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# Abemaciclib in the Adjuvant Setting for Breast Cancer: A Systematic Review

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***Author's contribution***

*Author SO designed the article, wrote the first draft of the manuscript, managed the literature searches.*

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***Systematic Review Article***

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## ABSTRACT

The combination of adjuvant Abemaciclib with endocrine therapy (ET) has emerged as a significant advancement in the management of HR+, HER2-, node-positive, high-risk early breast cancer, as demonstrated by the findings of the MonarchE trial. This innovative treatment approach yielded not only statistically significant but also clinically meaningful improvements in invasive disease-free survival.

Moreover, the benefits of this treatment combination were sustained over time, with a median follow-up of 27 months revealing continued clinically meaningful advantages in both invasive disease-free survival and distant recurrence-free survival. Importantly, these benefits extended beyond the initial 2-year treatment period, highlighting the durable efficacy of Abemaciclib and ET in preventing disease progression and distant metastasis.

Furthermore, the safety profile of the combination therapy was found to be manageable and tolerable. This aspect is crucial for ensuring patient adherence to treatment and minimizing the burden of adverse effects. Overall, these findings underscore the potential of adjuvant Abemaciclib with ET as a valuable therapeutic option for patients with high-risk early breast cancer, offering both efficacy and tolerability in the long-term management of the disease. More studies are required, especially in the elderly, in order to know how to counteract diarrhea and to make Abemaciclib more tolerated.

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## 1. INTRODUCTION

"For women, the most commonly diagnosed cancer and leading cause of cancer death was breast cancer, whereas it was lung cancer for men" [1].

Breast cancer continues to be a significant global health challenge, with adjuvant therapy playing a crucial role in reducing recurrence and improving survival rates.

"Approximately 70% of breast cancer are hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-)" [2]. The typical approach to treatment fluctuates based on the risk of recurrence. It typically involves surgery, radiotherapy, adjuvant/neoadjuvant chemotherapy, and endocrine therapy (ET).

Among the newer therapeutic options, Abemaciclib has emerged as a promising agent in the treatment landscape. Abemaciclib is a selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6), key regulators of the cell cycle, offering a novel approach to targeting proliferative signaling pathways in breast cancer.

This literature review aims to evaluate the existing evidence on the use of Abemaciclib in the adjuvant treatment of breast cancer. Furthermore, we aim to identify gaps in knowledge and highlight areas for future research to optimize the integration of Abemaciclib into adjuvant treatment algorithms.

## 2. METHODOLOGY

### 2.1 Literature Search Strategy

- A systematic search was conducted on the PubMed database to identify relevant studies published within the last 5 years. The search strategy utilized Medical Subject Headings (MeSH) terms
- The following search terms were used: ((("abemaciclib" [Supplementary Concept]) AND "Breast Neoplasms"[Mesh]) NOT "Neoplasm Metastasis"[Mesh].

### 2.2 Inclusion and Exclusion Criteria

- Studies were included if they met the following criteria: [1] investigated the use of abemaciclib in breast neoplasms that are hormone receptor-positive (HR+)/human epidermal growth factor receptor-2 negative (HER2-), [2] focused on breast cancer without metastasis, [3] were written in English, and [4] were published within the last 5 years.
- Exclusion criteria encompassed studies not available in full text and those not meeting the specified criteria.

### 2.3 Data Collection

- Initially, titles and abstracts of retrieved articles were screened to assess relevance to the research topic.
- Full-text articles meeting the inclusion criteria were obtained and reviewed for further analysis.

### 2.4 Data Extraction

- Relevant data from the included studies were extracted, focusing on key variables such as study design, patient characteristics, treatment regimens, outcomes, and conclusions.

## 3. RESULTS AND DISCUSSION

A total of 169 full-length articles satisfied the terms of our search. After duplicates removal and full eligibility assessment 38 records were included.

### 3.1 Abemaciclib Efficacy

"Cyclin-dependent kinase-4 and 6 (CDK4/6) are important in the process of cell proliferation. An impairment in CDK4/6-retinoblastoma pathway is involved in breast cancer" [3,4]. "Cyclins D1, D2 and D3 regulate the CDK4 and CDK6 kinases" [5]. "Cyclin D1 (CCND1) is a transcriptional target of the estrogen receptor and is overexpressed in about half of breast cancers" [4,6]. "CDK4/6 inhibitors induce cell cycle arrest in retinoblastoma protein competent cells" [7].

Abemaciclib is a cell growth inhibitor, inhibiting preferentially the CDK4/CyclinD1 complex, leading to cell senescence and cell death.

The phase III trial evaluating adjuvant Abemaciclib plus endocrine therapy (ET) in HR+ /HER2- early breast cancer (MonarchE).

"The study included women and men, with HR+, HER2-, with early breast cancer (EBC) at high risk of recurrence according to clinicopathological features. Patients meeting the following criteria were included in the study: ≥4 positive axillary lymph nodes (ALN) , or 1-3 ALN and at least one of the following criteria : ▫ Tumor size ≥5 cm ▫ Histologic grade 3 ▫ Centrally tested Ki-67 ≥20%. Patients diagnosed with inflammatory breast cancer or who had a history of thrombo-embolism disease were excluded" [8].

"Patients were randomized to receive adjuvant Abemaciclib plus endocrine therapy (ET) or ET alone for 2 years, with ET prescribed for at least 5 years. ET was prescribed based on the discretion of the treating physician including tamoxifen or aromatase inhibitors, with or without ovarian suppression. Abemaciclib + ET reduced the risk of developing an invasive disease-free survival (IDFS) event. There was an absolute improvement of 3.0% in the 2-year IDFS rates (Abemaciclib + ET: 92.3% versus ET alone: 89.3%). The treatment benefit was statistically valid beyond the 2-year treatment period with Abemaciclib" [9]. "The treatment benefit was also observed after neoadjuvant chemotherapy regardless of the residual tumor size" [10].

"US Food and Drug Administration Expanded Adjuvant Indication of Abemaciclib in High-Risk Early Breast Cancer" [11].

## 3.2 Safety Profile

"Abemaciclib dose holds and reductions due to adverse events occurred in 61.7% and 43.4% of patients, respectively, generally related to diarrhea, neutropenia, or fatigue. Most patients continued on Abemaciclib and only a small proportion of patients with dose reductions discontinued Abemaciclib due to Adverse events [8.9%]" [12].

### 3.2.1 Gastrointestinal toxicities

The most common adverse event with Abemaciclib was diarrhea.

Others effects of Abemaciclib include nausea, abdominal pain, constipation and vomiting. Diarrhea manifested early in treatment, with a median onset time of 8 days for any grade. It typically lasted for a brief period, with a median duration of 5 to 6 days for grades 2 and 3, classified according to the Common Terminology Criteria for Adverse Events (CTCAE) [8].

"Diarrhea was mainly managed with antidiarrheal medication (79%) and <25% of patients required dose modifications" [12]. Abemaciclib withdrawal due to diarrhea occurred in 5.3% of patients.

"Abemaciclib primarily inhibits cyclin-dependent kinases 4 and 6 (CDK4/6). While it has been shown to have some off-target effects on other CDKs, such as CDK9, its potency against CDK9 is significantly lower compared to its activity against CDK4/6 inhibits CDK9, an important regulator of intestinal cell proliferation" [6,13]. "In the intestinal mucosa of rats treated with Abemaciclib, pathological findings included proliferative changes in crypt cells and villous atrophy" [14]. "These findings are different from histological findings, such as necrosis of crypt cells and loss of microvilli and intestinal mucosal epithelium, which are typically observed in mucosal damage caused by cytotoxic anticancer agents or radiation" [15].

"The MERMAID is the first prospective study to evaluate the efficacy of probiotics and trimebutine. No superior therapeutic efficacy of Trimebutine was evident, indicating that oral loperamide remains pivotal in managing diarrhea. Importantly, the combination of probiotic Bifidobacterium with Trimebutine, in conjunction with loperamide, contributed to decreasing the occurrence of grade 3 diarrhea" [16]. The study's limitations encompass its non-comparative nature, as it did not evaluate two distinct groups of patients, one receiving probiotic Bifidobacterium and the other not.

### 3.2.2 Hematological toxicities

"Neutropenia, a prevalent side effect of CDK 4/6 inhibitors, arises from their impact on hematopoietic bone marrow function. Despite Abemaciclib demonstrating a lower incidence of neutropenia compared to other CDK 4/6 inhibitors, it remains the most frequently reported severe (grade ≥3) side effect associated with its usage. Management of abemaciclib-induced grade ≥3 neutropenia typically involves treatment discontinuation and dose reduction. Thus, it is imperative to identify patients at high risk of grade ≥3 neutropenia at baseline" [17].

Close monitoring of blood counts was an important strategy for mitigating these toxicities.

### 3.2.3 Hepatotoxicity

Because of significant hepatic metabolism via the CYP3A4 pathway, CDK 4/6 inhibitors have been

demonstrated to have a notable impact on liver enzymes.

The use of potent inhibitors of CYP3A4 with Abemaciclib should be avoided (The same goes for CYP3A4 inducers due to concerns about reduced efficacy of the treatment [18].

Elevations in liver enzymes have been observed with Abemaciclib treatment, and rare cases of severe hepatotoxicity have been reported. Liver function tests should be monitored regularly during treatment, and dose adjustments may be necessary in patients with pre-existing liver impairment [18].

### 3.2.4 Fatigue and musculoskeletal symptoms

Abemaciclib treatment may also be associated with fatigue and musculoskeletal symptoms, including arthralgia and myalgia. These symptoms can impact patient quality of life and may require supportive care interventions.

Bisphosphonates are widely used as valuable antiresorptive agents for the treatment of post-menopausal osteoporosis [19].

More studies about the of Abemaciclib in the adjuvant setting are warranted to evaluate the risk of osteonecrosis of the jaw and renal impairment.

### 3.2.5 Cardiovascular events

While Abemaciclib has shown a favorable cardiovascular safety profile overall, cases of myocardial infarction and arterial thromboembolic events have been reported [20].

CDK4/6 had different profiles of thromboembolism. Abemaciclib showed a weak association with the risk of thromboembolism [21].

Chappell et al. evaluated “the relationship between QT interval and exposure after oral administration of single ascending doses of abemaciclib”. “Inclusion criteria accepted healthy, males and females, aged 18 – 70 years, with a body mass index (BMI) between 18 and 32 kg/m2 with acceptable clinical laboratory test results and acceptable blood pressure. There were no significant changes in heart rate determined by central electrocardiogram analysis after 200, 300, 400, or 600 mg Abemaciclib. Single doses of Abemaciclib up to 400 mg had no statistically or clinically relevant effects on QT interval, and Abemaciclib was well tolerated up to a dose of 400 mg” [22].

### 3.2.6 Lung disease

“Interstitial lung disease/pneumonitis was infrequent and treated with corticosteroids and/or antibiotics” [23].

### 3.2.7 Renal safety

Chappell et al. found that “increases in serum creatinin following Abemaciclib administration are likely caused by inhibition of renal transporters and that Abemaciclib does not affect renal function as assessed by measured glomerular filtration rate, or increase in concentrations of urinary biomarkers of renal injury”. “The findings suggested that patients dosed with Abemaciclib will experience a mild (~10–40%) reversible increase in serum creatinin due to renal transport inhibition” [24].

### 3.2.8 Safety profile of abemaciclib with concurrent radiation therapy

“In MonarchE trial, the majority of patients (95.4%) had received postoperative radiation therapy (RT). However, radiation should have been completed prior to enrolment, and a washout period of at least 14 days was required between the end of RT and the trial randomization. An analysis of patient-reported outcomes from the MonarchE trial, conducted with a median follow-up of 27 months, revealed comparable rates of radiation pneumonitis in patients previously treated with radiation therapy (RT) across both treatment arms. The potential consideration of concurrent administration of RT during adjuvant Abemaciclib therapy may warrant further investigation” [25].

## 4. CONCLUSION

In summary, the combination of adjuvant Abemaciclib with endocrine therapy (ET) showed notable enhancements in both statistical significance and clinical relevance regarding invasive disease-free survival (IDFS) for patients with HR+, HER2-, node-positive, high-risk early breast cancer. Additionally, the combination therapy's safety profile was determined to be manageable and well-tolerated, a critical factor in promoting patient adherence to treatment and reducing the impact of adverse effects. These results highlight the potential of adjuvant

Abemaciclib with ET as a valuable therapeutic choice for high-risk early breast cancer patients, providing both effectiveness and tolerability in long-term disease management. Further research is needed, particularly focusing on the elderly population, to better understand strategies for managing diarrhea and enhancing the tolerability of Abemaciclib.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

This study was exempt from ethics board approval since it used publicly available data exclusively.

## COMPETING INTERESTS

Author has declared that no competing interests exist.

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