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Targeted and cytotoxic inhibitors used in the treatment of breast cancer

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ABSTRACT

Breast cancer is the most commonly diagnosed malignancy and the fifth leading cause of cancer deaths worldwide. Surgery and radiation therapy are localized therapies for early-stage and metastatic breast cancer. The management of breast cancer is determined in large part by the HER2 (human epidermal growth factor receptor 2), HR (hormone receptor), ER (estrogen receptor), and PR (progesterone receptor) status. Our views of breast cancer are evolving as its molecular hallmarks are examined, which now include immunohistochemical markers (ER, PR, HER2, and proliferation marker protein Ki-67), genomic markers (*BRCA1/2* and *PIK3CA*), and immunomarkers (tumor-infiltrating lymphocytes and PDL1). About two-thirds of malignancies of the breast are HR-positive/HER2-negative; accordingly, endocrine-based therapy is a major treatment option for these patients. Hormonal or endocrine therapy includes selective estrogen receptor modulators (SERMs) such as raloxifene, tamoxifen and toremifene, selective estrogen-receptor degraders (SERDs) including elacestrant and fulvestrant, and aromatase inhibitors such as anastrozole, letrozole, and exemestane. A variety of cytotoxic chemotherapeutic agents are used to treat HR-negative breast cancer patients. These agents include taxanes (docetaxel, nab-paclitaxel, and paclitaxel), anthracyclines (doxorubicin, epirubicin), anti-metabolites (capecitabine, gemcitabine, fluorouracil, methotrexate), alkylating agents (carboplatin, cisplatin, and cyclophosphamide), and drugs that target microtubules (eribulin, ixabepilone, ado-trastuzumab emtansine). Patients with ER-positive tumors are treated with 5–10 years of endocrine therapy and chemotherapy. For patients with metastatic breast cancer, standard first-line and follow-up therapy options include targeted approaches such as CDK4/6 inhibitors, PI3K inhibitors, PARP inhibitors, and anti-PDL1 immunotherapy, depending on the tumor type and molecular profile.

1. An overview of breast cancer

Sung et al. reported that female breast cancer is the most diagnosed cancer worldwide with an incidence of 2261,419 (11.7 % of all cancers) in 2020 and an overall death tally of 684,996 (6.9 % of all cancer deaths) [1]. They also report that female breast cancer is the most diagnosed malignancy (accounting for 11.7 % of total cases), followed by lung (11.4 %), colorectal (10.0 %), prostate (7.3 %), and stomach (5.6 %) cancers. Female breast cancer is the fifth leading cause of cancer mortality worldwide, with 685,000 deaths. Among women, breast cancer accounts for one in four cancer cases and for one in six cancer deaths, ranking first for incidence and mortality in the majority of countries. For 2024, Siegel et al. estimated that 310,720 women and 2790 men in the United States will develop breast cancer and 42,250 women and 530 men will die of the disease [2]. For women, breast cancer, lung cancer, and colorectal cancer in that order account for 51 % of all new cancer diagnoses, with breast cancer alone accounting for 32 % of cases. The overall probability of a female developing breast cancer in the United States during her lifetime is one in eight and the probability of dying from the disease is one in 43 [3]. Breast cancer mortality among women in the United States peaked in 1989 and has since decreased by 42 % through 2021, translating to the avoidance of more than 490,000 deaths. This progress is ascribed to earlier diagnosis through mammography, increased awareness, and is linked to improvements in treatment [2]. As noted above, women are 100 times more likely to develop breast cancer than men. The data indicate that the incidence of

Abbreviations: ArI, aromatase inhibitor; CDK, cyclin-dependent protein kinase; CNS, central nervous system; DCIS, ductal carcinoma in situ; DFd, diflourodeoxy; EGFR, epidermal growth factor receptor; ER, estrogen receptor; FDA, Food and Drug Administration of the United States; 5-FU, 5-flourouracil; HER2, human epidermal growth factor receptor-2 aka ErbB2; HR, hormone receptor; MAPK, mitogen activated protein kinase; PARP, a poly ADP-ribose polymerase; PD1, programed cell death protein 1; PDL1, programed cell death protein 1 ligand 1; PI3K, phosphatidylinositol 3-kinase; PKA, protein kinase A; PKB, protein kinase B aka AKT; PKC, protein kinase C; PR, progesterone receptor; Ro5, Lipinski's rule of 5; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator; TNBC, triple-negative breast cancer.

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breast cancer increases between the ages of 35 and 75 years, plateaus between 75 and 80 years, and then decreases [3]. The median age at the time of breast cancer diagnosis is 62 and the median age at the time of death is 68 years.

Risk factors for developing breast cancer include female gender, age, germline mutations of high penetrance, strong family history, and a high breast density [4]. Other risk factors include early menarche (age less than 12 years), a late menopause (an age greater than 55 years), late first pregnancy (an age greater than 35 years), nulliparity, absence of breastfeeding, high alcohol intake, cigarette smoking, and exogenous postmenopausal hormone therapy. Many women with breast cancer do not have any known risk factors and the relative probability associated with each of the above correlative factors is usually modest. The relative risk of breast cancer is reduced by 7.0 % for each birth and 4.3 % for every 12 months of breastfeeding. Higher rates of breast cancer have occurred alongside increases in potentially-modifiable risk factors such as obesity. An increasing body-mass index (BMI) is associated with heightened probability of developing postmenopausal breast cancer, but with a decreased chance of developing premenopausal breast cancer. Risk is lower in those with higher levels of self-reported physical activity. Current evidence suggests that breast-cancer survivors should avoid weight gain, be physically active, and eat a healthy diet for overall wellbeing. When a genetic aberration is found, it is usually a loss of function in the *BRCA1* or the *BRCA2* gene. About 70 % of women with loss of function *BRCA1/2* mutations develop breast cancer by the age of 80 years.

Common breast-related symptoms that prompt patients to seek medical care include pain (in about 25 % of patients), nipple discharge (15 % of patients), inflammation (2 %), palpable mass (24 %), and lumpiness or other symptoms (34 %) [5]. Although these symptoms cause concern, only (i) 5 % of patients that present with pain have breast cancer, (ii) 7 % with nipple discharge, (iii) < 1 % with inflammation, (iv) 5 % with a palpable mass, and (v) 1 % with lumpiness. Mammographic screening was initiated in the 1980s with the goal of detecting non-palpable asymptomatic breast cancers and it is currently the most commonly used screening procedure. The average size of invasive breast cancers detected by mammography is about 1 cm and this is significantly smaller than cancers that can be detected by palpation. However, about 10 % of invasive carcinomas are not observed by standard mammography.

Nearly all invasive breast cancers are ductal adenocarcinomas [5]. Invasive breast carcinomas are graded using the Nottingham Histologic Score [5,6]. They are evaluated for tubule formation, nuclear pleomorphism, and mitotic rate. Grade I tumors are well-differentiated cancers that grow in a cribriform or tubular pattern, have small uniform nuclei, and have a low proliferative rate. Grade II carcinomas are moderately differentiated with cells growing in solid clusters or single infiltrating cells with nuclear polymorphisms and high numbers of mitotic figures. Grade III malignancies invade as solid sheets or ragged nests of cells with enlarged irregular nuclei exhibiting a high proliferative rate often with areas of tumor necrosis. Furthermore, breast cancers are separated into three major groups based upon the expression of two proteins, the estrogen receptor (ER) and HER2 (also known as ErbB2). Luminal A cancers are ER-positive and HER2-negative with a low level of Ki67 expression, a protein found in the nucleus of dividing cells. Luminal B cancers are ER-positive cancers and HER-negative with a high level of Ki67 expression (Ki is an abbreviation for the German city Kiel and 67 is the number of the original clone found in a 96-well plate). Triple-negative breast cancers (TNBCs) are negative for ER and HER2; they are called triple negative because they also fail to express the progesterone receptor (PR), which is under the control of the estrogen receptor. These three groups of invasive breast cancers differ with respect to pathological features, metastatic patterns, treatment responses, time to relapse, and clinical outcomes.

The outcome for women with breast cancer depends upon the stage of the disease at the time of diagnosis and the biologic features of the carcinoma (the molecular and histologic type) [7,8]. The 8th edition American Joint Committee on Cancer (AJCC) staging system combined the anatomic stage (AS) with the receptor status and cancer grade to construct a prognostic stage (PS). The anatomic staging is given in Table 1. The AJCC staging system for breast cancer is dependent on tumor size (T), nodal status (N), and metastases (M) to guide patient management and to predict patient outcomes. The 8th edition staging combines the traditional TNM system with ER status, PR status, HER2 status, and tumor grade. When available, Oncotype® multigene assays are incorporated into the prognostic staging system, the genes of which are listed in Table 2. Of these genes, Ki67 has attracted the most attention. Based upon the biological and molecular features of breast cancer, some patients have a normal life expectancy whereas others have a 10 % chance of being alive in five years. Patients who present with distant metastases (5 %) or with an inflammatory carcinoma (1–5 %) have a poor prognosis. Metastasis beyond the axillary lymph nodes is the most important negative prognostic indicator followed by spread to the axillary and regional lymph nodes. Moreover, survival decreases with a higher histologic tumor grade. Survival is highest for ER-positive, PR-positive, and HER2-negative disease and is lowest for triple negative disease. The percentage of patients that are ER-positive is about 80 %, about 65 % of patients are both ER- and PR-positive, about 15–20 % are HER2-positive, and 10–20 % are triple negative (ER-negative, PR-negative, and HER2-negative).

2. Treatment options for breast cancer

2.1. An overview of treatment modalities

Surgery and radiation therapy represent localized therapies for primary and metastatic breast cancer [9,10]. Moreover, a variety of systemic treatments are prescribed for breast cancer therapy. The management of breast cancer is determined in large part by the HER2 and HR status [11,12]. Nearly two-thirds of breast cancers are HR-positive/HER2-negative and endocrine therapy is a major treatment option for these patients. The clinical profile of endocrine therapeutic drugs with their high efficacy and tolerability facilitated their widespread adoption. Endocrine therapy encompasses different classes of drugs including selective estrogen receptor modulators (SERMs) such as raloxifene, tamoxifen and toremifene, the selective estrogen-receptor degraders (SERDs) like elacestrant and fulvestrant, the gonadotrophin-releasing hormone (GnRH) agonists like goserelin and leuprolide, and the aromatase inhibitors including anastrozole, exemestane, and letrozole. Although SERMS are widely used for patients with breast cancer, their efficacy is limited and almost 25 % of patients with primary and advanced-stage disease develop resistance during their treatment.

A variety of cytotoxic chemotherapeutic agents are used to treat HR-negative breast cancer patients or patients whose tumors are growing rapidly [10]. These agents include the taxanes (docetaxel, nab-paclitaxel, and paclitaxel), the anthracyclines (doxorubicin, epirubicin), anti-metabolites (capecitabine, gemcitabine, fluorouracil, methotrexate), alkylating agents (carboplatin, cisplatin, and cyclophosphamide), and drugs that target microtubules (eribulin, ixabepilone, ado-trastuzumab emtansine). Several targeted inhibitors are used for the treatment of HER2-positive breast cancers including fam-trastuzumab deruxtecan-nxki, margetuximab-cmkb, the small molecule kinase blockers of HER2 including lapatinib, neratinib, and tucatinib, the CDK4/6 inhibitors such as abemaciclib, palbociclib, and ribociclib, the AKT kinase antagonist capivasertib, the mTOR antagonist everolimus, and the PI3K blockers alpelisib and inavolisib.

2.2. Endocrine-based therapy

Aromatase inhibitors (ArIs) block the action of aromatase or estrogen synthase [13]. It is a member of the cytochrome P450 superfamily of

Table 1
The 8th edition American Joint Committee on Cancer (AJCC) staging system[a].

Stage	T: Tumor		N: Lymph nodes		M: Distant metastasis		Clinical Group	10-Year Survival (%)
0	Ductal carcinoma in situ		No metastases	N0	None	M0	Primary operable breast cancer	97
I	Invasive carcinoma ≤ 2 cm	T1	No metastases	N0	None	M0		87
IIA	Invasive carcinoma > 2 cm	T0	1–3 positive	N1	None	M0		65
		T1		N1	None	M0		
		T2		N0	None	M0		
IIB	Invasive carcinoma > 5 cm	T2	0–3 positive	N1	None	M0		
		T3		N0	None	M0		
IIIA	Invasive carcinoma > 5 cm	T3	Negative or positive	N1	None	M0		40
		T0		N2	None	M0	Locally advanced breast cancer	
		T1		N2	None	M0		
		T2		N2	None	M0		
		T3		N2	None	M0		
IIIB	Any size invasive carcinoma	T4	≥ 4 positive	N0	None	M0		
		T4		N1	None	M0		
		T4		N2	None	M0		
IIIC	Invasive carcinoma with skin or chest wall involvement or inflammatory carcinoma	Any T	Negative or positive	N3	None	M0		
IV	Any size invasive carcinoma	Any T	Negative or positive	Any N	Positive	M1	Metastatic disease	5

[a] Adapted from Refs. [7,8]

Table 2
The Oncotype DX Breast Recurrence Score® test includes the following 21 genes.

Proliferation-related genes	*Ki67, STK15, BIRC5, CCNB1, MYBL2*
Metastasis-related genes	*MMP11, CTSL2*
HER2-related genes	*GRB7, HER2*
Sex hormone-related genes	*ER, PR, BCL2, SCUBE2, GSTM1, BAG1, CD68*
Internal control genes	*ACTB, GAPDH, GUS, RPLPO, TFRC*

monooxygenases and it catalyzes the demethylation of androgen carbon 19 thereby producing phenolic aromatic 18-carbon estrogens. The human aromatase gene, *CYP19*, has a 93 kb 5′-regulatory region and a 30 kb 3′-coding region. The regulatory region contains tissue-specific promoters that control local estrogen biosynthesis. In postmenopausal women, the conversion of androgens to estrogens via this pathway in adipose tissue, the adrenal glands, muscle, and skin is the primary source of estrogen. Aromatase inhibitors including anastrozole, exemestane, and letrozole (Table 3) block this pathway and consequently suppress estrogen levels in postmenopausal women. Breast cancer cells also demonstrate aromatase activity, a likely source of local estrogen for the tumor cells. The inhibition of aromatase lowers plasma estrogen levels by about 90 %, which decreases estrogen-mediated cancer cell proliferation in HR-positive breast cancer. In premenopausal women, aromatase inhibitors induce an increase in pituitary gonadotropin secretion resulting from reduced negative estrogen feedback, producing ovarian stimulation. This action precludes the use of aromatase inhibitors for the treatment of HR-positive breast cancer in premenopausal women.

Tamoxifen binds to and blocks the binding of estrogen to the ER in breast cancers [9,10]. The drug alters the three-dimensional shape of the receptor and blocks its binding to estrogen response elements on DNA. It also decreases the production of insulin-like growth factor 1 (IGF-1), a paracrine growth factor. In breast cancer cells, tamoxifen is an ER antagonist, and the breast cancer cells die owing to this effect. In other tissues such as liver, uterus, and bone, tamoxifen acts as an ER agonist accounting for its classification as a selective estrogen receptor modulator (SERM). Owing to its ER agonist activity in bones, for example, tamoxifen prevents osteoporosis and bone fractures as compared with placebo or aromatase blockers. Raloxifene and toremifene are also SERMs with similar mechanisms of action [14]. Fulvestrant is a modified derivative of estradiol with an added alkyl-sulfinyl moiety, which is given intramuscularly [12,15]. In contrast with tamoxifen, it has complete anti-estrogenic effects and is devoid of agonistic effects. It exhibits a 100-fold greater affinity to ER than tamoxifen and initiates selective estrogen receptor degradation (SERD), which ultimately leads to the complete blockade of estrogen-sensitive gene transcription. Fulvestrant is FDA-approved for the treatment of ER-positive advanced (metastatic) breast cancer in postmenopausal women with disease progression after anti-estrogen therapy (either ArI or tamoxifen). Elacestrant is a non-steroid that is orally bioavailable and, like fulvestrant, leads to the degradation of the estrogen receptor. Unlike fulvestrant, elacestrant readily crosses the blood-brain-barrier, where it can target breast cancer metastases in the brain.

2.3. Agents directly targeting DNA

Carboplatin and cisplatin are platinum-containing DNA alkylating agents that are used to treat a wide variety of cancers including those of the breast [16]. Anticancer chemotherapy with these platinum-containing drugs is based on the inhibition of tumor cell growth with DNA being the main target. The efficacy of these agents is associated with the suppression of DNA synthesis and repair because of the modification of the three-dimensional structure of DNA that is induced by these metal adducts. The antitumor effect of platinum-containing medications has been best studied for cisplatin. It binds preferentially to (i) the N7 atom of guanine, (ii) the N3 and the 4-amino group of cytosine, and (iii) the N1 and 6-amino group of adenine residues in DNA. The resulting interstrand and intrastrand DNA adducts alter the structure of DNA, inhibit replication and transcription, prolong the G2 phase of the cell cycle, and lead to programmed cell death (apoptosis). Moreover, cross-linking of two adjacent guanines on the same strand is a common modification. Carboplatin and cisplatin are usually given in combination with monoclonal antibodies and/or other drugs including cyclophosphamide, another alkylating agent [9,10,16]. Cyclophosphamide is orally bioavailable and is converted to aldophosphamide by the CYP2B group of P450 enzymes; this compound is transported by the circulation to cells where it undergoes non-enzymatic conversion to acrolein and a nitrogen mustard (phosphoamide mustard), the latter of which is the active agent [17]. Nitrogen mustards are cytotoxic organic compounds with the bis (2-chloroethyl) amino ($(ClC_2H_4)_2NR$) functional group. Nitrogen mustards are not related to the mustard plant; the name refers to their pungent odor.

Table 3
Classes of drugs used in the treatment of breast cancer.

(A) Antracyclines	**(H) Selected protein kinase blockers**
Doxorubicin	Capivasertib – AKT1/2/3 aka PKB
Epirubicin	Everolimus – mTOR
(B) Anti-metabolites	**(I) Alkylating agents**
Capecitabine – 5FU pro-drug	Carboplatin
Gemcitabine – dFdCTP into DNA	Cisplatin
Fluorouracil	Cyclophosphamide
Methotrexate	
(C) Taxanes – 20 carbon diterpene	**(J) CDK4/6 inhibitors**
Docetaxel	Abemaciclib
Nab-paclitaxel	Palbociclib
Paclitaxel	Ribociclib
(D) Microtubule inhibitors	**(K) PI3K blockers**
Ado-trastuzumab emtansine	Apelisib
Docetaxel – taxane	Inavolisib
Eribulin – macrocyclic compound	
Ixabepilone – macrocyclic compound	
Nab-paclitaxel – albumin-bound taxane	**(L) PARP inhibitors**
Paclitaxel – taxane	Olaparib
Vinorelbine – a vinca alkaloid	Talazoparib
(E) Aromatase inhibitors	**(M) GnRH desensitizers**
Anastrozole	Goserelin – a decapeptide – pre- and
Exemestane	perimenopausal patients
Letrozole	Leuprolide – a nonapeptide (appr prostate Ca)
(F) ER inhibitors	**(N) Anti-PD1 antibody**
Elacestrant – SERD	Pembrolizumab
Fulvestrant – SERD	
Raloxifene – SERM	
Tamoxifen – SERM	
Toremifene – SERM	
(G) HER2 antagonists	**(O) Calcium ion chelators used for the treatment of hypercalcemia of malignancy and bone pain**
Ado-trastuzumab emtansine	
Fam-trastuzumab deruxtecan-nxki	Pamidronate
Margetuximab-cmkb	Zoledronate
Lapatinib – ErbB1/2	
Neratinib – ErbB1/2/4	
Trastuzumab	
Tucatinib – ErbB2	

Doxorubicin and epirubicin, which are cornerstones in the treatment of breast cancer, are isomers and anthracycline derivatives with a tetracycline ring attached to a positively charged amino sugar [18]. These agents first form a complex with DNA by intercalating their planar rings between nucleotide base pairs; the rings insert between base pairs and lie perpendicular to the long axis of DNA and the amino sugar binds electrostatically to the DNA phosphate backbone. Naturally occurring DNA exists with negative supercoils with a counterclockwise twist. For every 10 deoxyribonucleotides added during replication, the parental double helix must make one complete turn around its axis. The rate of human DNA synthesis is about 3000 nucleotides per minute and each strand at each growing replication fork would have to rotate 300 times. To avoid this topological dilemma, DNA topoisomerases alter the superhelical structure of duplex DNA to obviate the need for rotation of the entire strand. There are two classes of topoisomerase: I and II. Topoisomerase I makes a nick in only one strand and allows the intact strand to pass through the nick, which is then closed. Topoisomerase II makes a nick in two strands and allows a duplex segment of DNA to pass through the open segment. One action of the topoisomerases is to relax negative supercoils during replication. Intercalation by doxorubicin or epirubicin inhibits replication and transcription and triggers DNA cleavage by topoisomerase II. The drugs also stabilize the topoisomerase II-DNA complex, resulting in irreversible DNA strand breakage, leading to cell death. One of the chief toxicities of these anthracyclines is cardiotoxicity. Despite considerable work, the mechanism for this side effect is unclear.

2.4. Taxanes and other microtubule targeted therapies

Taxanes were originally isolated and identified from plants of the genus *Taxus* (yews) and possess a taxadiene core [19]. They are a class of diterpenes composed of four isoprene units. Paclitaxel (Taxol) and docetaxel (Taxotere) are widely used chemotherapeutic agents that block the action of microtubules. The toxic effects of yew extracts have been known since ancient times. Not only are the poisonous properties of *Taxus* reported in the scientific literature but also in the Shakespeare play "Macbeth" and the Agatha Christie book "Pocket Full of Rye." Microtubules are polymeric heterodimers consisting of α-tubulin and β-tubulin. They are filamentous tube-shaped protein polymers that maintain cell shape and transport proteins and organelles such as mitochondria and vesicles. They also play an important role in cell migration, maintaining cell shape, and cell polarity. In addition, they play an essential role in cell division where tubulin undergoes alternating periods of structural growth and erosion known as dynamic instability. Microtubules extend outward from duplicated centrosomes during mitosis forming the mitotic spindle, which is responsible for chromosome separation and their allocation to daughter cells. Taxanes disrupt dynamic instability thereby promoting mitotic arrest that results in cell death by apoptosis. One problem with the taxanes is their insolubility in aqueous solutions. To increase efficacy, nab-paclitaxel (nanoparticle paclitaxel albumin-stabilized formulation), which is given intravenously, was developed. The paclitaxel is suspended in albumin instead of organic solvents, which makes it easier to tolerate than other taxanes.

Eribulin and ixabepilone are macrolides known as epothilones that are unrelated to taxanes but with functional groups properly positioned to mimic critical tubulin-binding groups. These agents destabilize microtubules by interfering with the elongation phase of dynamic instability promoting mitotic arrest and apoptosis. Ado-trastuzumab emtansine is an antibody-drug conjugate that consists of a monoclonal antibody (trastuzumab) targeting HER2, a non-cleavable thioether linker (4-[*N*-maleimidomethyl] cyclohexane1-carboxylate), and a microtubule inhibitor [20]. After binding to HER2-positive cells, the complex is internalized and degraded in lysosomes and releases DM1, a synthetic derivative of maytansine, a microtubule-targeted agent. DM1 produces mitotic arrest and apoptotic cell death. Various neuropathies are associated with treatment of drugs that target microtubules including the taxanes, macrocylic compounds, and DM1; these may result from the inhibition of microtubule-mediated neuronal axoplasmic transport.

2.5. Anti-metabolites

Like uracil, 5-flourouracil (5-FU) enters cells by facilitated transport [21]. Once inside, 5-FU is converted to 5-fluorouridine monophosphate (FUMP). FUMP is converted to the diphosphate and triphosphate in reactions involving ATP. FUTP can be incorporated into RNA and this incorporation diminishes the posttranscriptional processing and physiological activity of RNA leading to cellular toxicity. Fluorouridine diphosphate can be converted to fluorodeoxyuridine diphosphate (FdUDP) as catalyzed by ribonucleotide reductase. The dephosphorylation of FdUDP generates an inhibitor of thymidylate synthase (FdUMP). FdUMP binds to the nucleotide-binding site of thymidylate synthase, forming a stable, long-lasting ternary complex of the enzyme and N^5,N^{10}-methylene tetrahydrofolate thereby preventing the biosynthesis of dTMP. Consequently, the concentration of dTTP, a substrate for DNA polymerase, is lessened and the biosynthesis of DNA is impaired.

Depletion of dTTP affects the levels of other deoxyribonucleotides, including dATP. Imbalanced concentrations of deoxyribonucleotides can severely interfere with DNA synthesis and DNA repair and these effects result in cell death.

Capecitabine is an orally bioavailable carbamylated analogue of cytidine that is converted to fluorouracil in three steps [22,23]. Thymidine phosphorylase catalyzes the last step, which involves the conversion of 5'-deoxyfluoruridine to fluorouracil and a sugar phosphate. This enzyme is much more active in tumor cells than normal cells, which improves the tumor-selective generation of fluorouracil [24]. Concentrations of the active drug in tumor cells can be more than 3.5-fold higher than in the surrounding cells leading to a lower incidence of toxicity compared with fluorouracil therapy. The mechanism of action of 5-FU as given above involves its incorporation into RNA and its inhibition of thymidylate synthase.

Gemcitabine is another member of the anti-metabolite class of chemotherapeutics [25] including pharmaceuticals like 5-fluorouracil and capecitabine. The drug enters the cell via active nucleoside transporters and deoxycytidine kinase catalyzes its phosphorylation to yield difluorodeoxycytidine monophosphate from which point it is converted to difluorodeoxycytidine di- and triphosphate (dFdCDP/dFdCTP). The cytotoxic activity results from the competitive inhibition of dFdCTP with dCTP for DNA polymerase. Additionally, dFdCDP inhibits ribonucleotide reductase thereby depleting the pools of deoxyribonucleotide required for DNA synthesis. Following the incorporation of dFdCTP into DNA, DNA polymerase is released, the replication fork collapses, and the cell succumbs to apoptosis. Additionally, dFdCTP also adversely affects the ability of the cell to mediate DNA repair.

Methotrexate is an orally bioavailable folate antagonist that competes with 7,8-dihydrofolate for the dihydrofolate reductase enzyme [26]. The direct inhibition of the latter enzyme results in an increase in the concentration of cellular 7,8-dihydrofolate, which results in the feedback inhibition of thymidylate synthase. Consequently, the concentration of dTTP, a substrate for DNA polymerase, is diminished and the biosynthesis of DNA is impaired. Additionally, methotrexate blocks the activity of glycinamide ribonucleotide formyl transferase (GAR), an important enzyme in purine nucleotide biosynthesis. The resulting decreases in nucleotides and deoxyribonucleotides inhibits cell replication. Rapidly dividing cells are more sensitive to methotrexate than non-dividing cells, but normal cells are also subject to the inhibitory effects of methotrexate, which result in toxicity. If it were not for the conversion of the tetrahydro form of folate to the dihydro form of folate during the methyl transfer reaction catalyzed by thymidylate synthase, the inhibition of dihydrofolate reductase would not exert such a powerful effect on dividing cells.

2.6. *HER2 inhibitors*

Fam-trastuzumab deruxtecan-nxki is an antibody-drug conjugate consisting of a monoclonal antibody (trastuzumab) targeting HER2, a tetrapeptide-based protease-cleavable chemical linker, and a cytotoxic topoisomerase I inhibitor (deruxtecan) that is given by intravenous infusion in 21-day cycles [27,28]. Following binding to HER2 on tumor cells, fam-trastuzumab deruxtecan-nxki undergoes internalization and intracellular linker cleavage by lysosomal enzymes. Upon release from the lysosomes, the membrane-permeable topoisomerase blocker impairs the ability of the cell to replicate at the time of cell division and produces DNA damage and apoptotic cell death. Of interest, this medicine is effective in patients with tumors that express trace levels of HER2 (HER2 low). Ado-trastuzumab emtansine is another antibody-drug conjugate that targets HER2 whose mechanism of action is given in Section 2.3.

Margetuximab is an engineered fragment crystallizable (Fc) HER2-targeted IgG1 monoclonal antibody [29]. The Fab (fragment antigen-binding) domain of this antibody is derived from the same parental murine antibody as trastuzumab and both monoclonal antibodies bind to HER2 with high affinity. Direct binding of margetuximab to HER2 on the surface of tumor cells disrupts HER2 signaling and produces antiproliferative effects that are comparable with those mediated by trastuzumab. The engineered Fc region of margetuximab includes five amino acid substitutions (L235V, F243L, R292P, Y300L, and P396L) when compared with the trastuzumab. These modifications enhance antibody binding to FcγRIIIa (CD16A), an activating Fc gamma receptor (FcγR) while decreasing binding to FcγRIIb (CD32B), an inhibitory FcγR. As a result of these modifications, margetuximab stimulates Fc-dependent innate immune responses that include antibody-dependent cellular cytolysis (ADCC) mediated by natural killer (NK) cells, more effectively than the parent trastuzumab.

Lapatinib is a reversible orally effective 4-anilinoquinazoline inhibitor of ErbB1/EGFR, ErbB2/HER2, ErbB4/HER4 with IC_{50} values of 2.4, 7, and 54 nM, respectively [30]. Medicinal chemists and pharmacologists have studied the physicochemical properties of drugs that are orally effective. Lipinski's rule of five (Ro5) is a computational and experimental methodology that is used to assess water and lipid solubility, membrane permeation, and pharmacologic effectiveness in the drug-discovery setting [31]. This procedure is a rule of thumb that determines whether a drug has properties indicating that it would be orally bioavailable. The Lipinski rules stem from results showing that most orally effective drugs are relatively small and moderately lipophilic substances.

The Ro5 criteria indicate that less than ideal oral efficacy is more likely to occur when (i) the ALogP (atom-based calculated Log P) is larger than 5, when (ii) there are more than 5 hydrogen-bond donors, when (iii) there more than 5×2 or 10 hydrogen-bond acceptors, and when (iv) the molecular weight is more than 5×100 or 500 [30]. The partition coefficient (P) is the ratio of the concentration of the un-ionized drug in the organic phase divided by its concentration in the aqueous phase of water-saturated *n*-octanol. The P value reflects the hydrophobicity of a compound; the larger the P value, the greater the hydrophobicity. The number of hydrogen-bond donors represents the sum of NH and OH groups. The number of hydrogen bond acceptors is the sum of oxygen and nitrogen atoms. Lapatinib has two Ro5 violations; its molecular weight is 580 and its partition coefficient is 6.14 [32].

Neratinib is an orally bioavailable 4-anilino quinolidine irreversible inhibitor of EGFR/ErbB1, HER2/ErbB2, and HER4/ErbB4 with IC_{50} values of 1.1, 6, and 2.4 nM, respectively [33]. The mechanism of action of this medicinal involves the addition of a protein cysteine thiolate anion (protein—$S:^-$) to an acrylamide derivative ($CH2=CHC(=O)N(H)R$) where R denotes the pharmacophore. Such covalent modifications are commonly called Michael additions and each reaction results in the formation of a covalent bond between sulfur and carbon yielding a thioether. Covalent modification occurs in two discrete steps; the first step involves the reversible association of the drug with HER2 so that a weakly electrophilic functionality, a warhead, is bound near the appropriately positioned nucleophilic cysteine (C805 of HER2). In the second step, a reaction occurs between the warhead and C805 to form a covalently modified and inactive kinase. For this procedure to work, the warhead must be appropriately positioned near the cysteinyl thiolate so that the covalent modification can occur. Like lapatinib, neratinib has two Ro5 violations; its molecular weight is 557 and its atom-based partition coefficient is 5.93.

Tucatinib is an orally bioavailable quinazoline-4,6-diamine reversible competitive inhibitor of HER2 with an IC_{50} values of 450, 8, and 310 nM for EGFR, HER2, and HER4, respectively [30,34]. It has an atom-based calculated log P value of 5.09; otherwise, its makeup is within the Ro5 criteria. The *HER2* gene is overexpressed or amplified in approximately 15–20 % of breast cancer patients, which is linked with an unfavorable prognosis, tumor relapse, and worse outcomes, such as shorter progression-free survival (PFS) and overall survival (OS). The FDA approval of the drug for the treatment of HER2-positive breast cancer in 2020 adds to the various treatment modalities for this disorder. For a comprehensive review of the enzymology of the ErbB family, see Refs. [35–37].

2.7. CDK4/6 inhibitors

Cyclins and their associated CDKs (cyclin-dependent protein kinases) are required for traversing the cell division cycle [38,39]. People possess 13 cyclin groups (A, B, C, D, E, F, G, H, J, K, L, T, and Y) and 20 CDKs (1–20). Cyclins interact with CDKs as the first step in protein kinase activation. After forming the CDK-cyclin complex, the CDK undergoes phosphorylation at a conserved threonine residue in the activation segment that is catalyzed by CDK7 and results in the full expression of CDK-cyclin enzyme activity. The concentration of the CDKs are rather constant throughout the cell cycle. The catalytic activity of the CDKs that control passage through the cell cycle is regulated by the cyclins, proteins whose concentrations vary during the cell cycle. This oscillation of cyclin concentrations accounts for their names as they cycle up and down during cell growth and cell division. CDKs are regulated by a process that relies on the biosynthesis (which increases protein kinase activity) and degradation (which decreases enzyme activity) of their corresponding cyclins.

Human cyclins are a large family made up of about 13 groups of proteins with molecular weights extending from 35 to 90 kDa [38,39]. These proteins are expressed in specific stages of the cell cycle and are then broken down by an intricately controlled process that involves interactions with ubiquitin ligases (E3s) and proteasomes. To ensure proper progression through the cell cycle, cells have a series of checkpoints that block them from proceeding into the next phase before they have successfully completed their existing phase. The first checkpoint takes place at G1-S (which is named start, restriction point, or R-point) where G1-S and S-phase CDK-cyclins are activated during G1. After transiting the first checkpoint, completion of the cell cycle is independent of growth factors and mitogens. The G1-S enzymes include CDK4, CDK6, and the D1/2/3 cyclins, the different forms of which are expressed in a cell and tissue-specific fashion. The CDK2-cyclin E complex is needed for the S-phase transition. The second checkpoint occurs at G2-M as the M-phase CDK1-cyclin A/B complex undergoes activation and carries the cell to metaphase during mitosis. The metaphase-to-anaphase transition constitutes the third checkpoint, which goes on to sister-chromatid segregation, completion of mitosis, and cytokinesis as a parental cell completes cell division and forms two daughter cells. Progression occurs when the M-phase cyclin-CDK complexes activate the anaphase-promoting complex, which mediates the proteolysis of proteins that hold the sister chromatids together.

Following mitogenic stimulation, one or more cyclin D components – depending upon the cell type – are generated and lead to the activation of CDK4/6, which are crucial regulators of the G1-S transition [38,39]. The CDK4/6-cyclin D complexes mediate the phosphorylation of the retinoblastoma (Rb) protein at a unique site among 14 potential phosphorylation sites to produce monophosphorylated Rb that lasts for several hours in the G1-phase. CDK4 and CDK6 are protein kinases that possess narrow substrate specificity; these enzymes mediate the phosphorylation of Rb (RB1) and two other Rb-like family proteins (p107 or RBL1 and p130 or RBL2). The biosynthesis of cyclin D proteins is followed by the biosynthesis of cyclin E, cyclin A, and cyclin B along with the activation of their cognate CDKs. The production of cyclin E activates CDK2 later in the G1-phase thereby leading to (i) the hyperphosphorylation of Rb at all 14 sites and (ii) its deactivation.

Abemaciclib, palbociclib, and ribociclib are orally bioavailable reversible inhibitors of CDK4 and CDK6 [38,39]. The IC_{50} value of abemaciclib for CDK4-cyclin D1 is 2 nM and that for CDK6-cyclin D1 is 10 nM, respectively. The values for CDK1-cyclin B1, CDK2-cyclin E, and CDK7 cyclin H are greater than 1000 nM. The IC_{50} value of palbociclib for CDK4-cyclin D1 and CDK6-cyclin D2 are 11 nM and 15 nM, respectively. It is ineffective against CDK1-cyclin B, CDK2-cyclin E2, and CDK2-cyclin A with IC_{50} values greater than 10 μM. The IC_{50} value of ribociclib for CDK4-cyclin D1 is 10 nM and that for CDK6-cyclin D3 is 39 nM. The values for the three drugs were determined by different procedures and cannot be directly compared. Except for the molecular weight of abemaciclib of 507, all other parameters of these three drugs are in line with Lipinski's Ro5.

2.8. Other protein kinase antagonists

The PI3K/AKT/mTOR (phosphatidylinositol 3-kinase/AKT/mammalian target of the rapamycin) pathway participates in several crucial cellular functions including growth, proliferation, metabolism, and survival [30]. Stimulation of this signaling pathway is mediated by G protein-coupled receptors and receptor protein-tyrosine kinases located in the plasma membrane, which facilitate the recruitment of class I PI3Ks by adaptor proteins, such as the insulin receptor substrate (IRS). PI3K mediates the conversion of PIP_2 (phosphatidylinositol 4,5-bisphosphate) to PIP_3 (phosphatidylinositol 3,4,5-trisphosphate) as the phosphoryl group is linked to the 3' position of the inositol ring. PIP_3 functions as a second messenger that recruits and activates PKB/AKT, which in turn catalyzes the phosphorylation and inactivation of TSC1/2 (tuberous sclerosis complex 1/2), negative regulators of mTORC1 (mammalian target of rapamycin complex-1). Colocalization of AKT with PDK1 (3-phosphoinositide-dependent protein kinase 1) at the plasma membrane promotes the phosphorylation of AKT1 T308 within its activation segment leading to increased enzyme activity. These activities mediate cell growth and proliferation. The downstream consequences of PI3K activation can be blocked by PTEN (tumor suppressor phosphatase and tensin homolog) by the dephosphorylation of PIP_3 to regenerate PIP_2.

Everolimus binds to the FK Binding Protein-12 (FKBP-12 with a molecular weight of 12 kDa) to generate a complex that binds to and blocks the activity of mTOR, which is a protein-serine/threonine kinase that is a component of a signaling pathway involved in cell growth and metabolism [40]. Despite its high molecular weight (958 Da), everolimus is given orally. mTOR exists in two multiprotein complexes, mTORC1 and mTORC2, both of which are inhibited by everolimus. Allosteric inhibitors are those that do not bind to the active site of their target enzyme. In contrast to type III allosteric inhibitors that bind within the cleft of protein kinases between the small and large enzyme lobes, everolimus is a type IV allosteric antagonist that produces inhibition by binding to residues that are far from the ATP-binding site. Through its downstream effectors 4E-BP1 and S6K, mTOR participates in the initiation of the ribosomal translation of mRNA into proteins required for cell growth, cell cycle progression, and metabolism.

Capivasertib is an orally effective pyrrolo[2,3-*d*]pyrimidine derivative that blocks the activity of the AKT family of protein-serine/threonine kinases [30]. The AKT family consists of AKT1, AKT2, and AKT3. These three enzymes, which belong to the ACG protein kinase family (PKA, PKC, and PKG) have IC_{50} values of 3 nM, 7 nM, and 7 nM, respectively. The AKT family regulates cell proliferation, survival, migration, gene expression, and metabolism. AKT is commonly activated through signaling through PI3K as described above. Its physicochemical properties are in line with Lipinski's Ro5. Unlike most FDA approved protein kinase inhibitors, capivasertib is freely soluble in aqueous solutions.

2.9. PI3K blockers

The discovery of the PI3K (phosphatidylinositol 3-kinase) pathways was a major advance in deciphering eukaryotic signal transduction [41]. The substantial frequency of mutations in PI3K in many cancers fostered the development of drugs targeting these oncogenic mutants. The PI3Ks are divided into three classes; the Class I PI3Ks mediate the phosphorylation of PI-4,5-P_2 (phosphatidylinositol-4,5-bisphosphate) to generate PIP_3 (phosphatidylinositol-3,4,5-trisphosphate) according to the following equation.

$$ATP + \text{PI-4,5-}P_2 \rightarrow \text{PI-3,4,5-}P_3 + ADP$$

The class I PI3Ks consist of p110α, p110β, p110δ, and p110γ catalytic subunits and are encoded by the following genes: *PIK3CA, PIK3CB,*

PIK3CD, and *PIK3CG*, respectively. These enzymes bind constitutively to regulatory subunits including p85α, p85β, p55γ, p101, and p87. The p55/p85 regulatory subunits form heterodimers with p110α or p110δ that are regulated largely by receptor protein-tyrosine kinases. The p87 and p101 regulatory subunits form complexes with p110γ that are regulated chiefly by GPCRs (G protein-coupled receptors). Complexes containing the p110β subunit are activated by GPCRs as well as receptor protein-tyrosine kinases. Following the generation of PIP_3, the AKT and mTOR protein-serine/threonine kinases are activated leading to cell growth, proliferation, and survival. Class II PI3Ks mediate the conversion of PI-4-P to PI-3,4-P_2 and Class III PI3Ks catalyze the conversion of PI to PI-3-P. Our main concern relating to breast cancer focuses on the Class I enzymes.

Mutations involving the PI3K pathways are among the most common gene alterations observed in cancers. *PI3KCA* is the second most highly mutant protein observed in cancer following only p53 [42]. About 80 % of breast cancers are ER-positive and about 40 % of ER-positive/HER2-negative breast cancer patients bear *PIK3CA* mutations so that the number of potential breast cancer patients that could be treated with PI3K blockers corresponds to about 32 % of all breast cancer patients [43]. Alpelisib is a thiazo-pyrrolidine derivative that reversibly blocks the activity of PI3Kα with an IC_{50} value of 4.6 nM. The IC_{50} values for PI3Kβ (1160 nM), PI3Kδ (290 nM), and PI3Kγ (250 nM) are considerably greater. Inavolisib is a dihydroimidazo [1,2-*d*][1,4] benzoxazepine derivative that antagonizes the activity of PI3Kα with an IC_{50} value of 0.038 nM. Besides blocking the activity of PI3Kα, the medicinal induces the degradation of the enzyme. The drug is 1/300th as potent against PI3Kβ/δ/γ. Both drugs are orally bioavailable and possess physicochemical properties within Lipinski's Ro5. Hyperglycemia is a major side effect of these two medicinals and is an on-target side effect associated with PI3K pathway inhibitors [44,45].

2.10. PARP inhibitors

DNA undergoes continual damage resulting from the generation of reactive oxygen species and electromagnetic radiation; maintaining genome stability is required for cell survival as the accumulation of errors leads to cell death [45–48]. PARP1 (NAD^+ ADP-ribosyltransferase 1) and PARP2 (NAD^+ ADP-ribosyltransferase 2) are the two most studied members of a family of 16 PARP enzymes with varied actions. For example, PARP1/2 are involved in DNA repair and PARP5a/5b (also known as tankyrases 1/2) regulate Wnt signaling; both of these processes are involved in malignant transformation. PARP1/2 catalyze the conversion of NAD^+ (nicotinamide adenine dinucleotide) to polymers that are covalently linked to PARP1/2 and to other proteins; these polymers can contain up to 200 ribonucleoside units. PARP1, the most abundant and well-studied member, participates in key pathways that (i) repair single-strand breaks (SSB), (ii) repair double-strand breaks (DSB), and (iii) stabilize DNA replication forks. PARP1 attaches poly (ADP-ribose) to itself and other proteins by PARylation, which attracts other enzymes before PARP dissociates, thereby facilitating access to the site of DNA damage. PARP2, which is less abundant than PARP1, acts in a similar fashion.

Cancers with greater degrees of homologous recombination deficiency (HRD) are more sensitive to PARP inhibitors than tumors with robust homologous recombination activity [46]. The genetic interaction between PARP action and *BRCA1/2* mutation is synthetic lethal, which describes a situation in which the action of the drug combined with the action of the BRCA1/2 gene product together result in cell death, but inhibition by the drug or the presence of a *BRCA1/2* mutation does not [48]. Owing to synthetic lethality, defects in BRCA1/2 render cells vulnerable to PARP antagonists. PARP enzymes preferentially promote double-strand break (DSB) repair through the high-fidelity homologous recombination pathway, which includes *BRCA*1 and *BRCA*2 tumor suppressor proteins – thereby foregoing the error-prone alternate non-homologous end-joining pathway. When this high-fidelity pathway is compromised in cancers with homologous recombination deficiency (HRD), including tumors harboring *BRCA1* and *BRCA2* mutations, PARP inhibitors display greater efficacy. The specific mechanisms of action of PARP inhibitors are intricate. Besides blocking PARP polymerase activity, the formation and trapping of PARP-DNA complexes at single strand breakpoints prevent DNA repair, leading to additional formation and accumulation of lethal double strand breaks. PARP trapping is a mechanism where the PARP molecule is trapped on the DNA, which interferes with the ability of the cell to replicate.

Olaparib is a phthalazine derivative and talazoparib is a 1,2,4 triazole derivative that blocks the action of human PARP1/2 [45,48]. Both drugs bind to the nicotinamide binding site of their target enzymes. The former drug has IC_{50} values of 5 nM and 1 nM and the latter drug has IC_{50} values of 0.57 nM and 0.87 nM for PARP1 and PARP2, respectively. Both drugs are orally effective small molecules and their physicochemical properties fall within preferred Lipinski Ro5 values. Talazoparib, the most cytotoxic FDA-approved PARP inhibitor, traps PARP to DNA with ~100-fold greater potency relative to olaparib, but it has a similar catalytic inhibitory potency as compared with olaparib. Although PARP trapping is the chief mechanism of cytotoxicity, a combination of both PARP catalytic inhibition and trapping is important in their therapeutic activity.

3. Treatment of breast cancer

3.1. Ductal carcinoma in situ

Ductal carcinoma in situ (DCIS) is characterized by the clonal proliferation of epithelial cells limited to breast ducts and lobules by the basement membrane [49]. Essentially all molecular changes found in invasive carcinomas occur in these neoplasms. DCIS is usually detected by mammography as a result of calcifications associated with necrosis (cell death). It can develop into invasive cancer, with a rate of approximately 30 % for low and intermediate grade and 60 % for high-grade disease, within 5–20 years. Many of these patients are treated either with breast-conserving surgery (lumpectomy) or mastectomy. They may also have radiotherapy and endocrine therapies to decrease the risk of malignant transformation. There is a growing controversy about the overdiagnosis and overtreatment for mammography-screen-detected low-risk DCIS in patients with low histologic grade and small non-palpable lesions. As reported by Chen et al., the pooled invasive ipsilateral breast tumor event (iIBTE) rate in women with low-risk DCIS was 3.3 % at 5 years and 5.9 % at 10 years [9]. Compared to patients who did not receive surgery, those who underwent surgery for low-risk DCIS had lower ipsilateral tumor rates and there was also a trend toward improved 10-year breast cancer specific survival rates (BCSS). In comparison to these survival rates, mastectomy and additional radiation therapy after breast conserving surgery were also associated with a reduced rate of ipsilateral tumor events.

As for DCIS in general, current treatment options for low-risk disease involve surgery, often followed by radiation therapy and endocrine treatment [50]. About half of the recurrences among these patients are invasive carcinoma and a benefit for radiation therapy was observed (50 Gy in 25 fractions where Gy – gray – is the energy of one joule per kilogram) with a reduction of both invasive and non-invasive recurrences. Whether breast-conserving surgery (lumpectomy) is followed by whole breast radiotherapy, partial breast radiotherapy, or no radiotherapy is an important decision that focuses on the magnitude of risk reduction that is important to each patient and the level of treatment burden and toxicity that she is willing to accept. About 80 % of DCIS lesions are ER-positive and endocrine therapy reduces local recurrence after breast-conserving therapy and prevents the development of new primary breast cancers in the contralateral breast. Tamoxifen reduces ipsilateral events with or without radiation therapy and substantially reduces contralateral events. The addition of tamoxifen to radiation therapy is especially useful in younger patients with ER-positive DCIS in

whom the risk of local recurrence is higher and the toxicity of tamoxifen may be less than that observed in older people. The use of an aromatase inhibitor such as anastrozole is as effective as tamoxifen for DCIS in postmenopausal women.

3.2. Early-stage breast cancer

Early-stage breast cancer includes cancers that have not spread beyond the breast or the axillary lymph nodes [51,52]. These include ductal carcinoma in situ and stage I, stage IIA, stage IIB, and stage IIIA breast cancers. From the initial description of radical mastectomies by William S. Halstead in 1894, to the current standard of multimodal therapy for breast cancer (neoadjuvant and adjuvant treatment, radiation therapy, and surgery), women diagnosed with breast cancer are living longer with improved cancer-related mortality rates. For women with early-stage breast cancer, mastectomy and breast conservation therapy (lumpectomy plus radiation) have equivalent disease free and overall survival rates. About 5 % of breast cancer patients undergo oncoplastic breast surgery that entails the immediate reconstruction of a partial mastectomy defect using general plastic surgery principles for tissue rearrangement. Such techniques allow for increased excisional volumes without compromising aesthetic quality and they minimize the potential for poor cosmesis (concerning appearance) following surgery.

The rationale for using neoadjuvant therapy in breast cancer is to reduce the size of tumors before surgery [53]. It was initially employed in locally advanced inoperable breast cancer, but it is currently used in other situations. This procedure can make the surgery easier to perform, less invasive, and more successful. Neoadjuvant therapy can also allow a patient to have a lumpectomy instead of a mastectomy. Recommended neoadjuvant regimens generally consist of anthracyclines and a taxane, with dose-dense (standard doses at shorter intervals between cycles) anthracyclines and weekly paclitaxel [54]. For patients with HER2-positive cancers, combined anti-HER2 therapy (pertuzumab and trastuzumab) is indicated together with neoadjuvant therapy in women with an increased risk of recurrence. For women with triple-negative disease, the addition of carboplatin to neoadjuvant therapy improves the pathological complete response rate (no tumor cells in the breast and lymph nodes after treatment) and the survival rate. The use of platinum salts is one of the standard treatments of triple-negative breast cancer with more effective benefit in younger patients [53]. The addition of immune checkpoint inhibitors is also of benefit in triple negative breast cancer. Other neoadjuvant regimes include cyclophosphamide with doxorubicin or epirubicin. For HR-positive/HER2-negative cancers, neoadjuvant therapy with immune checkpoint inhibitors may increase the therapeutic efficacy in high-risk breast cancer patients (those with *BRCA1/2, PTEN,* or *TP53* mutations). Fam-trastuzumab deruxtecan-nxki and pembrolizumab are monoclonal antibodies that are also used in the neoadjuvant setting for breast cancer (Table 4).

3.3. Treatment of metastatic breast cancer

3.3.1. HR-positive and HER2-negative/positive tumors ± visceral crisis

The goals in the treatment of metastatic disease are to alleviate symptoms, enhance the quality of life, and extend survival [9]. Patients with stage IV breast cancer that are HR-positive and HER2-negative are evaluated for therapy depending on whether they have a visceral crisis. The latter exhibits signs and symptoms of severe organ dysfunction and rapid disease progression. There are different types of visceral crises including those of the liver, lung, bone marrow, and other organs. The most common type involves the liver, which accounts for about 30–50 % of all such cases. These patients have a poor prognosis and require aggressive treatment. The recommended therapies are linked to minimal toxicity together with improved overall survival. The first-line treatment of patients with HER2-negative recurrent unresectable (local or regional) breast cancer or stage IV disease in postmenopausal patients or premenopausal patients receiving ovarian suppression with a visceral crisis and a germline *BRCA1/2* mutation includes the use a PARP blocker (Table 5). Systemic chemotherapy is recommended for those patients without a *BRCA1/2* mutation. Monoclonal antibodies and chemotherapy are used for second-line and third-line therapies.

HER2-negative postmenopausal women or premenopausal patients receiving ovarian suppression that are not in a visceral crisis are treated with an aromatase inhibitor or fulvestrant with a CDK4/6 blocker in the first-line setting (Table 6) [9]. Everolimus and endocrine therapy represent a recommended second-line therapy. HER2-positive postmenopausal women or premenopausal patients receiving ovarian suppression not in a visceral crisis are treated with an aromatase inhibitor ± trastuzumab or ± lapatinib, or with both. Fulvestrant ± trastuzumab or tamoxifen ± trastuzumab are additional therapeutic options. Endocrine therapy is less toxic than chemotherapy. However, chemotherapy is recommended for individuals whose cancers no longer respond to endocrine therapy or for those patients who need a rapid treatment response for a visceral crisis.

3.3.2. HR-negative/HER2-negative (triple negative) breast cancer

Triple-negative (ER/PR/HER2-negative) breast cancer (TNBC), which constitutes about 10–20 % of all breast tumors, has the poorest prognosis among breast cancer subtypes [9,55]. It often occurs in young women and is an aggressive disease with a high mortality rate. Conventional chemotherapy has shown significant efficacy against this disorder. However, its adverse side effects are problematic and some people fail to achieve any meaningful clinical improvements from systemic treatment. Systemic chemotherapeutic agents that have been used in patients with low PDL1 expression include anti-metabolites (5-flourouracil, capecitabine, gemcitabine), topoisomerase II blockers (doxorubicin, epirubicin), microtubule-directed agents (eribulin, ixabepilone, vinorelbine – used off label), taxanes (docetaxel, paclitaxel), and cyclophosphamide (Tables 3 and 7). Chemotherapy with carboplatin and cisplatin continues to be one of the primary options for treating patients with TNBC. In patients with high PDL1 expression, pembrolizumab and chemotherapy with nab-paclitaxel, paclitaxel, or gemcitabine are recommended first-line treatments. For patients with germline *BRCA1/2* mutations, PARP blockers (olaparib or talazoparib) and/or chemotherapy (cisplatin or carboplatin) are recommended first-line treatments. Sacituzumab govitecan is an antibody-drug conjugate that is approved for the third-line treatment of triple-negative disease.

3.3.3. HER2-positive and HR-positive or HR-negative breast cancer

Gradishar et al. report that the preferred first-line treatment options for HER2-positive and HR-positive or HR-negative metastatic disease include pertuzumab, trastuzumab, and a taxane (docetaxel or paclitaxel) (Table 8) [9]. They also report that fam-trastuzumab is effective in the treatment of HER2-positive breast cancer in the second-line setting and ado-trastuzumab is efficacious for the treatment of these cancers in the third-line setting. Furthermore, these authors conclude that tucatinib in combination with trastuzumab and capecitabine is appropriate as a third-line therapy for HER2-positive patients and they are preferred for those patients with CNS metastases. This review panel noted that tucatinib may be considered in the second-line setting if the patient has CNS metastases. For patients that are HR-positive/HER2-negative with *PI3KCA* or *ESR1* mutations, the panel recommends (a) apelisib with fulvestrant and (b) elacestrant therapy, respectively (Table 9). Patients bearing tumors with deficient mismatch repair, a high tumor mutation burden, or microsatellite instability are treated with pembrolizumab.

3.3.4. Endocrine-based therapy for HR-positive patients

Abemaciclib and palbociclib are CDK4/6 inhibitors that are used for the treatment of HR-positive/HER2-negative patients (i) in combination with an aromatase inhibitor as a first-line therapy, and (ii) in combination with fulvestrant as a second-line therapy (Table 4) [9]. Abemaciclib alone is also approved for the third-line treatment of metastatic

Table 4
FDA-approved medicinals, their targets, and therapeutic indications for breast cancer[a].

Drug	Properties	Company	Trade name	Year approved	Targets	Therapeutic indications
Abemaciclib	MW = 507	Eli Lilly	Verzenio	2017	CDK4/6	This medicine is a kinase inhibitor used for the treatment of patients with HR-positive, HER2-negative breast cancer (i) in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of node-positive, early breast cancer with a high risk of recurrence, (ii) in combination with an aromatase inhibitor as initial endocrine-based therapy for advanced or metastatic disease, (iii) in combination with fulvestrant for advanced or metastatic cancer with disease progression following endocrine therapy, and (iv) as a monotherapy for advanced or metastatic cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.
Ado-trastuzumab emtansine	Humanized IgG1κ	Lonza	Kadcyla	2023	ErbB2	This agent is a HER2-targeted antibody and microtubule inhibitor conjugate (DM1) that is prescribed as a single agent for (i) the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination (patients should have either received prior therapy for metastatic disease or developed disease recurrence during or within six months of completing adjuvant therapy) and (ii) the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment. The drug undergoes receptor-mediated internalization into target cells and is catabolized in lysosomes where DM1-containing catabolites are released and bind tubulin to cause mitotic arrest and cell death.
Anastrozole	MW = 293	ANI Pharm.	Arimidex	1995	Aroma-tase	This drug is used for the (i) adjuvant treatment of postmenopausal women with HR-positive early breast cancer, (ii) first-line treatment of postmenopausal women with HR-positive or HR-status unknown locally advanced or metastatic breast cancer, (iii) second-line treatment of advanced breast cancer that has progressed on tamoxifen therapy, and (iv) second-line treatment for the prevention of HR-positive breast cancer.
Alpelisib	MW = 441	Novartis	Piqray	2019	PI3K	This compound is a kinase inhibitor that is prescribed in combination with fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative, *PIK3CA*-mutated metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.
Capecitabine	MW = 359	Genentech	Xeloda	1998	DNA Bio-synthesis	This agent is used for the treatment of metastatic breast cancer (i) in combination with docetaxel after failure of prior anthracycline-containing therapy and (ii) as a monotherapy in patients resistant to both paclitaxel and an anthracycline-containing regimen. This pro-drug is metabolized to 5-fluorouracil, the active ingredient.
Capivasertib	MW = 429	AstraZeneca	Truqap	2023	AKT1/2/3	This medicinal is a kinase inhibitor that is prescribed in combination with fulvestrant for the treatment of patients with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with one or more *PIK3CA/AKT1/PTEN*-alterations as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.
Carboplatin	MW = 371	Hospira	Paraplatin	1989	DNA	This agent is used for the treatment of locally advanced metastatic triple-negative breast cancer in combination with other chemotherapeutic agents. It promotes the formation of DNA intra- and inter-strand cross-links and inhibits DNA replication and transcription.
Cisplatin	MW = 301	Bristol Myers Squibb	Platinol	1978	DNA	This DNA cross-linking reagent is used for the treatment of (i) metastatic breast cancer and (ii) triple-negative breast cancer, often given with gemcitabine. It promotes the formation of DNA intra- and inter-strand cross-links and inhibits DNA replication and transcription.
Cyclophos-phamide	MW = 261	Baxter	Cyclophos-phamide	1959	DNA	This alkylating agent is used for the neoadjuvant and adjuvant treatment of breast cancer. It modifies and cross links purine bases in DNA, thus inhibiting DNA, RNA and protein synthesis and causing cell death in rapidly dividing cells.
Docetaxel	MW = 808	Sanofi-Aventis	Taxotere	2004	Micro-tubule	This compound is FDA-approved (i) as a single agent for the treatment of for locally advanced or metastatic breast cancer after chemotherapy failure and (ii) with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive breast cancer. This drug blocks the function of microtubules and is a G2/M phase anti-mitotic.
Doxorubicin	MW = 544	Pfizer	Adria mycin	1974	Topo-II	This drug is an anthracycline topoisomerase II inhibitor that is used as a component of multiagent adjuvant chemotherapy for the treatment of women with axillary lymph node involvement following resection of primary breast cancer. It inhibits the action of the topoisomerase II-DNA complex thereby blocking replication.
Elacestrant	MW = 459	Stemline Therapeutics	Orserdu	2023	ER	This medicinal is an ER antagonist that is prescribed for the treatment of postmenopausal women with advanced or metastatic ER-positive, HER2-negative, estrogen receptor−1 gene (*ESR1*) mutated breast

(*continued on next page*)

Table 4 (*continued*)

Drug	Properties	Company	Trade name	Year approved	Targets	Therapeutic indications
						cancer with disease progression following at least one line of endocrine therapy.
Epirubicin	MW = 544	Pfizer	Ellence	1999	Topo-II	This medicine is an anthracycline topoisomerase II inhibitor that is employed as a component of adjuvant therapy in patients with evidence of axillary node involvement following primary breast cancer resection. It is given with cyclophosphamide and fluorouracil. The mechanism of action is the same as that of doxorubicin.
Eribulin	MW = 730	Eisai	Halaven	2012	Micro-tubule	This compound is a microtubule inhibitor used for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.
Everolimus	MW = 958, given IV	Novartis	Afinitor	2009	mTOR	This drug is a kinase inhibitor that is prescribed for the treatment of postmenopausal women with advanced HR-positive, HER2-negative breast cancer in combination with exemestane after the failure of letrozole or anastrozole therapy.
Exemestane	MW = 296	Upjohn Co.	Aromasin	1999	Aroma-tase	The medicinal is an aromatase inhibitor used for (i) the adjuvant treatment of postmenopausal women with ER-positive early breast cancer who have received two to three years of tamoxifen and are switched to exemestane for completion of a total of five consecutive years of adjuvant hormonal therapy and (ii) the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy.
Fam-trastuzumab deruxtecan-nxki	Humanized IgG1κ	AstraZeneca	Enhertu	2022	ErbB2 Topo-I	This agent is a HER2-directed antibody and topoisomerase I inhibitor conjugate (deruxtecan) that is prescribed for the treatment of (i) patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either (a) in the metastatic setting or (b) in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy and (ii) patients with unresectable or metastatic HER2-low breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Trastuzumab binds to and blocks signaling through ErbB2. Once bound to ErbB2, the antibody is internalized by the cell carrying the bound deruxtecan that interferes with the ability of the cell to replicate its DNA, leading to DNA damage and apoptosis.
Fluoro-uracil	MW = 130	Fresenius Kabi	Fluoro-uracil	1962	DNA RNA	This nucleoside is approved for the treatment of adenocarcinoma of the breast. This substance interferes with the synthesis of DNA and to a lesser extent inhibits the formation of RNA leading to cell death. Fluorouracil is converted to three main active metabolites: (i) FdUMP, (ii) 5–10 FUTP and (iii) FdUTP. These metabolites have several effects including the inhibition of thymidylate synthase by FdUMP, incorporation of FUTP into RNA and incorporation of FdUTP into DNA.
Fulvestrant	MW = 607	AstraZeneca	Faslodex	2002	ER	This medicine is an ER antagonist used for the treatment of HR-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. Fulvestrant (i) binds to ERs with high affinity and blocks the dimerization of the receptor, (ii) promotes ER degradation which impedes estrogen signaling and inhibits the activity of estrogen-regulated genes, and (iii) prevents ERs from entering in the nucleus.
Gemcitabine	MW = 263	Sun Pharm.	Infugem	1996	DNA	This nucleoside metabolic inhibitor is used in combination with paclitaxel, for the first-line treatment of metastatic breast cancer after the failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated. This agent blocks DNA elongation, inhibits thymidylate synthase, and reduces dCTP concentrations.
Goserelin	MW = 1269	TerSera Therapeutics	Zoladex	1989	GnRH	This compound is a decapeptide gonadotropin releasing hormone antagonist that desensitizes GnRH pituitary receptors and inhibits the production of luteinizing hormone and follicle-stimulating hormone, which reduces the production of estrogen and progesterone, and is prescribed in the palliative treatment of advanced breast cancer in pre- and perimenopausal women.
Inavolisib	MW = 407	Genentech	Itovebi	October 2024	PI3K	The FDA approved inavolisib with palbociclib and fulvestrant for patients with endocrine-resistant, *PIK3CA*-mutated, HR-positive, HER2-negative metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy.
Ixabepilone	MW = 507	R-Pharm US	Ixempra	2007	Micro-tubule	This substance is a microtubule inhibitor used for the treatment (i) as a single agent for patients with metastatic or locally advanced breast cancer after failure of an anthracycline, a taxane, or capecitabine and (ii) in combination with capecitabine for patients with metastatic or locally advanced breast cancer resistant to treatment with an

(*continued on next page*)

Table 4 (*continued*)

Drug	Properties	Company	Trade name	Year approved	Targets	Therapeutic indications
						anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated.
Lapatinib	MW = 581	Novartis	Tykerb	2007	ErbB1/2	This agent is a kinase inhibitor that is prescribed in combination with (i) capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab – patients should have disease progression on trastuzumab prior to the initiation of treatment with this regimen and (ii) letrozole for the treatment of postmenopausal women with HR-positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated.
Letrozole	MW = 285	Novartis	Femara	1997	Aroma-tase	This drug is an aromatase inhibitor that is prescribed for the (i) adjuvant treatment of postmenopausal women with HR-positive early breast cancer, (ii) extended adjuvant treatment of postmenopausal women with early breast cancer who have received prior standard adjuvant tamoxifen therapy, and (iii) first and second-line treatment of postmenopausal women with HR-positive or HR-status unknown advanced breast cancer.
Leuprolide	MW = 1269	Tolmer, Inc.	Eligard	2016	GnRH	The FDA approved the use of this nonapeptide as an ovarian suppressor for premenopausal breast cancer; the drug works by desensitizing GnRH pituitary receptors and inhibiting the production of luteinizing hormone and follicle-stimulating hormone, which reduces the production of estrogen and progesterone.
Margetuximab-cmkb	Chimeric mouse/ Human IgG1	Macrogenics	Margenza	2020	ErbB2	This antibody is a HER2/neu receptor antagonist indicated, in combination with chemotherapy, for the treatment of patients with metastatic HER2-positive breast cancer in patients who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.
Methotrexate	MW = 454	Hospira	Metho-trexate	1953	Anti-folate	This folate antagonist is used for the treatment of patients with breast cancer as part of a combination chemotherapy regimen. The agent inhibits (i) dihydrofolate reductase, (ii) thymidylate synthase, and (iii) purine synthesis *de novo*.
Nab-paclitaxel	MW = 854 for paclitaxel	Celgene	Abraxane	2005	Micro-tubules	This drug-albumin derivative is employed for the treatment of metastatic breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated. The mechanism of action is the same as that of docetaxel.
Neratinib	MW = 557	Puma	Nerlynx	2017	ErbB1/2/4	This medicine is a kinase inhibitor that is prescribed (i) as a single agent, for the extended adjuvant treatment of patients with early stage HER2-positive breast cancer, to follow adjuvant trastuzumab-based therapy and (ii) in combination with capecitabine, for the treatment of patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting.
Olaparib	MW = 434	AstraZeneca	Lynparza	2014	PARP	The medicinal is FDA-approved for (i) the adjuvant treatment of patients with deleterious or suspected deleterious germline *BRCA* mutant, HER2-negative, high-risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy, (ii) the treatment of germline *BRCA* mutant, HER2-negative metastatic breast cancer patients with deleterious or suspected deleterious HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting, and (iii) for the treatment of patients with HR-positive breast cancer that have been treated with a prior endocrine therapy or are considered inappropriate for endocrine therapy.
Paclitaxel	MW = 854	Celgene	Abraxane	1992	Micro-tublues	This microtubule inhibitor is approved for the treatment of metastatic breast cancer after the failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.
Palbociclib	MW = 447	Pfizer	Ibrance	2015	CDK4/6	This drug is a kinase inhibitor that is prescribed for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with (i) an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or (ii) fulvestrant in women with disease progression following endocrine therapy.
Pamidronate	MW = 235	Novartis	Aridia	1991	Ca^{2+}	This bisphosphonate binds calcium ions and is used for the treatment of hypercalcemia of malignancy; it relieves bone pain.
Pembrolizumab	Humanized IgG4κ	Merck	Keytruda	2014	PD1	This agent is employed for the treatment of patients with (i) high-risk early-stage triple negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment and then continued as a single agent as adjuvant treatment after surgery and (ii) locally recurrent unresectable or metastatic TNBC whose tumors express PDL1 (Combined Positive Score $\geq$10) as determined by an FDA approved test in combination with chemotherapy. This antibody is

(*continued on next page*)

Table 4 (*continued*)

Drug	Properties	Company	Trade name	Year approved	Targets	Therapeutic indications
						also approved for cancers exhibiting deficient mismatch repair, microsatellite instability, or with a high mutation burden.
Pertuzumab	Humanized IgG1κ	Genentech	Perjeta	2012	HER2	This antibody is a HER2/neu receptor antagonist indicated for use (i) in combination with trastuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease, (ii) in combination with trastuzumab and chemotherapy (a) as a neoadjuvant treatment for patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer or (b) as an adjuvant treatment for patients with HER2-positive early breast cancer at high risk of recurrence.
Raloxifene	MW = 474	Eli Lilly	Evista	1997	ER	This medicinal is an estrogen agonist/antagonist that is prescribed for the reduction in the risk of invasive breast cancer in postmenopausal women with (i) osteoporosis or (ii) at high risk for invasive breast cancer.
Ribociclib	MW = 435	Novartis	Kisqali	2017	CDK4/6	This medicine is a kinase inhibitor that is used for the treatment of HR-positive, HER2-negative patients (i) in combination with an aromatase inhibitor for the adjuvant treatment of stage II and III early breast cancer at high risk of recurrence, (ii) advanced or metastatic breast cancer in combination with (a) an aromatase inhibitor as initial endocrine-based therapy or (b) fulvestrant as initial endocrine-based therapy or (c) following disease progression on endocrine therapy.
Sacituzumab govitecan	Humanized IgG1κ	Immuno-medics	Trodelvy	2020	Trop−2	This antibody is a directed at Trop−2 (trophoblast cell-surface antigen 2) and is linked (conjugated) to a topoisomerase I inhibitor that is employed for the treatment of patients with unresectable locally advanced or metastatic triple-negative breast cancer who have received two or more prior systemic therapies, at least one of them for metastatic disease.
Talazoparib	MW = 380	Pfizer	Talzenna	2023	PARP	This medicine is used as a single agent for the treatment of patients with deleterious or suspected deleterious germline *BRCA*-mutated HER2-negative locally advanced or metastatic breast cancer.
Tamoxifen	MW = 372	AstraZeneca	Soltamox	1977	ER	This medicine is an estrogen agonist/antagonist that is prescribed (i) for the treatment of with ER-positive metastatic breast cancer, (ii) for the adjuvant treatment of adult patients with early stage ER-positive breast cancer, (iii) to reduce the risk of invasive breast cancer following breast surgery and radiation in women with ductal carcinoma in situ, and (iv) to reduce the incidence of breast cancer in women at high risk. The agonist/antagonist effects are dependent upon the target tissue and the physiological context.
Toremifene	MW = 406	Orion	Fareston	1997	ER	This agent is an estrogen agonist/antagonist used for the treatment of metastatic breast cancer in postmenopausal women with ER-positive or ER-status unknown tumors.
Trastuzumab	Humanized IgG1κ	Genentech	Herceptin	1998	HER2	Trastuzumab binds with high affinity to the extracellular domain of HER2 and mediates antibody-dependent cellular cytotoxicity as Fc receptor-bearing effector cells recognize and kill antibody-coated target cells expressing HER2 on their surface.
Tucatinib	MW = 481	Seattle Genetics	Tukysa	2020	ErbB2 or HER2	The medicine is a kinase inhibitor used in combination with trastuzumab and capecitabine for the treatment of patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.
Vinorelbine	MW = 1079	Pierre Fabre Pharm. Inc.	Navelbine	1994	Micro-tubule	Interferes with microtubule function during mitosis at metaphase.
Zoledronic acid	MW = 272	Novartis	Zometa	2001	Ca^{2+}	This bisphosphonate binds calcium ions and is used for the treatment of hypercalcemia of malignancy; it relieves bone pain.

[a] www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

breast cancer. Anastrozole is an aromatase inhibitor that is used for the first- and second-line treatments of HR-positive metastatic breast cancers. Alpelisib and inavolisib are PI3K blockers that are approved in combination with fulvestrant for the second-line treatment of HR-positive metastatic breast cancer patients bearing a *PIK3CA* mutation. The AKT protein kinase blocker capivasertib is used for the second-line treatment of HR-positive metastatic breast cancer bearing *PIK3CA/AKT1/PTEN*-alterations. The mTOR antagonist everolimus is prescribed for the second-line treatment of HR-positive metastatic cancer in combination with exemestane after failure with an aromatase inhibitor (anastrozole, letrozole). Moreover, the selective estrogen receptor degrader fulvestrant is employed for the second-line treatment of HR-positive metastatic breast cancer in postmenopausal women.

Lapatinib is an ErbB1/2 protein kinase antagonist that is used for the first-line treatment of HR-positive/HER2-positive metastatic breast cancer in combination with letrozole (Table 4) [9]. It is also used with capecitabine for the second-line treatment of HR-positive/HER2-positive metastatic breast cancer after failure of trastuzumab therapy. Letrozole is used for the first and second-line treatment of postmenopausal women with HR-positive metastatic breast cancer. Olaparib is a PARP antagonist that is used for the second-line treatment of patients with HR-positive metastatic breast cancer that have been treated previously with endocrine therapy.

3.3.5. *Additional therapies for HER2-positive breast cancer*

Ado-trastuzumab emtansine is used for the treatment of patients with

Table 5
Systemic therapy for recurrent unresectable (local or regional) stage IV breast cancer that is HR-positive and HER2-negative with a visceral crisis[a].

Setting	Subtype/Biomarker	Regimen
First line	Germline *BRCA1/2* mutation	PARP inhibitor (olaparib, talazoparib)
	No germline *BRCA1/2* mutation	Systemic chemotherapy
Second line	HER2 low	Fam-trastuzumab deruxtecan-nxki
	Not a candidate for Fam-trastuzumab deruxtecan-nxki	Sacituzumab govitecan or systemic chemotherapy
Third line and beyond	Any	Systemic chemotherapy
	Biomarker positive NTRK, RET	Targeted agents

[a] Adapted from Ref. [9].

HER2-positive, metastatic breast cancer who previously received an anti-HER2 regimen consisting of trastuzumab and a taxane (Table 4) [9]. Fam-trastuzumab deruxtecan-nxki is a HER2-directed antibody and topoisomerase I inhibitor conjugate (deruxtecan) that is prescribed for the second-line treatment of patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2 regimen. Margetuximab-cmkb is a HER2/neu receptor antagonist indicated, in combination with chemotherapy, for the treatment of patients with metastatic HER2-positive breast cancer in patients who have received two or more prior anti-HER2 regimens. The ErbB1/2/4 protein kinase antagonist neratinib is prescribed in combination with capecitabine for the treatment of patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens. Neratinib is also employed (i) as a single agent for the extended adjuvant treatment of patients with early stage HER2-positive breast cancer after adjuvant trastuzumab-based therapy and (ii) in combination with the anti-metabolite capecitabine for the treatment of patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens. Tucatinib is an ErbB2/HER2 protein kinase antagonist that is used in combination with capecitabine and trastuzumab for the management of women with advanced unresectable or metastatic HER2-positive breast cancer, including those patients with CNS metastases, who have received one or more prior anti-HER2 regimens in the metastatic setting.

3.3.6. Systemic chemotherapy for metastatic breast cancer

The cytotoxic drugs used in the treatment of metastatic and non-metastatic breast cancers include the anthracyclines, taxanes, anti-metabolites, and microtubule disrupters (Table 10). For HER2-negative patients, the combination of (i) doxorubicin, cyclophosphamide, and paclitaxel and (ii) docetaxel and cyclophosphamide are recommended in the neoadjuvant and adjuvant settings [10]. For triple-negative breast cancer patients, various combinations of an anthracycline, a taxane, an alkylator, and capecitabine has proven useful. The combination of paclitaxel and carboplatin or docetaxel and carboplatin has also been prescribed. For HER2-positive patients, the combination of (i) paclitaxel

Table 7
Systemic therapy for recurrent unresectable (local or regional) stage IV breast cancer that is HR-negative and HER2-negative (triple negative) breast cancer[a].

Setting	Subtype/Biomarker	Regimen
First line	PDL1 Combined Positive Score < 10 no *BRCA1/2* mutations	Systemic chemotherapy
	With or without *BRCA1/2* mutations	Cisplatin or carboplatin
	PDL1 Combined Positive Score ≥ 10 with or without BRCA*1/2* mutations	Pembrolizumab + chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine)
	PDL1 Combined Positive Score < 10 with *BRCA1/2* mutations	Olaparib or talazoparib
Second line	Germline *BRCA1/2* mutants	Olaparib or talazoparib
	Any	Sacituzumab govitecan
	Any	Systemic chemotherapy

[a] Adapted from Ref. [9].

Table 8
Systemic therapy for HER2-positive and HR-positive or HR-negative recurrent unresectable (local or regional) stage IV breast cancer[a].

Setting	Regimen
First line	Pertuzumab + trastuzumab + docetaxel
	Pertuzumab + trastuzumab + paclitaxel
Second line	Fam-trastuzumab deruxtecan-nxki
Third line	Tucatinib + trastuzumab + capecitabine
	Ado-trastuzumab emtansine
Fourth line and beyond	Trastuzumab + docetaxel or vinorelbine
	Trastuzumab + paclitaxel + carboplatin
	Trastuzumab or lapatinib + capecitabine
	Trastuzumab + lapatinib
	Neratinib + capecitabine
	Margetuximab-cmkb + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)

[a] Adapted from Ref. [9].

Table 6
Systemic therapy for recurrent unresectable (local or regional) stage IV breast cancer[a].

HER2-negative and postmenopausal or premenopausal receiving ovarian suppression
First-line therapy
Aromatase inhibitor (ArI) or fulvestrant + CDK4/6 blocker
ArI or fulvestrant with ribociclib
ArI or fulvestrant with abemaciclib
Ari or fulvestrant with palbociclib
Second- and subsequent-line therapy
Fulvestrant + CDK4/6 blocker (abemaciclib, palbociclib, or ribociclib) if CDK blocker not previously used
Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)
Other recommended regimens
Fulvestrant
Fulvestrant plus non-steroidal aromatase inhibitor (anastrozole, letrozole)
Non-steroidal aromatase inhibitor (anastrozole, letrozole)
Selective ER modulator (tamoxifen)
Steroidal aromatase inhibitor (exemestane)
HER2-positive and postmenopausal or premenopausal receiving ovarian suppression
ArI ± trastuzumab
ArI ± lapatinib
ArI ± lapatinib + trastuzumab
Fulvestrant ± trastuzumab
Tamoxifen ± trastuzumab

[a] Adapted from Ref. [9].

Table 9
Selected targeted therapies and biomarker testing for recurrent unresectable (local or regional) or stage IV (M1) disease[a].

Breast Cancer	Biomarker	FDA-approved Agents
HR-positive/HER2-negative	*PI3KCA* activating mutation	Apelisib + fulvestrant
HR-positive/HER2-negative	*ESR1* mutation	Elacestrant
Any	Deficient mismatch repair	Pembrolizumab
Any	High tumor mutation burden	Pembrolizumab
Any	Microsatellite instability	Pembrolizumab
Any	NTRK fusion protein	Larotrectinib or entrectinib

[a] Adapted from Ref. [9].

Table 10
Systemic chemotherapy for HR-positive or HR-negative and HER2-negative breast cancer[a].

Preferred Regimens	Other Recommended Regimens	Useful under Certain Circumstances
Anthracyclines	Cyclophosphamide	AC[b] (doxorubicin/cyclophosphamide)
Doxorubicin	Docetaxel	EC (epirubicin/cyclophosphamide)
Liposomal doxorubicin	Nab-paclitaxel	CMF (cyclophosphamide/methotrexate/fluorouracil)
Taxanes	Epirubicin	Docetaxel/capecitabine
Paclitaxel	Ixabepilone	GT (gemcitabine/paclitaxel)
Antimetabolites		Gemcitabine/carboplatin
Capecitabine		
Gemcitabine		
Microtubule inhibitors		
Vinorelbine		
Eribulin		

[a] Adapted from Ref. [9].
[b] Doxorubicin aka Adriamycin.

and trastuzumab, (ii) docetaxel, carboplatin, and trastuzumab, (iii) docetaxel/carboplatin/trastuzumab/pertuzumab, (iv) docetaxel/cyclophosphamide/trastuzumab, and (v) paclitaxel/carboplatin/-trastuzumab/pertuzumab have been employed. The variations and possibilities are endless.

4. Concluding remarks

Owing to the frequency and importance of breast cancer worldwide, clinicians and basic science investigators have studied the biology and clinical course of this disorder for more than a century. Our views of breast cancer have undergone significant change since its molecular hallmarks were extensively characterized, which now include immunohistochemical markers (ER, PR, HER2, and proliferation marker protein Ki-67), genomic markers (*BRCA1/2* and *PIK3CA*), and immunomarkers (tumor-infiltrating lymphocytes and PDL1). The formulation of new biomarker combinations form the basis for progressively more complex diagnostic and therapeutic algorithms. Neoadjuvant combination therapy, which frequently includes targeted agents, is a standard of care (especially in triple-negative breast cancer and in HER2-positive breast cancer). Moreover, radiotherapy continues to be an important component of breast cancer management. Patients with ER-positive tumors are treated with 5–10 years of endocrine therapy and chemotherapy. For patients with metastatic breast cancer, standard first-line and follow-up therapy options include targeted approaches such as CDK4/6 inhibitors, PI3K inhibitors, PARP inhibitors, and anti-PDL1 immunotherapy, depending on the tumor type and molecular profile. This range of treatment options underscores the complexity of today's breast cancer therapy. Combining CDK4/6 inhibitors with PI3K inhibitors or immune-modulating anticancer drugs is an attractive possibility [55].

The selection of management protocols is based upon patient demographics, clinical features, and the biomarker profile of tumor samples. Such information is used in the delivery of personalized medicine. Of all potential biomarkers, HR and HER2 status are the most important. HR-positivity is found in 70–80 %, HER2 positivity occurs in 15–20 %, and triple negativity is found in 10–20 % of breast cancer patients [56–58]. HR-positive patients are treated with aromatase inhibitors and selective estrogen receptor degraders or modulators. The selection of treatment modalities is increasingly complex as therapeutic modalities are numerous and they continue to evolve. Also of importance is an accurate tumor and lymph node assessment because treatment decisions and prognosis are dependent on the stage of the disease.

The armamentarium of first-line systemic therapy for patients with metastatic breast cancer has expanded significantly in recent years. Molecularly targeted therapy, immune checkpoint inhibitor therapy, and the use of antibody-drug conjugates have improved progression-free and overall survival with favorable toxicity profiles. PI3K, PKB, PARP, and protein kinase inhibitors are orally bioavailable, a property that eases treatment (not requiring a visit to a hospital or clinic) and is appreciated by the patient. All immune therapies are given by injection as are most of the cytotoxic drugs. As indicated in Table 4, endocrine-based therapies, systemic chemotherapies, and antibody-based therapy alone or in combination with cytotoxic drugs or with a second antibody are dependent upon breast cancer staging.

The road from a basic science discovery applicable to clinical care is often circuitous. The discovery of the estrogen receptor is a case in point. It was discovered by Elwood V. Jensen of the Ben May Laboratory at the University of Chicago [59]. He used ^{3}[H]-estradiol of high specific activity and sucrose density gradient centrifugation to characterize rat uterine proteins, "estrogen receptors" or "estrophiles", that bound to this ligand. He demonstrated that the hormone bound reversibly to the receptor and that estradiol per se did not undergo any chemical transformation during this process. He also demonstrated that the hormone was found in both the cytosol and nucleus and he characterized its transport into the nucleus. At the time these experiments were performed (late 1960s), they were not accepted by the scientific community because the idea of a receptor for a molecule was novel and lacked precedence.

Most of the early studies on the estrogen receptor were performed on rat uteri and only later was the receptor studied in breast [60]. Jensen reported that the determination of estrophilin (estrogen receptor) in both primary and metastatic breast cancers can furnish useful information regarding the choice of optimal therapy for a patient with advanced disease [61]. He noted that most patients with significant tumor estrogen receptor levels will respond favorably to endocrine ablation therapy in 85–90 percent of the cases. In the 1970s, endocrine ablation usually involved bilateral oophorectomy and salpingectomy. Furthermore, Jensen reported that the analysis of the tumor at the time of mastectomy serves as a guide to subsequent therapy if metastases should appear. He further reported that patients whose breast cancers lack the estrogen receptor have little chance of benefit from endocrine ablation and should be treated by alternative therapies. As noted in this review, the estrogen receptor status is one of the most important breast cancer biomarkers.

In the modern era, the estimated five-year survival of breast cancers, excluding triple-negative disease, is about 90 % (https://www.cancer.org/cancer/types/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-survival-rates.html). The estimated five-year survival for patients with triple-negative disease is about 75 %. Several planned and ongoing clinical trials with new drug combinations are exploring treatment effectiveness in the neoadjuvant and adjuvant settings. However, there are many uncertainties about drug combinations, the optimal treatment sequence, and personalized therapies depending on biomarker expression, disease stage, and other patient-specific

factors. Addressing these problems will help in reducing breast cancer-related morbidity and mortality.

CRediT authorship contribution statement

Robert Roskoski: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization.

Declaration of Competing Interest

Elwood V. Jensen was one of my instructors at the University of Chicago and members of his laboratory aided me with my dissertation research. The author is unaware of any affiliations, memberships, or financial holdings that might be perceived as affecting the objectivity of this review.

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Data availability

No data was used for the research described in the article.

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