Long-Term Follow-Up of the Anthracyclines in Early Breast Cancer Trials (USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 [NRG Oncology])

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ABSTRACT

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

The primary joint efficacy analysis of the Anthracyclines in Early Breast Cancer (ABC) trials reported in 2017 failed to demonstrate nonanthracycline adjuvant therapy was noninferior to anthracycline-based regimens in high-risk, early breast cancer. Full analyses of the studies had proceeded when the prespecified futility boundary was crossed at a planned futility analysis for the ability to demonstrate noninferiority of a nonanthracycline regimen with continued follow-up. These results were presented with 3.3 years of median follow-up. This manuscript reports results of the final analyses of the study efficacy end points conducted with 6.9 years of median follow-up. Long-term analysis of invasive disease-free survival (IDFS), the primary end point of the ABC trials, remains consistent with the original results, as noninferiority of the nonanthracycline regimens could not be declared on the basis of the original criteria. The secondary end point of recurrence-free interval, which excluded deaths not due to breast cancer as events, favored anthracycline-based regimens, and tests for heterogeneity were significant for hormone receptor status ($P = .02$) favoring anthracycline regimens for the hormone receptor–negative cohorts. There was no difference in overall survival, and review of the type of IDFS events in the groups suggested reductions in cancer recurrences achieved with anthracycline regimens were offset by late leukemias and deaths unrelated to breast cancer.

ACCOMPANYING CONTENT

Data Supplement

Protocol

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INTRODUCTION

The aim of the joint analysis of the Anthracyclines in Early Breast Cancer (ABC) trials was to determine if six cycles of docetaxel with cyclophosphamide (TC6) was noninferior to standard regimens of docetaxel or paclitaxel with cyclophosphamide and doxorubicin (TaxAC). A hazard ratio (HR) for invasive disease-free survival (IDFS) of 1.18 was the prespecified margin of inferiority. The ABC trials were three sequential adjuvant trials that randomly assigned women to receive TC6 or TaxAC. The definitive analysis was planned when 668 IDFS events had been reported across the three trials, with a single interim analysis (IA) for futility when 50% of events required for the definitive analysis were reported. The IA conducted with a median follow-up of 3.3 years demonstrated an HR of 1.20, so the data monitoring committee recommended full analysis, which demonstrated TC6 was inferior to TaxAC (HR, 1.23).[1] Herein, with a median follow-up of 6.9 years and 731 IDFS events, we report updated results of IDFS and secondary end points of recurrence-free interval (RFI) and overall survival (OS).

METHODS

Study Design

Designs of the individual ABC trials and the joint analysis were reported previously.[1]

End Point Definitions

The primary end point was IDFS and secondary end points included RFI and OS. Definitions were provided previously.[1]

TABLE 1. Patient and Tumor Characteristics by Parent ABC Protocol Data as of September 30, 2020

Patient or Tumor Characteristic	USOR 06-090 (n = 1,287)	B-46-I/07132 (n = 1,051)	B-49 (n = 1,843)	Total (N = 4,181)	P[a]
Follow-up, years, median	9.4	6.5	6.7	6.9	NA
Age, years, %					
≤49	37	38	32	35	
50-59	38	35	35	36	<.0001
≥60	26	27	34	30	
Race, %					
White	88	83	84	85	
Black or African American	10	12	11	11	
Asian	2	2	2	2	<.0001
Other/unknown	1	3	3	2	
Ethnicity, %					
Hispanic or Latino	11	11	8	10	
Not Hispanic or Latino	89	85	90	88	<.0001
Unknown	0	4	2	2	
Hormonal receptor status, %					
ER- or PgR-positive	71	67	69	69	
ER- and PgR-negative	29	33	31	31	.15
No. of positive nodes, %					
0	35	38	46	40	
1-3	51	43	40	44	
4-9	11	14	11	11	<.0001
≥10	3	5	4	4	
Histologic grade, %					
Low	12	10	9	10	
Intermediate	38	37	36	37	
High	45	52	55	51	<.0001
Unknown	5	1	<0.5	2	

Abbreviations: ABC, anthracyclines in early breast cancer; ER, estrogen receptor; NA, not applicable; PgR, progesterone receptor.
[a]Chi-square test.

An HR >1.18 was predefined as demonstrating inferiority, corresponding to an absolute difference of ≥2% in the 5-year IDFS rate of TC6 relative to TaxAC, using a Cox model stratified for the parent trial, nodal status, and hormone receptor status. Noninferiority was to be tested at alpha 10% one-sided error, equivalent to an 80% CI for the IDFS HR, excluding 1.18 for the final analysis.[1]

Statistical Analysis

All patients with follow-up were analyzed according to randomized treatment assignment (intention to treat [ITT]). *P* values are two-sided (unless otherwise specified), not controlled for multiple comparisons, and are provided as a measure of strength of evidence. Time to event was measured from random assignment and time-to-event plots were estimated by the Kaplan-Meier (K-M) method.[2] HRs were estimated from stratified Cox models and *P* values for time to event were obtained from stratified log-rank tests. Strata used for analyses were parent trial, nodal status, and hormone receptor status, or the appropriate subset of factors for subset analyses. Fisher's exact or chi-square tests were used to test for differences in proportions.[3]

RESULTS

Patient Characteristics

Between May 2007 and November 2013, a total of 4,243 patients enrolled in the common arms of the three trials. Of these, 4,181 were analyzed, with 2,102 women assigned to TC6 and 2,079 to TaxAC (Data Supplement, Fig S1). Patient and tumor characteristics are described in Table 1. Median follow-up is 6.9 years for the combined studies. Although the distribution of characteristics differs statistically by protocol, absolute differences are small and not clinically relevant.

Update of the Primary End Point, IDFS

The observed HR for IDFS on the basis of ITT analysis using all available information through September 30, 2020, for TC6 versus TaxAC is 1.14. Figure 1A shows KM plots of IDFS.

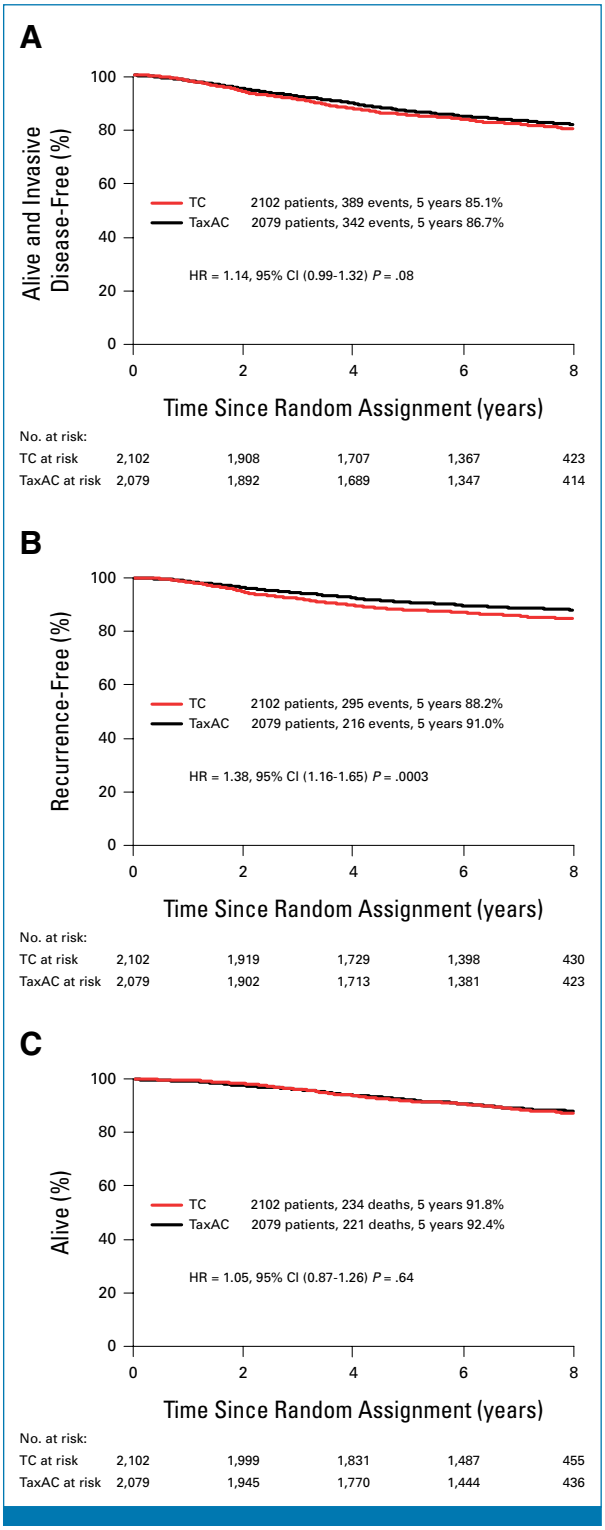

FIG 1. Kaplan-Meier plots of time-to-event: (A) IDFS, (B) RFI, and (C) OS. IDFS, invasive disease-free survival; OS, overall survival; RFI, recurrence-free interval; TaxAC, docetaxel or paclitaxel with cyclophosphamide and doxorubicin; TC, docetaxel with cyclophosphamide.

Five-year IDFS rates were 85.1% for TC6 and 86.7% for TaxAC. The 80% CI for the HR of 1.14 is 1.04 to 1.25, the upper boundary of which does not exclude the prespecified inferiority threshold of 1.18; therefore, noninferiority of TC6 was not demonstrated in the ITT population.

The Data Supplement (Table S2) provides number and type of IDFS first events by treatment. TaxAC significantly reduced any recurrence as a first event compared with TC6 (P = .0012) but was associated with increased leukemias (P = .03) and non–breast cancer deaths (P = .003). The Data Supplement (Table S3) summarizes reported causes of non–breast cancer deaths for 58 patients from B-46-I/07132 and B-49 as the first IDFS event. Deaths were numerically higher in the TaxAC arms for cardiac (8 *v* 3), neurologic (4 *v* 0), and unknown (18 *v* 8) causes, respectively. Cause of death data were not available for USOR 06090.

Secondary End Points

There is a statistically significant difference in RFI in favor of TaxAC, with 295 events in the TC6 group and 216 events in the TaxAC arms (HR, 1.38 [95% CI, 1.16 to 1.65]; P = .0003; Fig 1B). Five-year RFI rates were 88.2% for TC6 and 91.0% for TaxAC. However, there is no significant difference in OS with 234 deaths in the TC6 groups and 221 deaths in the TaxAC groups (HR, 1.05 [95% CI, 0.87 to 1.26]; P = .64; Fig 1C). Five-year OS rates are 91.8% and 92.4%, respectively.

Subset Analyses

Subset analyses are presented in Table 2 and the Data Supplement (Fig S1). Planned exploratory tests for treatment interaction by protocol, hormone receptor status, and nodal status were conducted along with race and histologic grade and were negative for IDFS (Data Supplement, Fig S1A) and OS (Data Supplement, Fig S1C) but significant (P = .02) for treatment by hormone receptor status interaction for RFI (Data Supplement, Fig S1B). The HR for RFI for TC6 versus TaxAC in the receptor-negative subset was 1.90 (95% CI, 1.39 to 2.61; P < .0001) demonstrating superiority for TaxAC. The HR for IDFS was 1.30 (95% CI, 1.02 to 1.67; P = .04) in the receptor-negative subset, also favoring TaxAC.

The Data Supplement (Table S4) provides results of exploratory subset analysis of nodal status by hormone receptor status with absolute 5-year point estimates for IDFS, RFI, and OS for each cohort.

DISCUSSION

Long-term analysis of IDFS, the primary end point of the ABC trials, remains consistent with the original analysis, although conclusions on the basis of prespecified criteria for demonstrating noninferiority of docetaxel with cyclophosphamide (TC) relative to TaxAC for each analysis were slightly different. The HR of 1.23 in the original analysis exceeded the prespecified HR of 1.18 for inferiority, consistent with the inferiority of TC6.[1] With 332 additional events for this analysis, the HR of 1.14 with an upper boundary of the 80% CI of 1.25 does not exclude the

TABLE 2. Subset Analyses: ABC Protocols

IDFS End Point

	Patients		Events				
	TaxAC	TC	TaxAC	TC	HR (95% CI)	*P*	Interaction *P* Value
Protocol[a]							
USOR 06-090	642	645	97	140	1.39 (1.07 to 1.80)	.01	
B-46-I/07132	522	529	75	88	1.21 (0.89 to 1.65)	.23	.11
B-49	915	928	170	161	0.96 (0.78 to 1.20)	.74	
Hormone receptor[a]							
Negative	657	647	114	139	1.30 (1.02 to 1.67)	.04	.21
Positive	1,422	1,455	228	250	1.06 (0.89 to 1.27)	.50	
Positive nodes[a]							
0	824	866	120	141	1.10 (0.86 to 1.40)	.45	
1-3	934	914	130	145	1.16 (0.91 to 1.47)	.23	.82
4+	321	322	92	103	1.14 (0.86 to 1.51)	.36	
Race[b]							
White	1,747	1,803	280	331	1.17 (1.0 to 1.37)	.06	.58
Black	223	238	43	50	1.09 (0.71 to 1.68)	.69	
Histologic grade[b]							
Low/intermediate	977	994	138	153	1.08 (0.86 to 1.36)	.51	.71
High	1,062	1,073	199	230	1.15 (0.95 to 1.39)	.15	
Overall	2,079	2,102	342	389	1.14 (0.99 to 1.32)	.08	

RFI End Point

	Patients		Events				
	TaxAC	TC	TaxAC	TC	HR (95% CI)	*P*	Interaction *P* Value
Protocol[a]							
USOR 06-090	642	645	61	111	1.76 (1.29 to 2.40)	.0003	
B-46-I/07132	522	529	50	68	1.40 (0.97 to 2.03)	.07	.13
B-49	915	928	105	116	1.15 (0.88 to 1.49)	.32	
Hormone receptor[a]							
Negative	657	647	62	107	1.90 (1.39 to 2.61)	<.0001	.02
Positive	1,422	1,455	154	188	1.19 (0.96 to 1.47)	.11	
Positive nodes[a]							
0	824	866	64	104	1.52 (1.11 to 2.07)	.008	
1-3	934	914	84	105	1.30 (0.97 to 1.73)	.08	.41
4+	321	322	68	86	1.29 (0.94 to 1.77)	.12	
Race[b]							
White	1,747	1,803	177	249	1.40 (1.15 to 1.70)	.0007	.87
Black	223	238	27	40	1.52 (0.90 to 2.54)	.11	
Histologic grade[b]							
Low/intermediate	977	994	86	110	1.23 (0.93 to 1.64)	.15	.41
High	1,062	1,073	127	181	1.44 (1.15 to 1.82)	.002	
Overall	2,079	2,102	216	295	1.38 (1.16 to 1.65)	.0003	

OS End Point

	Patients		Events				
	TaxAC	TC	TaxAC	TC	HR (95% CI)	*P*	Interaction *P* Value
Protocol[a]							
USOR 06-090	642	645	71	89	1.18 (0.87 to 1.62)	.29	
B-46-I/07132	522	529	45	58	1.27 (0.86 to 1.88)	.23	.21
B-49	915	928	105	87	0.85 (0.64 to 1.13)	.27	

(continued on following page)

TABLE 2. Subset Analyses: ABC Protocols (continued)

OS End Point	Patients		Events				
	TaxAC	TC	TaxAC	TC	HR (95% CI)	*P*	Interaction *P* Value
Hormone receptor[a]							
Negative	657	647	75	94	1.30 (0.96 to 1.77)	.09	.10
Positive	1,422	1,455	146	140	0.92 (0.73 to 1.16)	.49	
Positive nodes[a]							
0	824	866	76	84	1.01 (0.74 to 1.38)	.93	
1-3	934	914	77	80	1.08 (0.79 to 1.48)	.64	.92
4+	321	322	68	70	1.02 (0.73 to 1.43)	.90	
Race[b]							
White	1,747	1,803	181	196	1.06 (0.86 to 1.30)	.58	.94
Black	223	238	28	34	1.12 (0.66 to 1.90)	.67	
Histologic grade[b]							
Low/intermediate	977	994	78	80	0.98 (0.72 to 1.35)	.91	.84
High	1,062	1,073	141	150	1.03 (0.81 to 1.30)	.82	
Overall	2,079	2,102	221	234	1.05 (0.87 to 1.26)	.64	

Abbreviations: ABC, anthracyclines in early breast cancer; HR, hazard ratio; IDFS, invasive disease-free survival; OS, overall survival; RFI, recurrence-free interval; TaxAC, docetaxel or paclitaxel with cyclophosphamide and doxorubicin; TC, docetaxel with cyclophosphamide.
[a]Prespecified subset analysis.
[b]Exploratory subset analysis.

inferiority threshold of 1.18, so noninferiority of TC6 for IDFS is not demonstrated. Both the original analysis and this updated analysis of the ABC trials are consistent with the recent meta-analysis reported by the EBCTCG.[4]

RFI, which excluded deaths not due to breast cancer as events, favored TaxAC with an HR of 1.38 with corresponding 5-year RFI rates of 88.2% for TC6 versus 91.0% for TaxAC. Tests for heterogeneity for RFI were significant for hormone receptor status ($P = .02$) favoring TaxAC for the hormone receptor–negative cohorts. However, with nearly 7 years of median follow-up and 455 deaths across both arms, the HR for OS is 1.05 ($P = .64$), corresponding to 5-year OS rates of 91.8% versus 92.4%, respectively. Review of the type of first IDFS events demonstrate 290 versus 213 total recurrences with TC relative to TaxAC, offset by one versus seven leukemias and 34 versus 62 deaths without recurrence or second cancers, respectively, suggesting reductions of recurrent breast cancers with TaxAC were offset by increases in late leukemias and deaths unrelated to breast cancer.

A comparison of IDFS by hormone receptor and nodal status in the original manuscript suggested clinically important benefit from TaxAC might be limited to hormone receptor–negative patients and hormone receptor–positive patients with four or more positive nodes. An update in the Data Supplement (Table S4) suggests clinically important benefit from inclusion of doxorubicin was limited to hormone receptor–negative breast cancer. Although not definitive, the long-term results suggest TC6 may be sufficient for most patients with hormone receptor–positive breast cancer who derive substantial benefit from endocrine therapy. However, biomarker analyses are planned to identify subsets of patients who could benefit from inclusion of anthracyclines.

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