Response of Therapy in Cell-Cycle Regulatory Genes in Breast Cancer

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16.1 Introduction

Cancerous cells bypass the cell cycle's multiple shielding and checkpoints, allowing them to multiply indefinitely despite aneuploidy as well as other abnormalities that can stop non-malignant cells from proliferating. This behavior is acquired by accumulating a variety of genetic or epigenetic genomic changes that hyper-activate or deactivate key elements of the cell cycle that put unique cellular demands on cancerous cells in order to maintain abnormal growth. Diverse subtypes of breast cancer have various molecular changes and reliance on the cell cycle as well as its checkpoints. Tumor cells in ER (+) /HER2 (−) "luminal" breast tumors still rely on estrogen for oncogenic actions. When estrogen binds to hormonal receptors, it triggers a signaling cascade that results in receptor-driven gene expression which promotes cellular growth, survival, and multiplication. Cyc D1 is an ER targeting gene which promotes cell cycle progress across the limitation point by permitting CDK4/6/cyclin D interactions (Platet et al. 2004). ESR1, the gene that encodes the estrogen receptors, and its related protein, are overexpressed in ER+ tumors. Augmentation of the CCND1 gene is also common in luminal tumors. In ER+ breast tumors, activating alterations in PIK3CA are prevalent, and they lead to the progression of cell cycle via oncogenic AKT/mTOR signaling. ER+/luminal cancers, unlike TNBC and HER2+ types, usually have functional p53 and Rb tumor suppressor mechanisms as well as are gnomically stable due to their major reliance on estrogen signaling. TNBCs, on the other hand, have RB1 alterations or deletions that disrupt

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the stability of the Rb/E2F/CDK4/6 pathway's cell cycle regulation, and also frequent changes in DNA damage reaction genes like BRCA1. Such tumors are also extremely aneuploid, with almost ubiquitous TP53 loss, recurring CCNE1 DNA multiplications, or decreased PTEN function (Curtis et al. 2012; Xu et al. 2014; Bianchini et al. 2016). TNBC tumors are dependent on the spindle assembly checkpoints and express elevated amount of mitotic checkpoint proteins (e.g., BUB1, TKK, AURKB, and MAD2) and DNA repairing proteins, according to numerous cellular dependency investigations (Yuan et al. 2006; Brough et al. 2011; Daniel et al. 2011; Curtis et al. 2012; Mehraj et al. 2021a). This is apparently due to their significant levels of genomic instabilities. CDK4 copy increases are widespread in all forms of breast cancers, although they are most common in HER2+ tumors. Furthermore, PIK3CA, TP53, and PTEN alterations, as well as CCND1 DNA duplication, are all common in this subtype.

Dysregulation of a cell cycle caused by tumor suppressor deactivation and abnormal stimulation of cyclins and CDKs is a hallmark of breast carcinoma. Given how important this biological mechanism is for cancer cell growth, it is no surprise that it is a prospective treatment target (Ignatiadis and Sotiriou 2013; Dominguez-Brauer et al. 2015; Mir et al. 2020). Nevertheless, because of the loss of target selectivity and dose-limiting toxicity, previously cell cycle targeted medicines performed badly in the clinic. Despite earlier medications' poor clinical performance, improvement of the treatment approach to increase therapeutic efficacy and the introduction of novel potent and specific inhibitors have reawakened interest in using the cell cycle as an antitumor therapy approach.

16.2 Treatment Response of the HER-2 Oncogene in Breast Cancer

HER-2, commonly called as HER-2/neu or erbB-2, is a 185-kDa transmembrane tyr kinase growth regulator receptor that is found on chromosome 17q (Yarden and Sliwkowski 2001; Mir et al. 2022a; b; c; d). Growth factor receptors are activated by attaching to targeting ligands or, if expressed in adequate receptors concentration on the cell membrane, by themselves, following by dimerization or receptors autophosphorylation, that results in various transduction pathways functioning via a number of routes. Angiogenesis, proliferation, abnormal cell interactions, enhanced cell mobility, metastasis, and apoptosis inhibition are all induced by the MAP kinase or 3-kinase (PI3K)/Akt routes (Oved and Yarden 2002; Wadhwa et al. 2020). The finding of HER-2 gene duplication and higher expression in early human breast carcinoma, as well as its link to more severe therapeutic behavior (Slamon et al. 1987), sparked initial interest in diagnosis and treatment applications. HER-2 gene is infrequently elevated in benign breast carcinoma, and its expression differs by histological subtype, as it is nearly exclusively detected in ductal vs. lobular initial breast malignancies. The HER-2 gene is increased and highly expressed in 20%–30% of aggressive cases of BC, as well as in the most of elevated Ductal carcinoma in situ patients (van de Vijver et al. 1988). Numerous researches have

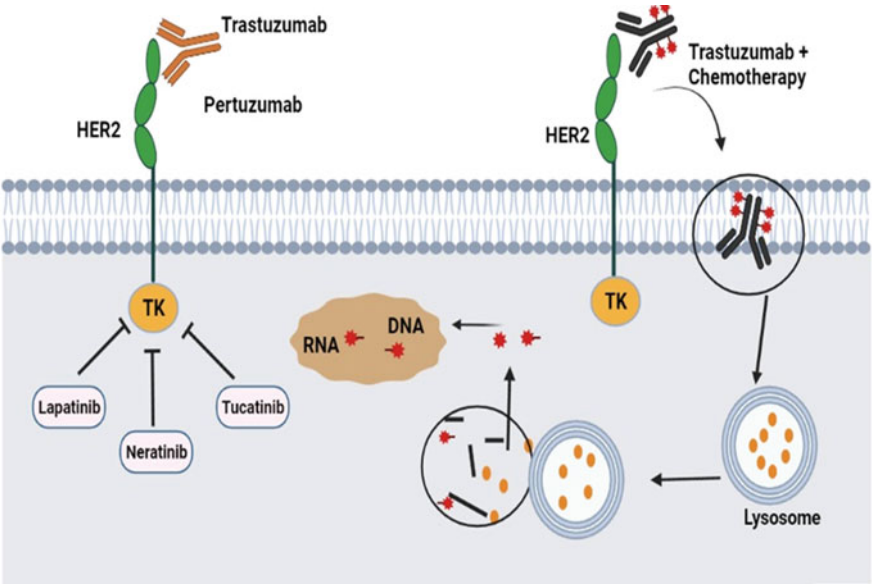

Fig. 16.1 Mechanism of action of anti-HER2 therapies

linked it to an elevated relapse in early breast malignancy, as well as greater resistance to endocrine treatment (possibly more with tamoxifen than it is with aromatase antagonists), resistance to non-anthracycline treatment, improved responsiveness to doxorubicin, as well as, in some cases, taxane-based treatment (Ross et al. 2003; Mehraj et al. 2021b). Nevertheless, apart from identifying individuals for trastuzumab treatment, HER-2 expression is not widely advised for decision-making at this time. It raises the likelihood of tumor relapse in early breast carcinoma and may thus affect adjuvant therapy selection.

Antibodies targeting growth hormone receptors have been proven in experimental animals to suppress growth. Trastuzumab is a humanized synthetic monoclonal antibody that targets the HER-2 protein's extracellular region (Carter et al. 1992). Trastuzumab's mode of activity is thought to involve modulatory impacts on cell signaling in animal systems, although there are additional indications of an immunological impact (Clynes et al. 2000) (Fig. 16.1). The findings of the earliest trastuzumab studies are summarized in Tables 16.1 and 16.2 (Baselga et al. 1996; Cobleigh et al. 1999; Slamon et al. 2001; Vogel et al. 2002). When trastuzumab was given as a single drug, response percentages ranged from 11% to 26%, and this effectiveness was greater (35%) in individuals who, in retrospect, had really HER-2+ tumors based on improved immunohistochemistry (IHC) or gene amplification standards. When trastuzumab was coupled with chemotherapy, it showed increased effectiveness, including increases in reaction rates, time to progression of the disease, durability of response, and survival in the major randomized study. With using trastuzumab, particularly in conjunction with anthracycline treatment,

Table 16.1 Trials of trastuzumab as a monotherapy treatment

Prior chemotherapeutic treatment for advanced illness	No. of individuals	Response rate	Median duration of response	Median survival	References
Any	43	12%	6.6	14	Baselga et al. (1996)
None	114	26%	>12	24	Vogel et al. (2002)
One or two previous regimens	222	15%	9.1	13	Cobleigh et al. (1999)

Table 16.2 The outcomes of the major randomized study evaluating chemotherapy alone versus chemotherapy + trastuzumab (Slamon et al. 2001)

Treatment	No. of individuals	Response rate	Median duration of response	Median survival
Chemotherapy	234	32%	6.1	20.3
Trastuzumab + chemotherapy	235	50%	9.1	25.1
Subgroups				
Anthracycline + cyclophosphamide	138	42%	6.7	21.4
Anthracycline + cyclophosphamide + trastuzumab	143	56%	9.1	26.8
Paclitaxel	96	17	4.5	18.4
Trastuzumab + paclitaxel	92	41	10.5	22.1

cardiomyopathy that is generally temporary and resolves over time has also observed. This is an example of how difficult it is to forecast the effects of tailored medicine. While HER-2 expression in mature myocytes is modest, the HER signaling cascade is known to have a role in embryonic cardiac and neural growth, as well as stress reactions and remodeling in the mature heart (Schneider et al. 2002)

Growth hormone receptor systems interact with additional routes, including those implicated in hormone-receptor signaling and DNA repairing, indicating that trastuzumab as well as other traditional breast carcinoma treatments could be additive or synergistic in some cases. Platinum medicines, vinorelbine, and docetaxel were reported to have the highest levels of synergy in preclinical studies, although differing outcomes were found by other scientists using various cell lines (Pegram et al. 1999). Trastuzumab had showed the most efficacies when combined with docetaxel, vinorelbine, and, to a smaller extent, gemcitabine in phase II experimental studies, although broader comparative studies are needed to enhance these combinations (O'Shaughnessy 2003; Esteva et al. 2002; Burstein et al. 2003). The combination of carboplatin with chemotherapy has been demonstrated to improve responsiveness and duration to progression in one research (Robert 2002). Trastuzumab as well as related HER-family-targeted medicines is also

being utilized to overcome resistance to hormonal therapies or increase their efficacy (Johnston et al. 2003a).

Pertuzumab (2C4), a novel anti-HER-2 Mab, binds the external region of HER-2 as well, but it produces steric interference and inhibits receptors dimerization. This antibody was found in preclinical studies to suppress the development of cells that express reduced amounts of HER-2, likely by interacting with the production of HER family heterodimers (Agus et al. 2002). In solid tumors, phase I screening revealed efficacy (3/21 patients, 15%) (Agus et al. 2003), and research in breast carcinoma, including HER-2– or trastuzumab-refractory HER-2+ breast malignancy, are currently ongoing.

16.3 Endocrine Resistance

Because antiestrogens, a commonly utilized and successful treatment for hormone-responsive BCs, quickly downregulate cyc D1, unregulated transcription of this cyclin may be supposed to impact susceptibility to these drugs. Several clinical evidence supports the concept that individuals with elevated cyclin D1 have a shorter length of responsiveness to antiestrogen treatment, and that higher expression of cyc D1 in breast tumor cultured cells leads to transient antiestrogen resistance (Butt et al. 2005; Qayoom et al. 2021). More evidence from laboratory models and primary breast tumors would be needed to answer the issue of whether cyclin D1 overexpression impacts antiestrogen responsiveness. Despite the fact that cyclin E upregulation in breast carcinoma cells has only a minor impact on antiestrogen responsiveness in vitro, one research discovered that elevated cyc E expression has been linked with worse RFS in patient populations treated with hormonal therapies (Sutherland and Musgrove 2004).

p27 mediates the cell-cycle stop of breast carcinoma cells by therapeutically effective pharmaceutical drugs that impede estrogen activity (Sutherland and Musgrove 2004). Administration of MCF-7 BC cells with synthetic steroidal antiestrogen ICI 182780 (Mir 2015) (Faslodex), for instance, resulted in enhanced p27 expression, increased p27–cyclin E–Cdk2 interaction, or cell-cycle halt. Moreover, this antiestrogen's high stimulation of p27 helps to induce a quiescent, growth factor-insensitive condition. Antiestrogen sensitivity is conferred in breast tumor cells in vitro when p21 or p27 is downregulated by antisense oligonucleotides or when Skp2 is overexpressed. MEK inhibition recovers p27 suppression of cyclin E–Cdk2 complex and treatment response in antiestrogen sensitive breast tumor cells, demonstrating that antiestrogen responsiveness may be regained in resistant cells by treating with specific signal cascade inhibitors. In a therapeutic setting, tumor p21 and p27 status could be prognostic of antiestrogen response. Elevated p27 expression has been linked with enhanced relapse-free as well as overall survival in a research of premenopausal females with initial phase breast tumor obtaining combinational endocrine treatment of tamoxifen and goserelin (Pohl et al. 2003), and p21 levels had also been linked with reaction to antiestrogens in several, but not every, clinical research (Butt et al. 2005).

16.4 Early Generation Cell Cycle/CDK Inhibitors and Microtubule Binding Drugs

Microtubule binding agents (MTBAs) are a cornerstone in cancer treatment that work by stabilizing (taxanes, such as docetaxel and paclitaxel) or disrupting (eribulin, vinca alkaloids) microtubules during mitosis of multiplying cancerous cells (Dumontet and Jordan 2010). These drugs trigger the spindle assembly/mitotic checkpoints (SAC) that inhibit anaphase and mitotic escape till all chromosomes had established bipolar adhesion to the spindle. MTBAs cause cell cycle stop in mitosis as a result of this, and persistent mitotic pause results in apoptosis (Dumontet and Jordan 2010; Mehraj et al. 2022a). Numerous MTBAs have been licensed for breast carcinoma treatment, either individually or in conjunction with additional chemotherapy drugs (or HER2-targeted MABs). When utilized as adjuvant therapy for early-stage breast carcinoma, taxanes were shown to boost treatment efficacy, and substantial increase in tumor responsiveness can be attained in initial lines of treatment for metastatic cancer (De Laurentiis et al. 2008; Gradishar 2012; Mir et al. 2022a; b; c; d) (Fig. 16.2).

The cell cycle's first-generation targeted inhibitors, in comparison to MTBAs, showed minimal effectiveness in the management of solid tumors (Dumontet and Jordan 2010). Dinaciclib, flavopiridol, and seliciclib (Finn et al. 2016) are non-selective multi-CDK antagonists, as are many similar mitotic kinase blockers like those inhibiting AURKB and PLK1. The surprising insufficiency of such medicines had been ascribed in large portion to dose-limiting effects produced by unwanted target suppression in non-malignant tissues, such as neurotoxicity, myelosuppression, and gastrointestinal issues (Dumontet and Jordan 2010; Finn et al. 2016). The absence of prognostic biomarkers to guide patient choice for these medications may possibly had led to their failure (Finn et al. 2016; Mir et al. 2022a; b; c; d). Although preclinical research suggests that some of these medicines,

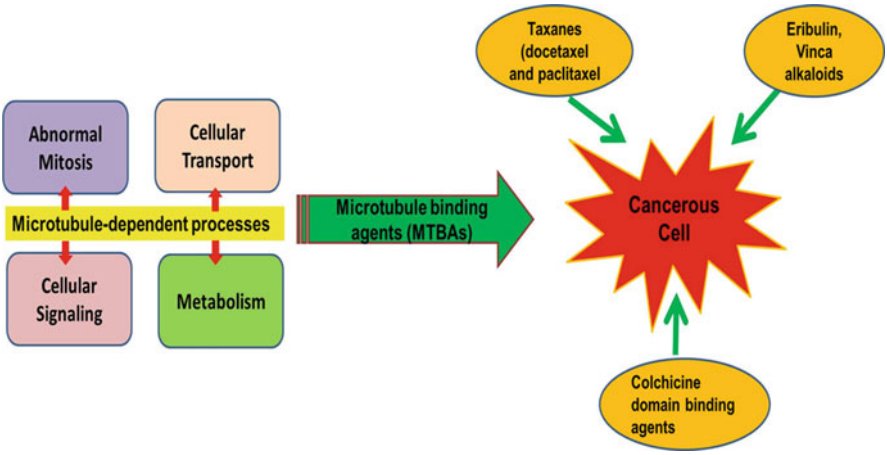

Fig. 16.2 Different microtubule binding drugs

like dinaciclib, could be repurposed, the processes are dependent on transcriptional suppression instead of cell cycle-related actions (Johnson et al. 2016).

In order to accomplish a treatment efficacy for breast cancer specificity, these experiences formalized the necessity of utilizing cancer- and subtype-specific vulnerabilities (such as genetic instability and anomalies in cell-cycle proteins which are not crucial in non-malignant cells). This need has directed the advancement of the latest generation of agents that target cell cycle.

16.4.1 Inhibitors of TTK

TTK protein kinases (TTK), also called as MPS1 (monopolar spindle 1), is an important modulator of the SAC (Spindle checkpoint assembly) (Lara-Gonzalez et al. 2012; Liu and Winey 2012; Musacchio 2015) (Fig. 16.3). TTK establishes and maintains the mitotic checkpoint by phosphorylating its substrate and recruiting checkpoint protein to kinetochores throughout mitosis. Because it delays anaphase and the commencement of mitotic escape till all chromosomes had attained bipolar linkage to the mitotic spindle, the checkpoint is crucial for preserving genomic integrity throughout mitosis (Lara-Gonzalez et al. 2012). TTK promotes proper chromosomal segregation and genetic stability by regulating the SAC. TTK is frequently abundantly expressed in cancerous cells, that also might be due to its role in mitosis, as aggressive tumors with elevated mitotic indicators naturally have elevated expression rates of cell-cycle genes; nevertheless, it may also be due to tumor cells' reliance on the SAC to facilitate feasible separation of their aneuploid as well as unreliable genomes into new cells (Yuan et al. 2006; Daniel et al. 2011; Curtis et al. 2012; Patel et al. 2018a). TNBCs were shown to have a gene expression profile linked with "aggressiveness," which was elevated for genes associated with

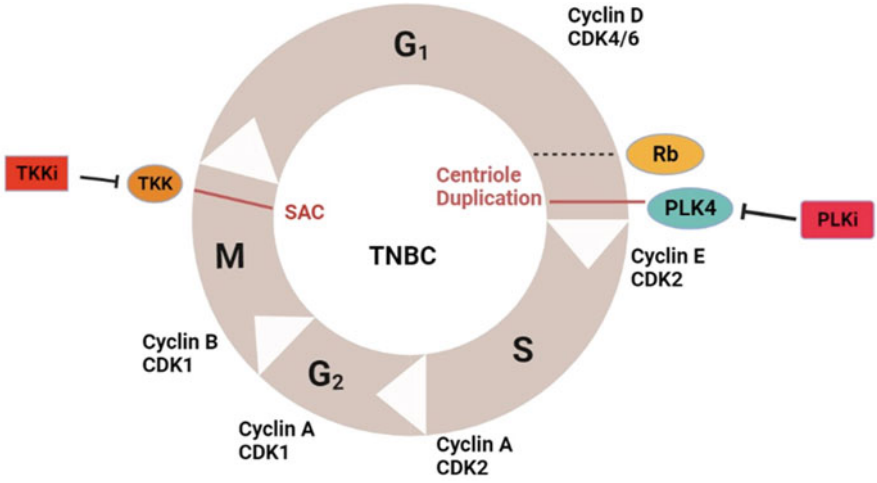

Fig. 16.3 Cell cycle vulnerabilities of TNBC tumors

Table 16.3 TTK inhibitors in clinical trials

Drug	Phase	Patient Cohort	Trail ID
BOS172722 (CCT289346) ± paclitaxel	Phase I	Advanced solid tumors	NCT03328494
BAY1161909 + paclitaxel	Phase I	Advances cancers	NCT021138812
BAY 1217389 + paclitaxel	Phase I	Advanced cancers	NCT02366949
CFI-402257	Phase I	Advanced cancers	NCT02792465
S81694 + paclitaxel	Phase I/II	TNBC	NCT03411161

genomic instability, notably TTK (Liu and Winey 2012). TNBC cells' reliance on TTK was also validated in this investigation. TTKs expression differentiates aneuploid cancerous cells from non-malignant diploid cells which have supplemental competent paths protecting integrity of the genome, and offers a treatment efficacy to target breast tumor cells, irrespective of whether its upregulation reflects a correlation with extremely aggressive tumor physiology or a functional reliance of cancerous cells on the SAC. The idea behind using TTK inhibitors to cure genetically unstable tumors like TNBC is to bypass the SAC and force cells to undergo mitosis when the chromosomes could be properly segregated. In susceptible cancerous cells, this leads to mitotic segregation faults and unbearable levels of genetic instability, eventually resulting in cell death. Numerous TTK inhibitors, like CFI-402257 (Table 16.3), are now being examined in initial stage clinical studies as individual medicines or in conjunction with taxane therapy. AZ3146, CCT271850, NMS-P715, CCT251455, MPI-0479605, and MPS1-IN-3 are some of the other TTK inhibitors in experimental research, highlighting the interest and therapeutic promise of this family of anti-cancer drugs (Naud et al. 2013; Tannous et al. 2013; Kusakabe et al. 2015; Faisal et al. 2017).

Gatekeeper alterations in the active region of TTK were shown to give resistance in in vitro to TTK inhibitors, comparable to other therapeutic kinase inhibitors (Koch et al. 2016), though the clinical significance of these alterations in patients who acquire resistance (Fig. 16.4) should be verified prospectively.

Patient biopsies would become accessible for genetic sequencing as TTK inhibitors precede through clinical studies, allowing pharmacogenomics investigations to find molecular correlations linked with treatment responsiveness. Such data will be crucial in guiding patient treatment categorization. In the meanwhile, once tumor genetic and medication reaction data are accessible, possible TTK inhibitor biomarkers responsiveness could be developed in a preclinical context and examined for therapeutic relevance.

Zaman and coworkers found that activation alterations in CTNNB1 (β-catenin) were related with increased susceptibility to TTK inhibitors when contrasted to wild-type CTNNB1 mice (Zaman et al. 2017), despite only a basic assessment of the working effect of CTNNB1 mutant on TTK inhibitor sensitivity was carried in an in vitro. Moreover, the frequency of CTNNB1 alterations in BC restricts the use of this potential biomarker in this illness. p53−/− HCT-116 colon cancer cells were

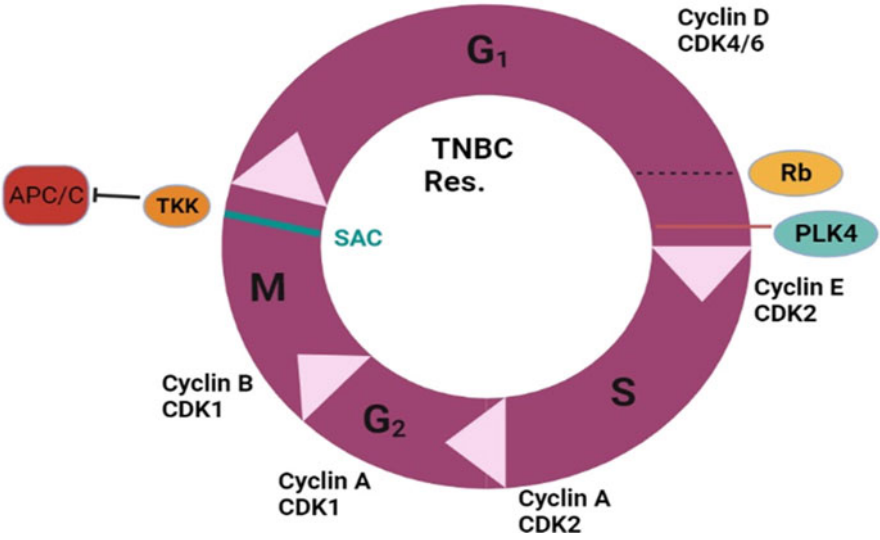

Fig. 16.4 Potent resistance mechanisms to TTK inhibition in TNBC

shown to be highly susceptible to the wide ranging S/T kinase inhibitors, SP600125, that suppress TTK with an IC50 = 1.95 μM (Jemaa et al. 2012), suggesting that p53 status might be linked to responsiveness to TTK suppression. The lack of specificity of SP600125, on the other hand, makes it difficult to understand the significance of TTK suppression in triggering selective p53-deficient cell death in this research. Furthermore, utilizing siRNA screenings to compare genetic dependence in PTEN-mutant versus wild-type BC cell lines, it was discovered that TTK inhibition is selectively detrimental in PTEN-deficient cancerous cells, implying that PTEN may be a biomarker for TTK inhibitor effectiveness (Dumontet and Jordan 2010; Mendes-Pereira et al. 2012).

16.4.2 PLK4 Inhibitors

Centrosomes, which are made up of 2 barrel-like structures termed centrioles, are primary microtubule organizing centers in cells. In G1, the centrosome's centrioles detach from each other. Centriole replication begins at the same time as the G1/S shift. In the S and G2 stages, procentriole synthesis and extension occur, and centrosome development and division occur, resulting in 2 centrosomes that constitute the mitotic spindle (Wang et al. 2014; Nigg and Holland 2018). PLK4 (Polo-like kinase 4) is the controller of centriole replication. The activation of centrosome biology proteins by PLK4 is an upstream step in the centriole formation signaling cascades, which is necessary for centrosome synthesis (Wang et al. 2014; Maniswami et al. 2018; Nigg and Holland 2018). PLK4 transcription is strictly controlled to maintain the numeric integrity of centrioles and centrosomes, as

reduction of PLK4 prevents centriole doubling and overexpression causes centriole expansion. PLK4 upregulation and centrosome anomalies are prevalent in cancers, particularly breast carcinoma, and are linked to disease aggressiveness (Chan 2011; Pannu et al. 2015; Denu et al. 2016; Marteil et al. 2018). PLK4-driven centrosome multiplication is hypothesized to have a function in the chromosomal instabilities linked with cancer. Even though previous research discovered no increased prevalence of spontaneous tumor development in p53+/− or p53−/− mice after PLK4 increased expression and centrosome multiplication (Vitre et al. 2015), a latest research discovered increased tumor growth in an APCMin/+ model of intestinal malignancy after PLK4-mediated centrosome multiplication (Levine et al. 2017), strengthening the case for using PLK4 as a targeted therapy. Suppression of PLK4 would amplify aneuploidy and genetic instability; ultimately result in cancer cell mortality, according to the proposed process of PLK4 over-activation promoting centrosome multiplication (Dominguez-Brauer et al. 2015; Mir et al. 2022a; b; c; d).

Depending on a siRNA screen targeted kinases, PLK4 was considered as a potential option with specific potency in TNBC cell lines. CFI-400945 has distinct phenotypic impacts at distinct doses, which is consistent with the inverse impacts mentioned for PLK4 removal and over-activation in the literature, with depletion of centrosome at elevated doses as well as centriole over-duplication (and subsequent centrosome overexpression) at small doses. PLK4 was partially inhibited by CFI-400945 at low doses, blocking auto-regulation through trans-autophosphorylation of its degron, resulting in enhanced PLK4 proteins expression (Cunha-Ferreira et al. 2013; Mason et al. 2014; Bedard et al. 2016). CFI400945 administration causes chromosomal segregation abnormalities due to the production of abnormal mitotic spindles (for example, multi-polar spindles), elevated DNA content associated with genetic instability, or finally death of cells in several cancer types (Mason et al. 2014; Lohse et al. 2017; Kawakami et al. 2018).

Employing in vitro models of cancer, researchers have yet to find significant pathways of developed resistance to CFI-400945, and this remained an important field of research. In diploid non-malignant RPE1 cells, cell resistance to centrosome loss generated by the tool chemical centrinone, a relatively specific inhibitor of PLK4, was revealed to be controlled by a p53-dependent 53BP1-USP28 pathway. In two classical investigations that created models of RPE1 in which natural PLK4 was substituted by an analog-sensitive variant that is inhibited following chemical stimulation to promote centrosome removal, this result of 53BP1 and USP28 deactivation generating resistance toward centrosome loss was similarly seen (Fong et al. 2016; Lambrus et al. 2016). Although this mechanism of resistance may exist in cancers with good p53 signaling, its therapeutic significance is unknown. TP53-independent processes would likely promote resistance in tumors with elevated amounts of genetic instability, centrosomal abnormalities, and common TP53 alterations, such as TNBC (Marteil et al. 2018).

Early functional assessment of CFI400945 impacts in breast tumor cell lines suggested a possible link among PTEN status and drug responsiveness, with PTEN loss being linked to response (Mason et al. 2014). This result was in line with a study that found inactivation of PLK4 was synthetically fatal in breast cancers with PTEN

mutation (Brough et al. 2011), implying that PTEN status might be used as a marker for CFI-400945. PTEN as a possible biomarker in BC PDX with characterized reactions to CFI-400945, as well as other postulated biomarkers dependent on PLK4 biology, like instability of chromosomes or copy numbers of centrosomes, is now being investigated. Surprisingly, a recent thorough evaluation of centrosome multiplication in the NCI-60 tumor cell line panel revealed richness of centrosome multiplication in aggressive TNBC and microsatellite stable colorectal malignancy (vs MSI CRC) that are 2 diseases for which CFI-400945 has shown substantial preclinical and clinical antitumor action (Marteil et al. 2018). Clinically tumor samples from existing clinical studies will be used to examine the possible connections among PTEN inactivation, centrosome duplication, and CFI-400945 responsiveness.

16.5 Modulators for Downstream Signal Transduction

Signaling pathway controlled by growth factors stimulates several major kinases which operate as master regulators, controlling multiple routes. Because alternative receptors can potentially initiate signals, targeting downstream messengers may produce therapeutically favorable benefits which growth factor channel inhibition cannot, but it can also lead to extra toxicities. The mTOR is a critical downstream regulator that regulates the cell cycle by coupling growth impulses from receptor or cytosolic kinases. Rapamycin as well as its equivalents suppress mTOR activation, preventing downstream stimulation of S6 kinase or 4E binding protein-1, and thereby reducing translation of essential protein biosynthesis machinery elements and cell cycle transcription factors (like c-Myc or cyclin D1) (Mita et al. 2003; Khan et al. 2022b; Mir et al. 2022a; b; c; d). CCI-779 is a rapamycin analog which had been through stage I research and has shown toxicities such as dermatitis, myelosuppression, and elevated liver enzymes. Improvements were observed in numerous tumor types, particularly breast, on a weekly frequency, which looked to be the most tolerated (Hidalgo et al. 2000). A phase-2 trial comparing 75 mg CCI779 intravenously weekly versus 250 mg CCI779 intravenously once a week for DOXO and/or taxane-refractory BC had shown preliminary cumulative outcomes of 9 responses from 106 patient populations (8.5%), with a 10% occurrence of level III/IV hepatocellular, skin, as well as hematological toxicities (Chan et al. 2003). More research is required to establish its efficacy when administered early in the development of the illness or in combination treatment, as well as whether biological subtypes of individuals are somewhat more likely to benefit. The MAP kinase and PI3K/Akt cascades are activated by Ras, a downstream main signaling protein. FTIs (farnesyl transferase inhibitors) block Ras from reaching the inner layer, where it is triggered. Even though certain oncogenic variants of Ras are poorly suppressed by FTIs, and RAS alterations are rarely shown in breast carcinoma, FTIs could still have a role in breast cancer because Ras is involved in growth factor receptors and other processes. In a stage II study of 76 individuals, the FTI tipifarnib produced a 12% reaction rate as well as a 24% therapeutic improvement rate, with thrombocytopenia,

neurotoxicity, and granulocytopenia as adverse effects (Johnston et al. 2003b). Small molecules or antisense inhibitor of Ras downstream elements (for example, Raf, MEK kinase) are being studied, however no outcomes in breast cancer have been reported yet.

16.6 Cell Cycle Modulators and Cyclins

The process of entering cell cycle and active multiplication is strongly regulated. CDKs are a set of proteins that are appropriately distributed throughout the cell cycle. When CDKs are triggered, they enhance the activation of other proteins, particularly pRb, a key gatekeeper which enables the cell to transition from G0 to dynamic cycling and mitosis. Cyclins control CDKs favorably, while CDK inhibitors inhibit them negatively (CKIs). Cyc D1 and cyc E expression rates fluctuate with the cell cycle and both are important in the cell's transition from G1 to S stage (Vermeulen et al. 2003; Sofi et al. 2022a).

The cyclin D1 gene which is located on chromosome 11q13 had been shown to be highly expressed in 40%–50% of aggressive breast tumors and increased in 10%–20% of instances (Steeg and Zhou 1998; Mehraj et al. 2022b). The pRb tumor suppressor factor is activated when cyclin D1 is bonded with its CDK counterpart, liberating the transcription component E2F and stimulating proteins essential for DNA replication. Elevated levels of cyclin D1 expression seem to be linked to ER positivity and a higher proliferation index (Loden et al. 2002). The cyclin E gene is found on 19q12 chromosome and is only slightly increased in breast carcinoma (2%); nevertheless, upregulation and changes in the breakdown pathway leading to the aggregation of limited-molecular-weight variants have been observed in 20%–30% of breast malignancies (Keyomarsi et al. 2002). Occasionally, both cyclin D1 and cyclin E are abundantly expressed at the same time. Overexpression of cyc E, like cyc D1, causes hyper-phosphorylation of pRb and enhanced proliferation. In comparison to elevated cyc D1 cancers, strong cyclin E tumors are also capable of inducing S phase without pRb phosphorylation or E2F stimulation. Overall, there is a large loss in cell cycle regulation as well as a substantial deregulation of multiplication as a consequence of this. Elevated cyc E cancers are much more prone to be of a greater grade than elevated cyc D1 tumors, are HR (−), possess a greater proliferation score, and had a worse prognosis (Keyomarsi et al. 2002; Loden et al. 2002; Mir 2022). Many characteristics linked to elevated cyclin E levels could indicate why this phenotype is highly aggressive. As previously stated, tumors that overexpress cyclin E are likely to skip the pRb node, enabling for more rapid cell cycle. Furthermore, higher cyc E levels had been linked to greater genetic instability, as compared to higher cyclin D1 levels. Moreover, the enzyme, elastase that breaks down cyclin E to its low-molecular-weight variants, has been linked to a higher propensity for infiltration and metastasis, which may help to elucidate the aggressive phenotype (Keyomarsi et al. 2002; Mir and Agrewala 2008; Khan et al. 2022a). Yet, there is no evidence that cyclins or their variants should be used routinely for predictive or therapeutic purposes.

Cell cycle control is an attractive target because it is a critical end point for many signaling cascades (Dai and Grant 2003). Flavopiridol is a nonspecific CDK blocker and a semi-synthetic flavone derivative of rohitukine, an antitumor drug derived from an Indian plant (Tan and Swain 2002). This chemical seems to cause apoptosis by interfering with CDKs for ATP binding and disrupting P-TEFb (the CDK9-cyclin T complexes), perhaps as a result of downregulation of anti-apoptotic proteins. Secretory diarrhea and hypotension were found to be dosage limiting in phase I investigations. In a phase II study in mantle cell lymphoma, that is linked to cyclin D1 amplification, 3 patients (11%) responded, with diarrhea, lethargy, and nausea typical side effects, as well as modest hematologic damage (Kouroukis et al. 2003). In breast carcinoma, trials of Flavopiridol in conjunction with a variety of chemotherapeutic drugs are continuing, and preliminary outcomes from a stage I study of Flavopiridol plus docetaxel showed that this conjunction is well accepted (Patel et al. 2018b; Mir et al. 2022a; b; c; d). Because growth hormone-receptor signaling ultimately leads to cell cycle entry, addressing the distal and proximal elements of this pathway with trastuzumab in conjunction with Flavopiridol was examined in HER-2+ cell lines, and combinatorial cytotoxicity was shown (Nahta et al. 2002). Therefore, experiments that combine early and middle signaling with specific cell cycle modulators could be likely to produce improved cell deaths while causing less host damage.

Ro 31-7453 is a nonspecific oral cell-cycle blocker that has been shown to be effective against a variety of tumor cell lines in vitro. It induces loss of mitotic spindle assembly in dividing cells, resulting to M-phase halt, by slightly inhibiting CDK2, CDK1, and CDK4 and tubulin assembly. Two of 32 (6 percent) individuals in a phase II trial of tax and anthracycline-resistant BC reacted, with diarrhea and nausea being the most common adverse effects (Osborne et al. 2004). UCN-01 (7hydroxy-staurosporine) is similarly a wide blocker of CDKs and PDK1, exhibiting hypotension as an adverse effect in stage I studies and no reactions in renal cell carcinoma (Shaw et al. 2009; Sofi et al. 2022b). Chemotherapeutic combinations are being investigated. CDK4 and CDK6 inhibitors with greater specificity have been designed and are tested in clinical studies.

Proteasomal inhibitors had become of interest (Nalepa and Harper 2003; Qayoom et al. 2022) because numerous CKIs as well as similar negative regulating molecules are generally controlled by ubiquitin–proteasome degradation. They are currently being tested in clinical trials for breast carcinoma. These medications impact not just CKIs but also a variety of many additional short-lived proteins, like the repressor of NF-κB, a critical mediator of stress and immune system response systems, and so may block other signaling routes as well. In anthracycline-pretreated breast carcinoma, a phase-2 trial of the proteasome blocker bortezomib in conjunction with docetaxel generated response in 6 out of 14 patients (43%) (Albanell et al. 2004).

16.7 Summary

Based on the initial clinical achievement of CDK4/6 inhibitors as well as the hopeful anti-cancer properties of TTK inhibitors as well as CFI-400945, the upcoming rational stages in the advancement of these molecules are to better comprehend treatment resistance, recognize biomarkers for patient choice, and advise treatment sequence data. Long-term therapy of terminal metastatic malignancies with these novel drugs will very certainly accelerate tumor evolution and give selection pressure for drug-resistant clones to spread. Knowing how this evolving process alters tumor genomes to produce treatment resistance phenotypes would be crucial in developing approaches to counteract progression of the disease. Understanding resistance processes and drug-induced biological changes could lead to the development of biomarkers that can forecast innate tumor responses. The proportion of persons with developed tolerance to CDK 4 and 6 inhibitors, that are currently conventional of care for the management of metastatic ER +/HER2+ BCs, would continue to rise. Multiple attempts are being made to explain the genetic evolution of therapeutic resistance utilizing both liquid (i.e., ctDNA) and paired tumor tissues, and testing of advancing illness will be critical for discovering resistance pathways.

16.8 Further Reading

The readers can further read about the role of CDKs in breast cancer by going through the following papers

- https://www.nature.com/articles/s41523-017-0009-7
- http://egetipdergisi.com.tr/en/pub/issue/36515/414615

The following visual presentations are also available for the readers to view for a better conceptual grasp of CDKs and their function in breast cancer

- https://www.youtube.com/watch?v=0Sj3rbJPeXQ
- https://www.youtube.com/watch?v=vEe3lBduckE
- https://www.youtube.com/watch?v=9Rd74mqd-jw

For more insights about the topic, we would suggest detailed findings from the books of (Mir MA, 2022) https://doi.org/10.1016/C2021-0-02565-7, https://doi.org/10.1016/C2014-0-02898-5 (Mir MA, 2021) https://doi.org/10.52305/WXJL6770, from cancer.net website, https://www.cancer.net/cancer-types/breast-cancer/types-treatment

For diagrammatic illustrations, descriptive tables, (Lazzeroni, 2012) http://www.eurekaselect.com/article/49928

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