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Targeted therapy for breast cancer in older patients

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ABSTRACT

Older patients are one of the most relevant sub-groups of patients with breast cancer and will only gain in importance as demographic transition unfolds. Their management, in both the early and advanced settings, should take into consideration specific clinical needs and is made more difficult by the limited availability of evidence on the efficacy and safety of standard treatment regimens in older patients. At the root of this situation is the low rate of participation of older patients in clinical trials, often due to age limits for inclusion, and limitations on the participation of persons with significant comorbidities or organ dysfunction. Although this has begun to change in recent years, most agents currently in use have not been tested in a substantial number of older patients. This includes the targeted agents that have, in the last fifteen years, changed the prognosis of patients with early and advanced breast cancer. Most data guiding the use of targeted agents in older patients come from subanalysis of larger trials or small retrospective cohort studies. The goal of this review is to go over the available evidence regarding the efficacy and safety of targeted agents approved for use in breast cancer (trastuzumab, lapatinib, T-DM1, pertuzumab, neratinib, palbociclib, bevacizumab, ribociclib, abemaciclib, everolimus, olaparib, talazoparib), and place their side effects into an older-specific context in order to help medical oncologists when making treatment decisions and managing older patients with breast cancer.

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1. Introduction

Breast cancer (BC) is one of the most frequent and deadly forms of cancer [1]. Older patients represent, today, a large proportion of patients in diagnosed with BC [2]. Evidence-based management of older patients with BC is challenging as they are underrepresented in clinical trials [3,4]. End-points used in cancer trials, moreover, can be less relevant to older patients, who often focus on functionality rather than on increasing survival time [5,6]. Registration trials rarely focus on issues specific to older patients or place drug safety within a context appropriate to older patients, including investigating interactions, altered drug metabolism and what toxicity may entail for older patients. Today, due to the rarity of studies designed to study targeted agents in older populations, most of the efficacy and safety data which underpin treatment decisions is based on small case series, retrospective cohorts or sub-analysis of general population studies.

This review will provide a thorough and practical expert opinion-based assessment of the state of the evidence regarding approved targeted agents in older patients with BC (Tables 1 and 2). Particular attention will be given to drug-related adverse events (AEs), in putting the most clinically relevant AEs into a geriatric context (Supplementary Table 1), highlighting the special concerns that may arise due to common AEs in older patients as well as on potential drug-drug interactions (Table 3) in order to help medical oncologists make the most appropriate decisions.

2. Anti-HER2 Agents

Anti-human epidermal growth factor receptor 2 (HER2) agents comprise five agents, approved in the early and/or advanced setting [7,8]. These are trastuzumab, lapatinib, pertuzumab, T-DM1 and neratinib (see Table 1).

2.1. Trastuzumab

2.1.1. Metastatic Setting

Data on the efficacy and safety of trastuzumab in older patients in the metastatic setting is sparse. Kaufman et al. compared patients aged ≥75 (65 patients) with those aged between ≥65 and < 75 (144 patients) and those aged <65 (792 patients). Results suggest that the patients ≥75 receive trastuzumab less frequently (77% vs 81% vs 85%, respectively) and are more likely to receive it alone or in combination with endocrine therapy (ET) (18% vs 4.3% vs 5.3% respectively) [9]. Another study by Griffiths et al. used SEER-MEDICARE database data to identify 610 patients ≥66 years who received trastuzumab for metastatic BC. Their results suggest trastuzumab use is associated with reduced cancer-specific mortality (HR 0.67; 95% CI 0.51–0.88 $P < .01$). Interestingly, in this study, 31% of patients received trastuzumab alone while 48% received trastuzumab plus taxane-based chemotherapy (which was significantly associated with better outcomes) [10].

2.1.2. Adjuvant Setting

One meta-analysis of the adjuvant trials and one systematic review investigated outcomes in older (defined as ≥60) patients who participated in trastuzumab adjuvant trials and both publications show significant improvement in outcomes with the use of trastuzumab [11,12]. Additional data is available from retrospective cohort studies. The study by Dall et al. showed patients aged ≥65 had similar improvement in outcomes but a higher risk of early discontinuation (8% in <65 and 13% ≥75) and probability of receiving trastuzumab monotherapy (5% in <65 and 9% ≥75) when compared to younger patients [13]. Reeder-Hayes et al. investigated the comparative efficacy and toxicity of adjuvant regimens containing trastuzumab in older patients using SEER-Medicare data, showing that the two most commonly prescribed regimens – ACTH (doxorubicin, cyclophosphamide, paclitaxel, and trastuzumab) and TCH (docetaxel, carboplatin, and trastuzumab) led to comparably good survival outcomes in older patients. ACTH compared with TCH was, moreover, not associated with a higher rate of serious AEs or hospitalizations, but was associated with worse treatment completion [14].

One study prospectively evaluated trastuzumab in older patients - the RESPECT trial (NCT01104935), which randomized 275 patients between 70 and 80 years of age with stage I-IIIA HER2+ BC between adjuvant trastuzumab alone or trastuzumab plus chemotherapy. The goal of RESPECT was to determine whether trastuzumab monotherapy was non-inferior to trastuzumab + chemotherapy in older patients. Three-year disease-free survival (DFS) results were 94.8% (combination) vs 89.2% (trastuzumab alone), HR 1.42; 95% CI 0.68–2.95, $p = .35$. Trastuzumab monotherapy was better tolerated and was on the short term better in terms of quality of life (QoL), though no difference remained at three years, including, critically, on cognitive function [15–17]. The results are difficult to interpret since the study was clearly underpowered to confirm non-inferiority with clinically relevant borders.

The duration of adjuvant treatment with trastuzumab has been long debated [18]. Several trials had tested reduced treatment durations, all having failed until very recently [19]. The PERSEPHONE trial testing one year vs six months of trastuzumab showed non-inferiority between efficacy outcomes with the two regimens. Though the results of PERSEPHONE should be seen with caution, six month trastuzumab treatment could be considered as an option in older patients when

Table 1
FDA and/or EMA Approved target agents for use in breast cancer treatment.

Name	Year of Approval	Settings
Trastuzumab	1998	Early and Metastatic HER2+ Disease
Lapatinib	2007	Metastatic HER2+ Disease
Bevacizumab	2010	Metastatic HER2- Disease[b]
Everolimus	2010	Metastatic ER+ HER2- Disease
Pertuzumab	2012	Early and Metastatic HER2+ Disease
T-DM1	2013	Early and Metastatic HER2+ Disease
Palbociclib	2015	Metastatic ER+ HER2- Disease
Ribociclib	2017	Metastatic ER+ HER2- Disease
Neratinib	2017	Early HER2+ Disease
Olaparib	2018	Metastatic HER2- Disease in gBRCA mutated patients[a]
Talazoparib	2018	Metastatic HER2- Disease in gBRCA mutated patients[a]

FDA - Food and Drug Administration; EMA - European Medicines Agency; HER2 -human epidermal growth factor receptor 2; ER - Estrogen Receptor, gBRCA – Germline Breast Cancer Susceptibility Gene.
[a] FDA approved only.
[b] EMA approved only.

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Table 2
Phase III trials and reported older adult populations and results.

Drug	Trial	Indication	Treatment	Older population	Reported results in older adults
Trastuzumab	TAnDEM (NCT00022672) [92]	Metastatic	Trastuzumab+Anastrozole vs Anastrozole	Not reported.	Not reported
Trastuzumab	Slamon Trial [93]	Metastatic	Trastuzumab+CT vs CT	Not reported.	Not Reported
Trastuzumab	HERA (NCT00045032) [94]	Adjuvant	Trastuzumab 1 year vs Trastuzumab 2 years vs Observation	≥60 = 818 (16%)	≥60 1y vs observation DFS HR = 0.82 (CL, 0.62–1.08); 2y vs observation HR 0,78 (CL, 0.59–1.03)
Trastuzumab	BCIRG-006 (NCT00021255) [95]	Adjuvant	AC-T vs AC-TH vs TCH (1 year of trastuzumab)	Not reported.	Not Reported
Trastuzumab	NCCTG N9831 + NSABP B31	Adjuvant	AC-T vs AC-TH (1 year of trastuzumab)	≥60 = 683 (16.8%)	>60 DFS HR = 0.41 (95% CI, 0.24–0.68)
Trastuzumab	FNCLCC-PACS 04 [96]	Adjuvant	CT+ Trastuzumab vs CT (1 year of trastuzumab)	No patients above 65 allowed, above 60 not reported	Not reported
Trastuzumab	FinHER [18]	Adjuvant	Docetaxel or Vinorelbine with or without Trastuzumab for 9 weeks	No patients above 65 allowed, above 60 not reported	Not reported
Pertuzumab	CLEOPATRA (NCT00567190) [37]	Metastatic	Docetaxel+Trastuzumab+Pertuzumab vs Docetaxel+Trastuzumab+Placebo	≥65 = 127 (15,7%); ≥75 = 19 (2,3%)	PFS ≥65 HR 0,53 (CI 0,31-0,9); ≥75 HR 0,85 (CI 0,26-2,73)
Pertuzumab	Neosphere (NCT00545688) [44]	Neoadjuvant	Docetaxel+Trastuzumab; Pertuzumab+Docetaxel; Pertuzumab+Trastuzumab, Docetaxel +Trastuzumab+Pertuzumab	Not reported.	Not Reported
Pertuzumab	APHINITY (NCT01358877) [46]	Adjuvant	CT + Trastuzumab+Pertuzumab vs CT + Trastuzumab+placebo	≥65 = 608 (12.6%)	≥65 = 3y-IDFS 92,9% vs 90,6% HR 0,70 (CI0,41–1,17)
T-DM1	EMILIA (NCT00829166) [48]	Metastatic	T-DM1 vs Capecitabine + Lapatinib	65–74 = 113 (11,4%); ≥75 = 25 (2,5%)	65–74 HR 0,89 (CI 0,56-1,43); ≥75 HR 2,79 (0,99-7,88)
T-DM1	TH3RESA (NCT01419197) [49]	Metastatic	T-DM1 vs Physicians choice	65–74 = 74 (12,9%); ≥75 = 19 (3,1%)	OS: 65–74 = 18,2 m vs 13,5 m (HR 0,73 CI 0,40-1,34); ≥75 = 31,8 m vs 16,4 m (HR 0,27 CI 0,07-1,04)
T-DM1	KATHERINE (NCT01772472) [50]	Post-neoadjuvant	T-DM1 vs Trastuzumab	65–74 = 56 (7.5%); ≥75 = 2 (0.3)	iDFS ≥65 = 87.4% vs 81.1% HR 0.55 (CI 0.22–1.34)
Lapatinib	Geyer Trial [30] (NCT00078572)	Metastatic	Lapatinib+Capecitabine vs Capecitabine	Not reported.	Not Reported
Lapatinib	MA.31 (NCT00667251) [97]	Metastatic	Paclitaxel+Lapatinib vs Paclitaxel+Trastuzumab	60–69 = 143 (22%); ≥70 = 60 (9%)	Not Reported
Lapatinib	EGF104900 (NCT00320385) [29]	Metastatic	Lapatinib+Trastuzumab vs Trastuzumab	Not reported.	Not Reported
Lapatinib	ALTTO [32]	Adjuvant	CT + Trastuzumab vs CT + Lapatinib vs CT + Trastuzumab+Lapatinib vs CT + Trastuzumab-Lapatinib	≥65 = 855 (10%)	Not Reported
Neratinib	ExteNET (NCT00878709) [56]	Adjuvant	Neratinib+ Paclitaxel vs Trastuzumab+Paclitaxel	≥65 = 87 (18%)	IDFS ≥65 (HR 0,75 CI 0,43-1,30)
Everolimus	BOLERO-2 (NCT00863655) [63,98]	Metastatic	Everolimus+Examestane vs Placebo+Examestane	≥ 65 = 275; ≥ 70 = 164	PFS ≥ 70: 6,8 vs 1,5 m 0,45 (0,30-0,68); stomatitis 49%, fatigue 38%, decreased appetite 38%, diarrhea 36%
Palbociclib	PALOMA - 2 (NCT01740427) [78,80]	Metastatic	Letrozole+Palbociclib vs Letrozole+Placebo	≥ 65 = 262 (39.3%)	PFS ≥ 65: 26,2 vs 12,9 m HR 0.57 (CI 0,39-0,84)
Palbociclib	PALOMA - 3 (NCT01942135) [80,99]	Metastatic	Fulvestrant+Palbociclib vs Fulvestrant+Placebo	≥ 65 = 129 (24, 8%)	PFS ≥ 65: 9,9 vs 3,9 m HR 0.35 (CI 0,19-0,62)
Ribociclib	MONALEESA - 2 (NCT01958021) [83,100]	Metastatic	Ribociclib+Letrozole vs Letrozole	≥ 65 = 295 (44, 2%)	PFS ≥ 65: HR 0,61 (0,39-0,94)
Bevacizumab	AVADO (NCT00333775) [70,71]	Metastatic	Placebo+Docetaxel vs Docetaxel+Bevacizumab 7.5 mg vs Docetaxel+Bevacizumab 15 mg	≥ 65 = 127 (17, 2%)	PFS ≥ 65, placebo vs bev 7,5 mg HR 0, 83; placebo vs bev 15 mg HR 0, 58, CI not reported but both non-significant.
Bevacizumab	Ribbon-1 (NCT00262067) [101]	Metastatic	Capecitabine or AT+Placebo vs Capecitabine or AT +Bevacizumab	Capecitabine ≥65 = 153 (24, 8%); AT ≥65 = 124(19, 9%)	Capecitabine ≥65 PFS 6,2 vs 9,1 m (HR 0,69 95% CI 0,47-1,02); AT ≥65 PFS 8,5 vs 10,1 m (HR 0,83 95% CI 0,52-1,34)
Bevacizumab	E2100 (NCT00028990) [102]	Metastatic	Paclitaxel vs Paclitaxel+Bevacizumab	≥ 65–85 = 148 (20, 49%)	PFS ≥ 65–85: 7,9–11,9 m; HR 0,77 (95% CI 0,54-1,09)
Olaparib	OlympiAD (NCT02000622) [87]	Metastatic	Olaparib vs Physicians Choice	15 patients 65 or older (4.9%)	Not reported

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Table 2 (*continued*)

Drug	Trial	Indication	Treatment	Older population	Reported results in older adults
Talazoparib	EMBRACA (NCT01945775) [88]	Metastatic	Talazoparib vs Physicians Choice	Not reported	Not reported

HR = Hazard Ratio, PFS = Progression Free-Survival, iDFS = invasive Disease Free Survival, OS = Overall Survival; DFS = Disease Free Survival.

anthracycline/taxane chemotherapy will be used [20]. It is important to stress, however, that chemotherapy de-escalation, as per the APT trial, should take precedence over trastuzumab de-escalation in older patients [21].

2.1.3. Cardiac Toxicity

Trastuzumab-induced cardiotoxicity is a special concern in older patients [22] and can lead to loss in functionality. It is, however, often asymptomatic and generally resolves after interruption of trastuzumab use [23] but whether this is also true for frail older patients is not specifically studied. Recognized risk factors include age (specially above 80), duration of treatment, comorbidities (hypertension, diabetes, coronary disease), and previous anthracycline use [23–25]. Most available studies in older patients receiving trastuzumab in either the metastatic and early settings confirm that they are at higher risk of experiencing trastuzumab-related cardiac toxicity, with rates of up to 25.4% of treated patients [9–11,13,26,27].

2.1.4. Conclusion

Though the amount of data available in clinical trials for trastuzumab use in older patients is overall limited, it suggests that trastuzumab is effective in older populations in both early and metastatic settings and that trastuzumab monotherapy is a sub-optimal regimen that should not be considered as standard. Risk factors for trastuzumab-associated cardiac toxicity are well established, allowing for easier patient selection. Fit older patients with controlled cardiovascular comorbidities and without end-organ damage are good candidates for trastuzumab therapy. For less fit or frail patients, trastuzumab therapy can still be, nevertheless, of benefit, with de-escalated regimens being an option in parallel with careful follow-up.

2.2. Lapatinib

Lapatinib is a tirosine kinase inhibitor that blocks HER1 and HER2 and is approved for use in combination with letrozole, capecitabine or trastuzumab in metastatic HER2+ BC [28–30]. Limited data is available

Table 3
Targeted drugs and interactions with commonly use drugs

Targeted agent	Metabolism	Dose adjustments	Interactions
Trastuzumab	Plasmatic	No adjustments suggested for hepatic and renal dysfunction (not studied)	Increased cardiac toxicity with anthracycline use (wash out 20 weeks for trastuzumab)
Lapatinib	Major substrate of CYP3A4, moderate inhibitor of BCRP, CYP2C8 and weak inhibitor of CYP3A4 and P-Glycoprotein	Renal failure: As renal elimination is minimal therefore no adjustment is needed; Hepatic failure: Child-Pugh class C should have dose adjustment. With capecitabine dose should be reduced 750 mg and with letrozole 1000 mg.	To avoid: CYP 3A4, 2C8, 2C19 (grapefruit juice) inhibitors, inducers and substrates with a narrow therapeutic index, substances that increase gastric pH (avoid oral anti-acids within one-hour of a lapatinib dose), digoxin. Administer with caution when prescribing medications that can worsen heart function or increase QTc
Pertuzumab	Plasmatic	No adjustments suggested for hepatic and renal dysfunction (not studied)	To avoid: other monoclonal antibodies and immunosuppressant medications
T-DM1	Major substrate of CYP3A4	No adjustments suggested for hepatic and renal dysfunction (not studied)	Close watch to patients receiving anticoagulants. Inhibitors and inducers of 3A4 should be avoided, as well as PGP inhibitors.
Neratinib	Major substrate of CYP3A4; Inhibitor of P-glycoprotein/ABCB1	No dose adjustment needed. If severe hepatic function impairment reduce dose to 80 mg/day	Close watch to patients receiving anticoagulants. Inhibitors and inducers of 3A4 should be avoided, as well as PGP inhibitors.
Everolimus	Major substrate of CYP3A4; Inhibitor of P-glycoprotein/ABCB1, weak inhibitor of CYP3A4	No adjustment needed for renal impairment. Dose should be reduced to 7,5 mg if mild impairment, 5 mg if moderate and 2,5 mg if severe.	Drugs that increase stomach pH can alter absorption and reduce efficacy. If anti-acid use is necessary take neratinib 3 h before. Inhibitors and inducers of 3A4 should be avoided, as well as PGP/ABCB1 inhibitors and digoxin
Palbociclib	Major substrate of CYP3A4; weak inhibitor of CYP3A4, Inhibitor of PGP	No dose adjustments for renal or liver failure	Inhibitors, inducers and substrates of CYP 3A4 should be avoided. Also avoid in patients with galactose intolerance, Lapp lactase deficiency or glucose/galactose malabsorption syndrome.
Ribociclib	Major substrate of CYP3A4; moderate inhibitor of CYP3A4	No dose adjustments for renal failure, reduce dose to 400 mg/day if moderate or severe liver impairment	Avoid substrates, inducers and inhibitors of CYP 3A4 (moderate inhibition CYP3A4)
Bevacizumab	Plasmatic; Inhibitor of PGP	No dose adjustments for renal or liver failure	Can increase the toxicity of anthracyclines and myelosupressive effects of other cytotoxic agents.
Abemaciclib	Substrate of CYP3A4.	No dose adjustment necessary for renal failure; Child-Pugh class C: Reduce the abemaciclib frequency to once daily.	Avoid substrates, inducers and inhibitors of BCRP/ABCG2, CYP3A4 and PGP/ABCB1
Olaparib	Substrate of CYP3A; Inhibitor of PGP	Dose adjustment for CrCl below 50 mL/min. No adjustments for moderate or mild liver failure.	Avoid inhibitors and inducers of CYP3A4 as well as substrates. If a moderate inhibitor of CYP3A4 is absolutely necessary, dose should be reduced to either 300 mg (moderate) or 200 mg (strong)
Talazoparib	Substrate of BCRP/ABCG2, P-glycoprotein/ABCB1	CrCl 30 to 59 mL/min: Reduce dose to 0.75 mg once daily. No need of adjustment for mild liver function impairment, not studies in moderate to serious liver function impairment	P-glycoprotein/ABCB1 Inhibitors such as Amiodarone; Carvedilol; Clarithromycin; Itraconazole; Verapamil may increase the concentration of talazoparib. In case of concomitant use reduce talazoparib to 0.75 mg per day for the first 3–5 half lives

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on lapatinib use in older patients with BC. A series of 26 cases above age 65 showed a median progression-free survival (PFS) of seven months with lapatinib and capecitabine (close to the 8.4 months improvement in time to progression obtained in the registration trial) [31]. Though in this series, lapatinib was overall reasonably well tolerated with only two interruptions due to AEs and only one treatment discontinuation due to adverse event, this has not been the case in the adjuvant setting in which tolerability and treatment completion rates are major concerns [35]. More recently, a prospective study in older patients ($N = 40$, median age 72) testing trastuzumab + lapatinib in the advanced setting showed a response rate of 23% and a clinical benefit rate of 45%. 43% of patients needed a lapatinib dose reduction, and 20% had grade 3 or more AEs (diarrhea 5%) [33].

In combination with capecitabine, lapatinib increases the incidence of diarrhea and cutaneous rash [28,29,31,32]. Clinical tools for predicting the toxicity of this regimen were proposed, and advanced age (>65) is a known risk factor [34]. It is, moreover, a regimen that entails the intake of numerous pills or tablets per day, and is therefore cumbersome and can lead to confusion and wrong dosing [35]. Considering the existing regimen choices, the favored regimens in older patients with hormone receptor positive tumors should be in combination with trastuzumab or letrozole.

2.3. Pertuzumab

2.3.1. Metastatic Setting

Pertuzumab is a monoclonal anti-body that impedes the heterodimerization between the HER2 and HER3 receptors [36] and was registered following the results of the CLEOPATRA trial [37], in which 127 patients (15.7%) were 65 years of age or older. Pre-planned subgroup analyses by age group (<65, ≥65, <75, and ≥ 75 years) suggest that all age groups benefit from the regimen similarly. Safety data show, however, a higher number of docetaxel dose reductions and lower total number of docetaxel cycles for the population ≥ 65 years. Paradoxically, neutropenia was less common in older patients, likely because they received more growth factor support [38], but diarrhea (19% vs 8%) [39], anorexia, vomiting, dysgeusia and fatigue – all toxicities of significant functional impact in nutrition and hydration, were more common in older patients than in younger patients. An effective strategy to manage diarrhea should entail proactive follow-up and early intervention with antidiarrheal medications, dietary modifications, rehydration, dose delays, or reductions of the chemotherapy agent [40]. Additionally, a phase II trial showed that weekly paclitaxel, offers an alternative to docetaxel-based therapy for first and second-line older patients with BC [41].

The EORTC 75111-10114 randomized phase II evaluated trastuzumab combined with pertuzumab (TP) or TP plus metronomic chemotherapy (TPM – consisting of continuous 50 mg cyclophosphamide) in an old/frail HER2+ metastatic BC population. The population consisted of a true older population; median age was 77 years and a potential frailty profile was present in 56 patients (71%) of 79 as measured by the geriatric screening with the G8 tool (≤14). With 20.7 months of median follow-up this study has shown a seven months higher median PFS for TPM over TP alone without adding significant toxicity in this old and frail HER2+ advanced BC population. This difference in treatment efficacy went along with an acceptable toxicity profile for both arms and geriatric assessment evolution during the first year showed no relevant difference in functional evolution between treatment arms [42]. TPM constitutes, therefore, an alternative in this particularly frail population.

Regimens adding ET to the TP double are an interesting approach to older patients. In the PERTAIN study (aromatase inhibitor + trastuzumab + pertuzumab) patients received trastuzumab (with or without a taxane for 18–24 weeks) plus an aromatase inhibitor (anastrozole or letrozole), or trastuzumab (with or without a taxane for 18–24 weeks) plus pertuzumab and an aromatase inhibitor. Though double blockade plus aromatase inhibitor regimen appears to be effective, it is important to note that 57% of patients received induction chemotherapy (taxane) and thus it is strictly not possible to affirm TP without upfront taxane as a standard treatment option for the overall population of this study [43].

2.3.2. Early Setting

Pertuzumab is approved for use in the neoadjuvant setting (following the results of NEOSPHERE) and in adjuvant setting (APHINITY trial) [44–46]. No older-specific sub-analysis of these studies are available, and no studies in older patients using pertuzumab in the early setting have been published. Both studies have shown that pertuzumab causes a mild increase in toxicity when added to chemotherapy + trastuzumab – particularly diarrhea (mostly during chemotherapy) and rash. QoL results show meaningful declines in both the pertuzumab and placebo arms, with scores for diarrhea being the only significantly worse symptom in the pertuzumab group. A subgroup analysis of invasive disease-free survival (iDFS) in APHINITY – presented as part of the main results - suggests equivalent benefit for older patients – though still of marginal clinical meaning [46,47].

2.4. Trastuzumab-emtansine (T-DM1)

T-DM1 is an antibody drug conjugate approved for use in metastatic HER2+ BC following the results of the EMILIA and TH3RESA trials [48,49]. Both trials showed that T-DM1 was not only superior in terms of outcomes but less toxic than other treatment regimens. More recently, the KATHERINE trial has shown the benefit of T-DM1 in the post-neoadjuvant setting – which led to its rapid approval [50]. The most common grade 3/4 AEs reported with T-DM1 use were thrombocytopenia and liver enzyme elevation [48,50].

A pooled safety analysis of T-DM1 trials including 122 older patients (defined as ≥65 years of age) showed higher rate of grade 3–4 AEs in, as compared with patients with <65 years of age (51.6% vs 44%, respectively) [51]. An interim subgroup analysis of the KAMILLA Trial (NCT01702571) focused on 373 older patients (defined as those with ≥65) and confirms that patients ≥65 have a higher rate of grade 3–4 AEs, as well as higher rate of treatment discontinuations due to AEs. The increase in grade 3–4 AEs was not due to a specific AE but rather to small increases in the incidence of many different AEs. The most common AEs among older patients included asthenia (any grade 29.5%), nausea (27.6%), fatigue (23.1%), and decreased appetite (22.3%). Thrombocytopenia of any grade occurred in 12.9% (3.5% grade ≥ 3) and haemorrhage in 23.9% of older patients (1.6% grade ≥ 3) [52]. Cardiac toxicity, though generally not seen as associated with T-DM1, can still occur. A recent combined-analysis of 1961 patients showed that 66 patients experienced cardiac events, mostly low grade LVEF drops. Notably, age was a significant risk factor for cardiac events while using T-DM1 [53].

In the aforementioned EORTC-75111 randomized phase II trial, patients who had disease progression after TP or TPM were offered treatment with T-DM1. Among the 29 patients who continued on T-DM1, fifteen patients progressed, four patients died without progression and the median PFS after starting T-DM1 was about six months. During treatment, at least one grade 3–5 adverse event was reported in fourteen (48%) of the 29 patients. One patient died because of pneumonitis and one due to cachexia.

The thrombocytopenia associated with T-DM1 is caused by DM1 interference with the differentiation of megakaryocytes [54]. It is important to note that, though thrombocytopenia and coagulopathies are not considered a normal part of the aging process, multiple drugs used in older patients can cause thrombocytopenia and therefore should be used with care in tandem with T-DM1 (including furosemide, thiazide diuretics, ranitidine, aspirin, and anticoagulants). Lastly, older patients are at a higher risk for gastro-intestinal comorbidities which predispose to bleeding (such as diverticular disease and gastric ulcers) and with a higher risk of hospitalization and death [55].

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2.5. Neratinib

Neratinib is an oral, irreversible pan-HER TKI inhibitor and was approved following the results of the ExteNET trial testing one year of neratinib following standard adjuvant treatment, based on a significant yet small improvement in iDFS in the ITT population (2.3%) though a higher iDFS improvement was seen in the HR+ cohort (4.4%) [56]. Importantly, neratinib significantly increased the risk of diarrhea (grade 3 = 40% vs 2% in placebo arm) [56]. Systematic loperamide use with neratinib is now, therefore, considered as standard of care [57].

No data is yet available on older patients being treated with neratinib. Because of changes in body composition and loss of kidney function, diarrhea can be a significant problem for older patients [58]. Additionally, neratinib is major substrate of CYP3A4 and inhibitor of P-glycoprotein, leading to numerous drug-drug interactions, including with ciprofloxacin, digoxin and proton pump inhibitors. Taking all the currently available data, neratinib should not be considered as standard extended therapy for the general older population. There is an ongoing clinical trial to assess the safety and tolerability of neratinib treatment in patients with metastatic HER2-positive BC who are ≥60 years of age (NCT02673398).

3. mTOR Inhibitors

The PI3K/AKT/mTOR pathway is often implicated in primary and secondary resistance to endocrine treatment [59]. Therefore, drugs targeting this pathway are being extensively investigated [59]. Recently, after the severe toxicity associated with pan-PI3K inhibitors, such as buparlisib, most attention has been focused on testing alfa-specific PI3K inhibitors in PIK3CA-mutant tumors [60,61]. Alpelisib is, for the time being, the only clinically active drug in this class despite a substantial toxicity profile, as shown in the SOLAR-1 trial [62]. The mTOR inhibitor everolimus remains, for the time being, the sole approved drug targeting this pathway.

3.1. Everolimus

Everolimus was approved in combination with exemestane for treatment in patients having failed to a non-steroidal aromatase inhibitor (AI) alone after the results of the BOLERO-2 trial. Out of a total of 724 patients the BOLERO-2 trial [63,64], 275 were ≥ 65, 164 were ≥ 70 and 71 were ≥ 75 years. In a subgroup analysis, patients ≥70 years were shown to derive significant benefit from everolimus (absolute gain in PFS of 5.26 months, HR 0.45; 95% CI 0.38–0.54; $P < .0001$) [65]. The toxicity profile was overall similar to younger patients, with the most common AEs being stomatitis, fatigue, decreased appetite, and diarrhea. However older patients in the everolimus arm more commonly had decreased appetite, dyspnea, anemia, asthenia, increased creatinine levels, and urinary tract infections than younger patients. Also clinically significant was the mean weight loss of 4.8 kg among older patients receiving everolimus with exemestane (vs 1.7 kg with placebo). Though dose reductions were no more common in the older sub-group (67% for both age groups), treatment discontinuation due to AE (17.4% vs 6.3%) and voluntary withdrawal (19% vs 6.3%) were both more common in this group. Also, the number of serious AEs attributed to study treatment increased ten-fold (11% vs 1%), and patients using everolimus had an increased probability of fatal AEs, notably if ≥70 years [65,66].

The clinical significance of everolimus toxicity, therefore, cannot be ignored and is, in terms of magnitude, very similar to that of capecitabine, as the results of BOLERO-6 suggest (incidence of grade 3 and 4 AEs 74% vs 70s and of serious AEs 29% vs 36% in capecitabine and everolimus + examestane, respectively) [67]. Starting with a lower dose of 5 mg (and dose increase if well tolerated) may represent a good strategy to avoid clinical complications. Stomatitis prophylaxis with steroid mouthwash should be used systematically, and attention should be taken with patient hydration and nutritional status [68].

4. Anti-angiogenics

Angiogenesis is one of the critical elements of the development of BC [69]. Bevacizumab, a humanized monoclonal antibody that targets VEGF-A in circulation, is for the time being the most extensively studied antiangiogenic agent in BC, although it is currently not approved in the US due to a lack of benefit [70].

4.1. Bevacizumab

Given the lack of overall survival (OS) benefit, and the potential for increased toxicity, there is no evidence to support the use of bevacizumab in patients with metastatic BC. However, data is available on the comparative efficacy and toxicity of bevacizumab in older patients due to its long time in clinical use, and its approval for multiple diseases. In BC, a sub-analysis of the AVADO trial was conducted on 127 patients aged ≥65. Although the PFS benefit was not significant, it was numerically similar to the overall population results, and likely negative due to the small number of patients. Importantly, older patients did not seem to be at a higher risk of hypertension, proteinuria or cardiac events, with the number of neutropenia cases being the only toxicity with higher incidence in older patients [71]. These results bear a marked difference to the ATHENA trial investigating the safety of bevacizumab, which showed a greater incidence of grade 3 hypertension and proteinuria in older patients [72]. In both studies, the levels of bleeding, cardiac dysfunction and embolic events remained low overall, and similar in both younger and older patients.

5. CDK 4/6 Inhibitors

CDK 4/6 plays an important part in the regulation of the cell cycle [73]. The data on the oral CDK 4/6 inhibitors have led to considerable excitement, due to the improvement in PFS outcomes in combination with ET. Currently, this class has three approved agents – palbociclib, ribociclib and abemaciclib for use in patients with metastatic BC [74–77].

5.1. Palbociclib

Palbociclib is currently approved for use in first-line advanced ER+/HER2- BC in combination with letrozole, and in patients who have failed at least one line of ET in combination with fulvestrant. This approval was based on the PFS results of three pivotal trials – PALOMA-1, 2 and 3 [74,78,79]. The most common and clinically significant adverse event was neutropenia (66.4% of patients with grade 3 or 4). Febrile neutropenia was a rare event across the various trials.

Rugo et al conducted a combined analysis of efficacy and toxicity in patients with patients aged ≥65 in all Phase II and III trials of palbociclib. Among a total of 872 patients, 221 (25%) were between 65 and 74 years and 83 (10%) were ≥ 75 years. Their results confirm that palbociclib improves outcomes in all age groups. AEs in older patients were similar to those of younger patients – with neutropenia being the more common but rarely complicated by febrile neutropenia events. Patients in the ≥75 group, however, were at a significantly higher risk for myelosuppression [80].

Neutropenia is a major clinical issue, especially in older patients, as they are already infection-prone due to multiple factors. Even if febrile neutropenia levels remained overall low, it is important to note that 62% of patients between ages 65–74 and 60% aged ≥75 experienced infections during treatment. Though this number is close to that of younger patients (56%), infections among older patients, especially if they require hospitalization, may trigger delirium and cognitive dysfunction with acute functional decline which can lead to long-term sequelae [81].

OS benefit with the use of CDK 4/6 inhibitors remains to be shown. In PALOMA-3, no significant improvement was found, as the trial was underpowered, despite an absolute difference of 6.9 months [82].

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Furthermore, no strategy to select patients to use palbociclib is currently available. Since CDK 4/6 inhibitors are costly and can have toxic effects, especially in older patients, trials such as SONIA (NCT03425838) are currently investigating whether sequence matters when using CDK 4/6 inhibitors.

5.2. Ribociclib

Ribociclib was recently approved by the FDA for ER+/HER2- advanced BC in combination with letrozole, based on the results of the phase III randomized, double blind, placebo controlled MONALEESA-2 trial. Results showed a significant improvement in PFS as well as in other efficacy outcomes [75]. As expected, the most common grade 3/4 AEs were neutropenia and leukopenia. A subsequent sub-group analysis focused on older patients alone, defined as age ≥ 65, including 295 patients (44% of the total sample) found that a comparable number of patients in both age groups had discontinued due to AEs (respectively 7% and 9%) and that these were overall more common among older patients [83]. As ribociclib seems to prolong the QTc interval in a concentration-dependent manner, this treatment should be avoided in patients who already have QTc prolongation and in those using drugs known to prolong QTc. Special focus should be given to perform baseline ECG and repeat it during follow-up. Additionally, electrolytes should be measured, and drugs that can increase QTc should be avoided. For older patients, this is cause for concern as commonly used drugs can increase QTc. Advanced age, renal impairment, use of diuretics, and heart comorbidities are also risk factors for a prolonged QTc.

5.3. Abemaciclib

Abemaciclib differs from other CDK4/6 inhibitors by having a greater selectivity for CDK4. In practice, this translates into a continuous dosing schedule [84]; and important changes in the toxicity profile. In the registration MONARCH-3 trial diarrhea (any grade) occurred in 81.3% of patients (vs 29.8% in the control arm), neutropenia in 41.3% (vs 1.9%), fatigue 40.1% (31.7%) and vomiting 28.4% (vs 11.8%) [76]. Additionally, venous thromboembolic events occurred in 4.9% of patients in the abemacicilib arm vs 0.6% in the control arm. For older patients, this toxicity profile is particularly problematic – notably the increased incidence of VTEs, as older patients are often less mobile and already have a baseline increased risk of VTEs [85], though it is important to note that this could be a class concern rather than an abemaciclib concern.

Therefore, when a CDK inhibitor is considered for an older patient, palbociclib might be a better treatment option until further data specific to older patients is available. Abemaciclib, with adequate management of diarrhoea, can also be an interesting option as the continuous administration can reduce the risk of mistakes for patients with cognitive issues.

6. PARP Inhibitors

Poly ADP ribose polymerases (PARP) are a group of proteins that are vital to the process of DNA repair [86]. In clinical practice, this principle has been explored in patients harboring BRCA germline mutations, who typically develop BC at a very early age. This is well exemplified by the median age in the registration trials of the two approved PARP inhibitors for BC– Olaparib and Talazoparib, which were respectively 44 and 45. Both drugs drugs have been tested in BRCA mutant populations with advanced BC against treatment of physician's choice, and have shown superior clinical and patient-reported outcomes (including QoL), despite substantial toxicity which includes anemia, neutropenia, fatigue and nausea [87–89]. Therefore, some older women may profit from the comparative QoL benefits of PARP inhibitors, as long as nausea and vomiting are proactively handled and CYP3A inhibitors (for Olaparib) and their substrates are avoided (see Table 3).

7. Conclusion

Globally, data on the efficacy and safety of targeted agents in older patients is of limited quality. Older patients are underrepresented in clinical trials, and those that do participate are likely to be fit based on performance status. End-points and follow-up are not well suited to the needs of older patients. In order to advance in increasing the options available for the treatment of older patients, trials geared at this population are essential. Integrating the geriatric assessment in clinical trials will allow for a better understanding of older participants [90]. Also, recruitment in clinical trials of older patients might improve with the recommendations from ASCO and Friends of Cancer Research initiative, which strongly suggest less stringent inclusion criteria for patients with organ dysfunction, prior malignancies, and comorbidities [91].

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Conflicts of Interest

Dr. Noam Pondé has received travelling support from Roche/Genentech, Janssen-Cilag and Mundipharma, as well as speaker's fees from Mundipharma. The Institute he works for has received AstraZeneca, Lilly, MSD, Novartis, Pfizer, Roche-Genentech, Synthon, Radius and Servier.
Dr. Hans Wildiers received travel support from Roche and Pfizer, and his institution received consulting fees and honoraria from Roche, AstraZeneca, Amgen, Lilly, Novartis, Abbvie, Vifor Pharma, Pfizer, Celldex therapeutics, Janssen-CILAG, TRM Oncology, PUMA Biotechnology, ORION corporation and an unrestricted research grant from Roche.
Dr. Ahmad Awada has acted as advior, received fees for lectures and research grants from Roche, Lilly, Amgen, ESAI, BMS, Pfizer, Novartis, MSD.
Dr. Evandro de Azambuja has received honoraria and advisory board from Roche/GNE, Travel grants from Roche/GNE and GSK/Novartis. The Institute he works for has received AstraZeneca, Lilly, MSD, Novartis, Pfizer, Roche-Genentech, Synthon, Radius and Servier.
Coralie Deliens has no conflicts of interest to declare.
Dr. Lissandra Dal Lago has received travel grants from Roche/Genetench. The Institute she works for has received AstraZeneca, Lilly, MSD, Novartis, Pfizer, Roche-Genentech, Synthon, Radius and Servier.

Authors Contribution

Dr. Noam Pondé and Dr. Lissandra Dal Lago have conceived and written the original paper draft. Dr. Hans Wildiersn Ahmed Awada and Evandro de Azambuja have reviewed the manuscript, added content with their clinical experience and knlodge of the field. Coralie Deliens has contributed with pharmacological information on the different agents.

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