








Review Article

Impact of CDK4/6 Inhibitors on Aromatase Inhibitor-Associated Musculoskeletal Syndrome (AIMSS) in the Adjuvant Setting

Efthymia Skafida,¹ Angeliki Andrikopoulou ,¹ Evangelos Terpos ,¹ Christos Markellos,¹ Savvina Moustafa ,² Dimitrios Pectasides ,³ Meletios-Athanasios Dimopoulos ,¹ Flora Zagouri ,¹ and Dimitrios Vassilopoulos ,²

¹Department of Clinical Therapeutics, Alexandra Hospital, Medical School, Athens, Greece

²Clinical Immunology-Rheumatology Unit, 2nd Department of Medicine and Laboratory, National and Kapodistrian University of Athens School of Medicine, Hippokration General Hospital, Athens, Greece

³Oncology Section, Second Department of Internal Medicine, Hippokration Hospital, Athens, Greece

Correspondence should be addressed to Flora Zagouri; florazagouri@yahoo.co.uk

Efthymia Skafida and Angeliki Andrikopoulou contributed equally to this work.

Received 25 January 2022; Revised 20 September 2022; Accepted 28 March 2023; Published 31 May 2023

Academic Editor: Taobo Hu

Copyright © 2023 Efthymia Skafida et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background. Third-generation aromatase inhibitors (AIs) are the mainstay of treatment in hormone receptor (HR)-positive breast cancer. Even though it is considered to be a well-tolerated therapy, AI-induced musculoskeletal symptoms are common and may be accused for treatment discontinuation. Recently, selective cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors changed the therapeutic setting, and currently, ribociclib, palbociclib, and abemaciclib are all approved in combination with nonsteroidal AIs in patients with ER-positive, HER2-negative advanced or metastatic breast cancer. This systematic review aims to identify the frequency of aromatase inhibitor-associated musculoskeletal syndrome (AIMSS) in the adjuvant setting in patients under AI monotherapy compared to patients under combination therapy with AIs and CDK4/6 inhibitors and demonstrate the underlying mechanism of action. **Methods.** This study was performed in accordance with PRISMA guidelines. The literature search and data extraction from all randomized clinical trials (RCTs) were done by two independent investigators. Eligible articles were identified by a search of MEDLINE and ClinicalTrial.gov database concerning the period 2000/01/01–2021/05/01. **Results.** Arthralgia was reported in 13.2 to 68.7% of patients receiving AIs for early-stage breast cancer, while arthralgia induced by CDK4/6 inhibitors occurred in a much lower rate [20.5–41.2%]. Bone pain (5–28.7% vs. 2.2–17.2%), back pain (2–13.4% vs. 8–11.2%), and arthritis (3.6–33.6% vs. 0.32%) were reported less frequently in patients receiving the combination of CDK4/6 inhibitors with ET. **Conclusions.** CDK4/6 inhibitors might have a protective effect against joint inflammation and arthralgia occurrence. Further studies are warranted to investigate arthralgia incidence in this population.

1. Introduction

Breast cancer is the most common malignancy in females affecting more than 2,000,000 women each year [1]. Clinical practice has changed substantially in recent decades leading to a more prolonged survival. At the time of diagnosis, approximately 64% of patients have localized disease, while 6% of patients have already developed metastases. The 5-year survival rate of metastatic disease is

estimated to be around 27% [2]. Around 75% of all breast tumors express the estrogen receptor (ER) and/or the progesterone receptor (PgR) and are considered as hormone receptor-positive (HR) tumors [3]. HR-positive breast cancer demonstrates the best survival rates (90.3%–92.5% 4-year survival rate) compared with epidermal growth factor receptor 2 (HER2)-positive tumors (82.7% 4-year survival rate) and triple-negative subtype (survival rate 77.0%) [4].

Adjuvant endocrine therapy remains the mainstay of HR-positive early breast cancer along with chemotherapy and adjuvant radiation therapy. For postmenopausal women, next generation aromatase inhibitors (AIs) non-steroidal (anastrozole and letrozole) or steroidal (exemestane) are widely used in the adjuvant setting [5–7]. However, administration of AIs has been associated with joint pain and musculoskeletal symptoms that can even lead to treatment discontinuation. Aromatase inhibitor-associated musculoskeletal syndrome (AIMSS) is the most common adverse event encountered by breast cancer patients. In early-stage breast cancer, an incidence of 47% of arthralgias was reported in postmenopausal women treated with AI, including a 23.5% rate of new-onset arthralgia and a 23.5% rate of exacerbation of pre-existing arthralgias [8]. Another recent meta-analysis showed a 17.9% rate of AI-induced arthralgia in postmenopausal women which was lower in early-stage breast cancer compared with advanced disease [9]. Overall, approximately 13–25% of patients discontinue AI therapy mainly because of arthralgias [10, 11].

The development of selective cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors which regulate cell cycle progression has altered daily clinical practice. Currently, ribociclib (LEE011), palbociclib (PD0332991), and abemaciclib (LY2835219) are all approved in combination with nonsteroidal AIs as first-line therapy of ER-positive, HER2-negative advanced or metastatic breast cancer. Results from Phase III studies showed a 40–45% improvement in progression-free survival (PFS) from the addition of CDK4/6 inhibitors in the metastatic setting [12]. CDK4/6 inhibitors are currently under investigation in the adjuvant setting as well. Adverse events commonly reported after CDK4/6 inhibitor administration includes neutropenia (75–80%) upon ribociclib or palbociclib treatment, elevated amino-transferases (15%), and prolongation of corrected QT interval by Fredericia (QTcF) (3.3%) with ribociclib and diarrhea (81.3%) upon abemaciclib treatment. Remarkably, musculoskeletal symptoms have not been linked with CDK4/6 treatment despite the coadministration with AIs. Whether CDK4/6 inhibitors affect the arthralgia rate reported in Phase III trials of AIs remains unknown. We conducted this systematic review to identify the rate of musculoskeletal manifestations induced by AIs and CDK4/6 inhibitors in the adjuvant setting and the potential effect of CDK4/6 inhibitors on joint symptoms. We have previously published the musculoskeletal toxicity of CDK4/6 and aromatase inhibitors in the metastatic setting, so we are now presenting the existing data in the adjuvant setting [13].

2. Materials and Methods

This systematic review was performed in accordance with PRISMA guidelines [14]. The protocol of this systematic review has been submitted to the Institutional Review Board of Alexandra Hospital and Medical School of Athens and is available upon request. All eligible studies were identified using MEDLINE and ClinicalTrial.gov database for search concerning the period 2000/01/01–2021/05/01. The search

algorithm applied consisted of the following words: (breast AND (cancer OR neoplasm) and (aromatase inhibitors OR letrozole OR anastrozole OR exemestane OR CDK4/6 OR palbociclib OR ribociclib OR abemaciclib) AND (phase III) AND (adjuvant)). Language restrictions were not applied. In order to maximize the amount of synthesized information, we systematically examined the reference lists of the articles retrieved for potentially eligible studies.

Eligible studies included all randomized controlled Phase III trials exploring third-generation AI monotherapy treatment in early-stage breast cancer in postmenopausal women and all randomized controlled Phase III trials evaluating AIs in combination with CDK4/6 inhibitors in the adjuvant setting. Phase I-II trials, case reports, and reviews were excluded. Trials of AIs in combination with other antineoplastic drugs, e.g., trastuzumab, or in combination with bone-protective therapies [15–19] were also excluded. In case of overlapping publications emerging from the same study, the larger sample size study was evaluated, e.g., TEAM trial and N-SAS BC 04 trial [6, 20]. In case of additional information provided from multiple papers from the same trial, each article was evaluated separately [5, 21].

From each of the eligible studies, the following data were extracted: first author, year of publication, trial number, treatment arms, sample size, median age, median follow-up time, disease-free survival, overall survival, arthralgia rate, myalgia rate, backpain rate, bone pain rate, arthritis rate, osteoporosis, and osteoporotic fracture rates. Two investigators (ES and AA), working independently, searched the literature, and extracted data from each eligible study. Only data when AIs were administered as monotherapy treatment were considered eligible, and thus, data emerging from the sequential administration of tamoxifen and AIs were not included in our final results. In addition, whenever study results were available on ClinicalTrials.gov, results extracted from eligible articles were updated according to ClinicalTrials.gov data. Any differences in extracted data were resolved via within-pair consensus. Odds Ratio (OR) with 95% confidence interval (CI) was applied as an effect estimate of arthralgia occurrence when CDK4/6 inhibitors were added to ET therapy. Pooled OR with 95% CI was calculated using the random-effects model due to the underlying variations across the included trials. Heterogeneity across included trials was assessed using I^2 and Q statistics, and significant heterogeneity was defined as $I^2 > 50.0\%$ or $P < 0.10$. Statistical analysis was conducted using Review Manager (RevMan) v.5.4.1 software.

3. Results

Overall, 291 articles were identified and screened in the MEDLINE database. Among them, 16 studies were considered eligible for our review [5, 6, 21–38]. After investigating the references of the eligible articles, four more studies were added (ITA [39], ARNO-95 [40, 41], ABCSG-6a [42], NSABP B-33 [43]). An additional search in ClinicalTrials.gov recruited five additional studies (PENELOPE-B

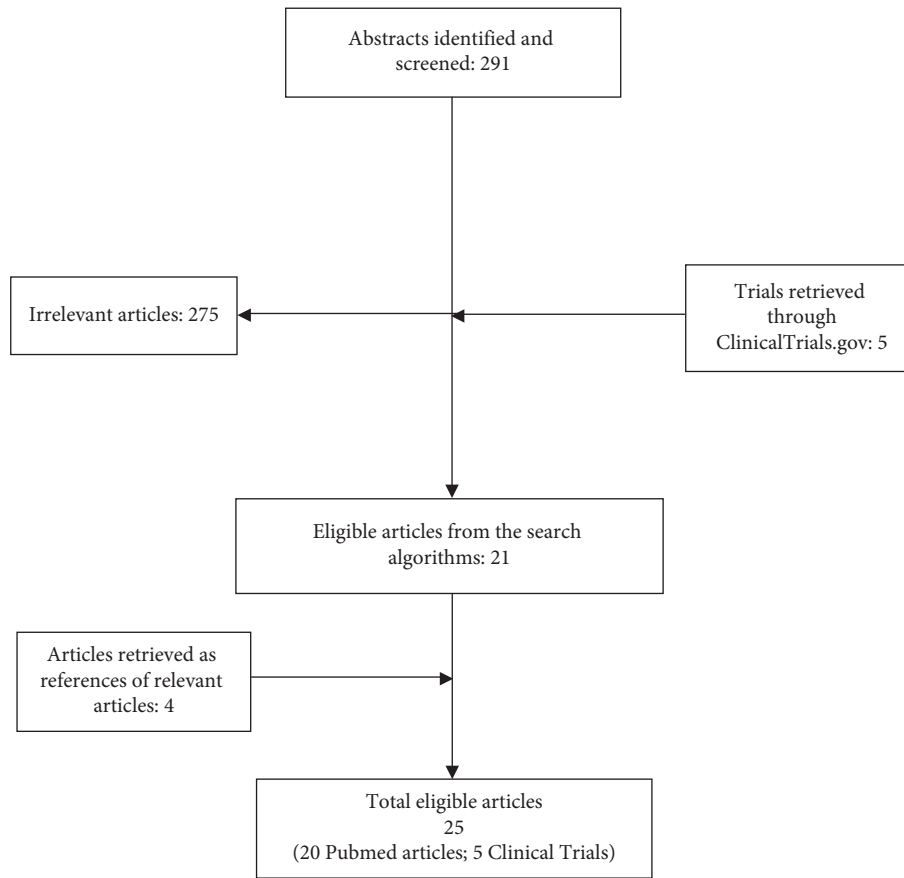


FIGURE 1: Flowchart presenting the successive steps during the selection of studies.

[44], ATAC [7, 45], IES [46], GIM4 LEAD [47], SALSA [48]). Overall, 25 studies were considered as eligible for this systematic review. The flow diagram of literature search and study selection is shown in Figure 1. There are no data about whether the manifestations of AIMSS were defined according to a specific protocol or by investigator's judgment in each trial.

3.1. Arthralgia. In the adjuvant setting, the reported percentage of arthralgias in patients under monotherapy with AIs ranged from 13.2 to 68.7%, while in patients receiving therapy with tamoxifen, the reported arthralgia rates ranged from 11.8 to 31.8% and in patients receiving placebo from 15 to 50% (Table 1). The highest rates of arthralgias were observed in studies when 4–6 years of AI treatment had preceded before enrolment, such as MA.17R study and SOLE study where arthralgia was reported in 53% and 68.7% of patients, respectively [32, 36]. Anastrozole and letrozole were associated with approximately the same arthralgia rate (48.2% vs. 47.9%, respectively) according to the FACE trial [28]. More specifically, letrozole monotherapy induced arthralgia with an incidence of 13.2–68.7%, while the incidence of arthralgia in anastrozole and exemestane monotherapy was 24.5–57.7% and 24–55.4% respectively. Overall, the occurrence of exemestane-induced arthralgia is lower than those of letrozole and anastrozole.

Data from MonarchE, PALLAS, and PENELOPE-B Phase III trials of CDK4/6 inhibitors plus endocrine therapy (ET) versus ET in the adjuvant setting were just published [35, 37, 38, 44] (Table 2). Arthralgia rate was 20.5–41.2% of patients receiving CDK4/6 inhibitor plus ET. In all of the trials, arthralgia rate was lower in patients receiving CDK4/6 inhibitors compared to the control arm (MonarchE: 20.5% vs. 31.3%; PALLAS: 34.9% vs. 41.6%; PENELOPE-B: 41.2% vs. 46.8%). The odds ratio of arthralgia incidence ranged from 0.56 to 0.82 across these trials. Pooled analysis of these trials showed that adding CDK4/6 inhibitor to ET significantly reduced arthralgia incidence (OR: 0.70; 95% CI: 0.56–0.87; $P < 0.05$; Figure 2) compared to ET alone despite the heterogeneity observed across the trials ($I^2 = 87%$; $P < 0.05$). Of note, arthralgia incidence was lower in abemaciclib treatment (20.5%) compared to palbociclib (34.9–41.2%) [35, 37, 38, 44].

3.2. Myalgias. In the adjuvant setting, the incidence of myalgia reported in 9 of RCT was 7.5–37.1% in patients receiving AIs as monotherapy, 7% in patients receiving tamoxifen, and 6–25% in patients receiving placebo. The highest myalgia rates were reported in MA.17R trial (28%) and SOLE trial (35.9%/37.1%) where patients enrolled had received 4 to 5 years of previous endocrine therapy with AIs [32, 36]. In the rest of RCTs, the myalgia rate reported was lower than 20% (7.5–17.7%). Myalgia incidence was

TABLE 1: Phase III randomized trials of AIs in postmenopausal women with early-stage breast cancer.

| Reference | Trial | Treatment arms | Study sample | Median age | Median follow-up (month) | DFS | OS | Arthralgia (%) | Myalgia (%) | Bone pain (%) | Back pain (%) | Arthritis (%) | Osteoporosis (%) | Fracture (%) | Carpal tunnel syndrome |
|--------------------------|---------------------------------|---|-----------------------|----------------|--------------------------|---|--|----------------|-------------|---------------|---------------|---------------|------------------|--------------|------------------------|
| Colleoni et al. [21] | BIG 1-98 (NCT00004205) | Tamoxifen 5 years vs. letrozole 5 years | 4922 (2459/2463) | 61.7/61.9 | 51 | 81.1%/84% IPCW: 82.1/85.6 | 90.4/91.8 | 16.6/22.5 | 7/8.4 | NR | NR | NR | 2.2/5.1 | 6.7/10 | 0.2/0.8 |
| Regan et al. [5] | | | | | | | | | | | | | | | |
| Buzdar et al. [45] | ATAC (NCT00849030) | Tamoxifen for 5 years vs. anastrozole for 5 years vs. combination for 5 years | 9366 (3116/3125/3125) | 64.1/64.1/64.3 | 68 | 575 vs. 651 events; HR: 0.87 | Similar; HR: 0.97 | 29.4/35.6 | NR | NR | NR | NR | 7/11 | 7.7/11 | 1/3 |
| Howell et al. [7] | | | | | | | | | | | | | | | |
| Van de Velde et al. [6] | TEAM (NCT00036270, NCT00279448) | Tamoxifen for 2.5-3 years plus exemestane until 5 years vs. exemestane for 5 years | 9779 (4875/4904) | 64 | 61 | 5-year: 86%/87%; HR: 0.93 10-year: 67%/67%; HR: 0.96 | 5-year: 91%/91%; HR: 1.0 10-year: 73%/74%; HR: 0.98 | 20.9/24 | 7.4/7.5 | 4.8/5.4 | 5.7/5.7 | 2.9/3.6 | 6/10 | 3/5 | NR |
| Derks et al. [22] | | | | | | | | | | | | | | | |
| Coombes et al. [46] | IES (NCT00038467) | Tamoxifen for 2-3 years plus exemestane until 5 years vs. tamoxifen for 5 years | 4724 (2352/2372) | 63.7/63/6 | 55.7 | 5-year: 354 vs. 455 events; adjusted HR: 0.75 | 5-year: 222 vs. 261 deaths; adjusted HR: 0.85 | 18.6/11.8 | NR | NR | NR | 14.1/12 | 7.3/5.5 | 4.3/3.1 | 2.8/0.3 |
| Goss et al. [23, 24] | NCIC CTG MA-17 (NCT00003140) | Letrozole vs. placebo for 5 years (after 5 years of tamoxifen) | 5187 (2593/2594) | 62.4/62 | 30 | 4-year: 94.4%/89.8%; HR: 0.58 | 4-year: 95.4%/95%; HR: 0.82 | 25/21 | 15/12 | 5/6 | NR | 6/5 | 8.1/6 | 5.3/4.6 | NR |
| Goss et al. [36] | MA.17R (NCT00754845) | Letrozole vs. placebo for 4.5-6 years of AI treatment preceded or not by tamoxifen) | 1918 (959/959) | 65.6/64.8 | 75 | 5-year: 96%/91%; HR: 0.66 | 5-year: 93%/94%; HR: 0.97 | 53/50 | 28/25 | 18/14 | NR | 33/30 | 11/6 | 14/9 | NR |
| Mamounas et al. [25, 26] | NSABP-B42 (NCT00382070) | Letrozole vs. placebo for 5 years (after 5 years of tamoxifen or AI) | 3966 (1983/1983) | NR | 83 | 7-year: 84.7%/81.3%; HR: 0.85 | 7-year: 91.8%/92.3%; HR: 1.15 | 18/15 | 8/6 | NR | 2/2 | NR | NR | 3/2 | NR |
| Smith, et al. [28] | FACE (NCT00248170) | Letrozole vs. anastrozole for 5 years | 4136 (2061/2075) | 62/62 | 65 | 5-year: 84.9%/82.9%; HR: 0.93 | 5-year: 89.9%/89.2%; HR: 0.98 | 48.2/47.9 | 11.4/10.3 | 6.7/5.9 | 10.3/9.4 | NR | 10.9/10.9 | NR | 0/0.05 |

TABLE 1: Continued.

| Reference | Trial | Treatment arms | Study sample | Median age | Median follow-up (month) | DFS | OS | Arthralgia (%) | Myalgia (%) | Bone pain (%) | Back pain (%) | Arthritis (%) | Osteoporosis (%) | Fracture (%) | Carpal tunnel syndrome |
|--------------------------|--|---|------------------|------------|--------------------------|---|--|----------------|-------------|---------------|---------------|---------------|------------------|--------------|------------------------|
| Boccardo et al. [39] | ITA trial (NCT00286117) | Tamoxifen for 2-3 years plus anastrozole until 5 years vs. tamoxifen for 5 years | 448 (223/225) | 63/63 | 36 | 94.6%/85.8% | 10 deaths vs. 4 deaths | NR | NR | NR | NR | NR | NR | 1/1.3 | NR |
| Jakesz et al. [42] | ABCSG 6a (NCT00300508) | Anastrozole for 3 years vs. placebo (after 5 years of tamoxifen) | 856 (387/469) | 67.8/68.5 | 62.3 | 5-year: 7.15 vs. 11.8%; 16 vs. 35 events (HR=0.53; P=0.034) | 5-year: 40 deaths (10.3%) vs. 55 deaths (11.7%); HR: 0.89; P=0.570 | NR | NR | NR | NR | NR | NR | 0.8/1.1 | NR |
| Dubsky et al. [27] | ABCSG-8 (NCT00291759) | Tamoxifen for 2 years plus anastrozole for 3 years vs. tamoxifen for 5 years | 3714 (1865/1849) | 63.6/64 | 60 | 5-year: 83 vs. 94 deaths; HR: 0.87 | 83 vs. 94 deaths; HR: 0.87 | NR | NR | 19/16 | NR | NR | NR | 2.3/1.5 | NR |
| Jakesz et al. [40] | ABCSG-8 (NCT00291759) ARNO 95 (NCT00287534) | Tamoxifen for 2 years plus anastrozole for 3 years vs. tamoxifen for 5 years | 3224 (1618/1606) | 60.9/60.5 | 28 | 3-year: 95.8%/92.7%; HR: 0.60 | 3-year: 97%/96%; HR: 0.53 | NR | NR | NR | NR | NR | NR | 2/1 | NR |
| Tjan-Heijnen et al. [29] | DATA (NCT00301457) | Anastrozole for 3 years vs. 6 years (after 2-3 years of tamoxifen) | 1860 (929/931) | 57.6/57.7 | 51 | 5-year: 79.4%/83.1%; HR: 0.79 | 5-year: 90.4%/90.8%; HR: 0.91 | 52.5/57.7 | NR | NR | NR | NR | 16.4/20.9 | 7.5/10 | NR |
| Colleoni et al. [32] | SOLE (NCT00553410) | Letrozole intermittently or continuously for 5 years (after 4-6 years of endocrine therapy) | 4851 (2425/2426) | 60/60 | 60 | 5-year: 85.8%/87.5%; HR: 1.08 | 5-year: 94.3%/93.7%; HR: 0.85 | 65.7/68.7 | 35.9/37.1 | 27.2/28.7 | NR | NR | 47.4/46.8 | 8.1/8.8 | NR |
| Blok et al. [31] | IDEAL (BOOG 2006-05) | Letrozole for 2.5 years vs. 5 years (after 5 years of endocrine therapy) | 1824 (909/915) | 79 | 79 | 5-year: 82%/83.4%; HR: 0.92 | HR: 1.04 | 13.2/14.7 | NR | NR | NR | NR | 7.5/12.7 | 2.8/5 | NR |

TABLE 1: Continued.

| Reference | Trial | Treatment arms | Study sample | Median age | Median follow-up (month) | DFS | OS | Arthralgia (%) | Myalgia (%) | Bone pain (%) | Back pain (%) | Arthritis (%) | Osteoporosis (%) | Fracture (%) | Carpal tunnel syndrome |
|---------------------------|------------------------------|--|--------------------|---------------|--------------------------|------------------------------------|---|-----------------------|-------------------|---------------------|---------------|---------------|------------------|--------------|------------------------|
| De Placido et al. [30] | FATA-GIM3 (NCT00541086) | Anastrozole or exemestane or letrozole 5 years vs. tamoxifen for 2 years plus anastrozole or letrozole or exemestane for 3 years | 3697 (1847/1850) | 64/64 | 60 | 5-year: 89.8%/ 88.5%; HR: 0.89 | 5-year: 96.8%/ 95.3%; HR: 0.72 | NR | 17/13 | 27.3/ 21.9 | NR | 33.6/25.8 | 23.8/19.4 | 4/5 | NR |
| Del Mastro et al. [47] | GIM4 LEAD (NCT01064635) | Letrozole for 2-3 years vs. 5 years (after 2-3 years of tamoxifen) | 2056 (1030/1026) | 60/61 | 120 | 8-year: 80%/ 85%; HR: 0.82 | NR | NR | NR | NR | NR | NR | 4.8/8.3 | 0.5/0.9 | NR |
| NCT00295620 [48, 49] | SALSA (ABCSSG 16) | Anastrozole for 2 years vs. 5 years (after 5 years of endocrine therapy) | 3470 (1732/1738) | 65/65 | | 5-year: 78%/ 78%; HR 0.99 | NR | NR | NR | NR | NR | NR | NR | 4/6 | NR |
| Mamounas et al. 2008 [43] | NSABP B-33 (NCT00016432) | Exemestane for 5 years vs. placebo for 5 years (after 5 years of tamoxifen) | 1598 (799/799) | | 30 | 4-year: 91%/ 89%; $P = 0.07$ | 16 vs. 13 deaths | 1/0.5 (Grade 3/4) | NR | 0.5/0.7 (Grade 3/4) | NR | NR | NR | NR | NR |
| Aihara et al. [33] | N-SAS BC03 | Tamoxifen for 1-4 years plus anastrozole until 5 years vs. tamoxifen for 5 years | 706 (354/3520) | 59.5/ 60.2 | 42 | 3-year: 94.3%/90.7% HR: 0.69 | 3-year: 99.6%/ 98.8% | 50.4/31.8 | NR | NR | NR | NR | NR | 1.4/2.6 | NR |
| Ruiz-Borrego et al. [34] | GEICAM/2006-10 (NCT00543127) | Anastrozole vs. anastrozole plus fulvestrant | 870 (437/433) | 62/62 | 75 | 7-year: 83.3%/ 86.9%; HR: 0.84 | 5-year: 95.8%/ 94.3%; $P = 0.558$ | 14.6/13.4 (Grade 2-4) | 2.7/5 (Grade 2-4) | 3/6.5 (Grade 2-4) | NR | NR | NR | NR | NR |
| Goss et al. [23, 64] | NCIC CTG MA.27 (NCT00066573) | Exemestane for 5 years vs. anastrozole for 5 years | 7576 (3,789/3,787) | 64.1 | 49 | 4-year: 91 vs. 91.2; HR: 1.02 | 4-year: 94.5%/94.1; HR: 0.93 | 55.4/55.4 | 17.7/16.7 | 10.1/ 10.9 | 12.7/ 13.4 | 7/6.4 | 33/36.4 | 4/4 | NR |

NR = not reported.

TABLE 2: Phase III randomized trials of CDK4/6 inhibitors in postmenopausal women with early-stage breast cancer.

| Reference | Trial | Treatment arms | Study sample | Median age | Median follow-up (month) | iDFS | OS | Arthralgia (%) | Myalgia (%) | Bone pain (%) | Back pain (%) | Arthritis (%) | Osteoporosis (%) | Fracture (%) | Carpal tunnel syndrome |
|--------------------------|------------|--|------------------|------------|--------------------------|---|---|----------------|-------------|---------------|---------------|---------------|------------------|--------------|------------------------|
| Johnston et al. [35, 38] | MonarchE | Abemaciclib plus endocrine therapy (ET) vs. ET (AIs, tamoxifen) | 5637 (2808/2829) | 51/51 | 15.5 | 2-year: 92.2% vs. 88.7% ^e (P = 0.01; HR: 0.75) | — | 20.5%/31.3% | 5.98%/5.92% | 2.22%/3.32% | 8%/9.7% | 0.32%/1.04% | 1.61%/2.54% | NR | NR |
| | | | | | | 3-year: 81.2% vs. 77.7% (HR: 0.93; P = 0.525) | — | 34.9%/41.6% | NR | NR | NR | NR | NR | NR | |
| Mayer et al. [37] | PALLAS | Palbociclib plus endocrine therapy (ET) vs. ET (AIs, tamoxifen) | 5760 (2883/2877) | 52/52 | 23.7 | 3-year: 88.2% vs. 88.5% (p = 0.51; HR: 0.93) | — | NR | NR | NR | NR | NR | NR | NR | NR |
| | | | | | | 3-year: 81.2% vs. 77.7% (HR: 0.93; P = 0.525) | — | 41.2%/46.8% | 20.2%/18.5% | 17.2%/19.1% | 11.2%/13.3% | NR | NR | NR | NR |
| Loibl et al. [44] | PENELOPE-B | Palbociclib plus endocrine therapy (ET) vs. ET (AIs, tamoxifen) after taxane-containing NACT | 1250 (631/619) | 49/48 | 42.8 | 3-year: 81.2% vs. 77.7% (HR: 0.93; P = 0.525) | 3-year: 93.6%/90.5% (HR: 0.87; P = 0.420) | 41.2%/46.8% | 20.2%/18.5% | 17.2%/19.1% | 11.2%/13.3% | NR | NR | NR | NR |

NR = not reported; iDFS: invasive disease-free survival; NACT: neoadjuvant chemotherapy.

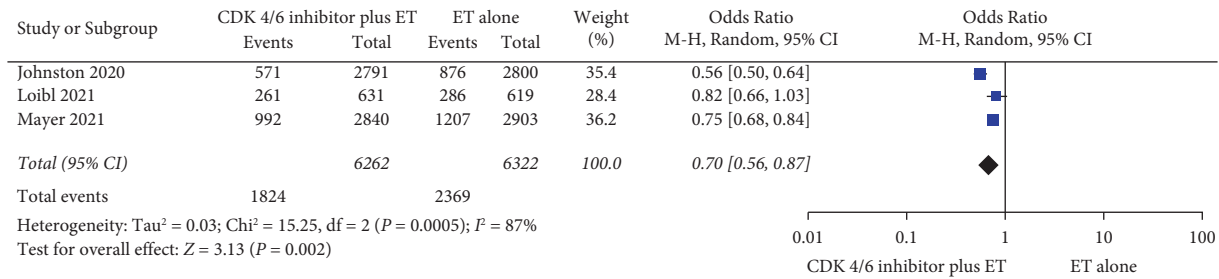


FIGURE 2: Forest plot of the arthralgia incidence in patients receiving CDK4/6 inhibitors plus ET versus ET alone.

8–37.1%, 10.3–16.7%, and 7.5–17.7% in early breast cancer patients treated with letrozole, anastrozole, and exemestane, respectively. There are no data of myopathy or elevated CPK in any of the trials.

Myalgia incidence was reported in only two of the trials of CDK4/6 inhibitors in the adjuvant setting [38, 44]. Myalgia rate ranged from 5.98 to 20.2% in patients treated with CDK4/6 inhibitors plus ET for early breast cancer which was comparable to myalgia rates reported in the control arms (MonarchE: 5.98% vs. 5.92%; PENELOPE-B: 20.2% vs. 18.5%).

3.3. Bone Pain. Data concerning bone pain emerge from 9 RCTs and affect 5–28.7% of patients receiving AIs in the adjuvant setting, while 6–14% and 16% of patients suffered from bone pain in the placebo and tamoxifen groups, respectively. The incidence of bone pain in exemestane group was 5.4–10.1%, whereas it was 5–28.7% and 5.9–10.9% in the letrozole and anastrozole groups.

Bone pain was reported by 2.2–17.2% of patients receiving CDK4/6 inhibitors [38, 44]. In accordance with arthralgia rate, the incidence of bone pain was also lower in patients receiving the combination of CDK4/6 inhibitors with ET compared to ET alone (MonarchE: 2.2% vs. 3.3%; PENELOPE-B: 17.2% vs. 19.1%).

3.4. Backpain. The percentage of backpain observed in patients treated with AIs in the adjuvant setting was 2–13.4% according to reported data emerging from 5 RCTs. The incidence of backpain for letrozole was 2–10.3% compared with 9.4–13.4% and 5.7–12.7% reported in anastrozole and exemestane arms.

Backpain was reported in 8–11.2% of patients treated with abemaciclib or palbociclib [38, 44]. Backpain was less frequently identified in patients receiving CDK4/6 inhibitors compared to the control arms (MonarchE: 8% vs. 9.7%; PENELOPE-B: 11.2% vs. 13.3%).

3.5. Arthritis. Arthritis is of major concern in patients treated with AIs, and data concerning arthritis were reported in 6 trials. In the adjuvant setting, AIs induced arthritis in 3.6–33.6% of women, which was higher than the 12% and 5–30% rates, reported in tamoxifen monotherapy and placebo groups, respectively. However, the rate of AI-induced arthritis was 6–7% in the majority of RCTs [6, 22–24] with the exception of

MA.17R trial where AI treatment for 4.5–6 years preceded the enrolment (33%) [36]. The arthritis rate caused by letrozole was 6–33%, while arthritis was reported in 6.4% of women in anastrozole group and 3.6–7% in exemestane group.

Only one trial has reported the incidence of arthritis induced by CDK4/6 inhibitors in the adjuvant setting [38]. Arthritis was identified in 0.32% of patients receiving abemaciclib plus ET in the adjuvant setting.

3.6. Osteoporosis-Osteoporotic Fractures. Data concerning osteoporosis and osteoporotic fractures were eligible in 13 and 19 of the 25 RCTs, respectively. In breast cancer patients receiving letrozole, osteoporosis was confronted in 4.8–46.8% of patients. Osteoporosis incidence was 10.9–36.4% and 10–33% in patients receiving anastrozole and exemestane, respectively. The highest rates of osteoporosis were reported in SOLE trial where about half of patients treated with letrozole for five years after prior endocrine therapy for 4–6 years developed osteoporosis. Osteoporosis incidence increased consistently with duration of AI treatment according to results of DATA, IDEAL, and GIM4 LEAD trials [29, 31, 47]. CDK4/6 inhibitors (abemaciclib) plus ET induced osteoporosis less commonly (1.61%) than ET alone (4.8–46.8%) in MonarchE trial [38].

Fractures represent one of the serious adverse events in AI treatment. In the adjuvant setting, incidence of fractures observed in patients treated with AIs ranged from 0.5% to 14%. The highest fracture rate (14%) was reported in MA.17R trial where patients received AIs for a total of 10 years while the lowest rate (0.5%) was reported in GIM4 LEAD trial where patients received AI treatment for a maximum of 5 years after treatment with tamoxifen for 2 to 3 years [36, 47]. In contrast, incidence of fracture was 1–7.7% and 1.1–9% in patients treated with tamoxifen or placebo, respectively. The incidence of fracture was greater in patients treated with AIs compared with tamoxifen treatment as shown in BIG 1–98, ATAC, TEAM, IES, ABCSG-6a, and ABCSG-8/ARNO-95 trials [5–7, 21, 22, 40, 42, 45, 46]. The duration of AI treatment seemed to correlate with fracture rate. DATA trial reported an 7.5% and 10% fracture rate in patients treated with anastrozole for 3 and 6 years, respectively [29]. Consistently, patients administered with letrozole for 2.5 and 5 years presented with fractures in a rate of 2.8% and 5% respectively in IDEAL trial [31]. SALSA trial demonstrated an increase from 4% to 6% of fracture rate in patients receiving anastrozole for 2 versus 5 years,

respectively [48, 49]. Overall, letrozole induced fractures in 0.5–14% of patients, whereas the same rates were 0.8–11% and 4–5% for anastrozole and exemestane population.

3.7. Carpal Tunnel Syndrome. Carpal tunnel syndrome was reported in 0–3% of patients treated with AIs in the adjuvant setting in contrast with 0.2–1% incidence reported in tamoxifen arms according to data reported in 4 RCTs. There are no data of the incidence of carpal tunnel syndrome in patients receiving CDK4/6 inhibitors in the adjuvant setting.

4. Discussion

Aromatase inhibitor-induced musculoskeletal syndrome (AIMSS) has emerged as a major cause of treatment discontinuation in hormone receptor-positive patients treated with AIs. In our systematic review of phase III RCTs, arthralgias were reported in 13.2 to 68.7% of patients receiving AIs for early-stage breast cancer, while arthralgias induced by CDK4/6 inhibitors occurred in a much lower rate [20.5–41.2%]. Pooled analysis of three trials evaluating CDK4/6 inhibitors plus ET in the adjuvant setting demonstrated an odds ratio of arthralgia in favor of the population receiving CDK4/6 inhibitors (OR: 0.70; 95% CI: 0.56–0.87; $P < 0.05$) although the populations included were quite heterogeneous. Bone pain (5–28.7% vs. 2.2–17.2%), back pain (2–13.4% vs. 8–11.2%), and arthritis (3.6–33.6% vs. 0.32%) were reported less frequently in patients receiving the combination of CDK4/6 inhibitors with ET. Our results are consistent with data emerging from previous studies. Crew et al. reported a 47% rate of AI-related joint pain and 44% rate of joint stiffness in postmenopausal women with early-stage breast cancer [8]. Consistently, 45% of women with early-stage breast cancers experienced joint symptoms according to results from COBRA trial [50]. Median time to onset of symptoms was 1.6 months although joint symptoms could appear as early as a few days after initiation of treatment [50]. Laroche et al. reported an initial appearance of joint pain after 6 weeks of treatment and a consequent more diffuse pain after 12 months of treatment [51]. Whatever the time course, AI-induced musculoskeletal syndrome remains of major clinical significance in women with breast cancer.

AIs may lead to joint symptoms via three different mechanisms. Estrogen deprivation seems to be the most likely mechanism of AIMSS [52]. Treatment with AIs results in a decrease in serum estrogen levels below postmenopausal levels. The expression of the two estrogen receptors alpha and beta ($ER\alpha$ and $ER\beta$) in human articular cartilage provides evidence that estrogens modulate the metabolism of chondrocytes [53]. Concentrations of $ER\alpha$ and $ER\beta$ receptors are increased in men, and thus, male joints may be more protected against the development of arthritis [53]. Animal studies demonstrated that estrogen deficiency may accelerate cartilage turnover and increase cartilage surface erosion [54]. Exogenous estrogen or SERM administration suppresses the progression of cartilage erosion exerting a chondroprotective effect on articular cartilage. Moreover,

hormone replacement therapy results in a reduction up to three-fold of osteoarthritis incidence [55, 56]. In addition, estrogen has direct effects on opioid pain fibers in the central nervous system [57]. Estrogen receptors are localized in opioid-containing neurons in the spinal cord and brain. Apart from their role in central nervous system, estrogens enhance neural transmission of peripheral nociceptive input by inducing an inflammatory environment within the joint. As a result, transmission of stimuli produced from articular structures is facilitated via estrogen mediation.

The second mechanism of AI-induced arthralgia might implicate an autoimmune process [52]. Morel et al. described a case of rheumatoid arthritis in a woman treated with exemestane [58]. Moreover, AI treatment may lead to autoimmune diseases in patients with breast cancer, including rheumatoid arthritis, subacute cutaneous lupus erythematosus (SCLE), and vasculitis [59]. This could be due to AI-induced inhibition of differentiation of naïve T-cells to regulatory T-cells and increased interferon- γ (IFN- γ) and interleukin-12 (IL-12) cytokine levels. In some cases, autoimmune disorders including arthralgias reversed upon AI cessation, along with a decrease in autoantibody levels, such as antinuclear antibodies (ANA) and rheumatoid factor (RF) [60]. The last and less likely mechanism of AI-induced musculoskeletal syndrome is through a direct off target effect of the AI medication or one of its metabolites [52].

CDK4/6 inhibitors have been widely applied in everyday clinical practice in patients with HR-positive disease. Cyclin-dependent kinase 4 or 6 (CDK4/6) modulates cell cycle progression to the S phase via catalyzing retinoblastoma (RB) protein hyperphosphorylation [12]. In the hypophosphorylated state, RB exerts a repressive effect on the E2F family of transcription factors blocking cell cycle progression through the G1-S checkpoint. In response to mitogenic signals, including ER pathway, cyclin D associates with the protein kinases CDK4 and CDK6, and the cyclin D-CDK4/6 complex subsequently phosphorylates the RB protein. Phosphorylation induces structural changes in RB protein rendering it unable to interact with E2F transcription factors. CDK4/6 inhibitors restore the onco-suppressive effect of RB by preventing its hyperphosphorylation by CDK4/6 kinases.

The mechanism through which CDK4/6 inhibitors might reduce the rate of AIMSS remains unclear. Handschick et al. demonstrated that CDK6 physically and functionally interact with NF- κ B subunit p65 [61]. Aberrant CDK6 expression contributes to NF- κ B p65 phosphorylation and NF- κ B-induced gene expression. NF- κ B is activated upon stimulation from proinflammatory cytokines, such as interleukin-1 (IL-1) or tumor necrosis factor alpha (TNF- α). It was shown that 34–45% of IL-1-induced genes required CDK4 or CDK6, while RNAi-mediated knockdown of CDK6 suppressed several IL-1-induced genes such as IL-8, IL-6, and NFKB1A [61]. Moreover, CDK6 colocalized with NF- κ B p65 subunit at several binding sites modulating the expression of many NF- κ B target genes. CDK4/6 inhibitors might attenuate CDK6-dependent inflammatory gene expression and the development of an intraarticular inflammatory microenvironment. The inhibition of AI-

induced inflammation by CDK4/6 inhibitors could contribute to the decreased arthralgia rate observed in this population.

CDK4/6 inhibitors reinstate the suppressive effect of RB on the E2F family of transcription factors. Wang et al. demonstrated that E2F2 regulates the inflammation produced via STAT1 and PI3K/AKT/NF- κ B pathways in a rheumatoid arthritis animal model [62]. Indeed, NF- κ B associates with the promoter region of E2F2, and activated E2F2 subsequently binds to the promoter of IL-6, which in turn leads to the development of arthritis. siRNA-mediated knockdown of E2F2 attenuates the expression of inflammatory cytokines in rheumatoid arthritis synovial fibroblasts. E2F2 regulates nuclear translocation of STAT1 and activation of PI3K/AKT/NF- κ B pathway, inhibiting the expression of inflammatory cytokines such as IL-1 and TNF- α . This effect of E2F2 is further supported by the fact that E2F2 is overexpressed in RA synovial tissues [62]. CDK4/6 inhibitors might suppress E2F2 through an RB-dependent way and thus inhibit the hyperplasia of RA synovial fibroblasts and joint damage caused by E2F2-induced inflammatory factors. Tomita et al. reported a decrease in cartilage erosion by infiltrating synovium upon transfection with E2F decoy oligodeoxynucleotides (ODN) [63]. The production of IL-1, IL-6, and MMP-1 proinflammatory factors was also impaired by E2F decoy ODN. CDK4/6 inhibitors might have a similar protective function against articular cartilage invasion.

5. Conclusion

Overall, we report a decreased incidence of AI-induced arthralgia in postmenopausal breast cancer patients treated with AI and CDK4/6 inhibitor combination in the adjuvant setting. CDK4/6 inhibitors might have a protective effect against joint inflammation and arthralgia occurrence although the exact mechanism remains unknown. Ongoing Phase III trials of CDK4/6 inhibitors in the adjuvant setting remain to address this issue.

Data Availability

The data supporting our findings can be found in PubMed MEDLINE bibliographical and ClinicalTrial.gov database.

Conflicts of Interest

MAD has received honoraria from participation in advisory boards from Amgen, Bristol-Myers-Squibb, Celgene, Janssen, Takeda. FZ has received honoraria for lectures and has served in an advisory role for Astra-Zeneca, Daiichi, Eli-Lilly, Merck, Novartis, Pfizer, and Roche. Evangelos Terpos received honoraria from Amgen, Astra/Zeneca, Bristol Myers Squibb, Eusa Pharma, GSK, Integris Pharma, Janssen, Pfizer, Sanofi, and Takeda, research grants from Amgen, GSK, Janssen, Sanofi and Takeda, and travel grants from Amgen, Eusa Pharma and Takeda. The remaining authors declare that they have no conflicts of interest.

Authors' Contributions

Angeliki Andrikopoulou, Efthymia Skafida, Christos Markellos, and Moustafa S contributed data curation. Angeliki Andrikopoulou, Efthymia Skafida, Christos Markellos, and Moustafa S contributed formal analysis. Angeliki Andrikopoulou, Efthymia Skafida, Christos Markellos, and Moustafa S performed investigation. Meletios-Athanasios Dimopoulos and Flora Zagouri performed project administration; Pectasides D, Dimopoulos MA, Zagouri F, Vasilopoulos D, Terpos E. Visualization, Flora Zagouri, Dimopoulos MA, and Vassilopoulos D did supervision. Angeliki Andrikopoulou and Efthymia Skafida wrote the original draft. Angeliki Andrikopoulou, Efthymia Skafida, and Terpos E wrote the article, and reviewed and edited the article. All the authors have read and approved the final manuscript. All authors agree with the content, and all give consent to submit the manuscript in the current form. FZ is the corresponding author and guarantor of the review. Efthymia Skafida and Angeliki Andrikopoulou contributed equally to this work.

Acknowledgments

This study was supported by a non-profit organization of Greek Society of Cancer Biomarkers and Targeted Therapy. The authors have no conflicts of interest that are directly relevant to the content of this article.

References

- [1] Cancer Today, "Cancer today," 2020, <https://gco.iarc.fr/today/online-analysis-multi-bars>.
- [2] Survival Rates for Breast Cancer, "Survival rates for breast cancer," 2020, <https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-survival-rates.html>.
- [3] N. Howlader, S. F. Altekruse, C. I. Li et al., "US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status," *Journal of the National Cancer Institute*, vol. 106, no. 5, Article ID dju055, 2014.
- [4] N. Howlader, K. A. Cronin, A. W. Kurian, and R. Andridge, "Differences in breast cancer survival by molecular subtypes in the United States," *Cancer Epidemiology, Biomarkers & Prevention*, vol. 27, no. 6, pp. 619–626, 2018.
- [5] M. M. Regan, K. N. Price, A. Giobbie-Hurder, B. Thürlimann, and R. D. Gelber, "Interpreting breast international group (BIG) 1-98: a randomized, double-blind, phase III trial comparing letrozole and tamoxifen as adjuvant endocrine therapy for postmenopausal women with hormone receptor-positive, early breast cancer," *Breast Cancer Research*, vol. 13, no. 3, 2011.
- [6] C. J. Van De Velde, D. Rea, C. Seynaeve et al., "Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial," *The Lancet*, vol. 377, no. 9762, pp. 321–331, 2011.
- [7] A. Howell, J. Cuzick, M. Baum, A. Buzdar, M. Dowsett, and J. F. Forbes, "Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer," *Lancet*, vol. 365, no. 9453, pp. 60–62, 2005.

- [8] K. D. Crew, H. Greenlee, J. Capodice et al., "Prevalence of joint symptoms in postmenopausal women taking aromatase inhibitors for early-stage breast cancer," *Journal of Clinical Oncology*, vol. 25, no. 25, pp. 3877–3883, 2007.
- [9] D. Hong, L. Bi, J. Zhou et al., "Incidence of menopausal symptoms in postmenopausal breast cancer patients treated with aromatase inhibitors," *Oncotarget*, vol. 8, no. 25, pp. 40558–40567, 2017.
- [10] N. L. Henry, F. Azzouz, Z. Desta et al., "Predictors of aromatase inhibitor discontinuation as a result of treatment-emergent symptoms in early-stage breast cancer," *Journal of Clinical Oncology*, vol. 30, no. 9, pp. 936–942, 2012.
- [11] Q. Shi, S. H. Giordano, H. Lu, A. K. Saleeba, D. Malveaux, and C. S. Cleeland, "Anastrozole-associated joint pain and other symptoms in patients with breast cancer," *The Journal of Pain*, vol. 14, no. 3, pp. 290–296, 2013.
- [12] C. G. Murphy and M. N. Dickler, "The role of CDK4/6 inhibition in breast cancer," *The Oncologist*, vol. 20, no. 5, pp. 483–490, 2015.
- [13] A. Andrikopoulou, O. Fiste, M. Lontos, M. A. Dimopoulos, and F. Zagouri, "Aromatase and CDK4/6 inhibitor-induced musculoskeletal symptoms: a systematic review," *Cancers*, vol. 13, no. 3, pp. 465–516, 2021.
- [14] A. Liberati, D. G. Altman, J. Tetzlaff et al., "The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration," *Journal of Clinical Epidemiology*, vol. 62, no. 10, pp. e1–e34, 2009.
- [15] M. Gnant, G. Pfeiler, P. C. Dubsy et al., "Adjuvant denosumab in breast cancer (ABCSCG-18): a multicentre, randomised, double-blind, placebo-controlled trial," *The Lancet*, vol. 386, no. 9992, pp. 433–443, 2015.
- [16] C. Markopoulos, E. Tzoracoleftherakis, A. Polychronis et al., "Management of anastrozole-induced bone loss in breast cancer patients with oral risedronate: results from the ARBI prospective clinical trial," *Breast Cancer Research*, vol. 12, no. 2, p. R24, 2010.
- [17] N. D. Wagner-Johnston, J. A. Sloan, H. Liu et al., "5-year follow-up of a randomized controlled trial of immediate versus delayed zoledronic acid for the prevention of bone loss in postmenopausal women with breast cancer starting letrozole after tamoxifen: N03CC (Alliance) trial," *Cancer*, vol. 121, no. 15, pp. 2537–2543, 2015.
- [18] G. K. Ellis, H. G. Bone, R. Chlebowski et al., "Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer," *Journal of Clinical Oncology*, vol. 26, no. 30, pp. 4875–4882, 2008.
- [19] C. Van Poznak, R. A. Hannon, J. R. Mackey et al., "Prevention of aromatase inhibitor-induced bone loss using risedronate: the SABRE trial," *Journal of Clinical Oncology*, vol. 28, no. 6, pp. 967–975, 2010.
- [20] H. Takei, S. Ohsumi, K. Shimozuma et al., "Health-related quality of life, psychological distress, and adverse events in postmenopausal women with breast cancer who receive tamoxifen, exemestane, or anastrozole as adjuvant endocrine therapy: national Surgical Adjuvant Study of Breast Cancer 04 (N-SAS BC 04)," *Breast Cancer Research and Treatment*, vol. 133, no. 1, pp. 227–236, 2012.
- [21] M. Colleoni, A. Giobbie-Hurder, M. M. Regan et al., "Analyses adjusting for selective crossover show improved overall survival with adjuvant letrozole compared with tamoxifen in the BIG 1-98 study," *Journal of Clinical Oncology*, vol. 29, no. 9, pp. 1117–1124, 2011.
- [22] M. G. M. Derks, E. J. Blok, C. Seynaeve et al., "Adjuvant tamoxifen and exemestane in women with postmenopausal early breast cancer (TEAM): 10-year follow-up of a multicentre, open-label, randomised, phase 3 trial," *The Lancet Oncology*, vol. 18, no. 9, pp. 1211–1220, 2017.
- [23] P. E. Goss, J. N. Ingle, K. I. Pritchard et al., "Exemestane versus anastrozole in postmenopausal women with early breast cancer: NCIC CTG MA.27 - a randomized controlled phase III trial," *Journal of Clinical Oncology*, vol. 31, no. 11, pp. 1398–1404, 2013.
- [24] P. E. Goss, J. N. Ingle, S. Martino et al., "Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17," *Journal of the National Cancer Institute: Journal of the National Cancer Institute*, vol. 97, no. 17, pp. 1262–1271, 2005.
- [25] E. P. Mamounas, B. Lembersky, J. H. Jeong et al., "Nsbp B-42: a clinical trial to determine the efficacy of five years of letrozole compared with placebo in patients completing five years of hormonal therapy consisting of an aromatase inhibitor (AI) or tamoxifen followed by an AI in prolonging disease-free survival in postmenopausal women with hormone receptor-positive breast cancer," *Clinical Breast Cancer*, vol. 7, no. 5, pp. 416–421, 2006.
- [26] E. P. Mamounas, H. Bandos, B. C. Lembersky et al., "Use of letrozole after aromatase inhibitor-based therapy in postmenopausal breast cancer (NRG Oncology/NSABP B-42): a randomised, double-blind, placebo-controlled, phase 3 trial," *The Lancet Oncology*, vol. 20, no. 1, pp. 88–99, 2019.
- [27] P. C. Dubsy, R. Jakesz, B. Mlineritsch et al., "Tamoxifen and anastrozole as a sequencing strategy: a randomized controlled trial in postmenopausal patients with endocrine-responsive early breast cancer from the Austrian Breast and Colorectal Cancer Study Group," *Journal of Clinical Oncology*, vol. 30, no. 7, pp. 722–728, 2012.
- [28] I. Smith, D. Yardley, H. Burris et al., "Comparative efficacy and safety of adjuvant letrozole versus anastrozole in postmenopausal patients with hormone receptor-positive, node-positive early breast cancer: final results of the randomized phase III femara versus anastrozole clinical evaluation (FACE) trial," *Journal of Clinical Oncology*, vol. 35, no. 10, pp. 1041–1048, 2017.
- [29] V. C. G. Tjan-Heijnen, I. E. G. van Hellemond, P. G. M. Peer et al., "Extended adjuvant aromatase inhibition after sequential endocrine therapy (DATA): a randomised, phase 3 trial," *The Lancet Oncology*, vol. 18, no. 11, pp. 1502–1511, 2017.
- [30] S. De Placido, C. Gallo, M. De Laurentiis et al., "Adjuvant anastrozole versus exemestane versus letrozole, upfront or after 2 years of tamoxifen, in endocrine-sensitive breast cancer (FATA-GIM3): a randomised, phase 3 trial," *The Lancet Oncology*, vol. 19, no. 4, pp. 474–485, 2018.
- [31] E. J. Blok, J. R. Kroep, E. Meershoek-Klein Kranenbarg et al., "Optimal duration of extended adjuvant endocrine therapy for early breast cancer; results of the IDEAL trial (BOOG 2006-05)," *Journal of the National Cancer Institute: Journal of the National Cancer Institute*, vol. 110, no. 1, pp. 40–48, 2018.
- [32] M. Colleoni, W. Luo, P. Karlsson et al., "Extended adjuvant intermittent letrozole versus continuous letrozole in postmenopausal women with breast cancer (SOLE): a multicentre, open-label, randomised, phase 3 trial," *The Lancet Oncology*, vol. 19, no. 1, pp. 127–138, 2018.
- [33] T. Aihara, Y. Takatsuka, S. Ohsumi et al., "Phase III randomized adjuvant study of tamoxifen alone versus sequential

- tamoxifen and anastrozole in Japanese postmenopausal women with hormone-responsive breast cancer: N-SAS BC03 study,” *Breast Cancer Research and Treatment*, vol. 121, no. 2, pp. 379–387, 2010.
- [34] M. Ruiz-Borrego, A. Guerrero-Zotano, B. Bermejo et al., “Phase III evaluating the addition of fulvestrant (F) to anastrozole (A) as adjuvant therapy in postmenopausal women with hormone receptor-positive HER2-negative (HR+/HER2-) early breast cancer (EBC): results from the GEICAM/2006–10 study,” *Breast Cancer Research and Treatment*, vol. 177, no. 1, pp. 115–125, 2019.
- [35] S. R. D. Johnston, N. Harbeck, R. Hegg et al., “Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2-, node-positive, high-risk, early breast cancer (monarchE),” *J Clin Oncol. September*, vol. 38, no. 34, pp. 3987–3998, 2020.
- [36] P. E. Goss, J. N. Ingle, K. I. Pritchard et al., “Extending aromatase-inhibitor adjuvant therapy to 10 years,” *New England Journal of Medicine*, vol. 375, no. 3, pp. 209–219, 2016.
- [37] E. L. Mayer, A. C. Dueck, M. Martin et al., “Palbociclib with adjuvant endocrine therapy in early breast cancer (PALLAS): interim analysis of a multicentre, open-label, randomised, phase 3 study,” *The Lancet Oncology*, vol. 22, no. 2, pp. 212–222, 2021.
- [38] Clinicaltrials.Gov, “Endocrine therapy with or without abemaciclib (LY2835219) following surgery in participants with breast cancer - study results - ClinicalTrials.gov,” 2021, <https://clinicaltrials.gov/ct2/show/results/NCT03155997>.
- [39] F. Boccardo, A. Rubagotti, M. Puntoni et al., “Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: preliminary results of the Italian Tamoxifen Anastrozole Trial,” *Journal of Clinical Oncology*, vol. 23, no. 22, pp. 5138–5147, 2005.
- [40] R. Jakesz, W. Jonat, M. Gnant et al., “Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years’ adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial,” *The Lancet*, vol. 366, no. 9484, pp. 455–462, 2005.
- [41] M. Kaufmann, W. Jonat, J. Hilfrich et al., “Improved overall survival in postmenopausal women with early breast cancer after anastrozole initiated after treatment with tamoxifen compared with continued tamoxifen: the ARNO 95 study,” *Journal of Clinical Oncology*, vol. 25, no. 19, pp. 2664–2670, 2007.
- [42] R. Jakesz, R. Greil, M. Gnant et al., “Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a,” *JNCI Journal of the National Cancer Institute*, vol. 99, no. 24, pp. 1845–1853, 2007.
- [43] E. P. Mamounas, J. H. Jeong, D. L. Wickerham et al., “Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention-to-treat analysis of the national surgical adjuvant breast and bowel project B-33 trial,” *Journal of Clinical Oncology*, vol. 26, no. 12, pp. 1965–1971, 2008.
- [44] S. Loibl, F. Marmé, M. Martin et al., “Palbociclib for residual high-risk invasive HR-positive and HER2-negative early breast cancer—the penelope-B trial,” *Journal of Clinical Oncology*, vol. 39, no. 14, pp. 1518–1530, 2021.
- [45] Arimidex Tamoxifen Alone or in Combination Trialists’ Group, A. Buzdar, A. Howell et al., “Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial,” *The Lancet Oncology*, vol. 7, no. 8, pp. 633–643, 2006.
- [46] R. Coombes, L. Kilburn, C. Snowdon et al., “Survival and safety of exemestane versus tamoxifen after 2-3 years’ tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial,” *The Lancet*, vol. 369, no. 9561, pp. 559–570, 2007.
- [47] L. Del Mastro, M. Mansutti, G. Bisagni et al., “Benefit from letrozole as extended adjuvant therapy after sequential endocrine therapy: a randomized, phase III study of Gruppo Italiano Mammella (GIM),” *Journal of Clinical Oncology*, vol. 37, p. 504, 2019.
- [48] Clinicaltrials.Gov, “Secondary adjuvant long term study with arimidex - study results - ClinicalTrials.gov,” 2020, <https://clinicaltrials.gov/ct2/show/results/NCT00295620>.
- [49] M. Gnant, G. Steger, R. Greil, F. Fitzal, B. Mlineritsch, and D. Manfreda, “Abstract GS3-01: a prospective randomized multi-center phase-III trial of additional 2 versus additional 5 years of anastrozole after initial 5 years of adjuvant endocrine therapy – results from 3,484 postmenopausal women in the ABCSG-16 trial,” *Cancer Research*, vol. 78, 2018.
- [50] N. L. Henry, J. T. Giles, D. Ang et al., “Prospective characterization of musculoskeletal symptoms in early stage breast cancer patients treated with aromatase inhibitors,” *Breast Cancer Research and Treatment*, vol. 111, no. 2, pp. 365–372, 2008.
- [51] F. Laroche, J. Coste, T. Medkour et al., “Classification of and risk factors for estrogen deprivation pain syndromes related to aromatase inhibitor treatments in women with breast cancer: a prospective multicenter cohort study,” *The Journal of Pain*, vol. 15, no. 3, pp. 293–303, 2014.
- [52] N. L. Henry, J. T. Giles, and V. Stearns, “Aromatase inhibitor-associated musculoskeletal symptoms: etiology and strategies for management,” *Oncology*, vol. 22, no. 12, pp. 1401–1408, 2008.
- [53] T. Ushiyama, H. Ueyama, K. Inoue, I. Ohkubo, and S. Hukuda, “Expression of genes for estrogen receptors α and β in human articular chondrocytes,” *Osteoarthritis and Cartilage*, vol. 7, no. 6, pp. 560–566, 1999.
- [54] P. Høegh-Andersen, L. B. Tankó, T. L. Andersen et al., “Ovariectomized rats as a model of postmenopausal osteoarthritis: validation and application,” *Arthritis Research and Therapy*, vol. 6, no. 2, pp. R169–R180, 2004.
- [55] M. C. Nevitt, S. R. Cummings, N. E. Lane, M. C. Hochberg, J. C. Scott, and A. R. Pressman, “Association of estrogen replacement therapy with the risk of osteoarthritis of the hip in elderly white women. Study of Osteoporotic Fractures

- Research Group,” *Archives of Internal Medicine*, vol. 156, no. 18, pp. 2073–2080, 1996.
- [56] T. D. Spector, D. Nandra, D. J. Hart, and D. V. Doyle, “Is hormone replacement therapy protective for hand and knee osteoarthritis in women?: the Chingford Study,” *Annals of the Rheumatic Diseases*, vol. 56, no. 7, pp. 432–434, 1997.
- [57] D. T. Felson and S. R. Cummings, “Aromatase inhibitors and the syndrome of arthralgias with estrogen deprivation,” *Arthritis & Rheumatism*, vol. 52, no. 9, pp. 2594–2598, 2005.
- [58] B. Morel, H. Marotte, and P. Miossec, “Will steroidal aromatase inhibitors induce rheumatoid arthritis? [1],” *Annals of the Rheumatic Diseases*, vol. 66, no. 4, pp. 557–558, 2006.
- [59] G. Zarkavelis, A. Kollas, E. Kampletsas et al., “Aromatase inhibitors induced autoimmune disorders in patients with breast cancer: a review,” *Journal of Advanced Research*, vol. 7, no. 5, pp. 719–726, 2016.
- [60] M. Laroche, M. Seniow, H. Roché, and A. Ruysen-Witrand, “Arthralgia associated with autoimmune abnormalities under aromatase inhibitor therapy: outcome after cessation of treatment,” *Journal of Rheumatology*, vol. 43, no. 10, pp. 1945–1946, 2016.
- [61] K. Handschick, K. Beuerlein, L. Jurida et al., “Cyclin-dependent kinase 6 is a chromatin-bound cofactor for NF- κ B-Dependent gene expression,” *Molecular Cell*, vol. 53, no. 2, pp. 193–208, 2014.
- [62] S. Wang, L. Wang, C. Wu, S. Sun, and J. H. Pan, “E2F2 directly regulates the STAT1 and PI3K/AKT/NF- κ B pathways to exacerbate the inflammatory phenotype in rheumatoid arthritis synovial fibroblasts and mouse embryonic fibroblasts,” *Arthritis Research and Therapy*, vol. 20, no. 1, 2018.
- [63] T. Tomita, Y. Kunugiza, N. Tomita, and H. Takano, “E2F decoy oligodeoxynucleotide ameliorates cartilage invasion by infiltrating synovium derived from rheumatoid arthritis - PubMed,” 2020, <https://pubmed.ncbi.nlm.nih.gov/16820932/>.
- [64] Clinical Trials Group, “Exemestane or anastrozole in treating postmenopausal women who have undergone surgery for primary breast cancer - study results - ClinicalTrials.gov,” 2020, <https://clinicaltrials.gov/ct2/show/results/NCT00066573>.