Identification and Management of Medical Comorbidities in Patients With HR+/HER2– Metastatic Breast Cancer Treated With CDK4/6 Inhibitors: Literature Review and Recommendations From Experts in Spain Opinion

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Abstract

Approximately one-third of patients with breast cancer have comorbidities at the time of their diagnosis. Recommendations for managing metastatic breast cancer are usually based on the results of clinical trials, which often limit patients with comorbidities. However, comorbidities greatly influence the quality of life, patient survival rate and treatment choice, particularly in older patients. The objective of this review was to identify clinically relevant comorbidities in patients with metastatic breast cancer, analyze the clinical approach to the treatment of these comorbidities, and propose recommendations from experts. An expert panel of eight medical oncologists identified seven therapeutic areas associated with the most relevant comorbidities in metastatic breast cancer: cardiovascular, gastrointestinal, endocrine/metabolic, renal, geriatric, psychological, and pain related. A clinical specialist from each therapeutic area specific to the relevant comorbidities ($n = 8$) joined the panel of experts ($n = 8$) to provide guidance on the appropriate management of these comorbidities. The specific comorbidities analyzed were hypertension, atrial fibrillation, venous thromboembolism, obesity, diabetes mellitus, cancer cachexia, chronic kidney disease, age-related disorders, arthritis, and fibromyalgia. In most cases, patients with metastatic breast cancer and medical comorbidities are polymedicated and/or vulnerable to toxicity. The oncologists provided recommendations on initial assessment and monitoring, follow-up recommendations, and warning signs and symptoms for referral to corresponding specialists based on their experience. The panel of experts also explored clinical scenarios related to each comorbidity and recommended a preferred CDK4/6 inhibitor based on available evidence regarding drug–drug interactions and potential for toxicity.

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Introduction

In 2020, female breast cancer became the most diagnosed cancer worldwide, with an estimated 2.3 million new cases that year. Female breast cancer is associated with considerable mortality, as it is the fourth leading cause of cancer death overall and the most common cause of cancer death among women. In Spain, the total number of incident cases estimated for 2024 is 36,395 cases.[1] In 2018, the worldwide age-standardized rate (ASR) of incidence for breast cancer was 46.3 per 100,000 people.[2] Breast cancer incidence rates vary by region, with the highest rates in Australia/New Zealand (ASR = 94.2), Western Europe (ASR = 92.6), Northern Europe (ASR = 90.1), and North America (ASR = 84.8), and the lowest rates in South-Central Asia (ASR = 25.9), Middle, Eastern, and Western Africa (ASR = 27.9-37.3), South-Eastern Asia (ASR = 38.1), and Central America (ASR = 38.3).[2]

Breast cancer is a heterogeneous disease with diverse clinical and pathological factors and multiple molecular subtypes that influence prognosis and therapeutic decision-making. Molecular profiling of breast cancer typically includes assessment of hormone receptor (HR) status (including both estrogen receptor [ER] and progesterone receptor status) and human epidermal growth factor receptor 2 (HER2) status. According to an analysis of data from a United States of America (USA) registry of patients with breast cancer, HR-positive (HR+)/HER2-negative (HER2–) breast cancer was the most common molecular subtype, identified in 72.7% ($n = 36,810$) of patients.[3] Although many advances have been made in diagnosis, monitoring, and treatment, an estimated 10%-41% of patients with HR+ breast cancer will develop metastases within 5-20 years of diagnosis.[4] Mortality among patients with metastatic breast cancer (mBC) is high, with only 30% of US women with mBC surviving 5 years after diagnosis, and mortality may be affected by certain factors such age, health status, and treatment. The mortality rate is increased in patients with clinical risk factors, such as comorbidities.[5]

First- and second-line therapies for patients with HR+/HER2– mBC consist of endocrine-based therapy, including aromatase inhibitors, selective ER modulators, and selective ER downregulators that are given alone or in combination with targeted therapies, depending on patient- and tumor-specific factors.[6] Cyclin-dependent kinases 4 and 6 (CDK4/6) are important regulators of cancer cell proliferation, and have been implicated in endocrine resistance in HR+ breast cancer. When CDK4/6 forms a complex with cyclin D, hyperphosphorylation and inactivation of retinoblastoma result, which prevents cell-cycle progression and leads to uncontrolled cell division. Based on this mechanism of resistance, several pharmacologic agents have been developed that target this pathway and inhibit CDK4/6. Currently, 3 CDK4/6 inhibitors are approved in Spain and the USA for the treatment of HR+/HER2– advanced or mBC: palbociclib, ribociclib, and abemaciclib.[5,7]

Approximately 32% of patients with breast cancer have comorbidities at the time of their diagnosis, with the prevalence reported to be higher (42%) in older patients.[8] Because strict eligibility criteria are employed in the clinical trial setting, inclusion of patients with medical comorbidities is often restricted, which limits the generalizability of study results to real-world patient populations.[9] This is particularly problematic for patients with mBC, many of whom have at least one medical comorbidity.[10] In a large-scale retrospective study of patients with mBC, researchers observed that roughly one-third of patients were ineligible for clinical trials based on the presence of comorbidities.[11] Additionally, certain comorbidities may predispose patients with breast cancer to an increased risk of mortality. Furthermore, comorbidities greatly influence the quality of life, patient survival rate, and treatment choice, particularly in older patients.[8] The objective of this review was to identify clinically relevant comorbidities in patients with HR+/HER2– mBC treated with CDk4/6 inhibitors, analyze the clinical approach to the treatment of these comorbidities, and propose recommendations based on the opinion of experts with clinical management of cancer patients in Spain.

Material and Methods

A targeted review of the medical literature was conducted using the Medline/PubMed databases and the Web of Science. The search was performed in July 2023, and articles in English and Spanish were included; the search strategy is summarized in Supplemental Table S1. The initial search included terms related to breast cancer (eg, advanced breast cancer, metastatic breast cancer), comorbidities (eg, comorbidity, hypertension, diabetes), and treatment (eg, CDK4/6 inhibitor, palbociclib, ribociclib, abemaciclib).

An expert panel of eight medical oncologists was recruited in Spain. Each oncologist had a minimum of 16 years of experience in the diagnosis and treatment of breast cancer and managed at least 80 patients with mBC each year. The oncologists evaluated results from the literature review and identified relevant comorbidities for patients with advanced or mBC based on their clinical expertise and experience. Other medical experts specializing in the treatment of diseases affecting the body system associated with the identified comorbidities (eg, cardiovascular and endocrine/metabolic systems) were then recruited to complete the review panel. A total of 16 medical experts (eight oncologists and eight physicians from other specialties) took part in the review. The expert panel collaborated to develop recommendations for managing the relevant identified comorbidities in patients with HR+/HER2– advanced or mBC and for recommending an appropriate CDK4/6 inhibitor based on product labelling and current scientific evidence. Consensus was reached through structured meetings organized in three phases: (1) individual analysis of comorbidities based on the results of the scientific literature and personal clinical experience; (2) collective discussion of the results and proposal of a list of the most frequent comorbidities; (3) selection of recommendations and comorbidities to be addressed in this study by voting.

Results and Discussion

Several studies have identified medical comorbidities among patients with HR+/HER2– breast cancer. In a small-scale, prospective, observational study in Italy of 54 women with HR+/HER2– advanced breast cancer who were planning to begin treatment with a CDK4/6 inhibitor plus endocrine therapy, most patients (79.3%) had at least one comorbidity of any severity. Many patients reported a clinically relevant comorbidity, defined as a disease requiring chronic medical therapy and causing moderate or greater disability, in the following body systems: vascular (46.3%; eg, hyper-

tension, atherosclerosis); upper gastrointestinal (22.2%; eg, gastroesophageal reflux disease, gastritis); psychiatric (14.8%; eg, insomnia, anxiety, depression); musculoskeletal/cutaneous (12.9%); or endocrine/metabolic/mammary (11.1%; eg, diabetes).[10] In a retrospective, population-based study of 46,027 women age 65 years and older diagnosed with stage I–III HR+/HER2– breast cancer in the USA,[12] patients had multiple comorbidities at diagnosis, with all patients having a National Cancer Institute-Charlson Comorbidity Index score of at least 3, and 39% with a score of 6 or greater. The most common baseline comorbidities reported were hypertension (73.9%), dyslipidemia (66.5%), diabetes (34.6%), and chronic obstructive pulmonary disease (19.8%); other baseline comorbidities included stroke or transient ischaemic attack (10.6%), coronary heart failure (8.2%), and chronic kidney disease (7. 9%).[12] In a USA survey of 2542 adult women who had survived breast cancer and were enrolled in a randomized dietary trial, patients were asked about baseline comorbidities across various body systems for which they were currently receiving treatment, including cardiovascular, metabolic, gastrointestinal, and musculoskeletal systems.[13] Patients most often reported obesity (25.7%), arthritis (19.3%), and hypertension (14.3%).

Based on the findings of these studies and the clinical experience and expertise of the panel, the panel focused their review on comorbidities across seven therapeutic areas: cardiovascular, digestive, endocrine/metabolic, renal, geriatric, psychological, and pain related.

Review and Management of Comorbidities by Therapeutic Area

Pharmacological treatment of patients with metastatic breast cancer requires a multidisciplinary approach focused on individualization of therapy. Below we address management for each comorbidity.[14]

Cardiovascular Comorbidities. Cardiovascular disease (CVD), defined as any disease that affects the heart or blood vessels, is the leading cause of death among women worldwide. Ischemic heart disease is the leading cause of death worldwide, accounting for 13% of all deaths.[15] Among breast cancer survivors, CVD has been identified as the most common noncancer cause of death, and studies have shown that breast cancer survivors with preexisting CVD are at a higher risk of death than those without CVD.[16] The intersection between CVD and breast cancer may be related to common risk factors, such as smoking and obesity, as well as cardiovascular toxicities associated with many breast cancer treatments.[17] In addition, patients with cardiac involvement tend to receive suboptimal cancer treatment and may have worse overall survival.[16] A small-scale retrospective study of CVD among breast cancer survivors identified hypertension as the most common cardiovascular comorbidity observed; other cardiovascular comorbidities included congestive heart failure, myocardial infarction, arrhythmias, ischaemic heart disease, and venous thrombosis.[18]

Hypertension. As hypertension is the most common cardiovascular comorbidity among patients with breast cancer,[19] oncologists may need to manage it in conjunction with breast cancer treatment. Hypertension is defined by the International Society of Hypertension as a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg, with two blood pressure readings taken at separate visits. Treatment of hypertension typically includes lifestyle modifications, such as dietary changes, exercise, and smoking cessation, as well as administration of one or more pharmacologic agents. Treatment options include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor antagonists (ARBs), beta-blockers, calcium channel blockers (CCBs), and diuretics, among others. Choice and number of pharmacologic agents may depend on baseline blood pressure, concomitant health conditions, underlying risk factors, and patient age. Expert recommendations for management of hypertension in patients with mBC are shown in Figure 1.

Atrial Fibrillation. Atrial fibrillation (AF), is the most common sustained arrhythmia in the general population, and it is associated with an increased risk of stroke, congestive heart failure, and venous thromboembolism (VTE) as well as increased morbidity and mortality. Atrial fibrillation was more prevalent in patients with cancer (3.6%).[21] Studies have shown that patients with breast cancer have a higher likelihood of being diagnosed with AF than the general population, especially during the first few months following a cancer diagnosis. The relationship between cancer and AF has not been fully elucidated but the proinflammatory state associated with cancer may play a role in the development of AF.[22] Patients with AF are typically treated with oral anticoagulants such as vitamin K antagonists (including acenocoumarol and warfarin) and nonvitamin K antagonist (apixaban, dabigatran, edoxaban, and rivaroxaban)[23]; although treatment choices also depend on other comorbidities that the patient may have.

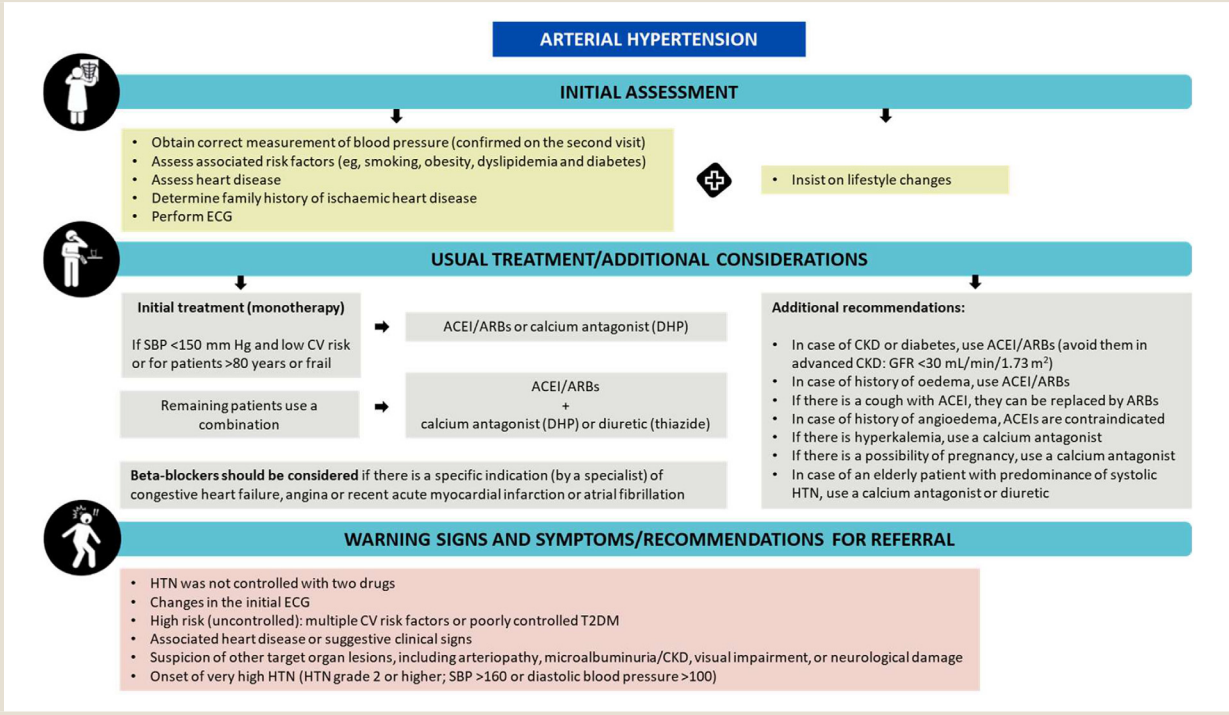
Venous Thromboembolism. Additionally, patients with breast cancer are 3 to 4 times more likely to develop VTE, especially during treatment.[24] The incidence of VTE among patients with cancer receiving outpatient treatment has been observed to be higher than in the general population, and VTE is a leading cause of death among patients with cancer.[25] VTE treatment options in patients with cancer include anticoagulants such as heparin, direct oral anticoagulant (DOACs) and vitamin K antagonists.[26]

Recommendations. Expert recommendations for the management of AF and VTE in patients with mBC are shown in Supplemental Figure 1.

Endocrine/Metabolic Comorbidities

According to the World Health Organization 2016 data, 13% of adults globally were obese (body mass index ≥30 kg/m2), and the prevalence has risen steadily since 1975.[27] Obesity has been identified as a major risk factor for several diseases, including diabetes mellitus, CVD, arthritis, and cancer. Numerous studies have shown that obesity is associated with increased incidence of patients with breast cancer, together with a greater degree of severity and mortality.[28] Furthermore, sarcopenic obesity, characterized by the combination of obesity and low skeletal muscle mass and muscle function, is an emerging problem in cancer patients.[29] In 1 observational

Figure 1 Recommendations for the management of hypertension in patients with mBC. ACEI = angiotensin converting enzyme inhibitors; ARBs = angiotensin II receptor antagonists; CKD = chronic kidney disease; CV = cardiovascular; DHP = dihydropyridine; DM2 = diabetes mellitus type 2; ECG = electrocardiogram; GFR = glomerular filtration rate; HBP = high blood pressure; HTN = hypertension; mBC = metastatic breast cancer; SBD = systolic blood pressure. Figure based on ESC/ESH 2018 guidelines for the management of arterial hypertension guidelines [20] and the authors' experiences.



study of women with breast cancer, an estimated 37% had low muscle mass at the time of breast cancer diagnosis.[30] Additionally, sarcopenic obesity is a poor prognostic factor for patients with cancer due to its association with dose-limiting toxicity to treatments, postoperative complications, deterioration of functional status, and lower rate of survival.[31]

Diabetes Mellitus. Management of type 2 diabetes mellitus (T2DM) is an important consideration for clinicians treating patients with mBC. According to a USA claims database study of 9221 women under the age of 64 years and diagnosed with breast cancer, 16% had preexisting T2DM.[32] In another USA study of postmenopausal breast cancer survivors, nearly 10% women were diagnosed with T2DM following diagnosis and treatment of breast cancer.[33] The relationship between breast cancer and T2DM is complex, with numerous mechanisms proposed, and the 2 diseases share numerous risk factors, including obesity and advanced age.[34] A study of patients with mBC showed that patients with diabetes had worse overall survival among long-term survivors.[35]

Cachexia. Cancer cachexia is a complex syndrome characterized by weight loss and muscle wasting with or without loss of fat mass related to the underlying cancer that may affect more than half of cancer patients. Patients with cancer cachexia often experience dysfunction and inflammation across multiple organ systems, and nutritional imbalances and/or malnutrition may ultimately develop. In a French study of 1903 inpatients, the prevalence of malnutrition among patients with breast cancer was reported to be 20.5%.[36] Cancer cachexia seriously threatens the lives of cancer patients, worsens the quality of life, increases functional deterioration, causes loss of autonomy and surgical complications, and exacerbates the adverse effects of chemotherapy.[37]

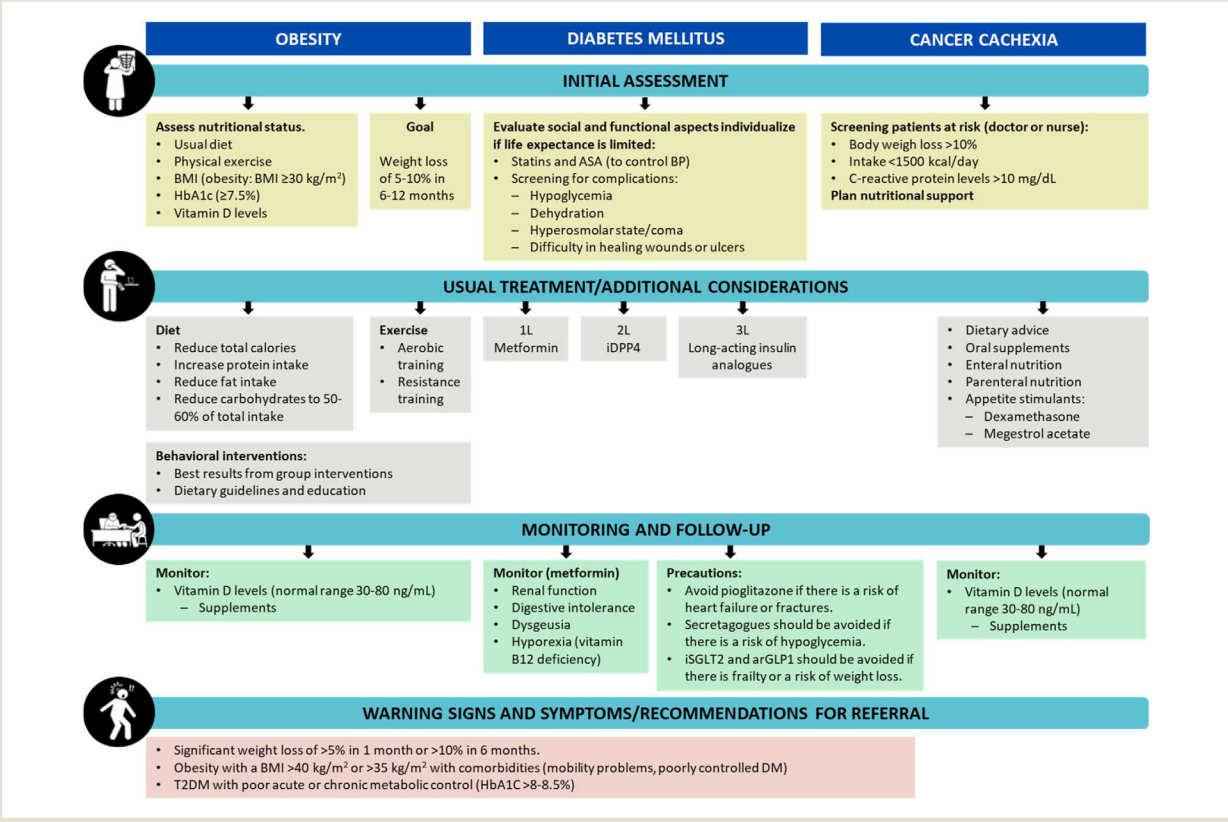
Vitamin D Deficiency. Levels of vitamin D have also been shown to impact the survival rates of patients with breast cancer.[38] A meta-analysis of 5 observational studies of vitamin D levels and breast cancer risk showed that higher levels of vitamin D were associated with lower breast cancer mortality. Risk factors for vitamin D deficiency include obesity, poor health status, and hypertension.[39]

Recommendations. Expert recommendations for the management of select endocrine/metabolic comorbidities in patients with mBC are shown in Figure 2.

Gastrointestinal Comorbidities

Liver Diseases. Patients with liver comorbidities or breast cancer that has metastasized in the liver may have poor liver function,[43] which may predispose them to experience more adverse events when

Figure 2 Recommendations for the management of select endocrine/metabolic comorbidities in patients with mBC. 1L = first-line treatment; 2L = second-line treatment; 3L = third-line treatment; arGLP1 = glucagon-like peptide 1 receptor agonists; ASA = acetylsalicylic acid; BMI = body mass index; BP = blood pressure; DM = diabetes mellitus; T2DM = diabetes mellitus type 2; HbA1c = glycated hemoglobin; iDPP4 = inhibitors of dipeptidyl peptidase 4; iSGLT2 = sodium-glucose cotransporter type 2 inhibitors; mBC = metastatic breast cancer. Figure based on recommendations from the European Society for Clinical Nutrition and Metabolism [40], the American Diabetes Association [41], an Endocrine Society Scientific Statement [42], and the authors' experiences.



treated with CDK4/6 inhibitors. For example, hepatoxicity and hypertransaminasemia are associated with hormonal treatments that are administered together with CDK4/6 inhibitors.[44–46] An asymptomatic elevation of bilirubin, glutamic oxaloacetic transaminase, and glutamic pyruvic transaminase may occur, which in most cases is reversible with dose adjustment.[25]

Dyspepsia. Dyspepsia is a mild comorbidity experienced by 4% to 9% of patients with mBC and can also be associated with treatment; it is characterized by an uncomfortable, often painful, sensation in the stomach resulting from poor digestion. Symptoms include heartburn, bloating, nausea, and vomiting. In some cases, it requires medical treatment.[47] Management of dyspepsia depends on its origin: treatment can include antacids, H-2 receptor antagonists, proton pump inhibitors (PPIs), prokinetics or antibiotics (if the cause is *Helicobacter pylori* infection).[48]

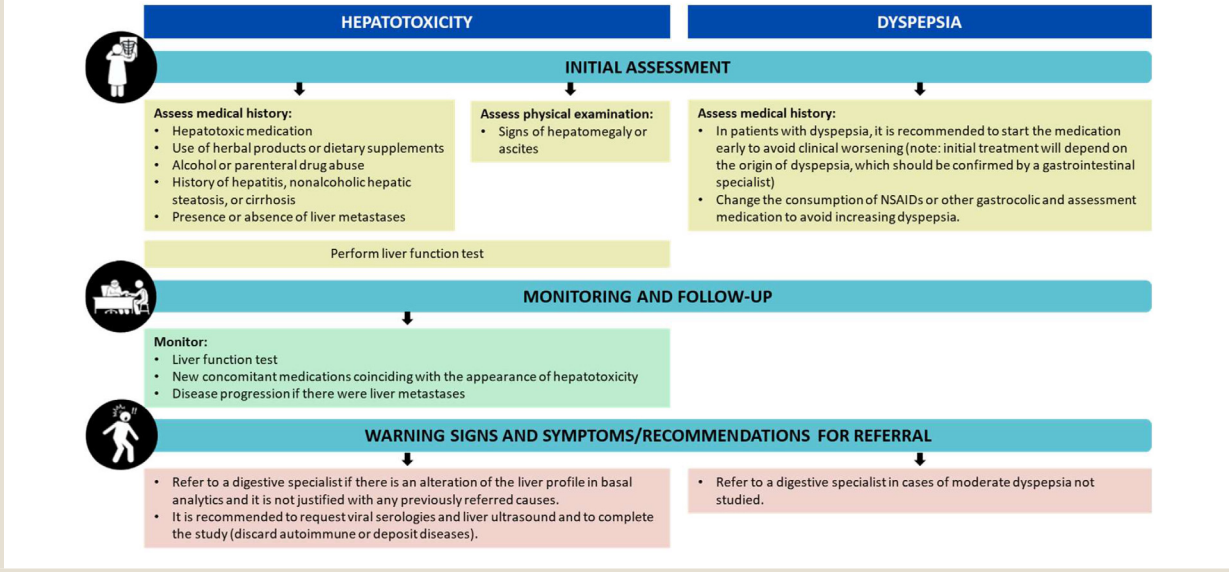
Nonalcoholic Fatty Liver Disease. Between 2.3% and 45.2% of patients with breast cancer will have nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH).[49] In addition to advanced liver disease, NAFLD is associated with metabolic diseases including impaired fasting glucose, diabetes, and cardiovascular disease, resulting in decreased overall survival.[50] The effect of NAFLD on prognosis of patients with breast cancer is unclear, with some studies reporting the presence of NAFLD is associated with a poorer prognosis[51] but others reporting that NAFLD may be associated with improved survival.[52] Lifestyle modification to achieve weight loss is the main target in the management of NAFLD.[53]

Recommendations. The expert recommendations for the management of select gastrointestinal comorbidities in patients with mBC are shown in Figure 3.

Renal Comorbidities

Chronic Kidney Disease. Chronic kidney disease (CKD) is a complex disease. The prevalence of CKD is approximately 7.2% in people aged 30 years or older and can reach 35.8% in people aged 64 years or older[55]; women experience a higher prevalence of CKD

Figure 3 Management guidelines related to select gastrointestinal comorbidities in patients with mBC. mBC = metastatic breast cancer; NSAIDs = nonsteroidal anti-inflammatory drugs. Figure based on European Association for the Study of the Liver (EASL) guidelines[54] and the authors' experiences.



than men.[56] Patients with CKD have an increased risk of cardiovascular morbidity, premature mortality, and a decrease in their quality of life.[57] CKD stratification is based upon the estimated glomerular filtration rate (GFR) and albuminuria level. In early CKD stages, treatment strategies aim to reduce the risk of CVD via nonpharmacological (diet and exercise) and pharmacological (antihypertensive and antihyperglycemic drugs) interventions.[58] In advanced stages of the disease, when kidney function is significantly impaired, patients are treated with dialysis or a transplant. Patients with CKD have worse breast cancer-specific survival than patients with other comorbidities. Furthermore, renal function deterioration is an independent poor prognostic factor, even if tumor factors and the age of the patient were considered.[59]

Kidney Transplant Patients. Patients who have undergone previous kidney transplantation may have a higher risk of developing breast cancer because of immunosuppressive treatment.[60] Furthermore, immunosuppression may increase the biological aggressiveness and mortality of breast cancer.[61]

Recommendations. Expert recommendations for the management of CKD in patients with mBC are shown in Figure 4.

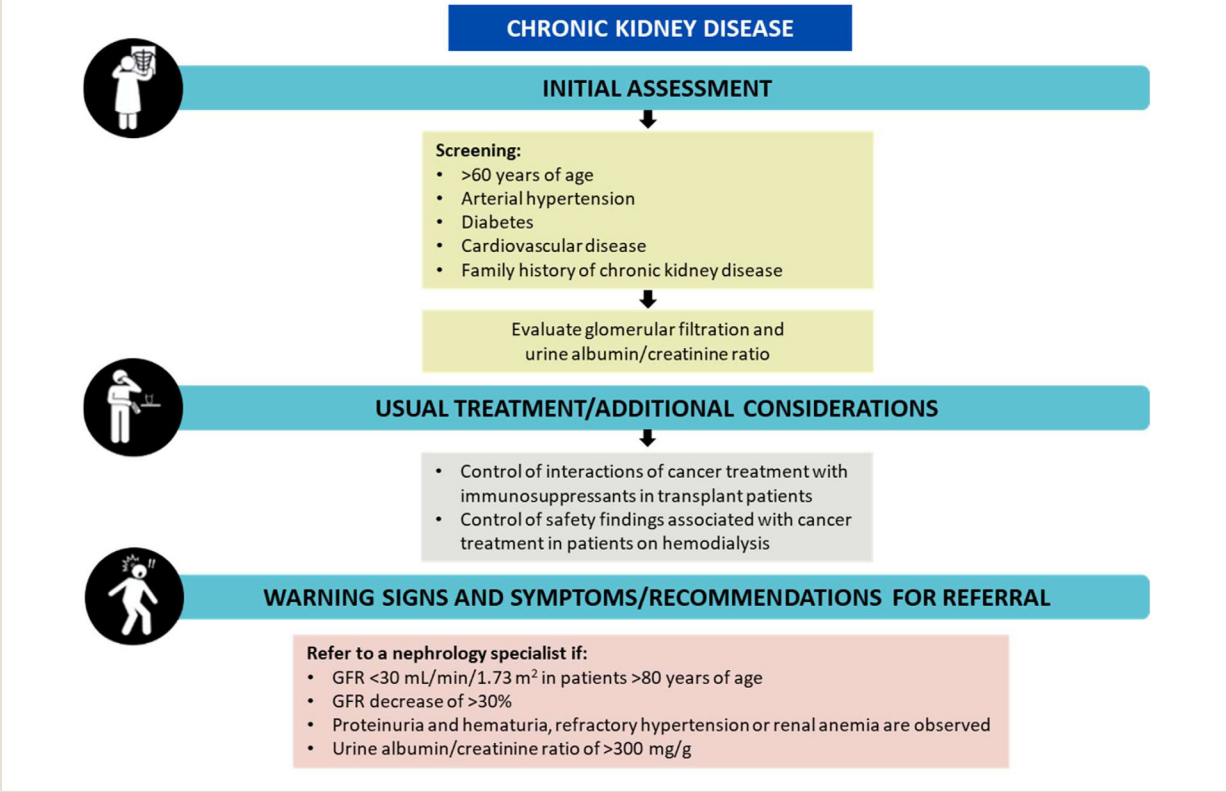
Geriatric Comorbidities and Polypharmacy

Comorbidities are common among the elderly; most people (80%) have at least one comorbid condition, with the most frequently reported comorbidities being CVD, diabetes, and arthritis.[63] Comorbidities and advanced age contribute to reduced survival. In addition, polypharmacy, functional capacity, cognitive status, and psychological factors influence therapeutic decisions. Nevertheless, older patients are underrepresented in clinical trials.[64] The International Society of Geriatric Oncology recommends using tools to assess functionality, cognitive status, and life expectancy before starting a specific cancer treatment.[65] Functional assessment is insufficient to predict mortality in older cancer patients. Therefore, it is recommended to carry out a comprehensive geriatric evaluation (including but not limited to the Mini Nutritional Assessment [MNA], Lawton Instrumental Activities of Daily Living Scale, Barthel Index, Short Physical Performance Battery [SPPB], Mini-Mental State Examination [MMSE], Montreal Cognitive Assessment [MoCA], Geriatric Depression Scale [GDS], Charlson comorbidity index [CCI], and STOPP-START toolkit) in older patients that may provide more information than a standard evaluation (an assessment that physicians perform in nongeriatric patients) and lead to a modification of the initial therapeutic approach in a notable percentage of cases.[65]

Polypharmacy. The impact of polypharmacy is also an essential factor to evaluate.[66] According to a study of 352 women with breast cancer, the frequency of polypharmacy (≥5 drugs per day) was 50% in nonelderly (aged <65 years) patients and up to 74% in elderly (aged ≥65 years) patients. The most common drugs for older populations were ACEI/ARBs, PPIs, nonsteroidal anti-inflammatory drugs, and diuretics.[67]

Sarcopenia. Sarcopenia in older patients accounts for 20%-70%. It is a progressive and generalized musculoskeletal disorder associated with a higher probability of adverse outcomes, including falls, fractures,[68] and physical dependence.[69] This comorbidity is

Figure 4 Recommendations for the management of chronic kidney disease in patients with mBC. GFR = glomerular filtration rate; mBC = metastatic breast cancer. Figure based on recommendations from consensus document from KDIGO[62] and the authors' experiences.



associated with a negative prognosis in patients with advanced or mBC.[30,70]

Recommendations. Expert recommendations for the management of select geriatric comorbidities in older patients with mBC are shown in Figure 5.

Psychological and Mental Comorbidities

Psychological Disorders. According to a retrospective database study of 279 patients with breast cancer, 28.7% had a comorbid mental health diagnosis; patients most often had depression, anxiety, and chronic pain conditions, and a small number had dementia, schizophrenia, bipolar disorder, or substance abuse conditions.[81] While some of these conditions are not strictly classified as psychological disorders, all have a considerable impact on the emotional well-being of patients and can exacerbate the psychological stress induced by cancer diagnosis and treatment. Knowing that life expectancy is shortened, the tumor has progressed, or invasive diagnostic and therapeutic procedures are necessary may cause further psychological stresses impacting compliance and the patient's coping potential. Therefore, psychological disorders may not only be associated with the cancer itself but also possibly related to its diagnosis and treatment. A meta-analysis of studies including over 280,000 patients with breast cancer demonstrated that both anxiety and depression were associated with higher recurrence and all-cause mortality.[82]

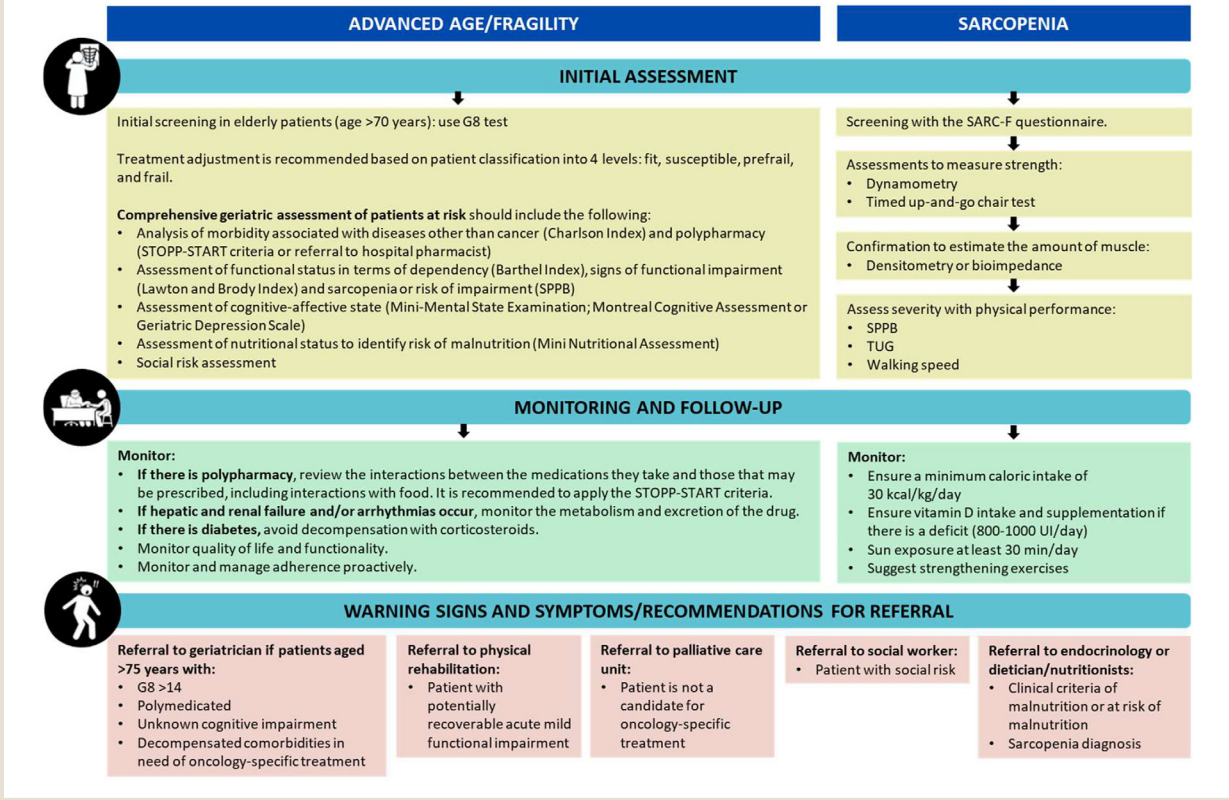
Insomnia. Additionally, more than two-thirds of women with mBC experience insomnia,[83] which harms physical and mental health and potentially also impacting survival.[84] *Recommendations:* Expert recommendations for the management of psychological comorbidities in patients with mBC are shown in Figure 6.

Pain-Related Comorbidities

Pain is not a common symptom in early breast cancer, but pain in the muscles and limbs may develop in advanced disease.[85] In a small cross-sectional study of 410 breast cancer survivors, 74% reported chronic pain.[86] Younger patients with cancer reported pain more often, and rated it as more severe.[87] In any case, poor control of cancer pain may affect a patient's quality of life.[88] Persistent pain after cancer treatment affects an estimated 25%-60% of patients.[85] Pain and numbness and reduced range of motion in the arm, hand, and shoulder may occur following surgical procedures and radiotherapy leading to chronic suffering.[89]

Fibromyalgia. In a small-scale study of 101 patients with breast cancer, the prevalence of fibromyalgia was higher than that observed

Figure 5 Expert recommendations for the management of select geriatric comorbidities in patients with mBC. G8 test = geriatric test; mBC = metastatic breast cancer; SARC-F = Strength, assistance with walking, rising from a chair, climbing stairs, and falls; SPPB = Short Physical Performance Battery; START = Screening Tool to Alert doctors to Right Treatment; STOPP = Screening Tool of Older Person's Prescriptions; TUG = Timed Up and Go. Figure based on guidelines/literature reviews for managing cancers or conditions in older patients[66,71,72] and sarcopenia[73–80], and the authors' experiences.



in the general population.[90] Fatigue and pain, the most common symptoms of fibromyalgia, may impact both functional status and quality of life for cancer patients, so achieving a correct diagnosis is highly relevant, and its management must be interdisciplinary.[90]

Osteoarthritis. Another possible cause of joint pain in patients with cancer is osteoarthritis, which was the third most common comorbidity observed among cancer survivors in 1 study.[91] Obesity and being overweight are shared risk factors for hip and knee osteoarthritis and breast cancer in postmenopausal women.[92] In addition, osteoarthritis seems to be more prevalent in breast cancer patients who develop febrile neutropenia associated with chemotherapy.[93]

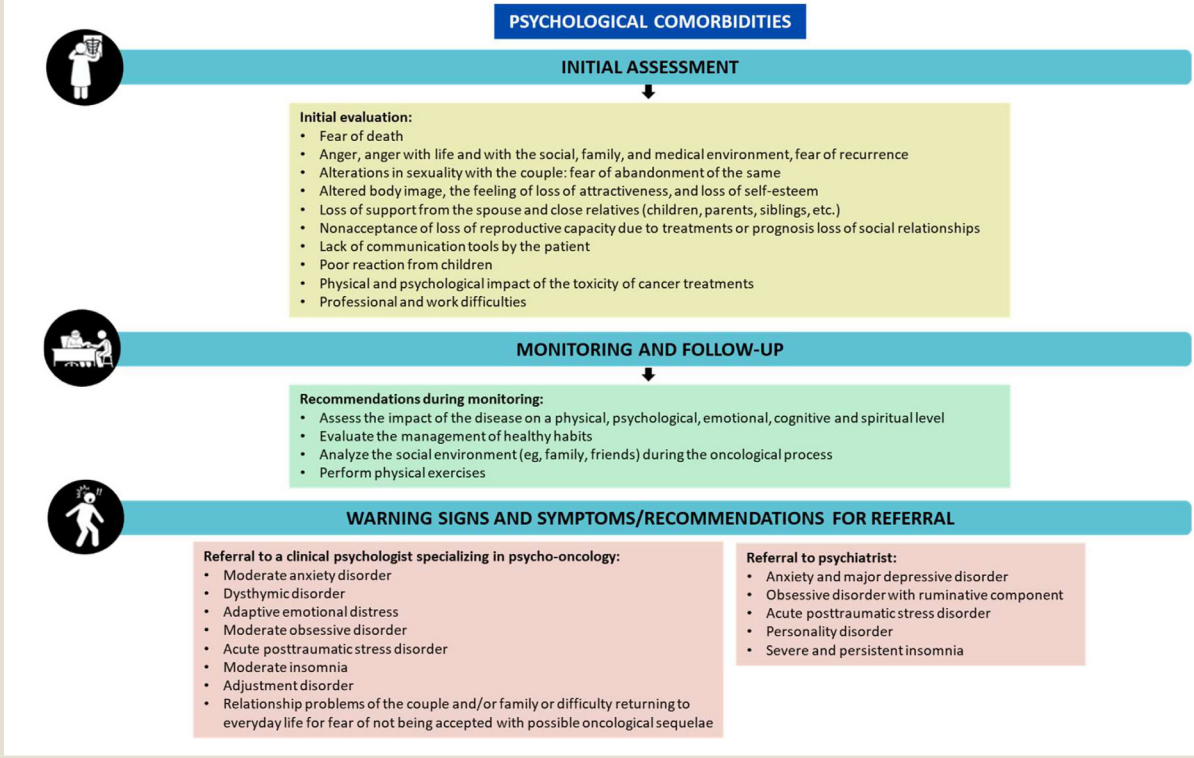
Recommendations. Expert recommendations for the management of pain and select related comorbidities in patients with mBC are shown in Figure 7.

Selection of a CDK4/6 Inhibitor. According to the European Society for Medical Oncology guidelines,[102] CDK4/6 inhibitors combined with endocrine therapy are the current established standard of care for patients with HR+/HER2– advanced breast cancer. The following recommendations are based on the evidence available from the randomized controlled trials that investigated the CDK4/6 inhibitors and the review of their approved labels. Patients' comorbidities and on-going concomitant medications should be taken into consideration when prescribing a CDK4/6 inhibitor. Prescribers should consult the approved labels[44–46] for full information, and other healthcare members (eg, pharmacists for drug–drug interactions [DDIs]) or specialists (eg, cardiologists) based on the type of comorbidities and patients.

Cardiovascular and Hematological Comorbidities

Hypertension Management and CDK4/6 Inhibitors. When treating patients with hypertension, clinicians should use caution when prescribing the CCBs diltiazem and verapamil because these drugs are moderate inhibitors of the cytochrome P450 3A4 (CYP3A4) enzyme, which metabolizes CDK4/6 inhibitors; therefore, coadministration of CYP3A4 inhibitors with any CDK4/6 inhibitor may increase the risk of toxicity.[44–46] According to the product labelling for ribociclib, coadministration with verapamil should be avoided, but if they must be used together, the dose of ribociclib should be

Figure 6 Expert recommendations for the management of psychological comorbidities in patients with mBC. mBC = metastatic breast cancer. Figure based on Spiegel et al.[84] and the authors' experiences.

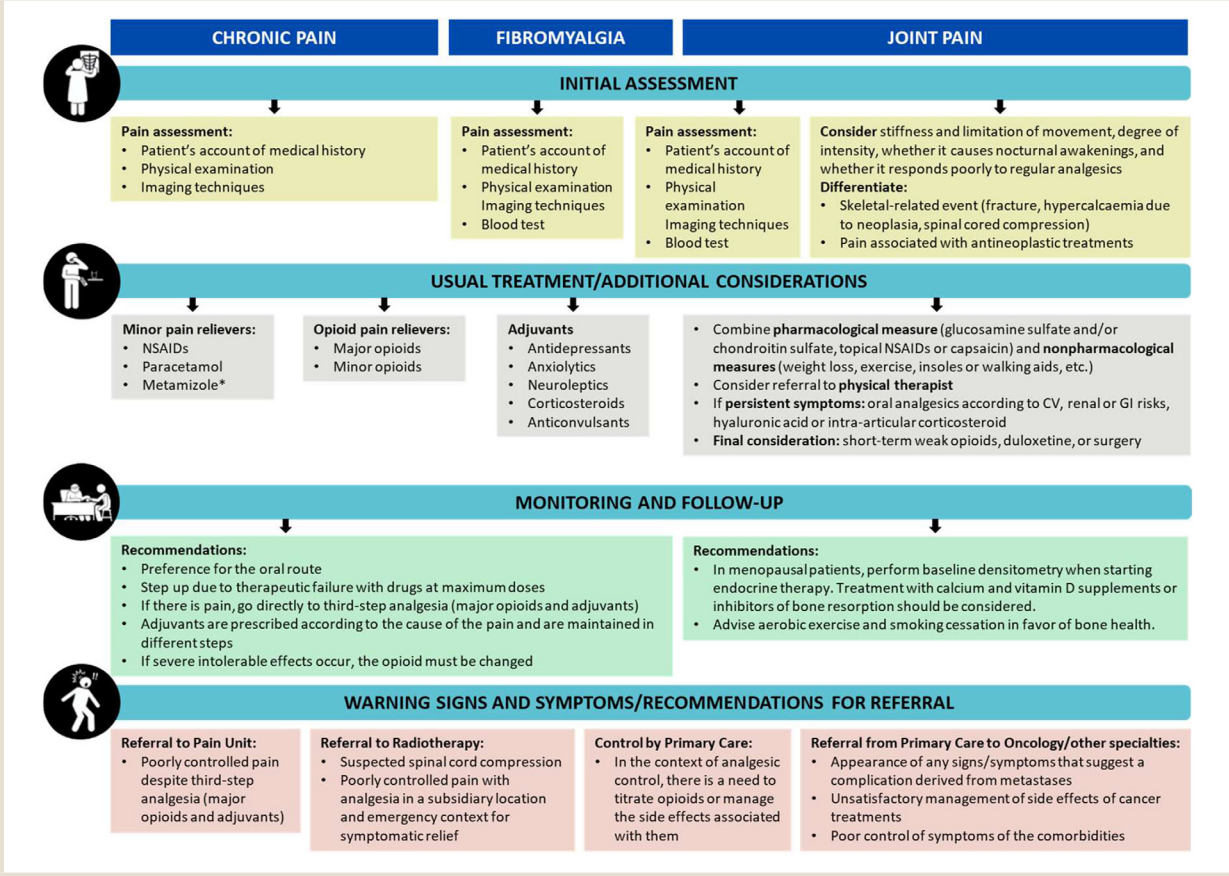


reduced.[44] Palbociclib or abemaciclib should be used with caution in combination with verapamil or diltiazem, and the patient should be monitored for signs and symptoms of toxicity, including nausea, vomiting, diarrhea, peripheral neuropathy, and neutropenia.[103]

QT Interval Considerations and CDK4/6 Inhibitors. In general, palbociclib or abemaciclib may be better choices of CDK4/6 inhibitor for patients with arrhythmias because ribociclib was shown to prolong the QT interval in clinical trials.[44,46] In contrast, neither palbociclib nor abemaciclib are associated with an increased risk of QT prolongation. The effect of palbociclib on the QT interval was evaluated in 77 patients with advanced breast cancer, and no clinically relevant change was observed.[46] Similarly, the effect of abemaciclib on QT interval was evaluated in 144 patients with advanced breast cancer, and no clinically relevant change was observed.[45] Notably, the palbociclib label mentions that the dose of sensitive CYP3A substrates such as quinidine, an antiarrhythmic agent, may need to be reduced when co-administered with palbociclib because palbociclib may increase their exposure[46]; whereas the ribociclib and abemaciclib labels recommend avoiding co-administration with such CYP3A substrates/inhibitors.[44,45]

Specific Drug Interactions With CDK4/6 Inhibitors. The use of ribociclib should be avoided in patients who already have, or who are at significant risk of developing, QTc prolongation, such as patients with long QT syndrome; with uncontrolled or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina and bradyarrhythmias; or patients with electrolyte abnormalities. According to the product labelling, an electrocardiogram (ECG) should be performed before initiating treatment with ribociclib only in patients with QTcF (QT corrected for heart rate by Fridericia's cube root formula) values <450 msec, and ECG should be repeated at approximately day 14 of the first cycle and at the beginning of the second cycle, then as clinically indicated. In case of QT prolongation observed during treatment, ribociclib treatment may need to be interrupted, reduced, or discontinued. The dose should be interrupted in the case of ECGs with QTcF interval >480 msec. If QTcF prolongation resolves to <481 msec, treatment can be restarted at a lower dose. Finally, ribociclib treatment should be discontinued with a QTcF interval >500 msec or where there is an increase of >60 msec from baseline.[44] Additionally, appropriate monitoring of serum electrolytes (including potassium, calcium, phosphorus, and magnesium) should be performed before starting treatment with ribociclib, at the beginning of the first 6 cycles, and then as clinically indicated; any serum electrolyte abnormality should be corrected before initiating treatment and during treatment with ribociclib. Further, the use of ribociclib in combination with drugs having a known potential to prolong the QT interval, such as antiarrhythmic medicinal products (including, but not limited to, amiodarone, disopyramide,

Figure 7 Expert recommendations for the management of pain and select related comorbidities in patients with mBC. CV = cardiovascular; GI = gastrointestinal; mBC = metastatic breast cancer; NSAIDs = nonsteroidal anti-inflammatory drugs. *Note: metamizole is banned in several countries. Figure based on NCCN clinical practice guidelines[94], SEOR, SEOM and ESCEO guidelines,[95,96], SERGAS protocols[97], EULAR recommendations[98,99], ESMO handbook[100], reviews into the management and treatment on pain[101], and the authors' experiences.



procainamide, quinidine and sotalol), and other medicinal products that are known to prolong the QT interval (including, but not limited to, chloroquine, halofantrine, clarithromycin, ciprofloxacin, levofloxacin, azithromycin, haloperidol, methadone, moxifloxacin, bepridil, pimozide and intravenous ondansetron) should be avoided. Furthermore, ribociclib is not recommended to be used in combination with tamoxifen; data from a clinical study in patients with breast cancer indicated that tamoxifen exposure was increased approximately 2-fold following co-administration with ribociclib.[44]

For patients receiving treatment with DOACs, such as those with AF, palbociclib may be the CDK4/6 inhibitor of choice. Apixaban and rivaroxaban, which are 2 DOACs indicated for the prevention of thrombotic events such as stroke or VTE, are metabolized via CYP3A4, and they should be used cautiously with ribociclib, which is a strong CYP3A4 inhibitor at the 600 mg dose and a moderate CYP3A4 inhibitor at the 400 mg dose.[44] Concomitant use of ribociclib and apixaban or rivaroxaban may lead to increased serum concentrations of apixaban or rivaroxaban, which may result in toxicity and increased risk of bleeding. In contrast, palbociclib is a weak, time-dependent inhibitor of CYP3A; however, the dose of sensitive CYP3A substrates may need to be reduced when co-administered with palbociclib.[46] According to the product labelling, interactions of abemaciclib, palbociclib, and ribociclib with narrow-therapeutic-index substrates of P-glycoprotein (a drug transporter), such as digoxin or dabigatran etexilate, may occur—caution and monitoring for toxicity are advised.[44–46]

Patients with cardiovascular comorbidities such as hypertension have increased risk of VTE when treated with a CDK4/6 inhibitor.[104] Both abemaciclib and palbociclib labels list VTE as a common adverse reaction (defined as a reaction occurring in 1% to 10% of patients in clinical trials).[44–46] Analyses of the USA Food & Drug Administration Adverse Event Reporting System have identified VTE as a potential class effect with all three currently approved CDK4/6 inhibitors.[105]

Hematological Toxicities With CDK4/6 Inhibitors. In terms of patients with haematological comorbidities such as anaemia associated with chronic renal disease or thrombocytopenia in chronic liver disease, palbociclib and ribociclib show high affinity for cell division protein kinase 6 (involved in haematopoiesis), increasing

the risk of haematological toxicity. Cases of neutropenia have been reported among the frequent adverse effects with the use of palbociclib. Before initiating treatment with palbociclib, confirming an absolute neutrophil count of ≥1000 mm3 and a platelet count of ≥50,000 mm3 are recommended. Grade 1-2 haematologic toxicity can be monitored by complete blood counts conducted every three months; thereafter, at the start of each cycle or if clinically indicated—but no dose adjustment is needed. If neutropenia is grade 3-4 severity, dose modifications will be necessary according to the product specifications.[46]

Similar precautions should be taken with ribociclib: a complete blood count should be performed before starting treatment and every 2 weeks for the first 2 cycles, at the beginning of the next 4 cycles, and as clinically indicated. No dose adjustment is required in grade 1 or 2 severity neutropenia, but adjustment is required in more-severe cases.[44] Despite its lower affinity for cell division protein kinase 6, abemaciclib can also be associated with the occurrence of neutropenia with some frequency, and a dose modification is recommended if toxicity is grade 3-4.[45]

Recommendations for CDK4/6 Inhibitors Selection. Palbociclib and ribociclib can be administered in patients who are receiving ACEIs, with the exception of losartan,[47] a CYP3A4 substrate that should be avoided in patients taking ribociclib[44] and abemaciclib,[45] and used with caution in patients taking palbociclib.[46] CCBs are major substrates for CYP3A4 and also moderate inhibitors; hence, clinically relevant DDIs with palbociclib, and particularly with ribociclib, are expected and concomitant administration should be avoided.[47] For example, it is recommended that nifedipine or nicardipine should be replaced with another calcium agonist in patients treated with palbociclib or abemaciclib. Similarly, the beta blockers bisoprolol and verapamil should be avoided and, instead, substituted with beta blockers such as carvedilol that have a low risk of interaction with palbociclib and ribociclib.[47]

There is a low risk of DDI between CDK4/6 inhibitors, low molecular weight heparins, and vitamin K analogues. Apixaban and rivaroxaban should be avoided in patients taking ribociclib and palbociclib owing to the high risk of DDIs.[47]

Endocrine/Metabolic Comorbidities

Specific Drug Interactions With CDK4/6 Inhibitors. Decreased appetite is a common adverse effect of palbociclib, abemaciclib, and ribociclib treatment.[44–46,106] Coadministration of metformin with either ribociclib or abemaciclib may result in elevated levels of metformin according to the product labelling for both drugs,[44,45] which may lead to toxicities such as lactic acidosis, as has been reported in 1 patient taking ribociclib with metformin.[107] In vitro data suggest that palbociclib may inhibit the uptake transporter organic cationic transporter 1 and then may increase the exposure of medical product substrates of this transporter (eg, metformin).[46]

Differentiation between the endocrine and direct effects of CDK4/6 inhibitors is necessary to manage associated toxicities. Endocrine toxicities, particularly those related to estrogen deprivation (such as genitourinary syndrome of menopause and bone density loss) during adjuvant endocrine therapy, can significantly impact quality of life and treatment adherence.[108] In addition, direct adverse effects of CDK4/6 inhibitors, such as neutropenia and diarrhea, need to be considered. Differences in toxicity profiles between abemaciclib, palbociclib, and ribociclib influence selection based on comorbidities and patient preferences.[109]

In a consensus workshop on the management of concomitant medication with palbociclib and ribociclib in breast cancer, it was concluded that palbociclib and ribociclib can be administered with insulin analogues, sulfonylureas, alpha glycosidase inhibitors, glucagon-like peptide 1 (GLP1) agonists and with some dipeptidyl peptidase OV (DPP-4) inhibitors (such as vildagliptin, alogliptin and sitagliptin).[47]

Recommendations for CDK4/6 Inhibitors Selection. A real-life study of 701 patients found that the combination of CDK4/6 inhibitors in combination with endocrine therapy in first-line treatment is effective. However, cases of endocrine resistance were identified, with tumors with primary resistance showing the worst outcomes in terms of time to treatment discontinuation and overall survival. In addition, the study data highlight no significant differences in the efficacy of second-line treatments, including taxane-based chemotherapy, capecitabine, fulvestrant, and exemestane plus everolimus. Therefore, it is essential to consider factors such as the duration of first-line treatment and the aggressiveness of metastatic disease when selecting the second-line therapy.[110]

Gastrointestinal Comorbidities

Low-grade severity gastrointestinal disorders that may occur with ribociclib and palbociclib are stomatitis, nausea, diarrhea, and vomiting.[44,46] For abemaciclib, similar gastrointestinal disorders are also common, together with dispepsia.[45] A higher risk of diarrhea has been reported with abemaciclib compared with palbociclib and ribociclib.[111]

Hepatotoxicity is listed as a common adverse reaction in the three key phase 3 clinical studies investigating the safety and efficacy of ribociclib and was observed during postmarketing experience, especially in patients with NASH.[44] Therefore, liver function tests and dose adjustments or discontinuations are required if hepatotoxicity is in the moderate to severe range.[103] Abnormalities in liver blood tests are also listed as very common side effects in the palbociclib and abemaciclib labels.[45,46] Palbociclib and abemaciclib require dose modification in cases of severe liver failure.[45,46] However, abemaciclib can interact more with medications that inhibit cytochromes or other agents with a narrow therapeutic margin due to their high affinity for plasma proteins.[45] Researchers have hypothesized that liver damage in patients taking CDK4/6 inhibitors may be related to toxic metabolites, immunogenic intermediates, or direct damage to hepatocytes.[112]

Specific Drug Interactions With CDK4/6 Inhibitors. Palbociclib, administered as a capsule, has been reported to have a moderate risk of interaction with PPIs,[46] which may be concomitantly administered in patients with dyspepsia or other gastrointestinal comorbidities.[48] Under fasting conditions, the coadministration of the PPI rabeprazole (used to treat symptoms of gastro-oesophageal reflux disease) with a single dose of palbociclib 125 mg in a capsule form, decreased the extent and rate of absorption of palbociclib.

Domperidone, an antiemetic used to manage dyspepsia, should be avoided in combination with CDK4/6 inhibitors.[113] Domperidone has a high risk of interaction with ribociclib, which could possibly increase the risk of QT prolongation.[114] *Recommendations for CDK4/6 inhibitors selection*

Palbociclib capsules are taken with a meal. However, when palbociclib is administered in the tablet form, coadministration of the PPI rabeprazole had no effect on the rate and extent of absorption of palbociclib and this formulation can be taken with or without food.

Renal Comorbidities

Tolerability of CDK4/6 Inhibitors. For patients with mild, moderate, or severe renal impairment (creatinine clearance rates of ≥15 mL/min), palbociclib has been shown to be well tolerated, and no dose adjustment is required.[46] Ribociclib and abemaciclib do not require dose adjustment in patients with mild or moderate renal impairment.[44,45] Although ribociclib has not been studied in patients with severe renal impairment, the product labelling recommends a lower starting dose.[44] Similarly, abemaciclib has not been studied in patients with severe renal impairment, and the manufacturer recommends caution and monitoring when administering the drug to this patient population.[45] It is important to note that none of the currently approved CDK4/6 inhibitors has been studied in patients on haemodialysis.[44–46] Both ribociclib and abemaciclib have been observed to increase serum creatinine (SCr) levels, although they do so through different mechanisms.[44,45] Abemaciclib increases SCr via the inhibition of renal tubular secretion transporters without affecting glomerular function (as measured by iohexol clearance).[45] Ribociclib has been shown to increase SCr via inhibition of the renal transporters organic cation transporter 2 and multidrug toxin extrusion protein 1, which are involved in active creatinine secretion from the proximal tubules; SCr increases during treatment would necessitate an extensive evaluation of renal function to exclude renal failure.[44] Based on the available evidence, palbociclib would be an appropriate CDK4/6 inhibitor for patients with any level of renal impairment not requiring haemodialysis. It should be noted that measuring serum cystatin C levels may be better at estimating GFR than SCr levels in patients with solid tumors.[115]

*Recommendations for CDK4/6 inhibitors selection*Patients who have undergone kidney transplant require immunosuppressants, some of which are sensitive CYP3A substrates with a narrow therapeutic index such as tacrolimus, everolimus, cyclosporine, or sirolimus.[46] Palbociclib is a weak, time-dependent inhibitor of CYP3A4, and ribociclib is a moderate to strong inhibitor of CYP3A4.[44,46] Concomitant use with narrow therapeutic index drugs that are substrates of CYP3A4 may necessitate dose adjustments. For example, patients who are taking palbociclib or ribociclib with the calcineurin inhibitors cyclosporin or tacrolimus for immunosuppression following a kidney transplant may require lower doses of their calcineurin inhibitor. Similarly, those who are taking palbociclib or ribociclib with the mammalian target of rapamycin inhibitor sirolimus or everolimus for prophylaxis of organ rejection in adult patients receiving a renal transplant may require a reduced dose of sirolimus or everolimus. Abemaciclib is not an inhibitor of CYP3A4 and would not require dose adjustments when used in combination with cyclosporine, tacrolimus, or everolimus.[45]

Geriatric Comorbidities

Tolerability of CDK4/6 Inhibitors. Age is associated with alterations in pharmacokinetics.[103] Since one-third of patients diagnosed with breast cancer are over 70 years of age, as the HR+/HER2– breast cancer subtype is the most common subtype in patients ≥65 years,[116] and given that this is a medically fragile population with a higher risk of adverse events owing to both their oncological disease and their age, the use and dose of CDK4/6 inhibitors must be appropriate.[103] Palbociclib, abemaciclib, and ribociclib do not require dose adjustment in patients ≥65 years of age.[44–46]

Recommendations for CDK4/6 Inhibitors Selection. Palbociclib may be a good option in polymedicated patients (>5 drugs) due to its lower incidence of clinically meaningful DDIs; this is particularly important in older patients, in whom hypoalbuminaemia, renal insufficiency, and polypharmacy frequently occur together.[103]

Psychological Comorbidities

Specific Drug Interactions With CDK4/6 Inhibitors. Certain antidepressants (eg, trazodone, mirtazapine, and escitalopram) and antipsychotics (eg, ziprasidone, aripiprazole, and haloperidol) should be avoided with palbociclib and ribociclib due to the potential for serious interactions.[47] All 3 currently approved CDK4/6 inhibitors may interact with the herbal supplement St. John's Wort, which is used to treat mild anxiety and depression.[44–46] The antidepressant nefazodone may also interact with palbociclib and ribociclib.[44,46] Ribociclib may interact with triazolam, which is used to treat sleep disturbances.[44] It has been well documented that some tricyclic antidepressants (eg, amitriptyline, maprotiline) may lead to QTc prolongation.[117] As previously mentioned, ribociclib should be avoided in patients who already have, or who are at significant risk of developing, QTc prolongation, including those receiving medicinal products known to prolong the QT interval.[46] Conversely, no clinically relevant change in QT interval has been observed in patients with advanced breast cancer receiving palbociclib or abemaciclib.[44,45]

Recommendations for CDK4/6 Inhibitors Selection. Palbociclib and abemaciclib are generally appropriate options in patients with psychological disorders but some specific interactions should be considered.

Pain-Related Comorbidities

Specific Drug Interactions With CDK4/6 Inhibitors. Following the application of radiotherapy, CDK4/6 inhibitors slow down tissue repair after the end of the treatment cycle, which may result in impaired pain relief.[118] Generally, opioids that have a low risk of interaction with palbociclib and ribociclib (considered the safest therapeutic options) are morphine, hydromorphone, tapentadol, and codeine.

Recommendations for CDK4/6 Inhibitors Selection. With ribociclib, tramadol, buprenorphine, and oxycodone may be used with caution, while fentanyl is not recommended.[47,103] In addition, the

concomitant use of ribociclib and methadone is not recommended owing to the potential of methadone to prolong the QT interval.[44] The product labelling for abemaciclib does not list any interactions with opioid pain relievers.[45]

Limitations

It is important to note that the recommendations are based on a review of the evidence from literature, expert opinion, and experience. For all these reasons, there may be biases, such as the authors' own clinical experience, access to treatments, and training. Additionally, relying on retrospective data and expert opinion introduces limitations inherent to this approach, including potential selection and recall bias. Future prospective studies are needed to validate these findings and provide robust evidence, particularly in long-term outcomes in patients with multiple comorbidities and the impact of multidisciplinary interventions. These limitations should be taken into account when interpreting the experts' findings and recommendations.

Conclusion

The expert panel involved in this review identified the main comorbidities in patients with HR+/HER2- metastatic breast cancer, based on their prevalence and their impact on therapeutic decisions and patient quality of life. Among the most relevant comorbidities are hypertension, which affects treatment tolerance; chronic kidney disease, which influences therapeutic selection; and depression, which impairs patient adherence and general well-being. The experts provided key recommendations for initial patient assessment, monitoring, and follow-up, highlighting warning signs that should lead to referral to appropriate specialists. In addition, clinical scenarios related to each comorbidity were explored, proposing a reference CDK4/6 inhibitor based on the available evidence on drug interactions and the toxicity profile of each drug.

Despite the progress, there are still areas for improvement and future research. In particular, prospective studies addressing the long-term impact of comorbidities on treatment outcomes with CDK4/6 inhibitors are needed, as well as research focused on optimizing the management of emerging comorbidities. Identifying patient subgroups who might benefit from more targeted and personalized interventions also represents an important direction for future research.

Disclosure

Carmen Hinojo: Received consulting fees and honoraria from Pfizer, Lilly and Gilead; advisory roles for Pfizer, Lilly, AstraZeneca-Daiichi -Sankyo and Seagen; travel grants from Pfizer, Roche, Novartis and AstraZeneca

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Manuel Barral: Received consulting fees and honoraria from the pharmaceutical industry, but never related with metastatic breast cancer.

María Piedra León: Received consulting fees for advisory boards from Sanofi; and has received fees for non-CME services received directly from commercial interest or their agents (eg, speakers' bureaus) and congress grants from NovoNordisk, Lilly, Pfizer, Sanofi, Astra Zeneca, Novartis and Amgen.

Susana de la Cruz: Received consulting fees and honoraria from Pfizer, Lilly, Novartis and Gilead; advisory roles for Pfizer, AstraZeneca-Daiichi -Sankyo and Seagen; travel grants from Pfizer, Novartis and AstraZeneca.

All other authors state that they have no conflicts of interest.

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References

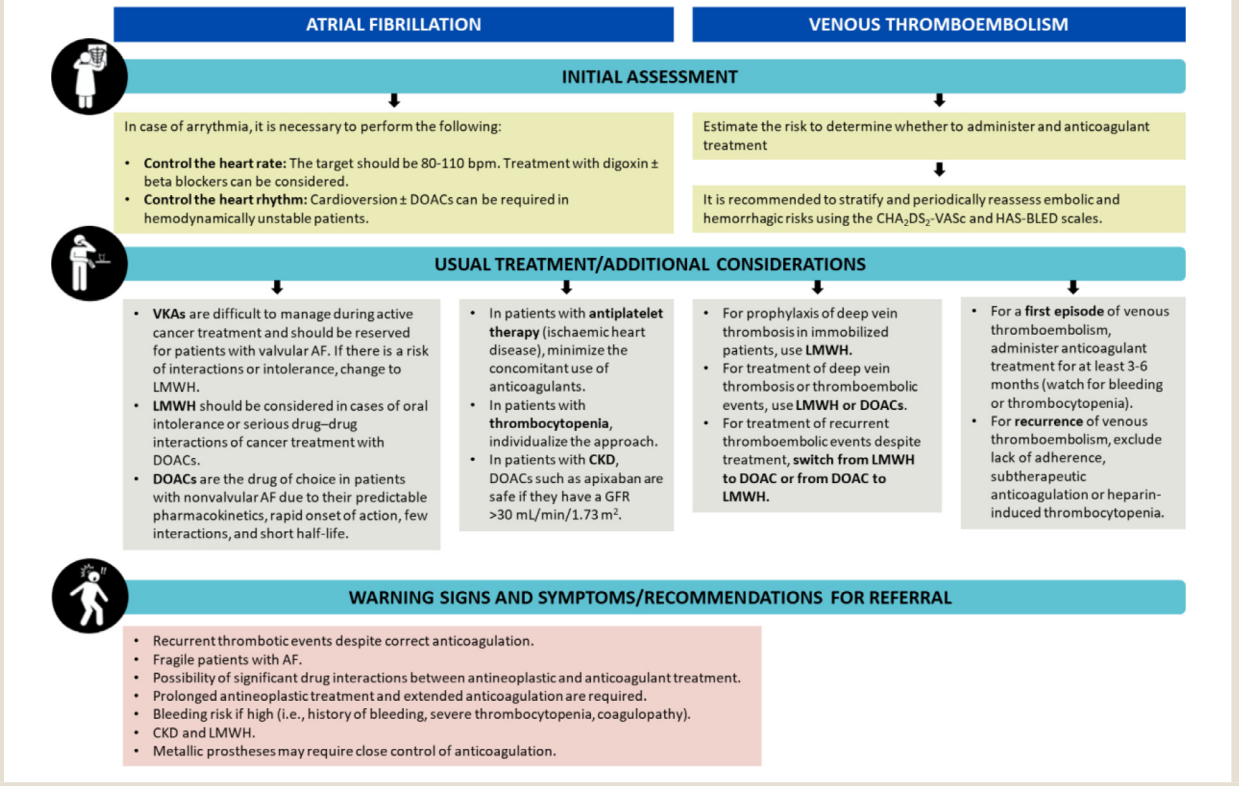
1. REDECAN. Estimaciones de la incidencia del cáncer en España, 2024. Published online 2024. Accessed June 30, 2024. https://redecan.org/storage/documents/09a96a55-6939-419d-ba3e-202d7ae76e1d.pdf.
2. Huang J, Chan PS, Lok V, et al. Global incidence and mortality of breast cancer: a trend analysis. *Aging (Albany NY)*. 2021;13(4):5748–5803. doi:10.18632/aging.202502.
3. Howlader N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J Natl Cancer Inst*. 2014;106(5):dju055. doi:10.1093/jnci/dju055.
4. Pan H, Gray R, Braybrooke J, et al. 20-year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. *N Engl J Med*. 2017;377(19):1836–1846. doi:10.1056/NEJMoa1701830.
5. Reddy S, Barkhane Z, Elmadi J, Satish Kumar L, Pugalenthi LS, Ahmad M. Cyclin-dependent kinase 4 and 6 inhibitors: a quantum leap in the treatment of advanced breast cancers. *Cureus*. 2022;14(4):e23901. doi:10.7759/cureus.23901.
6. Rugo HS, Rumble RB, Macrae E, et al. Endocrine therapy for hormone receptor-positive metastatic breast cancer: American society of clinical oncology guideline. *J Clin Oncol Off J Am Soc Clin Oncol*. 2016;34(25):3069–3103. doi:10.1200/JCO.2016.67.1487.
7. Garcia-Saenz JA, Blancas I, Echavarria I, et al. SEOM–GEICAM–SOLTI clinical guidelines in advanced breast cancer (2022). *Clin Transl Oncol*. 2023;25(9):2665–2678. doi:10.1007/s12094-023-03203-8.
8. Patnaik JL, Byers T, Diguiseppi C, Denberg TD, Dabelea D. The influence of comorbidities on overall survival among older women diagnosed with breast cancer. *J Natl Cancer Inst*. 2011;103(14):1101–1111. doi:10.1093/jnci/djr188.
9. Karim S, Xu Y, Kong S, Abdel-Rahman O, Quan ML, Cheung WY. Generalisability of common oncology clinical trial eligibility criteria in the real world. *Clin Oncol (R Coll Radiol)*. 2019;31(9):e160–e166. doi:10.1016/j.clon.2019.05.003.
10. Tagliaferri B, Mollica L, Palumbo R, et al. Health-related quality of life and clinical complexity of a real-life cohort of patients with advanced HR(+)/HER2(-) breast cancer treated with CDK4/6 inhibitors and endocrine therapy. *Drugs Context*. 2023;12:2023-1-7. doi:10.7573/dic.2023-1-7.
11. Batra A, Kong S, Cheung WY. Eligibility of real-world patients with metastatic breast cancer for clinical trials. *Breast*. 2020;54:171–178. doi:10.1016/j.breast.2020.10.005.
12. Zhou J, Cueto J, Ko NY, et al. Population-based recurrence rates among older women with HR-positive, HER2-negative early breast cancer: clinical risk factors, frailty status, and differences by race. *Breast*. 2021;59:367–375. doi:10.1016/j.breast.2021.08.005.
13. Patterson RE, Flatt SW, Saquib N, et al. Medical comorbidities predict mortality in women with a history of early stage breast cancer. *Breast Cancer Res Treat*. 2010;122(3):859–865. doi:10.1007/s10549-010-0732-3.
14. Roncato R, Gerratana L, Palmero L, et al. An integrated pharmacological counselling approach to guide decision-making in the treatment with CDK4/6 inhibitors for metastatic breast cancer. *Front Pharmacol*. 2022;13:897951. doi:10.3389/fphar.2022.897951.
15. The top 10 causes of death. Accessed June 30, 2024. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.
16. Abdel-Rahman O, Xu Y, Kong S, et al. Impact of baseline cardiovascular comorbidity on outcomes in women with breast cancer: a real-world, population-based study. *Clin Breast Cancer*. 2019;19(2):e297–e305. doi:10.1016/j.clbc.2018.12.005.
17. Mehta LS, Watson KE, Barac A, et al. Cardiovascular disease and breast cancer: where these entities intersect: a scientific statement from the american heart association. *Circulation*. 2018;137(8):e30–e66. doi:10.1161/CIR.0000000000000556.
18. Coughlin SS, Ayyala D, Majeed B, Cortes L, Kapuku G. Cardiovascular disease among breast cancer survivors. *Cardiovasc Disord Med*. 2020;2(1). doi:10.31487/j.cdm.2020.01.01.
19. Edwards BK, Noone A-M, Mariotto AB, et al. Annual Report to the Nation on the status of cancer, 1975-2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. *Cancer*. 2014;120(9):1290–1314. doi:10.1002/cncr.28509.
20. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Rev Esp Cardiol (Engl Ed)*. 2019;72(2):160. doi:10.1016/j.rec.2018.12.004.
21. Lateef N, Kapoor V, Ahsan MJ, et al. Atrial fibrillation and cancer; understanding the mysterious relationship through a systematic review. *J community Hosp Intern Med Perspect*. 2020;10(2):127–132. doi:10.1080/20009666.2020.1726571.
22. Jakobsen CB, Lamberts M, Carlson N, et al. Incidence of atrial fibrillation in different major cancer subtypes: a Nationwide population-based 12 year follow up study. *BMC Cancer*. 2019;19(1):1105. doi:10.1186/s12885-019-6314-9.
23. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the Europe. *Eur Heart J*. 2021;42(5):373–498. doi:10.1093/eurheartj/ehaa612.
24. Khan UT, Walker AJ, Baig S, Card TR, Kirwan CC, Grainge MJ. Venous thromboembolism and mortality in breast cancer: cohort study with systematic review and meta-analysis. *BMC Cancer*. 2017;17(1):747. doi:10.1186/s12885-017-3719-1.
25. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost*. 2007;5(3):632–634. doi:10.1111/j.1538-7836.2007.02374.x.
26. Falanga A, Ay C, Di Nisio M, et al. Venous thromboembolism in cancer patients: ESMO clinical practice guideline. *Ann Oncol Off J Eur Soc Med Oncol*. 2023;34(5):452–467. doi:10.1016/j.annonc.2022.12.014.
27. Obesity and overweight. Accessed June 30, 2024. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
28. Jiralerspong S, Goodwin PJ. Obesity and breast cancer prognosis: evidence, challenges, and opportunities. *J Clin Oncol Off J Am Soc Clin Oncol*. 2016;34(35):4203–4216. doi:10.1200/JCO.2016.68.4480.
29. Prado CMM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol*. 2008;9(7):629–635. doi:10.1016/S1470-2045(08)70153-0.
30. Caan BJ, Cespedes Feliciano EM, Prado CM, et al. Association of muscle and adiposity measured by computed tomography with survival in patients with nonmetastatic breast cancer. *JAMA Oncol*. 2018;4(6):798–804. doi:10.1001/jamaoncol.2018.0137.
31. Carneiro IP, Mazurak VC, Prado CM. Clinical implications of sarcopenic obesity in cancer. *Curr Oncol Rep*. 2016;18(10):62. doi:10.1007/s11912-016-0546-5.
32. Lawrence WR, Hosler AS, Gates Kuliszewski M, et al. Impact of preexisting type 2 diabetes mellitus and antidiabetic drugs on all-cause and cause-specific mortality among Medicaid-insured women diagnosed with breast cancer. *Cancer Epidemiol*. 2020;66:101710. doi:10.1016/j.canep.2020.101710.
33. Lipscombe LL, Chan WW, Yun L, Austin PC, Anderson GM, Rochon PA. Incidence of diabetes among postmenopausal breast cancer survivors. *Diabetologia*. 2013;56(3):476–483. doi:10.1007/s00125-012-2793-9.
34. Eketunde AO. Diabetes as a risk factor for breast cancer. *Cureus*. 2020;12(5):e8010. doi:10.7759/cureus.8010.
35. Cheung Y-MM, Hughes M, Harrod J, et al. The effects of diabetes and glycemic control on cancer outcomes in individuals with metastatic breast cancer. *J Clin Endocrinol Metab*. 2022;107(9):2511–2521. doi:10.1210/clinem/dgac375.
36. Hébuterne X, Lemarié E, Michallet M, de Montreuil CB, Schneider SM, Goldwasser F. Prevalence of malnutrition and current use of nutrition support in patients with cancer. *JPEN J Parenter Enteral Nutr*. 2014;38(2):196–204. doi:10.1177/0148607113502674.
37. Donohoe CL, Ryan AM, Reynolds J V. Cancer cachexia: mechanisms and clinical implications. *Gastroenterol Res Pract*. 2011;2011:601434. doi:10.1155/2011/601434.
38. Mohr SB, Gorham ED, Kim J, Hofflich H, Garland CF. Meta-analysis of vitamin D sufficiency for improving survival of patients with breast cancer. *Anticancer Res*. 2014;34(3):1163–1166.
39. Forrest KYZ, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in US adults. *Nutr Res*. 2011;31(1):48–54. doi:10.1016/j.nutres.2010.12.001.
40. Arends J, Bachmann P, Baracos V, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr*. 2017;36(1):11–48. doi:10.1016/j.clnu.2016.07.015.
41. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2022. *Diabetes Care*. 2022;45(Suppl 1):S125–S143. doi:10.2337/dc22-S009.
42. Bray GA, Heisel WE, Afshin A, et al. The science of obesity management: an endocrine society scientific statement. *Endocr Rev*. 2018;39(2):79–132. doi:10.1210/er.2017-00253.
43. Leser C, Dorffner G, Marhold M, et al. Liver function indicators in patients with breast cancer before and after detection of hepatic metastases-a retrospective study. *PLoS One*. 2023;18(3):e0278454. doi:10.1371/journal.pone.0278454.
44. Kisqali®. Technical data sheet of the medication. US Food and Drug Administration (FDA). Accessed November 3, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/ribociclib-kisqali.
45. Verzenios®. Technical data sheet of the medication. US Food and Drug Administration (FDA). Accessed November 3, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208716s006s007s008lbl.pdf.
46. Ibrance®. Technical data sheet of the medication. US Food and Drug Administration (FDA). Accessed November 3, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/palbociclib-ibrance.
47. Bellet M, Ahmad F, Villanueva R, et al. Palbociclib and ribociclib in breast cancer: consensus workshop on the management of concomitant medication. *Ther Adv Med Oncol*. 2019;11:1758835919833867. doi:10.1177/1758835919833867.
48. Gosson C, Gorard L, Goel R. Recommended management of dyspepsia in primary care. *Prescriber*. 2019;30:11–15.
49. Nseir W, Abu-Rahmeh Z, Tsipis A, Mograbi J, Mahamid M. Relationship between non-alcoholic fatty liver disease and breast cancer. *Isr Med Assoc J*. 2017;19(4):242–245.
50. Musso G, Gambino R, Cassader M, Pagano G. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. *Ann Med*. 2011;43(8):617–649. doi:10.3109/07853890.2010.518623.

51. Lee J Il, Yu J-H, Anh SG, Lee HW, Jeong J, Lee KS. Aromatase inhibitors and newly developed nonalcoholic fatty liver disease in postmenopausal patients with early breast cancer: a propensity score-matched cohort study. *Oncologist*. 2019;24(8):e653–e661. doi:10.1634/theoncologist.2018-0370.
52. Taroeno-Hariadi KW, Putra YR, Choridah L, Widodo I, Hardianti MS, Aryandono T. Fatty liver in hormone receptor-positive breast cancer and its impact on patient's survival. *J Breast Cancer*. 2021;24(5):417–427. doi:10.4048/jbc.2021.24.e41.
53. Aller R, Fernández-Rodríguez C, Lo Iacono O, et al. Consensus document. Management of non-alcoholic fatty liver disease (NAFLD). Clinical practice guideline. *Gastroenterol Hepatol*. 2018;41(5):328–349. doi:10.1016/j.gastrohep.2017.12.003.
54. EASL clinical practice guidelines: drug-induced liver injury. *J Hepatol*. 2019;70(6):1222–1261. doi:10.1016/j.jhep.2019.02.014.
55. Zhang Q-L, Rothenbacher D. Prevalence of chronic kidney disease in population-based studies: systematic review. *BMC Public Health*. 2008;8:117. doi:10.1186/1471-2458-8-117.
56. Tomlinson LA, Clase CM. Sex and the incidence and prevalence of kidney disease. *Clin J Am Soc Nephrol*. 2019;14(11):1557–1559. doi:10.2215/CJN.11030919.
57. Hill NR, Fatoba ST, Oke JL, et al. Global prevalence of chronic kidney disease - a systematic review and meta-analysis. *PLoS One*. 2016;11(7):e0158765. doi:10.1371/journal.pone.0158765.
58. NICE. National Institute for Health Care Excellence: Management of chronic kidney disease. Accessed June 30, 2024. https://www.nice.org.uk/guidance/conditions-and-diseases/kidney-conditions/chronic-kidney-disease.
59. Evans A, Petty R, Macaskill J. Why is renal impairment associated with poorer cancer specific survival in breast cancer patients?: a comparison with patients with other comorbidities. *Int J Clin Oncol*. 2020;25(10):1786–1792. doi:10.1007/s10147-020-01733-7.
60. Kwak H-Y, Chae B-J, Bae J-S, Jung S-S, Song B-J. Breast cancer after kidney transplantation: a single institution review. *World J Surg Oncol*. 2013;11:77. doi:10.1186/1477-7819-11-77.
61. Buell JF, Hanaway MJ, Trofe J, et al. De novo breast cancer in renal transplant recipients. *Transplant Proc*. 2002;34(5):1778–1779. doi:10.1016/s0041-1345(02)03063-4.
62. García-Maset R, Bover J, Segura de la Morena J, et al. Information and consensus document for the detection and management of chronic kidney disease. *Nefrologia*. 2022;42(3):233–264. doi:10.1016/j.nefroe.2022.07.003.
63. Crouch A, Champion VL, Von Ah D. Comorbidity, cognitive dysfunction, physical functioning, and quality of life in older breast cancer survivors. *Support care cancer Off J Multinatl Assoc Support Care Cancer*. 2022;30(1):359–366. doi:10.1007/s00520-021-06427-y.
64. Crome P, Lally F, Cherubini A, et al. Exclusion of older people from clinical trials: professional views from nine European countries participating in the PREDICT study. *Drugs Aging*. 2011;28(8):667–677. doi:10.2165/11591990-000000000-00000.
65. Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol Off J Am Soc Clin Oncol*. 2014;32(24):2595–2603. doi:10.1200/JCO.2013.54.8347.
66. Torregrosa-Maicas MD, Del Barco-Berrón S, Cotes-Sanchís A, Lema-Roso L, Servitja-Tormo S, Gironés-Sarrió R. Expert consensus to optimize the treatment of elderly patients with luminal metastatic breast cancer. *Clin Transl Oncol Off Publ Fed Spanish Oncol Soc Natl Cancer Inst Mex*. 2022;24(6):1033–1046. doi:10.1007/s12094-021-02766-8.
67. Topaloğlu US, Özaslan E. Comorbidity and polypharmacy in patients with breast cancer. *Breast Cancer*. 2020;27(3):477–482. doi:10.1007/s12282-019-01040-8.
68. Schaap LA, van Schoor NM, Lips P, Visser M. Associations of sarcopenia definitions, and their components, with the incidence of recurrent falling and fractures: the longitudinal aging study Amsterdam. *J Gerontol A Biol Sci Med Sci*. 2018;73(9):1199–1204. doi:10.1093/gerona/glx245.
69. Malmstrom TK, Miller DK, Simonsick EM, Ferrucci L, Morley JE. SARC-F: a symptom score to predict persons with sarcopenia at risk for poor functional outcomes. *J Cachexia Sarcopenia Muscle*. 2016;7(1):28–36. doi:10.1002/jcsm.12048.
70. Deluche E, Leobon S, Desport JC, Venat-Bouvet L, Usseglio J, Tubiana-Mathieu N. Impact of body composition on outcome in patients with early breast cancer. *Support care cancer Off J Multinatl Assoc Support Care Cancer*. 2018;26(3):861–868. doi:10.1007/s00520-017-3902-6.
71. Droz J-P, Aapro M, Balducci L, et al. Management of prostate cancer in older patients: updated recommendations of a working group of the International Society of Geriatric Oncology. *Lancet Oncol*. 2014;15(9):e404–e414. doi:10.1016/S1470-2045(14)70018-X.
72. Antonio M, Saldaña J, Carmona-Bayonas A, et al. Geriatric assessment predicts survival and competing mortality in elderly patients with early colorectal cancer: can it help in adjuvant therapy decision-making? *Oncologist*. 2017;22(8):934–943. doi:10.1634/theoncologist.2016-0462.
73. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing*. 2019;48(1):16–31. doi:10.1093/ageing/afy169.
74. Fuggle N, Shaw S, Dennison E, Cooper C. Sarcopenia. *Best Pract Res Clin Rheumatol*. 2017;31(2):218–242. doi:10.1016/j.berh.2017.11.007.
75. Veronese N, Stubbs B, Punzi L, et al. Effect of nutritional supplementations on physical performance and muscle strength parameters in older people: a systematic review and meta-analysis. *Ageing Res Rev*. 2019;51:48–54. doi:10.1016/j.arr.2019.02.005.
76. Volkert D, Beck AM, Cederholm T, et al. ESPEN guideline on clinical nutrition and hydration in geriatrics. *Clin Nutr*. 2019;38(1):10–47. doi:10.1016/j.clnu.2018.05.024.
77. Nascimento CM, Ingles M, Salvador-Pascual A, Cominetti MR, Gomez-Cabrera MC, Viña J. Sarcopenia, frailty and their prevention by exercise. *Free Radic Biol Med*. 2019;132:42–49. doi:10.1016/j.freeradbiomed.2018.08.035.
78. Valenzuela PL, Castillo-García A, Morales JS, et al. Physical exercise in the oldest old. *Compr Physiol*. 2019;9(4):1281–1304. doi:10.1002/cphy.c190002.
79. Landi F, Marzetti E, Martone AM, Bernabei R, Onder G. Exercise as a remedy for sarcopenia. *Curr Opin Clin Nutr Metab Care*. 2014;17(1):25–31. doi:10.1097/MCO.0000000000000018.
80. Gao S, Li Y, He Z, et al. Thromboembolism profiles associated with cyclin-dependent kinase 4/6 inhibitors: a real-world pharmacovigilance study and a systematic review. *Expert Opin Drug Saf*. 2023;22(7):599–609. doi:10.1080/14740338.2023.2181338.
81. Woelfel IA, Fernandez LJ, Idowu MO, Takabe K. A high burden of comorbid conditions leads to decreased survival in breast cancer. *Gland Surg*. 2018;7(2):216–227. doi:10.21037/gs.2018.02.03.
82. Wang X, Wang N, Zhong L, et al. Prognostic value of depression and anxiety on breast cancer recurrence and mortality: a systematic review and meta-analysis of 282,203 patients. *Mol Psychiatry*. 2020;25(12):3186–3197. doi:10.1038/s41380-020-00865-6.
83. Palesh OG, Roscoe JA, Mustian KM, et al. Prevalence, demographics, and psychological associations of sleep disruption in patients with cancer: University of Rochester Cancer Center-Community Clinical Oncology Program. *J Clin Oncol Off J Am Soc Clin Oncol*. 2010;28(2):292–298. doi:10.1200/JCO.2009.22.5011.
84. Spiegel D, Riba MB. Managing anxiety and depression during treatment. *Breast J*. 2015;21(1):97–103. doi:10.1111/tbj.12355.
85. Sunilkumar MM, Finni CG, Lijimol AS, Rajagopal MR. Health-related suffering and palliative care in breast cancer. *Curr Breast Cancer Rep*. 2021;13(4):241–246. doi:10.1007/s12609-021-00431-1.
86. Hamood R, Hamood H, Merhasin I. Keinan-Boker L. Chronic pain and other symptoms among breast cancer survivors: prevalence, predictors, and effects on quality of life. *Breast Cancer Res Treat*. 2018;167(1):157–169. doi:10.1007/s10549-017-4485-0.
87. Broemer L, Hinz A, Koch U, Mehnert-Theuerkauf A. Prevalence and severity of pain in cancer patients in Germany. *Front pain Res (Lausanne, Switzerland)*. 2021;2:703165. doi:10.3389/fpain.2021.703165.
88. Jara C, Del Barco S, Grávalos C, et al. SEOM clinical guideline for treatment of cancer pain (2017). *Clin Transl Oncol Off Publ Fed Spanish Oncol Soc Natl Cancer Inst Mex*. 2018;20(1):97–107. doi:10.1007/s12094-017-1791-2.
89. Hidding JT, Beurskens CHG, van der Wees PJ, van Laarhoven HWM, Nijhuis-van der Sanden MWG. Treatment related impairments in arm and shoulder in patients with breast cancer: a systematic review. *PLoS One*. 2014;9(5):e96748. doi:10.1371/journal.pone.0096748.
90. Akkaya N, Atalay NS, Selcuk ST, Alkan H, Catalbas N, Sahin F. Frequency of fibromyalgia syndrome in breast cancer patients. *Int J Clin Oncol*. 2013;18(2):285–292. doi:10.1007/s10147-012-0377-9.
91. Roy S, Vallepu S, Barrios C, Hunter K. Comparison of comorbid conditions between cancer survivors and age-matched patients without cancer. *J Clin Med Res*. 2018;10(12):911–919. doi:10.14740/jocmr3617w.
92. Ward MM, Alehashemi S. Risks of solid cancers in elderly persons with osteoarthritis or ankylosing spondylitis. *Rheumatology (Oxford)*. 2020;59(12):3817–3825. doi:10.1093/rheumatology/keaa166.
93. Li X, Luthra R, Morrow PK, et al. Comorbidities among patients with cancer who do and do not develop febrile neutropenia during the first chemotherapy cycle. *J Oncol Pharm Pract Off Publ Int Soc Oncol Pharm Pract*. 2016;22(5):679–689. doi:10.1177/1078155215603229.
94. Swarm RA, Paice JA, Anghelescu DL, et al. Adult cancer pain, version 3.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2019;17(8):977–1007. doi:10.6004/jnccn.2019.0038.
95. Bruyère O, Cooper C, Pelletier J-P, et al. An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: a report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). *Semin Arthritis Rheum*. 2014;44(3):253–263. doi:10.1016/j.semarthrit.2014.05.014.
96. Recomendaciones para el seguimiento de las mujeres supervivientes de Cáncer de Mama. *SEOM*. 2017. PublishedAccessed June 30, 2024. https://seom.org/publicaciones/publicaciones-seom/largos-supervivientes/106161-recomendaciones-para-el-seguimiento-de-las-mujeres-supervivientes-de-cancer-de-mama .
97. Saúde Sg. *Guía Técnica Del Proceso de Atención a La Fibromialgia.*; 2009. https://www.sergas.es/Asistencia-sanitaria/Documents/45/G11Fibro.pdf.
98. Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. *Ann Rheum Dis*. 2017;76(2):318–328. doi:10.1136/annrheumdis-2016-209724.
99. Alcántara Montero A, Sánchez Carnerero CI. Recomendaciones revisadas de la EULAR para el manejo de la fibromialgia. *Med Fam Semer*. 2017;43(6):472–473. doi:10.1016/j.semerg.2016.07.016.
100. Catane R. *Handbook of Advanced Cancer Care*. for Medical Oncology ES. Taylor & Francis; 2006. https://books.google.es/books?id=IBgDbSMFmGEC.

101. Torcal Baz M, Ventoso Mora SA. Manejo y tratamiento del dolor en cuidados paliativos. *Rev Clínica Med Fam*. 2020;13(3):203–211. https://www.redalyc.org/articulo.oa?id=169664978005.
102. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol Off J Eur Soc Med Oncol*. 2020;31(12):1623–1649. doi:10.1016/j.annonc.2020.09.010.
103. Roncato R, Angelini J, Pani A, et al. CDK4/6 inhibitors in breast cancer treatment: potential interactions with drug, gene, and pathophysiological conditions. *Int J Mol Sci*. 2020;21(17):6350. doi:10.3390/ijms21176350.
104. Bolzacchini E, Pomero F, Fazio M, et al. Risk of venous and arterial thromboembolic events in women with advanced breast cancer treated with CDK 4/6 inhibitors: A systematic review and meta-analysis. *Thromb Res*. 2021;208:190–197. doi:10.1016/j.thromres.2021.11.009.
105. Yan M-M, Wu S-S, Qi Y-P, et al. Association between cyclin-dependent kinase 4/6 inhibitors and venous thromboembolism: analysis of F.A.E.R.S. data. *Expert Opin Drug Saf*. 2022;21(2):277–283. doi:10.1080/14740338.2021.1981856.
106. Roncato R, Peruzzi E, Gerratana L, et al. Clinical impact of body mass index on palbociclib treatment outcomes and effect on exposure. *Biomed Pharmacother*. 2023;164:114906. doi:10.1016/j.biopha.2023.114906.
107. Lagampan C, Poovorawan N, Parinyanitikul N. Lactic acidosis, a potential toxicity from drug-drug interaction related to concomitant ribociclib and metformin in preexisting renal insufficiency: a case report. *Cancer reports (Hoboken, NJ)*. 2022;5(8):e1575. doi:10.1002/cnr2.1575.
108. Cucciniello L, Garufi G, Di Rienzo R, et al. Estrogen deprivation effects of endocrine therapy in breast cancer patients: incidence, management and outcome. *Cancer Treat Rev*. 2023;120:102624. doi:10.1016/j.ctrv.2023.102624.
109. Di Lauro V, Barchiesi G, Martorana F, et al. Health-related quality of life in breast cancer patients treated with CDK4/6 inhibitors: a systematic review. *ESMO open*. 2022;7(6):100629. doi:10.1016/j.esmoop.2022.100629.
110. Molinelli C, Bruzzone M, Blondeaux E, et al. The journey of patients affected by metastatic hormone receptor-positive/HER2-negative breast cancer from CDK 4/6 inhibitors to second-line treatment: a real-world analysis of 701 patients enrolled in the GIM14/BIOMETA study. *Eur J Cancer*. 2024;213:115113. doi:10.1016/j.ejca.2024.115113.
111. Jhaveri K, Burris Rd HA, Yap TA, et al. The evolution of cyclin dependent kinase inhibitors in the treatment of cancer. *Expert Rev Anticancer Ther*. 2021;21(10):1105–1124. doi:10.1080/14737140.2021.1944109.
112. Fuentes-Antrás J, de Luna A, López de Sá A, Ocaña A, García-Sáenz JÁ, Moreno F. Safety and efficacy of cyclin-dependent kinase inhibitor rechallenge following ribociclib-induced limiting hypertransaminasemia. *Breast*. 2020;54:160–163. doi:10.1016/j.breast.2020.10.007.
113. Pharmacist US. Drug interactions associated with CDK 4/6 inhibitors. Published 2023. Accessed June 30, 2024. https://www.uspharmacist.com/article/drug-interactions-associated-with-cdk-4-6-inhibitors.
114. National Institute for Health and Care Excellence. Ribociclib interactions. Accessed October 27, 2023. https://bnf.nice.org.uk/interactions/ribociclib/.
115. Vanhoutte T, Sprangers B. Serum cystatin C level can be used to estimate GFR in patients with solid tumors: moderator commentary. *J Onco-Nephrol*. 2022;6(3):119–124. doi:10.1177/23993693221114901.
116. Rugo HS, Turner NC, Finn RS, et al. Palbociclib plus endocrine therapy in older women with HR+/HER2- advanced breast cancer: a pooled analysis of randomised PALOMA clinical studies. *Eur J Cancer*. 2018;101:123–133. doi:10.1016/j.ejca.2018.05.017.
117. Rochester MP, Kane AM, Linnebur SA, Fixen DR. Evaluating the risk of QTc prolongation associated with antidepressant use in older adults: a review of the evidence. *Ther Adv drug Saf*. 2018;9(6):297–308. doi:10.1177/2042098618772979.
118. Bosacki C, Bouleftour W, Sotton S, et al. CDK 4/6 inhibitors combined with radiotherapy: a review of literature. *Clin Transl Radiat Oncol*. 2021;26:79–85. doi:10.1016/j.ctro.2020.11.010.
119. López-Fernández T, Martín-García A, Roldán Rabadán I, et al. Abordaje de la fibrilación auricular en pacientes con cáncer activo. Documento de consenso de expertos y recomendaciones. *Rev Española Cardiol*. 2019;72(9):749–759. doi:10.1016/J.RECESP.2019.03.017.
120. Muñoz Martín AJ, Gallardo Díaz E, García Escobar I, et al. SEOM clinical guideline of venous thromboembolism (VTE) and cancer (2019). *Clin Transl Oncol Off Publ Fed Spanish Oncol Soc Natl Cancer Inst Mex*. 2020;22(2):171–186. doi:10.1007/s12094-019-02263-z.

Supplemental Material

Supplemental Figure S1 Recommendations for the management of atrial fibrillation and venous thromboembolism in patients with mBC. AF = atrial fibrillation; CKD = chronic kidney disease; DOACs = direct-acting oral anticoagulants; GFR = glomerular filtration rate; LMWH = low-molecular-weight heparin; LVEF = left ventricular ejection fraction; mBC = metastatic breast cancer; VKAs = vitamin K antagonists. Figure based on recommendations from expert consensus document from the Cardio-Onco-Hematology and Thrombosis groups of the Spanish Society of Cardiology for AF,[119] the Spanish Society of Medical Oncology clinical guideline of venous thromboembolism,[120] and the authors' experiences.



Supplemental Table S1 Search Strategy

Breast Cancer	*and Comorbidities*	*and Treatment*
• Luminal breast cancer OR progesterone-receptor and/or estrogen-receptor positive AND human epidermal growth factor receptor 2–negative "HER2–" advanced breast cancer OR metastatic breast cancer	• Comorbidity OR comorbid condition • Hypertension OR cardiovascular disorder OR heart disease • Endocrine disorder OR diabetes OR obesity OR malnutrition • Impaired renal function OR renal impairment OR renal failure OR renal insufficiency • Liver failure OR hepatic impairment • Gastrointestinal disorder • Elderly OR geriatrics • Depression OR anxiety OR stress disorder • Anticoagulant treatment OR atrial fibrillation OR venous thromboembolism OR pulmonary embolism • Osteoarthritis OR pain	• CDK4/6 inhibitor OR palbociclib OR ribociclib OR abemaciclib • Polypharmacy OR concomitant medication