Endocrine Therapy Plus Anti-HER2 Therapy as Adjuvant Systemic Therapy for Luminal HER2-Positive Breast Cancer: An Analysis of the National Cancer Database

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ABSTRACT

BACKGROUND: Guidelines regarding the usage of adjuvant systemic therapy in patients with small human epidermal growth factor receptor 2 (HER2)-positive and estrogen receptor/progesterone receptor–positive (luminal HER2 positive) tumors are nonspecific. Outcomes of chemotherapy followed by endocrine therapy (ET), with or without anti-HER2 therapy, vs ET alone (no chemotherapy) have not been widely studied in this disease subtype. We sought to examine the usage and outcomes of adjuvant systemic therapy (ET vs chemotherapy with or without trastuzumab) in stage I luminal HER2-positive breast cancer (BC), based on the large National Cancer Database.

METHODS: We conducted a retrospective analysis of patients with luminal HER2-positive stage I BC, diagnosed between 2010 and 2015, in the United States, using univariable and multivariable logistic regression analyses. The Kaplan-Meier method estimated overall survival (OS).

RESULTS: A total of 37 777 patients were included in the analysis; of these, n = 32 594 (86%) received adjuvant ET and n = 5183 (14%) received chemotherapy. Around 40% of all patients received anti-HER2 therapy (trastuzumab). Patients who received trastuzumab had a better 5-year OS (93.4% vs 92.0%, $P = .0002$) compared with those who did not. Patients who received anti-HER2 therapy plus ET had the best OS rate at 5 years (93.5%, confidence interval [CI]: 89.2%-98%, $P < .0001$) compared with those receiving anti-HER2 therapy plus chemotherapy (92.7%, CI: 89.4%-96.1%, $P < .0001$).

CONCLUSIONS: Most patients in the United States, with stage I luminal HER2 positive BC, received ET, not chemotherapy but most of them do not receive anti-HER2 therapy resulting in inferior outcome. Future trials exploring the de-escalation of systemic adjuvant therapy for early-stage luminal HER2-positive BC to ET plus anti-HER2 therapy would be desirable.

KEYWORDS: Breast cancer, early stage, adjuvant therapy, anti-HER2, survivorship

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Background

The incidence of small, node-negative breast tumors continues to grow significantly as an overall proportion of invasive breast cancer (BC) diagnoses. Approximately half of human epidermal growth factor receptor 2 (HER2)-positive tumors also express hormone receptors (HRs), estrogen receptors (ERs), or progesterone receptors (PgRs), making these malignancies favorable targets for adjuvant therapy.[1] Recently, the addition of humanized monoclonal anti-HER2 antibody (trastuzumab) to chemotherapy regimens, for treatment of early-stage BC, has shown improved survival.[2-5] However, patients with small node-negative breast tumors, who present with HER2-positive disease subtypes, were predominantly *excluded* from these pivotal adjuvant trastuzumab trials. Yet, because they remain at increased risk of recurrence, they are still offered systemic adjuvant therapy.[6,7]

Patients with early-stage disease often undergo chemotherapy with prolonged treatment using an anti-HER2 regimen.[1,8,9] In addition, systemic treatment recommendations are constantly evolving as clinical management continues to progress toward more individualized therapy.[3,10] Due to the uncertain benefit of trastuzumab therapy in the HER2-positive subgroup, 2019 national guidelines recommend either (1) adjuvant endocrine therapy (ET) without trastuzumab or (2) adjuvant chemotherapy with trastuzumab, subsequently followed by ET, for PT1cPN0/PN1mi HR-positive or HER2-positive disease.[11] However, the benefit of chemotherapy with trastuzumab for all node-negative HER2+ tumors <1 cm is unknown due to a current lack of information from clinical trials and historical cohort studies which examine risk of relapse for pT1a and pT1b tumors.

Preferred usage and clinical outcomes of adjuvant systemic therapy (ET vs cytotoxic chemotherapy), in small HER2-positive and ER/PgR-positive (luminal HER2 positive) tumors, remain unclear. Similarly, the benefit of adding anti-HER2 therapy to ET (with no chemotherapy) in the adjuvant setting remains understudied.

When cytotoxic chemotherapy is chosen as the first adjuvant treatment, guidelines are not specific regarding the type of chemotherapy provided, or whether it is best to administer single-agent (eg, weekly paclitaxel + trastuzumab) or multi-agent drugs (eg, TCH-docetaxel, carboplatin, trastuzumab). The St Gallen International Breast Cancer Conference panel previously recommended adjuvant chemotherapy and anti-HER2 therapy for HER2-positive, stage pT1b pN0 and higher BCs. However, it has recommended *against* routine adjuvant chemotherapy and anti-HER2 therapy for HER2-positive, stage pT1a pN0 disease. The decision of the panel was based on the consensus that the paclitaxel-trastuzumab regimen was sufficient for treatment of most stage I disease.[12,13]

A thorough understanding of current clinical practices, and potential disparities in treatment delivery, would greatly help identify knowledge gaps and new areas for research. Therefore, in this analysis, we sought to evaluate real-world clinical practice experiences in the treatment of early-stage, luminal HER2-positive BC. We identified patterns of variation and de-escalation in treatment delivery, as well as its impact on prognosis, using data from the National Cancer Database (NCDB), which captures an estimated 70% of all diagnosed malignancies in the United States, as reported by facilities participating in this registry.

Methods

Patient data

This retrospective study evaluated patients diagnosed with clinical or pathologic stage I BC, between January 2004 and January 2015, using de-identified data from the NCDB. The NCDB is a hospital-based registry, established as a joint project of both the American Cancer Society and the Commission on Cancer (CoC) of the American College of Surgeons. Approximately 1400 hospitals contribute data to the NCDB, and represent the source of the de-identified data used in this study, which was accessed based on a grant award (PI ZN). The study was approved by the Cleveland Clinic Institutional Review Board, and a waiver of informed consent was granted.

Records from women and men, with stage I BC, diagnosed and treated between 2010 and 2015, were identified within the NCDB output. Prior to 2010, HER2 information was not consistently captured; as such, we harvested data from the point of HER2 inclusion, onward. Individuals with a diagnosis of luminal HER2-positive BC (by immunohistochemical stains, fluorescence in situ hybridization [FISH], or both) were included in the analysis. We also extracted the treatment received, including chemotherapy, biologic therapy (which indicates anti-HER2 therapy [trastuzumab]), and/or ET.

In addition, complete data were assessed regarding the type of chemotherapy received (single-agent or multi-agent). The independent variables for this analysis included age (grouped by <50, 50-70, >70 years), sex, stage I (TNM, American Joint Committee on Cancer [AJCC]), year of diagnosis, Charlson-Deyo comorbidity score (0-3), diagnosis of HER2 (immunohistochemistry, FISH, or both), adjuvant first-line treatment (ET vs chemotherapy), chemotherapy type (single, multiple), anti-HER2 therapy (yes, no), race/ethnicity groups (white, African American, Asian, Hispanic/Latinos, Native Americans, Others), distance from treatment center—divided into 4 quartiles (4 miles, 4-9 miles, 9-18 miles, or >18 miles), facility type (academic/research, community cancer, or comprehensive community program), insurance type (private insurance, government-provided insurance [including Medicaid and Medicare, Tricare Health/Veterans Affairs], or not insured), and income level—divided into quartiles based on national census data (<38K, 38-68K, ⩾68K). In addition, type of therapy received was stratified by tumor size (T1a/T1b or T1c).

Statistical analysis

Descriptive statistics were used to summarize patterns of care regarding the use of systemic therapy (ET, chemotherapy), type of chemotherapy (single, combination), and anti-HER2 therapy, as well as other variables including facility type. Univariable and multivariable logistic regression analyses were used to identify factors that correlated with first treatment received (ET vs chemotherapy). Overall survival (OS) was estimated by the Kaplan-Meier method, and stratified groups were compared using the log-rank test. All tests were 2-sided and *P* values of .05 or less were considered statistically significant. Statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.4 (R Foundation, Vienna, Austria).

Results

The study included a total of n = 37 777 patients with pathologic stage I (AJCC seventh edition), luminal HER2-positive BC. Within this data set, n = 37 527 (99%) patients were women and 250 (1%) patients were men. Patient and tumor characteristics are shown in Table 1. Patient ethnicity was distributed as follows: white 79%, African Americans 10%, Hispanic/Latinos 5%, Asian Americans 4%, Native Americans 0.26%, Others 0.48%, and Unknown 0.67%. Age groups were distributed as follows: 56.8% were between 50 and 70 years, 25.7% younger than 50 years, and 17.5% older than 70 years.

When evaluating the adjuvant therapy received (Table 2), n = 32 594 (86%) of patients were treated with ET not with chemotherapy, and 5183 (14%) received chemotherapy—883 received a single-agent chemotherapy, 3883 received multi-agent chemotherapy, and 417 were listed as chemotherapy type unknown. In this data set, 14 849 (39%) of patients overall received anti-HER2 therapy; 2412 (6%) patients received

Table 1. Characteristics of patients with luminal HER2-positive stage I breast cancer.

	NCDB TREATMENT GROUP		ALL
	CHEMOTHERAPY	ENDOCRINE THERAPY	–
	N (%)	N (%)	N (%)
Biomarker status			
ER–/PgR+/HER2+	375 (44.91)	460 (55.09)	835 (2.21)
ER+/PgR–/HER2+	1529 (17.18)	7369 (82.82)	8898 (23.55)
ER+/PgR+/HER2+	3279 (11.69)	24 765 (88.31)	28 044 (74.24)
Chemotherapy			
No chemotherapy	417 (1.26)	32 594 (98.74)	33 011 (87.38)
Single agent	883 (100)	0 (0)	883 (2.34)
Multi-agents	3883 (100)	0 (0)	3883 (10.28)
Trastuzumab (anti-HER2)			
Unknown	41 (29.5)	98 (70.5)	139 (0.37)
No	2730 (11.98)	20 059 (88.02)	22 789 (60.33)
Yes	2412 (16.24)	12 437 (83.76)	14 849 (39.31)
Age			
<50	1483 (15.29)	8214 (84.71)	9697 (25.67)
50 to 70	3039 (14.17)	18 412 (85.83)	21 451 (56.78)
>70	661 (9.97)	5968 (90.03)	6629 (17.55)
Sex			
Female	5131 (13.67)	32 396 (86.33)	37 527 (99.34)
Male	52 (20.8)	198 (79.2)	250 (0.66)
Grade			
Unknown	304 (13.19)	2000 (86.81)	2304 (6.1)
Poorly/Undifferentiated/Anaplastic	2335 (15.81)	12 437 (84.19)	14 772 (39.1)
Well/Moderately differentiated	2544 (12.29)	18 157 (87.71)	20 701 (54.8)
Charlson-Deyo score			
0	4472 (13.9)	27 705 (86.1)	32 177 (85.18)
1	606 (12.98)	4063 (87.02)	4669 (12.36)
2	82 (11.26)	646 (88.74)	728 (1.93)
⩾3	23 (11.33)	180 (88.67)	203 (0.54)
Race			
Unknown	41 (16.14)	213 (83.86)	254 (0.67)
African American	567 (14.79)	3267 (85.21)	3834 (10.15)
Asian	216 (14.01)	1326 (85.99)	1542 (4.08)
Hispanic/Latinos	337 (16.85)	1663 (83.15)	2000 (5.29)

(Continued)

Table 1. (Continued)

	NCDB TREATMENT GROUP		ALL
	CHEMOTHERAPY	ENDOCRINE THERAPY	–
	N (%)	N (%)	N (%)
Native American	13 (13)	87 (87)	100 (0.26)
Others	31 (17.22)	149 (82.78)	180 (0.48)
White	3978 (13.32)	25 889 (86.68)	29 867 (79.06)
Insurance			
Others	87 (20.14)	345 (79.86)	432 (1.14)
Government	1782 (12.55)	12 415 (87.45)	14 197 (37.58)
Not insured	110 (17.83)	507 (82.17)	617 (1.63)
Private	3204 (14.22)	19 327 (85.78)	22 531 (59.64)
Income			
Unknown	12 (12.24)	86 (87.76)	98 (0.26)
<38K	753 (14.63)	4395 (85.37)	5148 (13.63)
38 to 62K	2374 (13.39)	15 358 (86.61)	17 732 (46.94)
⩾68K	2044 (13.81)	12 755 (86.19)	14 799 (39.17)
Cancer center type			
Others	830 (13.09)	5513 (86.91)	6343 (16.79)
Community cancer program	500 (13.67)	3158 (86.33)	3658 (9.68)
Comprehensive community cancer program	2342 (14.21)	14 140 (85.79)	16 482 (43.63)
Academic/Research program	1511 (13.38)	9783 (86.62)	11 294 (29.9)
Distance to facility (miles)			
<4	1120 (13.45)	7208 (86.55)	8328 (22.05)
4 to 9	1478 (14.35)	8819 (85.65)	10 297 (27.26)
9 to 18	1256 (13.53)	8026 (86.47)	9282 (24.57)
⩾18	1329 (13.47)	8541 (86.53)	9870 (26.13)
Year of diagnosis			
2010	688 (13.48)	4414 (86.52)	5102 (13.51)
2011	656 (11.95)	4833 (88.05)	54 891 (4.53)
2012	747 (12.91)	5040 (87.09)	5787 (15.32)
2013	871 (13.54)	5560 (86.46)	6431 (17.02)
2014	979 (13.08)	6507 (86.92)	7486 (19.82)
2015	1242 (16.6)	6240 (83.4)	7482 (19.81)
Subtotal	5183 (13.72)	32 594 (86.28)	37 777 (100)

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; NCDB, National Cancer Database; PgR, progesterone receptor.

Table 2. Treatment distribution characteristics of patients with luminal HER2-positive stage I breast cancer.

ADJUVANT TREATMENT	N	%
Unknown	139	0.37
Chemotherapy with anti-HER2	2412	6.38
Chemotherapy with no anti-HER2	2730	7.23
ET with anti-HER2 and no chemotherapy	12437	32.92
ET with no anti-HER2 and no chemotherapy	20059	53.10
Total	37777	100

Abbreviations: ET, endocrine therapy; HER2, human epidermal growth factor receptor 2.

chemotherapy + anti-HER2, and 12437 (32%) patients received hormone therapy + anti-HER2. In addition, 20059 (53%) patients received ET alone, without chemotherapy or anti-HER2 therapy. Of all patients with pathologic stage I disease who received chemotherapy (n = 5142), 17% received a single-agent chemotherapy, 75% of patients received multiagent chemotherapy, and 8% were indicated as "unknown." Of 9961 patients diagnosed at either a pathologic TNM stage T1aN0M0 or T1bN0M0, 16% patients received adjuvant chemotherapy, while 84% received no chemotherapy.

With respect to insurance and payer type, 38% of patients had government-provided insurance, 60% had private insurance, and 2% were listed as "not insured." In addition, 44% were treated in a comprehensive community cancer program, 10% in a community cancer program, and 30% in an academic/research program, per the NCDB designation.

In univariable logistic analysis, patients older than 70 years had a significantly higher chance of receiving ET not chemotherapy ($P < .0001$). Male patients had a significantly higher chance of receiving chemotherapy compared with women ($P = .01$). Patients with poorly differentiated cancer had a higher chance of receiving chemotherapy ($P < .0001$). African American and Hispanic patients were significantly less likely to be treated by ET ($P = .005$ and $P = .0001$, respectively). Treatment choice was not significantly associated with the year of diagnosis.

Results of the multivariable logistic regression analysis are shown in Table 3. Patients older than 70 years had a significantly higher chance of receiving adjuvant ET not chemotherapy, when compared with patients younger than 70 years ($P < .0001$). Male patients had significantly higher chance of receiving chemotherapy compared with female patients ($P = .003$). Patients with poorly differentiated tumors had significantly higher chance of receiving chemotherapy ($P < .0001$). Patients who did not receive anti-HER2 therapy were more likely to be treated with ET. Academic centers were significantly more likely to treat patients with ET, not chemotherapy, compared with community cancer centers ($P = .002$).

The OS data were available for n = 28643 patients. The OS rate at 5 years was 92% (95% confidence interval [CI]: 0.918-0.928). Median OS was not reached. Median follow-up of patients reported alive was 34.6 months (range: 0.01-82.6 months). The OS plots, by factor, were as follows: Figure 1A shows OS for all patients with stage I BC and the 5-year OS rate was 92.3% (CI: 91.8-92.8). Figure 1B shows Kaplan-Meier estimated OS by anti-HER2 therapy group. Patients treated by anti-HER2 therapy had a small but significantly better OS ($P = .0002$) compared with those who were not treated with anti-HER2 therapy (5-year OS rates, 93.4% vs 92%, $P = .0002$). Figure 1C illustrates the small but statistically significant difference noted between the 2 main groups, favoring the nonchemotherapy group: 5-year OS rates of 91% (CI: 89.6%-92.4%) for those who received adjuvant chemotherapy and 92.5% (CI: 91.9%-93%), $P < .0001$, for those who received adjuvant ET. Figure 1D illustrates the comparison among all 4 treatment groups. Patients who received anti-HER2 therapy plus ET had a small but statistically significant increased OS rate at 5 years, 93.5% (CI: 89.2%-98%), compared with anti-HER2 therapy plus chemotherapy OS rate at 5 years, 92.7% (CI: 89.4%-96.1%), $P < .0001$.

When evaluating patient characteristics, older patients had significantly worse OS ($P < .0001$). Figure 2A shows that patients older than 70 years had significantly worse 5-year OS at 79.2%, compared with ages 50 to 70 years at 94% and <50 years at 96.9% ($P < .0001$). Kaplan-Meier analysis estimated OS by Charleson-Deyo score (Figure 2B) shows that patients with more comorbidities had significantly worse OS ($P < .0001$), as would be expected. Specifically, a higher Charlson-Deyo comorbidity score was associated with significantly decreased OS for those with a score of 3 with a 57.2% 5-year OS (CI: 5.9-71.4) compared with those with a score of 0 with a 93.5% 5-year OS (CI: 93%-94%). There were only 12 of 190 men compared with 1205 women (of 28629) Figure 2C shows Kaplan-Meier estimated OS by sex group. No significant difference was noted based on sex ($P = .12$). For men, 5-year OS was 92% (CI: 87.1-97.2) and for women, 5-year OS was 92.3% (CI: 91.8-92.8, $P = .1187$).

With respect to patient race/ethnicity, Figure 2D shows the Kaplan-Meier estimated OS, noting a significant difference between the groups with respect to OS ($P < .0001$). Asian and

Table 3. Univariable and corresponding multivariable logistic regression analysis results.

UNIVARIABLE REGRESSION RESULTS		
FACTOR	COMPARISON OF VARIABLES	OVERALL *P* VALUE
Age	(<50, 50-70) vs >70	<.0001*
Sex	Female vs Male	.01*
Grade	Poorly vs Well/Moderately differentiated	<.0001*
Charleson-Deyo score	(0, 1, 2) vs 3	.10
Race/Ethnicity	(All groups) vs white	.0006*
Year of diagnosis	(2010, 2011, 2012, 2013) vs 2014	.07
Trastuzumab	No vs Yes	<.0001
Insurance	(Not insured, Government) vs Private	<.0001*
Income	(<38K, 38-68K) vs ⩾68K	.25
Cancer center type	(Community, Comprehensive) vs Academic	.09
Distance to cancer center	(<4, 4-9, 9-18) vs ⩾18 miles	.23
MULTIVARIABLE REGRESSION RESULTS		
FACTOR	COMPARISON OF VARIABLES	*P*-VALUE
Age	<50 vs >70	<.0001*
	50 to 70 vs >70	<.0001*
Sex	Female vs Male	.003*
Grade	Poorly/Undifferentiated/Anaplastic vs Well/Moderately differentiated	<.0001*
Year of diagnosis	2010 vs 2014	.003*
	2011 vs 2014	.27
	2012 vs 2014	.02*
	2013 vs 2014	.35
Trastuzumab	No vs Yes	<.0001*
Center type	Community vs Academic	.25
	Comprehensive vs Academic	.002*

*indicates observed significance.

Hispanic groups showed longer OS than white and African American groups. Native Americans exhibited the worst OS as follows: the 5-year OS was the highest in Asian Americans at 98% (CI: 96.8%-99.3%), followed by Hispanic/Latino Americans 96.4% (CI: 94.8%-98%), African Americans 92% (CI: 90.7%-93.7%), and white 91.8% (CI: 91.2%-92.4%), while Native Americans had the lowest 5-year OS rate at 84% (CI: 76%-93%), $P < .001$ (Figure 2D).

Figure 3 shows survival based on patient demographics and insurance status. When analyzing OS by insurance groups, patients covered by government-provided insurance showed significantly worse OS than patients on private insurance or no insurance ($P < .0001$; Figure 3A). Patients using government-provided insurance had a significantly lower 5-year OS rate at 86.1% (CI: 91.2%-92.4%) compared with those with private insurance with OS 96.1% (CI: 95.6%-96.6%) and those categorized as not insured with OS 94.8% (CI: 91.8%-98%), $P < .0001$ (Figure 3A).

Kaplan-Meier estimated OS by income group (Figure 3B) showed patients from lower income communities had significantly worse OS ($P < .0001$). Specifically, patients in the higher income group (⩾68K) had a significantly higher 5-year OS at 94.2% (CI: 93.4-94.9) compared with those with the lowest income (<38K) with 5-year OS at 90.4% (CI: 89-91.8),

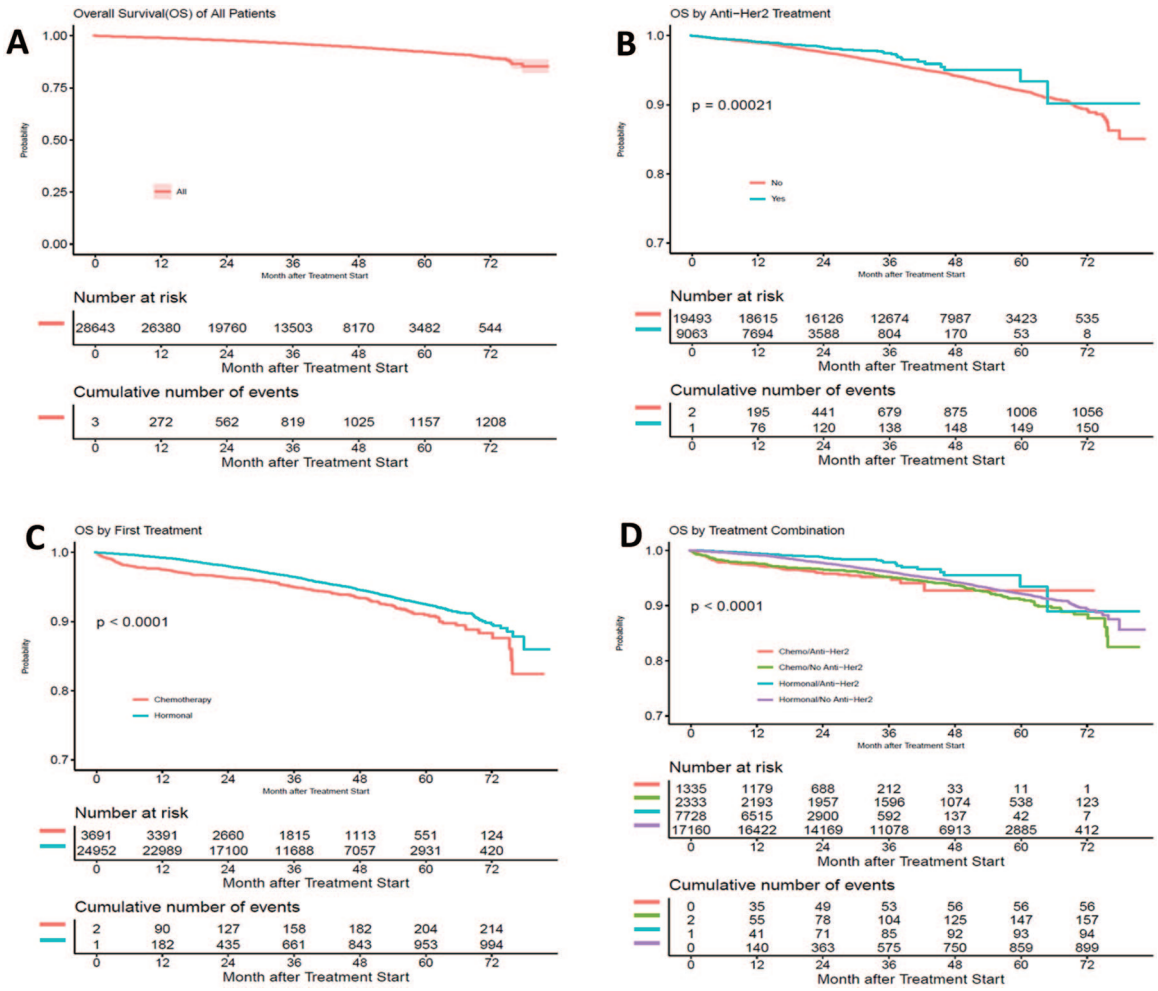

Figure 1. (A) Kaplan-Meier estimated overall survival of all stage I breast cancer. Kaplan-Meier estimated overall survival by the treatment group: (B) adjuvant chemo vs adjuvant endocrine/nonchemo group, (C) anti-HER2 group vs non anti-HER2, and (D) combination therapy.

$P < .0001$ (Figure 3B). Kaplan-Meier estimated OS by cancer center type is shown in Figure 3C. Patients treated at academic/research cancer centers had significantly better OS ($P < .0001$) as follows: patients treated in an academic/research program had the best 5-year OS at 93.8% (CI: 93%-94.6%) followed by comprehensive community cancer programs with 5-year OS at 91% (CI: 90.2%-91.8%) and community cancer programs with 5-year OS at 90.8% (CI: 89%-92.6%), $P < .0001$ (Figure 3C). There was no significant difference in OS between the year of diagnosis ($P = .22$). Also, no significant difference was noted based on the tumor grade for all stage I groups ($P = .66$).

To control for possible confounders, propensity score matching was performed between the chemo-first and hormone-first group. Matching was conducted using age, sex, T1 subgroup (ie, tumor size), lymph node status, and grade (Table 4). A Cox proportional hazard model was used with matching variables as stratification factors. The hazard ratio (HZR) of chemotherapy vs hormone therapy was 1.78 (95% CI: 1.44-2.20, $P < .0001$) by matched analysis. These findings indicate that patients treated with chemotherapy first exhibited significantly worse OS than those treated with hormone therapy first (Table 5). This effect is similar to the results observed without matching (HZR = 1.76, 95% CI: 1.48-2.08, $P < .0001$).

Discussion

This analysis of a large national database (NCDB) provides an updated understanding of current real-world clinical practices, preferred treatment approaches, and early survival outcomes for patients with node-negative, early-stage, luminal HER2-positive BC. Most patients in the United States received adjuvant ET alone, not chemotherapy, as reported in this setting based on the NCDB (database output estimated to capture 70% of all diagnosed malignancies).

As expected, our data confirmed that patients treated with anti-HER2 therapy had a significantly better OS compared with those who did not receive anti-HER2 therapy. Furthermore, this study suggests that patients who received anti-HER2 therapy plus ET exhibited a slightly increased OS rate compared with anti-HER2 therapy plus chemotherapy, supporting the clinical benefit of trastuzumab in combination with ET in this setting. However, it is important to note that the TH regimen paclitaxel and trastuzumab studied

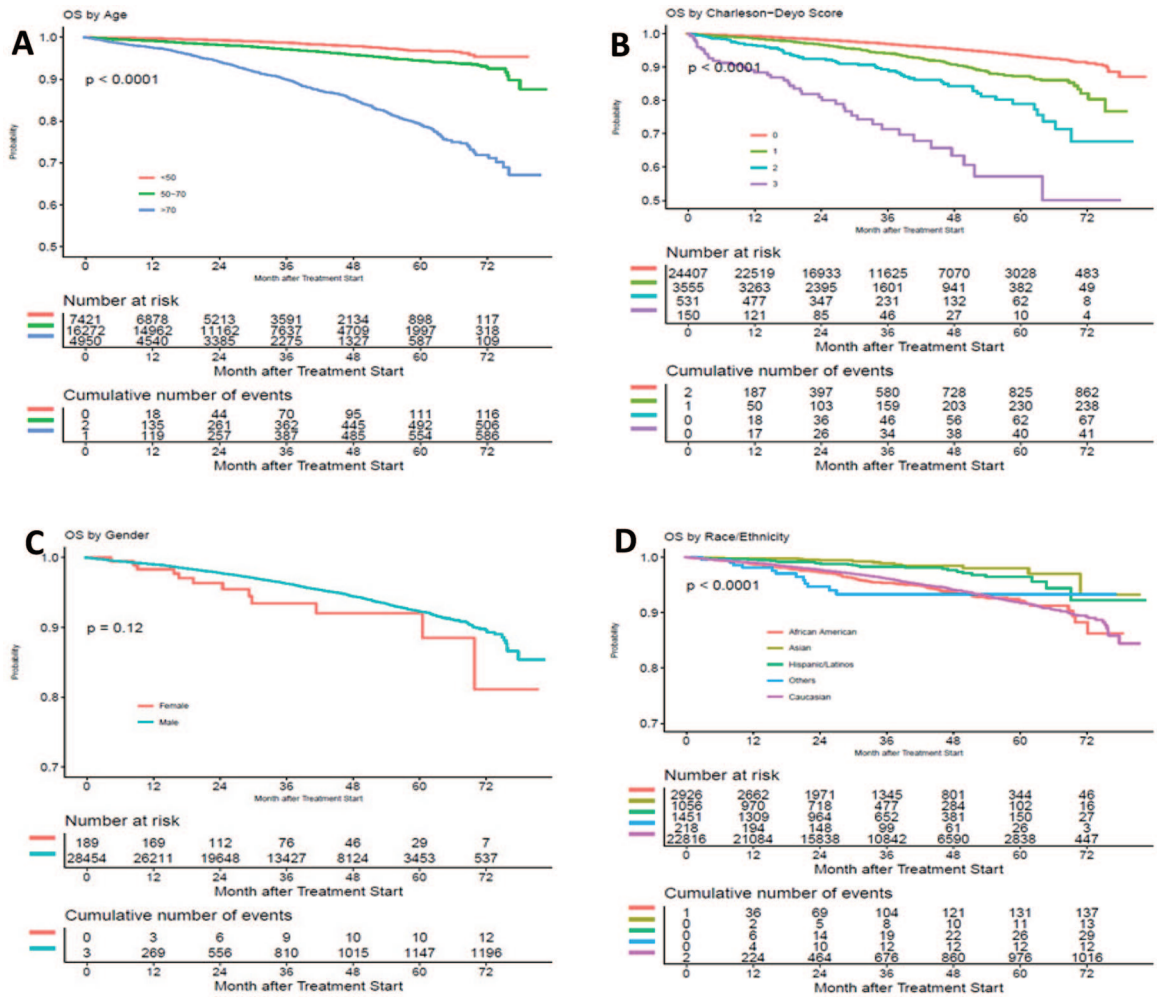

Figure 2. Kaplan-Meier estimated overall survival by patient characteristics: (A) age, (B) comorbidity, (C) sex, and (D) race/ethnicity. OS indicates overall survival.

in the APT trial[14] for use in T1, N0, M0 HER2+ cancer, and subsequently included in the National Comprehensive Cancer Network (NCCN[15]; and the recently released St Gallen guidelines),[13] was published in 2015. Thus, usage of this regimen likely increased after the time frame of our data set cut-off.

In the APT, single-arm trial, results showed that the combination of paclitaxel plus trastuzumab was associated with a low risk of disease recurrence and favorable outcomes (3-year disease-free survival: 98.7%), particularly in patients who were HR–. In addition, the ATEMPT trial indicated improved quality of life in an arm of patients treated with trastuzumab and cytotoxic emtansine (T-DM1) when compared with TH. These trials both indicate that a chemotherapy-immunotherapy combination may be associated with less adverse effects and could thus be a viable treatment option.[16]

Several clinical trials support our findings and the efficacy of trastuzumab in combination with ET. The TAnDEM trial was the first randomized, phase III study that combined hormonal agents with trastuzumab, without chemotherapy, for the management of HER2+/HR+ metastatic BC.[17] This study evaluated the progression-free survival (PFS) benefits of managing HER+/HR+ BC, in postmenopausal women, with an aromatase inhibitor (AI) and trastuzumab. Of note, ~60% had previously received ET; ~45% and ~30% had lung and liver metastasis, respectively. Combination therapy (trastuzumab plus anastrozole) resulted in a median PFS of 4.8 months vs 2.4 months in the anastrozole monotherapy group ($P = .0016$). In addition, the results of the TAnDEM trial demonstrated improvement in PFS and a trend toward prolonged OS in patients treated with trastuzumab plus anastrozole, vs anastrozole alone. These promising outcomes, associated with combination therapy, have since led to the initiation of additional clinical trials.

Our results revealed that those who received trastuzumab has a better 5-year OS compared with those who did not, emphasizing the survival benefits associated with the inhibition of the HER2 pathway. In the evaluation of luminal HER2-positive BC, the PERTAIN trial assessed the efficacy of pertuzumab plus trastuzumab in patients with metastatic BC who had received no prior systemic therapy, with the exception of ET.[18] The PERTAIN trial is the first controlled

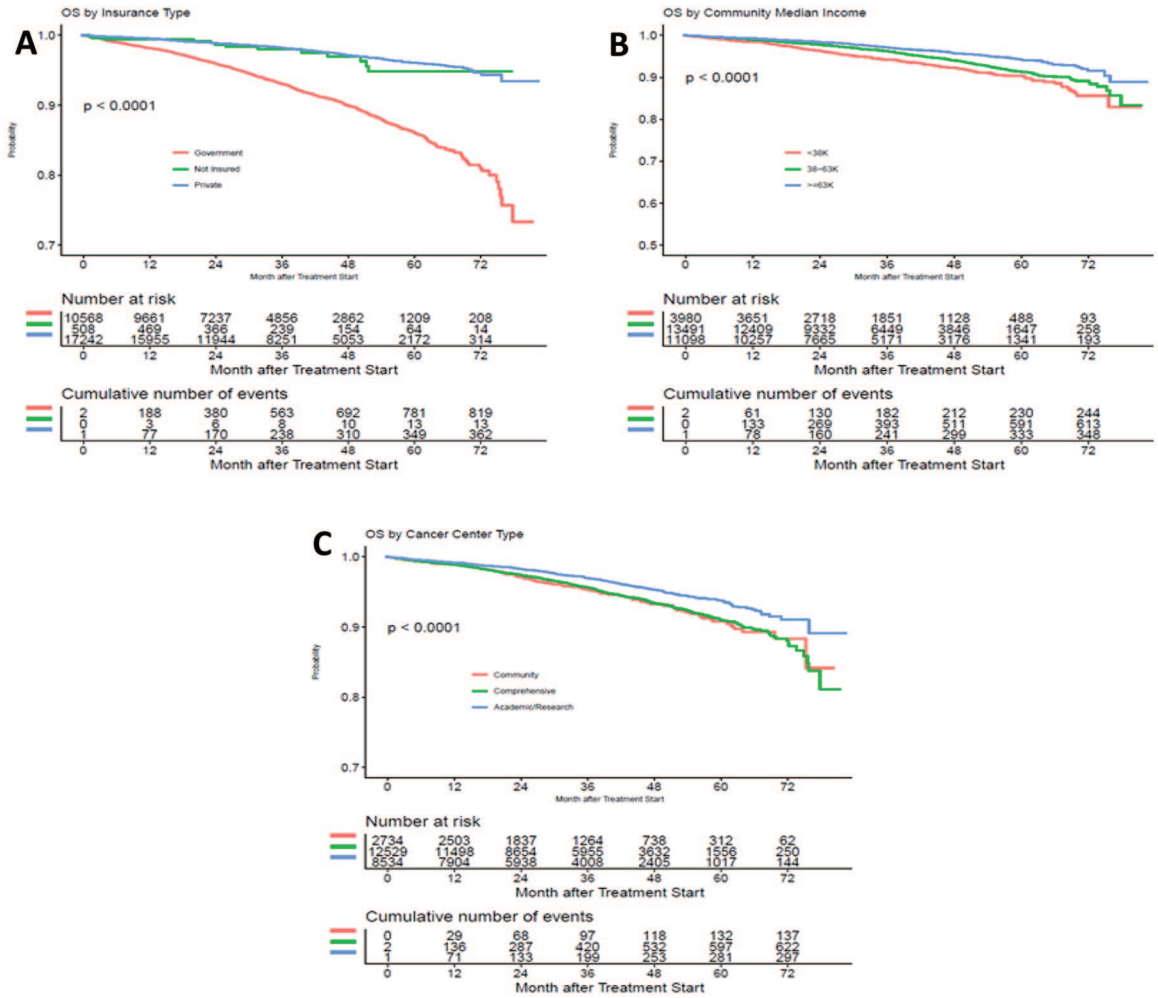

Figure 3. Overall survival by demographics: (A) insurance type, (B) income, and (C) cancer center type. OS indicates overall survival.

trial reporting the results of combining HER2-targeting, cytotoxic, and hormonal treatment simultaneously.[19] The median PFS for those receiving trastuzumab plus an AI plus pertuzumab (experimental arm) exceeded 27.1 months vs 15.1 months for patients with metastatic BC who received only trastuzumab plus an AI. The results of the PERTAIN trial offer significant hope for patients with metastatic BC, and have also led to additional clinical trials.

The ALTERNATIVE trial is a phase III clinical trial that assigned patients to treatment with lapatinib (which interrupts the HER2/neu and epidermal growth factor receptor pathway) plus trastuzumab and an AI (experimental arm), or trastuzumab plus an AI.[20] The PFS for patients with metastatic BC in the experimental arm was 11 months vs 5.7 months ($P = .0064$). The findings from this trial confirm the survival benefit of hormonal therapy plus an AI, in addition to highlighting the benefits of dual anti-HER2 therapy in the management of patients with metastatic BC.

The use of dual anti-HER2 therapy plus ET for BC has also proven beneficial in the preoperative setting. The PAMELA trial is a phase II trial of previously untreated HER2+ early BC patients. The study examined the prospect that those with HER2+ enriched BC subtypes received more benefit from dual HER2 blockade, without the implementation chemotherapy.[21] Patients either received lapatinib plus trastuzumab, or lapatinib plus trastuzumab plus letrozle if they were HER2+ (experimental arm). The PAMELA trial found that dual HER2 blockade led to a decrease in CCND1 mRNA in HER2+/HR+ breast tumors (experimental arm), suggesting that the combination therapy was more efficient at arresting the cell cycle and preventing tumor growth in patients with BC.[22]

Our study also discovered an association between insurance type and outcome; patients using government-provided insurance exhibited OS, when compared with patients using other types of insurance coverage. While these findings are likely a product of multiple sociodemographic and/or socioeconomic factors and require further exploration, they appear consistent with previously reported literature suggesting that patients with Medicaid had higher mortality rates than privately insured patients following colorectal cancer surgery,[23] and that primary payer status affects patient mortality for most major cancer surgical operations.[24] On analyzing 893 658 major surgical operations from 2003 to 2007, LaPar

Table 4. Summary of matched cohort by matching factors.

	FIRST TREATMENT				*P* VALUE
	CHEMO		HORMONE		
	N	%	N	%	
Age					
<50	888	20.12	3525	79.88	.88
50 to 70	2012	19.88	8108	80.12	
>70	450	20.30	1767	79.70	
Sex					
Female	3311	19.96	13279	80.04	.16
Male	39	24.38	121	75.63	
T1 subgroup					
T1a/b N0	1475	19.92	5930	80.08	.82
T1c	1875	20.06	7470	79.94	
Lymph Node status					
Negative	3129	20.01	12507	79.99	.89
Positive	221	19.84	893	80.16	
Grade					
Poorly differentiated, undifferentiated, anaplastic	1606	20.08	6391	79.92	.80
Well/Moderately differentiated	1744	19.92	7009	80.08	

Abbreviation: LN, lymph node.
Chemo:Hormone ratio = 1:4. *P* values were obtained by the chi-square test.

Table 5. Treatment regimen usage, by stage.

		T1 STAGE			
		T1A/B N0		T1C	
		N	%	N	%
First treatment	Anti-HER2				
Chemo	No	866	8.72	1092	5.82
	Yes	744	7.49	967	5.15
	All	1610	16.22	2059	10.96
Hormone	Anti-HER2				
	No	5567	56.07	9616	51.21
	Yes	2752	27.72	7103	37.83
	All	8319	83.78	16719	89.04
All		9929	100.00	18778	100.00

Abbreviation: HER2, human epidermal growth factor receptor 2.

et al[24] found that Medicaid insurance status confers an increased risk-adjusted mortality. The role of socioeconomic factors, such as the type of insurance used, has influenced health policy for years.[25,26] Therefore, future research, examining additional socioeconomic characteristics of patients with government-based insurance, is needed to identify

confounding factors that might be directly related to prognosis, including poverty and decreased access to care.

Patients treated at academic/research cancer centers appeared to have a significantly better survival compared with patients treated in community centers. This also warrants further evaluation in future studies, and perhaps evaluation of adherence to guidelines and measures to improve the implementation of standardized treatment pathways in all CoC-accredited cancer centers. Similar findings have been previously reported in a variety of cancer types. In analyzing the patient records of 27 120 patients with intrahepatic cholangiocarcinoma, Wu et al[27] found that patients who received treatment at academic cancer centers had improved OS. Similarly, Lassig et al[28] found that patients with head and neck cancer, with similar treatment breaks and treatment completion, at both academic and community centers, had higher 5-year OS rates if they received treatment in an academic setting. In addition, after the examination of 138 019 patients in the NCDB, diagnosed with nonmetastatic, high-risk prostate cancer, Mahal et al[29] found that the likelihood of receiving definite therapy was higher at academic vs community centers. Through further analysis, they also discovered that African Americans and Hispanic patients were more likely to experience significant delays before receiving treatment, and were less likely to receive definitive therapy, when compared with non-Hispanic whites, across both academic and community centers.[29] These findings demonstrate that while academic cancer centers did perform better than community cancer centers, academic centers may not be outperforming community cancer centers in treating patients among nonwhite, racial, and ethnic minority populations.

In this study, no significant variation in outcome among ethnic and racial groups was noted, possibly due to the short follow-up in this early-stage cohort. In focusing on patients with HER2 status reported in the NCDB, our follow-up period and survivor analysis was limited to 5 years (2010-2015). However, the significantly increased OS in Asian Americans, and worse OS in Native Americans compared with other ethnic and racial groups with early-stage BC, is of interest and calls for further evaluation of the underlying social risk factors and interplay of other potential comorbidities in these groups (eg, diabetes and lifestyle habits).

The strengths of our study included the following: (1) an analysis of data extracted from a large, national database, reflecting real-world practices in the United States, with the inclusion of relatively standardized methods of documentation from centers that have received accreditation by the American College of Surgeons CoC; (2) the data were based on documented treatment records with less than 3% of missing/unknown treatment data; and (3) the study has practical, clinical implications and revealed most patients analyzed are receiving a suboptimal treatment consisting of ET without anti-HER2 therapy. A preferred approach for those patients who are not provided chemotherapy and who have no contraindication to anti-HER2 therapy is likely a combination of ET plus trastuzumab. A randomized controlled trial is warranted to explore these adjuvant nonchemotherapy options in women with early-stage, luminal HER2-positive BC.

The limitations of this study include the following: (1) the general restrictions of any retrospective de-identified database analysis that is subject to the accuracy of documentation provided by the individual participating facilities; (2) the relatively short follow-up interval available due to the implementation of HER2 data reporting only since the year 2010 through 2015 in CoC sites, thus limiting a longer term survival analysis; (3) OS was based on the records with complete staging data; however, around 23% of records noted unknown AJCC clinical stage and 16% unknown pathologic AJCC stage; and (4) not having patient information on PFS in the NCDB data set.

Conclusions

This study provides real-world data that advance our understanding of the current clinical practices and preferred treatment approaches for patients with node-negative, early-stage luminal HER2-positive BC, as practiced in most facilities in the United States. This study supports the consideration of combining anti-HER2 therapy (trastuzumab) with ET in patients with small, node-negative, luminal HER2-positive BC, to mitigate chemotherapy side effects in the setting of longer follow-up. Future studies focusing on identifying subsets of patients with early-stage, luminal HER2-positive BC, who would derive a significant benefit from adjuvant chemotherapy, would be desirable. The relatively common practice, as shown in this analysis, of treating patients with ET without an anti-HER2 agent is likely to yield an inferior outcome compared with chemotherapy or ET plus anti-HER2 therapy. De-escalating systemic adjuvant therapy for luminal HER2-positive BCs to ET plus anti-HER2 therapy (with no chemotherapy) would be desirable and aligned with the current clinical practice, particularly when longer follow-up and more robust temporal analysis can be achieved. The possible disparity in outcomes based on treatment facility (academic vs community) and insurance status (government-provided vs others), albeit small, also warrants further evaluation.

Authors' Note

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Author Contributions

ZAN and CNB are major contributors in writing the manuscript and design, EBE participated in writing the manuscript, LCE participated in writing the manuscript and data interpretation, BH participated in design, participated in manuscript writing, and conducted statistics. WW participated in manuscript writing and conducted statistics. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Ethical approval was obtained from the Cleveland Clinic Institutional Review Board prior to conducting this study. All patient data were strictly de-identified and provided, with approval, from the American College of Surgeons as part of the National Cancer Database.

Consent for Publication

No individual person's data included; all data are reported in an aggregate manner.

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Availability of Data and Material

The data that support the findings of this study are available from the American College of Surgeons/American Cancer Society but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors on reasonable request and with permission of the American College of Surgeons/American Cancer Society.

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