European Journal of Cancer 185 (2023) 69–82

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Clinical outcomes of adjuvant taxane plus anthracycline versus taxane-based chemotherapy regimens in older adults with node-positive, triple-negative breast cancer: A SEER–Medicare study

Savannah Roy [a,*], Stephanie Lakritz [a], Anna R. Schreiber [b], Elizabeth Molina [c], Peter Kabos [b], Marie Wood [b], Anthony Elias [b], Lavanya Kondapalli [d], Cathy J. Bradley [e], Jennifer R. Diamond [b]

[a] *Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, USA*
[b] *Division of Medical Oncology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA*
[c] *Population Health Shared Resource, University of Colorado Cancer Center, Aurora, CO, USA*
[d] *Division of Cardiology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA*
[e] *Department of Health Systems, Management, and Policy, University of Colorado Anschutz Medical Campus, Aurora, CO, USA*

Received 5 October 2022; received in revised form 10 February 2023; accepted 14 February 2023
Available online 28 February 2023

KEYWORDS
Breast cancer;
Older adults;
Chemotherapy;
Triple-negative breast cancer;
Anthracyclines

Abstract ***Background:*** Triple-negative breast cancer (TNBC) is a subtype of breast cancer associated with an aggressive clinical course. Adjuvant chemotherapy reduces the risk of recurrence and improves survival in patients with node-positive TNBC. The benefit of anthracycline plus taxane (ATAX) regimens compared with non-anthracycline-containing, taxane-based regimens (TAX) in older women with node-positive TNBC is not well characterised.
Methods: Using the Surveillance, Epidemiology, and End Results–Medicare database, we identified 1106 women with node-positive TNBC diagnosed at age 66 years and older between 2010 and 2015. We compared patient clinical characteristics according to adjuvant chemotherapy regimen (chemotherapy versus no chemotherapy and ATAX versus TAX). Logistic regression was performed to estimate the odds ratios (OR) and 95% confidence intervals (CIs). Kaplan–Meier survival curves were generated to estimate 3-year overall survival (OS) and cancer-specific survival (CSS). Cox proportional hazard models were used to analyse OS and CSS while controlling for patient and tumour characteristics.
Results: Of the 1106 patients in our cohort, 767 (69.3%) received adjuvant chemotherapy with ATAX (364/767, 47.5%), TAX (297/767, 39%) or other regimens (106/767, 13.8%).

* *Corresponding author*: University of Colorado Anschutz Medical Campus, 12801 East 17th Ave, Mailstop 8117, Aurora, CO 80045, USA.
E-mail address: savannah.roy@cuanschutz.edu (S. Roy).

https://doi.org/10.1016/j.ejca.2023.02.014
0959-8049/Published by Elsevier Ltd.

Independent predictors of which patients were more likely to receive ATAX versus TAX included more extensive nodal involvement (≥4), age, marital/partner status and non-cardiac comorbidities. There was a statistically significant improvement in 3-year CSS (81.8% versus 71.4%) and OS (70.7% versus 51.3%) with the use of any chemotherapy in our cohort ($P < 0.01$). Three-year CSS and OS for patients who received ATAX versus TAX were similar at 82.8% versus 83.7% ($P = 0.80$) and 74.2% versus 72.7% ($P = 0.79$), respectively. There was a trend towards improved CSS and OS in patients with four or more positive lymph nodes who received ATAX versus TAX (hazard ratio 0.66, 95% CI: 0.36–1.23, $P = 0.19$ and hazard ratio 0.68, 95% CI: 0.41–1.14, $P = 0.14$, respectively).

Conclusion: Among older women with node-positive TNBC, a majority of patients received adjuvant chemotherapy, which was associated with an improvement in CSS and OS. When compared with TAX chemotherapy, there was a trend towards better outcomes with ATAX for patients with ≥4 nodes.

Published by Elsevier Ltd.

1. Introduction

Breast cancer is the most diagnosed cancer worldwide in women, and triple-negative breast cancer (TNBC), defined as negative for estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor 2 (HER2), accounts for approximately 15% of cases [1]. TNBC is associated with a more aggressive clinical course, including advanced stage at initial diagnosis, early metastatic spread and decreased overall survival (OS) [2,3].

Approximately 35% of patients diagnosed with TNBC are aged >65 years; however, data show decreased use of chemotherapy in this population and few aged >65 years enrolled in clinical trials [2,4–11]. The Bridging the Age Gap Study, a prospective cohort study, recently demonstrated that there are a significant number of older but fit patients with high-risk early breast cancer who are not receiving chemotherapy and that some of these patients, particularly those with ER-negative disease, may derive benefit from therapy [12]. The European Society of Breast Cancer Specialists and the International Society of Geriatric Oncology have recently updated and expanded the previous 2012 evidence-based recommendations for the management of breast cancer in older individuals, which should be used to select such patients for treatment [13].

Anthracycline and taxane-based chemotherapy (ATAX) has historically been the standard of care adjuvant therapy for patients with node-positive, HER2-negative, early-stage breast cancer. In this patient population, ATAX significantly reduces the risk of breast cancer recurrence, breast cancer mortality, and overall mortality compared with omission of adjuvant chemotherapy [14]. In the Early Breast Cancer Trialists' Collaborative Group meta-analysis, the addition of four cycles of taxanes to anthracyclines improved the 8-year breast cancer mortality rate from 21.1% to 23.9% (RR 0.86, 95% CI]: 0.79–0.93) and 8-year overall mortality rate from 23.5% to 26.7% (RR 0.86, 95% CI: 0.79–0.93) compared with the anthracyclines control group [14]. When compared head-to-head, TC (docetaxel, cyclophosphamide) was superior to AC (doxorubicin, cyclophosphamide) with a benefit in disease-free survival and OS [15].

Given the benefit of taxanes and the risk of cardiac toxicity and secondary leukaemias with anthracyclines, a series of phase III randomised trials were conducted to evaluate the impact of anthracyclines in taxane-containing regimens. The ABC trials demonstrate improved invasive disease-free survival for ATAX compared with TAX chemotherapy, with more benefit in patients with TNBC and those with node-positive disease [16]. However, a benefit was not demonstrated for ATAX compared with TAX in a combined analysis of PlanB and SUCCESS C trials [17]. Importantly, most patients enrolled in these trials were aged <66 years, and the benefit of ATAX compared with TAX in older patients remains underexamined. Two prospective clinical trials assessing the effect of chemotherapy versus no therapy in older patients with breast cancer, the CASA and ACTION studies, were closed prematurely because of poor accrual and demonstrate the challenges of conducting prospective randomised clinical trials in this patient population [19,20].

We recently completed a retrospective analysis of adjuvant chemotherapy in older women with node-negative TNBC and found that ATAX was associated with inferior 3-year OS and cancer-specific survival (CSS) compared with TAX [18]. The purpose of this study was to evaluate the benefit of adjuvant chemotherapy with ATAX compared with TAX in older women with node-positive TNBC.

2. Methods

Using the Surveillance, Epidemiology, and End Results (SEER)–Medicare database, we identified 178,228

patients diagnosed with primary breast cancer from 2010 to 2015. We then identified 1106 women with node-positive TNBC diagnosed at age ≥66 years meeting eligibility criteria for inclusion in this study/analysis (see Fig. 1). Individuals with missing data of interest were excluded from the analysis; this occurred in less than 1% of the data. Data regarding year of diagnosis, age, race, marital/partnered status, reporting registry region,

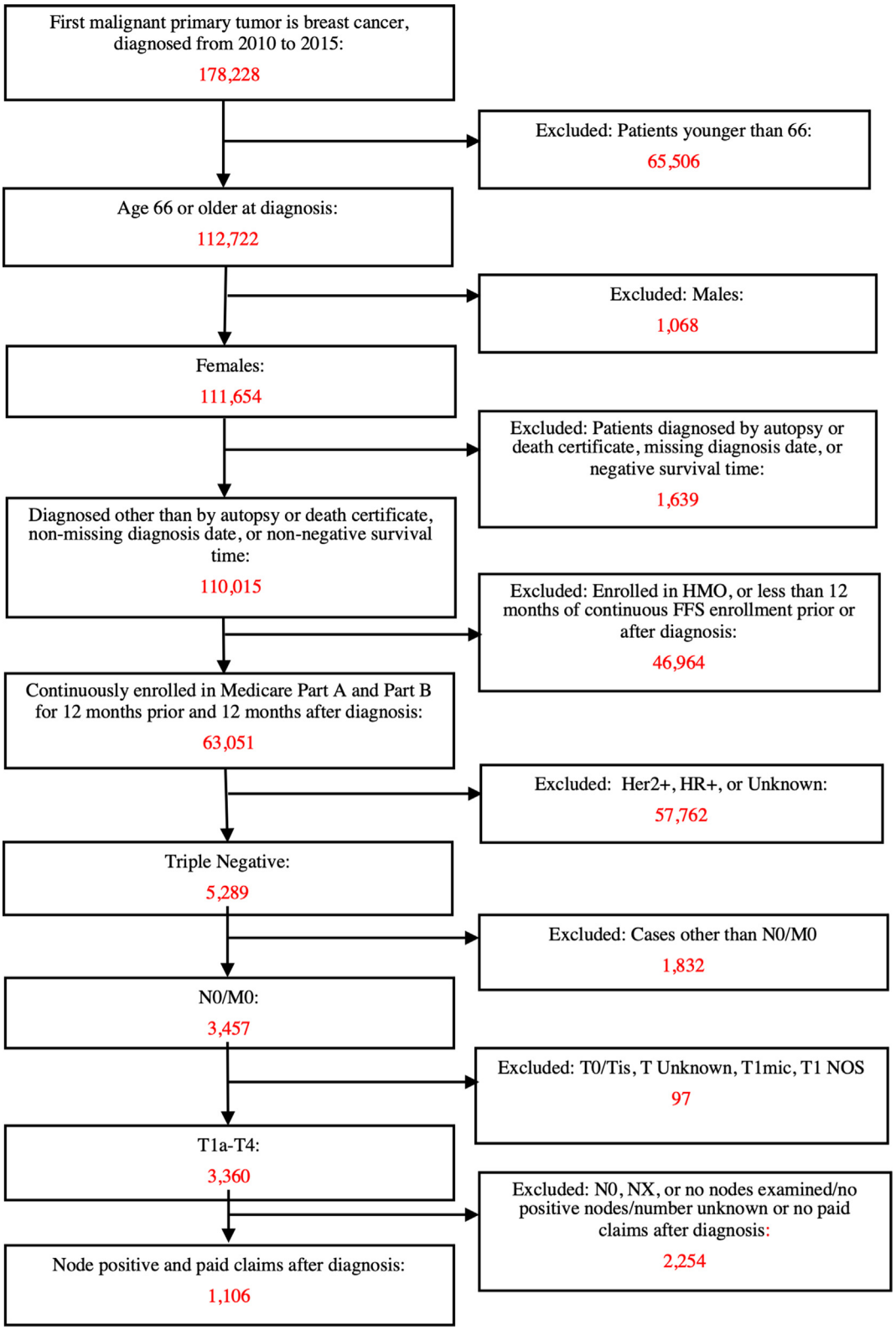

Fig. 1. Sample selection. Newly diagnosed node-negative triple-negative breast cancer in women aged ≥66 years between 2010 and 2015 in Surveillance, Epidemiology, and End Results–Medicare. FFS, fee-for-service; HMO, health maintenance organization.

urban/rural residency, tumour stage, number of positive nodes, census poverty level, facilities visited in the first 6 months, Charlson Comorbidity Index (CCI), treatment, presence of heart failure before diagnosis, presence of heart failure after diagnosis and presence of non-cardiac conditions were extracted. Heart failure after diagnosis could be before or after chemotherapy was received. The CCI was calculated based on claims 1 year before diagnosis. As all patients were aged ≥66 years, the CCI was not further age adjusted. Patients with a T1a and T1b disease and T3 and T4 disease were analysed together in T1a/b and T3/4 groups because of few patients in these groups. Patients were categorised into 1–3 (N1) and ≥4 positive lymph nodes (N2).

The administration of neoadjuvant or adjuvant chemotherapy was determined using current procedural terminology (CPT) and healthcare common procedure coding system (HCPCS) procedure codes for commonly used chemotherapy drugs. Comorbid conditions were defined by International Classification of Diseases, Ninth Revision, and International Classification of Diseases, Tenth Revision, codes (Appendix). Patients were identified as receiving ATAX if they received doxorubicin or epirubicin plus paclitaxel, docetaxel or nab-paclitaxel and as receiving TAX if they received docetaxel, paclitaxel or nab-paclitaxel without doxorubicin or epirubicin. Receipt of other drugs in combination with these agents was not included in this analysis.

Descriptive statistics were used to summarise demographic features across the treatment groups. Chi-square analysis was used to determine statistical significance of differences in descriptive characteristics across treatment groups. OS was defined as death due to any cause determined by the time from the month of diagnosis to death. CSS was defined as death from cancer determined by the time from the month of diagnosis to death. Kaplan–Meier 3-year all-cause and CSS curves were generated for treatment groups and for patients by age groups. OS and CSS between chemotherapy regimens were estimated using adjusted Cox proportional hazards models. Forest plots were generated using multivariate analysis and adjusted Cox proportional hazards models. Logistic regression was used to estimate odds ratios (ORs) and 95% CIs for the association between covariates and treatment groups. The CSS and OS analyses were adjusted for CCI to account for the impact of comorbidities as competing factors of mortality.

3. Results

3.1. Patient characteristics

Baseline patient characteristics are summarised in Table 1. Patients were well distributed between our age groups, with 54.1% aged 66–75 years and 45.9% aged ≥76 years. Most patients were non-Hispanic White (76.4%), followed by Black (13.5%), or other (10.3%). Most patients had T2 tumours (49.1%), and there were more patients with N1 versus N2 disease (64.6% versus 35.4%). Most patients were free of comorbidities with a CCI score of 0 (53.1%), followed by a CCI score of 2 or more (25.0%) and CCI score of 1 (22.0%). Patients more commonly visited teaching hospitals (53.6%) than National Cancer Institute (NCI) centres (12.8%) or other facilities (33.6%). Most patients did not have prior heart failure or heart failure after diagnosis (91.1% and 75.4%, respectively).

3.2. Patterns of chemotherapy administration

Of the 1106 patients in our cohort, 767 (69.3%) received any type of adjuvant chemotherapy (Table 1). Patients aged 66–75 years ($N = 598$) received chemotherapy at a much higher frequency (530/598, 88.6%) compared with patients aged ≥76 years ($N = 508$, 237/508, 46.7%, $P < 0.001$). Of those patients receiving adjuvant chemotherapy ($N = 767$), 364 (47.5%) received ATAX, 297 (38.7%) received TAX and 106 (13.8%) received another regimen. The most common other agents included cyclophosphamide, carboplatin, capecitabine, **5**-Fluorouracil (5-FU) and methotrexate. Our data did not delineate if these other agents were used as single agents or in combination with one another. Of the patients aged 66–75 years who received a taxane-containing regimen ($N = 485$), the majority (309/485, 63.7%) received ATAX compared with a minority of patients aged ≥76 years ($N = 176$, 55/176, 31.3%).

3.3. Factors associated with the use of adjuvant chemotherapy

3.3.1. Patient characteristics

Logistic regression analysis revealed that patients aged ≥76 years were less likely to receive adjuvant chemotherapy when compared with those aged 66–70 years (OR 0.12, 95% CI: 0.08–0.16, $P < 0.01$). Older patients aged ≥76 years were also less likely to receive ATAX versus TAX compared with patients aged 66–75 years (OR 0.24, 95% CI: 0.16–0.35, $P < 0.01$). Compared with the patients who were married or partnered, patients who were not married were less likely to receive adjuvant chemotherapy (OR 0.42, 95% CI: 0.30–0.58, $P < 0.01$). Patients who were non-married were also less likely to receive ATAX than TAX (OR 0.69, 95% CI: 0.44–0.88, $P < 0.01$). Patients in the Northeast were more likely to receive treatment with ATAX than TAX compared with those in the West (OR 2.20, 95% CI: 1.30–3.72, $P < 0.01$). Patients who sought care at an NCI-designated centre were more likely to receive adjuvant chemotherapy (OR 1.91, 95% CI: 1.10–3.33, $P = 0.02$) compared with other facilities. Table 2 provides additional analysis.

Table 1
Descriptive characteristics and statistics, women diagnosed with TNBC by chemotherapy administration, SEER–Medicare 2010–2015.

Variable	All patients				Patients who received ATAX and TAX			
	Overall, N	No chemotherapy, *n* (%)	Any chemotherapy, *n* (%)	*P* value	Overall, *n*	Taxane, *n* (%)	Taxane + anthracycline, *n* (%)	*P* value
All patients	1106	339 (30.6)	767 (69.3)		661	297	364	
Year of diagnosis								
2010	196 (17.7)	67 (19.8)	129 (16.8)	0.0558	114 (17.3)	49 (16.5)	65 (17.9)	0.9223
2011	217 (19.6)	70 (20.7)	147 (19.2)		132 (20.0)	58 (19.5)	74 (20.3)	
2012	192 (17.4)	66 (19.5)	126 (16.4)		110 (16.6)	52 (17.5)	58 (15.9)	
2013	158 (14.3)	45 (13.3)	113 (14.7)		91 (13.8)	45 (15.2)	46 (12.6)	
2014	175 (15.8)	56 (16.5)	119 (15.5)		102 (15.4)	44 (14.8)	58 (15.9)	
2015	168 (15.2)	35 (10.3)	133 (17.3)		112 (16.9)	49 (16.5)	63 (17.3)	
Age category								
66–75	598 (54.0)	68 (20.1)	530 (69.1)	**<0.0001**	485 (73.4)	176 (59.3)	309 (85.9)	**<0.0001**
≥76	508 (45.9)	271 (80.0)	237 (30.9)		176 (26.6)	121 (40.7)	55 (15.1)	
Race/ethnicity category								
White NH	832 (75.2)	259 (76.4)	573 (74.7)	0.7721	493 (74.6)	217 (73.1)	276 (75.8)	0.6043
Black NH	149 (13.5)	45 (13.3)	104 (13.6)		88 (13.3)	40 (13.5)	48 (13.2)	
Other	125 (11.3)	35 (10.3)	90 (11.7)		80 (12.1)	40 (13.5)	40 (11.0)	
Marital status category								
Non-married	625 (56.5)	250 (73.8)	375 (48.9)	**<0.0001**	317 (48.0)	164 (55.2)	153 (42.0)	**0.0007**
Married or partnered	481 (43.5)	89 (26.3)	392 (51.1)		344 (52.0)	133 (44.8)	211 (58.0)	
Registry region at diagnosis								
Northeast	200 (18.1)	50 (14.8)	150 (19.6)	0.2463	125 (18.9)	42 (14.1)	83 (22.8)	**0.0067**
Midwest	141 (12.8)	44 (13.0)	97 (12.7)		83 (12.6)	33 (11.1)	50 (13.7)	
South	319 (28.8)	98 (28.9)	221 (28.8)		198 (30.0)	90 (30.3)	108 (29.7)	
West	446 (40.3)	147 (43.4)	299 (39.0)		255 (38.6)	132 (44.4)	123 (33.8)	
Patient urban/rural recode category								
Urban commuting area	965 (87.3)	299 (88.2)	666 (86.8)	0.5292	567 (85.8)	254 (85.5)	313 (86.00)	0.8642
Non-urban commuting area	141 (12.8)	40 (11.8)	101 (13.2)		94 (14.2)	43 (14.5)	51 (14.0)	
DAJCC 7th Ed T category								
T1a/T1b	64 (5.8)	23 (6.8)	41 (5.4)	**0.0468**	35 (5.3)	18 (6.1)	17 (4.7)	0.4831
T2	543 (49.1)	149 (44.0)	394 (51.4)		337 (51.0)	156 (52.5)	181 (49.7)	
T3/T4	277 (25.1)	101 (29.8)	176 (23.0)		153 (23.2)	61 (20.5)	92 (25.3)	
Number of positive nodes								
1–3 nodes positive	714 (64.6)	220 (64.9)	494 (64.4)	0.8752	419 (63.4)	201 (67.7)	218 (59.9)	**0.0387**
≥4 nodes positive	392 (35.4)	119 (35.1)	273 (35.6)		242 (36.6)	96 (32.3)	146 (40.1)	
Charlson Comorbidity Index category								
0	587 (53.1)	142 (41.9)	445 (58.0)	**<0.0001**	392 (59.3)	156 (52.5)	236 (64.8)	**<0.0001**
1	243 (22.0)	75 (22.1)	168 (21.9)		140 (21.2)	61 (20.5)	79 (21.7)	
≥2	276 (25.0)	122 (36.0)	154 (20.1)		129 (19.5)	80 (26.9)	49 (13.5)	
Census poverty level								
0% to <20% poverty	841 (76.0)	256 (75.5)	585 (76.3)	0.7862	501 (75.8)	217 (73.1)	284 (78.0)	0.1388
≥20% poverty	265 (24.0)	83 (24.5)	182 (23.7)		160 (24.2)	80 (26.9)	80 (22.0)	
Facilities visited in first 6 months								
NCI centre	141 (12.8)	27 (8.0)	114 (14.9)	**0.0025**	97 (14.7)	44 (14.8)	53 (14.6)	0.4621
Teaching hospital	593 (53.6)	182 (53.7)	411 (53.6)		359 (54.3)	154 (51.9)	205 (56.3)	
Other	372 (33.6)	130 (38.4)	242 (31.6)		205 (31.0)	99 (33.3)	106 (29.1)	
Treatment								
Surgery alone	210 (19.0)	210 (62.0)	0 (0.0)	**<0.0001**				
Surgery and RT	129 (11.7)	129 (38.1)	0 (0.0)					
Surgery and chemotherapy	180 (16.3)	0 (0.0)	180 (23.5)		137 (20.7)	74 (24.9)	63 (17.3)	**0.0164**
Surgery, RT and chemo	587 (53.1)	0 (0.0)	587 (76.5)		524 (79.3)	223 (75.1)	301 (82.7)	
Prior heart failure								
No	1007 (91.1)	286 (84.4)	721 (94.0)	**<0.0001**	624 (94.4)	272 (91.6)	352 (96.7)	**0.0044**
Yes	99 (9.0)	53 (15.6)	46 (6.0)		37 (5.6)	25 (8.4)	12 (3.3)	
Heart failure after Dx								
No	834 (75.4)	223 (65.8)	611 (79.7)	**<0.0001**	529 (80.0)	221 (74.4)	308 (84.6)	**0.0011**
Yes	272 (24.6)	116 (34.2)	156 (20.3)		132 (20.0)	76 (25.6)	56 (15.4)	

ATAX, anthracycline plus taxane; NCI, National Cancer Institute; NH, non-Hispanic; SEER, Surveillance, Epidemiology, and End Results; TAX, taxane-based regimens; TNBC, triple-negative breast cancer; DAJCC, derived american joint committee on cancer; RT, radiation therapy. Bolded values are statistically significant findings.

3.3.2. Tumour size and nodal status

Patients with four or more positive lymph nodes were not statistically more likely to receive adjuvant chemotherapy compared with those with 1–3 positive nodes (OR 1.29, 95% CI: 0.93–1.80, $P = 0.13$). However, among patients who received a taxane-based chemotherapy regimen, patients with four or more positive lymph nodes were more likely than patients with 1–3 positive lymph nodes to receive ATAX versus TAX (OR 1.63, 95% CI: 1.13–2.37, $P < 0.01$).

3.3.3. Medical comorbidities

Patients with previously diagnosed heart failure were less likely to receive adjuvant chemotherapy compared with those without heart failure (OR 0.54, 95% CI: 0.31–0.94, $P = 0.03$). However, among patients with prior heart failure who received adjuvant chemotherapy, there was no significant difference between the proportion who received ATAX versus TAX (OR 0.93, 95% CI: 0.39–2.24, $P = 0.88$). There was no statistically significant difference in heart failure onset after cancer diagnosis in those who received adjuvant chemotherapy versus those who did not receive adjuvant chemotherapy (OR 0.87, 95% CI: 0.59–1.28, $P = 0.45$). Those with heart failure after diagnosis were statistically significantly less likely to receive ATAX versus TAX (OR 0.61, 95% CI: 0.38–0.98, $P = 0.04$). Those with a prior non-cardiac comorbid condition were statistically significantly less likely to receive chemotherapy in general and ATAX over TAX (OR 0.49, 95% CI: 0.31–0.79, $P < 0.01$ and OR 0.45, 95% CI: 0.25–0.79, $P < 0.01$, respectively).

3.3.4. Analysis of chemotherapy type and survival

Chemotherapy significantly improved both CSS and OS (seeFig. 2A and B). However, for patients who received a taxane-containing regimen, there was no difference in CSS or OS for patients receiving ATAX compared with TAX (Fig. 2C and D). In patients with four or more lymph nodes, there was a trend towards improved CSS and OS with ATAX compared with TAX (Fig. 2E–H), which was not seen in patients with 1–3 positive lymph nodes.

3.3.4.1. Analysis of CSS and OS controlling for covariates. We evaluated factors that might influence the previously mentioned findings (Fig. 3). Although treatment with any chemotherapy was associated with improved CSS (HR: 0.71, 95% CI: 0.51–0.98, $P = 0.04$), we saw a trend towards benefit for older (>76) versus younger patients and 1–3 versus ≥ 4 lymph nodes positive. When stratified by age, a trend towards benefit for CSS was seen in those aged ≥76 years (HR: 0.68, 95% CI: 0.46–1.00, $P = 0.05$) but was not statistically significant in those aged 66–75 years (HR: 0.68, 95% CI: 0.35–1.29, $P = 0.24$). Those with 1–3 positive lymph nodes had a trend towards benefit for CSS in those who received any adjuvant chemotherapy (HR: 0.63, 95% CI: 0.38–1.00, $P = 0.05$) but was not significant for those with four or more involved lymph nodes (HR: 0.78, 95% CI: 0.48–1.26; $P = 0.31$).

When compared with TAX, ATAX did not improve CSS (HR: 0.94, 95% CI: 0.61–1.45, $P = 0.79$) However, when stratified by age and number of positive lymph nodes, a trend emerged specifically in CSS. Improved CSS was seen in older patients ages 76 years and older with four or more positive lymph nodes who were treated with ATAX versus TAX (HR: 0.09, 95% CI: 0.01–0.73, $P = 0.02$). Conversely, a trend towards worse CSS was seen in older patients with less lymph node involvement, 1–3 positive lymph nodes when treated with ATAX versus TAX (HR: 12.33, 95% CI: 0.99–154.24, $P = 0.05$; Fig. 3).

Trends were similar for OS, with significant benefit observed for chemotherapy (HR: 0.71, 95% CI: 0.55–0.91, $P = 0.01$; Fig. 4). This trend of improved 3-year OS was seen when stratified by age in those aged ≥76 years (HR: 0.71, 95% CI: 0.53–0.96, $P = 0.03$) and those aged 66–75 years (HR: 0.61, 95% CI: 0.38–0.97, $P = 0.04$). The OS was also significant when stratified by 1–3 positive lymph nodes (HR: 0.71, 95% CI: 0.55–0.91, $P < 0.01$) and four or more positive lymph nodes (HR: 0.66, 95% CI: 0.45–0.97, $P = 0.03$). There was no 3-year OS benefit with ATAX compared with TAX (HR: 0.98, 95% CI: 0.70–1.37, $P = 0.90$). There was no statistically significant difference in 3-year OS between ATAX versus TAX in those with 1–3 positive lymph nodes (HR: 1.33, 95% CI: 0.82–2.14, $P = 0.25$). Similarly, there was no statistically significant difference in 3-year OS between ATAX versus TAX in those with four or more positive lymph nodes (HR: 0.68, 95% CI: 0.41–1.14, $P = 0.14$).

4. Discussion

Using the SEER–Medicare database, we retrospectively evaluated practice patterns and survival for older women treated for node-positive TNBC with ATAX or TAX chemotherapy. We conducted this study as older patients are commonly under-represented in randomised controlled trials yet make up an important patient population clinically. Because of lack of randomised control trials in this patient population, retrospective secondary analysis can be useful to guide treatment decisions in this older population and support future clinical trials.

Consistent with prior reports, our study confirmed the benefit of adjuvant chemotherapy in older women with node-positive TNBC with improved CSS and OS [21,22]. Patients aged ≥76 years were less likely to receive adjuvant chemotherapy, but when they did, they derived benefit in terms of both CSS and OS. This may

Table 2
Logistic regression analysis estimating OR of chemotherapy versus no chemotherapy and taxane + anthracycline-containing regimen versus taxane-containing regimen across variables, SEER–Medicare 2010–2015.

Variable	Chemotherapy versus no chemotherapy		Taxane + anthracycline versus taxane	
	OR (95% CI)	*P value*	OR (95% CI)	*P value*
Year of diagnosis				
2011 versus 2010	1.00 (0.61, 1.65)	0.9911	0.93 (0.53, 1.63)	0.7986
2012 versus 2010	1.09 (0.66, 1.79)	0.7454	0.94 (0.52, 1.70)	0.8275
2013 versus 2010	1.34 (0.78, 2.29)	0.2947	0.76 (0.41, 1.41)	0.3870
2014 versus 2010	1.00 (0.59, 1.67)	0.9874	0.96 (0.52, 1.75)	0.8892
2015 versus 2010	1.82 (1.04, 3.19)	**0.0353**	0.92 (0.51, 1.66)	0.7847
Age at diagnosis				
66–75 (ref)				
≥76 versus 66–75	0.12 (0.08, 0.16)	**<0.0001**	0.24 (0.16, 0.35)	**<0.0001**
Race/ethnicity				
White NH (ref)				
Black NH versus White NH	1.17 (0.72, 1.89)	0.5279	1.13 (0.65, 1.96)	0.6649
Other versus White NH	1.06 (0.63, 1.80)	0.8225	0.79 (0.45, 1.36)	0.4118
Marital status				
Married or partnered (ref)				
Non-married versus married or partnered	0.42 (0.30, 0.58)	**<0.0001**	0.69 (0.44, 0.88)	**0.0078**
Charlson comorbidity index				
0 (ref)				
1 versus 0	1.15 (0.74, 1.78)	0.5306	1.37 (0.84, 2.25)	0.2090
2 or more versus 0	0.96 (0.56, 1.63)	0.8698	0.76 (0.41, 1.43)	0.3953
Census-level poverty				
0–20% poverty (ref)				
≥20% or higher poverty versus 0% to <20% poverty	0.98 (0.67, 1.43)	0.9199	0.91 (0.59, 1.41)	0.6797
Region				
West (ref)				
Midwest versus West	0.81 (0.48, 1.36)	0.4231	1.30 (0.71, 2.38)	0.3878
Northeast versus West	1.55 (0.97, 2.47)	0.0665	2.20 (1.30, 3.72)	**0.0032**
South versus West	0.95 (0.64, 1.42)	0.8166	1.12 (0.71, 1.77)	0.6309
Urban/rural category				
Urban commuting area (ref)				
Non-urban commuting area versus urban commuting area	1.09 (0.67, 1.78)	0.7263	0.99 (0.59, 1.65)	0.9709
DAJCC7 T category				
T1a/T1b (ref)				
T1c versus T1a/T1b	1.40 (0.69, 2.85)	0.3526	1.29 (0.57, 2.93)	0.5439
T2 versus T1a/T1b	1.90 (0.98, 3.68)	0.0557	1.65 (0.77, 3.57)	0.2014
T3/T4 versus T1a/T1b	1.22 (0.61, 2.44)	0.5717	2.11 (0.92, 4.81)	0.0770
Number of positive nodes				
1–3 nodes positive (ref)				
≥4 nodes positive versus 1–3 nodes positive	1.29 (0.93, 1.80)	0.1292	1.63 (1.13, 2.37)	**0.0099**
Facility type				
Other (ref)				
NCI centre versus other	1.91 (1.10, 3.33)	**0.0227**	0.92 (0.52, 1.60)	0.7550
Teaching hospital versus other	1.14 (0.81, 1.62)	0.4500	1.04 (0.69, 1.57)	0.8487
Prior heart failure				
No (ref)				
Yes versus No	0.54 (0.31, 0.94)	**0.0296**	0.93 (0.39, 2.24)	0.8792
Heart failure after diagnosis				
No (ref)				
Yes versus No	0.87 (0.59, 1.28)	0.4741	0.61 (0.38, 0.98)	**0.0411**
Prior non-cardiac comorbid condition				
No (ref)				
Yes versus No	0.49 (0.31, 0.79)	**0.0029**	0.45 (0.25, 0.79)	**0.0053**

CI, confidence interval; NH, non-Hispanic; OR, odds ratio; SEER, Surveillance, Epidemiology, and End Results. Bolded values are statistically significant findings.

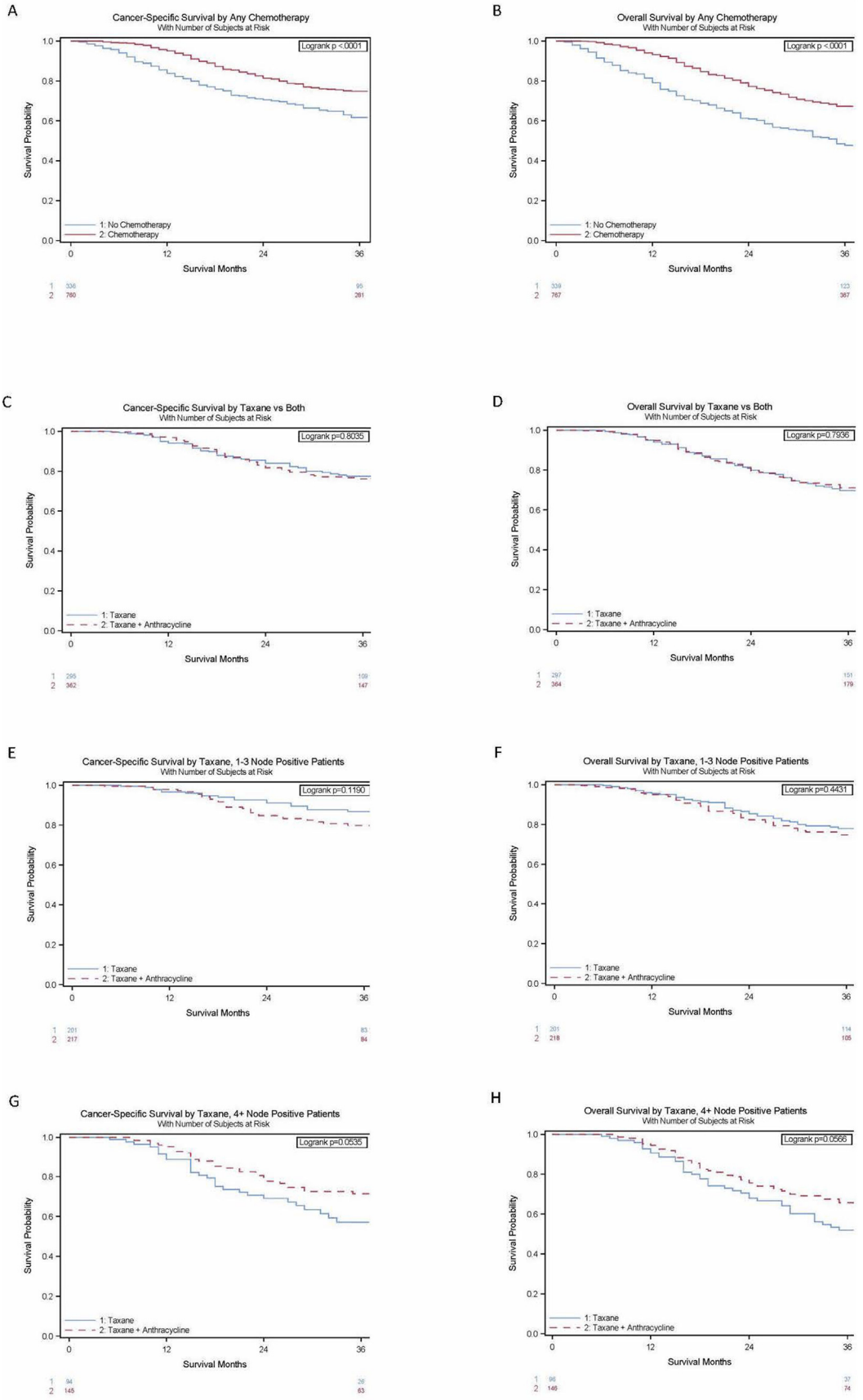

Fig. 2. Kaplan–Meier survival curves demonstrating survival probability over 3 years. Total number at risk is reflected at 0 months and 36 months for all curves. (A) Cancer-specific survival (CSS) for patients who received chemotherapy versus those who did not. (B) Overall

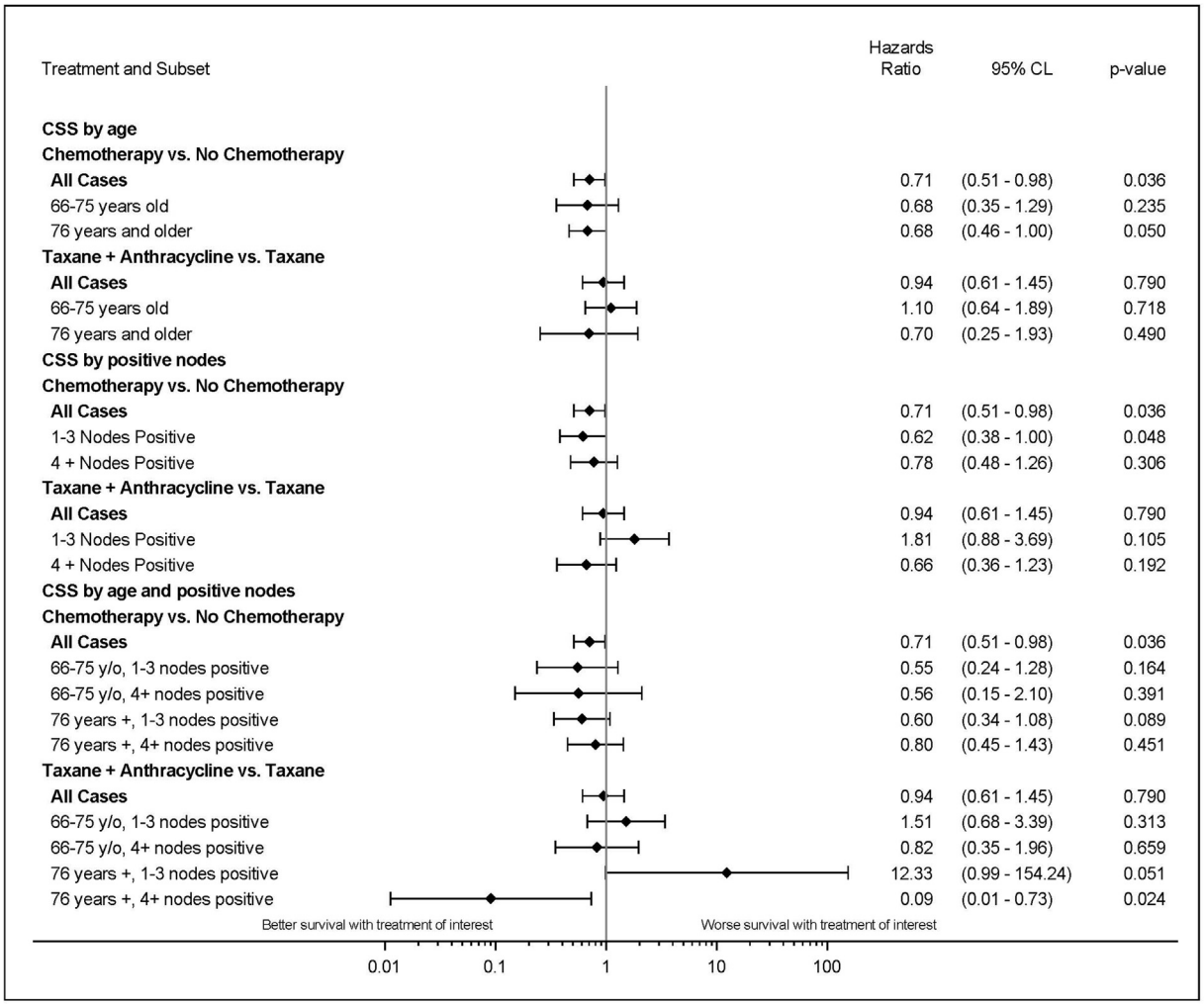

Fig. 3. Forest plots for multivariate analysis of cancer-specific survival (CSS). Hazard ratios shown overall and by stage after reflecting for all covariates.

reflect careful patient selection on the part of treating physicians, given the potential for severe chemotherapy toxicity in older patients who may have medical comorbidities or impaired functional status. Although chemotherapy does have an impact on quality of life, these effects are temporary and have been shown to largely resolve within 2 years [23]. Geriatric assessment tools are available that can be used for the physician to take an objective approach based on multidimensional assessment and not on age alone [24]. These assessment tools, such as the Comprehensive Geriatric Assessment by SIOG or the ESTIMATE can refine prognostication and enable better patient-centric decision-making [13,25].

We found that independent variables predicting the use of ATAX versus TAX included younger age, higher lymph node burden, having a marital partner and the absence of non-cardiac comorbid conditions. Although acute toxicity is more frequent in older patients receiving anthracycline-based chemotherapy that may result in treatment delay or interruption, overall treatment has been shown to be reasonably well-tolerated with 88.1% of older patients completing the planned anthracycline regimen in one study [26]. That said, it should be noted that anthracyclines carry a small but important risk of cardiotoxicity [27]. Cardiotoxicity is specifically a concern in the older population, as age >60 years is considered an independent risk factor as is having pre-

survival (OS) for patients who received chemotherapy versus those who did not. (C) CSS for patients who received anthracycline + taxane (ATAX) containing chemotherapy versus taxane-containing (TAX). (D) OS for patients who received ATAX versus TAX. (E) CSS for patients with 1–3 positive lymph nodes who received ATAX versus TAX. (F) OS for patients with 1–3 positive lymph nodes who received ATAX versus TAX. (G) CSS for patients with ≥4 positive lymph nodes who received ATAX versus TAX. (H) OS for patients with ≥4 positive lymph nodes who received ATAX versus TAX.

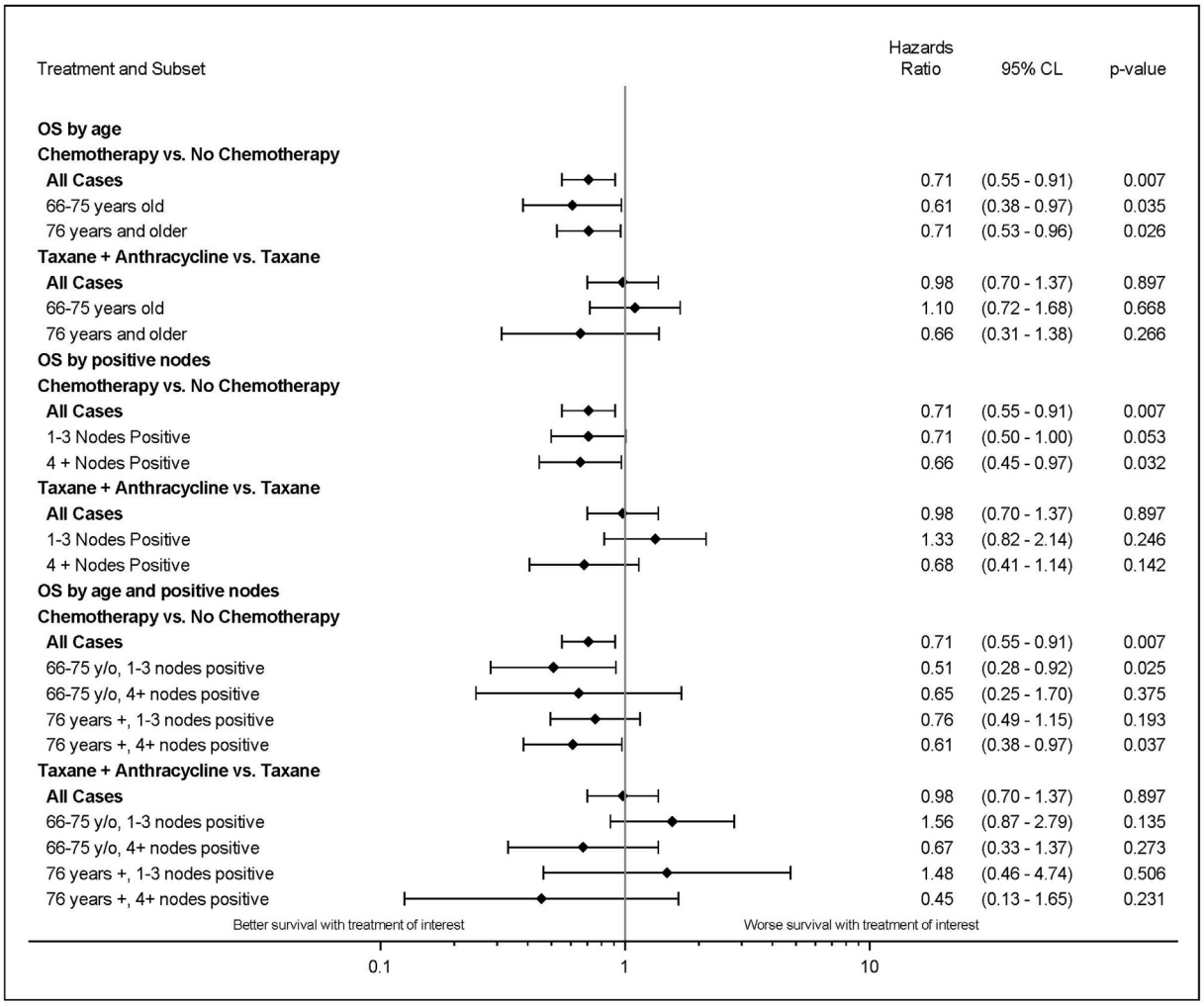

Fig. 4. Forest plots for multivariate analysis of overall survival (OS). Hazard ratios shown overall and by stage after reflecting for all covariates.

existing CV conditions such as hypertension, diabetes and prior myocardial infarction, which are more common as people age [28,29]. This may partly explain why older patients are less likely to receive an anthracycline-based regimen. It has been shown that there is significant overlap between cardiovascular disease and potentially curable cancer diagnoses, including breast cancer [30]. For patients who may be at elevated risk of cardiotoxicity, partnering with a cardiologist or cardio-oncologist can be helpful and allow these patients to receive cardiotoxic chemotherapy. Although specialised cardio-oncology services have been developed to meet this growing clinical demand, they are largely confined to large institutions, which are often academic referral centres [31]. More work needs to be done to increase awareness and expand access to cardio-oncology services to a larger proportion of the cancer population [32].

Those patients with four or more positive lymph nodes were more likely to receive ATAX over TAX, which highlights the important balance between tumour- and patient-related concerns that clinicians consider when choosing a chemotherapy regimen.

Interestingly, patients in our study with prior diagnosis of heart failure who received adjuvant chemotherapy were just as likely to receive ATAX as TAX. Those with heart failure after diagnosis were, however, statistically significantly less likely to receive ATAX over TAX. This was a surprising result; however, it highlights a limitation of our study. Given that guidelines emphasise a baseline echocardiogram for patients receiving anthracyclines [33,34], what our study defined as 'heart failure after diagnosis' could be before or after chemotherapy, and it is likely that patients with abnormal cardiac function on echocardiogram before treatment did not receive an anthracycline.

Previous studies have identified that married patients are more likely to receive definitive treatment [35], and for patients with breast cancer, marital status is an independent prognostic factor for survival [35,36]. Our study confirms the association between marital status and undertreatment, as non-married patients were less likely to receive adjuvant chemotherapy. They were also less likely to receive ATAX than TAX [14,16]. Indeed, it has been shown that the survival benefit of marriage is more significant in older people than younger people [37]. Therefore, it is particularly crucial that physicians probe about social support and provide appropriate social and psychological resources to non-married older breast cancer patients.

Our study sheds an important light on the issue of cancer disparities among older adults with cancer. Further investigation is needed, such as the analysis of chemotherapy use rates adjusted for different variables such as CCI, heart failure diagnosis, ethnicity, NCI-designated versus community centre, geographical location and marital status across different institutions. This should be further investigated.

Our study is consistent with the PlanB and SUCCESS C trials in finding no overall difference in CSS or OS for patients receiving ATAX versus TAX [17,38]. This contrasts with the ABC trials, which do show improved invasive disease-free survival with ATAX compared with TAX. However, similar to the ABC trials, our study reflected a trend to improved survival with ATAX compared with TAX when stratified by number of positive lymph nodes. In the pooled analysis of both PlanB and SUCCESS C, the median age of chemotherapy-treated patients was 55 years. Similarly, older patients are under-represented in the ABC trials, with only 29% of patients aged >60 years [16].

Our group recently reported that the use of ATAX compared with TAX is associated with inferior 3-year OS and CSS in older women with node-negative TNBC [18]. In the present study, we similarly found that among patients with 1–3 positive lymph nodes who received ATAX versus TAX, there was a trend towards worse OS and CSS. This trend became even more apparent when stratified by age, showing that in patients older than age 76 with 1–3 positive lymph nodes, CSS was inferior in those treated with ATAX versus TAX. This suggests that in this older patient population with limited nodal involvement, there appears to be no benefit to the addition of an anthracycline to a taxane-containing regimen [39].

Conversely, among patients with four or more positive lymph nodes in our study, there was a trend towards improved OS and CSS among patients who received ATAX versus TAX. When stratified by age, patients aged >76 years with four or more positive lymph nodes indeed had a statistically significant benefit in CSS with ATAX versus TAX. Other studies have recommended an adjuvant anthracycline in those with significant nodal involvement or higher risk triple-negative disease [39]. Our study, however, is the first to demonstrate a survival benefit among a subgroup of older patients.

The treatment of patients with node-positive TNBC has evolved over the last few years due largely to the results of the phase III KEYNOTE-522 trial, demonstrating an improvement in pathologic complete response (pCR) rate and event-free survival with the addition of pembrolizumab to an anthracycline, taxane and platinum-based neoadjuvant chemotherapy regimen in patients with T2+ or node-positive TNBC [40]. In KEYNOTE-522, however, >88% of patients were aged <65 years. It is important to specifically evaluate the benefit of cancer therapies in older patients, as the ageing population is heterogenous. Age alone should not be considered a barrier to the recommendation of chemotherapy, however, with the escalation of chemotherapy to include anthracyclines that have the potential for cardiac toxicity in older patients and now platinum agents that can cause more myelosuppression, there is the potential for these chemotherapy choices to impact clinical outcomes in older patients differently.

Non-anthracycline-containing platinum and taxane-based regimens, including docetaxel carboplatin, have been evaluated with similar pCR rates when compared with ATAX. For example, the NeoCART trial showed that compared with ATAX, docetaxel carboplatin resulted in a higher pCR rate in patients with T2+ or node-positive TNBC [41]. However, it is important to note that previous geriatric clinical trials, such as the ADVANCE trial, show that for TNBC, the platinum and taxane-based regimen paclitaxel carboplatin did not achieve targeted threshold for feasibility, or in other words, more than 80% of patients did not receive more than 80% of intended weeks/doses of therapy [42]. The NEOPACT trial demonstrated no better safety profile with platinum and taxane-based regimens in combination with immunotherapy than AC-like regimens. Therefore, currently, there is no data to recommend platinum compounds instead of anthracycline-containing or TC-like regimens for older patients, including to administer pembrolizumab in the early setting [43]. Further investigation with clinical trials is needed to determine the safest regimen for this population.

Our study has limitations, which should be acknowledged. The use of a retrospective data set may increase bias in our results. Our study did not consider specific chemotherapy toxicities or changes in quality of life. We evaluate age ranges, but it should be noted that no age threshold can determine the opportunity to treat or to not to treat with chemotherapy. In other words, these age ranges are not necessarily an appropriate proxy for functional status or tolerance of therapy. Finally, unobservable differences in health status may have driven some treatment decisions such that women in more compromised health were not given ATAX, which may impact differences in survival.

5. Conclusion

To our knowledge, this is the largest cohort study to evaluate the administration of ATAX versus TAX and examine clinical outcomes in older patients treated for TNBC with lymph node involvement. Older patients with TNBC are less likely to receive adjuvant chemotherapy, although there is a clear survival benefit for this group. Although we did not find a survival benefit with the use of ATAX compared with TAX overall, there was a benefit from an anthracycline and taxane-containing regimen for older patients with four or more positive lymph nodes. Clinical trials evaluating non-anthracycline-containing regimens, such as docetaxel carboplatin in combination with pembrolizumab, should be designed to include older patients.

Funding

This study was funded by the Women's Cancer Developmental Therapeutics (WCDT) Program at the University of Colorado Cancer Center. C.B. and E.M. are supported by the Cancer Center Support Grant P30CA046934.

Availability of data and materials

The data sets used to conduct this study are available on approval of a research protocol from the National Cancer Institute. Instructions for obtaining these data are available at https://healthcaredelivery.cancer.gov/seermedicare/obtain/.

Code availability

Not applicable.

Authors' contributions

S.R., S.L., A.S., C.B. and J.D. contributed to study design and concept. S.R., S.L., A.S., E.M., C.B. and J.D. contributed to analysis and interpretation of data. S.R. and J.D. wrote and edited the original draft. All authors contributed to the critical revision of the article. All authors read and approved the final article.

Ethics approval and consent to participate

This study was conducted following local institutional review board approval, and a limited data set was obtained via the National Cancer Institute's Surveillance, Epidemiology and End Results programme's policies.

Consent for publication

Not applicable.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This study used the linked SEER–Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the National Cancer Institute; Information Management Services (IMS), Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumour registries in the creation of the SEER–Medicare database.

The collection of cancer incidence data used in this study was supported by the California Department of Public Health pursuant to California Health and Safety Code Section 103885; Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries, under cooperative agreement 1NU58DP007156; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract HHSN261201800032I awarded to the University of California, San Francisco, contract HHSN2612018000 15I awarded to the University of Southern California, and contract HHSN261201800009I awarded to the Public Health Institue. The ideas and opinions expressed herein are those of the author(s) and do not necessarily reflect the opinions of the State of California, Department of Public Health, the National Cancer Institute and the Centers for Disease Control and Prevention or their Contractors and Subcontractors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2023.02.014.

References

[1] DeSantis CE, Ma J, Gaudet MM, et al. Breast cancer statistics, 2019. CA Cancer J Clin 2019;69(6):438–51. https://doi.org/10.3322/caac.21583.

[2] Dent R, Trudeau M, Pritchard KI, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res 2007;13(15 Pt 1):4429–34. https://doi.org/10.1158/1078-0432.CCR-06-3045.

[3] Boyle P. Triple-negative breast cancer: epidemiological considerations and recommendations. Ann Oncol 2012;23(Suppl. 6): vi7–12. https://doi.org/10.1093/annonc/mds187.

[4] Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-

based study from the California cancer registry. Cancer 2007; 109(9):1721–8. https://doi.org/10.1002/cncr.22618.
[5] Haffty BG, Yang Q, Reiss M, et al. Locoregional relapse and distant metastasis in conservatively managed triple negative early-stage breast cancer. J Clin Oncol 2006;24(36):5652–7. https://doi.org/10.1200/JCO.2006.06.5664.
[6] Tischkowitz M, Brunet JS, Bégin LR, et al. Use of immunohistochemical markers can refine prognosis in triple negative breast cancer. BMC Cancer 2007;7:134. https://doi.org/10.1186/1471-2407-7-134.
[7] Harris LN, Broadwater G, Lin NU, et al. Molecular subtypes of breast cancer in relation to paclitaxel response and outcomes in women with metastatic disease: results from CALGB 9342. Breast Cancer Res 2006;8(6):R66. https://doi.org/10.1186/bcr1622.
[8] Morris GJ, Naidu S, Topham AK, et al. Differences in breast carcinoma characteristics in newly diagnosed African-American and Caucasian patients: a single-institution compilation compared with the National Cancer Institute's Surveillance, Epidemiology, and End Results database. Cancer 2007;110(4): 876–84. https://doi.org/10.1002/cncr.22836.
[9] Scott LC, Mobley LR, Kuo TM, Il'yasova D. Update on triple-negative breast cancer disparities for the United States: a population-based study from the United States Cancer Statistics database, 2010 through 2014. Cancer 2019;125(19):3412–7. https://doi.org/10.1002/cncr.32207.
[10] Hutchins LF, Unger JM, Crowley JJ, Coltman CA, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med 1999;341(27):2061–7. https://doi.org/10.1056/NEJM199912303412706.
[11] Barthélémy P, Heitz D, Mathelin C, et al. Adjuvant chemotherapy in elderly patients with early breast cancer. Impact of age and comprehensive geriatric assessment on tumor board proposals. Crit Rev Oncol Hematol 2011;79(2):196–204. https://doi.org/10.1016/j.critrevonc.2010.06.005.
[12] Ring A, Battisti NML, Reed MWR, et al. Bridging the age gap: observational cohort study of effects of chemotherapy and trastuzumab on recurrence, survival and quality of life in older women with early breast cancer. Br J Cancer 2021;125(2):209–19. https://doi.org/10.1038/s41416-021-01388-9.
[13] Biganzoli L, Battisti NML, Wildiers H, et al. Updated recommendations regarding the management of older patients with breast cancer: a joint paper from the European Society of Breast Cancer Specialists (EUSOMA) and the International Society of Geriatric Oncology (SIOG). Lancet Oncol 2021;22(7):e327–40. https://doi.org/10.1016/S1470-2045(20)30741-5.
[14] Peto R, Davies C, Godwin J, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet 2012;379(9814):432–44. https://doi.org/10.1016/S0140-6736(11)61625-5.
[15] Jones SE, Savin MA, Holmes FA, et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. J Clin Oncol 2006;24(34):5381–7. https://doi.org/10.1200/JCO.2006.06.5391.
[16] Blum JL, Flynn PJ, Yothers G, et al. Anthracyclines in early breast cancer: the ABC trials-USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG oncology). J Clin Oncol 2017; 35(23):2647–55. https://doi.org/10.1200/JCO.2016.71.4147.
[17] de Gregorio A, Janni W, Friedl TWP, et al. The impact of anthracyclines in intermediate and high-risk HER2-negative early breast cancer-a pooled analysis of the randomised clinical trials PlanB and SUCCESS C. Br J Cancer 2022;126(12):1715–24. https://doi.org/10.1038/s41416-021-01690-6.
[18] Schreiber AR, Kagihara J, Eguchi M, et al. Evaluating anthracycline + taxane versus taxane-based chemotherapy in older women with node-negative triple-negative breast cancer: a SEER-Medicare study. Breast Cancer Res Treat 2022;191(2):389–99. https://doi.org/10.1007/s10549-021-06424-z.
[19] Crivellari D, Gray KP, Dellapasqua S, et al. Adjuvant pegylated liposomal doxorubicin for older women with endocrine nonresponsive breast cancer who are NOT suitable for a 'standard chemotherapy regimen': the CASA randomized trial. Breast 2013; 22(2):130–7. https://doi.org/10.1016/j.breast.2013.01.015.
[20] Leonard R, Ballinger R, Cameron D, et al. Adjuvant chemotherapy in older women (ACTION) study – what did we learn from the pilot phase? Br J Cancer 2011;105(9):1260–6. https://doi.org/10.1038/bjc.2011.377.
[21] Klepin HD, Pitcher BN, Ballman KV, et al. Comorbidity, chemotherapy toxicity, and outcomes among older women receiving adjuvant chemotherapy for breast cancer on a clinical trial: CALGB 49907 and CALGB 361004 (alliance). J Oncol Pract 2014;10(5):e285–92. https://doi.org/10.1200/JOP.2014.001388.
[22] Crozier JA, Pezzi TA, Hodge C, et al. Addition of chemotherapy to local therapy in women aged 70 years or older with triple-negative breast cancer: a propensity-matched analysis. Lancet Oncol 2020;21(12):1611–9. https://doi.org/10.1016/S1470-2045(20)30538-6.
[23] Battisti NML, Reed MWR, Herbert E, et al. Bridging the age gap in breast cancer: impact of chemotherapy on quality of life in older women with early breast cancer. Eur J Cancer 2021;144: 269–80. https://doi.org/10.1016/j.ejca.2020.11.022.
[24] Luque M, Arranz F, Cueva JF, et al. Breast cancer management in the elderly. Clin Transl Oncol 2014;16(4):351–61. https://doi.org/10.1007/s12094-013-1113-2.
[25] Leone JP, Graham N, Tolaney SM, et al. Estimating long-term mortality in women with hormone receptor-positive breast cancer: the 'ESTIMATE' tool. Eur J Cancer 2022;173:20–9. https://doi.org/10.1016/j.ejca.2022.06.029.
[26] Monteiro AR, Garcia AR, Póvoa S, et al. Acute toxicity and tolerability of anthracycline-based chemotherapy regimens in older versus younger patients with breast cancer: real-world data. Support Care Cancer 2021;29(5):2347–53. https://doi.org/10.1007/s00520-020-05766-6.
[27] Singal PK, Iliskovic N. Doxorubicin-induced cardiomyopathy. N Engl J Med 1998;339(13):900–5. https://doi.org/10.1056/NEJM199809243391307.
[28] Bash LD, Weitzman D, Blaustein RO, Sharon O, Shalev V, Chodick G. Comprehensive healthcare resource use among newly diagnosed congestive heart failure. Isr J Health Policy Res 2017;6: 26. https://doi.org/10.1186/s13584-017-0149-0.
[29] McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012;14(8):803–69. https://doi.org/10.1093/eurjhf/hfs105.
[30] Battisti NML, Welch CA, Sweeting M, et al. Prevalence of cardiovascular disease in patients with potentially curable malignancies: a national registry dataset analysis. JACC CardioOncol 2022;4(2):238–53. https://doi.org/10.1016/j.jaccao.2022.03.004.
[31] Fradley MG, Brown AC, Shields B, et al. Developing a comprehensive cardio-oncology program at a cancer institute: the Moffitt cancer center experience. Oncol Rev 2017;11(2):340. https://doi.org/10.4081/oncol.2017.340.
[32] Sadler D, Arnold A, Herrmann J, et al. Reaching across the Aisle: cardio-oncology advocacy and program building. Curr Oncol Rep 2021;23(6):64. https://doi.org/10.1007/s11912-021-01059-1.
[33] Armenian SH, Lacchetti C, Barac A, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice guideline. J Clin Oncol 2017;35(8):893–911. https://doi.org/10.1200/JCO.2016.70.5400.

[34] Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship care guideline. J Clin Oncol 2016;34(6):611–35. https://doi.org/10.1200/JCO.2015.64.3809.

[35] Aizer AA, Chen MH, McCarthy EP, et al. Marital status and survival in patients with cancer. J Clin Oncol 2013;31(31): 3869–76. https://doi.org/10.1200/JCO.2013.49.6489.

[36] Osborne C, Ostir GV, Du X, Peek MK, Goodwin JS. The influence of marital status on the stage at diagnosis, treatment, and survival of older women with breast cancer. Breast Cancer Res Treat 2005; 93(1):41–7. https://doi.org/10.1007/s10549-005-3702-4.

[37] Ding W, Ruan G, Lin Y, Zhu J, Tu C, Li Z. Dynamic changes in marital status and survival in women with breast cancer: a population-based study. Sci Rep 2021;11(1):5421. https://doi.org/10.1038/s41598-021-84996-y.

[38] Nitz U, Gluz O, Clemens M, et al. West German study PlanB trial: adjuvant four cycles of epirubicin and cyclophosphamide plus docetaxel versus six cycles of docetaxel and cyclophosphamide in HER2-negative early breast cancer. J Clin Oncol 2019;37(10):799–808. https://doi.org/10.1200/JCO.18.00028.

[39] Shah AN, Gradishar WJ. Adjuvant anthracyclines in breast cancer: what is their role? Oncologist 2018;23(10):1153–61. https://doi.org/10.1634/theoncologist.2017-0672.

[40] Schmid P, Cortes J, Dent R. Pembrolizumab in early triple-negative breast cancer. N Engl J Med 2022;386(18):1771–2. https://doi.org/10.1056/NEJMc2203316.

[41] Zhang L, Wu ZY, Li J, et al. Neoadjuvant docetaxel plus carboplatin vs epirubicin plus cyclophosphamide followed by docetaxel in triple-negative, early-stage breast cancer (NeoCART): results from a multicenter, randomized controlled, open-label phase II trial. Int J Cancer 2022;150(4):654–62. https://doi.org/10.1002/ijc.33830.

[42] Freedman RA, Li T, Sedrak MS, et al. 'ADVANCE' (a pilot trial) ADjuVANt chemotherapy in the elderly: developing and evaluating lower-toxicity chemotherapy options for older patients with breast cancer. J Geriatr Oncol 2022. https://doi.org/10.1016/j.jgo.2022.09.006.

[43] Sharma P, Stecklein SR, Yoder R, et al. Clinical and biomarker results of neoadjuvant phase II study of pembrolizumab and carboplatin plus docetaxel in triple-negative breast cancer (TNBC) (NeoPACT). J Clin Oncol 2022;40(Suppl. 16): 513–513. https://doi.org/10.1200/JCO.2022.40.16_suppl.513.