HHS Public Access

Author manuscript

*Drugs Aging*. Author manuscript; available in PMC 2021 May 01.

Published in final edited form as:

*Drugs Aging*. 2020 May ; 37(5): 349–358. doi:10.1007/s40266-020-00758-x.

# The Evolving Complexity of Treating Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor-2 (HER2)-Negative Breast Cancer: Special Considerations in Older Breast Cancer Patients—Part II: Metastatic disease

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## Abstract

Breast cancer is a disease of aging, and the incidence of breast cancer is projected to increase dramatically as the global population ages. The majority of breast cancers that occur in older adults are hormone-receptor positive, HER2-negative phenotypes, with favorable tumor biology; yet, because of underrepresentation in clinical trials, less evidence is available to guide the complex care for this population. Providing care for older patients with metastatic breast cancer, with coexisting medical conditions, increased risk of treatment toxicity, and frailty, remains a clinical challenge in oncology. This review provides an overview of the current evidence from clinical trials and subanalyses of older adults with hormone receptor-positive, HER2-negative metastatic breast cancer. We highlight data on the safety and efficacy of oral therapies including, endocrine therapy alone or in combination with CDK 4/6 inhibitors, PI3K inhibitors, or mTOR inhibitors, noting the significant underrepresentation of older and frail adults in these studies. We also discuss current and future directions in research for this special population, highlighting significant knowledge gaps, including the need to improve long-term adherence to hormonal and targeted therapy, prospective clinical trials that capture clinical and biological aging endpoints, and the need for a multidisciplinary approach with integration of geriatric and oncology principles.

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**Conflict of Interests:** Dr. Hill, Dr. Gutierrez, Ms. Liu, and Dr. Sedrak declare that they have no conflicts of interest that might be relevant to the contents of this manuscript. Dr. Sammons has served on scientific advisory boards for Foundation Medicine, Eli Lilly, Novartis and Sermonix. She receives institutional research funding from Eli Lilly and Astra Zeneca. Dr. Kimmick has served on Scientific Advisory Boards for Boehringer Ingelheim, Eisai, Genomic Health, and Agendia, is on the speakers bureau for Eisai, has consulted or advised Genomic Health, AstraZeneca, Novartis, and Pfizer, has had a key role in research at her institution funded by Bionovo, PUMA, Roche, and Novartis, received Royalties from UpToDate and Springer, and has attended dinner functions funded by Seattle Genetics, Novartis, and Foundation Medicine.

## 1. Introduction

Breast cancer is the second most common cause of death from cancer in women [1], with metastatic breast cancer accounting for a large portion of breast cancer-related morbidity and mortality [1,2]. About 6% of women have metastatic breast cancer when they are first diagnosed [2], and more than 150,000 women are living with metastatic breast cancer [1, 3]. Aging remains one of the single greatest risk factors for breast cancer, and as the global population ages, the number of older adults with breast cancer is expected to rise dramatically worldwide [4]. Nearly 80% of breast cancers that occur in older adults have hormone-receptor positive, HER2-negative histologies, with more indolent features and favorable tumor biology compared with those that arise in younger women [5-7].

Despite this, older age in itself is associated with early mortality in patients presenting with metastatic disease [8-11] and breast cancer outcomes for older patients are inferior compared to younger post-menopausal women [1, 11, 12]. One of the major contributors for this disparity is that older adults are often undertreated or receive non-standard care as a result of concerns for multi-morbidity, treatment toxicity, and frailty [13-15]. However, aging is heterogeneous, and how to individualize treatment around patients' functional or biological age remains a clinical challenge [16]. Moreover, age-related changes influence anti-neoplastic drug distribution, metabolism, and excretion which may contribute to changes in treatment tolerance between older and younger patients [17-21]. Yet, older adults remain vastly underrepresented in cancer clinical trials that establish standard care treatment dosing, safety, and efficacy [22, 23]. In addition, few studies have investigated how accumulation of cellular and molecular damage associated with anti-neoplastic drags may accelerate or accentuate the rate of aging compared with expected aging in the absence of cancer, and there is limited data on the long-term and late-emerging effects of cancer therapies on aging. [18, 24, 25].

In this review, we highlight several major issues related to management of hormone receptor-positive, HER2-negative, metastatic breast cancer in older patients. We describe current knowledge gaps related to drug safety and efficacy, postulate the potential impact of therapies on the aging process, and underscore limitations of the current evidence and need for more research related to anti-neoplastic drug therapy in older adults.

## 2. Endocrine therapy

There have been multiple trials evaluating the efficacy of aromatase inhibitors compared to tamoxifen in postmenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer [26-28]. These trials have shown superiority of anastrozole, letrozole, and exemestane when compared to tamoxifen in this setting. However, although aromatase inhibitors are commonly used in clinical practice for older adults based on this data, most of the data is heavily weighted towards younger postmenopausal females. The average age of patients included in these trials ranges from 63 to 67 and nearly 90% of these patients have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) rated as 0-1.

Fulvestrant alone has been shown to be a safe and effective endocrine therapy for older adults in the first and second line metastatic setting, and it may be more efficacious than aromatase inhibitors. Fulvestrant improved the time to progression compared to anastrozole in the first line setting with comparable overall response rate and clinical benefit rate [29, 30]. Fulvestrant is also an effective therapy after progression on an aromatase inhibitor [31, 32]. However, the patients included in these trials had an average age from 64-68 and were heavily weighted towards younger postmenopausal women with good performance status. One systematic review reported improved progression free survival (PFS) with fulvestrant 500 mg compared to an aromatase inhibitor and a subgroup analysis of patients 65 and older had a greater PFS benefit [33]. In postmenopausal women, fulvestrant 500 mg has demonstrated increased efficacy compared to the initially approved dose of 250 mg [34].

Adherence to endocrine therapy remains a problem, with unique challenges in the older adult population. Although most work on adherence has been done in the adjuvant setting, these studies have shown that the majority of patients with breast cancer receiving endocrine treatment (up to 90%) experience an adverse event including hot flashes, nausea, arthralgias, fatigue, mood changes, and fractures with endocrine therapy [27, 35]. Due to the high percentage of patients who experience side effects from these medications, adherence can be a challenge, especially with oral endocrine agents. In the adjuvant setting, postmenopausal women were estimated to be only 69% compliant with aromatase inhibitors [36]. In a broader analysis from a systematic review of adherence to recommended treatment for various cancers in an older adult population, adherence rates ranged from 52%-100% [37]. Further investigation is needed to understand the causes of nonadherence and potential remedies. In our practice, if there is concern that an older adult may struggle with adherence, perhaps due to dementia or other functional limitations, we consider using fulvestrant, which is administered in the clinic, rather than an oral aromatase inhibitor.

## 3. CDK4/6 inhibitors

Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors reduce proliferation of breast cancer cell lines by preventing progression from the G1 to S cell cycle phase [38-40]. With the development of the CDK4/6 inhibitors, palbociclib, ribociclib, and abemaciclib, the treatment landscape of hormone receptor-positive, HER2-negative metastatic breast cancer has dramatically changed. In combination with endocrine therapy, all three agents have improved PFS in the first line metastatic setting when compared to an aromatase inhibitor (AI) [41-44] or fulvestrant alone [45-48]. Furthermore, both ribociclib and abemaciclib combined with endocrine therapy have shown an improvement in overall survival (OS) when compared to endocrine therapy alone [49, 50], and we await further data on survival for palbociclib. While the three CDK4/6 inhibitors appear to be similar in terms of efficacy [51], there are significant differences in terms of toxicity, which may be especially relevant for oncologists who use these agents in the geriatric population. Palbociclib commonly causes neutropenia, leukopenia, fatigue, and nausea with up to 56% of patients experiencing grade 3 or greater neutropenia [41, 42, 38]. Ribociclib also frequently causes neutropenia (grade 3 or higher in 49.7%) but in contrast to the other CDK4/6 inhibitors, it carries an increased risk of QTC prolongation, requiring ECG monitoring [43, 39]. Abemaciclib causes less neutropenia but more diarrhea, with 81% of patients experiencing any grade of diarrhea and

27% experiencing grade 3 or higher [44, 40]. Most trials evaluating the CDK4/6 inhibitors are heavily weighted towards younger postmenopausal women in good health, and despite adverse events that may be more limiting for older adults, there is no detailed toxicity report for the older adult population [52]. In fact, in all of the above mentioned studies, only 8-11% of study participants were age 75 or older and all participants had an ECOG PS of 0-1 (Table 1).

Abemaciclib deserves additional mention since abemaciclib monotherapy is approved for the treatment of hormone receptor-positive, HER2-negative metastatic breast cancer after progression through hormonal therapy and chemotherapy. Abemaciclib has shown promise in this heavily pretreated population with a median PFS of 6 months and median OS of 17.7 months (Table 2) [53]. However, these patients were relatively young with an average age of 58 and fairly healthy with an ECOG PS of 0-1 (Table 1). Only 32% were over the age of 64.

Aside from the small sample of older adults in the above mentioned pivotal studies, Howie and colleagues performed a retrospective pooled analysis of patients age 70 or older from the PALOMA-2 (palbociclib), MONALEESA-2 (ribociclib), and MONARCH-3 (abemaciclib) trials [54]. Across these three trials, approximately 25% of study participants were age 70 or greater (n=456) and approximately 10% of study participants were age 75 or greater (n=198). Older adults did benefit from a CDK4/6 inhibitor plus an AI with a median PFS improvement from 13.7 months to 31.1 months with the combination compared to an AI alone in patients age 75 or greater. Older adults had greater toxicity with the combination. The dose reduction rate in patients 75 or older was 81.6% and the CDK4/6 inhibitor discontinuation rate was 32% compared to 71% and 12% in patients younger than 75 years, respectively. Patients age 75 or older reported greater diarrhea and fatigue relative to younger patients. In the group age 70 or greater, 56% of patients needed two or more dose reductions, generally due to neutropenia, diarrhea, kidney injury, and fatigue.

Furthermore, older adults had a similar decline in quality of life regardless of treatment with the combination or an aromatase inhibitor alone. An exploratory analysis found that patients aged 75 or greater had a more rapid decline in mobility, self-care, and functionality regardless of treatment arm. This analysis suggests that CDK4/6 inhibitors markedly improve PFS in this population and that toxicity is manageable with dose reductions [54]. However, this analysis has several limitations. First, it is a retrospective design, and prospective studies are needed. Second, the differential toxicity profiles of the CDK4/6 inhibitors examined makes it challenging to pool data on specific adverse events, and the authors were unable to pool data from additional studies of CDK4/6 inhibitors due to heterogeneity of patient populations and study design. Third, the current studies do not capture endpoints that may be most meaningful for older adults, such as function or cognition [54]. Many oncologists have reservations concerning the use of CDK4/6 inhibitors in the geriatric population [55].

Ongoing studies evaluating CDK4/6 inhibitors in the geriatric oncology population include a phase II study evaluating palbociclib plus letrozole or fulvestrant in patients age 70 or older with hormone receptor-positive, HER2-negative metastatic breast cancer (NCT03633331). This trial will provide prospective data in older adults with metastatic, hormone receptor-

positive breast cancer, allowing insight into the experience of older patients, which has historically been lacking in our traditional clinical trials. Given that CDK4/6 inhibitors are oral therapies, older adults who may have cognitive impairment or limited social support may face challenges with adherence. Finally, CDK4/6 inhibitors, by inducing cell cycle arrest, may promote a state of cellular senescence, which is a hallmark of aging [56]. This may not just apply to the tumor itself, but also to normal healthy tissue, possibly contributing to accelerated aging commonly seen in patients receiving anticancer therapy, and providing an opportunity to learn more about the aging process from studying this class of drug [57]. Further studies are warranted to understand the effect of CDK4/6 inhibitors on the biology of aging.

## 4. PI3K Inhibitors

The phosphatidylinositol 3-kinase (PI3K) pathway is a frequently altered growth factor receptor signaling pathway in breast cancer with *PIK3CA* mutations observed in approximately 40% of patients with hormone receptor-positive, HER2-negative breast cancer [58-61]. Alpelisib, an orally bioavailable α-specific PI3K inhibitor, was recently approved by the FDA to be used in combination with fulvestrant for the treatment of hormone receptor-positive, HER2-negative advanced breast cancer that has progressed or relapsed during or after endocrine therapy in postmenopausal women. This approval is based on the findings of the SOLAR-1 trial which demonstrated that alpelisib with fulvestrant significantly prolonged PFS and improved overall response in patients with *PIK3CA*-mutated, hormone receptor-positive, HER2-negative advanced breast cancer when compared to fulvestrant alone [62]. The median PFS of patients treated with alpelisib was 11 months compared to the placebo group with 5.7 months (Table 2). The most common adverse events amongst patients within the treatment group were hyperglycemia (63.7%), diarrhea (57.7%), nausea (44.7%), loss of appetite (35.6%), and rash (35.6%) [63]. The most common grade 3 or 4 adverse events were hyperglycemia (36.6%), rash (9.9%), maculopapular rash (8.8%), and diarrhea (6.7%). Notably, 25% of patients in the alpelisib group had to permanently discontinue treatment due to adverse events with hyperglycemia being the most common reason for early discontinuation.

There is limited prospective data on the safety and efficacy of alpelisib in older adults. This is because the average age of patients enrolled in this study was 62, and a vast majority had an ECOG PS of 0-1 (Table 1). Furthermore, it was noted that within the treatment group the incidence rate of grade 3 or 4 hyperglycemia was 44% in patients greater than 65 years of age relative to 32% in patients younger than 65 years of age [64]. Given that older patients are at a higher risk of developing hyperglycemia, and diabetes mellitus is a disease associated with aging [65], providers administering this medication must closely monitor their patient’s blood glucose, titrate their dose as needed, and manage any hyperglycemia with metformin, insulin sensitizers, or insulin as recommended [64]. This pivotal trial, SOLAR-1, showed no observable differences in the effectiveness of alpelisib on patients greater than 65 years of age compared to younger patients, however, there was a limited number (n= 34 of 284) of patients who received alpelisib greater than 75 years of age to determine any significant differences in safety or efficacy.

Other PI3K inhibitors, such as buparlisib, have been investigated but had a poor safety profile and thus were not pursued further, highlighting the challenge of tolerability of these agents, which could be especially problematic in a geriatric population [66]. Oncologists understandably have reservations in their use and we need more prospective data to understand how to safely utilize PI3K inhibitors in older adults. As with all oral therapies prescribed to older adults, adherence concerns regarding PI3K inhibitors are relevant. Finally, PI3K inhibitors, by reducing phosphorylation of downstream targets such as AKT, may affect cellular nutrient sensing, and deregulated nutrient sensing is a complex metabolic hallmark of aging [56], highlighting the potential of this drug class to impact the aging process [57].

## 5. mTOR Inhibitors

In hormone receptor-positive breast cancer, activation of the mammalian target of rapamycin (mTOR) pathway is associated with resistance to endocrine therapy and a worse prognosis [67-70]. The oral therapy, everolimus, is a mTOR inhibitor with anti-proliferative and anti-angiogenic properties [71]. Everolimus plus exemestane is an effective treatment for hormone receptor-positive, HER2-negative metastatic breast cancer and there is evidence that it is effective in an elderly population as well. The BOLERO-2 randomized controlled trial evaluated everolimus plus exemestane versus exemestane alone in postmenopausal women after progression on an aromatase inhibitor and demonstrated improved PFS from 3.2 months to 7.8 months (Table 2) [72, 73]. However, the patient population was weighted more towards younger postmenopausal women with the average age of patients in this trial being 61-62 years old [72]. Pritchard and colleagues did a retrospective analysis of patients age 65 or older on the BOLERO-2 trial, including 275 patients age 65 or older and 164 patients age 70 or older [74]. PFS improved in both age groups (HR 0.59 and 0.45 respectively). However, adverse events, such as stomatitis, infection, rash, pneumonitis, and hyperglycemia, were common, and 67% of patients in both age groups required dose reductions. Approximately 15% of patients in both age groups required more than one dose reduction. In 71 patients age 75 or older, the most common adverse events were stomatitis (49%), fatigue (48%), anorexia (41%), diarrhea (38%), nausea (38%), dyspnea (34%), rash (34%), weight loss (31%), and anemia (28%). The most common grade 3 or 4 adverse events in patients age 75 or older were fatigue (14%), stomatitis (10%), dyspnea (10%), and anemia (10%). The authors concluded that everolimus plus exemestane is an effective treatment in the elderly but there are frequent adverse events requiring dose reductions [74].

Furthermore, everolimus plus fulvestrant has demonstrated improved PFS when compared to fulvestrant alone after treatment with an aromatase inhibitor. However, while the average age in this study was 65-66, all patients were ECOG PS 0-1 (Table 1) [75]. In summary, there is evidence supporting the use of mTOR inhibitors in combination with endocrine therapy for older patients with hormone receptor-positive, HER2-negative disease, however, older adults may struggle with adherence and require more frequent monitoring for dose adjustments and responses. More investigation may be needed to explore the appropriate dosing of mTOR inhibitors in this population; these agents are an excellent example of potential clinical limitations set by pursuing the maximum tolerated dose rather than minimum effective dose during drug development [76]. Finally, mTOR inhibitors, like PI3K inhibitors, can affect

deregulated nutrient sensing, which is a hallmark of aging. Inhibition of mTOR can lead to aspects of the aging phenotype, potentially accelerating aging, but can also increase longevity in mammalian models, making it an interesting area of investigation in cancer and aging [56, 57].

## 6. Chemotherapy

Chemotherapy is an important treatment modality for older adults and should especially be considered in specific clinical scenarios such as the presence of life-threatening or rapidly progressive visceral disease [77] or in the setting of endocrine refractory metastatic disease [78]. Capecitabine has been shown to be effective in older adults with metastatic breast cancer both in the first line [79] and after prior anthracyclines [80]. However, the standard dose of 1250 mg/m$^2$ often cannot be tolerated in patients, regardless of age [81]. Older adults especially have greater risk of toxicity with capecitabine 1250 mg/m$^2$, with 30% of patients requiring dose reductions [82]. Since capecitabine 1000 mg/m$^2$ leads to dose reductions in only 5% of patients, this dose is now commonly used and often considered the standard of care practice in the U.S. [82, 83].

Taxanes are another commonly utilized chemotherapy class for older adults. Taxanes are generally considered as effective in older adults compared to younger adults, but they are associated with greater toxicity, likely due to decreased clearance of the drug [84, 85, 78]. Docetaxel is associated with greater grade 3 or 4 fatigue in patients 65 and older [86], paclitaxel is associated with more leukopenia, peripheral neuropathy, and cardiotoxicity with age [87, 88], and while nab paclitaxel has not shown increased toxicity with age in breast cancer, less than 2% of patients studied were 75 years or older [89, 90]. Numerous other chemotherapeutic agents are available and can be considered for use in older adults, weighing their individual toxicity profiles. Finally, chemotherapy classically is thought to create genomic instability leading to cell death, and genomic instability is a hallmark of aging [56]. A future area to explore may be how these agents accelerate aging, providing insights into the mechanisms and process of aging [56, 57].

## 7. Special Considerations in Older Patients

Treating older adults with metastatic breast cancer requires additional and often unique considerations in contrast to treating a younger population. It is helpful to use tools, such as ePrognosis, to estimate a patient's lifespan [91, 15, 92, 93] to inform a discussion on risks and benefits of therapeutic options. Furthermore, patient comorbidities and geriatric-specific domains need to be taken into account to better understand functional age as opposed to chronological age. A comprehensive geriatric assessment, which consists of an evaluation of functional status, co-morbid medical conditions, cognitive function, nutritional status, social support, and psychological state, and a review of medications, has been shown to be beneficial in predicting toxicity and survival in older adults [94]. ASCO guidelines now recommend that older patients receiving chemotherapy should have a geriatric assessment [15]. This assessment can help identify opportunities for interventions that may improve patient function and ability to tolerate treatment. Furthermore, including a geriatric

assessment in oncology clinical visits improves provider-patient communication about aging-related concerns [95].

Similar to principals often utilized in a general breast cancer patient population, older adults may benefit more from a single chemotherapeutic agent at a time rather than multi-agent chemotherapy. If adherence to therapy is a concern, perhaps because a patient struggles to remember or struggles to physically open bottles and does not have a caregiver, then an intravenous or injectable therapy may be preferred. Given the many facets of care of the older adult, a multidisciplinary approach, perhaps including a geriatrician, palliative care physician, or primary care physician, in addition to the oncologist and pharmacist, is ideal [95]. More data is needed to advise us on the optimal ways to approach treatment of metastatic, hormone receptor-positive breast cancer in the older adult population. Furthermore, endpoints that are more pertinent to older adults, such as functional outcomes or degree of impairment in addition to the traditional PFS and OS may provide the most relevant information to inform improvements in clinical practice.

## 8. Conclusions

The treatment landscape of metastatic breast cancer has evolved over time with many new oral treatment options being integrated into standard care, including endocrine therapy, with or without concurrent treatment with a CDK4/6 inhibitor, PI3K inhibitors, and mTOR inhibitors. For older women with hormone receptor-positive, HER2-negative metastatic breast cancer, these oral treatment options are promising, but prospective data in this particular patient population would aid in optimal dosing strategies and toxicity management. Endocrine therapy has been shown to be safe, tolerable, and effective in older adults. CDK4/6 inhibitors in combination with endocrine therapy appear to have excellent efficacy in terms of prolonging PFS in older adults (median PFS of 31.1 months) [54], but more data in older adults is needed to aid in optimal toxicity management and dosing and to understand best sequencing of endocrine and targeted therapy agents. PI3K inhibitors require cautious use in an older adult population due to a greater incidence of hyperglycemia. mTOR inhibitors are efficacious in older adults but require frequent dose reductions due to poor tolerability. Chemotherapy is considered safe and effective in older adults, but clearance may be lower requiring added attention to dosing. When treating older adults, it is important to balance efficacy of treatment with potential side effects in consideration of quality of life. Issues that factor into the risk/benefit discussion are more numerous and complex, and a multidisciplinary approach with a geriatric perspective can be particularly helpful. Finally, we enthusiastically encourage the inclusion of older adults in clinical trials, which not only present novel treatment options, but may also fill gaps in our knowledge to guide the complex clinical decision-making required in the care of the older adult.

## Acknowledgments

**Funding:** No external funding was used in the preparation of this manuscript.

## References


1. SEER Cancer Stat Facts: Female Breast Cancer. Bethesda, MD: National Cancer Institute.
2. American Cancer Society. Breast Cancer Facts & Figures 2019-2020. Atlanta: American Cancer Society2019 2019.
3. Waks AG, Winer EP. Breast Cancer Treatment: A Review. JAMA. 2019;321(3):288–300. doi:10.1001/jama.2018.19323 %J JAMA. [PubMed: 30667505]
4. Smith BD, Smith GL, Hurria A, Hortobagyi GN, Buchholz TA. Future of Cancer Incidence in the United States: Burdens Upon an Aging, Changing Nation. 2009;27(17):2758–65. doi:10.1200/jco.2008.20.8983.
5. Gennari R, Curigliano G, Rotmensz N, Robertson C, Colleoni M, Zurrida S et al. Breast carcinoma in elderly women. 2004;101(6):1302–10. doi:10.1002/cncr.20535.
6. Diab SG, Elledge RM, Clark GM. Tumor characteristics and clinical outcome of elderly women with breast cancer. Journal of the National Cancer Institute. 2000;92(7):550–6. doi:10.1093/jnci/92.7.550. [PubMed: 10749910]
7. Rodrigues NA, Dillon D, Carter D, Parisot N, Haffty BG. Differences in the pathologic and molecular features of intraductal breast carcinoma between younger and older women. 2003;97(6):1393–403. doi:10.1002/cncr.11204.
8. Schonberg MA, Marcantonio ER, Ngo L, Li D, Silliman RA, McCarthy EP. Causes of death and relative survival of older women after a breast cancer diagnosis. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011;29(12):1570–7. doi:10.1200/JCO.2010.33.0472. [PubMed: 21402602]
9. Vaz-Luis I, Lin NU, Keating NL, Barry WT, Winer EP, Freedman RA. Factors Associated with Early Mortality Among Patients with De Novo Metastatic Breast Cancer: A Population-Based Study. The oncologist. 2017;22(4):386–93. doi:10.1634/theoncologist.2016-0369. [PubMed: 28242790]
10. Rosso S, Gondos A, Zanetti R, Bray F, Zakelj M, Zagar T et al. Up-to-date estimates of breast cancer survival for the years 2000–2004 in 11 European countries: The role of screening and a comparison with data from the United States. European Journal of Cancer. 2010;46(18):3351–7. doi:10.1016/j.ejca.2010.09.019. [PubMed: 20943375]
11. Smith BD, Jiang J, McLaughlin SS, Hurria A, Smith GL, Giordano SH et al. Improvement in Breast Cancer Outcomes Over Time: Are Older Women Missing Out? 2011;29(35):4647–53. doi:10.1200/jco.2011.35.8408.
12. Kimmick G Treatment of metastatic breast cancer in older women. UpToDate 2019.
13. Muss HB, Berry DA, Cirrincione C, Budman DR, Henderson IC, Citron ML et al. Toxicity of older and younger patients treated with adjuvant chemotherapy for node-positive breast cancer: the Cancer and Leukemia Group B Experience. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25(24):3699–704. doi:10.1200/jco.2007.10.9710. [PubMed: 17704418]
14. Hurria A, Mohile S, Gajra A, Klepin H, Muss H, Chapman A et al. Validation of a Prediction Tool for Chemotherapy Toxicity in Older Adults With Cancer. 2016;34(20):2366–71. doi:10.1200/jco.2015.65.4327.
15. Mohile SG, Dale W, Somerfield MR, Schonberg MA, Boyd CM, Burhenn PS et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. 2018;36(22):2326–47. doi:10.1200/jco.2018.78.8687.
16. Hurria A, Wildes T, Blair SL, Browner IS, Cohen HJ, Deshazo M et al. Senior adult oncology, version 2.2014: clinical practice guidelines in oncology. Journal of the National Comprehensive Cancer Network : JNCCN. 2014; 12(1):82–126. doi:10.6004/jnccn.2014.0009. [PubMed: 24453295]
17. Baker SD, Grochow LB. Pharmacology of cancer chemotherapy in the older person. Clinics in geriatric medicine. 1997;13(1):169–83. [PubMed: 8995106]
18. Yuen GJ. Altered pharmacokinetics in the elderly. Clinics in geriatric medicine. 1990;6(2):257–67. [PubMed: 2184922]

19. Vestal RE. Aging and pharmacology. Cancer. 1997;80(7):1302–10. doi:10.1002/(sici)1097-0142(19971001)80:7<1302::aid-cncr16>3.0.co;2-b. [PubMed: 9317183]

20. Sawhney R, Sehl M, Naeim A. Physiologic aspects of aging: impact on cancer management and decision making, part I. Cancer journal (Sudbury, Mass). 2005;11(6):449–60. doi:10.1097/00130404-200511000-00004.

21. Lichtman SM, Wildiers H, Launay-Vacher V, Steer C, Chatelut E, Aapro M. International Society of Geriatric Oncology (SIOG) recommendations for the adjustment of dosing in elderly cancer patients with renal insufficiency. European journal of cancer (Oxford, England : 1990). 2007;43(1):14–34. doi:10.1016/j.ejca.2006.11.004.

22. Hurria A, Naylor M, Cohen HJ. Improving the Quality of Cancer Care in an Aging Population: Recommendations From an IOM Report. JAMA. 2013;310(17):1795–6. doi:10.1001/jama.2013.280416 %J JAMA. [PubMed: 24193075]

23. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2004;22(22):4626–31. doi:10.1200/jco.2004.02.175. [PubMed: 15542812]

24. Hurria A, Lichtman SM. Pharmacokinetics of chemotherapy in the older patient. Cancer control : journal of the Moffitt Cancer Center. 2007;14(1):32–43. doi:10.1177/107327480701400105. [PubMed: 17242669]

25. Balducci L, Corcoran MB. Antineoplastic chemotherapy of the older cancer patient. Hematology/oncology clinics of North America. 2000;14(1):193–212, x-xi. doi:10.1016/s0889-8588(05)70284-7. [PubMed: 10680078]

26. Thurlimann B, Hess D, Koberle D, Senn I, Ballabeni P, Pagani O et al. Anastrozole ('Arimidex') versus tamoxifen as first-line therapy in postmenopausal women with advanced breast cancer: results of the double-blind cross-over SAKK trial 21/95--a sub-study of the TARGET (Tamoxifen or 'Arimidex' Randomized Group Efficacy and Tolerability) trial. Breast cancer research and treatment. 2004;85(3):247–54. doi:10.1023/B:BREA.0000025420.78346.f9. [PubMed: 15111763]

27. Mouridsen H, Gershanovich M, Sun Y, Perez-Carrion R, Boni C, Monnier A et al. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2001;19(10):2596–606. doi:10.1200/jco.2001.19.10.2596. [PubMed: 11352951]

28. Paridaens RJ, Dirix LY, Beex LV, Nooij M, Cameron DA, Cufer T et al. Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008;26(30):4883–90. doi:10.1200/jco.2007.14.4659. [PubMed: 18794551]

29. Robertson JF, Llombart-Cussac A, Rolski J, Feltl D, Dewar J, Macpherson E et al. Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: results from the FIRST study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(27):4530–5. doi:10.1200/jco.2008.21.1136. [PubMed: 19704066]

30. Ellis MJ, Llombart-Cussac A, Feltl D, Dewar JA, Jasiówka M, Hewson N et al. Fulvestrant 500 mg Versus Anastrozole 1 mg for the First-Line Treatment of Advanced Breast Cancer: Overall Survival Analysis From the Phase II FIRST Study. 2015;33(32):3781–7. doi:10.1200/jco.2015.61.5831.

31. Johnston SR, Kilburn LS, Ellis P, Dodwell D, Cameron D, Hayward L et al. Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicentre, phase 3 randomised trial. The Lancet Oncology. 2013;14(10):989–98. doi:10.1016/s1470-2045(13)70322-x. [PubMed: 23902874]

32. Blancas I, Fontanillas M, Conde V, Lao J, Martinez E, Sotelo MJ et al. Efficacy of fulvestrant in the treatment of postmenopausal women with endocrine-resistant advanced breast cancer in routine clinical practice. Clinical & translational oncology : official publication of the Federation

of Spanish Oncology Societies and of the National Cancer Institute of Mexico. 2018;20(7):862–9. doi:10.1007/s12094-017-1797-9.

33. Wang CX, Guo SL, Han LN. Successful treatment of accessory breast cancer with endocrine therapy(). Journal of Zhejiang University Science B. 2017; 18(1):70–5. doi:10.1631/jzus.B1600220. [PubMed: 28070998]
34. Leo AD, Jerusalem G, Petruzelka L, Torres R, Bondarenko IN, Khasanov R et al. Results of the CONFIRM Phase III Trial Comparing Fulvestrant 250 mg With Fulvestrant 500 mg in Postmenopausal Women With Estrogen Receptor–Positive Advanced Breast Cancer. 2010;28(30):4594–600. doi:10.1200/jco.2010.28.8415.
35. Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF et al. Results of the AT AC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet (London, England). 2005;365(9453):60–2. doi:10.1016/s0140-6736(04)17666-6.
36. Ziller V, Kalder M, Albert US, Holzhauer W, Ziller M, Wagner U et al. Adherence to adjuvant endocrine therapy in postmenopausal women with breast cancer. Annals of oncology : official journal of the European Society for Medical Oncology. 2009;20(3):431–6. doi:10.1093/annonc/mdn646. [PubMed: 19150950]
37. Puts MT, Tu HA, Tourangeau A, Howell D, Fitch M, Springall E et al. Factors influencing adherence to cancer treatment in older adults with cancer: a systematic review. Annals of oncology : official journal of the European Society for Medical Oncology. 2014;25(3):564–77. doi:10.1093/annonc/mdt433. [PubMed: 24285020]
38. Pfizer Inc. IBRANCE (palbociclib) [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207103s004lbl.pdf. Revised 3 2017 Accessed October 31, 2019.
39. Novartis Pharmaceuticals Corporation. KISQALI (ribociclib) [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209092s000lbl.pdf. Revised 3 2017 Accessed October 31, 2019.
40. Eli Lilly and Company. VERZNIO (abemaciclib) [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208716s000lbl.pdf. Revised 9 2017 Accessed October 31, 2019.
41. Finn RS, Martin M, Rugo HS, Jones S, Im S-A, Gelmon K et al. Palbociclib and Letrozole in Advanced Breast Cancer. 2016;375(20):1925–36. doi:10.1056/NEJMoa1607303.
42. Finn RS, Crown JP, Ettl J, Schmidt M, Bondarenko IM, Lang I et al. Efficacy and safety of palbociclib in combination with letrozole as first-line treatment of ER-positive, HER2-negative, advanced breast cancer: expanded analyses of subgroups from the randomized pivotal trial PALOMA-1/TRIO-18. Breast cancer research : BCR. 2016;18(1):67. doi:10.1186/s13058-016-0721-5. [PubMed: 27349747]
43. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. The New England journal of medicine. 2016;375(18):1738–48. doi:10.1056/NEJMoa1609709. [PubMed: 27717303]
44. Goetz MP, Toi M, Campone M, Sohn J, Paluch-Shimon S, Huober J et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2017;35(32):3638–46. doi:10.1200/jco.2017.75.6155. [PubMed: 28968163]
45. Turner NC, Ro J, Andre F, Loi S, Verma S, Iwata H et al. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. The New England journal of medicine. 2015;373(3):209–19. doi:10.1056/NEJMoa1505270. [PubMed: 26030518]
46. Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, Masuda N et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. The Lancet Oncology. 2016;17(4):425–39. doi:10.1016/s1470-2045(15)00613-0. [PubMed: 26947331]
47. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. Journal of clinical

oncology : official journal of the American Society of Clinical Oncology. 2018;36(24):2465–72. doi:10.1200/jco.2018.78.9909. [PubMed: 29860922]

48. Sledge GW Jr., Toi M, Neven P, Sohn J, Inoue K, Pivot X et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2− Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2017;35(25):2875–84. doi:10.1200/jco.2017.73.7585. [PubMed: 28580882]
49. Im SA, Lu YS, Bardia A, Harbeck N, Colleoni M, Franke F et al. Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer. The New England journal of medicine. 2019;381(4):307–16. doi:10.1056/NEJMoa1903765. [PubMed: 31166679]
50. Sledge GW Jr, Toi M, Neven P, Sohn J, Inoue K, Pivot X et al. The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor–Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy—MONARCH 2: A Randomized Clinical Trial. JAMA Oncol. 2019. doi:10.1001/jamaoncol.2019.4782 %J JAMA Oncology.
51. Giuliano M, Schettini F, Rognoni C, Milani M, Jerusalem G, Bachelot T et al. Endocrine treatment versus chemotherapy in postmenopausal women with hormone receptor-positive, HER2-negative, metastatic breast cancer: a systematic review and network meta-analysis. The Lancet Oncology. 2019;20(10):1360–9. doi:10.1016/s1470-2045(19)30420-6. [PubMed: 31494037]
52. Battisti NML, De Glas N, Sedrak MS, Loh KP, Liposits G, Soto-Perez-de-Celis E et al. Use of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors in older patients with ER-positive HER2-negative breast cancer: Young International Society of Geriatric Oncology review paper. Ther Adv Med Oncol. 2018;10:1758835918809610-. doi:10.1177/1758835918809610.
53. Dickler MN, Tolaney SM, Rugo HS, Cortes J, Dieras V, Patt D et al. MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR(+)/HER2(−) Metastatic Breast Cancer. Clinical cancer research : an official journal of the American Association for Cancer Research. 2017;23(17):5218–24. doi:10.1158/1078-0432.Ccr-17-0754. [PubMed: 28533223]
54. Howie LJ, Singh H, Bloomquist E, Wedam S, Amiri-Kordestani L, Tang S et al. Outcomes of Older Women With Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor–Negative Metastatic Breast Cancer Treated With a CDK4/6 Inhibitor and an Aromatase Inhibitor: An FDA Pooled Analysis.0(0):JCO.18.02217. doi:10.1200/jco.18.02217.
55. Mahtani RL, Vogel CL. Addressing physician barriers to administering cyclin-dependent kinases 4 and 6 inhibitors in first-line treatment of hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer. Cancer Manag Res. 2019;11:513–24. doi:10.2147/CMAR.S186658. [PubMed: 30655702]
56. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013;153(6):1194–217. doi:10.1016/j.cell.2013.05.039. [PubMed: 23746838]
57. Hill A, Sadda J, LaBarge MA, Hurria A. How cancer therapeutics cause accelerated aging: Insights from the hallmarks of aging. Journal of geriatric oncology. 2019. doi:10.1016/j.jgo.2019.03.007.
58. Miller TW, Balko JM, Arteaga CL. Phosphatidylinositol 3-kinase and antiestrogen resistance in breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011;29(33):4452–61. doi:10.1200/JCO.2010.34.4879. [PubMed: 22010023]
59. Cancer Genome Atlas N Comprehensive molecular portraits of human breast tumours. Nature. 2012;490(7418):61–70. doi:10.1038/nature11412. [PubMed: 23000897]
60. Mollon L, Aguilar A, Anderson E, Dean J, Davis L, Warholak T et al. Abstract 1207: A systematic literature review of the prevalence of PIK3CA mutations and mutation hotspots in HR+/HER2− metastatic breast cancer. 2018;78(13 Supplement):1207-. doi:10.1158/1538-7445.AM2018-1207 %J Cancer Research.
61. Goncalves MD, Hopkins BD, Cantley LC. Phosphatidylinositol 3-Kinase, Growth Disorders, and Cancer. 2018;379(21):2052–62. doi:10.1056/NEJMra1704560.
62. André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS et al. Alpelisib for PIK3CA-Mutated, Hormone Receptor–Positive Advanced Breast Cancer. 2019;380(20):1929–40. doi:10.1056/NEJMoa1813904.

63. Juric D, Janku F, Rodón J, Burris HA, Mayer IA, Schuler M et al. Alpelisib Plus Fulvestrant in PIK3CA-Altered and PIK3CA-Wild-Type Estrogen Receptor-Positive Advanced Breast Cancer: A Phase 1b Clinical Trial. JAMA Oncol. 2019;5(2):e184475–e. doi:10.1001/jamaoncol.2018.4475. [PubMed: 30543347]
64. Novartis Pharmaceuticals Corporation. PIQRAY (alpelisib) [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212526s000lbl.pdf. Revised 5 2019 Accessed October 31, 2019.
65. Lee PG, Halter JB. The Pathophysiology of Hyperglycemia in Older Adults: Clinical Considerations. Diabetes care. 2017;40(4):444–52. doi:10.2337/dc16-1732. [PubMed: 28325795]
66. Di Leo A, Johnston S, Lee KS, Ciruelos E, Lonning PE, Janni W et al. Buparlisib plus fulvestrant in postmenopausal women with hormone-receptor-positive, HER2-negative, advanced breast cancer progressing on or after mTOR inhibition (BELLE-3): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Oncology. 2018;19(1):87–100. doi:10.1016/s1470-2045(17)30688-5. [PubMed: 29223745]
67. Yue W, Fan P, Wang J, Li Y, Santen RJ. Mechanisms of acquired resistance to endocrine therapy in hormone-dependent breast cancer cells. J Steroid Biochem Mol Biol. 2007;106(1-5):102–10. doi:10.1016/j.jsbmb.2007.05.008. [PubMed: 17616457]
68. Miller TW, Hennessy BT, González-Angulo AM, Fox EM, Mills GB, Chen H et al. Hyperactivation of phosphatidylinositol-3 kinase promotes escape from hormone dependence in estrogen receptor-positive human breast cancer. J Clin Invest. 2010;120(7):2406–13. doi:10.1172/JCI41680. [PubMed: 20530877]
69. Santen RJ, Song RX, Zhang Z, Kumar R, Jeng MH, Masamura S et al. Adaptive hypersensitivity to estrogen: mechanisms and clinical relevance to aromatase inhibitor therapy in breast cancer treatment. J Steroid Biochem Mol Biol. 2005;95(1-5):155–65. doi:10.1016/j.jsbmb.2005.04.025. [PubMed: 16024245]
70. Meric-Bernstam F, Chen H, Akcakanat A, Do K-A, Lluch A, Hennessy BT et al. Aberrations in translational regulation are associated with poor prognosis in hormone receptor-positive breast cancer. Breast cancer research : BCR. 2012;14(5):R138–R. doi:10.1186/bcr3343. [PubMed: 23102376]
71. Novartis Pharmaceuticals Corporation. AFINITOR (everolimus) [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022334s040,203985s013lbl.pdf. Revised 4 2018 Accessed October 31, 2019.
72. Yardley DA, Noguchi S, Pritchard KI, Burris HA 3rd, Baselga J, Gnant M et al. Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. Advances in therapy. 2013;30(10):870–84. doi:10.1007/s12325-013-0060-1. [PubMed: 24158787]
73. Baselga J, Campone M, Piccart M, Burris HA 3rd, Rugo HS, Sahmoud T et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. The New England journal of medicine. 2012;366(6):520–9. doi:10.1056/NEJMoa1109653. [PubMed: 22149876]
74. Pritchard KI, Burris HA 3rd, Ito Y, Rugo HS, Dakhil S, Hortobagyi GN et al. Safety and efficacy of everolimus with exemestane vs. exemestane alone in elderly patients with HER2-negative, hormone receptor-positive breast cancer in BOLERO-2. Clinical breast cancer. 2013;13(6):421–32.e8. doi:10.1016/j.clbc.2013.08.011 [PubMed: 24267730]
75. Kornblum N, Zhao F, Manola J, Klein P, Ramaswamy B, Brufsky A et al. Randomized Phase II Trial of Fulvestrant Plus Everolimus or Placebo in Postmenopausal Women With Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer Resistant to Aromatase Inhibitor Therapy: Results of PrE0102. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2018;36(16):1556–63. doi:10.1200/jco.2017.76.9331. [PubMed: 29664714]
76. Hurria A, Dale W, Mooney M, Rowland JH, Ballman KV, Cohen HJ et al. Designing therapeutic clinical trials for older and frail adults with cancer: U13 conference recommendations. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2014;32(24):2587–94. doi:10.1200/JCO.2013.55.0418. [PubMed: 25071116]

77. Wilcken N, Hornbuckle J, Ghersi D. Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer. The Cochrane database of systematic reviews. 2003(2):Cd002747. doi:10.1002/14651858.Cd002747. [PubMed: 12804433]

78. Shachar SS, Hurria A, Muss HB. Breast Cancer in Women Older Than 80 Years. 2016;12(2):123–32. doi:10.1200/jop.2015.010207.

79. Oshaughnessy JA, Blum J, Moiseyenko V, Jones SE, Miles D, Bell D et al. Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs. a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer. Annals of oncology : official journal of the European Society for Medical Oncology. 2001;12(9):1247–54. doi:10.1023/a:1012281104865. [PubMed: 11697835]

80. Talbot DC, Moiseyenko V, Van Belle S, O'Reilly SM, Alba Conejo E, Ackland S et al. Randomised, phase II trial comparing oral capecitabine (Xeloda) with paclitaxel in patients with metastatic/advanced breast cancer pretreated with anthracyclines. British journal of cancer. 2002;86(9):1367–72. doi:10.1038/sj.bjc.6600261. [PubMed: 11986765]

81. Zielinski C, Gralow J, Martin M. Optimising the dose of capecitabine in metastatic breast cancer: confused, clarified or confirmed? Annals of Oncology. 2010;21(11):2145–52. doi:10.1093/annonc/mdq069. [PubMed: 20332132]

82. Bajetta E, Procopio G, Celio L, Gattinoni L, Torre SD, Mariani L et al. Safety and Efficacy of Two Different Doses of Capecitabine in the Treatment of Advanced Breast Cancer in Older Women. 2005;23(10):2155–61. doi:10.1200/jco.2005.02.167.

83. O'Shaughnessy JA, Kaufmann M, Siedentopf F, Dalivoust P, Debled M, Robert NJ et al. Capecitabine monotherapy: review of studies in first-line HER-2-negative metastatic breast cancer. The oncologist. 2012;17(4):476–84. doi:10.1634/theoncologist.2011-0281. [PubMed: 22418569]

84. Yardley DA. Taxanes in the elderly patient with metastatic breast cancer. Breast Cancer (Dove Med Press). 2015;7:293–301. doi:10.2147/BCTT.S87638. [PubMed: 26379446]

85. Wildiers H, Paridaens R. Taxanes in elderly breast cancer patients. Cancer treatment reviews. 2004;30(4):333–42. doi:10.1016/j.ctrv.2003.12.001. [PubMed: 15145508]

86. Hainsworth JD, Burris HA 3rd, Yardley DA, Bradof JE, Grimaldi M, Kalman LA et al. Weekly docetaxel in the treatment of elderly patients with advanced breast cancer: a Minnie Pearl Cancer Research Network phase II trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2001;19(15):3500–5. doi:10.1200/jco.2001.19.15.3500. [PubMed: 11481356]

87. Lichtman SM, Hurria A, Cirrincione CT, Seidman AD, Winer E, Hudis C et al. Paclitaxel efficacy and toxicity in older women with metastatic breast cancer: combined analysis of CALGB 9342 and 9840. Annals of oncology : official journal of the European Society for Medical Oncology. 2012;23(3):632–8. doi:10.1093/annonc/mdr297. [PubMed: 21693770]

88. Del Mastro L, Perrone F, Repetto L, Manzione L, Zagonel V, Fratino L et al. Weekly paclitaxel as first-line chemotherapy in elderly advanced breast cancer patients: a phase II study of the Gruppo Italiano di Oncologia Geriatrica (GIOGer). Annals of oncology : official journal of the European Society for Medical Oncology. 2005;16(2):253–8. doi:10.1093/annonc/mdi056. [PubMed: 15668279]

89. Aapro M, Tjulandin S, Bhar P, Gradishar W. Weekly nab-paclitaxel is safe and effective in >/=65 years old patients with metastatic breast cancer: a post-hoc analysis. Breast (Edinburgh, Scotland). 2011;20(5):468–74. doi:10.1016/j.breast.2011.07.005.

90. Abraxis Bioscience. ABRAXANE (nab-paclitaxel) [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021660s022lbl.pdf. Revised 5 2009 Accessed October 31, 2019.

91. Shachar SS, Muss HB. Internet tools to enhance breast cancer care. npj Breast Cancer. 2016;2(1):16011. doi:10.1038/npjbcancer.2016.11. [PubMed: 28721377]

92. Glaser R, Marinopoulos S, Dimitrakakis C. Breast cancer treatment in women over the age of 80: A tailored approach. Maturitas. 2018;110:29–32. doi:10.1016/j.maturitas.2018.01.014. [PubMed: 29563032]

93. Kimmick GG, Major B, Clapp J, Sloan J, Pitcher B, Ballman K et al. Using ePrognosis to estimate 2-year all-cause mortality in older women with breast cancer: Cancer and Leukemia Group B

(CALGB) 49907 and 369901 (Alliance A151503). Breast cancer research and treatment. 2017;163(2):391–8. doi:10.1007/s10549-017-4188-6. [PubMed: 28283904]

94. Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP et al. Predicting Chemotherapy Toxicity in Older Adults With Cancer: A Prospective Multicenter Study. 2011;29(25):3457–65. doi:10.1200/jco.2011.34.7625.
95. Mohile SG, Epstein RM, Hurria A, Heckler CE, Canin B, Culakova E et al. Communication With Older Patients With Cancer Using Geriatric Assessment: A Cluster-Randomized Clinical Trial From the National Cancer Institute Community Oncology Research Program. JAMA Oncol. 2019:1–9. doi:10.1001/jamaoncol.2019.4728.
96. Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. The Lancet Oncology. 2015;16(1):25–35. doi:10.1016/s1470-2045(14)71159-3. [PubMed: 25524798]

**Key Points**

- Endocrine therapy is a safe, tolerable and effective treatment in older patients with hormone-receptor positive, HER2-negative metastatic breast cancer.
- CDK4/6 inhibitors, PI3K inhibitors, and mTOR inhibitors in combination with endocrine therapy are promising for the treatment of older adults, but prospective data is limited.
- There is a need to explore ways to improve adherence to hormonal and targeted therapy in older patients, which may be different than interventions designed for younger patients.
- Chemotherapy is considered safe and effective in older adults but may require added attention to dosing in this vulnerable population.
- Treating older adults requires a multidisciplinary approach that integrates geriatric and oncology principles.

**Table I.**

Age and ECOG PS of adults with breast cancer included in registration studies of targeted therapies

| Class | Agent | Trial | Age | | | ECOG PS | | |
|---|---|---|---|---|---|---|---|---|
| | | | Total | ≥ 65 years | ≥ 70 years | 0 | 1 | 2 |
| CDK 4/6 Inhibitor | Abemaciclib | **MONARCH-1** [53] | 132 | 42 (31.8%) | NR | 73 (55.3%) | 59 (44.7%) | NR |
| | | **MONARCH-2** [48] | 493 | 222 (45%) | NR | 296 (60%) | 197 (39.9%) | NR |
| | | **MONARCH-3** [44] | 493 | 222 (45%) | NR | 296 (60%) | 197 (39.9%) | NR |
| | Palbociclib | **PALOMA-1** [96] | 165 | 76 (46%) | NR | 91 (55.2%) | 74 (44.8%) | NR |
| | | **PALOMA-2** [41] | 666 | 262 (39.3%) | NR | 359 (53.9%) | 295 (44.3%) | 12 (1.8%) |
| | | **PALOMA-3** [46] | 521 | NR | NR | 322 (61.8%) | 199 (38.2%) | NR |
| | Ribociclib | **MONALEESA-2** [39] | 668 | 295 (44.2%) | NR | 407 (60.9%) | 261 (39.1%) | NR |
| | | **MONALEESA-3** [47] | 726 | 339 (46.7%) | NR | 468 (64.5%) | 256 (35.3%) | NR |
| PI3K Inhibitor | Alpelisib | **SOLAR-1** [62] | 572 | NR | NR | 388 (67.8%) | 181 (31.6%) | NR |
| mTOR Inhibitor | Everolimus | **BOLERO-2** [71] | 724 | 275 (37.9%) | 164 (22.7%) | 435 (60.1%) | 258 (35.6%) | 16 (2.21%) |

NR = Not Reported

**Table II.**

Efficacy results of registration studies of targeted therapies

| Class | Agent | Trial | Progression Free Survival | | | Objective Response | | |
|---|---|---|---|---|---|---|---|---|
| | | | N | Number of events (%) | Median in months, (95% CI) | N | Objective Response Rate (%) | CI (%) |
| CDK 4/6 Inhibitor | Abemaciclib | **MONARCH-1** [53] | 132 | NR | 6.0, (4.2-7.5)<br>5.9, (3.7-8.1) | 132 | 26 (19.7)<br>23 (17.4) | 13.3-27.5<br>11.4-25.0 |
| | | **MONARCH-2** [48] | 446 | 222 (49.8) | 16.4, (14.4-19.3) | 318 | 153 (48.1) | 42.6-53.6 |
| | | **MONARCH-3** [44] | 328 | 108 (32.9) * | NR | 267 | 158 (59.2) | 53.3-65.1 |
| | Palbociclib | **PALOMA-1** [96] | 84 | 41 (48.8) | 10.2, (5.7-12.6) | 65 | 36 (55.4) | 43.0-68.0 |
| | | **PALOMA-2** [41] | 444 | 194 (43.7) | 24.8, (22.1-NE) | 338 | 55.3 (49.9) | 49.9-60.7 |
| | | **PALOMA-3** [46] | 347 | 145 (41.8) | 9.5, (9.2-11.0) | 268 | 66 (24.6) | 19.6-30.2 |
| | Ribociclib | **MONALEESA-2** [39] | 334 | 93 (27.8) | NR, (19.3-NR) | 256 | 52.7 (20.6) | 46.6-58.9 |
| | | **MONALEESA-3** [47] | 484 | 210 (43) | 20.5, (18.5-23.5) | 379 | 155 (40.9) | 35.9-45.8 |
| PI3K Inhibitor | Alpelisib | **SOLAR-1** [62] | 169 | 103 (61) | 11.0, (7.5-14.5) | 126 | 45.0 (35.7) | 27.4-44.7 |
| mTOR Inhibitor | Everolimus | **BOLERO-2** [71] | 485 | NR | 7.8, (6.9, 8.5)<br>11.0, (9.7, 15.0) | 485 | 61.1 (12.6) | 9.8-15.9 |

NR = Not Reported

NE = Not Estimable

* Number of patients with an event