ATJ
Advanced Therapies Journal

VOL.7/ ISSUE 22 / WINTER 2025
Online ISSN: 2676-7236
DOI: 10.22034/atj.2025.505495.1006

OPEN ACCESS

Pages: 7-20 / Review Article / Submit: 20 January 2025 / Accepted: 18 February 2025

Availablein: https://www.atjournal.ir

The Role of Hormonal Therapy in the Management of Hormone Receptor-Positive Breast Cancer: Current Trends and Future Directions

Kosar Helmi[1,*], Farnoosh Honarmand[2]

[1]Department of Pharmacology and Toxicology, School of Pharmacy, Ardabil University of Medical Sciences, Ardabil, Iran
[2]Department of Pathogenic Microorganisms, Faculty of Basic Sciences and Advanced Technologies in Biology, University of Sciences and Culture, Tehran, Iran.

Corresponding Author's E-mail: K.helmi1376@gmail.com

Abstract:
Breast cancer is responsible for more than 2.3 million newly diagnosed cases each year, according to the statistics. A hormonal imbalance, which is defined by unregulated activity of estrogen and progesterone, is often the cause of this type of cancer. It has become easier to handle patients who have HR+ breast cancer, particularly in women who have both advanced and early-stage disease, as a result of the deployment of estrogen-blocking hormone treatment. The permissiveness of tamoxifen, which was the first selective estrogen receptor modulator (SERM) to be commercialized, made it possible for more hormonal therapies to be developed. The cornerstone of breast cancer treatment is comprised of aromatase inhibitors (AIs), selective estrogen receptor degraders (SERDs), and cyclin-dependent kinase inhibitors (CDK) 4/6. These three types of drugs ultimately lead to improved patient outcomes. On the other hand, the inherent or acquired resistance of cancers to hormone therapy continues to be a serious cause for concern. Alterations in the genetic makeup of the tumor, as well as the activation of alternate pathways, make this situation even worse. The increasing development of molecular biology, precision medicine, and targeted therapies, on the other hand, is pointing to a new strategy for dealing with these problems. The purpose of this study is to investigate prospective treatment options and to shed light on the significant role that hormone therapy plays in the management of HR-positive breast cancer.

Keywords: Breast Cancer, Selective Estrogen Receptors Modulator (SERM), Aromatase Inhibitors (AIs), Cyclin-Dependent Kinase Inhibitors (CDK)

Introduction

More than two million new cases of breast cancer are discovered every year, making it the disease that affects most people all over the world. The prevalence of breast cancer is a major concern for the public's health. An overwhelming majority of these cases are classified as hormone receptor-positive breast cancer, sometimes known as HR+ breast cancer (1). An increase in the number of estrogen and/or progesterone receptors is one of the characteristics of HR+ breast cancer patients. Cellular hyperplasia is induced by these receptors when they are triggered

How to Cite this Article:
K.Helmi, F. Honarmand" The Role of Hormonal Therapy in the Management of Hormone Receptor-Positive Breast Cancer: Current Trends and Future Directions", Advanced Therapies Journal, vol. 7, no. 22, pp. 7-20, 2025.

by hormonal signals, which ultimately leads to an increase in the growth of tumors (2). Given that estrogen and progesterone signaling may contribute to the genesis and progression of HR+ breast cancer, there is rising interest in the development of new hormonal treatments that precisely target this important signaling pathway. Patients who do not have HI have demonstrated an improvement in their prognosis as a result of these treatments; on the other hand, patients who have early and metastatic disease have reported a better prognosis for HI (3).

Tamoxifen, which is a selective estrogen receptor modulator (SERM) and the first medicine to precisely target estrogen receptors (4), is the drug that marks the beginning of hormonal therapy for breast cancer (5). Tamoxifen can achieve this by affixing itself to the estrogen receptors that are known to be present in breast cancer cells. Because of this, estrogen is unable to activate the cells, which results in a reduction in the proliferation of tumors. Because of the multiple benefits that are associated with their application, other medications that target the endocrine system have been very successful. A few examples of these benefits are increased rates of survival and decreased rates of recurrence of HR+ breast cancer when the patient is receiving treatment (6).

Over the course of several decades, tamoxifen has been the primary treatment for HR+ breast cancer. It is a substantial therapeutic strategy that improves the prognosis and reduces the risk of recurrence in both early-stage and metastatic circumstances (7).

We have made significant progress in our understanding of hormone receptor signaling, which has resulted in the revolutionary introduction of aromatase inhibitors (8) into the treatment paradigm, particularly for women who have gone through menopause. To accomplish their purpose, aromatase inhibitors, which include anastrozole, letrozole, and exemestane, work by inhibiting the enzyme aromatase (9). Aromatase is responsible for catalyzing the conversion of androgens into estrogen within the body. Aromatase inhibitors can successfully deprive HR+ tumors of the hormone that can boost their growth. This is accomplished by lowering estrogen levels (10). The results of clinical trials indicate that artificial insemination (6) is superior to tamoxifen in terms of reducing the rates of recurrence and improving disease-free survival (DFS) in postmenopausal women, particularly in the early stages of the illness. This advancement, in conjunction with the subsequent development of SERDs and cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, has significantly expanded the variety of treatments available for HR+ breast cancer (11).

As a consequence, clinical results have been improved, and patients have managed to live for longer periods. A different approach is provided by SERDs, which include fulvestrant. These SERDs not only inhibit estrogen receptors but also make it easier for them to degrade, which further hinders the process of estrogen-mediated signaling (4). SERDs have shown to be successful in the treatment of early-stage as well as metastatic HR+ breast cancer, particularly in patients who have already developed resistance to tamoxifen or aromatase inhibitors. CDK4/6 inhibitors are a class of targeted medicines that work by inhibiting cyclin-dependent kinases that are related to the advancement of the cell cycle. Examples of these drugs include palbociclib, ribociclib, and abemaciclib. CDK4/6 inhibitors, when used in concert with AIs, have demonstrated significant improvements in progression-free survival (PFS) and overall survival (10) in patients with metastatic HR+ breast cancer. This is particularly true for individuals whose tumors have demonstrated resistance to endocrine therapy alone.

Nonetheless, despite these therapeutic advancements, the clinical landscape of HR+ breast cancer is confounded by endocrine resistance, which may be intrinsic (existing from the initiation of therapy) or acquired (growing over time) (12). Endocrine resistance is a significant obstacle in the treatment of HR+ breast cancer, as tumors that initially respond to hormonal therapy may ultimately recur due to the activation of alternative signaling pathways or genetic changes that circumvent estrogen receptor reliance (13). The principal causes contributing to endocrine resistance encompass tumor heterogeneity, mutations in the estrogen receptor (notably ESR1 mutations), activation of the PI3K/AKT/mTOR pathway, and modifications in other cell cycle regulators, including cyclin D1 and CDK4/6. The tumor microenvironment and the presence of inflammatory mediators can exacerbate resistance to treatment (14).

Recent advancements in molecular biology, genomics, and precision medicine have yielded profound insights into the mechanisms underlying hormone resistance. These developments are facilitating the creation of innovative therapeutic ways to surmount resistance and enhance patient outcomes (15). Targeted medicines focused on specific molecular modifications, such as PI3K inhibitors or combination therapy addressing several signaling pathways, demonstrate potential in surmounting resistance. Moreover, the incorporation of liquid biopsy and sophisticated genetic profiling in clinical practice facilitates more accurate, personalized therapy approaches tailored to the distinct genomic attributes of a patient's tumor (16).

This review seeks to elucidate the present role of hormonal therapy in the management of HR+ breast cancer, analyzing the diverse therapeutic choices, their clinical effectiveness, and the obstacles

presented by endocrine resistance. Furthermore, it will examine novel tools in precision medicine and molecular targeting that possess the potential to enhance the efficacy of hormone therapy and tackle the intricate problem of resistance. The integration of tailored treatment strategies, innovative targeted medicines, and enhanced comprehension of the molecular biology of HR+ breast cancer will be essential for improving outcomes and alleviating the worldwide burden of this illness.

Current Approaches to Hormonal Therapy

Aromatase Inhibitors: The Backbone of Therapy in Postmenopausal Women

Aromatase inhibitors, also known as AIs, are the principal treatment for hormone receptor-positive breast cancer in postmenopausal women who have passed through menopause. Adipose tissue, liver, and muscle are all examples of peripheral tissues that are affected by these drugs because they inhibit the aromatase enzyme, which is responsible for facilitating the conversion of androgens, which are precursors to estrogen, into estrogen (17). In women who have gone through menopause, the ovaries stop producing a significant amount of estrogen, and the majority of the estrogen that is found in the body comes from several peripheral conversion mechanisms (18). Aromatase inhibitors reduce the amount of estrogen that is circulating in the body, preventing estrogen receptor-positive (ER+) tumors from receiving the hormone that is necessary for their growth and proliferation (19).

The efficacy of artificial intelligence as a therapeutic agents has been undeniably demonstrated, particularly in the context of adjuvant treatment for early-stage HR+ breast cancer. In postmenopausal women, aromatase inhibitors are superior to tamoxifen in terms of reducing the risk of breast cancer recurrence and improving disease-free survival (DFS) (20). This has been demonstrated by a large number of substantial clinical trials that were conducted using randomised methods. Two studies, the ATAC (Arimidex, Tamoxifen, Alone or in Combination) experiment and the BIG 1-98 study, demonstrated that aromatase inhibitors, such as anastrozole, letrozole, and exemestane, significantly reduce the rates of recurrence and improve survival outcomes when administered as adjuvant therapy after surgery. This is in comparison to the use of tamoxifen (21).

In comparison to tamoxifen, artificial insemination can reduce estrogen levels in a more effective manner, which is one of the primary advantages of AIs. Tamoxifen is a SERM that blocks estrogen receptors in breast tissue while demonstrating partial estrogenic activities in other tissues, such as the bones and the uterus (22). Tamoxifen is used to treat breast cancer. On the other hand, artificial intelligence solutions offer a more comprehensive estrogen blockade by systematically lowering the production of estrogen. Artificial insemination treatment is particularly advantageous for postmenopausal women since it targets the primary source of estrogen in the body while simultaneously lowering the likelihood of uterine side effects that are linked with tamoxifen (6).

Although AIs have significantly improved outcomes for postmenopausal women who have HR+ breast cancer, the deployment of these technologies raises several challenges. AIs have been related to particular side effects, including decreased bone density, arthralgia, vasomotor symptoms, and an increased probability of fractures. These bad effects have been linked to prolonged administration of such medications (23). As a consequence of the fact that estrogen plays a crucial role in maintaining bone health, AIs have the potential to lower estrogen levels, which in turn can lead to a drop in bone mineral density (BMD). As a consequence of this, individuals who are receiving AI therapy typically require constant monitoring of their bone health. Certain bone-modifying medications, such as bisphosphonates or denosumab, may be utilized to mitigate the risk of bone fractures (24).

Furthermore, musculoskeletal disorders, which include joint stiffness, pain, and edema, are common side effects that can have a significant impact on the quality of life of a patient. These symptoms, which are sometimes referred to as “AI arthralgia,” have the potential to render certain individuals unable to function normally and perhaps lead to the termination of treatment (25). Consequently, it is crucial to regulate these adverse effects in the care of women who are receiving AI therapy. Controlling these symptoms involves utilizing a variety of strategies, including analgesics, physical therapy, and adaptations to the patient’s lifestyle, to improve patient comfort and adherence to treatment (26).

There are several cases in which artificial intelligence is applied in the management of advanced or metastatic HR+ breast cancer. It has been established that AIs can improve PFS and overall survival in patients who have metastatic sickness when they are taken in conjunction with other targeted therapies, such as cyclin-dependent kinase 4/6 (CDK4/6) inhibitors (27). Certain CDK4/6 inhibitors, such as palbociclib, ribociclib, and abemaciclib, perform their role by impeding the advancement of the cell cycle, which in turn inhibits the proliferation of cancer cells. The combination of artificial intelligence with CDK4/6 inhibitors has resulted in the establishment of a standard treatment protocol for metastatic HR+ breast cancer (28). This approach offers patients extended disease management and improved outcomes in comparison

to monotherapy.

Even though they are effective, a significant obstacle continues to exist in the form of endocrine resistance, which can develop either naturally or as a result of prolonged treatment (29). Alterations in the estrogen receptor or the activation of alternative signaling pathways can lead to the development of resistance to aromatase inhibitors in some malignancies over the course of treatment. This resistance represents a considerable impediment to the efficacy of treatment interventions over the long term, particularly in the case of metastatic sickness. New chances to overcome resistance and improve patient outcomes have arisen as a result of the development of innovative drugs. These therapies include SERDs and combination treatments that target alternative biochemical pathways (30).

Clinical Efficacy and Applications

Early-Stage Breast Cancer

While conventional treatments like tamoxifen are effective in reducing the risk of recurrence and improving DFS in patients with early-stage HR+ breast cancer, AIs are more effective in clinical settings (31). Anastrozole, letrozole, and exemestane are examples of artificial insemination drugs that work by lowering estrogen levels in the body, which in turn inhibits the growth of tumors that are mediated by estrogen. Because estrogen is primarily produced by the aromatase enzyme rather than the ovaries, this method is particularly useful for women who have gone through menopause (32).

The function of aromatase inhibitors in the adjuvant setting has been elucidated by significant clinical trials. In this context, aromatase inhibitors are supplied after surgery to reduce the likelihood of recurrence taking place (33). Through the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial, which was a significant study, it was determined that anastrozole, which is an aromatase inhibitor, was more effective than tamoxifen in reducing the recurrence rates of HR+ breast cancer in postmenopausal women (34). Following the administration of letrozole as adjuvant therapy, the BIG 1-98 study indicated that letrozole was more effective than tamoxifen in improving DFS and overall survival respectively. Artificial intelligence is an effective alternative to tamoxifen for the treatment of early-stage HR+ breast cancer, particularly in postmenopausal women. These studies have established the use of AIs as a standard treatment for breast cancer (35).

Extended Adjuvant Therapy

There have been several important studies that have demonstrated the benefits of extending adjuvant AI therapy beyond the traditional timeframe of five years. Women who had completed their original five years of treatment with tamoxifen were included in the MA.17 trial, which proved the significant advantages of extending the duration of letrozole medication for an additional five years of treatment (36). Notably among high-risk patients, such as those with lymph node-positive sickness or those diagnosed at a younger age, the prolonged therapy led to a considerable drop in the incidence of late recurrences. This was notably true for individuals who had advanced stages of the disease (37). It has become apparent that increasing the use of AI therapy for these patients is a potential strategy for further reducing the rates of recurrence and improving the outcomes of long-term survival. Nevertheless, the benefits of prolonged adjuvant therapy need to be weighed against the possibility of long-term detrimental repercussions, such as decreased bone density, cardiovascular events, and musculoskeletal difficulties, which calls for careful monitoring and administration of care services (8).

Metastatic Breast Cancer

In the context of metastatic breast cancer, aromatase inhibitors are crucial, especially for patients with hormone receptor-positive tumors. In advanced disease, the objective is to manage the cancer, extend survival, and preserve quality of life. Artificial intelligences are frequently utilized with other therapies to augment their effectiveness (38). A promising strategy in metastatic HR+ breast cancer is the utilization of AIs alongside targeted medicines, including cyclin-dependent kinase 4/6 (CDK4/6) inhibitors. Pharmaceuticals such as palbociclib, ribociclib, and abemaciclib, which inhibit the CDK4/6 pathway, function by obstructing cell cycle advancement, hence averting cancer cell multiplication. In conjunction with AIs, CDK4/6 inhibitors have demonstrated a substantial enhancement in PFS and overall survival for patients with metastatic HR+ breast cancer (39).

The integration of AIs with CDK4/6 inhibitors has emerged as a fundamental treatment for metastatic breast cancer, yielding enhanced clinical results relative to AIs alone. Additional targeted medicines, including PI3K inhibitors or mTOR inhibitors, may be utilized in conjunction with AIs for specific individuals, contingent upon the tumor's molecular features (40). This comprehensive therapeutic strategy has transformed the management of metastatic breast cancer, providing patients with enhanced options for disease control and prolonging survival with a comparatively advantageous side effect profile compared to chemotherapy.

Limitations and Side Effects

The use of aromatase inhibitors for an extended

period in the treatment of HR+ breast cancer has been associated with several adverse effects, particularly on bone health (41). To function, artificial intelligence inhibits the enzyme aromatase, which is responsible for catalyzing the conversion of androgens to estrogen. This results in a decrease in the amount of estrogen that is present in the body (42). Even though these treatments are effective in reducing the proliferation of tumors that are caused by estrogen, they may also cause a significant reduction in bone density. As a consequence, the risk of fractures and other musculoskeletal consequences, such as joint pain, stiffness, and edema, is increased. Estrogen deficiency, which is essential for maintaining bone density, is thought to be the cause of these adverse consequences (43).

When these risks are taken into consideration, it is necessary to carefully monitor the bone health of patients who are undergoing AI therapy. The degree of bone loss can be evaluated with the help of bone density examinations, such as DEXA scans, which are frequently recommended (44). To add insult to injury, medical professionals may recommend bone-modifying medications, such as bisphosphonates (for example, zoledronic acid) or denosumab (a monoclonal antibody), which reduce the likelihood of fractures by increasing bone density and reducing bone resorption (45). It is the goal of these therapies to reduce the bone-debilitating effects of AIs, which will allow patients to continue receiving treatment for their cancer while simultaneously minimizing the number of skeletal difficulties they have. Furthermore, managing musculoskeletal disorders is an essential component of patient care because these symptoms can harm a patient's quality of life as well as their ability to comply with treatment (46).

Selective Estrogen Receptor Modulators (SERMs): A Historical Perspective

In the treatment of ER+ breast cancer, selective estrogen receptor modulators, also known as SERMs, are an important component of hormonal therapy (47). The therapeutic approach for HR+ breast cancer was revolutionized by tamoxifen, which was the first SERM to be approved for clinical application when it was first introduced. Specifically, tamoxifen accomplishes its effect by attaching itself to estrogen receptors in breast cancer cells (48). This prevents estrogen from connecting to the receptors, which in turn promotes the proliferation of cancer cells. Tamoxifen acts as an estrogen antagonist in breast tissue, which means that it inhibits the proliferative effects of estrogen on tumor cells. As a result, it reduces the likelihood of recurrence in women who have HR+ breast cancer (49).

In addition to its effect on the breast, tamoxifen also demonstrates estrogenic activity in other tissues, such as the uterus and the bones. Because tamoxifen has the potential to protect bone density while simultaneously increasing the risk of endometrial cancer, the risk-benefit profile has become more complicated as a result of the dual action (50). Tamoxifen has been the cornerstone of breast cancer treatment for decades, despite the concerns that have been raised about its effectiveness. There is strong clinical evidence that supports its effectiveness in reducing the risk of breast cancer recurrence and improving overall survival rates in women who have ER+ tumors (51).

Recently, innovative selective estrogen receptor modulators SERMs with tissue-specific effects have been developed as our understanding of breast cancer biology has progressed. Along the same lines as tamoxifen, raloxifene is a drug that targets estrogen receptors. It is primarily used for the treatment of osteoporosis and the prevention of breast cancer in women who are at a high risk of developing the disease after menopause (52). The development of SERMs has been a significant technological accomplishment in the field of hormonal therapy for breast cancer. Furthermore, continuing research continues to investigate novel options that have improved efficacy and safety profiles (53).

Clinical Impact

Tamoxifen remains an essential treatment for premenopausal women with HR+ breast cancer and in certain postmenopausal contexts. Tamoxifen, a SERM, functions by attaching to estrogen receptors on cancer cells, inhibiting the proliferative effects of estrogen in breast tissue (54). Although newer medicines like aromatase inhibitors are accessible for postmenopausal women, tamoxifen continues to be a fundamental treatment, especially for premenopausal women who still synthesize estrogen from their ovaries. The enduring therapeutic advantages of tamoxifen have been thoroughly recorded in significant clinical trials, such as the NSABP P-1 (National Surgical Adjuvant Breast and Bowel Project P-1) and ATLAS (Adjuvant Tamoxifen: Longer Against Shorter) trials (55). The trials have shown that tamoxifen substantially decreases the incidence of breast cancer recurrence and contralateral breast cancer in women with HR+ breast cancer. The ATLAS trial, featuring extensive long-term follow-up, validated that tamoxifen maintains its efficacy beyond 10 years of treatment, decreasing the probability of relapse and enhancing DFS and overall survival (10). The NSABP P-1 study, which primarily examined tamoxifen as a prophylactic intervention for high-risk women, showed a significant decrease in the occurrence of both invasive breast cancer and non-invasive (ductal carcinoma in situ) illness. Additionally, tamoxifen

has demonstrated efficacy in diminishing the risk of contralateral breast cancer, which is particularly significant for women previously diagnosed with cancer in one breast (56). The clinical advantages have established tamoxifen as a standard treatment, providing an effective approach to enhance long-term survival and quality of life in women with HR+ breast cancer.

Challenges

Although tamoxifen is a crucial element in breast cancer therapy, its administration is linked to various side effects and constraints that may affect patient compliance and overall results. A significant adverse effect of tamoxifen is the heightened risk of thromboembolic events, such as deep vein thrombosis (DVT) and pulmonary embolism (57). These concerns are especially pertinent for older women, those with additional thrombosis risk factors, or individuals with pre-existing cardiovascular diseases. The risk of these life-threatening consequences necessitates meticulous screening and management of patients, especially those with concurrent comorbidities (58).

Furthermore, tamoxifen has been linked to a heightened risk of endometrial cancer, especially in postmenopausal women. Due to tamoxifen's role as an estrogen agonist in specific tissues, including the endometrium, it can promote the proliferation of endometrial cells, potentially resulting in hyperplasia or cancer (59). The risk of endometrial cancer is dose-dependent and seems to be elevated in older women on prolonged tamoxifen treatment. This requires vigilant observation for signs of endometrial cancer (such as atypical uterine bleeding) and consistent gynecological assessments, particularly for women who have undergone prolonged tamoxifen therapy (60).

A notable difficulty with tamoxifen is its restricted effectiveness in cancers that are inherently resistant to estrogen inhibition. Although tamoxifen is efficacious in numerous HR+ breast cancers, certain tumors may possess genetic mutations or modifications in the estrogen receptor (e.g., ESR1 mutations) that diminish tamoxifen's capacity to bind efficiently and impede estrogen signaling (61). In certain instances, the tumors may persist in their growth despite tamoxifen treatment. Furthermore, cancers that initially respond to tamoxifen may ultimately acquire resistance, resulting in disease recurrence. This inherent or developed resistance to tamoxifen poses a significant therapeutic obstacle in the treatment of HR+ breast cancer, particularly in advanced or metastatic cases (62).

Significant advancements have been made in the development of alternative therapies to address these constraints. Aromatase inhibitors are now the standard treatment for postmenopausal women with HR+ breast cancer, providing comprehensive estrogen suppression by decreasing estrogen synthesis. Patients with tamoxifen-resistant cancers can benefit from novel targeted medicines, including SERDs and CDK4/6 inhibitors, which offer alternative therapy choices to enhance outcomes and combat resistance mechanisms (63). In conclusion, although tamoxifen is a crucial therapy for premenopausal women and specific postmenopausal scenarios, its adverse effects, such as thromboembolic events, heightened risk of endometrial cancer, and restricted effectiveness in tamoxifen-resistant malignancies, pose considerable obstacles. Continued research aimed at addressing resistance, enhancing side effect profiles, and formulating combination medicines is crucial for optimizing treatment results in women with HR+ breast cancer (64).

Advancements in Hormonal Therapy: CDK4/6 Inhibitors and Beyond

The introduction of CDK 4/6 inhibitors has substantially altered the therapeutic approach for HR+ breast cancer, particularly in advanced and metastatic phases (65). These medications signify a significant advancement in enhancing outcomes for patients with restricted alternatives following progression on standard hormonal therapy, including aromatase inhibitors or tamoxifen. CDK4/6 inhibitors have transformed the treatment of HR+ breast cancer by introducing a new mode of action that improves the effectiveness of endocrine therapy (66).

Mechanism of Action

CDKs are crucial regulators of the cell cycle, particularly governing the transition from the G1 phase (cell proliferation) to the S phase (DNA synthesis). CDK4 and CDK6 are essential in facilitating this transition by phosphorylating the retinoblastoma (Rb) protein, a principal regulator that typically inhibits cell cycle advancement (67). The phosphorylation of Rb by CDK4/6 facilitates the release of E2F transcription factors, which initiate the expression of genes essential for the S phase of the cell cycle, culminating in cell division (68).

CDK4/6 inhibitors, including palbociclib, ribociclib, and abemaciclib, selectively inhibit CDK4 and CDK6 activity, obstructing Rb phosphorylation and impeding cell cycle progression from G1 to S phase (69). This strategy significantly inhibits cell proliferation in HR+ breast cancer cells, which is essential for malignancies driven by estrogen receptor signaling. Combining CDK4/6 inhibitors with conventional hormonal treatments, such as aromatase inhibitors or fulvestrant, enhances therapeutic efficacy by more efficiently inhibiting tumor proliferation (39).

Clinical Evidence

First-Line Therapy

It has been established time and again in clinical studies that the incorporation of CDK4/6 inhibitors into endocrine therapy results in a significant improvement in PFS and overall outcomes for patients who have advanced HR+ breast cancer (70). To demonstrate the clinical efficacy of these combinations, studies such as PALOMA-2, MONALEESA-2, and MONARCH-3 have been extremely important. The PALOMA-2 trial demonstrated that the combination of palbociclib and letrozole, which is an aromatase inhibitor, resulted in a significant improvement in progression-free survival (PFS) when compared to letrozole alone (71). This resulted in a considerable reduction in the likelihood of the illness progressing. The MONALEESA-2 trial, which included both ribociclib and letrozole, produced comparable results. These results indicated a considerable improvement in progression-free survival (PFS) in addition to a positive safety profile (72).

In the context of first-line treatment, the MONARCH-3 study evaluated the performance of abemaciclib in combination with letrozole, which resulted in the production of strong evidence for the benefits of combining CDK4/6 inhibitors with aromatase inhibitors. The results of these clinical trials make it abundantly evident that the incorporation of CDK4/6 inhibitors not only increases the efficacy of endocrine therapy but also provides patients with extended disease management and delays progression, hence improving both quality of life and overall survival rates (73).

Second-Line Therapy

The use of CDK4/6 inhibitors in second-line treatment regimens has been beneficial in patients whose illness has progressed after first-line hormone therapy. In patients with metastatic HR+ breast cancer who had previously had hormonal treatment, the MONARCH-2 study found that combining abemaciclib with fulvestrant, an estrogen receptor antagonist, significantly improved overall survival and PFS (74). For patients who have shown resistance to aromatase inhibitors or tamoxifen, the results of MONARCH-2 validated the use of abemaciclib as a second-line treatment. It has been shown that CDK4/6 inhibitors, when combined with other endocrine drugs, can overcome endocrine resistance and produce substantial therapeutic benefits, even at the late stages of the disease (75).

According to the results, CDK4/6 inhibitors are now more commonly used in combination therapy as a first-line and second-line treatment strategy for metastatic HR+ breast cancer. This has greatly improved survival rates and given patients fresh hope for controlling their disease in the long run (70).

Toxicities and Management

Even though CDK4/6 inhibitors are highly effective in the treatment of HR+ breast cancer, they are also associated with several undesirable side effects. Neutropenia, fatigue, diarrhea, and hepatic enzyme abnormalities are the most common adverse effects that have been associated with CDK4/6 inhibitors (76). Neutropenia is a significant cause for concern because it can contribute to an increased risk of infections and may require a reduction in the dosage of the medication or a temporary cessation of treatment. Consistent monitoring of blood counts is essential for the early discovery and management of neutropenia. Patients may require growth factor support or alterations to their treatment plan, depending on the severity of their condition (77).

One of the most common unpleasant effects, particularly one that is related to abemaciclib, is diarrhea, which can be quite severe in some individuals. It is common practice to treat this adverse effect with supportive treatment, which may involve the prescription of anti-diarrheal medications and the reduction of dosage as necessary. To prevent dehydration and maintain the patient's quality of life, it is essential to effectively manage diarrhea (78).

It has been observed that patients who have been treated with ribociclib and abemaciclib have displayed abnormalities in liver function, including elevated levels of liver enzymes (AST and ALT). It is recommended that liver function be evaluated regularly, particularly in the beginning stages of treatment. In cases where there is a significant amount of liver toxicity, patients may be forced to make adjustments to their dosage or perhaps stop receiving treatment altogether (79).

Even though fatigue is a common adverse effect, it is often manageable via the use of supportive care procedures and symptomatic therapy. Even though some individuals may experience symptoms such as nausea, headaches, or baldness, it is important to note that these symptoms are typically less severe than the toxicities that are associated with conventional chemotherapy (80).

Additionally, even though the introduction of CDK4/6 inhibitors has revolutionized the treatment of HR+ breast cancer, particularly in the later and metastatic stages of the disease, it is vital to address adverse effects to achieve the best possible outcomes for patients. The alleviation of these toxicities can be accomplished by the implementation of individualized treatment protocols, consistent observation, and supportive interventions (81). This will enable patients to continue receiving therapy and benefit from significant gains in disease management and survival rates. There is reason to be optimistic about

the possibility of improved long-term management of HR+ breast cancer, as the development of novel medications and combination therapies continues to advance (82).

Challenges in Hormonal Therapy: Mechanisms of Resistance

Resistance to hormonal therapy constitutes a major obstacle to the efficient management of (HR+) breast cancer, especially in late or metastatic phases. Notwithstanding the considerable clinical efficacy of therapies such as SERMs, AIs, and other endocrine-based treatments, a significant proportion of patients encounter either intrinsic or acquired resistance, resulting in disease progression (13). Comprehending the mechanisms underlying this resistance is essential for formulating innovative therapeutic techniques that can overcome these obstacles and enhance patient outcomes (83).

Intrinsic vs. Acquired Resistance

Intrinsic Resistance

Intrinsic resistance denotes cancers that are unresponsive to hormone therapy from the beginning. This form of resistance frequently arises from certain genetic mutations or modifications in essential signaling pathways that inhibit the efficacy of the therapy (84). For instance, certain HR+ cancers may include mutations that impair estrogen receptor signaling, or they may have anomalies in alternative growth-promoting pathways that reduce their dependence on estrogen for proliferation. These tumors exhibit a diminished likelihood of responding to standard hormonal therapy, like tamoxifen or aromatase inhibitors, from the onset of treatment (85).

Acquired Resistance

Acquired resistance occurs when cancers first react to hormonal therapy but subsequently establish methods to circumvent estrogen reliance. Over time, these tumor cells acclimate to the selective pressures of hormone therapy, resulting in disease progression despite ongoing treatment. This condition is particularly prevalent in metastatic contexts, where tumor cells undergo prolonged endocrine treatments (86). As the tumor progresses, it may activate alternate signaling pathways or acquire mutations that enable it to circumvent the requirement for estrogen, so rendering the therapy ineffective. Acquired resistance poses a significant difficulty in the management of advanced HR+ breast cancer, as it restricts the efficacy duration of previously effective medicines (87).

Key Mechanisms of Resistance

Several mechanisms have been identified that contribute to both intrinsic and acquired resistance to hormonal therapy in HR+ breast cancer. These include genetic mutations, activation of alternative signaling pathways, changes in hormone receptor expression, and epigenetic modifications (88). Below are some of the most prominent mechanisms that drive resistance:

1.**ESR1 Mutations**

A prominent cause of acquired resistance is the development of mutations in the ESR1. These mutations frequently occur in cancers that initially responded to tamoxifen or aromatase inhibitors but subsequently acquired resistance. ESR1 mutations result in ligand-independent activation of the estrogen receptor, indicating that the receptor remains active without the presence of estrogen or other activating ligands (89). This enables tumor cells to persist in proliferation independent of estrogen stimulation. Aromatase inhibitors, which function by diminishing estrogen synthesis, thus lose their efficacy. ESR1 mutations correlate with unfavorable prognosis and underscore the necessity for alternative treatments, such as SERDs, capable of targeting and degrading the mutated receptor (90).

2.**Alternative Pathway Activation**

A significant form of resistance involves the development of alternative signaling pathways that completely circumvent the estrogen receptor pathway. In HR+ breast cancer, tumors may enhance signaling pathways such as the PI3K/AKT/mTOR pathway, HER2 signaling, or fibroblast growth factor receptor (FGFR) signaling, all of which can facilitate tumor growth and survival independently of estrogen (91). Activation of the PI3K/AKT/mTOR pathway can promote cell proliferation and survival, even when medications that inhibit estrogen signaling are present. Likewise, HER2 overexpression or amplification may activate alternate growth signals, causing resistance to endocrine treatment. These alternative pathways present novel therapeutic targets, and combination therapies aimed at both estrogen signaling and these pathways are being explored to address resistance (92).

3.**Loss of ER Expression**

Certain malignancies may experience a significant alteration, completely losing estrogen receptor expression. The phenomenon termed “ER downregulation” frequently transpires with the advancement of breast cancer to a more aggressive and therapy-resistant phenotype (93). Tumors that exhibit a loss of ER expression become independent of estrogen for proliferation and are consequently resistant to hormonal treatments, like AIs or tamoxifen. The absence of ER expression is generally linked to an unfavorable prognosis and is indicative

of more aggressive, poorly differentiated neoplasms. This resistance mechanism is a considerable difficulty, as these cancers necessitate an entirely distinct treatment strategy, frequently incorporating chemotherapy or targeted medicines instead of hormone therapy (94).

4.**Epigenetic Modifications**

Epigenetic modifications, such as changes in DNA methylation and histone abnormalities, may also play a role in the resistance to hormone treatments in HR+ breast cancer. These alterations can influence the expression and functionality of the estrogen receptor without modifying the fundamental genetic sequence (95). Hypermethylation of the ESR1 gene promoter can result in decreased expression of the estrogen receptor, thereby reducing the efficacy of therapy aimed at the ER. Likewise, modifications in histone acetylation or methylation can influence chromatin architecture and gene expression, encompassing genes pertinent to cell cycle regulation and apoptosis. Epigenetic alterations enable tumor cells to circumvent the growth-inhibitory effects of hormone therapy, hence increasing their resistance to treatment (96).

Biomarker-Driven Personalized Medicine

Progress in genomic profiling has markedly improved the capacity to customize breast cancer therapies according to the specific molecular traits of the tumor. Personalized medicine, informed by biomarkers, is progressively establishing itself as a fundamental aspect of breast cancer care. By identifying particular genetic mutations, modifications in signaling pathways, and other molecular characteristics, clinicians can determine the best suitable medicine for each patient, so ensuring a more tailored and effective treatment approach (97).

Multi-Gene Assays

Multi-gene assays, including Oncotype DX and MammaPrint, have transformed the management of HR+ breast cancer by delivering essential insights regarding recurrence risk and the possible advantages of adjuvant therapies. These assays evaluate the expression of several genes in tumor specimens to forecast the probability of recurrence and inform treatment strategies. Oncotype DX evaluates the expression of 21 genes and generates a recurrence score that aids in determining the need for chemotherapy alongside hormonal therapy (98). MammaPrint, a prevalent genomic assay, assesses the expression of 70 genes and offers insights about the patient's recurrence risk and potential advantages of adjuvant chemotherapy. Utilizing these assays, oncologists can categorize patients into distinct risk groups, facilitating more tailored treatment strategies that prevent both overtreatment and undertreatment (99).

The integration of biomarker-driven medicines, shown by alpelisib for PIK3CA-mutated tumors, illustrates the influence of precision medicine on the future of breast cancer treatment. Advancements in biomarker research are expected to yield better-tailored medicines, enhancing patient outcomes and minimizing superfluous side effects (100).

Emerging Therapies

Several promising therapies are currently being investigated in clinical trials with the potential to complement or enhance existing treatments for HR+ breast cancer. These emerging therapies are focused on disrupting estrogen receptor signaling at multiple levels and overcoming the challenges associated with resistance to current therapies (101).

Selective ER Coregulator Modulators (SECRMs)

Selective estrogen receptor coregulator modulators (SECRMs) represent an innovative category of pharmaceuticals aimed at precisely and specifically modulating estrogen receptor function. In contrast to conventional SERMs, which either inhibit or stimulate ER signaling based on the tissue type, SECRMs function by modifying the recruitment of coregulatory proteins to the ER (102). This may result in the suppression of ER-mediated transcription in tumors while preserving normal estrogenic function in other tissues, including bone. SECRMs offer a promising treatment strategy for HR+ breast cancer by specifically inhibiting ER signaling in cancer cells while maintaining its function in normal tissues, especially for patients resistant to standard hormonal therapy (103).

Epigenetic Modulators

Epigenetic modulators represent a promising field of investigation focused on undoing or altering the epigenetic modifications that lead to resistance in HR+ breast cancer. Alterations in DNA methylation, histone modification, and chromatin remodeling can modify gene expression patterns in cancers, particularly those associated with estrogen receptor signaling, resulting in resistance to hormonal treatments (104). Epigenetic modulators aim to target and counteract these alterations, perhaps reinstating sensitivity to endocrine therapy. Agents that inhibit DNA methyltransferases or histone deacetylases are being evaluated in conjunction with hormone therapy to ascertain their potential to surmount resistance and enhance therapeutic efficacy (105).

Immune Checkpoint Inhibitors:

While immune checkpoint medications, including

PD-1 and PD-L1 inhibitors, have demonstrated significant potential across various malignancies, their effectiveness in HR+ breast cancer has been comparatively limited. HR+ breast cancer generally exhibits a reduced mutational burden and diminished immune cell infiltration, resulting in decreased responsiveness to immune checkpoint inhibitors. Researchers are investigating the integration of immune checkpoint inhibitors with hormone treatments to augment anticancer immunity (106). The objective of integrating immune checkpoint inhibition with endocrine therapy is to surmount the immunosuppressive tumor milieu and elicit a more robust immune response. Current early-phase clinical trials are in progress, and although the results to date have been inconsistent, this strategy possesses the potential to enhance outcomes for HR+ breast cancer patients, particularly those with metastatic illness (107).

Conclusion

Hormonal therapy has revolutionized the treatment of HR+ breast cancer, markedly enhancing survival rates and quality of life. Nonetheless, obstacles like as resistance, tumor heterogeneity, and treatment-associated toxicity highlight the necessity for further innovation. The future of HR+ breast cancer management is rooted in personalized medicine, with novel drugs such as oral SERDs, combination therapies, and biomarker-driven strategies providing renewed optimism. By overcoming the constraints of existing medicines and utilizing advancements in molecular biology, the forthcoming phase of hormonal therapy is poised to enhance results for patients with HR+ breast cancer.

Authors's Contribution

Kosar Helmi: Conceptualization and review, Farnoosh Honarmand: Writing and editing the draft. The authors read and confirmed the final manuscript.

Funding

This study is the outcome of self-directed research carried out without any financial assistance.

Ethics approval and consent to participate

Not applicable.

Conflict of Interest

The authors declared no conflict of interest.

Consent for publication

Not Applicable

References

1. Łukasiewicz S, Czeczelewski M, Forma A, Baj J, Sitarz R, Stanisławek A. Breast Cancer-Epidemiology, Risk Factors, Classification, Prognostic Markers, and Current Treatment Strategies-An Updated Review. Cancers. 2021;13(17).
2. Al-Shami K, Awadi S, Khamees A, Alsheikh AM, Al-Sharif S, Ala' Bereshy R, et al. Estrogens and the risk of breast cancer: A narrative review of literature. Heliyon. 2023;9(9):e20224.
3. Clusan L, Ferrière F, Flouriot G, Pakdel F. A Basic Review on Estrogen Receptor Signaling Pathways in Breast Cancer. International Journal of Molecular Sciences [Internet]. 2023; 24(7).
4. Gheysen M, Punie K, Wildiers H, Neven P. Oral SERDs changing the scenery in hormone receptor positive breast cancer, a comprehensive review. Cancer Treatment Reviews. 2024;130:102825.
5. Rasha F, Sharma M, Pruitt K. Mechanisms of endocrine therapy resistance in breast cancer. Molecular and Cellular Endocrinology. 2021;532:111322.
6. Criscitiello C, Fumagalli D, Saini KS, Loi S. Tamoxifen in early-stage estrogen receptor-positive breast cancer: overview of clinical use and molecular biomarkers for patient selection. OncoTargets and therapy. 2010;4:1-11.
7. Andrahennadi S, Sami A, Manna M, Pauls M, Ahmed S. Current Landscape of Targeted Therapy in Hormone Receptor-Positive and HER2-Negative Breast Cancer. Current oncology (Toronto, Ont). 2021;28(3):1803-22.
8. He X, Ji J, Qdaisat A, Esteva FJ, Yeung S-CJ. Long-term overall survival of patients who undergo breast-conserving therapy or mastectomy for early operable HER2-Positive breast cancer after preoperative systemic therapy: an observational cohort study. The Lancet Regional Health - Americas. 2024;32:100712.
9. Generali D, Berardi R, Caruso M, Cazzaniga M, Garrone O, Minchella I, et al. Aromatase inhibitors: the journey from the state of the art to clinical open questions. Frontiers in oncology. 2023;13:1249160.
10. Chan HJ, Petrossian K, Chen S. Structural and functional characterization of aromatase, estrogen receptor, and their genes in endocrine-responsive and -resistant breast cancer cells. The Journal of steroid biochemistry and molecular biology. 2016;161:73-83.
11. van Hellemond IEG, Geurts SME, Tjan-Heijnen VCG. Current Status of Extended Adjuvant Endocrine Therapy in Early Stage Breast Cancer. Current treatment options in oncology. 2018;19(5):26.
12. Nolan E, Lindeman GJ, Visvader JE. Deciphering breast cancer: from biology to the clinic. Cell. 2023;186(8):1708-28.
13. Hanker AB, Sudhan DR, Arteaga CL. Overcoming

Endocrine Resistance in Breast Cancer. Cancer cell. 2020;37(4):496-513.
14.Gao Y, Yu Y, Zhang M, Yu W, Kang L. Mechanisms of endocrine resistance in hormone receptor-positive breast cancer. Frontiers in oncology. 2024;14:1448687.
15.Siavashy S, Soltani M, Rahimi S, Hosseinali M, Guilandokht Z, Raahemifar K. Recent advancements in microfluidic-based biosensors for detection of genes and proteins: Applications and techniques. Biosensors and Bioelectronics: X. 2024;19:100489.
16.Bou Antoun N, Chioni AM. Dysregulated Signalling Pathways Driving Anticancer Drug Resistance. Int J Mol Sci. 2023;24(15).
17.Tenti S, Correale P, Cheleschi S, Fioravanti A, Pirtoli L. Aromatase Inhibitors-Induced Musculoskeletal Disorders: Current Knowledge on Clinical and Molecular Aspects. Int J Mol Sci. 2020;21(16).
18.Cui J, Shen Y, Li R. Estrogen synthesis and signaling pathways during aging: from periphery to brain. Trends in molecular medicine. 2013;19(3):197-209.
19.Caciolla J, Bisi A, Belluti F, Rampa A, Gobbi S. Reconsidering Aromatase for Breast Cancer Treatment: New Roles for an Old Target. Molecules [Internet]. 2020; 25(22).
20.Generali D, Berardi R, Caruso M, Cazzaniga M, Garrone O, Minchella I, et al. Aromatase inhibitors: the journey from the state of the art to clinical open questions. 2023;13.
21.Josefsson ML, Leinster SJ. Aromatase inhibitors versus tamoxifen as adjuvant hormonal therapy for oestrogen sensitive early breast cancer in post-menopausal women: Meta-analyses of monotherapy, sequenced therapy and extended therapy. The Breast. 2010;19(2):76-83.
22.Patel HK, Bihani T. Selective estrogen receptor modulators (SERMs) and selective estrogen receptor degraders (SERDs) in cancer treatment. Pharmacology & Therapeutics. 2018;186:1-24.
23.Cerulli C, Moretti E, Grazioli E, Emerenziani GP, Murri A, Tranchita E, et al. Protective role of exercise on breast cancer-related osteoporosis in women undergoing aromatase inhibitors: A narrative review. Bone reports. 2024;21:101756.
24.Noirrit-Esclassan E, Valera M-C, Tremollieres F, Arnal J-F, Lenfant F, Fontaine C, et al. Critical Role of Estrogens on Bone Homeostasis in Both Male and Female: From Physiology to Medical Implications. International Journal of Molecular Sciences [Internet]. 2021; 22(4).
25.Roberts KE, Adsett IT, Rickett K, Conroy SM, Chatfield MD, Woodward NE. Systemic therapies for preventing or treating aromatase inhibitor-induced musculoskeletal symptoms in early breast cancer. The Cochrane database of systematic reviews. 2022;1(1):Cd013167.
26.Roberts KE, Rickett K, Feng S, Vagenas D, Woodward NE. Exercise therapies for preventing or treating aromatase inhibitor-induced musculoskeletal symptoms in early breast cancer. The Cochrane database of systematic reviews. 2020;1(1):Cd012988.
27.Ahn JS, Shin S, Yang SA, Park EK, Kim KH, Cho SI, et al. Artificial Intelligence in Breast Cancer Diagnosis and Personalized Medicine. Journal of breast cancer. 2023;26(5):405-35.
28.Pavlovic D, Niciforovic D, Papic D, Milojevic K, Markovic M. CDK4/6 inhibitors: basics, pros, and major cons in breast cancer treatment with specific regard to cardiotoxicity - a narrative review. Therapeutic advances in medical oncology. 2023;15:17588359231205848.
29.Bekes I, Huober J. Extended Adjuvant Endocrine Therapy in Early Breast Cancer Patients-Review and Perspectives. Cancers. 2023;15(16).
30.Garcia-Martinez L, Zhang Y, Nakata Y, Chan HL, Morey L. Epigenetic mechanisms in breast cancer therapy and resistance. Nature Communications. 2021;12(1):1786.
31.Baek SY, Kwon JY, Lee YJ, Gwark S-c, Lee SB, Kim J, et al. Prediction of Late Breast Cancer-Specific Mortality in Recurrence-Free Breast Cancer Survivors Treated for Five Years with Tamoxifen. Journal of breast cancer. 2019;22(3):387-98.
32.Cao L-Q, Sun H, Xie Y, Patel H, Bo L, Lin H, et al. Therapeutic evolution in HR+/HER2- breast cancer: from targeted therapy to endocrine therapy. 2024;15.
33.Tjan-Heijnen VCG, Lammers SWM, Geurts SME, Vriens IJH, Swinkels ACP, Smorenburg CH, et al. Extended adjuvant aromatase inhibition after sequential endocrine therapy in postmenopausal women with breast cancer: follow-up analysis of the randomised phase 3 DATA trial. EClinicalMedicine. 2023;58:101901.
34.Geisler J. Differences between the non-steroidal aromatase inhibitors anastrozole and letrozole – of clinical importance? British Journal of Cancer. 2011;104(7):1059-66.
35.Ruhstaller T, Giobbie-Hurder A, Colleoni M, Jensen MB, Ejlertsen B, de Azambuja E, et al. Adjuvant Letrozole and Tamoxifen Alone or Sequentially for Postmenopausal Women With Hormone Receptor-Positive Breast Cancer: Long-Term Follow-Up of the BIG 1-98 Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2019;37(2):105-14.
36.Burstein HJ, Lacchetti C, Anderson H, Buchholz TA, Davidson NE, Gelmon KA, et al. Adjuvant Endocrine Therapy for Women With Hormone

Receptor–Positive Breast Cancer: ASCO Clinical Practice Guideline Focused Update. Journal of Clinical Oncology. 2018;37(5):423-38.
37.Pedersen RN, Esen B, Mellemkjær L, Christiansen P, Ejlertsen B, Lash TL, et al. The Incidence of Breast Cancer Recurrence 10-32 Years After Primary Diagnosis. Journal of the National Cancer Institute. 2022;114(3):391-9.
38.Roskoski Jr R. Targeted and cytotoxic inhibitors used in the treatment of breast cancer. Pharmacological Research. 2024;210:107534.
39.Braal CL, Jongbloed EM, Wilting SM, Mathijssen RHJ, Koolen SLW, Jager A. Inhibiting CDK4/6 in Breast Cancer with Palbociclib, Ribociclib, and Abemaciclib: Similarities and Differences. Drugs. 2021;81(3):317-31.
40.Gomes I, Abreu C, Costa L, Casimiro S. The Evolving Pathways of the Efficacy of and Resistance to CDK4/6 Inhibitors in Breast Cancer. Cancers. 2023;15(19).
41.Rugo HS. The breast cancer continuum in hormone-receptor–positive breast cancer in postmenopausal women: evolving management options focusing on aromatase inhibitors. Annals of Oncology. 2008;19(1):16-27.
42.Eissa MA, Gohar EY. Aromatase enzyme: Paving the way for exploring aromatization for cardio-renal protection. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2023;168:115832.
43.Hsu S-H, Chen L-R, Chen K-H. Primary Osteoporosis Induced by Androgen and Estrogen Deficiency: The Molecular and Cellular Perspective on Pathophysiological Mechanisms and Treatments. International Journal of Molecular Sciences [Internet]. 2024; 25(22).
44.Ong W, Liu RW, Makmur A, Low XZ, Sng WJ, Tan JH, et al. Artificial Intelligence Applications for Osteoporosis Classification Using Computed Tomography. Bioengineering (Basel, Switzerland). 2023;10(12).
45.Anastasilakis AD, Pepe J, Napoli N, Palermo A, Magopoulos C, Khan AA, et al. Osteonecrosis of the Jaw and Antiresorptive Agents in Benign and Malignant Diseases: A Critical Review Organized by the ECTS. The Journal of clinical endocrinology and metabolism. 2022;107(5):1441-60.
46. Galvano A, Gristina V, Scaturro D, Bazan Russo TD, Tomasello S, Vitagliani F, et al. The role of bone modifying agents for secondary osteoporosis prevention and pain control in post-menopausal osteopenic breast cancer patients undergoing adjuvant aromatase inhibitors. Frontiers in endocrinology. 2023;14:1297950.
47.Gnant M, Turner NC, Hernando C. Managing a Long and Winding Road: Estrogen Receptor–Positive Breast Cancer. American Society of Clinical Oncology Educational Book. 2023(43):e390922.
48.Park WC, Jordan VC. Selective estrogen receptor modulators (SERMS) and their roles in breast cancer prevention. Trends in molecular medicine. 2002;8(2):82-8.
49.Blakely B, Shin S, Jin K. Overview of the therapeutic strategies for ER positive breast cancer. Biochemical pharmacology. 2023;212:115552.
50.Xuerun L, Jianliu W, Jingyi Z. The role of oestrogen and oestrogen-calcium axis in endometrial carcinoma. Gynecology and Obstetrics Clinical Medicine. 2024;4(1):e000012.
51.Lopez-Tarruella S, Echavarria I, Jerez Y, Herrero B, Gamez S, Martin M. How we Treat HR-Positive, HER2-Negative Early Breast Cancer. Future Oncology. 2022;18(8):1003-22.
52.Lafront C, Germain L, Weidmann C, Audet-Walsh É. A Systematic Study of the Impact of Estrogens and Selective Estrogen Receptor Modulators on Prostate Cancer Cell Proliferation. Scientific Reports. 2020;10(1):4024.
53.Ye F, Dewanjee S, Li Y, Jha NK, Chen Z-S, Kumar A, et al. Advancements in clinical aspects of targeted therapy and immunotherapy in breast cancer. Molecular Cancer. 2023;22(1):105.
54.Miziak P, Baran M, Błaszczak E, Przybyszewska-Podstawka A, Kałafut J, Smok-Kalwat J, et al. Estrogen Receptor Signaling in Breast Cancer. Cancers [Internet]. 2023; 15(19).
55.Aromatase inhibitors versus tamoxifen in premenopausal women with oestrogen receptor-positive early-stage breast cancer treated with ovarian suppression: a patient-level meta-analysis of 7030 women from four randomised trials. The Lancet Oncology. 2022;23(3):382-92.
56.Buijs SM, Koolen SLW, Mathijssen RHJ, Jager A. Tamoxifen Dose De-Escalation: An Effective Strategy for Reducing Adverse Effects? Drugs. 2024;84(4):385-401.
57.DeCensi A, Puntoni M, Guerrieri-Gonzaga A, Caviglia S, Avino F, Cortesi L, et al. Randomized Placebo Controlled Trial of Low-Dose Tamoxifen to Prevent Local and Contralateral Recurrence in Breast Intraepithelial Neoplasia. Journal of Clinical Oncology. 2019;37(19):1629-37.
58.Rodgers JL, Jones J, Bolleddu SI, Vanthenapalli S, Rodgers LE, Shah K, et al. Cardiovascular Risks Associated with Gender and Aging. Journal of cardiovascular development and disease. 2019;6(2).
59.Emons G, Mustea A, Tempfer C. Tamoxifen and Endometrial Cancer: A Janus-Headed Drug. Cancers. 2020;12(9).
60.Mitra S, Lami MS, Ghosh A, Das R, Tallei TE, Fatimawali, et al. Hormonal Therapy for Gynecological Cancers: How Far Has Science

Progressed toward Clinical Applications? Cancers [Internet]. 2022; 14(3).
61.Brett JO, Spring LM, Bardia A, Wander SA. ESR1 mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer. Breast Cancer Research. 2021;23(1):85.
62.García-Becerra R, Santos N, Díaz L, Camacho J. Mechanisms of Resistance to Endocrine Therapy in Breast Cancer: Focus on Signaling Pathways, miRNAs and Genetically Based Resistance. International Journal of Molecular Sciences [Internet]. 2013; 14(1):[108-45 pp.].
63.Patel R, Klein P, Tiersten A, Sparano JA. An emerging generation of endocrine therapies in breast cancer: a clinical perspective. npj Breast Cancer. 2023;9(1):20.
64.Swerdlow AJ, Jones ME. Tamoxifen treatment for breast cancer and risk of endometrial cancer: a case-control study. Journal of the National Cancer Institute. 2005;97(5):375-84.
65.Johnston S, Emde A, Barrios C, Srock S, Neven P, Martin M, et al. Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors: existing and emerging differences. JNCI cancer spectrum. 2023;7(4).
66.Foffano L, Cucciniello L, Nicolò E, Migliaccio I, Noto C, Reduzzi C, et al. Cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i): Mechanisms of resistance and where to find them. The Breast. 2025;79:103863.
67.Goel S, Bergholz JS, Zhao JJ. Targeting CDK4 and CDK6 in cancer. Nature reviews Cancer. 2022;22(6):356-72.
68.Pellarin I, Dall'Acqua A, Favero A, Segatto I, Rossi V, Crestan N, et al. Cyclin-dependent protein kinases and cell cycle regulation in biology and disease. Signal Transduction and Targeted Therapy. 2025;10(1):11.
69.Yousuf M, Alam M, Shamsi A, Khan P, Hasan GM, Rizwanul Haque QM, et al. Structure-guided design and development of cyclin-dependent kinase 4/6 inhibitors: A review on therapeutic implications. International Journal of Biological Macromolecules. 2022;218:394-408.
70.Kimmick G, Pilehvari A, You W, Bonilla G, Anderson R. First- vs second-line CDK 4/6 inhibitor use for patients with hormone receptor positive, human epidermal growth-factor receptor-2 negative, metastatic breast cancer in the real world setting. Breast cancer research and treatment. 2024;208(2):263-73.
71.Rugo HS, Layman RM, Lynce F, Liu X, Li B, McRoy L, et al. Comparative overall survival of CDK4/6 inhibitors plus an aromatase inhibitor in HR+/HER2− metastatic breast cancer in the US real-world setting[☆]. ESMO Open. 2025;10(1).
72.Fasching PA, Decker T, Hartkopf A, Nusch A, Heinrich BJ, Kurbacher C, et al. Efficacy, safety, and prognosis prediction in patients treated with ribociclib in combination with letrozole: Final results of phase 3b RIBECCA study in hormone receptor positive, human epidermal growth factor receptor-2 negative, locally advanced or metastatic breast cancer. European Journal of Cancer. 2024;198:113480.
73.Goetz MP, Toi M, Huober J, Sohn J, Trédan O, Park IH, et al. Abemaciclib plus a nonsteroidal aromatase inhibitor as initial therapy for HR+, HER2- advanced breast cancer: final overall survival results of MONARCH 3. Annals of oncology : official journal of the European Society for Medical Oncology. 2024;35(8):718-27.
74.Mittal A, Molto Valiente C, Tamimi F, Schlam I, Sammons S, Tolaney SM, et al. Filling the Gap after CDK4/6 Inhibitors: Novel Endocrine and Biologic Treatment Options for Metastatic Hormone Receptor Positive Breast Cancer. Cancers. 2023;15(7).
75.Gehrchen ML, Berg T, Garly R, Jensen M-B, Eßer-Naumann S, Rønlev JD, et al. Real-world effectiveness of CDK 4/6 inhibitors in estrogen-positive metastatic breast cancer. BJC Reports. 2024;2(1):44.
76.Yang L, Xue J, Yang Z, Wang M, Yang P, Dong Y, et al. Side effects of CDK4/6 inhibitors in the treatment of HR+/HER2- advanced breast cancer: a systematic review and meta-analysis of randomized controlled trials. Annals of palliative medicine. 2021;10(5):5590-9.
77.Shi X, Sims MD, Hanna MM, Xie M, Gulick PG, Zheng YH, et al. Neutropenia during HIV infection: adverse consequences and remedies. International reviews of immunology. 2014;33(6):511-36.
78.Lim E, Boyle F, Okera M, Loi S, Goksu SS, van Hal G, et al. An open label, randomized phase 2 trial assessing the impact of food on the tolerability of abemaciclib in patients with advanced breast cancer. Breast cancer research and treatment. 2022;195(3):275-87.
79.Meunier L, De Martin E, Delire B, Jacot W, Guiu S, Zahhaf A, et al. CDK4/6 inhibitor-induced liver injury: Clinical phenotypes and role of corticosteroid treatment. JHEP reports : innovation in hepatology. 2024;6(7):101098.
80.Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2018;36(17):1714-68.
81.Petrelli F, Dottorini L, Di Menna G, Borgonovo K, Parati MC, Rea CG, et al. The role of CDK4/6

inhibitors in older and younger patients with breast cancer: A systematic review and meta-analysis. The Breast. 2023;71:138-42.
82.Lee EY, Lee DW, Lee KH, Im SA. Recent Developments in the Therapeutic Landscape of Advanced or Metastatic Hormone Receptor-Positive Breast Cancer. Cancer research and treatment. 2023;55(4):1065-76.
83.Garg P, Malhotra J, Kulkarni P, Horne D, Salgia R, Singhal SS. Emerging Therapeutic Strategies to Overcome Drug Resistance in Cancer Cells. Cancers. 2024;16(13).
84.Kinnel B, Singh SK, Oprea-Ilies G, Singh R. Targeted Therapy and Mechanisms of Drug Resistance in Breast Cancer. Cancers. 2023;15(4).
85.Clusan L, Ferrière F, Flouriot G, Pakdel F. A Basic Review on Estrogen Receptor Signaling Pathways in Breast Cancer. Int J Mol Sci. 2023;24(7).
86.Shete N, Calabrese J, Tonetti DA. Revisiting Estrogen for the Treatment of Endocrine-Resistant Breast Cancer: Novel Therapeutic Approaches. Cancers [Internet]. 2023; 15(14).
87.Zhou Y, Tao L, Qiu J, Xu J, Yang X, Zhang Y, et al. Tumor biomarkers for diagnosis, prognosis and targeted therapy. Signal Transduction and Targeted Therapy. 2024;9(1):132.
88.Alalhareth IS, Alyami SM, Alshareef AH, Ajeibi AO, Al Munjem MF, Elfifi AA, et al. Cellular Epigenetic Targets and Epidrugs in Breast Cancer Therapy: Mechanisms, Challenges, and Future Perspectives. Pharmaceuticals [Internet]. 2025; 18(2).
89.Dustin D, Gu G, Fuqua SAW. ESR1 mutations in breast cancer. Cancer. 2019;125(21):3714-28.
90.De Santo I, McCartney A, Migliaccio I, Di Leo A, Malorni L. The Emerging Role of ESR1 Mutations in Luminal Breast Cancer as a Prognostic and Predictive Biomarker of Response to Endocrine Therapy. Cancers [Internet]. 2019; 11(12).
91.Dong C, Wu J, Chen Y, Nie J, Chen C. Activation of PI3K/AKT/mTOR Pathway Causes Drug Resistance in Breast Cancer. Frontiers in pharmacology. 2021;12:628690.
92.Liu L, Graff SL, Wang Y. New Emerging Therapies Targeting PI3K/AKT/mTOR/PTEN Pathway in Hormonal Receptor-Positive and HER2-Negative Breast Cancer—Current State and Molecular Pathology Perspective. Cancers [Internet]. 2025; 17(1).
93.Diaz Bessone MI, Gattas MJ, Laporte T, Tanaka M, Simian M. The Tumor Microenvironment as a Regulator of Endocrine Resistance in Breast Cancer. Frontiers in endocrinology. 2019;10:547.
94.Saatci O, Huynh-Dam KT, Sahin O. Endocrine resistance in breast cancer: from molecular mechanisms to therapeutic strategies. Journal of molecular medicine (Berlin, Germany). 2021;99(12):1691-710.
95.Kim A, Mo K, Kwon H, Choe S, Park M, Kwak W, et al. Epigenetic Regulation in Breast Cancer: Insights on Epidrugs. Epigenomes. 2023;7(1).
96.Li JW, Deng QM, Zhu JL, Min W, Hu XY, Yu Chen H, et al. Methylation of ESR1 promoter induced by SNAI2-DNMT3B complex promotes epithelial-mesenchymal transition and correlates with poor prognosis in ERα-positive breast cancers. MedComm. 2023;4(6):e403.
97.Molla G, Bitew M. Revolutionizing Personalized Medicine: Synergy with Multi-Omics Data Generation, Main Hurdles, and Future Perspectives. Biomedicines. 2024;12(12).
98.Licata L, Cosentini D, De Sanctis R, Iorfida M, Caremoli ER, Vingiani A, et al. Multigene signatures for early breast cancer in clinical practice: A report of the Lombardy genomic assays for breast cancer working group. Frontiers in oncology. 2023;13:1081885.
99.Venetis K, Pescia C, Cursano G, Frascarelli C, Mane E, De Camilli E, et al. The Evolving Role of Genomic Testing in Early Breast Cancer: Implications for Diagnosis, Prognosis, and Therapy. International Journal of Molecular Sciences [Internet]. 2024; 25(11).
100.He J, Jia YJTBCR. The evolution and advances of biomarker use in clinical trials for breast cancer treatment—a narrative review. 2021. 2021;2.
101.Mercogliano MF, Bruni S, Mauro FL, Schillaci R. Emerging Targeted Therapies for HER2-Positive Breast Cancer. Cancers. 2023;15(7).
102.Martinkovich S, Shah D, Planey SL, Arnott JA. Selective estrogen receptor modulators: tissue specificity and clinical utility. Clinical interventions in aging. 2014;9:1437-52.
103.Miziak P, Baran M, Błaszczak E, Przybyszewska-Podstawka A, Kałafut J, Smok-Kalwat J, et al. Estrogen Receptor Signaling in Breast Cancer. Cancers. 2023;15(19).
104.Sarkar S, Venkatesh D, Kandasamy T, Ghosh SS. Epigenetic Modulations in Breast Cancer: An Emerging Paradigm in Therapeutic Implications. 2024;29(8).
105.Patnaik E, Madu C, Lu Y. Epigenetic Modulators as Therapeutic Agents in Cancer. Int J Mol Sci. 2023;24(19).
106.Chen F, Chen N, Gao Y, Jia L, Lyu Z, Cui J. Clinical Progress of PD-1/L1 Inhibitors in Breast Cancer Immunotherapy. Frontiers in oncology. 2021;11:724424.
107.Sun Q, Hong Z, Zhang C, Wang L, Han Z, Ma D. Immune checkpoint therapy for solid tumours: clinical dilemmas and future trends. Signal Transduction and Targeted Therapy. 2023;8(1):320.