https://doi.org/10.1245/s10434-026-19198-9 Annals of Surgical Oncology

Impact of Age on Use of Neoadjuvant Chemoimmunotherapy and Outcomes for Patients with Triple-Negative Breast Cancer

Zachary Schrank, BA[1] · Kelsey Landrum, PhD[2] · Chris B. Agala, PhD[2] · Kristalyn K. Gallagher, DO[1,2] · David W. Ollila, MD[1,2] · Philip M. Spanheimer, MD[1,2] · Julia M. Selfridge, MD[1,2]

Received: 8 December 2025 / Accepted: 20 January 2026

Abstract

Background Following KEYNOTE-522, there is limited population-level data regarding the use and outcomes of neoadjuvant chemoimmunotherapy (NACI) for triple-negative breast cancer (TNBC) management across patient ages. We examined trends in the use of NACI and neoadjuvant chemotherapy (NAC) without immunotherapy in TNBC patients stratified by age groups and impact on pathological complete response (pCR) and overall survival (OS).

Methods Adult women with nonmetastatic TNBC who underwent NAC/NACI between 2012 and 2022 were selected from the National Cancer Database. These patients were compared overall and stratified by age group (< 50 years, 50–70 years, and >70 years) based on receipt of NACI or NAC.

Results A total of 56,606 patients were included. Use of NACI significantly increased from 2012 to 2022 with a concomitant decrease in NAC ($p < 0.0001$), although women >70 years received significantly less NACI in 2022 than other age groups ($p < 0.0001$). Women had greater pCR rates in the breast and axillary lymph nodes with NACI compared with NAC overall (relative risk 1.405, $p < 0.0001$), with women >70 years receiving the greatest benefit (relative risk 1.56, $p < 0.0001$). All women had greater OS with NACI over NAC (hazard ratio 0.704, $p < 0.0001$), especially women 50–70 years.

Conclusions Use of NACI for TNBC patients has increased over the past decade. NACI was associated with higher pCR rates and greater OS over NAC in all women, especially > 70 years. These data suggest that older TNBC patients may achieve significant clinical benefit from this regimen.

Keywords Triple-negative breast cancer · Neoadjuvant · Immune checkpoint · Age

Although breast cancer remains the second most common malignancy for women, it is a heterogenous disease.[1–4] Triple-negative breast cancer (TNBC), a subtype without estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) overexpression, is associated with early onset, increased metastatic potential, and the worst prognosis of all breast cancers.[5,6] Given the historic lack of targeted therapies for these patients, chemotherapy administered in the neoadjuvant and adjuvant setting has been the mainstay of systemic therapy for TNBC.[7–12] Within the past two decades, immunotherapy has become an attractive treatment approach for the management of aggressive cancers bearing a high degree of immune cell infiltration. Strategies aimed at blocking the immune checkpoints PD-1, PD-L1, and CTLA-4 rejuvenate populations of exhausted tumor-infiltrating T cells and allow enhanced anticancer immune responses.[6,13–16] This immune checkpoint inhibitor (ICI) therapy has revolutionized the treatment of several "immune hot" malignancies, including melanoma, non-small cell lung cancer, and renal cell carcinoma.[17–20] Compared with other breast cancer subtypes, TNBC also has the highest degree of immune cell infiltration, which has spurred interest in leveraging immunotherapy, including ICIs, for TNBC treatment.[21–23]

Prior to 2021, neoadjuvant chemotherapy was the preferred treatment strategy for early-stage, high-risk TNBC.[12,24,25] The phase III KEYNOTE-522 trial enrolled women with previously untreated anatomic stage II or stage III TNBC to assess the efficacy of combined neoadjuvant pembrolizumab and chemotherapy for

✉ Julia M. Selfridge, MD
Julia_Selfridge@med.unc.edu

[1] Division of Surgical Oncology, Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC

[2] Department of Surgery, University of North Carolina, Chapel Hill, NC

Published online: 14 March 2026

early-stage TNBC, followed by adjuvant treatment with pembrolizumab alone, compared to the standard neoadjuvant chemotherapy (NAC) alone. The group receiving combined pembrolizumab and chemotherapy had an absolute improved pathological complete response (pCR) rate improvement of 7.5% compared with the group receiving only chemotherapy.[26] In addition, the chemoimmunotherapy group had increased event-free survival (EFS) over the chemotherapy only group at the median follow-up of 15.5 months.[27] These findings led to the FDA approval of neoadjuvant combination chemoimmunotherapy for high-risk early-stage TNBC patients in 2021.[28] Prior to approval, neoadjuvant chemoimmunotherapy (NACI) had also been used in a trial setting for TNBC, with the KN522 trial being most recent in the last 5 years.[29]

Some studies, often in other tumor types, suggest that older patients may have greater ICI benefit than younger patients,[30–33] despite the gradual decline of immune function that occurs naturally with age.[34] Despite this efficacy, older adults are less likely to receive immunotherapy for some solid malignancies.[30] Furthermore, data regarding efficacy of breast cancer therapies in older women are scarce, as older women are often underrepresented in clinical trials.[35,36] For example, only 11% of KEYNOTE-522 patients were 65 years or older. The number of adults older than 65 is expected to surpass those 18 and younger by 2035.[37] With 60% of new cancer diagnoses occurring in people older than 65 years and 70% of cancer-related deaths occurring in this population, it is imperative to investigate differential responses to immunotherapy as well as trends in adoption of these therapies across age groups to identify potential barriers to treatment.[33] Using the National Cancer Database (NCDB), we sought to examine trends in NACI utilization as well as adoption following FDA approval of NACI for the management of TNBC from 2012 to 2022.[38] We also sought to investigate differences in adoption of NACI, as well as rates of pCR and overall survival (OS), in women younger than 50 years, women 50 to 70 years old, and women older than 70 years.

Methods

Data Source

Data were obtained from the American College of Surgeons and American Cancer Society 2022 National Cancer Database (NCDB). This database is noted to include at least 70% of incident cancers in the United States.[38]

Study Design and Population

We utilized the NCDB participant user files for 2012 to 2022 for adult (≥18 years) female patients with clinical T0-4, N0-3, M0 TNBC. Patients with inflammatory breast cancer (T4d) were included. Patients with metastatic disease were excluded. Patients with T1 N0 disease were also excluded as these patients are typically not candidates for NACI in clinical practice. Characteristics of the overall study population are included in Table 1. A complete table of T and N staging included in the study population is available in Table 2. Triple-negative breast cancer status was determined by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression. In order to capture practice patterns during the study period, patients were evaluated based on treatment with neoadjuvant chemotherapy or neoadjuvant chemotherapy with neoadjuvant immunotherapy. Patients were stratified into three age groups based on age at diagnosis (<50 years, 50-70 years, >70 years).

Covariates

Clinical and demographic covariates were collected, including neoadjuvant therapy type in the NCDB file specific to neoadjuvant chemotherapy and neoadjuvant immunotherapy starting in 2012. Surgery type was included based on the annotations in the NCDB file specific to sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND) starting in 2012. Additional demographic information included age, rural status, race, comorbidity score using the Charlson Comorbidity Index (CCI), facility type, and insurance status. Tumor characteristics were also collected, including grade and stage information. Posttreatment T-stage was determined by using the TNM_POST_PATH_T variable when available (after 2018) and using the TNM_PATH_T variable only for patients who received NAC before 2018. Nodal PCR was evaluated for patients who received NAC and were found to have ypN0 disease. This was determined by using the TNM_POST_PATH_N variable when available (after 2018) and by using the TNM_PATH_N variable for only patients who received NAC before 2018.

Statistical Analysis

Frequencies were used to describe demographic and clinical characteristics of the cohort overall and stratified by exposure status (NACI vs. NAC). Chi-square tests of

Table 1 Characteristics of adult female breast cancer patients with triple-negative breast cancer who received neoadjuvant chemotherapy or neoadjuvant chemoimmunotherapy between 2012-2022 in the National Cancer Database (*n*=56606)

Characteristic	Categories	Overall (n=56606) Frequency (%)	Neoadjuvant Chemotherapy (NAC) (n= 44400, 78.4%) Frequency (%)	Neoadjuvant Chemoimmunotherapy (NAC) (n= 12206, 21.6%) Frequency (%)	*P*-value
Age (continuous)	Mean	53.7	53.7	53.4	0.011
Age (categorical)	< 50	23346 (41.2)	18221 (41)	5125 (42)	0.0097
	50-70	27349 (48.3)	21595 (48.6)	5754 (47.1)	
	> 70	5911 (10.4)	4584 (10.3)	1327 (10.9)	
Race	White	39297 (70)	30755 (69.8)	8542 (70.7)	<.0001
	Black	13331 (23.8)	10755 (24.4)	2576 (21.3)	
	Native American, Alaskan Native, Pacific Islander	375 (0.7)	276 (0.6)	99(0.8)	
	Asian	2273 (4)	1626 (3.7)	647 (54)	
	Other	848 (1.5)	624 (1.4)	224 (1.9)	
	Missing	482	364	118	
Ethnicity	Not Hispanic/Latino	50471 (90.8)	39705 (91.1)	10766 (89.7)	<.0001
	Hispanic/Latino	5110 (9.2)	3873 (8.9)	1237 (10.3)	
	Missing	1025	822	203	
Location	Metropolitan	46701 (85.6)	36640 (85.5)	10061 (85.6)	0.3644
	Urban	6809 (12.5)	5369 (12.5)	1440 (12.3)	
	Rural	1077 (2)	829 (1.9)	248 (2.1)	
	Missing	2019	1562	457	
Insurance	Uninsured	1581 (2.8)	1333 (3)	248 (2)	<.0001
	Private	33905 (60.5)	26460 (60.2)	7445 (61.4)	
	Government	20591 (36.7)	16159 (36.8)	4432 (36.6)	
	Missing	529	448	81	
Region	Midwest	12313 (21.8)	9702 (21.9)	2611 (21.4)	<.0001
	Northeast	16944 (29.9)	13106 (29.5)	3838 (31.4)	
	South	19935 (35.2)	15878 (35.8)	4057 (33.2)	
	West	7414 (13.1)	5714 (12.9)	1700 (13.9)	
Facility type	Community Cancer Program	2773 (5.8)	2176 (5.8)	597 (5.9)	0.0021
	Comprehensive Community Cancer Program	17518 (36.7)	13979 (37.1)	3539 (35.1)	
	Academic/ Research Program	16841 (35.3)	13177 (35)	3664 (36.3)	
	Integreated Network Cancer Program	10611 (22.2)	8318 (22.1)	2293 (22.7)	
	Missing	8863	6750	2113	
Median household income	< $46,277	8517 (17.9)	6950 (18.5)	1567 (15.5)	<.0001
	$46,277-$57,856	10039 (21.1)	8003 (21.3)	2036 (20.2)	
	$57,857-$74,062	11282 (23.7)	8883 (23.6)	2399 (23.8)	
	> $74,063	17811 (37.4)	13735 (36.6)	4076 (40.4)	
	Missing	8957	6829	2128	
Charlson Comorbidity Index	0	47628 (84.1)	37358 (84.1)	10270 (84.1)	0.8064
	1	6670 (11.8)	5247 (11.8)	1423 (11.7)	
	2	1467 (2.6)	1137 (2.6)	330 (2.7)	
	3	841 (1.5)	658 (1.5)	183 (1.5)	

Table 1 (continued)

Characteristic	Categories	Overall (n=56606) Frequency (%)	Neoadjuvant Chemotherapy (NAC) (n= 44400, 78.4%) Frequency (%)	Neoadjuvant Chemoimmunotherapy (NAC) (n= 12206, 21.6%) Frequency (%)	*P*-value
Histology	Ductal	52089 (92)	40660 (91.6)	11429 (93.6)	<.0001
	Lobular	559 (1)	423 (1)	136 (1.1)	
	Other	3958 (7)	3317 (7.5)	641 (5.3)	
Grade	1	243 (0.7)	178 (0.8)	65 (0.6)	0.0598
	2	5112 (14.7)	3444 (14.9)	1668 (14.5)	
	3	29314 (84.6)	19536 (84.4)	9778 (84.9)	
	Missing	21937	21242	695	
Clinical T Stage	0	142 (0.3)	127 (0.3)	15 (0.1)	<.0001
	1	4921 (8.7)	3872 (8.7)	1049 (8.6)	
	2	37570 (66.4)	29130 (66)	8260 (67.7)	
	3	9280 (16.4)	7278 (16.4)	2002 (16.4)	
	4	4693 (8.3)	3813 (8.6)	880 (7.2)	
Clinical N Stage	0	27323 (48.3)	21312 (48)	6011 (49.2)	<.0001
	1	22677 (40.1)	17852 (40.2)	4825 (39.5)	
	2	3382 (6)	2766 (6.2)	616 (5)	
	3	3224 (5.7)	2470 (5.6)	754 (6.2)	
Radiation Therapy Timing	No radiation	16247 (29.7)	12540 (29.1)	3797 (31.8)	<.0001
	Adjuvant radiation	37928 (69.3)	29922 (69.9)	8006 (67.1)	
	Unknown or alternative radiation sequence	554 (1)	426 (1)	128 (1.1)	
	Missing	1877	1602	275	
Breast Surgery Type	Mastectomy	32323 (57.1)	25551 (57.5)	6772 (55.5)	<.0001
	Breast conservation therapy	24283 (42.3)	18849 (45.3)	5434 (31.5)	
Axillary Surgery Type	SLNB only	32028 (56.6)	23742 (53.5)	8286 (67.9)	<.0001
	ALND only	14255 (25.2)	12335 (27.8)	1920 (15.7)	
	ALND & SLNB	9697 (17.1)	7777 (17.5)	1920 (15.7)	
	No surgery or biopsy/aspiration of regional lymph nodes	626 (1.1)	546 (1.2)	80 (0.7)	

*Chi Square Test of Independence, alpha = 0.05

**Wilcoxon Rank Sum Test, alpha = 0.05

independence (for categorical variables) and the Wilcoxon rank-sum test (for continuous variables) were used to assess differences in exposure status across baseline characteristics.

Trends in neoadjuvant immunotherapy were assessed by using the Cochran-Mantel-Haenszel test. Hazard ratios (HR) for the potential predictors of survival were estimated by using Cox proportional hazard regression models.

To compare risk of breast, nodal, and overall PCR by exposure status, log-risk regression was used to generate risk ratios (RRs) and their corresponding 95% confidence intervals. In our primary outcomes analysis (for PCR), we adjusted for age, breast surgery type, axillary surgery type, CCI, income, and hospital/facility type. We further estimated and compared risk of breast, nodal, and overall pCR within age groups (<50 years, 50-70 years, >70 years).

We used Kaplan-Meier methods to estimate and show graphically median survival time after diagnosis and estimate and compare hazard of death postdiagnosis by exposure status after adjusting for age, TNM clinical stage, breast surgery type, axillary surgery type, CCI, income, and facility type. Alpha of 0.05 was used for all measures. All analyses were conducted by using SAS version 9.4 (SAS Institute Inc., Cary, NC) and RStudio (R Core Team 2024). The University of North Carolina institutional

Table 2 T and N Staging of Study Population

Stage	Overall	Neoadjuvant Chemotherapy (NAC)	Neoadjuvant Chemoimmunotherapy (NACI)
	Frequency (%)	Frequency (%)	Frequency (%)
T0N1	84 (0.2)	80 (0.2)	4 (0)
T0N2	30 (0.1)	23 (0.1)	7 (0.1)
T0N3	28 (0.1)	24 (0.1)	4 (0)
T1N1	4109 (7.3)	3203 (7.2)	906 (7.4)
T1N2	450 (0.8)	382 (0.9)	68 (0.6)
T1N3	362 (0.6)	287 (0.7)	75 (0.6)
T2N0	22906 (40.5)	17823 (40.1)	5083 (41.6)
T2N1	12086 (21.4)	9458 (21.3)	2628 (21.5)
T2N2	1375 (2.4)	1124 (2.5)	251 (2.1)
T2N3	1203 (2.1)	905 (2)	298 (2.4)
T3N0	3493 (6.2)	2743 (6.2)	750 (6.1)
T3N1	4211 (7.4)	3322 (7.5)	889 (7.3)
T3N2	751 (1.3)	600 (1.4)	151 (1.2)
T3N3	825 (1.5)	613 (1.4)	212 (1.7)
T4N0	924 (1.6)	746 (1.7)	178 (1.5)
T4N1	2187 (3.9)	1789 (4)	398 (3 3)
T4N2	776 (1.4)	637 (1.4)	139 (1.1)
T4N3	806 (1.4)	641 (1.4)	165 (1.4)

review board determined this study to be exempt (IRB# 20-1493).

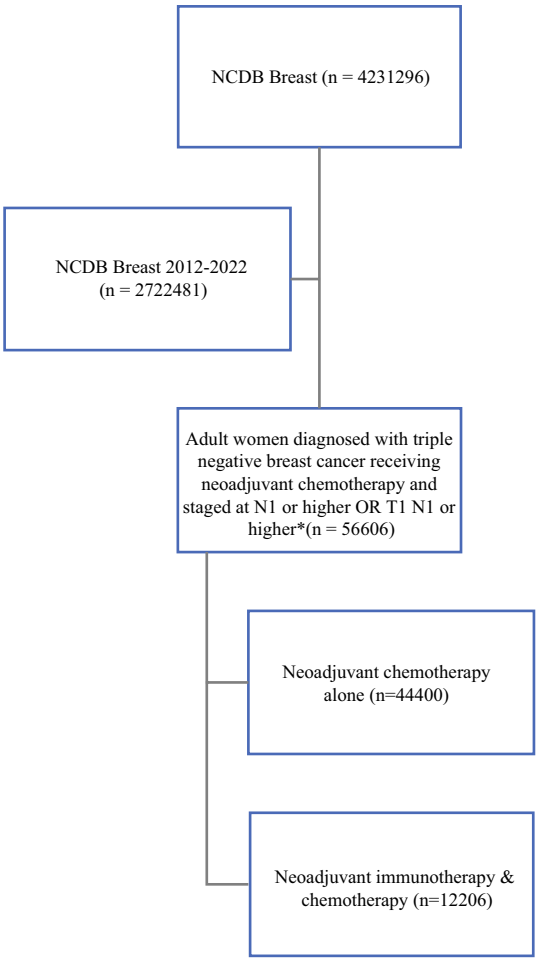

Fig. 1 Consort diagram

Results

Patient Characteristics

We identified 56,606 women diagnosed with non-metastatic triple-negative breast cancer between 2012 and 2022 who received NAC or NACI (Fig. 1). Demographic and clinical characteristics for the overall cohort provided in Table 1 were stratified by treatment group. The median age at diagnosis was 53.7 years and was similar between treatment groups. Patients were further separated into categorical age groups: <50 years (n = 23,346), 50-70 years (n = 27,349), and >70 years (n = 5,911).

Clinical T and N staging for the study population is included in Table 2. Patients most frequently presented with clinical T2 N0 disease (40.1% of NAC patients, 41.6% of NACI patients) or T2 N1 disease (21.3% of NAC patients, 21.5% of NACI patients). Clinical T4 tumors were most common in the NAC group (8.6% vs. 7.2% of NACI patients). Grade 3 disease was also noted most frequently and was similarly represented in both treatment groups (84.4% of NAC, 84.9% of NACI).

The majority of women in this study were considered healthy with a Charlson-Deyo comorbidity index (CCI) score of 0 (84.1%), which was similar between treatment groups. However, CCI scores were highest in the >70 years group. 90.0% of patients <50 years had a CCI of 0, compared to 81.4% of patients 50 to 70 and 73.5% of patients >70 ($p < 0.0001$). Overall, 70% of women were White, 23.8% were Black, and 6.2% were other races. Most women lived in metropolitan areas (85.6%), whereas 12.5% lived in urban areas and 2% lived in rural areas. Of patients included, 36.7% were treated at comprehensive community cancer programs, 35.3% were treated at academic/research institutions, 22.2% received treatment at an integrated network cancer program, and 5.8% were treated at a community cancer program. Most women (60.5%) were covered by private insurance or managed care, 36.7% were covered by Medicare and/or Medicaid, and 2.8% of women were uninsured.

Treatment Characteristics

Neoadjuvant chemotherapy alone was more common than NACI during the study period. Overall, 44,400 women (78.4%) received NAC, while 12,206 women (21.6%) received NACI. The proportion of patients in each age group was also similar between NAC and NACI treatment groups. Given the large cohort size, the difference in age was statistically significant ($p = 0.0097$). For women receiving NAC, 41% of women were <50 years, 48.6% were between 50 and 70 years, and 10.3% were >70 years. For women receiving NACI, 42% were <50 years, 47.1% were 50-70 years, and 10.9% were > 70 years.

Mastectomy was the most frequent surgical management of the breast during the study period; 57.5% of NAC patients and 55.5% of NACI patients underwent mastectomy ($p < 0.0001$). Sentinel lymph node biopsy (SLNB) was the most frequent axillary management strategy for patients during the study period and was more common in the NACI group, with 53.5% of NAC patients and 67.9% of NACI patients receiving SLNB only ($p < 0.0001$), and 17.5% of the NAC group received SLNB followed by completion ALND compared with 15.7% in the NACI group. Axillary lymph node dissection (ALND) alone was performed in 27.8% of the NAC group and 15.7% of the NACI group (Fig. 2a). This pattern was also observed in the age-stratified groups, with SLNB being the most common axillary procedure across age ranges. Interestingly, SLNB was most common in women <50 years in both treatment groups and least common in women >70 years (Fig. 2b). Similar use of adjuvant radiation was observed between treatment groups; 69.9% of NAC patients and 67.1% of NACI patients were treated with radiation in an adjuvant setting ($p < 0.0001$).

Trends in Neoadjuvant Chemoimmunotherapy

In 2012, 99.61% of patients overall received NAC alone, whereas only 0.39% received NACI (Fig. 3a). Stratifying by age group, 0.5% of women younger than 50 years and 0.33% of women 50–70 years received NACI in 2012, while no women older than 70 received NACI in 2012 (Figs. 3b-d). NACI increased over time from 2012 to 2022 ($p < 0.0001$) with a concomitant decrease in NAC alone. This trend was also observed in all three age groups ($p < 0.001$). There was a substantial increase in NACI treatment beginning in 2021, where 45.04% of women received NACI compared with NAC (54.96%). In 2022, NACI was more frequently utilized than NAC overall (81.78% vs. 18.22%). However, in 2022, 86.24% of women younger than 50 years and 82.43% of women aged 50–70 years were treated with NACI, whereas only 68.37% of women older than 70 years received NACI ($p < 0.0001$).

PCR Rate

Overall, 38.9% of women receiving NAC achieved pathological complete response (pCR) in the breast ($n = 17,524$), whereas a greater proportion of women receiving NACI achieved breast pCR (56.19%, n = 6,859; Table 3a). The overall risk ratio for breast pCR in women receiving NACI versus NAC was 1.39 (95% confidence interval [CI] 1.36-1.41, $p < 0.0001$). Stratifying by age group, women older than 70 were most likely to achieve breast pCR on NACI over NAC (RR 1.49, 95% CI 1.38–1.60, $p < 0.0001$), followed by women 50–70 years (RR 1.40, 95% CI 1.36–1.44, $p < 0.0001$), and women younger than 50 years (RR 1.36, 95% CI 1.33–1.40, $p < 0.0001$).

In the axillary lymph nodes, there was a marginal increase in rate of pCR for women receiving NACI over

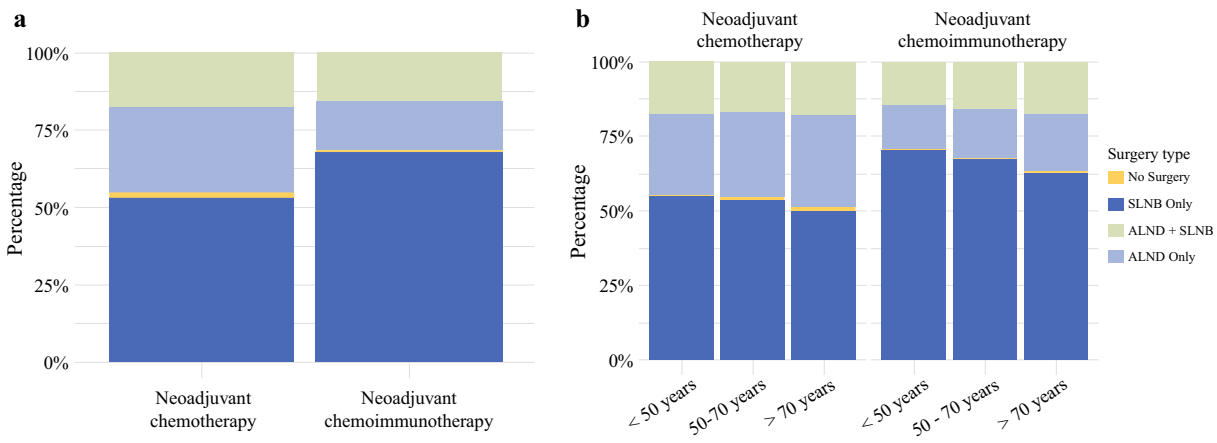

Fig. 2 Axillary surgery type by treatment overall (**a**) and by age group (**b**)

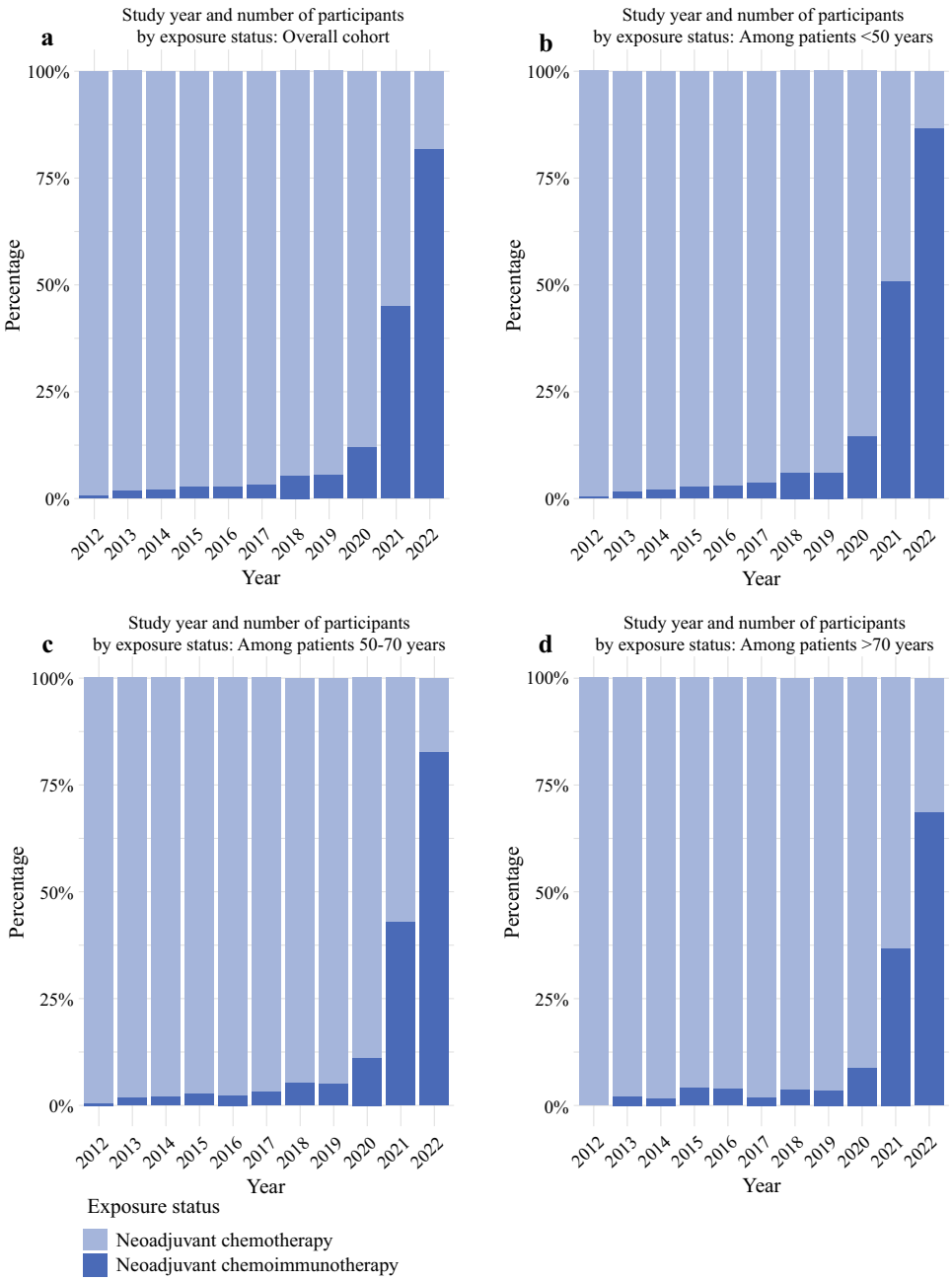

Fig. 3 Trends in the use of neoadjuvant chemotherapy and neoadjuvant chemoimmunotherapy for TNBC patients from 2012 to 2022 overall and by age group. **a** Overall cohort. **b** <50 years age group. **c** 50–70 years age group. **d** >70 years age group

those receiving NAC (RR 1.02, 95% CI 1.01–1.02, $p < 0.0001$; Table 3b). Similar modest effects were also seen when stratifying by age group. The risk ratio for nodal pCR in women younger than 50 receiving NACI vs. NAC was 1.02 (95% CI 1.00-1.03, $p = 0.0089$). For women 50–70 years, the risk ratio was 1.02 (95% CI 1.01–1.03, $p = 0.0002$). For women older than 70 years, the risk ratio for nodal pCR following NACI vs. NAC was 1.01 and not statistically significant (95% CI 0.99–1.04, $p = 0.161$). Women older than 70 years were also more likely to have residual nodal disease following neoadjuvant therapy; 64.7% of women older than 70 years were ypN0, whereas 70.8% of women 50–70 years and 74.4% of women < 50 years were ypN0.

Looking at overall tumor clearance in both the breast and lymph nodes, NACI was associated with higher rates of pCR in both sites than NAC overall (RR 1.41, 95% CI 1.38–1.43, $p < 0.0001$; Table 3c). Women > 70 years had the greatest benefit from NACI over NAC (RR 1.56, 95% CI 1.44–1.69, $p < 0.0001$), followed by women 50–70 years (RR 1.46, 95% CI 1.41–1.50, $p < 0.001$) and women <50 years (RR 1.38, 95% CI 1.35–1.42, $p < 0.0001$).

Table 3 Risk ratios for pathologic complete response in the breast and axillary lymph nodes after NACI versus NAC in TNBC patients

a. Risk ratios for pathologic complete response in the breast.

Comparison	Risk Ratio	95% CI	*p*-value
Overall			
NACI vs. NAC	1.39	1.36–1.41	<.0001
*Adjusted for: age, breast surgery type, axillary surgery type, CCI, TNM clinical stage (early vs. late)			
Age Groups			
<50 years			
NACI vs. NAC	1.36	1.33–1.4	<.0001
50–70 years			
NACI vs. NAC	1.4	1.36–1.44	<.0001
> 70 years			
NACI vs. NAC	1.49	1.38 – 1.6	<.0001
*Adjusted for: breast surgery type, axillary surgery type, CCI, TNM clinical stage (early vs. late)			

b. Risk ratios for pathologic complete response in the axillary lymph nodes.

Comparison	Risk Ratio	95% CI	*p*-value
Overall			
NACI vs. NAC	1.02	1.01–1.02	<.0001
*Adjusted for: age, breast surgery type, axillary surgery type, CCI, TNM clinical stage (early vs. late)			
Age Groups			
<50 years			
NACI vs. NAC	1.01	1.00– 1.03	0.0089
50–70 years			
NACI vs. NAC	1.02	1.01 – 1.03	0.0002
> 70 years			
NACI vs. NAC	1.01	0.99–1.04	0.1611
*Adjusted for: breast surgery type, axillary surgery type, CCI, TNM clinical stage (early vs. late)			

c. Risk ratios for overall pathologic complete response in the breast and lymph nodes.

Comparison	Risk Ratio	95% CI	*p*-value
Overall			
NACI vs. NAC	1.41	1.38– 1.43	<.0001
*Adjusted for: age, breast surgery type, axillary surgery type, CCI, TNM clinical stage (early vs. late)			
Age Groups			
<50 years			
NACI vs. NAC	1.38	1.35–1.42	<.0001
50–70 years			
NACI vs. NAC	1.46	1.41–1.50	<.0001
> 70 years			
NACI vs. NAC	1.56	1.44– 1.69	<.0001
*Adjusted for: breast surgery type, axillary surgery type, CCI, TNM clinical stage (early vs. late)			

Overall Survival

Multivariate analysis assessing factors associated with hazards for mortality showed that receiving NACI was associated with improved survival over patients receiving NAC (HR 0.704, 95% CI 0.645–0.768, $p < 0.0001$; Fig. 4). This model was adjusted for age, TNM clinical stage, breast surgery type, axillary surgery type, and Charlson-Deyo comorbidity score. Women aged 50–70 years had the strongest survival association from NACI (HR 0.653, 95% CI 0.573–0.745, $p < 0.0001$), followed by women younger than 50 years (HR 0.73, 95% CI 0.683–0.836, $p < 0.0001$) and women older than 70 years (HR 0.777, 95% CI 0.616 – 0.979, $p = 0.0323$).

Discussion

In this study, we found that immunotherapy use for TNBC has risen significantly from 2012 to 2022. The notable increase in the use of NACI in 2021 likely coincides with publication of the KEYNOTE-522 study and FDA approval of this regimen for high-risk early-stage TNBC, which became the predominant neoadjuvant therapy choice in 2022.[27] This trend was present across the age groups examined, though women older than 70 years were less likely to receive immunotherapy than younger women each year between 2017 and 2022. While there has been significant interest in the field to de-escalate surgical intervention especially for older patients, there may be hesitancy to provide additional therapy to older women over concern for their ability to tolerate it, as well as the under-representation of this group within clinical trials.[35,36] Immune function declines with age, partially owing to age-associated immune senescence, prompting concern that older patients may not respond as robustly to immune checkpoint therapy.[39–42] In addition, immune dysregulation related to aging may confer increased vulnerability to immune related adverse effects (irAEs) associated with immune checkpoint therapy.[43–45] This may partially explain the slightly reduced adoption of this regimen for older TNBC patients.

As was demonstrated in KEYNOTE-522 trial, we observed an improved breast, nodal, and overall pCR rate in women receiving NACI compared to NAC. Interestingly, we found that women older than 70 years who received NACI had the greatest benefit in achieving breast and total pCR over chemotherapy alone compared to women 50-70 years and younger than 50 years. Women <50 years and 50-70 years had a marginal but statistically significant benefit in achieving pCR in the axillary lymph nodes with NACI, but the benefit in women >70 years was not statistically significant. This discordance in response to neoadjuvant immunotherapy between the primary tumor and regional lymph

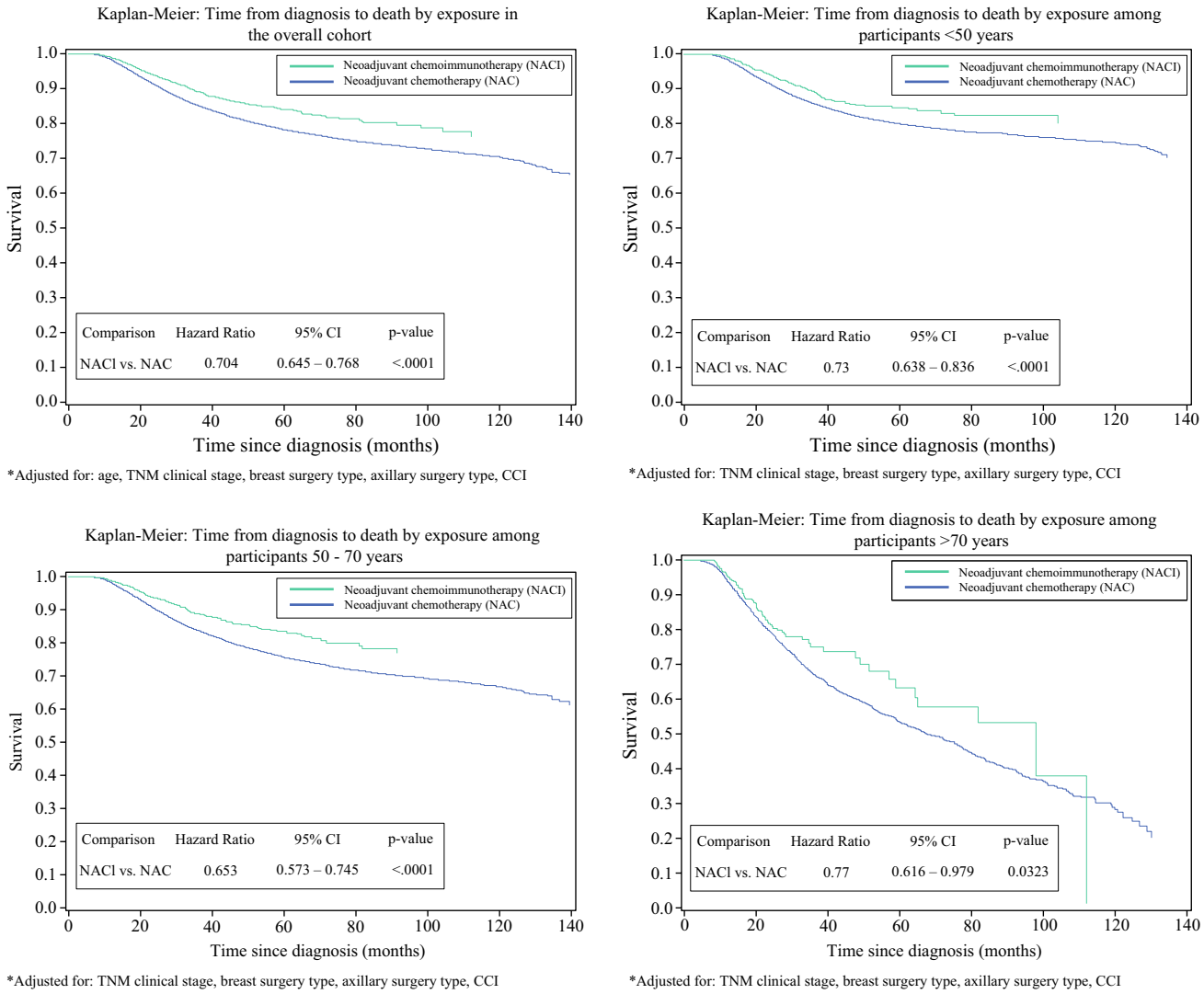

Fig. 4 Overall survival of TNBC patients receiving NACI versus NAC

nodes has been seen in other cancers, as well, and may be associated with differential compositions of the T-cell compartment between the lymph node and primary tumor.[46,47] The increased benefit in the >70 years group compared with the other age groups did not extend to overall survival, although all age groups had improved overall survival on NACI compared to NAC. This may partially be explained by increased rates of all-cause mortality in the oldest age group which may not be linked to their cancer diagnosis. These findings of improved immunotherapy benefit in the >70 years group are in line with other recent studies showing that older patients respond most robustly to ICI therapy in several cancers, including melanoma, non-small cell lung cancer, and renal cell carcinoma.[30,32]

De-escalation of medical and surgical intervention for elderly breast cancer patients has been an active area of research for the past decade. For example, the Society of Surgical Oncology's Choosing Wisely campaign recommends omitting SLNB in women older than 70 years with node negative, early stage ER/PR+ HER2− breast cancers.[48,49] Furthermore, recent updates to the American Society for Clinical Oncology guidelines recommend against routine SLNB in postmenopausal patients 50 years and older with low-grade, small, HR+ HER2− breast cancers and no evidence of axillary involvement on preoperative ultrasound.[50] It is interesting in this study that women > 70 years were more likely to receive an ALND, because older women are often more likely to receive de-escalated axillary management by SLNB.[51] It is unclear whether this is related to initial patient presentation or other patient selection factors. Notably, CCI scores were highest in the > 70 years group. However, women > 70 years were more likely to have residual axillary disease after neoadjuvant therapy, as well as had a higher proportion of completion ALNDs performed than the other age groups.

This may partially explain the predilection for ALND in this group. Some studies have also suggested that elderly breast cancer patients are less likely to achieve pCR following neoadjuvant chemotherapy.[52,53] However, these studies often included women with HR+ and HER2+ breast cancers, which are less likely to respond to chemotherapy and may deflate pCR rates in older women, for whom luminal tumors are more common.[54] The findings of this study overall are suggestive that women > 70 years may receive increased benefit from immunotherapy approaches compared with younger women and that de-escalation of medical therapy may not be warranted. Future prospective trials should aim to increase representation of this age group to evaluate therapeutic efficacy for older breast cancer patients, as well as assess rates of adverse effects that may warrant de-escalated management.

One limitation of this study is that there is only limited available data regarding neoadjuvant immunotherapy use for TNBC since FDA approval in 2021, which narrows analysis of survival associated with adoption of this regimen. Furthermore, patients in the oldest age group (>70 years) may have reduced survival due to age-associated confounding factors. There is also possible selection bias in the older age groups, where older patients with higher functional status who are more likely to have improved outcomes may be preferentially selected to receive NACI over NAC. However, adjusting for comorbidities with CCI helps mitigate this risk. Another limitation of this study is that NCDB does not contain data on the type and duration of neoadjuvant immunotherapy or chemotherapy administered, limiting comparisons of outcomes based on these factors. It is noteworthy that a substantial number of TNBC patients received neoadjuvant immunotherapy prior to its FDA approval in 2021. Immune checkpoint therapy was first approved for melanoma in 2011 following the publication of trials demonstrating the efficacy of ipilimumab, an anti-CTLA-4 antibody, in extending survival for patients with metastatic disease.[55,56] A gradual increase in off-label use of neoadjuvant immunotherapy for TNBC patients may coincide with the increase in immunotherapy use for other cancers. It is unclear whether certain TNBC patient populations were more likely to receive NACI in this setting or how this selection may have impacted overall survival analyses for this cohort. The NCDB contains retrospective data, and details regarding patient selection for NACI versus NAC are also not available. In addition, we are unable to comment on the decision-making related to surgical management and the false negative rate of nodal pCR for patients who received SLNB only following neoadjuvant therapy, although it has been shown that patients with cN1 disease who convert to cN0 after neoadjuvant therapy with nodal pCR have low rates of axillary recurrence.[57]

The use of immunotherapy for the treatment of solid malignancies continues to grow rapidly. As these modalities evolve for the management of breast cancer, it will be imperative to balance these promising treatments with medical de-escalation efforts. Prospective studies investigating which patient groups may benefit the most from these innovative approaches are critical to improve outcomes for this aggressive disease.

Conclusions

The addition of immunotherapy to NAC for TNBC management has been increasing and is now the standard-of-care for young and older TNBC patients. Use of NACI was associated with higher pCR rates than NAC in all patients, but women older than 70 years in this cohort may derive the greatest benefit from NACI over NAC compared with women 50-70 years and younger than 50 years. These results suggest that older women with TNBC may have greater benefit from chemoimmunotherapy than other age groups in the neoadjuvant setting.

Acknowledgments The National Cancer Database (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The CoC's NCDB and the hospitals participating in the CoC's NCDB are the source of the de-identified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

Funding Zachary Schrank is supported by funding from the National Institutes of Health (UNC-Integrated Translational Oncology T32-CA244125 to UNC/ZS). Dr. Philip Spanheimer is supported by funding from the National Institutes of Health (K08CA280388). This work was supported in part by P30CA016086 UNC Lineberger Comprehensive Cancer Center Core Support Grant.

References

1. Kim J, Harper A, McCormack V, et al. Global patterns and trends in breast cancer incidence and mortality across 185 countries. *Nat Med*. 2025;31(4):1154–62. https://doi.org/10.1038/S41591-025-03502-3.
2. Barzaman K, Karami J, Zarei Z, et al. Breast cancer: Biology, biomarkers, and treatments. *Int Immunopharmacol*. 2020. https://doi.org/10.1016/j.intimp.2020.106535.
3. Yin L, Duan JJ, Bian XW, Yu SC. Triple-negative breast cancer molecular subtyping and treatment progress. *Breast Cancer Res*. 2020. https://doi.org/10.1186/S13058-020-01296-5.
4. Waks AG, Winer EP. Breast Cancer Treatment: A Review. *JAMA - J Am Med Assoc*. 2019;321(3):288–300. https://doi.org/10.1001/JAMA.2018.19323.
5. Kumar N, Ehsan S, Banerjee S, et al. The unique risk factor profile of triple-negative breast cancer: a comprehensive meta-analysis. *JNCI J Natl Cancer Inst*. 2024;116(8):1210–9. https://doi.org/10.1093/JNCI/DJAE056.
6. Kakimi K, Sugie T. Why combine and why neoadjuvant? Tumor immunological perspectives on chemoimmunotherapy in

triple-negative breast cancer. *Breast Cancer*. 2025;32(4):676–88. https://doi.org/10.1007/S12282-025-01707-5/METRICS.
7. Li Y, Zhang H, Merkher Y, et al. Recent advances in therapeutic strategies for triple-negative breast cancer. *J Hematol Oncol*. 2022;15(1):121. https://doi.org/10.1186/S13045-022-01341-0.
8. Gradishar WJ, Moran MS, Abraham J, et al. Breast Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Cancer Network*. 2022;20(6):691–722. https://doi.org/10.6004/JNCCN.2022.0030.
9. Bou Zerdan M, Ghorayeb T, Saliba F, et al. Triple negative breast cancer: Updates on classification and treatment in 2021. *Cancers (Basel)*. 2022. https://doi.org/10.3390/CANCERS14051253.
10. Leon-Ferre RA, Hieken TJ, Boughey JC. The Landmark Series: Neoadjuvant chemotherapy for triple-negative and HER2-positive breast cancer. *Ann Surg Oncol*. 2021;28(4):2111–9. https://doi.org/10.1245/S10434-020-09480-9.
11. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2019;30(8):1194–220. https://doi.org/10.1093/annonc/mdz173.
12. Pusztai L, Foldi J, Dhawan A, DiGiovanna MP, Mamounas EP. Changing frameworks in treatment sequencing of triple-negative and HER2-positive, early-stage breast cancers. *Lancet Oncol*. 2019;20(7):e390–6. https://doi.org/10.1016/S1470-2045(19)30158-5.
13. Carlino MS, Larkin J, Long GV. Immune checkpoint inhibitors in melanoma. *Lancet*. 2021;398(10304):1002–14. https://doi.org/10.1016/S0140-6736(21)01206-X.
14. Rui R, Zhou L, He S. Cancer immunotherapies: advances and bottlenecks. *Front Immunol*. 2023. https://doi.org/10.3389/FIMMU.2023.1212476.
15. Mellman I, Chen DS, Powles T, Turley SJ. The cancer-immunity cycle: Indication, genotype, and immunotype. *Immunity*. 2023;56(10):2188–205. https://doi.org/10.1016/J.IMMUNI.2023.09.011.
16. Naimi A, Mohammed RN, Raji A, et al. Tumor immunotherapies by immune checkpoint inhibitors (ICIs); the pros and cons. *Cell Comm Signal*. 2022. https://doi.org/10.1186/S12964-022-00854-Y.
17. Wolchok JD, Chiarion-Sileni V, Rutkowski P, et al. Final, 10-year outcomes with nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med*. 2025;392(1):11–22. https://doi.org/10.1056/NEJMOA2407417.
18. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. *N Engl J Med*. 2015;373(17):1627–39. https://doi.org/10.1056/NEJMOA1507643/SUPPL_FILE/NEJMOA1507643_DISCLOSURES.PDF.
19. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer. *N Engl J Med*. 2015;372(21):2018–28. https://doi.org/10.1056/NEJMOA1501824/SUPPL_FILE/NEJMOA1501824_DISCLOSURES.PDF.
20. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2018;378(14):1277–90. https://doi.org/10.1056/NEJMOA1712126/SUPPL_FILE/NEJMOA1712126_DISCLOSURES.PDF.
21. Katz H, Alsharedi M. Immunotherapy in triple-negative breast cancer. *Med Oncol*. 2018;35(1):1–9. https://doi.org/10.1007/S12032-017-1071-6/TABLES/2.
22. Bareche Y, Buisseret L, Gruosso T, et al. Unraveling triple-negative breast cancer tumor microenvironment heterogeneity: Towards an optimized treatment approach. *J Natl Cancer Inst*. 2020;112(7):708–19. https://doi.org/10.1093/JNCI/DJZ208.
23. Keenan TE, Tolaney SM. Role of immunotherapy in triple-negative breast cancer. *JNCCN J Natl Compr Cancer Netw*. 2020;18(4):479–89. https://doi.org/10.6004/JNCCN.2020.7554.
24. Burstein HJ, Curigliano G, Loibl S, et al. Estimating the benefits of therapy for early-stage breast cancer: The St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. *Ann Oncol*. 2019;30(10):1541–57. https://doi.org/10.1093/annonc/mdz235.
25. Geurts V, Kok M. Immunotherapy for metastatic triple negative breast cancer: Current paradigm and future approaches. *Curr Treat Options Oncol*. 2023;24(6):628–43. https://doi.org/10.1007/S11864-023-01069-0.
26. Shah M, Osgood CL, Amatya AK, et al. FDA approval summary: pembrolizumab for neoadjuvant and adjuvant treatment of patients with high-risk early-stage triple-negative breast cancer. *Clin Cancer Res*. 2022;28(24):5249–53. https://doi.org/10.1158/1078-0432.CCR-22-1110.
27. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for early triple-negative breast cancer. *N Engl J Med*. 2020;382(9):810–21. https://doi.org/10.1056/NEJMOA1910549/SUPPL_FILE/NEJMOA1910549_DATA-SHARING.PDF.
28. Shah M, Osgood CL, Amatya AK, et al. FDA approval summary: Pembrolizumab for neoadjuvant and adjuvant treatment of patients with high-risk early-stage triple-negative breast cancer. *Clin Cancer Res*. 2022;28(24):5249–53. https://doi.org/10.1158/1078-0432.CCR-22-1110.
29. Debien V, De Caluwé A, Wang X, et al. Immunotherapy in breast cancer: an overview of current strategies and perspectives. *NPJ Breast Cancer*. 2023;9(1):1–10. https://doi.org/10.1038/S41523-023-00508-3.
30. Jain V, Hwang WT, Venigalla S, et al. Association of age with efficacy of immunotherapy in metastatic melanoma. *Oncologist*. 2019;25(2):e381. https://doi.org/10.1634/THEONCOLOGIST.2019-0377.
31. Kao C, Charmsaz S, Tsai HL, et al. Age-related divergence of circulating immune responses in patients with solid tumors treated with immune checkpoint inhibitors. *Nat Comm*. 2025;16(1):1–16. https://doi.org/10.1038/S41467-025-58512-Z.
32. Wu Q, Wang Q, Tang X, et al. Correlation between patients' age and cancer immunotherapy efficacy. *Oncoimmunology*. 2019;8(4):e1568810. https://doi.org/10.1080/2162402X.2019.1568810.
33. Hamilton JAG, Henry CJ. Aging and immunotherapies: New horizons for the golden ages. *Aging Cancer*. 2020;1(1–4):30. https://doi.org/10.1002/AAC2.12014.
34. Weyand CM, Goronzy JJ. Aging of the immune system: Mechanisms and therapeutic targets. *Ann Am Thorac Soc*. 2016;13(Suppl 5):S422–8. https://doi.org/10.1513/ANNALSATS.201602-095AW/SUPPL_FILE/DISCLOSURES.PDF.
35. Shachar SS, Hurria A, Muss HB. Breast cancer in women older than 80 years. *J Oncol Pract*. 2016;12(2):123–32. https://doi.org/10.1200/JOP.2015.010207.
36. Markopoulos C, Van De Water W, Van De Velde CJ. Breast cancer in the elderly: Reducing the losses. *Future Oncol*. 2013;9(9):1253–6. https://doi.org/10.2217/FON.13.120.
37. Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the "silver tsunami": Prevalence trajectories and comorbidity burden among older cancer survivors in the United States. *Cancer Epidemiol Biomarkers Prev*. 2016;25(7):1029–36. https://doi.org/10.1158/1055-9965.EPI-16-0133.
38. Bilimoria KY, Stewart AK, Winchester DP, Ko CY. The National Cancer Data Base: A powerful initiative to improve cancer care in the United States. *Ann Surg Oncol*. 2008;15(3):683–90. https://doi.org/10.1245/S10434-007-9747-3/FIGURES/2.

39. Lee KA, Flores RR, Jang IH, Saathoff A, Robbins PD. Immune senescence, immunosenescence and aging. *Front Aging*. 2022;3:900028. https://doi.org/10.3389/FRAGI.2022.900028/BIBTEX.
40. Shaw AC, Goldstein DR, Montgomery RR. Age-dependent dysregulation of innate immunity. *Nat Rev Immunol*. 2013;13(12):875. https://doi.org/10.1038/NRI3547.
41. Smith A, Boby JM, Benny SJ, Ghazali N, Vermeulen E, George M. Immunotherapy in older patients with cancer: A narrative review. *Int J Gen Med*. 2024;17:305. https://doi.org/10.2147/IJGM.S435001.
42. Kanesvaran R, Cordoba R, Maggiore R. Immunotherapy in older adults with advanced cancers: Implications for clinical decision-making and future research. *Am Soc Clin Oncol Edu Book*. 2018;38:400–14. https://doi.org/10.1200/EDBK_201435/ASSET/BE99A07C-48E6-41F1-9694-1A5EA0318C27/ASSETS/IMAGES/LARGE/EDBK_201435_TABLE2.JPG.
43. Zheng Y, Liu Q, Goronzy JJ, Weyand CM. Immune aging – A mechanism in autoimmune disease. *Semin Immunol*. 2023. https://doi.org/10.1016/j.smim.2023.101814.
44. Chen C, Zhang C, Wu B, Xu T. Immune-related adverse events in older adults: Data mining of the FDA Adverse Event Reporting System. *J Geriatr Oncol*. 2022;13(7):1017–22. https://doi.org/10.1016/j.jgo.2022.05.009.
45. Goronzy JJ, Weyand CM. Immune aging and autoimmunity. *Cell Mol Life Sci*. 2012;69(10):1615. https://doi.org/10.1007/S00018-012-0970-0.
46. Merlino DJ, Johnson JM, Tuluc M, et al. Discordant responses between primary head and neck tumors and nodal metastases treated with neoadjuvant nivolumab: Correlation of radiographic and pathologic treatment effect. *Front Oncol*. 2020;10:566315. https://doi.org/10.3389/FONC.2020.566315/FULL.
47. Grant C, Hagopian G, Nagasaka M. Neoadjuvant therapy in non-small cell lung cancer. *Crit Rev Oncol Hematol*. 2023;190:104080. https://doi.org/10.1016/J.CRITREVONC.2023.104080.
48. Whitrock JN, Pratt CG, Long SA, Carter MM, Lewis JD, Heelan AA. Implementation of Choosing Wisely guidelines: Omission of lymph node surgery. *Surgery (United States)*. 2024. https://doi.org/10.1016/j.surg.2024.08.047.
49. Egbert LK, Kosiorek H, Cronin P, Billar J, Bold R, Pockaj B. Trends in axillary staging for breast cancer in the elderly: Outcomes of choosing wisely at a high-usage institution. *Am J Surg*. 2025;250:116477. https://doi.org/10.1016/j.amjsurg.2025.116477.
50. Park KU, Somerfield MR, Anne N, et al. Sentinel lymph node biopsy in early-stage breast cancer: ASCO guideline update. *J Clin Oncol*. 2025. https://doi.org/10.1200/JCO-25-00099/SUPPL_FILE/2025-SLNB-EARLY-BREAST-VIS-ABS.PNG.
51. Ong CT, Thomas SM, Blitzblau RC, et al. Patient age and tumor subtype predict the extent of axillary surgery among breast cancer patients eligible for the American College of Surgeons Oncology Group Trial Z0011. *Ann Surg Oncol*. 2017;24(12):3559. https://doi.org/10.1245/S10434-017-6075-0.
52. Cabrera-Galeana P, Soto-Perez-de-Celis E, Reynoso-Noveron N, et al. Real-world outcomes among older Mexican women with breast cancer treated with neoadjuvant chemotherapy. *Oncologist*. 2020;25(12):1023. https://doi.org/10.1634/THEONCOLOGIST.2019-0891.
53. Chou HH, Kuo WL, Yu CC, et al. Impact of age on pathological complete response and locoregional recurrence in locally advanced breast cancer after neoadjuvant chemotherapy. *Biomed J*. 2019;42(1):66–74. https://doi.org/10.1016/J.BJ.2018.10.007.
54. Jenkins EO, Deal AM, Anders CK, et al. Age-specific changes in intrinsic breast cancer subtypes: A focus on older women. *Oncologist*. 2014;19(10):1076. https://doi.org/10.1634/THEONCOLOGIST.2014-0184.
55. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363(8):711. https://doi.org/10.1056/NEJMOA1003466.
56. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med*. 2011;364(26):2517–26. https://doi.org/10.1056/NEJMOA1104621.
57. Barrio AV, Montagna G, Mamtani A, et al. Nodal recurrence in patients with node-positive breast cancer treated with sentinel node biopsy alone after neoadjuvant chemotherapy—a rare event. *JAMA Oncol*. 2021;7(12):1851–5. https://doi.org/10.1001/JAMAONCOL.2021.4394.