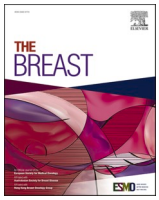
The Breast 80 (2025) 104428

Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast



# Antibody-drug conjugates in elderly patients with breast cancer

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ARTICLE INFO

*Keywords:*
Breast cancer
Antibody-drug conjugates
Age
Elderly
Treatment
Safety

ABSTRACT

Breast cancer remains a leading cause of cancer-related mortality worldwide, with elderly patients (aged >65 years) comprising a substantial portion of those affected. The treatment of breast cancer in this population is often complicated by frailty, comorbidities and polypharmacy. This review explores the application of antibody-drug conjugates (ADCs), such as trastuzumab emtansine (T-DM1), trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan (SG), in treating breast cancer among elderly populations. The underrepresentation of older patients in clinical trials complicates efficacy and safety assessments in this group. Current evidence indicates that ADCs are both effective and tolerable in elderly patients, demonstrating improved progression-free survival (PFS) and overall survival (OS) alongside a manageable safety profile. Data from several trials like the EMILIA, TH3RESA and DestinyBreast studies demonstrate that T-DM1 and T-DXd maintained benefit in PFS and OS for HER2-positive breast cancer in older patients, despite a slight increase in adverse events. The ASCENT and TROPiCS-02 trials further confirm that SG provides significant improvements in PFS and OS in elderly patients at the cost of an increase in some toxicity. Emerging ADCs, including datopotamab deruxtecan and ARX-788, show promise but lack extensive geriatric-specific data. While the ADCs offer encouraging results in terms of efficacy and safety, with appropriate dose adjustments, further research is needed to optimize their use in elderly patients with breast cancer.

## 1. Introduction

Breast cancer is the most diagnosed cancer and the leading cause of cancer-related mortality among females globally, accounting for an estimated 2.3 million new cases and 685.000 deaths in 2020. By 2040, the global incidence of female breast cancer is projected to rise to approximately 2.964.197 new cases, a 31 % increase compared to the 2.260.127 cases reported in 2020 [1].

Nearly half of all new breast cancer diagnoses occur in women over 65, a demographic frequently often burdened by frailty and comorbidities. As the incidence of breast cancer among older women continues to rise, managing the disease in frail elderly patients presents growing challenges [2–6].

The recommendations from the European Society of Breast Cancer Specialists (EUSOMA) and the International Society of Geriatric Oncology (SIOG) on treatment "personalization" primarily focus on chemotherapy. The 6th and 7th International Consensus Guidelines for the Management of Metastatic Breast Cancer (MBC) further propose extending these principles to emerging treatments, even in the absence of specific data for unfit patient populations [7–9].

In recent decades, the importance of geriatric assessment (GA) has been recognized as a tool for identifying specific vulnerabilities in the elderly. GA examines not only the oncological aspects of the disease but also factors such as functional status, physical conditions, comorbidities, and social and cognitive support. This integrated approach can be used to better predict outcomes and tailor oncological therapies to the patient's individual conditions [10,11].

Multidimensional geriatric assessment (GAM) is emerging as an effective method for improving oncological outcomes in elderly patients. Recent clinical studies have shown that the use of MGA, adopting tools like G8 score or G-CODE to measure geriatric parameters, can significantly reduce chemotherapy-related complications and toxicity. However, despite the benefits, the implementation of MGA remains limited and has not yet been standardized across all oncology settings

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https://doi.org/10.1016/j.breast.2025.104428
Received 18 December 2024; Received in revised form 19 February 2025; Accepted 21 February 2025
Available online 23 February 2025
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[12].

Antibody-drug conjugates (ADCs), such as trastuzumab emtansine (T-DM1), trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan (SG), have transformed MBC management, offering effective and tolerable alternatives to standard chemotherapy [13,14]. However, the underrepresentation of elderly patients in trials limits guidance. Studies now emphasize that age alone should not exclude elderly patients from active treatment options or clinical trials and the international guidelines recommend treatment be based on frailty assessments rather than age alone [7,15,16].

ADC therapies are generally recommended in elderly patients, with personalized adjustments to optimize both efficacy and quality of life [15,16].

The pharmacokinetics (PK) and pharmacodynamics (PD) of ADCs in elderly patients require careful consideration due to physiological changes associated with aging. Alterations in hepatic clearance, protein binding, and renal elimination can influence ADC metabolism, increasing susceptibility to toxicities such as interstitial lung disease, peripheral neuropathies, and cardiac dysfunction, especially with HER2- or TROP2-targeting ADCs. Frailty, coupled with the challenges of polypharmacy, compounds the risks, as the use of multiple medications heightens the probability of adverse drug reactions (ADRs). Additionally, comorbidities such as diabetes, smoking, or chronic lung disease may exacerbate these toxicities. Addressing these risks demands a tailored therapeutic approach to optimize outcomes while minimizing harm. In this vulnerable population, clinicians must carefully balance efficacy, safety, and the vulnerabilities posed by frailty and comorbid conditions [8,17,18].

In this review we collect and expose the available data on ADCs in older patients. A lot of these data derived from subgroup analysis and, in some cases, were found in the supplementary data. We also focused on pharmacokinetics aspects with particular attention to safety aspects.

## 2. Anti-HER2 ADCs in elderly population

### 2.1. Trastuzumab emtansine (T-DM1)

T-DM1 is an ADC that combines the HER2-targeted antitumor properties of trastuzumab with the cytotoxic activity of the microtubule-inhibitory agent DM1. T-DM1 allows for intracellular drug delivery specifically to HER2-overexpressing cells, improving the therapeutic index and minimizing exposure to normal tissue [19].

Metabolism of T-DM1 predominantly occurs via CYP3A4, with a lesser contribution from CYP3A5. The drug demonstrates an elimination half-life of approximately four days and is primarily excreted through the bile, with minimal renal clearance observed. Population pharmacokinetic analysis indicates that age does not have a clinically meaningful effect on the PK of T-DM1 [17,20].

One of the main studies that assessed the efficacy and safety of T-DM1 was the EMILIA clinical trial, a phase 3 trial comparing T-DM1 with lapatinib and capecitabine in patients with locally advanced or metastatic HER2-positive breast cancer previously treated with trastuzumab and a taxane. Among the 991 patients enrolled, only 13.9 % were over 65 years old, and 2.5 % were over 75 years old. In this study, T-DM1 significantly improved progression-free survival (PFS) compared to lapatinib and capecitabine, with a median PFS of 9.6 months versus 6.4 months. With limitation of a post-hoc subgroup analysis, the relative benefits in PFS were not evident in patients over 75 and in the 65–75 age range, where the wide confidence interval made it difficult to determine a clear and statistically significant benefit [21].

In the final analysis, median overall survival (OS) was 29.9 months for patients treated with T-DM1 compared to 25.9 months for the lapatinib-capecitabine group. In this case as well, the relative survival benefits were less clear in the over-65 population and nearly absent in the over-75 population [22].

In the TH3RESA trial, T-DM1 was compared to physician's choice treatment for HER2-positive patients previously treated with trastuzumab, lapatinib, and a taxane, who had progressed after at least two lines of anti-HER2 therapy. In this study, only 12.3 % of patients were between 65 and 74 years old, and 3.15 % were over 75. A trend of improvement of OS was observed also in older patients treated with TDM1 [23].

The specific data on the efficacy of T-DM1 in the EMILIA and TH3RESA clinical studies are shown in Tables 1 and 8.

Concerning safety, the results were not evaluated in terms of age in the two previously mentioned studies [21–23].

A more specific analysis regarding T-DM1 safety in the elderly population emerged from the KAMILLA study, which included 373 patients over 65 (18.6 %) and 101 patients over 75 (5 %). The higher proportion of elderly patients in the KAMILLA study underscores its relevance for assessing T-DM1 tolerability in this demographic [24].

In the over-65 subgroup, the treatment discontinuation rate due to AEs was 14.3 %, compared to 9.5 % in younger patients. Grade 3 or higher AEs were more frequent in older patients (42.9 %) than in younger ones (33.2 %), although no significant differences were observed in specific T-DM1-related side effects, such as thrombocytopenia, liver toxicity, and hemorrhages. Data are shown in Table 2 [25].

Additional data come from a 2013 meta-analysis combining several studies involving 884 patients treated with T-DM1. The most common AEs reported during T-DM1 treatment were asthenia (46.4 %), thrombocytopenia (32.2 %), headache (29.4 %) and constipation (26.5 %). Grade 3 or higher AEs mainly included thrombocytopenia (11.9 %) and increased transaminases (4.3 %). In 12 patients, AEs led to death. Subgroup analysis by age showed a higher incidence of grade 3 or higher AEs in patients over 65 (51.6 %) compared to younger patients (44 %) [26].

This trend was also confirmed by the EORTC 75111-10114 study, which examined patients with HER2-positive metastatic breast cancer (MBC) aged 70 and older. Patients were randomized to receive cyclophosphamide in combination with trastuzumab and pertuzumab versus trastuzumab and pertuzumab alone. Upon progression, all patients were offered T-DM1 treatment [27].

Of the 29 patients treated with T-DM1, PFS was 43.6 % at 6 months and 34.5 % at 12 months. Grade 3–5 AEs were observed in 45 % of patients, but no new toxicities emerged compared to previous studies [28].

The safety data of T-DM1 in relation to age were also analyzed in the age-specific analysis of the Destiny Breast studies, as will be discussed later [29].

Overall, the data showed that T-DM1 remains a safe and effective treatment choice, albeit with a higher frequency of AEs compared to younger patients.

### 2.2. Trastuzumab-deruxtecan (T-DXd)

T-DXd is an ADC targeting HER2, consisting of a monoclonal antibody, a tetrapeptide cleavable linker, and a topoisomerase I inhibitor as the cytotoxic payload. Compared to T-DM1, T-DXd has a higher drug-to-antibody ratio, delivering more cytotoxic drug per antibody. It also has the unique ability to cross cell membranes and target nearby cancer cells, regardless of HER2 expression, broadening its therapeutic potential [30].

T-DXd undergoes intracellular cleavage by lysosomal enzymes, leading to the release of DXd. The DXd metabolite is primarily metabolized by CYP3A4. After three treatment cycles, the elimination half-life of both T-DXd and DXd is approximately 7 days. Preclinical studies have demonstrated that the main route of elimination for the drug is via feces, through the biliary pathway [31].

The population pharmacokinetic analysis showed that age (range: 20–96 years) did not affect the PK of T-DXd [32].

The DestinyBreast clinical trials have explored the efficacy and safety profile of T-DXd in HER2-positive breast cancer, but data on the elderly

**Table 1**
Clinical outcomes by age subgroups from the EMILIA study of T-DM1 vs lapatinib and capecitabine in metastatic HER2-positive breast cancer and from TH3RESA study of T-DM1 vs treatment of physician's choice in metastatic HER2-positive breast cancer [18–20].

| | Outcome | Age | | | | | | Overall Population | |
|---|---|---|---|---|---|---|---|---|---|
| | | <65 years | | 65–74 years | | ≥75 years | | | |
| **EMILIA** | | **T-DM1** | **Lapatinib + capecitabine** | **T-DM1** | **Lapatinib + capecitabine** | **T-DM1** | **Lapatinib + capecitabine** | **T-DM1 (n = 495)** | **Lapatinib + capecitabine (n = 496)** |
| | *Median PFS, mo (95 % CI)* | / | / | / | / | / | / | 9.6 | 6.4 |
| | *HR (95 % CI)* | 0.62 (0.52–0.74) | | 0.88 (0.53–1.45) | | 3.51 (1.22–10.13) | | 0.65 (0.55–0.77) | |
| | *Median OS, mo (95 % CI)* | / | / | / | / | / | / | 29.9 (26.3-34-1) | 25.9 (22.7–28.3) |
| | *HR (95 % CI)* | 0.73 (0.61–0.86) | | 0.89 (0.56–1.43) | | 2.79 (0.99–7.88) | | 0.75 (0.64–0.88) | |
| | *ORR %* | / | / | / | / | / | / | / | / |
| **TH3RESA** | | **T-DM1 (n = 345)** | **TPC (n = 164)** | **T-DM1 (n = 46)** | **TPC (n = 28)** | **T-DM1 (n = 13)** | **TPC (n = 6)** | **T-DM1 (n = 404)** | **TPC (n = 198)** |
| | *Median PFS, mo (95 % CI)* | 5.8 | 3.4 | 6.9 | 3.2 | NE | 3 | 6.2 (5.59–6.87) | 3.3 (2.89–4.14) |
| | *HR (95 % CI)* | 0.55 (0.44–0.70) | | 0.42 (0.22–0.80) | | 0.14 (0.02–0.79) | | 0.52 (0.42–0.66) | |
| | *Median OS, mo (95 % CI)* | 23.1 (19.4–27.8) | 16.1 (13.9–22.2) | 18.2 (14.3–28.3) | 13.5 (11.5–21.9) | 31.8 (13.5-NE) | 16.4 (12.4–24.7) | 22.7 (19.4–27.5) | 15.8 (13.5–18.7) |
| | *HR (95 % CI)* | 0.71 (0.55–0.91) | | 0.73 (0.40–1.34) | | 0.27 (0.07–1.04) | | 0.68 (0.54–0.85) | |
| | *ORR %* | / | / | / | / | / | / | 31 | 9 |

CI confidence interval, HR hazard ratio, NE not estimable, ORR objective response rate, OS overall survival, PFS progression-free survival, T-DM1 trastuzumab emtansine, TPC treatment of physician's choice, TTR time to response.

**Table 2**
Safety outcomes by age subgroups from the KAMILLA study of TDM-1 in patients with HER2-positive advanced breast cancer [21].

| | Age | | Overall safety population |
|---|---|---|---|
| | <65 years | ≥65 years | |
| | T-DM1 (n = 1628) | T-DM1 (n = 373) | T-DM1 (n = 2002) |
| *Any TEAE, n (%)* | / | / | 1862 (93) |
| *Grade ≥3 (%)* | 540 (33.2) | 160 (42.9) | 816 (40.8) |
| *Leading to dose reduction (%)* | / | / | / |
| *Leading to drug interruption (%)* | / | / | / |
| *Leading to drug discontinuation (%)* | 112 (9.5) | 41 (14.3) | 237 (11.8) |
| *Leading to death (%)* | 17 (1) | 10 (2.7) | 45 (2.24) |

TEAE treatment emergent adverse event, SAE serious adverse event, T-DM1 trastuzumab emtansine.

population remain largely limited. In the clinical trials, older patients represent a minority, comprising 18 %–23.9 % of participants, depending on the study, with an even smaller proportion of patients over 75. This limited representation underscores the importance of targeted analysis to evaluate in detail the efficacy and safety of T-DXd in this cohort, which has specific clinical characteristics and needs associated with advanced age [29].

In the age-specific aggregate analysis conducted on the DestinyBreast01, DestinyBreast02 and DestinyBreast03 studies, a positive picture emerges for T-DXd efficacy even in the over-65 population. It is important to highlight that formal comparisons were not conducted between partecipants under 65 and those aged 65 or older, as the analysis was descriptive. A total of 851 patients were enrolled across all three studies, with 178 patients over 65 receiving T-DXd therapy, and only 34 patients aged over 75. Most patients had an ECOG PS of 0 or 1, with vascular disorders and hypertension more common in patients ≥65 [29].

Analyzing the individual study data, in DestinyBreast01, of the 184 patients enrolled to receive T-DXd after previous T-DM1 treatment, only 23.9 % were over 65, and only 4.9 % were over 75. Overall, T-DXd showed a response rate of 60.9 % and a median PFS of 16.4 months, with a duration of response of 14.8 months. These results were consistent regardless of age, with a median PFS of 18.1 months in the <65 years cohort and a median PFS of 19.4 months in the >65 years cohort [33].

Of the 816 patients with HER2-positive MBC, resistant or refractory to T-DM1, enrolled in the DestinyBreast02 clinical trial, only 21 % in the T-DXd arm and 19 % in the comparator arm were over 65. In this study, the T-DXd-treated group reported a median PFS of 17.8 months compared to 6.9 months for the control group. The PFS advantage was evident regardless of age, confirming T-DXd efficacy in older patients, with a median PFS of 17.9 in the <65 years cohort and 16.8 in the >65 years cohort. The median OS for the general population was 39.2 months for the T-DXd group compared to 26.5 months for the standard treatment group, demonstrating a survival benefit even in older age groups [34].

In the DestinyBreast03 study, patients with unresectable or metastatic HER2-positive breast cancer that had progressed during or after trastuzumab and taxane treatment were randomized 1:1 to receive T-DXd or T-DM1. Of the 524 total patients, only 18 % in the T-DXd arm and 21 % in the control arm were over 65. Of these, only 3–4% were over 75 [35].

This study demonstrated a significant improvement in median PFS in the T-DXd group, with 29.0 months compared to 7.2 months for T-DM1, as well as an OS benefit of 52.6 months versus 42.7 months. Treatment benefits with T-DXd were observed across all analyzed subgroups, with no age-related differences. The median PFS was 30.4 months in the <65

years cohort and 25.1 months in the >65 years cohort [35,36].

Regarding the HER2-low breast cancer population, data from the DestinyBreast04 study were analyzed, which included patients with unresectable or metastatic HER2-low hormone-responsive and hormone-negative disease. Patients were randomized 2:1 to receive T-DXd or physician's choice chemotherapy (TPC). A total of 557 patients were enrolled. Of these, only 23.5 % were over 65. In the HR-positive cohort, the median PFS was 10.1 months for the T-DXd group, compared to 5.4 months for the control group. Similarly, the median OS was 23.9 months in the T-DXd group, versus 17.5 months in the control group. A clear benefit in both PFS and OS was also observed in the overall population [37].

Data from a subgroup analysis highlight that the PFS benefit was maintained regardless of the patient's age. In the over-65 group, the median PFS for the overall population was 11.4 months in the T-DXd group compared to 6.2 months in the control group. In the hormone-positive population, the median PFS was 12 months in the T-DXd group versus 5.6 months in the control group [38].

The data related to the DestinyBreast studies are detailed in Table 3, Table 4 and Table 8.

From a safety perspective, treatment with T-DXd in elderly patients showed a similar AE profile to younger patients, though with a tendency towards greater severity and frequency of events. As of the cutoff date, the median duration of treatment with T-DXd was 13.1 months for patients under 65 and 12.4 months for those aged 65 and older. The most common side effects, regardless of age group and severity, were nausea, vomiting, and fatigue, followed by alopecia and neutropenia. Treatment-related adverse events (TRAEs), regardless of grade, occurred in 99.6 % of patients under 65 and in 100 % of patients aged 65 and over. Grade 3 or higher AEs were reported in 53.6 % of patients under 65 and in 65.5 % of patients aged 65 and older. The most common grade 3 or higher AEs were neutropenia, anemia, and fatigue. Drug-related interstitial lung disease (ILD) was observed in 11.8 % of patients under 65, compared to 17.5 % in patients aged 65 and older. Fortunately, most cases of ILD were low grade. Further details on toxicity profiles by age group are highlighted in Table 5 [29].

The results of this aggregate analysis demonstrate that T-DXd has a favorable benefit-risk profile even in patients aged 65 and older, with a slightly increased toxicity as expected [29].

The TREX-Old study provided further information on the tolerability profile of T-DXd in the elderly population. This retrospective European study evaluated the real-world use of T-DXd in patients aged 70 and older with advanced HER2-positive breast cancer. A total of 27 patients were enrolled: 63 % were aged 70–74, 30 % were aged 75–79, and only 7 % were over 80 years old. Most patients had an ECOG performance status of 0 or 1 (78 %). The 29.6 % of the patients started with a dose reduction, and the 29.6 % later had a dose adjustment. Overall, TRAEs of any grade occurred in 70.3 % of the cases. Among these, nausea was the most common adverse event (37 %), followed by fatigue (18 %). The 11.1 % of the patients developed ILD, all of grade 1 or 2. Only one patient experienced nausea as a grade 3 AE (Figs. 1 and 2) [39].

## 3. Sacituzumab govitecan and new ADCs in elderly population

### 3.1. Sacituzumab govitecan (SG)

SG is an ADC composed of an anti-Trop 2 antibody coupled to SN-38, a topoisomerase I inhibitor [40,41].

PK analyses in patients treated with SG did not identify an effect of age. The elimination of the drug occurs primarily via the biliary and fecal pathways, with renal excretion playing a minor role. Specifically, SN-38 is metabolized by the enzyme UGT1A1, whose activity is influenced by genetic polymorphisms. Patients homozygous for the UGT1A1*28 allele are at a higher risk of developing high-grade febrile neutropenia compared to those with the wild-type allele. Therefore, assessing the mutational status associated with UGT1A1 genetic polymorphisms may be clinically warranted [17].

Clinical trials have shown its efficacy in heavily pretreated MBC patients, leading to its FDA and EMA approval [42].

SG has been extensively evaluated in older patients with MBC through two major clinical trials: ASCENT and TROPiCS-02.

In a subgroup analysis by age, the ASCENT trial, which focused on heavily pre-treated metastatic triple negative breast cancer (TNBC), demonstrated that also older patients benefited significantly from SG compared to TPC. The recruited population was aged 27–82 years, and the median age was 54 years. About 20 % of the recruited population was over 65 years old. In general, patient disease characteristics were similar between patients aged <65 years and ≥65 years with some exceptions. Patients aged <65 years had a higher rate of negative germline BRCA mutations in those patients with known BRCA status than patients aged ≥65 years [43].

Focusing on efficacy outcomes on ≥65 years subgroup of patients, the trial revealed a median PFS of 7.1 months for the patients treated with SG, which was notably better compared to just 2.4 months with

**Table 3**
Clinical outcomes by age subgroups from the DestinyBreast study: trastuzumab deruxtecan (DB01); trastuzumab deruxtecan vs treatment of physician's choice (DB02) and trastuzumab deruxtecan vs TDM-01 (DB03) in metastatic HER2-positive breast cancer [26,30–33].

| | Outcome | Age | | | | Overall Population (ITT) | |
|---|---|---|---|---|---|---|---|
| | | <65 years | | ≥65 years | | | |
| DESTINYBREAST01 | | **T-DXd (n = 140)** | | **T-DXd (n = 44)** | | **T-DXd (n = 184)** | |
| | *Median PFS, mo (95 % CI)* | 18.1 | | 19.4 | | 16.4 (127-NE) | |
| | *HR (95 % CI)* | / | | / | | / | |
| | *Median OS, mo (95 % CI)* | 28.1 (23.2–36.2) | | 30.9 (21.9-NE) | | NE | |
| | *HR (95 % CI)* | / | | / | | / | |
| | *ORR, n (%)* | 62 % | | 61 % | | 60.9 % | |
| DESTINYBREAST02 | | **T-DXd (n = 321)** | **TPC (n = 164)** | **T-DXd (n = 85)** | **TPC (n = 38)** | **T-DXd (n = 406)** | **TPC (n = 202)** |
| | *Median PFS, mo (95 % CI)* | 17.9 | / | 16.8 | / | 17.8 (14.3–20.8) | 6.9 (5.5–8.4) |
| | *HR (95 % CI)* | / | | / | | 0.36 (0.28–0.45) | |
| | *Median OS, mo (95 % CI)* | NR (35.5–NE) | / | 30.2 (22.3–39.2) | / | 39.2 (32.7-NE) | 26.5 (21.0-NE) |
| | *HR (95 % CI)* | / | | / | | 0.66 (0.50–0.86) | |
| | *ORR %* | 70.7 | / | 65.9 | / | 69.7 | 29.2 |
| DESTINYBREAST03 | | **T-DXd (n = 212)** | **T-DM1 (n = 206)** | **T-DXd (n = 49)** | **T-DM1 (n = 57)** | **T-DXd (n = 261)** | **T-DM1 (n = 263)** |
| | *Median PFS, mo (95 % CI)* | 30.4 | / | 25.1 | / | 29.0 (23.7–40.0) | 7.2 (6.8–8.3) |
| | *HR (95 % CI)* | / | | / | | 0.30 (0.24–0.38) | |
| | *Median OS, mo (95 % CI)* | NR (40.5–NE) | / | NR (26.6-NE) | / | 52.6 (48.7–NE) | 42.7 (35.4–NE) |
| | *HR (95 % CI)* | / | | / | | 0.73 (0.56–0.94) | |
| | *ORR %* | 78.8 | / | 77.6 | / | 78.9 | 36.9 |

CI confidence interval, HR hazard ratio, NE not estimable, ORR objective response rate, OS overall survival, PFS progression-free survival, T-DXd trastuzumab deruxtecan, TPC treatment of physician's choice, T-DM1 trastuzumab emtansine, TTR time to response.

**Table 4**
Clinical outcomes by age subgroups from the DestinyBreast04 study of trastuzumab deruxtecan vs treatment of physician's choice in metastatic HER2-low breast cancer [34,35].

| | Outcome | Age | | | | | | | | Overall Population (ITT) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | <65 years | | | | ≥65 years | | | | | | | |
| | | Hormone Receptor–Positive Cohort | | All Patients | | Hormone Receptor–Positive Cohort | | All Patients | | Hormone Receptor–Positive Cohort | | All Patients | |
| | | **TDxd (n = 260)** | **TPC (n = 120)** | **TDxd (n = 290)** | **TPC (n = 136)** | **TDxd (n = 71)** | **TPC (n = 43)** | **TDxd (n = 83)** | **TPC (n = 48)** | **TDxd (n = 331)** | **TPC (n = 163)** | **TDxd (n = 373)** | **TPC (n = 184)** |
| DESTINYBREAST04 | *Median PFS, mo (95 % CI)* | 9.8 (8.4–11.3) | 5.4 (4.1–7.8) | 9.8 (8.4–11.1) | 4.6 (2.9–5.9) | 12.0 (9.5–14.7) | 5.6 (4.3–10.8) | 11.4 (8.3–13.3) | 6.2 (4.3–10.8) | 10.1 (9.5–11.5) | 5.4 (4.4–7.1) | 9.9 (9.0–11.3) | 5.1 (4.2–6.8) |
| | *HR (95 % CI)* | / | | 0.47 (0.37–0.61) | | / | | 0.57 (0.36–0.89) | | 0.51 (0.40–0.64) | | 0.50 (0.40–0.63) | |
| | *Median OS, mo (95 % CI)* | / | / | / | / | / | / | / | / | 23.9 (20.8–24.8) | 17.5 (15.2–22.4) | 23.4 (20.0–24.8) | 16.8 (14.5–20.0) |
| | *HR (95 % CI)* | / | | / | | / | | / | | 0.64 (0.48–0.86) | | 0.64 (0.49–0.84) | |
| | *ORR, n (%)* | / | / | / | / | / | / | / | / | 52.6 | 16.3 | 52.3 | 16.3 |

CI confidence interval, HR hazard ratio, NE not estimable, ORR objective response rate, OS overall survival, PFS progression-free survival, T-DXd trastuzumab deruxtecan, TPC treatment of physician's choice, TTR time to response.

**Table 5**
Safety outcomes by age subgroups from the DestinyBreast study: trastuzumab deruxtecan (DB01); trastuzumab deruxtecan vs treatment of physician's choice (DB02) and trastuzumab deruxtecan vs TDM-01 (DB03) in metastatic HER2-positive breast cancer [26,30–32].

| | Age | | | | | | | | | Overall safety population (n = 482) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <65 years | | | ≥65 years | | | ≥75 years | | | | | |
| | T-DXd (n = 668) | TPC, DB02 (n = 157) | TDM-1, DB03 (n = 204) | T-DXd (n = 177) | TPC, DB02 (n = 38) | TDM-1, DB03 (n = 57) | T-DXd (n = 33) | TPC, DB02 (n = 8) | TDM-1, DB03 (n = 8) | T-DXd (n = 845) | TPC, DB02 (n = 195) | TDM-1, DB03 (n = 261) |
| *Any TEAE, n (%)* | 665 (99.6) | 148 (94.3) | 194 (95.1) | 177 (100) | 37 (97.4) | 55 (96.5) | 33 (100) | 8 (100) | 8 (100) | 842 (99.7) | 185 (94.8) | 249 (95.4) |
| *Grade ≥3 (%)* | 358 (53.6) | 68 (43.3) | 100 (49.0) | 116 (65.5) | 18 (47.4) | 35 (61.4) | 17 (51.5) | 6 (75) | 4 (50) | 474 (56) | 86 (44.1) | 135 (51.7) |
| *Leading to dose reduction (%)* | 163 (24.4) | 67 (42.7) | 23 (11.3) | 51 (28.8) | 22 (57.9) | 15 (26.3) | 10 (30.3) | 7 (87.5) | 2 (25) | 214 (25.3) | 89 (45.6) | 38 (14.5) |
| *Leading to study drug interruption (%)* | 302 (45.2) | 73 (46.5) | 53 (26) | 94 (53.1) | 17 (44.7) | 23 (40.4) | 15 (45.5) | 5 (62.5) | 3 (37.5) | 396 (46.8) | 90 (46.1) | 76 (29.1) |
| *Leading to drug discontinuation (%)* | 125 (18.7) | 15 (9.6) | 13 (6.4) | 45 (25.4) | 4 (10.5) | 11 (19.3) | 8 (24.2) | 1 (12.5) | 3 (37.5) | 170 (20.1) | 19 (9.74) | 24 (9.2) |
| *Leading to death (%)* | 17 (2.5) | 6 (3.8) | 4 (2) | 10 (5.6) | 1 (2.6) | 2 (3.5) | 0 (0) | 0 (0) | 1 (12.5) | 27 (3.2) | 7 (3.58) | 6 (2.3) |
| *Any SAE (%)* | 162 (24.3) | 39 (24.8) | 33 (16.2) | 57 (32.2) | 7 (18.4) | 25 (43.9) | 10 (30.3) | 1 (12.5) | 4 (50) | 219 (25.9) | 46 (23.6) | 58 (22.2) |

TEAE treatment emergent adverse event, SAE serious adverse event, T-DXd trastuzumab deruxtecan, TPC treatment of physician's choice, T-DM1 trastuzumab emtansine.

**Table 6**
Clinical outcomes by age subgroups from the phase 3 ASCENT study of sacituzumab govitecan in metastatic triple-negative breast cancer and from the phase 3 TROPiCS-02 study of sacituzumab govitecan vs treatment of physician's choice in HR+/HER2− metastatic breast cancer [40,41].

| | Outcome | Age | | | | | | | | Overall Population (ITT) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | <65 years | | ≥65 years | | <75 years | | ≥75 years | | | |
| **ASCENT Trial** | | **SG (n = 218)** | **TPC (n = 210)** | **SG (n = 49)** | **TPC (n = 52)** | / | / | / | / | **SG (N = 267)** | **TPC (N = 262)** |
| | *Median PFS, mo (95 % CI)* | 4.2 (3.2–5.5) | 1.6 (1.5–2.5) | 7.1 (4.9–8.4) | 2.4 (1.5–2.9) | / | / | / | / | 4.8 (4.1–5.8) | 1.7 (1.5–2.5) |
| | *HR (95 % CI)* | 0.45 (0.35–0.57) | | 0.25 (0.14–0.43) | | / | / | / | / | 0.43 (0.35–0.54) | |
| | *Median OS, mo (95 % CI)* | 10.8 (9.5–13.0) | 6.7 (5.4–7.5) | 14.7 (12.2–22.5) | 8.9 (6.2–10.2) | / | / | / | / | 11.8 (10.5–13.8) | 6.9 (5.9–7.7) |
| | *HR (95 % CI)* | 0.54 (0.43–0.66) | | 0.54 (0.43–0.66) | | / | / | / | / | 0.51 (0.41–0.62) | |
| | *ORR, n (%)* | 61 (28) | 11 (5) | 22 (45) | 0 | / | / | / | / | 83 (31) | 11 (4) |
| **TROPiCS-02 Trial** | | **SG (n = 199)** | **TPC (n = 204)** | **SG (n = 73)** | **TPC (n = 67)** | **SG (n = 256)** | **TPC (n = 263)** | **SG (n = 16)** | **TPC (n = 8)** | **SG (n = 272)** | **TPC (n = 271)** |
| | *Median PFS, mo (95 % CI)* | 5.5 (4.1–6.9) | 4.1 (3–4.4) | 6.7 (4.2–9) | 3.5 (1.7–5.6) | 5.5 (4.1–6.9) | 4 (3.1–4.4) | 9 (3.8–NE) | 5.5 (0.3–NE) | 14.4 (13.0–15.7) | 11.2 (10.1–12.7) |
| | *HR (95 % CI)* | 0.69 (0.53–0.89) | | 0.59 (0.38–0.93) | | 0.7 (0.56–0.87) | | 0.3 (0.08–1.12) | | 0.79 (0.65–0.96) | |
| | *Median OS, mo (95 % CI)* | 14.1 (12.7–16.4) | 11.5 (10.3–13.3) | 14.9 (12–17.5) | 10.1 (7.6–14.2) | 14.6 (13–16) | 11.2 (10.1–12.9) | 12.3 (6.4–NE) | 11.6 (5.6–NE) | 14.4 (13.0–15.7) | 11.2 (10.1–12.7) |
| | *HR (95 % CI)* | 0.81 (0.64–1.02) | | 0.80 (0.54–1.19) | | 0.82 (0.67–1.01) | | 0.56 (0.2–1.56) | | 0.79 (0.65–0.96) | |
| | *ORR, n (%)* | 42 (21) | 28 (14) | 15 (21) | 10 (15) | 21 (16–27) | 14 (10–18) | 19 (4–4.6) | 25 (3–65) | 57 (21) | 38 (14) |

CI confidence interval, HR hazard ratio, NE not estimable, ORR objective response rate, OS overall survival, PFS progression-free survival, SG sacituzumab govitecan, TPC treatment of physician's choice.

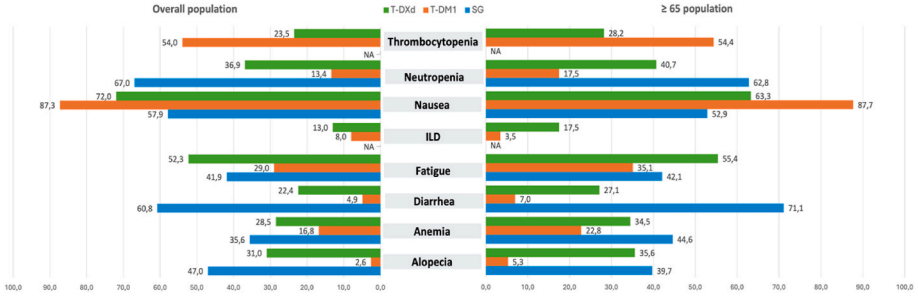


**Fig. 1.** Comparison of the frequency of the main adverse events related to T-DM1, T-DXd, SG in the general population and in the over-65 population according to the data from the reported studies [26,30–32,40,42].
T-DM1 trastuzumab emtansine, T-DXd trastuzumab deruxtecan, SG sacituzumab govitecan.

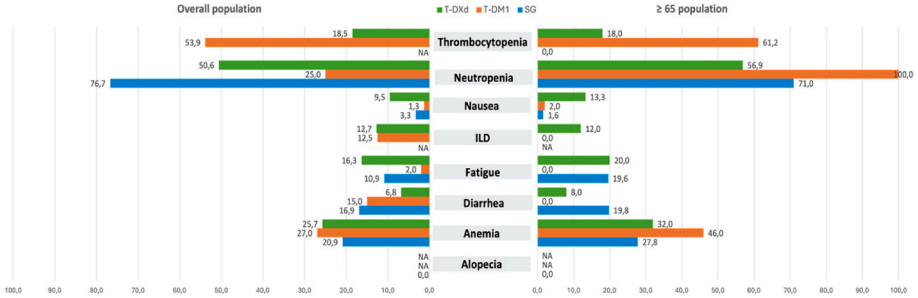


**Fig. 2.** Comparison of the frequency of the severe main adverse events (grade ≥3) related to main adverse events of any grade in T-DM1, T-DXd, SG in the general population and in the over-65 population according to the data from the reported studies [26,30–32,40,42].
T-DM1 trastuzumab emtansine, T-DXd trastuzumab deruxtecan, SG sacituzumab govitecan.

single-agent chemotherapy. Similarly, the median OS for older patients receiving SG was 14.7 months, significantly longer than the 8.9 months observed with chemotherapy. Notably, 45 % of older patients on SG showed a response to the treatment, a stark contrast to the 0 % response rate among those on chemotherapy. When comparing with the younger subgroup, patients under 65 years had a median PFS of 4.2 months with SG, while those 65 years and older showed a more substantial PFS improvement with SG, as explained above. Comparing efficacy outcomes by age subgroups, the median OS was also better in the older group: 14.7 months with SG compared to 10.8 months in younger patients. The objective response rate (ORR) was higher in the older group as well, at 45 % versus 28 % in younger patients. Overall, while both groups benefited from SG, the older patients showed greater improvements across all considered outcomes (see Tables 5 and 8) [43].

The TROPiCS-02 trial evaluated SG in patients with HR+ and HER2- locally recurrent inoperable or MBC who received at least one previous endocrine therapy, a taxane, and a CDK4/6 inhibitor in any setting and two to four previous chemotherapy regimens for metastatic disease. This trial recruited 543 patients aged 49–65 years in a median age of 56 years. About 26 % of the recruited population was over 65 years old. The trial showed positive results in this older population. In this study, the older patients treated with SG had a median PFS of 6.7 months, compared to 3.5 months with TPC. The median OS was 14.9 months for older patients with SG, versus 10.1 months with TPC. The clinical benefit rate with SG was 36 %, compared to 19 % with TPC, and the duration of response was longer with SG (6.9 months vs. 4.3 months with TPC), as shown in Tables 5 and 8 [44].

The ASCENT trial reported a more pronounced OS benefit in the older subgroup compared to the TROPiCS-02 trial, where the improvement was less striking. These discrepancies suggest that tumor subtype and prior treatments may significantly influence SG's overall impact (see Table 6).

Analyzing safety data, both trials indicate that SG is associated with a higher incidence of adverse events, particularly in older patients. In the ASCENT trial, 37 % of older patients required dose modifications due to treatment emergent adverse event (TEAEs), compared to 19 % in younger patients. Neutropenia, diarrhea and fatigue were the most common adverse effects in elderly people treated with SG respect to TPC. Severe TEAEs, such as neutropenia and diarrhea, were reported in 47 % and 12 % of older patients, respectively. Despite these challenges, the rate of treatment discontinuation due to TEAEs was relatively low at 2 %, suggesting that the side effects were manageable for many older patients. Focusing specifically on those aged 75 years and older, in the SG treatment group, all patients in this age bracket experienced TRAEs. Among them, 75 % had severe adverse events (grade ≥3), but only one patient required a dose reduction due to these events. Importantly, there were no instances of study drug discontinuation or death attributed to TRAEs in this age group (Table 7) [45].

The TROPiCS-02 trial also highlighted safety concerns. All older patients experienced at least one TEAE, with 75 % experiencing severe TEAEs when treated with SG, compared to 61 % in the TPC group. However, the rates of these TEAEs were similar to younger subgroups. Dose reductions and treatment interruptions were more frequent with SG, affecting 38 % and 68 % of older patients, respectively. Furthermore, 17 % of older patients discontinued treatment due to TEAEs, compared to 5 % in the TPC group. Discontinuation rate was significatively higher in older population respect to younger subgroup (17 % vs 3 %). Specific AEs such as neutropenia, diarrhea, and nausea were confirmed to be more pronounced with SG, respect to TPC. For example, 65 % of older patients experienced neutropenia, with 44 % having severe cases, while 75 % had diarrhea, including 17 % with severe cases. Alopecia and fatigue were also more frequent with SG (42 % and 38 % of patients, respectively). For patients aged 75 and older, all patients in SG group experienced severe AEs (Grade ≥3). Among these, the 50 % of cases require dose reductions, significative higher rate respect to TPC (29 %). This shows that dose adjustments were common in both groups, but more frequent in SG. Conversely, SG treatment was not associated with significative higher discontinuation rates (13 % vs 14 % in TPC group) as shown in Table 7 [44].

Summarizing, older patients, particularly those aged 65 and above, displayed better PFS, OS, and ORR compared to younger patients, especially in the ASCENT trial. This counterintuitive result suggests that age, often considered a risk factor for poorer treatment responses, does not diminish the therapeutic benefit of SG.

Despite the efficacy, safety concerns in older people are notable. Higher rates of severe TEAEs were observed in older patients, with dose reductions and treatment discontinuations more common in those aged 75 and above. While the toxicities were generally manageable, the frequent need for dose adjustments highlights the challenge of balancing efficacy and tolerability in this population, especially those with comorbidities (Figs. 1 and 2).

### 3.2. Datopotamab deruxtecan

Datopotamab-deruxtecan (Dato-DXd) is another Trop-2-directed ADC that has demonstrated potential in treating advanced breast cancer, including TNBC.

It is composed of an anti-TROP2 monoclonal antibody covalently linked to a highly potent topoisomerase I inhibitor, a derivative of exatecan [46].

The TROPION-PanTumor01 study is a phase I clinical trial evaluating Dato-DXd in 85 patients with previously treated solid tumors. This study aimed to assess the safety, tolerability, antitumor activity, and pharmacokinetics of Dato-DXd in advanced/unresectable or metastatic

**Table 7**
Safety outcomes by age subgroups from the phase 3 ASCENT study of sacituzumab govitecan in metastatic triple-negative breast cancer and from the phase 3 TROPiCS-02 study of sacituzumab govitecan vs treatment of physician's choice in HR+/HER2− metastatic breast cancer [40,42].

| | | Age | | | | Overall safety population | |
|---|---|---|---|---|---|---|---|
| | | <65 years | | ≥65 years | | | |
| **ASCENT Trial** | | **SG (n = 208)** | **TPC (n = 176)** | **SG (n = 49)** | **TPG (n = 48)** | **SG (n = 257)** | **TPC (n = 224)** |
| | *Any TEAE, n (%)* | 208 (100) | 171 (97) | 49 (100) | 48 (100) | 257 (100) | 219 (98) |
| | *Grade ≥3 (%)* | 154 (74) | 115 (65) | 34 (69) | 30 (63) | 188 (73) | 145 (65) |
| | *Leading to dose reduction (%)* | 39 (19) | 43 (24) | 18 (37) | 16 (33) | 57 (22) | 59 (26) |
| | *Leading to drug interruption (%)* | 137 (66) | 66 (38) | 25 (51) | 21 (44) | 162 (63) | 87 (39) |
| | *Leading to drug discontinuation (%)* | 11 (5) | 11 (6) | 1 (2) | 1 (2) | 12 (5) | 12 (5) |
| **TROPiCS-02 Trial** | | **SG (n = 196)** | **TPC (n = 188)** | **SG (n = 72)** | **TPG (n = 61)** | **SG (n = 268)** | **TPC (n = 249)** |
| | *Any TEAE, n (%)* | 196 (100) | 178 (95) | 72 (100) | 61 (100) | 268 (100) | 239 (96) |
| | *Grade ≥3* | 144 (73) | 113 (60) | 54 (75) | 37 (61) | 198 (74) | 150 (60) |
| | *Leading to dose reduction* | 63 (32) | 65 (35) | 27 (38) | 17 (28) | 90 (34) | 82 (33) |
| | *Leading to drug interruption (%)* | 129 (66) | 82 (44) | 49 (68) | 27 (44) | 178 (66) | 109 (44) |
| | *Leading to drug discontinuation (%)* | 5 (3) | 8 (4) | 12 (17) | 3 (5) | 17 (6) | 11 (4) |

TEAE treatment emergent adverse event, SAE serious adverse event, SG sacituzumab govitecan, TPC treatment of physician's choice.

**Table 8**
Characteristics of the main studies analyzed and results related to the subgroup analysis by age.

| Trial | Design | Population | Arms | Results | Age range | Subgroup analysis about age | Results of subgroup analysis | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Benefit in PFS in >65 years | Benefit in OS in >65 years |
| **EMILIA** | Randomised (1:1), open-label, phase 3 trial | HER2-positive unresectable, LA or MBC patients previously treated with trastuzumab and a taxane | - Experimental arm: T-DM1<br>- Control arm: lapatinib plus capecitabine | Improvement in PFS and OS in T-DM1 | **Experimental arm:**<br>Median age: 53 years<br>Age range: 28–83 years<br>**Control arm**:<br>Median age: 53 years<br>Range: 25–84 years | Yes (<65 years, 65–74 years, >75 years) | Unclear | Unclear |
| **TH3RESA** | Randomised (2:1), open-label, phase 3 trial | HER2-positive ABC patients previously treated with both trastuzumab and lapatinib (advanced setting) and a taxane (any setting) and with progression on two or more HER2-directed regimens in the advanced setting | - Experimental arm: T-DM1<br>- Control arm: TPC | Improvement in PFS and OS in T-DM1 | **Experimental arm:**<br>Median age: 54 years<br>Age range: 28–85 years<br>**Control arm**:<br>Median age: 53 years<br>Range: 27–89 years | Yes (<65 years, 65–74 years, >75 years) | Unclear | Unclear |
| **DESTINY BREAST02** | Randomised, open-label (2:1), multicentre, phase 3 trial | HER2-positive unresectable or MBC patients who had disease progression on or after trastuzumab emtansine | - Experimental arm: T-DXd<br>- Control arm: TPC | Improvement in PFS and OS in T-DXd | **Experimental arm:**<br>Median age: 54.2 years<br>Age range: 45.5–63.4 years<br>**Control arm**:<br>Median age: 54.7 years<br>Range: 48–63 years | Yes (<65 years, ≥65 years) | Similar to < 65 years (no formal comparison was made) | Similar to < 65 years (no formal comparison was made) |
| **DESTINY BREAST03** | Randomised, open-label (1:1), multicentre, phase 3 trial | Unresectable or HER2-positive metastatic BC patients whose disease progresses after treatment with a combination of anti-HER2 antibodies and a taxane | - Experimental arm: T-DXd<br>- Control arm: T-DM1 | Improvement in PFS and OS in T-DXd | **Experimental arm:**<br>Median age: 54.3 years<br>Age range: 27.9–83.1 years<br>**Control arm**:<br>Median age: 54.2 years<br>Range: 20.2–83 years | Yes (<65 years, ≥65 years) | Similar to < 65 years (no formal comparison was made) | Similar to < 65 years (no formal comparison was made) |
| **DESTINY BREAST04** | Randomised, open-label (2:1), multicentre, phase 3 trial | HER2-low MBC patients who had received one or two previous lines of chemotherapy | - Experimental arm: T-DXd<br>- Control arm: TPC | Improvement in PFS and OS in T-DXd, better results in HR + cohort | **Experimental arm:**<br>Median age: 57.5 years<br>Age range: 31.5–80.2 years<br>**Control arm**:<br>Median age: 55.9 years<br>Range: 28.4–80.5 years | Yes (<65 years, ≥65 years) | Similar to < 65 years (no formal comparison was made) | / |
| **ASCENT** | Randomised, open-label (1:1), multicentre, phase 3 trial | Metastatic TNBC patients whose disease relapsed or was refractory to two or more previous standard chemotherapy regimens for unresectable, locally advanced or metastatic disease; previous therapy had to include a taxane (for any indication) | - Experimental arm: SG<br>- Control arm: TPC | Improvement in PFS and OS in SG | **Experimental arm:**<br>Median age: 54 years<br>Age range: 29–82 years<br>**Control arm**:<br>Median age: 53 years<br>Range: 27–81 years | Yes (<65 years, ≥65 years) | Better to < 65 years (no formal comparison was made) | Better to < 65 years (no formal comparison was made) |
| **TROPiCS-02** | Randomised, open-label (1:1), multicentre, phase 3 trial | HR+ and HER2− locally recurrent inoperable or MBC after at least one previous endocrine therapy, a taxane, and a CDK4/6 inhibitor in any setting and | - Experimental arm: SG<br>- Control arm: TPC | Improvement in PFS and OS in SG | **Experimental arm:**<br>Median age: 57 years<br>Age range: 49–65 years | Yes (<65 years, 65–74 years, >75 years) | Better to < 65 years (no formal comparison was made) | Better to < 65 years (no formal comparison was made) |

(*continued on next page*)

**Table 8** (*continued*)

| Trial | Design | Population | Arms | Results | Age range | Subgroup analysis about age | Results of subgroup analysis | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Benefit in PFS in >65 years | Benefit in OS in >65 years |
| | | two to four previous chemotherapy regimens for metastatic disease | | | **Control arm**: Median age: 55 years Range: 48–63 years | | | |
| **TROPION-PanTumor01** | Phase I, two-part, multicenter, open-label, multiple-dose trial (ongoing) | Advanced HR+/HER2– BC or TNBC that had relapsed or progressed after local standard treatments or for which no standard treatment was available | - Experimental treatment: Dato-DXd | Promising clinical activity and a manageable safety profile | **HR+/HER2- BC cohort:** Median age: 57 Age range: 33–75 years **TNBC cohort:** Median age: 52.5 Age range: 32–82 years | No | / | / |
| **ICARUS-BREAST01** | Multi-center, academic, single-arm, phase II study (ongoing) | HR+ and HER2- ABC, unselected for HER3 expression, who progressed on CDK 4/6 inh, any line of targeted/ET and 1 line of chemotherapy for ABC | - Experimental treatment: HER3-DXd | Early signs of activity and a manageable safety profile | Median age: 56 years Age range: 28–82 years | No | / | / |

Dato-DXd Datopotomab deruxtecan, HER3-DXd patritumab deruxtecan, HR + hormone receptor-positive, LA locally advanced, MBC metastatic breast cancer, m months, SG Sacituzumab govitecan, T-DM1 trastuzuman emtansine, TPC treatment of physician's choice, T-DXd trastuzumab deruxtecan.

HR+/HER2-and TNBC breast cancer population. Median age in HR+/HER2-breast cancer population was 57 in a range from 33 to 75 years, while in TNBC median age was 52.5 in a range from 32 to 82 years. So, it was included a significative group of elderly people in the trial. Results showed at data cut-off an ORR of 26.8 % for HR+/HER2-breast cancer and 31.8 % for TNBC, with a median duration of response of 16.8 months in the TNBC cohort. The median PFS was 8.3 months for HR+/HER2-breast cancer and 4.4 months for TNBC. The median OS was not reached for the HR+/HER2- BC cohort and was 13.5 months in the TNBC cohort. Common AEs included stomatitis, nausea, and fatigue. Other less frequent TEAEs were diarrhea, anemia and neutropenia. Severe toxicities such as ILD and infusion-related reactions (IRRs) were noted, with about 10 % of patients experiencing ILD and approximately 20 % experiencing grade 3 or higher adverse events. Globally, the safety profile of Dato-DXd in both BC cohorts was manageable, with low incidences of grade ≥3 TEAEs, few dose modifications, and no drug-related deaths [46,47].

One of the major strengths of Dato-DXd is its higher selectivity in payload release. This mechanism theoretically limits off-target toxicity by reducing systemic exposure, which is particularly advantageous for older patients who are more vulnerable to adverse effects. However, despite the inclusion of elderly patients in the TROPION-PanTumor01 trial, no specific age-based analysis was reported. This lack of data limits conclusions about its safety and efficacy in this vulnerable group, where pharmacokinetics and comorbidities may influence outcomes. Comparatively, Dato-DXd shows fewer hematologic toxicities than SG, but long-term effects on quality of life in older patients remain unclear (Table 8).

### 3.3. Emerging ADCs

Disitamab vedotin (RC48) is an emerging ADC that pairs the HER2-targeting antibody disitamab with the microtubule inhibitor MMAE [48]. It has been evaluated in a recent retrospective study in heavily pre-treated patients with HER2+ MBC. The median age of the recruited population was 49 in a range from 34 to 83 years. The study showed a median real-world PFS of 5.9 months and an ORR of 29.6 % in the overall population, while the median OS had not been achieved at the time of the study. About safety, the study found that RC48 was generally well-tolerated, with the most common grades 3–4 AEs being neutropenia, leukopenia, and hypoesthesia. Specific data on the efficacy and safety of RC48 in elderly patients is limited [48,49].

RC48 demonstrated to have a competitive efficacy profile comparing with established therapies such as neratinib plus capecitabine and lapatinib plus capecitabine from the EMILIA study, and with T-DM1 from the TH3RESA study but despite these promising aspects, the reported efficacy outcomes are modest when compared to T-DXd, as seen in the DESTINY-Breast01 trial. Additionally, the small sample size further limits the statistical power of the study, particularly when analyzing subgroups such as elderly patients, for whom detailed safety and efficacy data are still lacking. Moreover, the safety profile of RC48, although generally manageable, remains a concern, particularly in elderly populations [48,49].

ARX-788 is another novel ADC targeting HER2, linking the antibody to the cytotoxic payload AS269. An interim analysis from a phase II/III trial demonstrated a median PFS of 11.33 months compared to 8.25 months for lapatinib plus capecitabine in HER2+ advanced breast cancer patients who progressed on trastuzumab-based therapies. Grade 3–5 AEs were comparable between treatments, but unique side effects included blurred vision, dry eye, and ILD, with the latter being mostly mild. No trial data on the median age of the participants or the age range considered have yet been released [50].

One of the most significant aspects of ARX-788 is its safety profile in terms of hematological and gastrointestinal toxicity, appearing more favorable compared to other ADCs targeting HER2 like T-DM1 and T-DXd. This characteristic may make ARX-788 a more suitable option for elderly patients or those with compromised health who may be unable to tolerate the more aggressive toxicity profiles of other ADCs. However, the current trial does not provide sufficient data to definitively assess the efficacy and safety of ARX-788 in older populations.

Patritumab deruxtecan (HER3-DXd) is a novel ADC, composed of an anti-HER3 monoclonal antibody coupled to a topoisomerase I inhibitor payload [51].

Two clinical trials explored the effects of HER3-DXd in advanced breast cancer patients who had already undergone extensive prior treatments. In the phase I/II trial U31402-A-J101 HER3-DXd demonstrated encouraging efficacy results among all breast cancer subtypes, particularly for patients with HER2-positive cancer who achieved the

highest ORR at 42.9 %, with a PFS of 11 months and an OS of 19.5 months. Side effects were frequent, with nausea and decreased blood cell counts being the most common. Many patients required adjustments to their treatment until treatment discontinuation occurred in 9.9 % of patients. This trial enrolled a population in a wide age range from 30 to 83 years with a median age of 57 years [52].

The phase II trial ICARUS-BREAST01 focused on HR+/HER2- MBC patients who had progressed despite multiple treatments, including CDK 4/6 inhibitors. The trial enrolled a population in a wide age range from 28 to 82 years with a median age of 56 years. Although the data is still preliminary, early analysis showed that 28.6 % of patients had a partial response, 53.6 % achieved stable disease, and 17.9 % experienced disease progression at data cut-off. Fatigue, alopecia and gastrointestinal issues, notably nausea and diarrhea, affected nearly all patients. Many of them required treatment adjustments with a small percentage (12.5 %) discontinuing treatment due to AEs [51].

HER3-DXd's performance may be comparable to SG: the median PFS and OS achieved with HER3-DXd are aligned with those observed in the TROPiCS-02 and ASCENT trials. The safety profile appears manageable, but the high incidence of TEAEs raises concerns. These events, often managed with dose delays or reductions, highlight the need for vigilant monitoring, especially in elderly or more vulnerable patients. The inclusion of elderly patients in these trials is commendable, yet detailed age-related safety data are lacking, which limits the ability to assess its full impact on older populations who are more prone to severe AEs (Table 8) [51].

Ladiratuzumab vedotin targets LIV-1 expressed in a moderate/high level in the majority of breast. It has been evaluated in the phase I SGNLVA-001 trial with patients with either first- or second-line endocrine therapy refractory HR+/HER2- MBC or second-line refractory metastatic TNBC, without a LIV-1 expression requirement. Preliminary results showed an ORR of 32 % with a median PFS of 11.3 weeks. Common grade 1 or 2 TRAEs included fatigue, nausea, peripheral neuropathy, and alopecia. The median age of the population was 55, while no data are still reported about age range or age subgroups analysis [53,54].

## 4. Conclusions

The development of ADCs has completely changed the treatment landscape for breast cancer. Several trials have shown their strong potential in terms of efficacy and safety in the overall population. There are also some data on their use in the geriatric population, which nowadays is becoming increasingly representative in the epidemiology of breast cancer.

The evaluation of anti-HER2 ADCs, particularly T-DM1 and T-DXd, in elderly patients highlights their efficacy and safety, albeit with some age-related nuances. T-DM1 can be considered a valid therapy for elderly patients with HER2-positive breast cancer, despite slightly lower tolerability compared to younger patients. Data from the DestinyBreast studies, confirmed by the results from the TREX-Old study, show that T-DXd represents a valid therapeutic option for elderly patients with HER2-positive breast cancer, with significant benefits in terms of PFS and OS. As expected, there is a tendency for a higher incidence of severe AEs in patients over 65 compared to younger patients, especially concerning neutropenia and ILD. These findings suggest that while T-Dxd is effective and tolerable in elderly patients, optimized safety requires closer monitoring and, in when necessary, dose adjustments.

Newest ADCs like SG and emerging agents have shown promise in elderly populations with MBC, too. Trials such as ASCENT and TROPiCS-02 highlight SG's efficacy in older patients, with notable improvements in PFS and OS compared to standard chemotherapy. However, safety profiles reveal higher rates of AEs, particularly in patients aged $\geq$75, emphasizing the need for careful dose management. Emerging ADCs like Dato-DXd and RC48 show potential, but limited age-specific data restricts robust conclusions about their applicability in elderly patients.

Managing ADCs in elderly breast cancer patients requires balancing efficacy with toxicity, often necessitating dose modifications, treatment interruptions, or discontinuation. Dose optimization strategies, including body weight (BW) cap dosing, treatment duration capping, dose scheduling adjustments, response-guided dosing, and randomized dose-finding studies, have been explored to improve efficacy and safety. In particular, treatment duration capping reduces the risk of cumulative toxicities while dose scheduling adjustments, such as adjusting frequency for trastuzumab emtansine, reduce toxicity while maintaining efficacy. ADCs remain effective in elderly patients, but careful monitoring and individualized adjustments are crucial to optimize benefits while minimizing toxicity [55].

In conclusion, ADC therapy in elderly MBC patients deserves careful clinical evaluation and risk benefit balance. Identifying and managing frailty is essential to improving clinical outcomes, personalizing treatment, and reducing complications. Despite advancements in frailty and geriatric assessments, challenges persist, including the integration of these tools into routine clinical practice and the establishment of comprehensive guidelines for frailty monitoring. Strengthening collaboration between oncologists and geriatricians and promoting personalized strategies could significantly enhance the quality of life and survival rates of elderly cancer patients. Further age-focused analyses are critical for advancing the therapeutic potential of ADCs in geriatric oncology.

Real world evidence or well-designed observational studies with geriatric assessment will help optimization of ADC use for older patients in daily practice.

## CRediT authorship contribution statement

**Marta Bonotto:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Giulia De Pieri:** Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation, Data curation, Conceptualization. **Rocco Esposto:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Data curation, Conceptualization. **Ludovica Lay:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Giuseppe Aprile:** Writing – review & editing, Visualization, Validation, Supervision. **Fabio Puglisi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Alessandro Marco Minisini:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Data curation, Conceptualization.

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