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ORIGINAL REPORT

Accrual of Older Patients With Breast Cancer to Alliance Systemic Therapy Trials Over Time: Protocol A151527

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A B S T R A C T

Purpose

Despite increasing awareness of accrual challenges, it is unknown if accrual of older patients to breast cancer treatment trials is improving.

Methods

We examined accrual of older patients to Alliance for Clinical Trials in Oncology systemic therapy breast cancer trials during 1985-2012 and compared disease characteristics and reasons for therapy cessation for older (age ≥ 65 years and ≥ 70 years) versus younger (age < 65 years and < 70 years) participants. To examine accrual trends, we modeled age as a function of time, using logistic regression.

Results

Overall, 17% of study participants were ≥ 65 years of age. Approximately 15%, 24%, and 24% of participants in adjuvant, neoadjuvant, and metastatic trials were age ≥ 65 years, and 7%, 15%, and 13% were age ≥ 70 years, respectively. The odds of a patient age ≥ 65 years enrolling significantly increased over time for adjuvant trials (odds ratio [OR] per year, 1.04; 95% CI, 1.04 to 1.05) but decreased significantly for neoadjuvant and metastatic trials (OR, 0.62; 95% CI, 0.58 to 0.67 and OR, 0.98, 95% CI, 0.97 to 1.00). Similar trends were seen for those age ≥ 70 years but these were statistically significant for adjuvant and neoadjuvant trials only (OR, 1.05, 95% CI, 1.04 to 1.07; and OR, 0.57, 95% CI, 0.52 to 0.62). In general, those age ≥ 65 years (*v* those < 65 years) in adjuvant studies had a higher mean number of lymph nodes involved and more hormone receptor-negative tumors, although tumor sizes were similar. Early protocol treatment cessation was also more frequent in those age ≥ 65 years (50%) versus < 65 years (35.9%) across trials.

Conclusion

Older patients with breast cancer remain largely underrepresented in cooperative group therapeutic trials. We observed some improvement in accrual to adjuvant trials but worsening of accrual for neoadjuvant/metastatic trials. Novel strategies to increase accrual of older patients are critical to meaningfully change the evidence base for this growing patient population.

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INTRODUCTION

Breast cancer is a disease of aging and nearly 72,000 breast cancers occur annually in US women ≥ 70 years of age.[1,2] Although most breast cancers in older women are lower-risk tumors and most older patients with breast cancer die of other causes,[3-5] approximately 19,000 breast cancer deaths occur yearly in US women ≥ 70 years of age, accounting for 47% of breast cancer deaths.[6]

Although most cancers occur in older patients, accrual of older patients to cancer clinical trials has been a persistent challenge. Consequently, the availability of prospective data for older patients with breast cancer is limited. Although some evidence suggests that older patients are just as likely to enroll in clinical trials as younger patients if one is offered,[7] multiple barriers to accrual have been identified, including comorbidity, physician/patient preferences, socioeconomic factors, insurance, concerns about loss of continuity with primary oncologists, lack of knowledge about clinical trials, and age itself.[7-18] In addition, others have cited time and travel considerations and trial phase as barriers for all patients.[16,19] Thus far, specific efforts to improve enrollment of older patients with cancer to clinical trials within the cooperative group setting have

ASSOCIATED CONTENT

Appendix
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Table 1. Alliance for Clinical Trials in Oncology

Trial	Agents Administered	Key Eligibility*	Total Patients in Study, No.	Age ≥ 65 Years, No. (% total accrual)	Age ≥ 70 years, No. (% total accrual)	Dates of Accrual
All trials combined	—	—	19,507	3,308 (17)	1,672 (9)	1985-2012
Adjuvant trials (overall)			15,297	2,277 (15)	1099 (7)	1985-2010
CALGB 40101[32,33]	A+C *v* T (4 *v* 6 cycles)	• 0-3 nodes involved • No locally advanced disease • ECOG PS not specified	3,871	468 (12)	177 (5)	6/2002-7/2010
CALGB 49907†[24]	A+C/C+M+F *v* capecitabine	• Age ≥ 65 years • Tumor > 1 cm • Life expectancy > 5 years • ECOG PS 0-2	633	633 (100)	415 (66)	6/2002-12/2006
NCCTG N9831[34]	A+C+T *v* A+C+T+H	• HER2 positive • Node positive or higher risk node negative • ECOG PS not specified	3,505	301 (9)	126 (4)	5/2000-4/2005
CALGB 9741[35]	A+C+T q2w *v* A+C+T q3w *v* sequential A+T+C q2w	• T0-T3, N1/2, M0 disease • ECOG PS not specified	2,005	162 (8)	54 (3)	10/1997-3/1999
CALGB 9344[36]	A+C with 3 different doses of A (60, 75, 90 mg/m^2) × 4 cycles ± T	• Node positive • ECOG PS not specified	3,170	182 (6)	55 (2)	5/1994-4/1997
NCCTG 89-30-52‡[37]	Tamoxifen ± fluoxymesterone	• Postmenopausal • Estrogen-receptor positive • T1 or T2 • If node negative, any age allowed • If node positive, required to be age ≥ 65 years • ECOG PS not specified	541	381 (70)	225 (42)	1/1991-4/1995
CALGB 8541[38]	C+A+F dosing (3 dose levels examined)	• Stage II (T1N0M0 or T2N1M0) • ECOG PS 0-1	1,572	150 (10)	47 (3)	1/1985-3/1991
Neoadjuvant trials (overall)			1,663	407 (24)	252 (15)	2006-2012
CALGB 40603[39]	A+C+T ± carboplatin ± bevacizumab	• Triple negative • Clinical stage II-III • ECOG PS not specified	454	40 (9)	10 (2)	7/2009-8/2012
CALGB 40601[40]	T+H *v* T+H+L *v* T+L	• HER2 positive • Clinical stage II-III • ECOG PS not specified	305	25 (8)	10 (3)	2/2009-2/2012
ACOSOG Z1041[41]	Preoperative F+E+C→T+H *v* T+H→F+E+C+H	• HER2 positive • T2 or node positive • ECOG PS 0-1	282	18 (6)	8 (3)	9/2007-12/2011
ACOSOG Z1031‡[42]	Preoperative exemestane *v* letrozole *v* anastrozole	• Postmenopausal • HR positive • HER2 negative • Clinical T2-T4c, N0-3, M0 • ECOG PS 0-2	622	324 (52)	224 (36)	01/2006-01/2009
Metastatic trials (overall)			2,547	624 (24)	321 (13)	1994-2011
CALGB 40502[43]	Weekly paclitaxel *v* nab-paclitaxel *v* ixabepilone	• HER2 negative • Stage IIIC or IV • First-line chemotherapy • ECOG PS 0-1	799	166 (21)	81 (10)	11/2008-11/2011
CALGB 40503[44]	Letrozole/tamoxifen ± bevacizumab	• HR positive • Metastatic • First-line patients only • ECOG PS 0-1	394	98 (25)	53 (13)	9/2008-11/2011
CALGB 40302‡[45]	Fulvestrant ± lapatinib	• HR positive • Postmenopausal • Noncurative stage III or stage IV • 1-2 prior endocrine therapies allowed • ECOG PS 0-2	295	84 (28)	47 (16)	12/2006-07/2010
CALGB 9342[46]	Paclitaxel dosing	• ≤ 1 prior line of chemotherapy • Metastatic disease • ECOS PS not specified	474	149 (31)	87 (18)	9/1998-11/2003

(continued on following page)

Table 1. Alliance for Clinical Trials in Oncology (continued)

Trial	Agents Administered	Key Eligibility*	Total Patients in Study, No.	Age ≥ 65 Years, No. (% total accrual)	Age ≥ 70 years, No. (% total accrual)	Dates of Accrual
CALGB 9840[47]	Paclitaxel schedules (weekly *v* q3w + trastuzumab if HER2 positive	• HER2 positive or negative • ≤ 1 prior line of chemotherapy for metastatic disease or locally advanced • ECOS PS not specified	585	127 (22)	53 (9)	2/1994-7/1997

NOTE. Adjuvant, neoadjuvant, and metastatic studies included (most recent to oldest). Dashes indicate not applicable.
Abbreviations: A, doxorubicin; ACOSOG, American College of Surgeons Oncology Group; CALGB, Cancer and Leukemia Group B; C, cyclophosphamide; E, epirubicin; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; F, 5-fluorouracil; H, trastuzumab; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; L, lapatinib; M, methotrexate; NCCTG, North Central Cancer Treatment Group; q2w, every 2 weeks; q3w, every 3 weeks; T, paclitaxel.
*Only key and relevant eligibility criteria are listed; this is not complete. "ECOG PS not specified" indicates this was not described in the publication, but it is possible this was on the list of exclusions/inclusions in protocol documents.
†Age ≥ 65 years was an eligibility requirement.
‡Postmenopausal status was an eligibility requirement.

included educational interventions,[20] focused committees, policy statements,[21-23] and the development of a limited number of trials dedicated to older patients.[24-26] Additional attempts to improve accrual across all ages have examined strategies to improve the consent process and the methods for opting in/out of enrollment.[27-29]

Because of keen awareness of accrual challenges for older patients, designing clinical trials specific to older patients with cancer has been a priority.[22,23,30] We have seen some successes with Cancer and Leukemia Group B (CALGB) trials 9343 and 49907,[24-26] though there is concern that we continue to struggle with enrollment of older patients.[22] The Alliance for Clinical Trials in Oncology ("Alliance"; formed by the merger of legacy groups CALGB, American College of Surgeons Oncology Group [ACOSOG], and North Central Cancer Treatment Group [NCCTG]) has a national therapeutic protocol program in breast cancer[31] and has completed many practice-changing, large-scale systemic trials to date. However, it is not known if accrual of older patients to these trials has improved. In this retrospective analysis (A151527), we examined whether enrollment of older patients with breast cancer to Alliance systemic therapy clinical trials has improved over time. We also examined disease characteristics and the reasons for study treatment cessation for those age ≥ 65 years and ≥ 70 years versus younger patients.

METHODS

Data Source

We reviewed the Alliance portfolio of accrued systemic therapy trials in neoadjuvant, adjuvant, and metastatic breast cancer therapeutic settings during 1985-2012. Because of specific concerns about the lack of enrollment of older patients in systemic treatment trials in particular, we focused our analysis on therapeutic systemic trials only and did not include local or supportive therapy protocols. Table 1 lists the trials included.

Variables of Interest

Our primary end point was the proportion of older patients enrolled in studies over time, using the date of protocol registration for each patient. We determined whether the probability of an older patient enrolling in a study changed significantly over time. We examined both the overall time trend for all studies and the time trends specific to trial type (separately) for adjuvant, neoadjuvant, and metastatic trials. Our secondary goal was to better understand whether disease characteristics for trial participants differed by age by examining tumor size, number of nodes involved, hormone receptor status, and human epidermal growth factor 2 (HER2) receptor status (when available) for older versus younger women in each adjuvant study. We limited comparisons of disease characteristics to adjuvant trials because neoadjuvant and metastatic trials primarily enrolled patients with homogeneous staging and tumor subtypes. When available, we also examined baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS)[48] and reasons for protocol therapy cessation by age.

Statistical Analysis

To determine whether the proportion of older patients enrolling in trials changed over time, we modeled age as a function of time, using logistic regression, both for age ≥ 65 years ($v < 65$ years) and age ≥ 70 years ($v < 70$ years). This was done separately for adjuvant, neoadjuvant, and metastatic trials, using data pooled across all available studies for each trial setting. Of note, CALGB 49907, NCCTG 89-30-52, and ACOSOG Z1031 primarily targeted postmenopausal and/or older women, enrolling patients age ≥ 65 years at rates of 100%, 70%, and 52%, respectively. Therefore, in a sensitivity analysis, we repeated analyses with these trials excluded.

To assess the degree to which disease characteristics differed with age for each adjuvant study, we compared subtype (estrogen receptor [ER], progesterone receptor [PR], and HER2 receptor status), tumor size, and the number of nodes involved for patients (when data were available) in each adjuvant study, using χ^2 tests for comparisons of receptor status and tumor size and paired t tests for comparison of nodes. We also examined differences in ECOG PS and reasons for protocol therapy cessation (overall and for each trial type separately) by age, using χ^2 tests.

Because this study used preexisting data, we received exemption from the Dana-Farber Cancer Institute Office for Human Research Studies for these analyses. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center.

RESULTS

Accrual Over Time

We included 16 Alliance protocols, which enrolled 19,507 patients. The proportion of patients age ≥ 65 years and ≥ 70 years enrolled in each study, agents administered, key eligibility, and

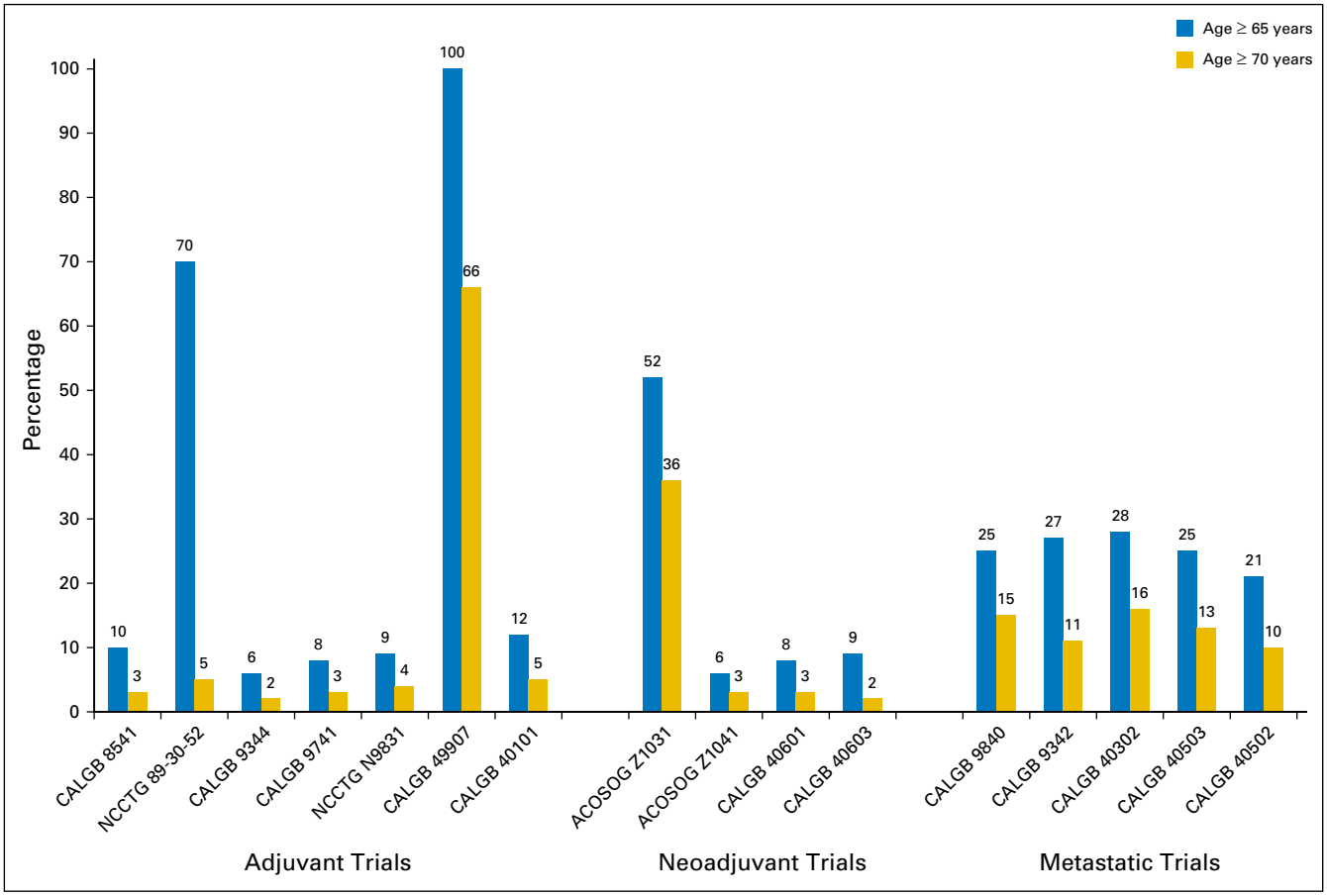

Fig 1. Proportions of patients age ≥ 65 years and ≥ 70 years enrolled in each clinical trial. ACOSOG, American College of Surgeons Oncology Group; CALGB, Cancer and Leukemia Group B; NCCTG, North Central Cancer Treatment Group.

dates of accrual are listed in Table 1. No trial had an upper limit for age as part of eligibility requirements. Overall, 3,308 (17%) of the 19,507 trial participants registered during 1985-2012 were age ≥ 65 years and 1,672 (9%) were age ≥ 70 years.

Among the 15,297 women who enrolled in adjuvant trials, 15% were age ≥ 65 years and 7% were ≥ 70 years. For the 1,663 women enrolled in neoadjuvant studies, 24% were age ≥ 65 years and 15% of participants were ≥ 70 years. Of the 2,547 participants in metastatic protocols, 24% were age ≥ 65 years and 13% were ≥ 70 years. Figure 1 displays the proportion of older women enrolled by trial. Distinct peaks in enrollment for older patients are visible for CALGB 49907 (adjuvant chemotherapy for patients age ≥ 65 years), NCCTG 89-30-52, and ACOSOG Z1031 (hormonal therapy-based trials for postmenopausal women).

The absolute numbers of patients age ≥ 65 years and age ≥ 70 years increased somewhat over the study period (Appendix Fig A1, online only), although this was not consistent over time. For example, the years with the lowest absolute numbers of enrolled patients age ≥ 65 years were 1991 (n = 7), 2012 (n = 15), and 1985 (n = 31), whereas the highest numbers of enrolled older patients occurred during 2000 (n = 467), 2010 (n = 282), and 2009 (n = 246).

Figure 2 displays the trends in overall accrual over time by age (Fig 2A), trends in accrual by trial type for age ≥ 65 years (Fig 2B) and ≥ 70 years (Fig 2C), and trends by ages ≥ 65 years and ≥ 70 years after excluding CALGB 49907/NCCTG 89-30-52/ACOSOG Z1031 (Fig 2D). To further illustrate potential trends in each of these plots, we included locally weighted scatterplot smoothing lines (a type of nonparametric regression).

Results from our logistic regression model indicate that the odds of a patient age ≥ 65 years enrolling slightly increased with each year in adjuvant trials, with an odds ratio (OR) for enrollment of 1.04 per year (95% CI, 1.04 to 1.05; $P < .001$). Thus, over 5 years, this translates into a 20% increase in the odds of enrolling patients age ≥ 65 years. In contrast, the odds of a patient age ≥ 65 years enrolling decreased significantly by year in neoadjuvant and metastatic trials (OR, 0.62; 95% CI, 0.58 to 0.67; $P < .001$; and OR, 0.98, 95% CI, 0.97 to 1.00, $P = .03$, respectively). Similar trends were seen for patients age ≥ 70 years, but these were statistically significant for adjuvant and neoadjuvant trials only (OR, 1.05; 95% CI, 1.04 to 1.07; and OR, 0.57; 95% CI, 0.52 to 0.62, respectively). After exclusion of patients enrolled in CALGB 49907/NCCTG 89-30-52/ACOSOG Z1031, results were unchanged for adjuvant and metastatic trials, but no significant time trend was found for neoadjuvant trials.

Disease Characteristics and ECOG PS by Age

Disease characteristics by age for adjuvant trials CALGB 40101, 49907, 9344, 9741, 9344, 8541, and N9831 are listed in Table 2 (detailed characteristics for NCCTG 89-30-52 were not available). In general, across adjuvant trials, the proportion of

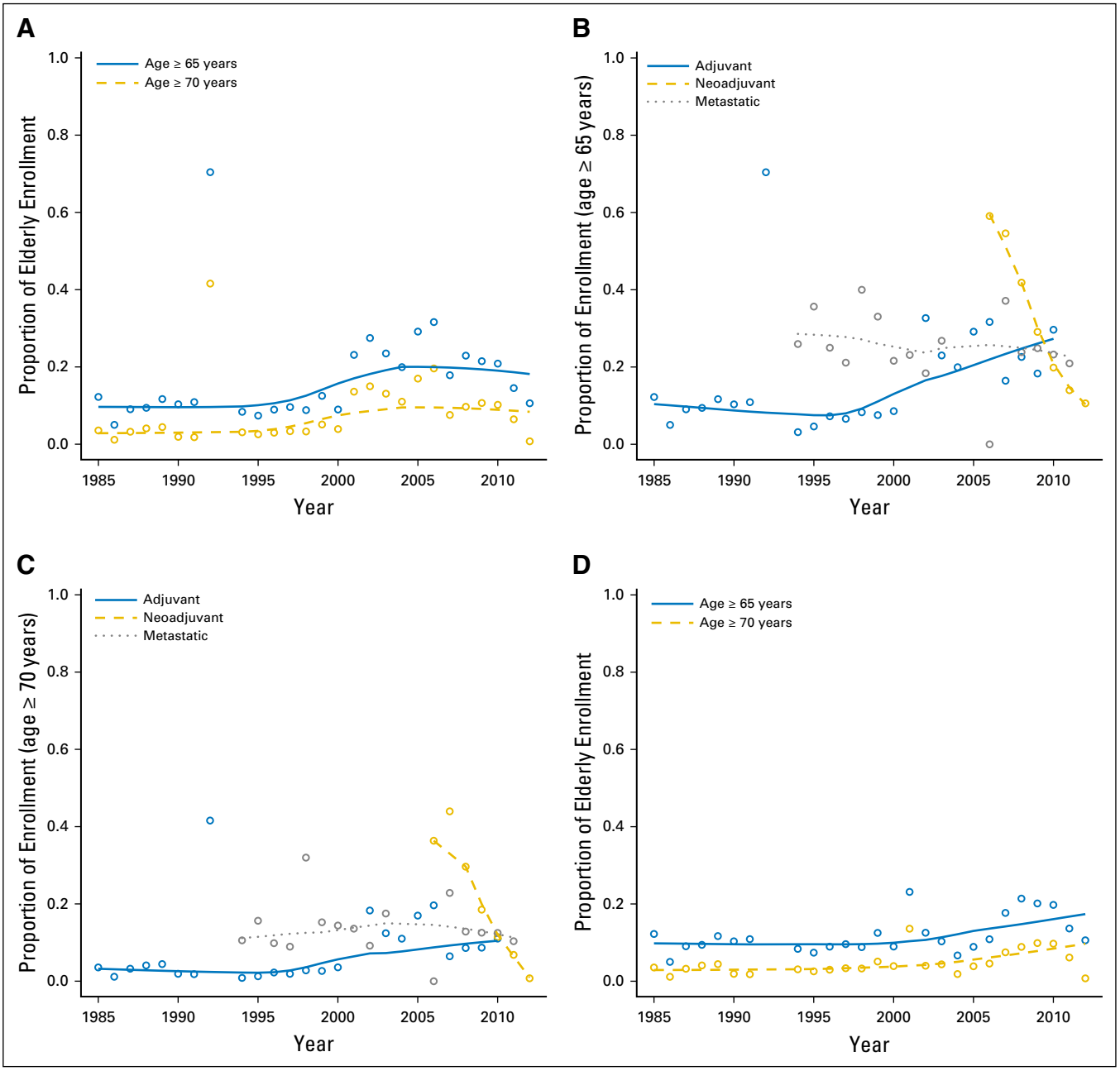

Fig 2. Unadjusted proportions of patients age ≥ 65 years and ≥ 70 years enrolled in all trials (A), by trial type for age ≥ 65 years and ≥ 70 years (B, C), and after exclusion of Cancer and Leukemia Group B (CALGB) 49907, North Central Cancer Treatment Group (NCCTG) 89-30-52, and American College of Surgeons Oncology Group (ACOSOG) Z1031 (D).

women with ER-negative and PR-negative tumors was significantly higher for older versus younger women. Comparisons by HER2 status were limited because these data were not routinely collected in older studies and because all patients in N9831 had HER2-positive disease. For CALGB studies 40101, 8541, 9344, and 9741, the mean number of nodes in women age ≥ 65 years was higher than in younger patients. Mean tumor sizes were similar by age for all adjuvant studies ($P > .05$ for all five protocols), although when categorized as < 2 cm or ≥ 2 cm, CALGB 40101 had a higher proportion of patients age ≥ 65 years with tumors ≥ 2 cm compared with those age < 65 years (49% *v* 44%, respectively; $P = .019$). Results for age ≥ 70 years were similar to those with a cutoff age of 65 years (data not shown). Patients age ≥ 65 years and ≥ 70 years had significantly higher proportions of participants with ECOG PS 1 (*v* 0) in CALGB studies 40101, 40302, and 40603 compared with younger women. ECOG PS was similar by age in CALGB 40502 and 9840 (Table 3).

Reasons for Protocol Treatment Cessation

Table 4 lists the reasons for stopping protocol treatment (based on trials with this information available). Overall, reasons for going off treatment differed significantly for women age ≥ 65

Table 2. Disease Characteristics by Adjuvant Trial for Older Versus Younger Women*

Variables by Protocol	Total*	Age < 65 Years	Age ≥ 65 Years	Age ≥ 70 Years†	P‡ (age < 65 years v ≥ 65 years)
CALGB 40101[32,33]	3,864	3,396	468	177	
ER					.024
Positive	2,564 (66)	2,275 (67)	289 (62)	103 (58)	
Negative	1,298 (34)	1,119 (33)	179 (38)	74 (42)	
Missing/unknown	2 (0)	2 (0)	0 (0)	0 (0)	
PR					.011
Positive	2,175 (56)	1,937 (57)	238 (51)	87 (49)	
Negative	1,681 (44)	1,452 (43)	229 (49)	90 (51)	
Missing/unknown	8 (0)	7 (0)	1 (0)	0 (0)	
HER2					.140
Positive	719 (19)	620 (18)	99 (21)	32 (18)	
Negative	3,017 (78)	2,662 (78)	355 (76)	138 (78)	
Missing/unknown	128 (3)	114 (3)	14 (3)	7 (4)	
Mean no. of nodes involved (range)	0.2 (0-17)	0.2 (0-17)	0.4 (0-8)	0.6 (0-8)	< .001
Tumor size, cm					.019
< 2	2,152 (56)	1,915 (56)	237 (51)	80 (68)	
≥ 2	1,712 (44)	1,481 (44)	231 (49)	97 (32)	
CALGB 49907	633	—	633	415	
ER		N/A			N/A
Positive	417 (66)	417 (66)	260 (63)		
Negative	214 (34)	214 (34)	155 (24)		
Missing/unknown	2 (0)	2 (0)	0 (0)		
PR		N/A			N/A
Positive	333 (53)	333 (53)	199 (48)		
Negative	296 (47)	296 (47)	214 (52)		
Missing/unknown	4 (1)	4 (1)	2 (0)		
HER2		N/A			N/A
Positive	76 (12)	76 (12)	48 (12)		
Negative	529 (84)	529 (84)	349 (84)		
Missing/unknown	28 (4)	28 (4)	18 (4)		
Mean no. of nodes involved (range)	2.0 (0-20)	N/A	2.0 (0-20)	2.3 (0-20)	N/A
Tumor size, cm		N/A			N/A
< 2	229 (36)	229 (36)	135 (33)		
≥ 2	401 (64)	401 (64)	279 (67)		
NCCTG N9831[34]	3,505	3,204	301	126	
ER					.014
Positive	1,841 (53)	1,707 (53)	134 (45)	55 (44)	
Negative	1,663 (47)	1,496 (47)	167 (55)	71 (56)	
Missing/unknown	0 (0)	1 (0)	0 (0)	0 (0)	
PR					.002
Positive	1,400 (40)	1,312 (41)	88 (29)	36 (29)	
Negative	2,096 (60)	1,883 (59)	213 (71)	90 (71)	
Missing/unknown	9 (0)	9 (0)	0 (0)	0 (0)	
HER2-positive	3,505 (100)	3,204 (100)	301 (100)	126 (100)	N/A§
Mean no. of nodes involved (range)	4.3 (0-41)	4.3 (0-41)	4.9 (0-39)	5.2 (0-39)	.053
Tumor size, cm					.621
< 2	1,143 (33)	1,041 (32)	102 (34)	45 (36)	
≥ 2	2,362 (67)	2,163 (68)	199 (66)	82 (64)	
CALGB 9741[35]	1,985	1,825	160	52	
ER					.127
Positive	1,283 (65)	1,026 (56)	114 (71)	37	
Negative	668 (34)	757 (41)	46 (29)	15	
Missing/unknown	34 (2)	34 (2)	0 (0)	0	
PR					.818
Positive	1,116 (56)	1,026 (56)	90 (56)	29	
Negative	826 (42)	757 (41)	69 (43)	23	
Missing/unknown	43 (2)	42 (2)	1 (1)	0 (0)	
HER2			Not reliably collected		
Positive					
Negative					
Missing/unknown					
Mean no. of nodes involved (range)	4.3 (0-34)	4.1 (0-30)	6.7 (1-34)	6.8 (1-26)	< .001
Tumor size, cm					.968
< 2	633 (33)	581 (33)	52 (33)	16 (31)	
≥ 2	1,311 (67)	1,204 (67)	107 (67)	36 (69)	

(continued on following page)

Table 2. Disease Characteristics by Adjuvant Trial for Older Versus Younger Women* (continued)

Variables by Protocol	Total*	Age < 65 Years	Age ≥ 65 Years	Age ≥ 70 Years†	P‡ (age < 65 years v ≥ 65 years)
CALGB 9344[36]	3,165	2,983	182	55	
ER					.367
Positive	1,871 (59)	1,757 (59)	114 (63)	32	
Negative	1,276 (40)	1,208 (40)	68 (37)	23	
Missing/unknown	18 (0)	18 (1)	0 (0)	0 (0)	
PR					.294
Positive	1,771 (56)	1,675 (56)	96 (53)	27	
Negative	1,364 (43)	1,278 (43)	86 (47)	28	
Missing/unknown	30 (1)	30 (1)	0 (0)	0 (0)	
HER2			Not collected		
Positive					
Negative					
Missing/unknown					
Mean no. of nodes involved (range)	5.0 (0-41)	4.9 (0-41)	7.4 (1-36)	7.3 (1-22)	< .001
Tumor size, cm					.127
< 2	821 (26)	765 (26)	56 (31)	18 (33)	
≥ 2	2,325 (74)	2,200 (74)	125 (69)	37 (67)	
CALGB 8541[38]	1,558	1,411	147	47	
ER/PR/HER2			Not collected		
Missing					
Mean no. of nodes involved (range)	4.6 (1-54)	4.4 (1-38)	6.1 (1-54)	6.6 (1-26)	.039
Tumor size, cm					.454
< 2	367 (24)	329 (23)	38 (26)	7 (16)	
≥ 2	1,182 (76)	1,075 (77)	107 (74)	38 (84)	

NOTE. Data are given as no. (%) unless otherwise indicated. Dashes indicate no data available.
Abbreviations: CALGB, Cancer and Leukemia Group B; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; N/A, not applicable; NCCTG, North Central Cancer Treatment Group; PR, progesterone receptor.
*Detailed tumor characteristics for NCCTG 89-30-52 were not available; some sample sizes are smaller than the overall protocol sample because of missing data on some patients. Comparisons were made among those with known tumor characteristics listed.
†*P* value not shown for age ≤ 70 years *v* ≥ 70 years.
‡Values are for χ^2 testing for ER/PR/HER2; *t* tests for tumor size and number of nodes.
§All patients had HER2-positive disease.

years versus those age < 65 years (overall $P < .0001$), and early protocol treatment cessation was more frequent in those age ≥ 65 years (50%) versus < 65 years (35.9%) across trials. For those treated in adjuvant trials (Table 4), small differences by age were seen in the percentage of women who went off protocol treatment because they completed therapy, with 80.1% of women age < 65 years completing therapy as planned versus 77.4% of women age ≥ 65 years (overall $P < .0001$). For neoadjuvant trials, comparisons were limited because 65% of patients did not have clearly documented reasons for stopping study therapy. Overall, deaths during a study were uncommon (1% of women age ≥ 65 years *v* 0.2% for those age < 65 years). Cessation of therapy because of adverse events occurred more frequently for those age ≥ 65 years compared with those < 65 years (7.9% *v* 6.4% overall; $P < .0001$), though differences were small.

DISCUSSION

The US population is aging and the number of older patients with breast cancer is expected to rise significantly in the coming decades.[49-53] Currently, the median age at diagnosis is 62 years and approximately 42% of all new breast cancer cases annually are diagnosed in women age ≥ 65 years.[1] On average, an 80-year-old woman currently living in the United States will live another 9 years[54] and will benefit from optimized systemic therapy for her breast cancer. Furthermore, nearly 10% of older patients present with stage III-IV disease,[55] and even more have node-positive/earlier-stage disease with a high probability of recurrence, where chemotherapy can provide benefit.[56-58] Improving the availability of prospective evidence for this growing number of patients is crucial to inform decision-making and to optimally serve patients' medical, emotional, and functional needs.[30]

In this analysis of Alliance systemic therapy studies during 1985-2012, we observed small increases in accrual of older patients to adjuvant trials but a significant decrease in accrual to trials in the neoadjuvant and metastatic disease settings. In general, with the exception of selected trials dedicated to older patients, the proportion of patients enrolling to clinical trials who were age ≥ 65 years and, in particular, ≥ 70 years remained low throughout the study period, with less than 20% of participants age ≥ 65 years and less than 10% of participants age ≥ 70 years. The absolute numbers of older patients enrolled over time also remained low, though some years saw higher accrual than others.

Of note, despite a trend for decreased accrual for metastatic and neoadjuvant trials for older patients, overall, numerically higher proportions of older patients enrolled in these trials compared with adjuvant studies, with approximately 24% of participants aged ≥ 65 years in both metastatic and neoadjuvant studies (*v* 15% on adjuvant trials). The reasons for this finding are not clear from the data available but may be related to a lower threshold for treatment in the neoadjuvant/metastatic settings

Table 3. Eastern Cooperative Oncology Group Performance Status for Patients in Included Studies, by Age and Trial

		Age Group					Age Group				
		< 65 Years		≥ 65 Years			< 70 Years		≥ 70 Years		
Study	PS	n	%	n	%	*P**	n	%	n	%	*P**
40101	0	3,047	89.5	394	84.2	.0006	3,296	89.2	145	81.9	.003
	1	356	10.5	74	15.8		398	10.8	32	18.1	
40302	0	154	73.0	44	52.4	.003	177	71.4	21	44.7	.001
	1	54	25.6	38	45.2		68	27.4	24	51.1	
	2	3	1.4	2	2.4		3	1.2	2	4.3	
40502	0	400	63.2	100	60.2	.485	448	62.4	52	64.2	.751
	1	233	36.8	66	39.8		270	37.6	29	35.8	
40503	0	208	70.3	56	57.1	.017	233	68.3	31	58.5	.157
	1	88	29.7	42	42.9		108	31.7	22	41.5	
40601	0	262	93.6	21	84.0	.076	274	92.9	9	90.0	.729
	1	18	6.4	4	16.0		21	7.1	1	10.0	
40603	0	376	90.8	32	80.0	.030	401	90.3	7	70.0	.035
	1	38	9.2	8	20.0		43	9.7	3	30.0	
49907	0	N/A		457	72.2	N/A	175	80.3	282	68.0	.004
	1			161	25.4		39	17.9	122	29.4	
	2			15	2.4		4	1.8	11	2.7	
9840	0	153	67.4	39	60.9	.602	169	66.8	23	60.5	.852
	1	67	29.5	24	37.5		77	30.4	14	36.8	
	2	6	2.6	1	1.6		6	2.4	1	2.6	
	3	1	0.4				1	0.4			

NOTE. Eastern Cooperative Oncology Group performance status (ECOG PS) for the protocols where this information available. ECOG PS 0 = full active, able to carry on all predisease performance without restriction; ECOG PS 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; ECOG PS 2 = ambulatory and capable of all self-care but unable to carry out any work activities.[48] Up and about more than 50% of waking hours.
Abbreviation: N/A, not applicable.
*By study, using χ^2 testing.

because of symptomatic or higher burden of disease. Furthermore, all the patients with metastatic disease in the trials included in this analysis received single-agent chemotherapy, which may be more appealing for providers and older patients than doublet treatment. Although there were some differences noted by age in PS for trial participants, essentially all patients across studies had ECOG PS of 0-1 and met trial eligibility criteria. It is possible that some older patients who would have otherwise participated in protocols were disproportionately not eligible because of poor PS, but we do not have information on patients not enrolled in studies. However, given that most older patients with cancer have life expectancies of > 16 years at age 70,[54] and that approximately half of older patients with breast cancer having three or fewer comorbid conditions,[4] it is unlikely that the majority of older patients not enrolled in trials were truly ineligible.

Not surprisingly, trials administering endocrine therapies also enrolled higher proportions of older participants, though results for accrual of older patients were similar even after excluding these trials. In contrast, in the adjuvant setting, there may be a higher threshold to treat older patients with chemotherapy in general, thus leading to fewer older patients enrolled in adjuvant studies. Consistent with this, we observed more nodal involvement and more hormone receptor-negative cancers for older (*v* younger) women enrolled in adjuvant studies. Although it is often appropriate to withhold adjuvant systemic therapy in older patients with significant comorbidity and/or low-to-intermediate risk tumors, there are likely many cases in which older women are being undertreated,[56,57,9-64] possibly reflected by their disproportionately low enrollment in adjuvant trials. For example, in CALGB 9344, an adjuvant trial for women with node-positive cancers, only 6% of trial participants were age ≥ 65 years and 2% were age ≥ 70 years. On average, older women on this trial had more than seven positive lymph nodes compared with an average of more than five nodes for patients age < 65 years, suggesting a higher threshold to treat despite similar mortality benefits from adjuvant chemotherapy for older and younger women.[55,57,58] However, we do not have information on whether older women received treatment off-study.

Reassuringly, we observed small differences in the proportion of patients who stopped therapy for adverse events by age, and ≤ 10% of all patients stopped therapy for this reason, regardless of age. Consistent with this, Muss et al[24] reported that 92% of patients age ≥ 65 years receiving anthracycline-based therapy on CALGB 49907 completed treatment. Deaths while participating in a study in our analysis were more common for older patients overall (1% for age ≥ 65 years *v* 0.2% for age < 65 years), but nearly half of deaths in older patients occurred in the metastatic setting and were likely related to disease progression. Less than 1% of older patients on adjuvant trials had death as the documented reason for therapy cessation.

Our results suggest that current strategies to increase enrollment of older adults to Alliance trials have had limited effectiveness. Although chemotherapy-based clinical trials targeting older women, such as CALGB 49907 and the local therapy trial CALGB 9343 (tamoxifen with or without radiation therapy for women undergoing breast conservation) have demonstrated the ability to accrue patients to large-scale, practice-changing trials on a national level, protocols dedicated to older patients remain few. Consequently, there has been new momentum to reassess how we approach accrual challenges across the cancer spectrum. Recently proposed, overarching strategies to improve prospective evidence have outlined strong recommendations for the following: (1) leverage trial designs by including

Table 4. Reasons for Study Therapy Cessation by Age for All Studies and by Trial Type

Reason for Going Off Study	All Ages, Total No. (%)	Age < 65 Years, No. (%)	Age ≥ 65 Years, No. (%)	*P*
All studies combined	13,763	11,336	2,427	< .001[1]
Adverse event	911 (6.6)	720 (6.4)	191 (7.9)	
Completed per protocol	8,481 (61.6)	7,267 (64.1)	1,214 (50.0)	
Death	43 (0.3)	19 (0.2)	24 (1.0)	
Disease progressed/new primary	1,274 (9.3)	994 (8.8)	280 (11.5)	
Never started	245 (1.8)	208 (1.8)	37 (1.5)	
Other disease; other therapy; other/missing	2,180 (15.9)	1,623 (14.3)	554 (22.9)	
Refused further treatment	616 (4.5)	494 (4.4)	122 (5.0)	
Adjuvant studies (n = 10,014)*				< .001
Adverse event	702 (7.0)	568 (6.7)	134 (8.8)	
Completed per protocol	7,981 (79.7)	6,806 (80.1)	1,175 (77.4)	
Death	21 (0.2)	8 (0.1)	13 (0.9)	
Disease progressed/new primary	86 (0.9)	75 (0.9)	11 (0.7)	
Never started	183 (1.8)	156 (1.8)	27 (1.8)	
Other disease; other therapy; other/missing	636 (6.4)	552 (6.5)	84 (5.5)	
Refused further treatment	405 (4.0)	330 (3.9)	75 (4.9)	
Neoadjuvant studies (n = 1,669)				.028
Adverse event	46 (2.8)	39 (3.1)	7 (1.7)	
Completed per protocol	493 (29.5)	456 (36.1)	37 (9.1)	
Disease progressed/new primary	12 (0.7)	11 (0.9)	1 (0.2)	
Never started	13 (0.8)	11 (0.9)	2 (0.5)	
Other disease; other therapy; other/missing	1,083 (64.9)	725 (57.4)	358 (88.0)	
Refused further treatment	22 (1.3)	20 (1.6)	2 (0.5)	
Metastatic studies† (n = 2,074)				< .001
Adverse event	163 (7.9)	113 (7.2)	50 (10.0)	
Completed per protocol	8 (0.4)	6 (0.4)	2 (0.4)	
Death	22 (1.1)	11 (0.7)	11 (2.2)	
Disease progressed/new primary	1,181 (56.9)	912 (57.9)	269 (54.0)	
Never started	50 (2.4)	41 (2.6)	9 (1.8)	
Other disease; other therapy; other/missing	461 (22.2)	349 (22.1)	112 (22.5)	
Refused further treatment	189 (9.1)	144 (9.1)	45 (9.0)	

*Excluding North Central Cancer Treatment Group (NCCTG) 89-30-52, Cancer and Leukemia Group B (CALGB) 8541, CALGB 9344, and CALGB 9342, for which this information was not available.
†Excluding CALGB 9342, for which this information was not available.

specific analyses of outcomes for older patients and (2) improve the research environment for enrollment (eg, nationally based incentives for enrolling older patients, improving the information collected for older patients).[23,30]

Additional ways to incorporate older patients[22] could include strategies that either mandate enrollment of a prespecified proportion or number of older patients in National Institutes of Health-supported studies or a dedicated "expansion cohort" of older patients where toxicity, functional decline, and outcomes can be closely monitored. An alternative strategy could require that all new National Clinical Trials Network (NCTN) protocols undergo review to ensure specific considerations and outcomes are included for older adults. Third, ensuring that clinical trials are extended to community sites rather than academic institutions will likely improve the appeal of clinical trials for older patients. With any of these approaches, we may not need to rely on dedicated clinical trials for older patients to gain prospective data. This would also reduce the need to pool clinical trial data from heterogeneous groups of patients to answer questions about the experiences, toxicities, and disease outcomes for older patients.[58,65]

We recognize several important limitations. We did not have information on the numbers of women approached or not approached, the characteristics of providers and practices, trial burden or requirements, or why patients did not enroll. Second, because the focus of our analysis was limited to Alliance systemic therapy trials, our results cannot be extrapolated across all breast cancer studies. Furthermore, we do not have information on how our results compare with those from other cooperative group settings or clinical trials in general, because of the lack of previously published data. Third, we did not have complete information on PS, reasons for therapy cessation, and tumor characteristics for some trials. Also, some tumor characteristics may be misclassified in some cases because they relied on previously collected data. Finally, interpretation of results from neoadjuvant trials may be limited by the smaller number of patients enrolled overall and the fact that two of these trials (CALGB 40603 and 40601) targeted patients with tumor subtypes that occur less frequently in older (*v* younger) patients.[66]

Despite these limitations, we were able to examine breast cancer systemic treatment trials over time on a national scale, further highlighting previous findings across all cancers[22,23] and identifying areas in urgent need of improvement within breast cancer NCTN trials. Our findings serve as an urgent call to action: Novel strategies for accrual of older patients to clinical trials are critical to meaningfully change the evidence-base for this growing group. The NCTN has the power to effect meaningful change on a national level with regard to the care of older patients with cancer and should seize this opportunity to forge a new path in clinical trial strategy.

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Appendix

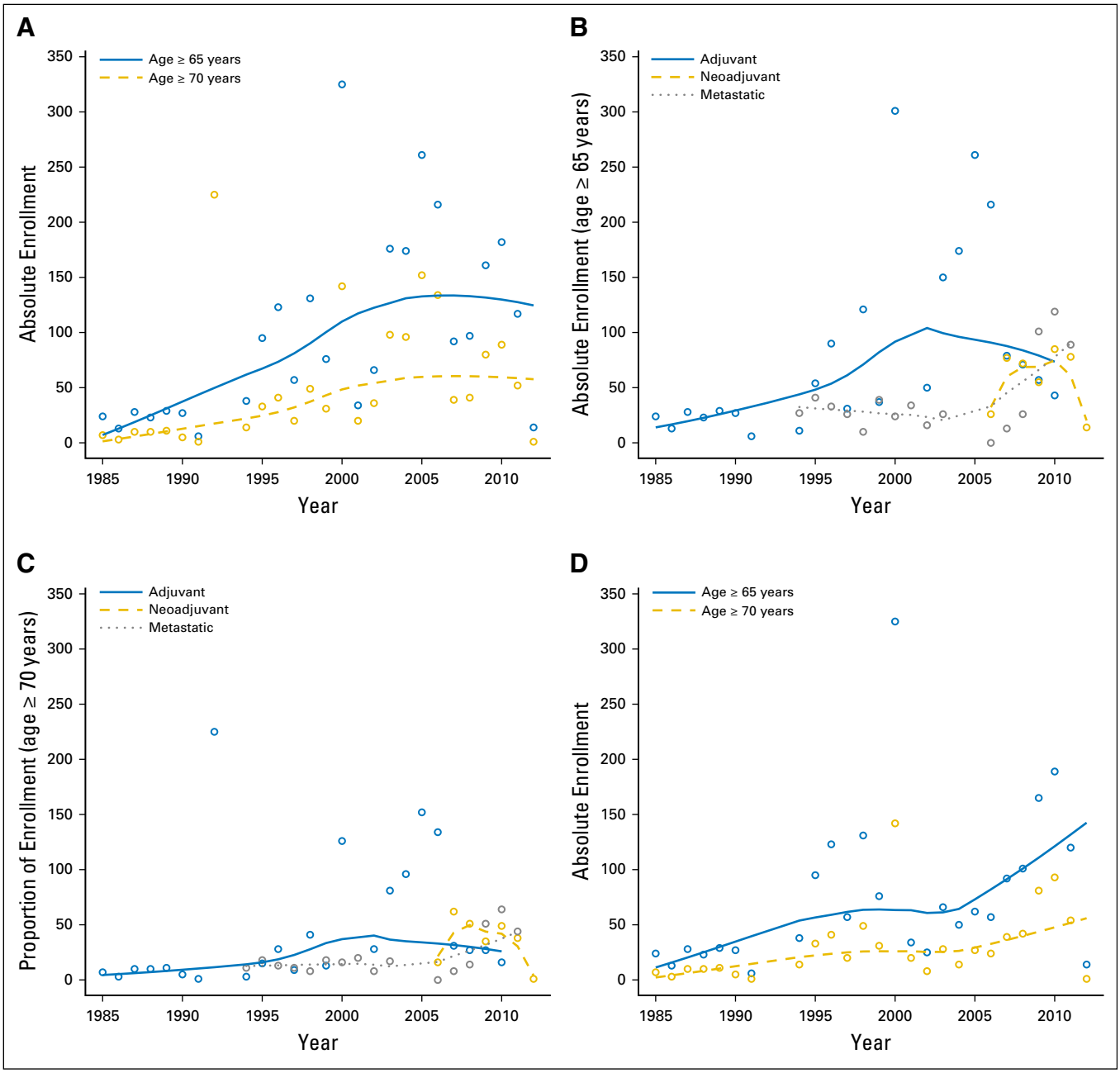

Fig A1. Absolute numbers of patients enrolled onto clinical trials for all patients age ≥ 65 years and age ≥ 70 years (A), by trial type for age ≥ 65 years and ≥ 70 years (B, C), and after exclusion of Cancer and Leukemia Group B (CALGB) 49907, North Central Cancer Treatment Group (NCCTG) 89-30-52, and American College of Surgeons Oncology Group (ACOSOG) Z1031 (D).