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Distinct targeted agents for breast cancer: trastuzumab and abemaciclib

Yuhan Zhang

Department of Green Collaborate Innovation Center, Zhejiang University of Technology, Huzhou, China

302023514220@zjut.edu.cn

Abstract. Breast cancer ranks among the most common malignancies affecting women globally, and can be stratified into multiple molecular subtypes that guide the selection of targeted therapeutic strategies. This review systematically compares two representative targeted agents: trastuzumab and abemaciclib, which act via completely different therapeutic paradigms for HER2+ and HR+/HER2- breast cancer respectively. Trastuzumab is a humanized intravenous monoclonal antibody targeting membrane HER2 extracellular domain IV, suppressing oncogenic HER2 signaling and exerting anti-tumour effects mainly through antibody-dependent cellular cytotoxicity, while its primary adverse effect is cardiac toxicity. Abemaciclib is an oral small-molecule CDK4/6 inhibitor capable of arresting G1/S cell-cycle shift via suppression of cyclin D-CDK4/6 kinase activity, with diarrhea and neutropenia as its major toxicities. Building upon published clinical evidence, this review contrasts their clinical applicability, efficacy and safety profiles across patient subgroups. It also outlines core resistance mechanisms underlying treatment failure for both modalities, highlighting key molecular differences that separate antibody based HER2-directed therapy from cell-cycle-targeted small-molecule inhibition. Despite both occupying critical positions in modern breast cancer treatment, the two agents are not interchangeable given their divergent targets, toxicity spectra and eligible patient populations. Integrating such comparative information supports better therapeutic decision-making and promotes personalized precision oncology for breast cancer patients.

Keywords: breast cancer, trastuzumab, abemaciclib, targeted therapy, comparison

1. Introduction

Breast cancer ranks first among all malignant tumors in terms of incidence among women worldwide[1]. It ranks as the second most common cause of cancer-related mortality among women worldwide, only surpassed by lung cancer [1]. In 2022, there were approximately 357,161 new cases of breast cancer and around 74,986 deaths among women in China [2]. Figure 1 depicts the global distribution of female breast cancer mortality rates across countries in 2023. About 300,590 individuals in the U.S. received a breast-cancer diagnosis in

[1] American Cancer Society. (2023). Key statistics for breast cancer. Available from: https://www.cancer.org/cancer/types/breast-cancer/key-statistics.html

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2023, whereas 43,700 patients succumbed to this malignancy [3], among whom 530 were men. Therefore, despite its relatively low incidence, male breast cancer remains a non-negligible clinical entity.

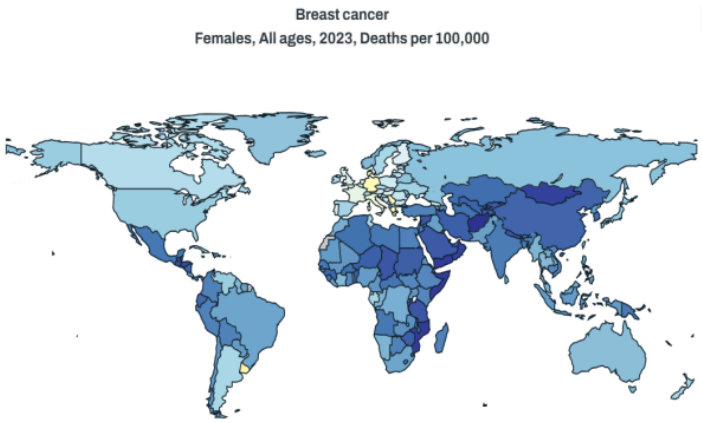


Figure 1. Global distribution of female breast cancer mortality rates in 2023 (deaths per 100,000 population; lighter colour represents higher mortality)[2]

Breast cancer has a higher incidence in developed countries, resulting from the combined effects of genetics, endogenous hormonal and reproductive factors, external environmental conditions, and lifestyle [4], which generates diverse molecular subtypes characterized by unique pathophysiological features. Clinically, breast cancer can be divided into three mainstream molecular subtypes: Hormone Receptor-positive (HR+), Human Epidermal Growth Factor Receptor 2-positive (HER2+), and triple-negative breast cancer [5] as shown in Figure 2.

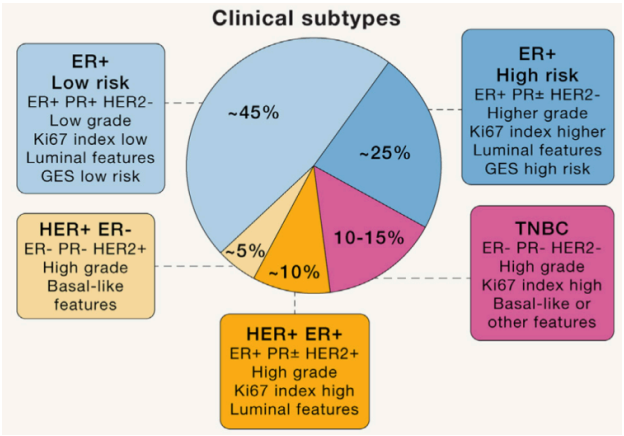


Figure 2. Clinical subtypes of breast cancer: population proportions [5]

HR+ breast cancer, which refers to breast cancers that test positive for Estrogen Receptor (ER) or Progesterone Receptor (PR), approximately 70% of all breast cancers fall into this subtype. Estrogen acts as the primary signal driving the proliferation and progression of luminal tumors. Oestrogen signalling serves as a key mitogenic stimulus driving luminal-type tumour expansion. Mammary luminal epithelial cells inherently

[2] Institute for Health Metrics and Evaluation (IHME). GBD Compare [Online visualization tool]. University of Washington, 2025. Retrieved 8 July 2026, from https://vizhub.healthdata.org/gbd-compare.

express ER protein, while chronic oestrogen exposure over a patient's lifespan renders these cell populations vulnerable to oncogenic transformation, which could partly explain why HR-positive cases dominate breast-cancer cohorts. HER2+ breast cancer refers to breast cancer with positive HER2 expression, accounting for approximately 15% of all breast cancers [6]. Recognition of such subtype disparities lays the foundation for tailored therapeutic regimens and accurate prognostic evaluation as shown in Figure 3 [7].

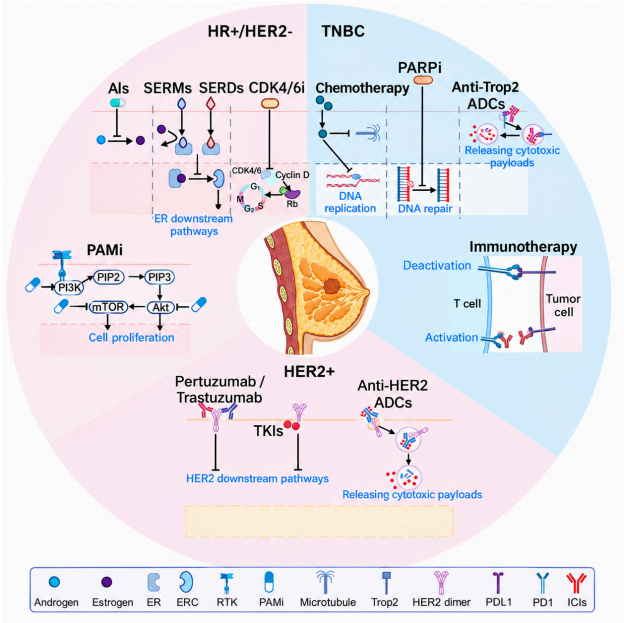


Figure 3. Treatment landscape of different breast cancer molecular subtypes [7]

Cross-talk between core oncogenic signaling pathways is illustrated in the middle of Figure 4. In HER2-positive breast cancer, ERBB2 gene amplification drives substantial overexpression of HER2 protein on the tumour-cell plasma membrane. These HER2 receptors can spontaneously assemble into ligand-independent homodimers, which in turn trigger intracellular tyrosine-kinase autophosphorylation. This event generates constitutive kinase activity and leads to persistent hyper-activation of the PI3K-AKT and RAS-MAPK signalling cascades. Accordingly, amplified HER2 serves as a primary therapeutic target for multiple agents including Trastuzumab.

In HR-positive luminal breast cancer, wild-type ESR1 encodes the oestrogen receptor (ER). This receptor undergoes nuclear translocation and triggers the transcription of proliferation-related genes only upon oestrogen-ligand binding. Recurrent activating PIK3CA mutations sustain persistent PI3K-AKT signalling activity. Downstream AKT kinase mediates ER phosphorylation, which enables ER nuclear translocation and proliferative transcriptional activation in an oestrogen-independent fashion. Oestrogen-bound ER then interacts with the p85 regulatory subunit of PI3K, elevating the expression of cyclin-D and growth-factor receptors. This event further potentiates PI3K-AKT signalling and establishes a pro-proliferative feed-forward feedback loop. Multiple upstream pro-proliferative signalling cascades converge onto the CDK4/6-governed cell-cycle axis to propel cell-cycle progression. Therefore, simultaneous targeting of HER2 and CDK4/6 can block key proliferative signals transmitted through this shared downstream effector node, providing a mechanistic rationale for selecting HER2 and CDK4/6 as combinatorial therapeutic targets [7].

In future clinical practice, an integrated AI-assisted diagnosis and treatment system for breast cancer can be constructed by combining the MIINet multimodal information-interconnected network [8] and the weakly supervised bilayer convolutional network [9].

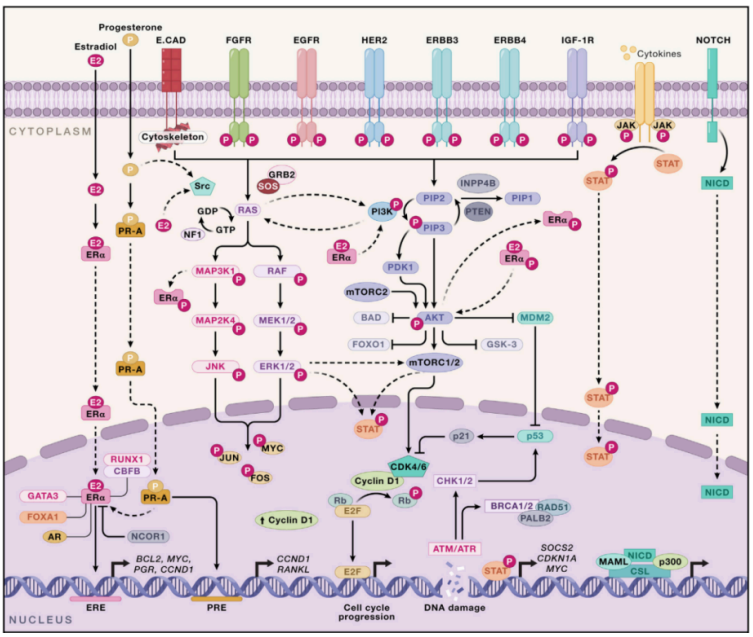


Figure 4. Driver pathways and mutation profiles of breast cancer molecular subtypes [5]

2. Trastuzumab

The first anti-HER2 monoclonal antibody for breast cancer was initially researched by Genentech, a member of the Roche Group. This humanized IgG1-kappa monoclonal antibody is produced via recombinant protein expression employing Chinese hamster ovary mammalian cell [10]. Marketed under the brand name Herceptin, Trastuzumab received its initial U.S. FDA approval for the treatment of HER2-overexpressing breast cancer in adults[3]. Figure 5 shows the structure of Trastuzumab Fab fragment.

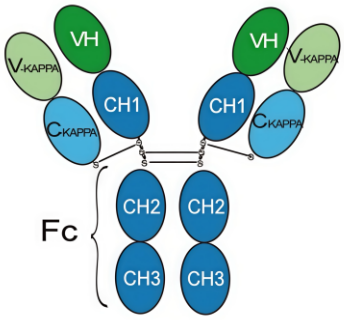


Figure 5. Structure of Trastuzumab Fab fragment. Based on two heavy-chain and two light-chain amino-acid sequences plus glycosylation modification, the intact antibody has an approximate molecular weight of 148 kDa[4]

[3] U.S. Food and Drug Administration. (2026). Herceptin (trastuzumab) full prescribing information, BLA 103792. Silver Spring, MD: U.S. Food and Drug Administration. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. Accessed 28 July 2026.

[4] Visual data retrieved from IMGT/mAb-DB (Version 2.0.8). Available at: https://imgt.org/mAb-DB/.

As illustrated in Figure 6, Trastuzumab primarily binds the juxtamembrane epitope within HER2 extracellular Domain IV. This epitope is composed of three distinct peptide loops spanning residues 557-561 (ARHCL), 570-573 (QNGS) and 593-603 (PPFCVARCPSG).

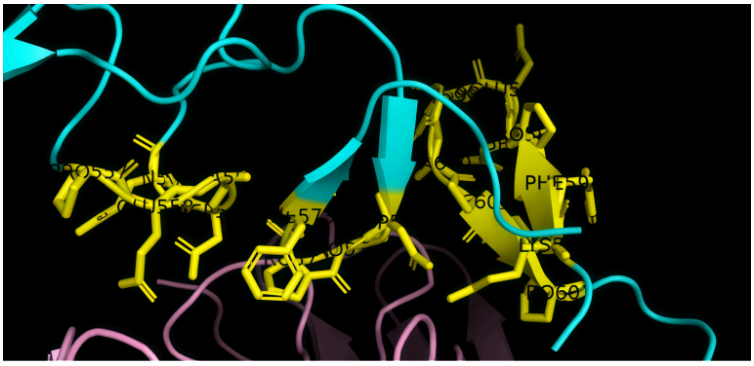


Figure 6. Binding sites and corresponding amino acid sequences visualized by PyMOL based on PDB entry 1N8Z. Yellow ribbon: Trastuzumab fab fragment; cyan ribbon: HER2 domain IV (Trastuzumab-binding epitope); magenta ribbon: HER2 extracellular domains I-III

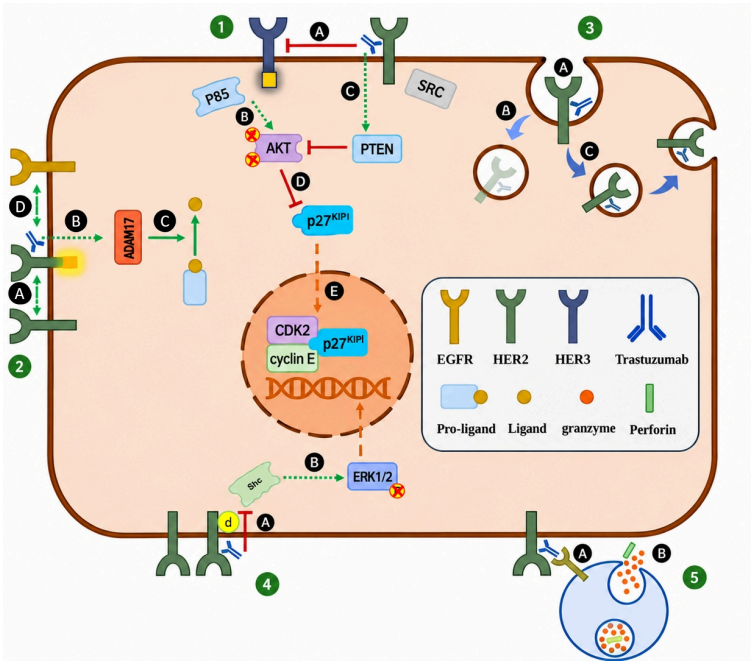


Figure 7. Pharmacological mechanisms of Trastuzumab [11]

The mechanism of action of Trastuzumab remains incompletely elucidated, and one of the prevailing viewpoints holds that the occupation of this Domain IV site positions the Fc segment of Trastuzumab away from the tumour cell surface, leaving it fully accessible for recognition by immune cell Fcγreceptors. In stark contrast to its multiple downstream signaling effects, which remain widely debated due to contradictory results across diverse experimental systems, antibody-dependent cellular cytotoxicity is a uniformly validated anti-tumour activity of Trastuzumab as shown in Figure 7. The interaction between Trastuzumab's Fc domain and Fcγreceptors activates SYK-driven signaling cascades, prompting immune cells to secrete perforin and granzymes and induce tumour cell apoptosis. Tumour antigens liberated from lysed cancer cells are

subsequently engulfed by dendritic cells, which further amplify systemic adaptive anti-tumour immune responses [11]. In addition, recent research has revealed that EGF is persistently secreted within the microenvironment of breast tumor lesions. Trastuzumab binds to the juxtamembrane domain IV of HER2 without blocking EGF-induced EGFR-HER2 heterodimer formation. Nevertheless, it impedes the translocation of such heterodimers into cell membrane lipid rafts, thereby disrupting the signal microenvironment required for AKT activation. This effect leads to potent suppression of the PI3K/AKT pathway and ultimately inhibited proliferation of HER2+ breast cancer cells [12].

3. Abemaciclib

Abemaciclib (commercial name Verzenio®) was approved by the U.S. FDA across early and late-stage HR-positive, HER2-negative breast cancer. In the adjuvant context, it is combined with tamoxifen or aromatase inhibitors for node-positive early-stage tumours with elevated recurrence risk. For advanced or metastatic disease, therapeutic strategies include first-line pairing with aromatase inhibitors, combination with fulvestrant after endocrine-treatment failure, and single-agent administration for individuals with metastatic disease whose tumours have advanced despite receiving both endocrine treatment and previous chemotherapy[5].

It is a fully synthetic oral selective small-molecule CDK4/6 inhibitor originally developed by Eli Lilly Company [13]. Derived from a pyrimidine-benzimidazole screening hit and optimized via systematic structure-activity relationship studies, the candidate LY2835219 exhibits balanced anti-tumour potency, kinase selectivity and desirable pharmacokinetic characteristics [14]. Figure 8 shows the chemical structure of Abemaciclib. It possesses a molecular formula of C27H32F2N8 with a molecular weight of 506.59 g/mol. It presents as a white-to-yellow solid powder and is practically insoluble in water while soluble in DMSO and ethanol. It has a predicted LogP of approximately 3.36-4.03, a topological polar surface area of 75 Å², one hydrogen-bond donor and nine hydrogen-bond acceptors, and a predicted basic pKa of 7.69; these physicochemical characteristics support its cell-membrane permeability for intracellular target engagement.

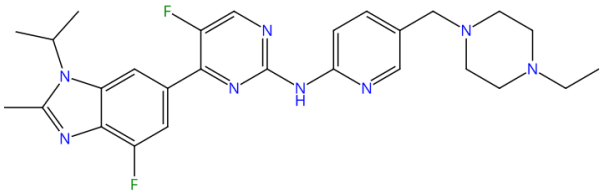


Figure 8. Chemical structure of Abemaciclib[6]

As described above, the core oncogenic driver pathway of breast cancer involves cyclin D1 forming active complexes with CDK4/6, which continuously catalyze hyperphosphorylation of Retinoblastoma (Rb) protein and release E2F transcription factors, thereby activating numerous key genes governing G1/S phase transition, DNA replication and cell division.

Rb activity is governed by cyclin-CDK complexes, a group of evolutionarily conserved serine-threonine protein kinases. For cells to transit from G1 into S phase, Rb must be phosphorylated by either CDK4 or its

[5] U.S. Food and Drug Administration. (2026). Verzenio (abemaciclib) full prescribing information, NDA 20834. Silver Spring, MD: U.S. Food and Drug Administration. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. Accessed 28 July 2026.

[6] Retrieved from SciFinder® (CAS Registry Number: 1231929-97-7).

close paralog CDK6. Both kinases become catalytically competent upon association with D-type cyclin activators cyclin D1, D2 or D3.

Abemaciclib competitively binds to the ATP-binding pockets of CDK4 and CDK6 and inhibits CDK4/6 kinase activity. Consequently, intracellular Rb remains hypophosphorylated and stably binds to and suppresses E2F transcription factors, silencing cell cycle-related genes and arresting tumour cells in the G1 phase to block sustained proliferation as shown in Figure 9. This canonical, core anti-proliferative activity fully relies on intact and functional Rb protein. In tumour cells carrying Rb gene deletion, truncating mutations or complete loss of Rb protein function, no free E2F is available for sequestration, thus, the cell cycle arrest effect induced by CDK4/6 inhibition cannot be achieved [15].

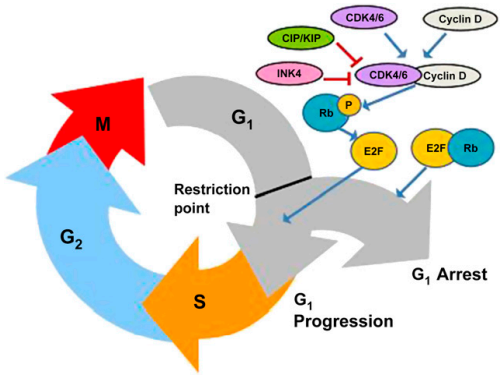


Figure 9. Mechanism of Abemaciclib-mediated CDK4/6 inhibition and G1 arrest [15]

4. Comparison

4.1. Drug type

Trastuzumab is a recombinant humanized monoclonal antibody administered via intravenous infusion. As a macromolecular protein, it can not cross cell membranes, acts predominantly at the extracellular cell-surface, and therefore requires parenteral delivery.

Abemaciclib is an oral small-molecule CDK4/6 kinase inhibitor. It is a low-molecular-weight organic compound that can pass through cell membranes and exert intracellular pharmacological effects after oral absorption.

4.2. Therapeutic target

Trastuzumab specifically targets the extracellular domain of HER2 on breast tumor cell membranes. It binds HER2 extracellular domain IV and suppresses HER2-driven signaling through multiple mechanisms.

Abemaciclib occupies the ATP-binding pocket of cyclin-dependent kinase 4 and 6 to suppress kinase catalytic activity, thereby restraining cell cycle transition from G1 to S phase.

4.3. Indicated breast cancer subtype

Trastuzumab targets HER2-overexpressing tumors for the treatment of HER2-overexpressing breast cancer.

Abemaciclib is indicated for HR-positive, HER2-negative early-stage high-risk adjuvant breast cancer as well as multiple settings of advanced or metastatic HR-positive, HER2-negative breast cancer.

They are approved for distinct breast cancer molecular subtypes; therefore, these two agents are not routinely interchangeable in clinical practice.

4.4. Mechanism

The mechanism of therapy introduced in this paper is shown in Figure 10. Trastuzumab targets the upstream HER2 signaling node, whereas Abemaciclib inhibits the downstream CDK4/6 cell-cycle effector axis.

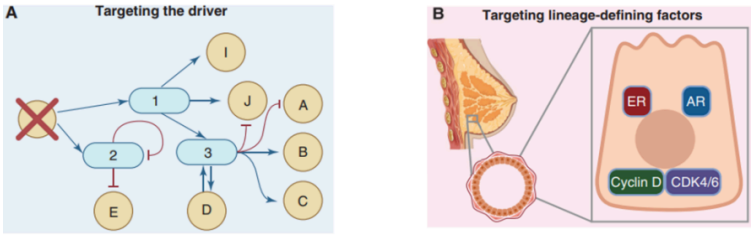


Figure 10. Mechanisms of two therapeutic approaches for breast cancer. (A) Targeting the driver. Therapies target unique oncogenic driver gene abnormalities specific to tumor cells. HER2 amplification represents such a driver event, just as the molecules marked with red crosses on the left side of the figure; Trastuzumab directly inhibits HER2, thereby suppressing oncogenic HER2 signaling in HER2-amplified breast cancer and exemplifying driver-targeted therapy. (B) Targeting lineage-defining factors. Therapies act on intrinsic physiological proliferative pathways of mammary epithelial cells. The schematic highlights core lineage-associated molecules including ER, Cyclin D and CDK4/6within mammary ductal cell nuclei. HR-positive breast cancer hijacks these native mammary developmental pathways to sustain malignant proliferation. Abemaciclib functions as a CDK4/6 inhibitor that impedes Cyclin D-CDK4/6 binding to trigger tumour-cell-cycle arrest. It targets proliferation dependency rather than a tumour-specific oncogenic driver [16]

So Trastuzumab and Abemaciclib represent two distinct and non-interchangeable therapeutic paradigms for breast cancer. Based on their distinct mechanisms of action, Abemaciclib can be combined with Trastuzumab, mainly applying to HR+/HER2+ breast cancer. The Abemaciclib monarcHER trial, a randomized, open-label phase II study conducted in heavily pretreated patients with hormone receptor-positive, HER2-positive advanced breast cancer (HR+/HER2+ ABC), stratified eligible women who had received at least two prior HER2-directed therapies into three 1:1 randomized treatment arms: Arm A (Abemaciclib combined with Trastuzumab and Fulvestrant), Arm B (Abemaciclib plus Trastuzumab), and Arm C (Trastuzumab paired with physician-selected single-agent chemotherapy as standard-of-care control). Investigator-assessed PFS per RECIST version 1.1 was defined as the primary endpoint. After a median follow-up of 52.9 months, updated survival analyses revealed only numerical improvements rather than statistically significant benefits for both PFS and OS across experimental cohorts. For the primary PFS endpoint, the triplet regimen of Abemaciclib, Trastuzumab and Fulvestrant (Arm A) yielded a median PFS of 8.3 months versus 5.7 months in the chemotherapy control arm (Arm C; Hazard Ratio [HR] = 0.72, nominal two-sided $p = 0.077$), while Arm B achieved identical median PFS (5.7 months) to Arm C with no clinical advantage. In terms of Overall Survival (OS), median OS reached 31.1 months in Arm A and 29.2 months in Arm B, compared with 20.7 months in Arm C (Arm A vs C: HR = 0.71, $p = 0.086$; Arm B vs C: HR = 0.83, $p = 0.365$). Pooled analysis of all Abemaciclib-containing arms (A+B) also demonstrated a roughly 10-month median OS prolongation (30.3 vs 20.7 months, HR = 0.77, $p = 0.127$), yet all inter-arm comparisons failed to reach conventional statistical significance at the $\alpha = 0.05$ threshold. Figure 11 presents survival data for patients enrolled in the monarcHER trial. Further large-scale phase III investigations are warranted to confirm these findings, owing to the limitations inherent to phase II research [17].

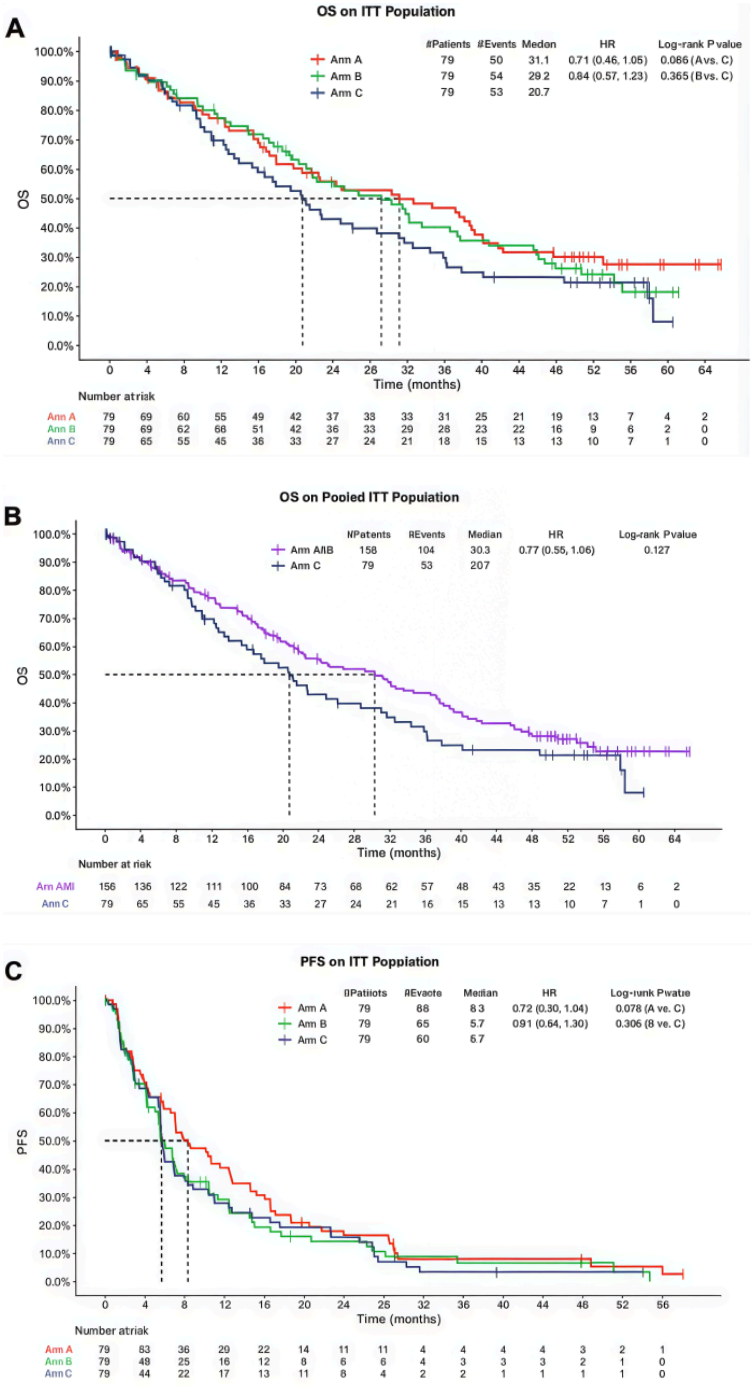


Figure 11. Survival outcomes from the monarcHER trial. (A) OS for the ITT population across individual study arms. (B) Pooled OS comparing combined Abemaciclib-containing arms (Arms A + B) versus control Arm C. (C) Updated investigator-assessed PFS for all separate study arms. HR, hazard ratio [17]

4.5. Therapeutic efficacy

Retrospective real-world single-center study from India focuses on adjuvant therapy for early HER2-positive breast cancer, comparing 1-year standard, 6-month and 9-week Trastuzumab regimens. Although there were subgroup differences in age at diagnosis, composite tumor stage, hormone receptor status, nodal involvement,

and duration of adjuvant Trastuzumab therapy, the 4-year Disease-Free Survival (DFS) rates of all patients receiving adjuvant Trastuzumab exceeded 90% as shown in Table 1 [18].

Table 1. Subgroup analysis of 4-year DFS [18]

Variables	4-year DFS (mo)	*p*-Value (confidence interval)
Age at diagnosis (less than 40 years vs. 40-60 years vs. more than 60 years)	100% vs. 97.3% vs. 96%	0.125
Composite stage (stage 1 vs. stage 2 vs. stage 3)	94.8% vs. 99.2% vs. 92.6%	0.003 (122.832-127.305)
Hormone receptor status (HR-positive vs. HR-negative)	96.5% vs. 98.3%	0.175
Nodal involvementNode negative vs. node positive	98.8% vs. 95.8%	0.243
Duration of adjuvant Trastuzumab therapy	96.7% vs. 98% vs. 98.4%	0.600

Phase III clinical trial targets metastatic HER2-positive breast cancer. It showed that the objective response rate of Trastuzumab monotherapy was approximately 17%-21%. Combination with chemotherapy significantly improved tumor response rates and prolonged time to disease progression. When combined with paclitaxel, the objective response rate reached 44% with a median duration of response of 7.1 months [19].

In addition, the multicentre Chinese phase III PHILA trial enroled previously untreated metastatic HER2-positive breast cancer patients. The triplet combination of Pyrotinib, Trastuzumab and Docetaxel delivered sustained anti-tumour activity, with a median PFS of 24.8 months observed in individuals harbouring intact wild-type HER2 signaling cascades as shown in Figure 12 [20].

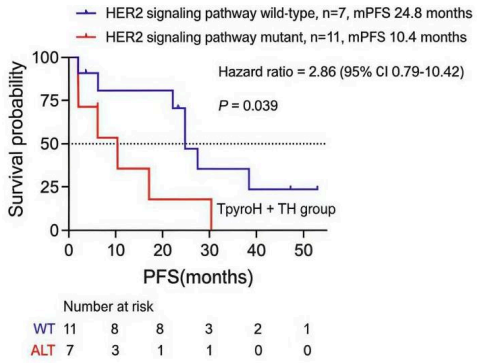


Figure 12. Kaplan-Meier analysis of PFS stratified by HER2-signaling-pathway status in patients receiving Pyrotinib-Trastuzumab-Docetaxel triplet therapy [20]

An observational retrospective multicenter single-arm TRACE study enrolled adult women with histologically confirmed HR+/HER2-locally advanced or metastatic breast cancer from Kuwait and Lebanon who received Abemaciclib (either monotherapy or combined regimen) for at least three months in routine clinical practice, excluding patients in Adjuvant settings, clinical trials or with concurrent other primary malignancies. Its primary endpoint was to characterize real-world Abemaciclib treatment patterns; secondary endpoints included patient demographics, PFS, and RECIST v1.1-based Objective Response Rate (ORR). In this Middle-Eastern real-world cohort, Abemaciclib monotherapy yielded a median PFS of 275 days with a 12-month PFS rate of 33.3%. By blocking estrogen signaling and downregulating Cyclin D1 to diminish

upstream Cyclin D-CDK4/6 complex formation, endocrine drugs are routinely combined with Abemaciclib clinically. Figure 13 illustrates that patients receiving Abemaciclib combination therapy attained a 12-month PFS rate of 79.6% and median PFS was not reached, demonstrating substantially superior disease-control efficacy for combination therapy while monotherapy provided limited anti-tumor benefit [21].

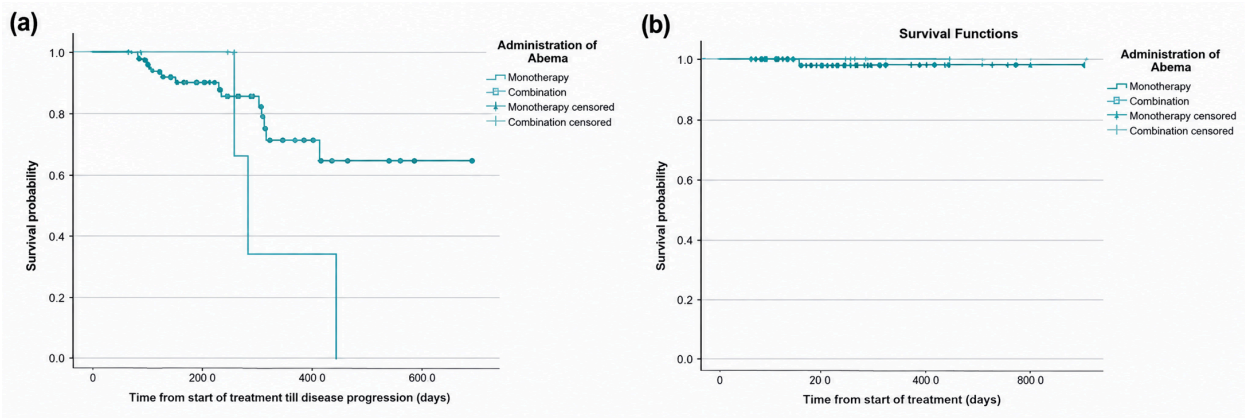


Figure 13. Kaplan-Meier curves for PFS (a) and OS (b) among patients receiving Abemaciclib monotherapy versus combination therapy [21]

For investigator-evaluated outcomes in MONARCH 3 was a global randomized, double-blind phase III trial, median PFS was not reached in the Abemaciclib arm versus 14.7 months in the placebo arm as presented in Figure 14. Consistent benefit was confirmed by blinded central imaging review. It proves that combining Abemaciclib with aromatase inhibitor brings significant, consistent PFS and response improvements for first-line treatment of postmenopausal HR+/ HER2- advanced breast cancer [22].

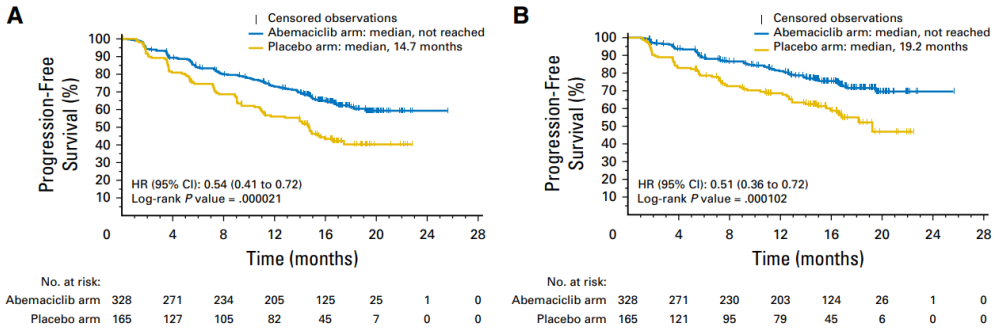


Figure 14. Kaplan-Meier analysis of PFS from MONARCH 3. (A) reflects real-world evaluation by treating physicians, while (B) uses blinded central imaging review to verify the efficacy result without subjective bias. Both analyses confirmed that Abemaciclib combination therapy significantly prolonged PFS versus placebo [22]

As shown in Figure 15, real-world studies across western cohorts like France, Italy, Spain demonstrate robust anti-tumour efficacy of Abemaciclib in HR+/HER2- advanced breast cancer. Even among unselected real-world patients with substantial prior chemo-or radiotherapy and heterogeneous baseline prognoses, first-line Abemaciclib delivered 1-year real-world PFS approaching or exceeding 78% across countries, with a remarkable median rwPFS of 26.0 months in Spain and not-reached median rwPFS in France, reflecting powerful long-term disease control in the front-line setting. Substantial benefit was also preserved in second-line setting, with median rwPFS consistently over 20 months. Although efficacy waned at later lines,

meaningful anti-tumour activity remained. Objective response rates ranged from 42.7% to 55.9%, confirming tangible tumour shrinkage under routine-practice conditions [23]. In Asian countries such as Japan, the unstratified real-world cohort showed that the median rwPFS was 13.0 months (95% CI, 10.1-15.8 months), with a 12-month rwPFS rate of 55.7% [24].

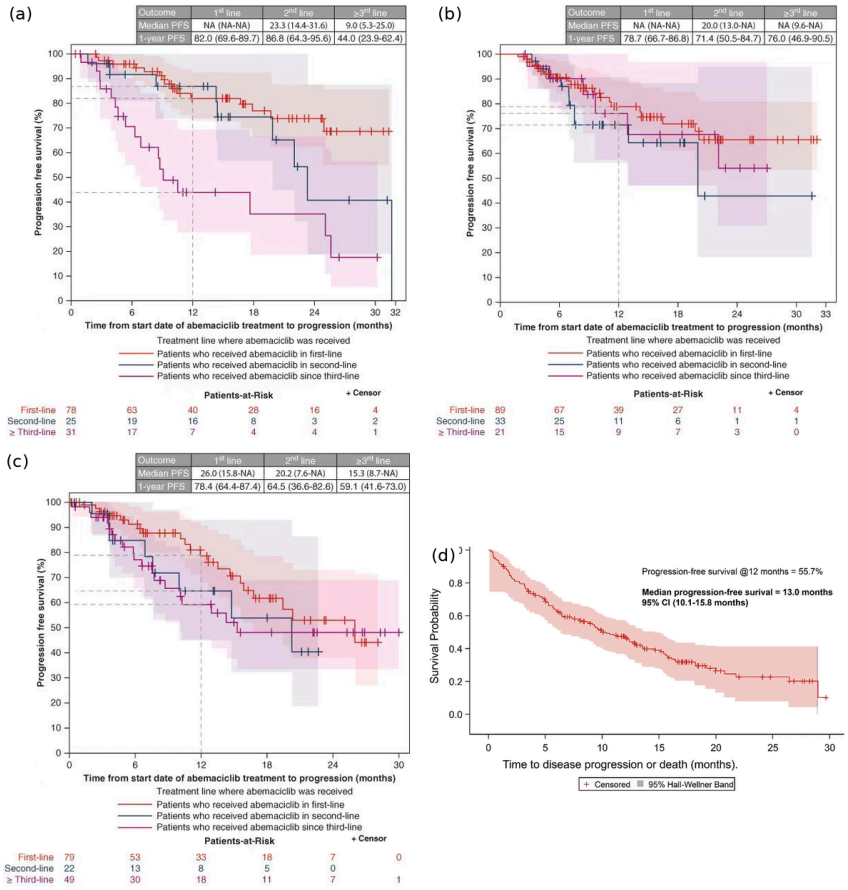


Figure 15. Kaplan-Meier curves of Abemaciclib real-world PFS: stratified analyses by line of therapy for France, Italy, Spain (a-c) [23] and overall survival outcome for the Japanese cohort (d) [24]

Both agents exhibit anti-tumor activity as monotherapy, and combination regimens markedly amplify their therapeutic efficacy. And consistent positive outcomes have been further validated by multi-country real-world clinical studies.

4.6. Adverse effects and mechanistic basis

According to real-world follow-up studies in Vietnam, cardiotoxicity is the primary adverse effect of Trastuzumab, predominantly occurring in the early phase of treatment [25]. According to real-world evidence from the *Japanese Adverse Drug Event Report* (*JADER*) database, routine cardiac follow-up during anti-HER2 therapy is recommended for the first 18 months from treatment initiation [26]. A single-center retrospective cohort study conducted at McMaster University in Canada demonstrated that after three years of follow-up, 14% of patients still presented persistent cardiotoxicity [27].

Subgroup analyses from the global phase III SafeHer trial demonstrate that Asian participants had numerically lower rates of any-grade adverse events (86.5% vs overall 88.7%), grade ≥ 3 adverse events

(15.3% vs overall 23.2%), and serious adverse events (11.4% vs overall 12.7%) [28]. This cardiac injury can be alleviated by optimizing therapeutic regimens, such as avoiding concurrent anthracycline administration or administering cardioprotective agents.

The exact mechanism of Trastuzumab-Induced Cardiotoxicity (TIC) remains incompletely elucidated. Inhibition of the NRG1/HER signaling pathway represents the prevailing hypothesis for TIC pathogenesis as shown in Figure 16. HER2, alongside other HER-family receptors HER1/3/4, is expressed not only in tumour cells but also in adult cardiomyocytes. NRG1, an essential ligand for cardiac homeostasis and cardiomyocyte maturation, is secreted by cardiac microvascular endothelium under hemodynamic stress. Via paracrine signaling, NRG1 binds to HER4 and triggers either HER4 homodimerization or protective HER4/HER2 heterodimerization, which further activates downstream PI3K-Akt and MAPK cascades. The PI3K-Akt cascade facilitates nitric oxide generation, counteracts oxidative stress, regulates mitochondrial respiration and reduces Reactive Oxygen Species (ROS) accumulation to maintain cardiomyocyte viability. Trastuzumab binds to the extracellular domain IV of HER2 and sterically hinders receptor dimerization, thus suppressing PI3K-Akt signaling, triggering massive ROS accumulation and ultimately inducing cardiomyocyte apoptosis [29].

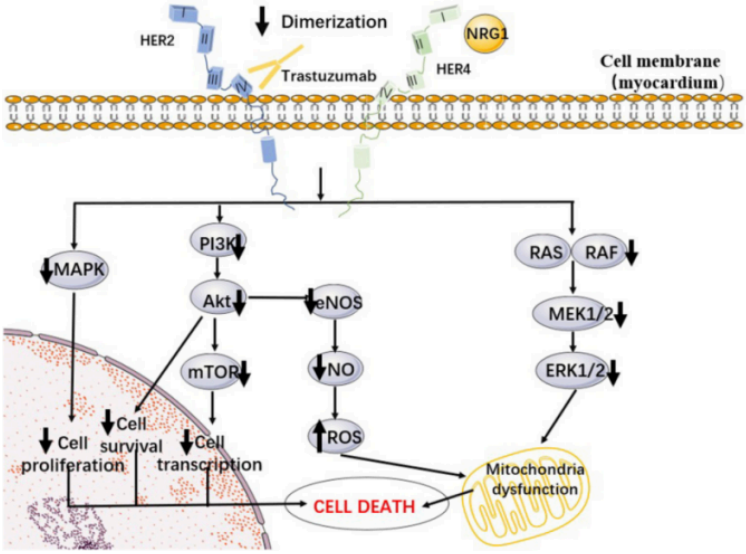


Figure 16. Proposed cellular mechanism of Trastuzumab-mediated cardiotoxicity [29]

According to retrospective real-world studies conducted in Greece and the United States, diarrhea is the most common adverse reaction associated with Abemaciclib. The all-grade incidence in Greece was as high as 51.0%, whereas clinically significant Grade 3-4 events that put patients at risk accounted for only 5.7% [30] and the all-grade incidence in the United States was 83.5%, with ≥ grade 3 events reported in 7.8% of patients [31].

Meanwhile, a multicenter retrospective observational study in China found that neutropenia was the most prominent adverse event, occurring in 39.9% of patients with high-risk early breast cancer and 34.5% of patients with metastatic advanced breast cancer receiving abemaciclib [32]. Also, in the Indian population, neutropenia is the main haematological adverse event, occurred in around 30% of patients, 18.9% experienced ≥ grade 3 neutropenia; Anaemia represented another common haematological adverse event, occurring in 23.5% of patients, 14.0% experienced ≥ grade 3 anaemia [33].

Neutropenia is a class-wide on-target adverse effect of all three CDK4/6 inhibitors, because the bone marrow hematopoietic progenitor cells highly express CDK4 and CDK6. The mechanism of diarrhea is that

Abemaciclib potently suppresses multiple off-target kinases including GSK3β. As a core component of the degradation complex, GSK3β mediates the phosphorylation of β-catenin to trigger its proteasomal breakdown and block its nuclear translocation. Once β-catenin enters the nucleus, it forms transcriptional complexes with TCF transcription factors to upregulate proliferative genes such as c-Myc, Cyclin D1 and Axin2. The β-catenin/TCF-4 complex functions as a central molecular switch that modulates the equilibrium between proliferation and differentiation of intestinal epithelial cells. Inhibition of GSK3β leads to aberrant hyperactivation of the canonical WNT signaling cascade and excessive cell proliferation. GSK3 is moderately expressed in gastrointestinal tissues. Given the abundant expression of intestinal GSK3β together with the characteristic crypt hyperplasia and defective epithelial differentiation observed after Abemaciclib exposure, hyperactivated Wnt/β-catenin signaling serves as a credible driver of Abemaciclib-related gastrointestinal toxicity [34]. Mild diarrhea can be managed with dietary modification and fluid supplementation or treated promptly with Loperamide [35].

Both drugs produce dose-dependent adverse toxicities that can be relieved by dose adjustment, symptomatic treatment, or optimized medication schedules. Their toxicity profiles differ substantially: Trastuzumab-related adverse events are dominated by cardiac toxicity and infusion-related reactions, whereas Abemaciclib frequently induces diarrhea, neutropenia, fatigue, hepatotoxicity, venous thromboembolism, with potential risk of interstitial lung disease/ pneumonitis. Ethnic disparities exist in the spectrum and incidence of adverse events for both medicines.

4.7. Economics accessibility

In 2022, the nationwide weighted-average retail price for originator Trastuzumab for injection (powder for injection, 150 mg/vial, manufacturer: Roche) costs about ¥5,496.09 per vial. For a 60 kg patient with HER2-positive early breast cancer receiving 52-week adjuvant monotherapy with Trastuzumab, the loading dose is 480 mg requiring four 150 mg vials, followed by 17 maintenance infusions of 360 mg each. A total of 55 vials are needed for the full treatment course.

For originator Abemaciclib tablets (tablet, manufacturer: Eli Lilly) covering its 50 mg, 100 mg and 150 mg tablet formulations, the national physical-pharmacy retail price stood at around ¥77.6 per tablet for a 2-year adjuvant treatment course.

Original-brand agents impose substantial economic burdens on patients, whereas generic alternatives can greatly reduce treatment-related costs. All prices above are retail prices from physical pharmacy sales statistics, which may differ from hospital procurement prices, post-reimbursement prices, and prices across different regions or time periods. Cost comparison between oral tablet Abemaciclib and injectable powder-for-injection Trastuzumab should be interpreted cautiously given their distinct dosage forms and administration regimens[7].

4.8. Drug resistance pathways

Figure 17 summarizes core pathways mediating Trastuzumab resistance in HER2-positive breast cancer.

ERBB2 mutations and nuclear localization. It often co-mutated with ERBB3, RAF1, PIK3CA, correlating with shorter PFS. Nuclear-localized HER2 forms transcriptional complex with HER3 to drive Cyclin D1 and

[7] Yaozhi Database. (2026) National physical-pharmacy sales statistics for pharmaceuticals. Available at: https://vip.yaozh.com/fdadrugnew/208855. Accessed: 12 August 2026.

cell-cycle progression. Trastuzumab only targets membrane HER2 and cannot block nuclear HER2 activity, leading to drug resistance.

d16-HER2 arises from ERBB2 exon-16-skipping. It forms constitutive-active homodimers on cell membrane, activates SRC kinase, enhances proliferation, migration and tumorigenesis, and reduces Trastuzumab sensitivity.

p95-HER2 is a truncated HER2 isoform lacking extracellular domain and Trastuzumab-binding epitope. Its prognostic role remains controversial; whether it directly causes Trastuzumab resistance needs further study.

Aberrant PI3K/AKT/mTOR pathway. Activated SRC amplifies PI3K/AKT signaling. Besides, Notch-Jagged1-STAT3 cascade sustains cancer stem-cell survival, upregulates cell-cycle, anti-apoptotic and angiogenic genes, and mediates Trastuzumab resistance [36].

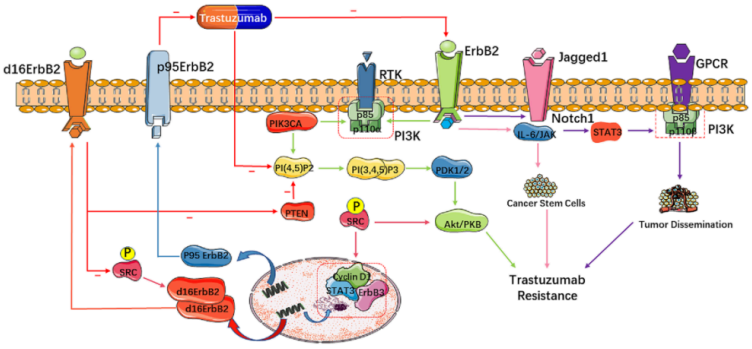


Figure 17. Signaling pathways driving of Trastuzumab resistance [36]

In addition, long-term Trastuzumab stimulation induces tumor autophagy, which degrades damaged organelles and recycles amino acids, lipids, and energy to sustain the continuous metabolism of tumor cells. This counteracts the pro-apoptotic and anti-proliferative effects of Trastuzumab, thereby maintaining tumor cell survival [37].

ErbB receptors contain four extracellular domains I-IV. Ligand binding induces receptor heterodimerization, which triggers tyrosine kinase phosphorylation and activates multiple signaling cascades including the RAS/MAPK and PI3K/AKT/mTOR pathways, driving cell proliferation, anti-apoptosis, angiogenesis and tumor invasion. Trastuzumab exerts its inhibitory function by targeting extracellular subdomain IV of HER2 to dampen receptor-driven activation. By contrast, Pertuzumab recognizes subdomain II and sterically hinders heterodimer formation between HER2 and other ErbB isoforms (HER1, HER3, HER4), consequently restraining tumour-cell growth, invasive potential and viability, thereby suppressing tumor proliferation, invasiveness and cancer cell survival. Therefore, Pertuzumab may enhance antitumour efficacy when combined with Trastuzumab in HER2-positive breast cancer [38].

Figure 18 illustrate that Abemaciclib resistance arises from multiple alterations:

Loss-of-function mutations in the RB1 gene lead to the inactivation of RB protein. Without physiologically active RB molecules to bind and repress E2F transcription factors, Abemaciclib, even with potent inhibitory effects against CDK4/6 kinase activity, cannot sequester E2F by maintaining RB in a hypophosphorylated state. Free E2F continuously activates downstream target genes and triggers the compensatory cyclin E-CDK2 signaling axis, which drives uncontrolled G1-to-S-phase cell-cycle transition in tumour cells and renders tumour proliferation entirely independent of CDK4/6 kinase function.

MiRNA-mediated and epigenetic regulation. Multiple microRNAs modulate sensitivity to CDK4/6 inhibitors by targeting core cell-cycle molecules. In ER-positive breast cancer, miR-432-5p represses the TGF-β pathway, upregulates CDK6 expression, and thereby weakens the therapeutic efficacy of CDK4/6 inhibitors.

Altered checkpoint adaptation. WEE1 is a serine-threonine kinase of the G2/M checkpoint, which prevents cells with DNA damage from entering mitosis. WEE1 overexpression reinforces the G2/M DNA-damage checkpoint, allowing tumour cells to evade G1-phase drug-imposed suppression and sustain proliferation. Loss-of-function of FZR1 destabilizes the APC/C complex, reduces p27 protein abundance, elevates overall CDK kinase activity, and abrogates cell-cycle repression [39].

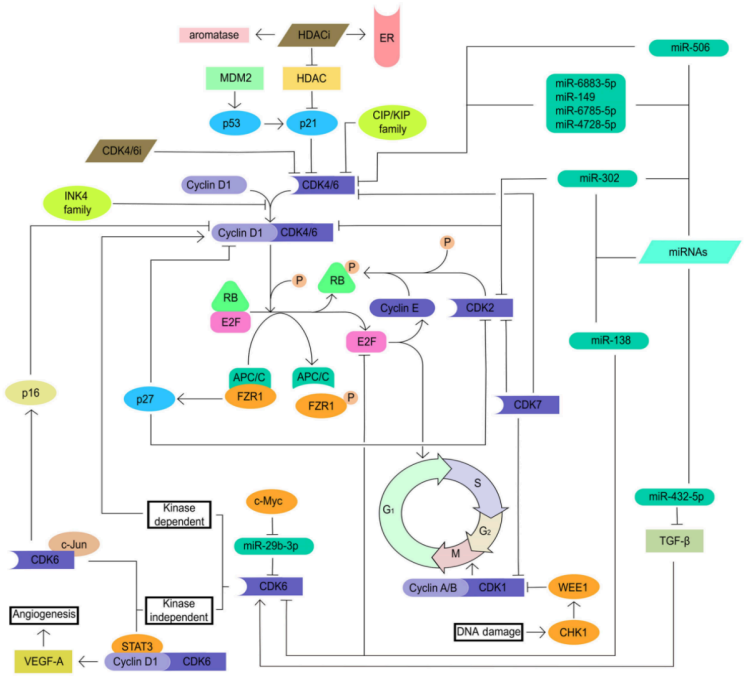


Figure 18. Signaling networks underlying Abemaciclib resistance in HR-positive breast cancer [39]

Recent studies also found activated Rb exerts tumour-suppressive effects by repressing E2F-target genes at promoter regions to induce G1-phase cell-cycle arrest. Meanwhile, it relocalizes to ER-rich chromatin enhancer transcriptional hubs, forming a ternary complex with ER and KDM5A. By inhibiting the histone-demethylase activity of KDM5A, activated Rb upregulates pro-proliferative ER-responsive genes including CCND1, triggering a compensatory pro-proliferative transcriptional programme that leads to incomplete drug response. This effect persists in ESR1-mutant cells and compromises the therapeutic efficacy of CDK4/6 inhibitors. This represents a transcriptional adaptive resistance mechanism under the condition of intact, functional Rb, which can be abrogated by SERD-mediated degradation of the ER protein [40].

Culmerciclib, newly developed by Chia Tai Tianqing Pharmaceutical, exerts simultaneous inhibitory effects on CDK2, CDK4 and CDK6, and thus has the potential to reverse therapeutic resistance. Its isopropylindole core structure not only enhances drug-binding affinity to target proteins, enabling highly selective and potent inhibition of CDK4, but also forms an extremely stable dihydrogen bond with the hinge region of CDK2 at the molecular level, ensuring sustained and effective blockade of CDK2 activity. This synergistic inhibition of both CDK2 and CDK4/6 fundamentally disrupts the drug resistance escape pathway dependent on CDK2-mediated bypass activation--a unique advantage absent in conventional CDK4/6 inhibitors [41]. It has received its first-global approval from China's NMPA for HR-positive, HER2-negative advanced breast cancer. Its clinical efficacy is underpinned by Level-1A evidence from random, double-blind, placebo-controlled Phase III trials. At present, this agent is only authorized in mainland China, with additional clinical trials for other indications ongoing [42].

Trastuzumab and Abemaciclib share several common resistance mechanisms: their drug resistance is driven by critical gene mutations, compensatory bypass signaling, microRNA and epigenetic regulation, as well as adaptive cellular remodeling after prolonged drug exposure, with hyperactivation of the PI3K/AKT and cell-cycle pathways serving as shared escape routes. Nevertheless, their root causes of resistance differ fundamentally. In Trastuzumab-resistant cells, persistent HER2 signaling ultimately upregulates Cyclin D1 to activate CDK4/6. In contrast, Abemaciclib resistance relies directly on Cyclin E-CDK2/E2F bypass independent of Cyclin D1.

5. Conclusion

This review systematically compares two core targeted agents for distinct breast cancer molecular subtypes: Trastuzumab and Abemaciclib, highlighting fundamental disparities in drug characteristics, antitumor mechanisms, eligible populations, clinical efficacy, toxicity spectra and drug resistance patterns, while discussing mechanistic rationale, existing clinical evidence and limitations for their combination strategy. Selected information is summarized in Table 2.

Table 2. Key comparative characteristics of trastuzumab and abemaciclib

Category	Trastuzumab	Abemaciclib
Origins & Structure	Genentech-derived humanized IgG1 monoclonal antibody (148kDa)	Eli Lilly-developed fully synthetic small-molecule CDK4/6 inhibitor (MW 506.6g/mol)
Route of Administration	Intravenous infusion (standard)/subcutaneous fixed dose; parenteral deliveryonly (macromolecule)	Oral administration (small molecule, high cell membrane permeability)
Target & Mechanism	Targets HER2 extracellular Domain IV; exerts anti-tumor effects via ADCC, Pl3K/AKT pathway suppression, and inhibition of HER2-driven oncogenic signaling	Targets CDK4/6 ATP-binding pockets; arrests tumor cells in G1 phase bymaintaining Rb protein hypophosphorylation, blocking G1/S transition.
Key Toxicity	Signature cardiotoxicity (early onset persistent risk up to 3 years)	Dominant gastrointestinal (diarrhea) and hematological (neutropenia) toxicities, low-grade ILD/pneumonitis risk.
Economics & Access	1-year adjuvant total cost = ¥76,500 (original 440mg/vial); included in China's NHl Category B, wide access for HER2-positive breast cancer.	2-year adjuvant total cost = ¥100,500; included in China's NHI Category B, approved for HR+/HER2-negative high-risk early and advanced breast cancer.

In terms of therapeutic positioning, Trastuzumab indicated for HER2-amplified breast tumors. It binds the extracellular domain IV to play its role. In contrast, Abemaciclib adopts for HR+/HER2- disease. It competitively blocks CDK4/6 ATP pockets to retain hypophosphorylated Rb protein, arresting tumor cells at the G1/S checkpoint. Conventionally, the two agents serve mutually-exclusive patient subgroups and are not interchangeable in routine clinical practice. Although statistically-significant OS improvement was not

achieved, the phase II monarcHER trial demonstrated marginal clinical benefit for heavily pretreated HR+/HER2-metastatic breast cancer. Robust phase III evidence is still required to validate the clinical value of this combinatorial regimen.

Trastuzumab and Abemaciclib share a key clinical limitation of insufficient single-agent efficacy, while exhibiting prominent differences in therapeutic performance and toxicity profiles. Both drugs demonstrate modest standalone antitumor activity in clinical practice. Trastuzumab achieves durable long-term disease control in HER2-positive early breast cancer, with adjuvant four-year DFS exceeding 90% across subgroups. Abemaciclib delivers prominent PFS benefits when combined with endocrine therapy for advanced HR+/HER2-disease, with consistent favorable real-world outcomes across Asian, European and Middle Eastern cohorts, though its single-agent activity is modest. Their toxicity landscapes both exhibits striking ethnic and mechanistic differences. Trastuzumab's signature adverse event is cardiac dysfunction induced by disrupted NRG1/HER4 cardiomyocyte protective signaling. Abemaciclib's dominant toxicities are gastrointestinal and hematological disorders. All adverse events of both agents are generally manageable via dose adjustment and supportive care.

While Trastuzumab and Abemaciclib share common resistance drivers like genetic aberrations, their core dominant resistance mechanisms differ substantially. Trastuzumab resistance is primarily driven by sustained oncogenic HER2 signaling induced by ERBB2 mutations, nuclear HER2 translocation, and truncated HER2 isoforms, which further activates the Cyclin D1–CDK4/6 cascade to maintain tumor proliferation. In contrast, the predominant mechanism of Abemaciclib resistance relies on RB1 loss-of-function mutations, which release E2F-mediated transcription and trigger compensatory Cyclin E–CDK2 bypass signaling, rendering cell cycle progression independent of Cyclin D1 and CDK4/6 activity. Notably, novel targeted agents represented by Pertuzumab and Culmerciclib can target the above key resistance pathways and reverse drug insensitivity, compensating for the limitations of traditional single-target therapeutic regimens.

Collectively, Trastuzumab and Abemaciclib embody two representative targeted-therapeutic paradigms. Clarifying their contrasting molecular actions, safety risks and resistance routes facilitates individualized subtype-specific treatment decisions, provides reference for cross-ethnic toxicity management, and inspires rational combinatorial strategies. Further prospective trials are urgently needed to define optimal patient subsets, dosing schedules and safety-monitoring standards for Trastuzumab plus Abemaciclib, translating pre-clinical synergism into tangible clinical gains for refractory HR+/HER2+ breast cancer.

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