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Overall Survival With Circulating Tumor Cell Count–Driven Choice of Therapy in Advanced Breast Cancer: A Randomized Trial

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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.

In patients with hormone receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer, the STIC CTC trial established that, for choosing between endocrine therapy (ET) or chemotherapy, the use of circulating tumor cell (CTC) count is noninferior to the investigator's choice in terms of progression-free survival. Here, we report overall survival (OS) results, a secondary end point. Patients were randomly assigned in a 1:1 ratio to have their first-line treatment (ET or chemotherapy) determined by investigators or CTC count (chemotherapy if ≥ 5 CTCs/7.5 mL; ET if low CTC count; CellSearch). OS was assessed at the discontinuation of follow-up. After a median follow-up of 4.7 years, 382 deaths (50.6%) had occurred among 755 patients. Median OS was 51.3 months (95% CI, 46.8 to 55.1) in the CTC arm and 45.5 months (95% CI, 40.9 to 51.1) in the standard arm (hazard ratio [HR] for death, 0.85; 95% CI, 0.69 to 1.03; $P = .11$). Among 189 patients (25.0%) with ET recommended by clinicians and high CTC count, chemotherapy was superior to ET (HR for death, 0.53; 95% CI, 0.36 to 0.78; $P = .001$). In case of a discordant estimate, OS data demonstrate the clinical utility of CTC count.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Protocol

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INTRODUCTION

In hormone receptor–positive metastatic breast cancer (MBC), endocrine therapy (ET) is the preferred option for first-line therapy, but in most international guidelines,[1,2] chemotherapy remains an option for patients with a rapidly evolving disease, the choice between ET and chemotherapy being eventually left to the clinician. In an effort to rationalize, standardize, and optimize the use of frontline chemotherapy, we designed and ran the STIC CTC study, a multicenter randomized phase III trial. This trial compared a choice of first-line therapy (ET or chemotherapy) on the basis of the circulating tumor cell (CTC) count in the experimental arm (CTC arm), with the investigator's choice in the standard arm. CTC count is a well-established independent prognostic factor in MBC,[3-5] but, to our knowledge, its clinical utility in terms of both progression-free survival (PFS) and overall survival (OS) has never been demonstrated.[3]

The study reached its primary end point, demonstrating that the CTC arm was noninferior to the clinician-driven arm in terms of 2-year PFS.[6] PFS was not significantly superior in the CTC arm, but analyses in the subgroups of patients with discordant Clinical/CTC features suggested the relevance of using the CTC count to choose between ET and chemotherapy. Here, we report the results of updated PFS and final OS (a secondary end point) analyses of the STIC CTC trial.

METHODS

The design of the STIC CTC trial has been published previously.[6] Detailed trial design and statistical analysis methods are available in the Data Supplement (online only). Briefly, women with a hormone receptor–positive, human epidermal growth factor receptor 2–negative MBC were randomly assigned to a clinician-driven choice of first-line therapy, or to a CTC-driven choice. Before random assignment, the preferred choice of investigators was recorded: chemotherapy (patients referred to as $Clin^{high}$) or ET (patients referred to as $Clin_{low}$).

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The baseline CTC count was then determined: patients with a CTC count ≥5 CTCs/7.5 mL were identified as CTC^{high} and those with a count <5 CTCs/7.5 mL as CTC_{low}. Patients randomly assigned in the standard arm received chemotherapy if they were $Clin^{high}$ or ET if they were $Clin_{low}$, while patients in the CTC arm received chemotherapy if they were CTC^{high} or ET if they were CTC_{low}.

Results for the primary end point, 2-year PFS, were previously reported.[6] PFS (with no time boundaries), OS, and subgroup analyses in patients with discordant Clin/CTC features were prespecified secondary end points. The final OS analysis was performed after the follow-up of patients was discontinued, on February 24, 2021.

RESULTS

From February 1, 2012, to July 28, 2016, 778 patients were randomly assigned to the standard arm (387 patients) or the CTC arm (391 patients; flowchart displayed in the Data Supplement). Patients' characteristics were balanced across the trial arms (Table 1).

Among the 755 participants in the per protocol population, 463 (61.3%) had concordant Clin/CTC features and received the same treatment whatever their allocated arm (ET if $CTC_{low}/Clin_{low}$, chemotherapy if $CTC^{high}/Clin^{high}$). In a first subgroup with discordant features ($Clin_{low}/CTC^{high}$), consisting of n = 189 (25.0%) participants, the 99 $Clin_{low}/CTC^{high}$ patients allocated to the standard arm received ET, whereas the 90 $Clin_{low}/CTC^{high}$ patients allocated to the CTC arm received upfront chemotherapy. In the other subgroup with discordant, but opposite, $Clin^{high}/CTC_{low}$ features (n = 103 [13.6%]), 51 were allocated to the standard arm and received chemotherapy, whereas 52 were allocated to the CTC arm and received ET.

This final analysis was performed after 664 PFS events (87.9% maturity) and 382 deaths (50.6%) had occurred: 197 deaths among 378 patients (52.1%) in the standard arm and 185 among 377 patients (49.1%) in the CTC arm. In the overall population, including all patients with either concordant or discrepant clinical/CTC estimate, the 377 patients of the CTC arm had a median PFS of 15.7 months (95% CI, 12.8 to 17.4) and a median OS of 51.3 months (95% CI, 46.8 to 55.1), whereas the 378 patients of the standard arm had a median PFS of 13.8 months (95% CI, 12.1 to 15.9; hazard ratio [HR] for progression or death, 0.94; 95% CI, 0.81 to 1.09) and a median OS of 45.5 months (95% CI, 40.9 to 51.1; HR for death, 0.85; 95% CI, 0.69 to 1.03; Fig 1A and Fig 1B).

We observed a statistically significant interaction for both PFS and OS between treatment arms and the four subgroups defined by clinical and CTC features (Data Supplement).

Patients with discordant $Clin_{low}/CTC^{high}$ features derived statistically better outcomes from receiving chemotherapy (in the CTC arm) rather than ET (in the standard arm): median PFS was 15.7 months (95% CI, 12.7 to 23.2) versus 10.0 months (95% CI, 8.2 to 15.4; HR for progression or death, 0.65; 95% CI, 0.48 to 0.87; $P = .005$), and median OS was 51.8 months (95% CI, 43.3.4 to not reached) versus 35.4 months (95% CI, 30.4 to 45.4; HR for death, 0.53; 95% CI, 0.36 to 0.78; $P = .001$), in the CTC arm and in the standard arm, respectively (Fig 2A and Fig 2B).

By contrast, there was no significant difference in outcomes for the other patient subgroup with discordant $Clin^{high}/CTC_{low}$ features, in which the CTC-driven decision allowed for a de-escalation from chemotherapy to ET in the CTC arm: median PFS was 9.3 months (95% CI, 6.1.8 to 17.2) versus 14.6 months (95% CI, 10.8 to 20.5; HR for progression or death, 1.14; 95% CI, 0.75 to 1.74; $P = .54$), and median OS was 49.4 months (95% CI, 35.4 to 65.4) versus 45.9 months (95% CI, 36.3 to 59.8; HR for death, 0.88; 95% CI, 0.51 to 1.51; $P = .64$), in the CTC arm and in the standard arm, respectively (Fig 2C and Fig 2D).

Several post hoc analyses were performed (Data Supplement): survival in patients with concordant Clin/CTC status, sensitivity analysis of PFS and OS, variables associated with a CTC^{high} status, and proportion of patients having received a CDK4/6 inhibitor as second or later line of therapy; their results did not undermine those of the preplanned analyses.

DISCUSSION

To our knowledge, the STIC CTC trial is the first contemporary trial that investigated the utility of a prognostic biomarker to drive treatment decision and compared ET or chemotherapy in predefined subgroups of patients with MBC. There was no significant OS benefit in the general population—which comprised a core of approximately 60% patients with concordant Clin/CTC estimate. In subgroup analyses, interaction tests showed that patients with discordant $Clin_{low}/CTC^{high}$ features, which accounted for about a quarter of the general population, benefited from the proposed strategy, with a clinically and statistically significant gain of 16.4 months in median OS. Interestingly, PFS and OS analyses in patients with $Clin^{high}/CTC_{low}$ features showed no statistically significant superiority of chemotherapy (in the standard arm) over ET (in the CTC arm), suggesting ET should remain the mainstay of treatment in these patients. Other relevant advantages of CTC count as treatment-driving biomarker over other methods are summarized in the Data Supplement. Importantly, although circulating tumor DNA (ctDNA) is often opposed to CTC, it is important to acknowledge that their clinical validity spectrum is not fully overlapping,[8] and, beyond tumor genotyping, ctDNA clinical utility remains to be formally established by randomized trials in MBC.

The most important limitation to the external validity of our trial is that it was run before the approval of CDK4/6 inhibitors which, given in combination with ET, have

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TABLE 1. Patients' Characteristics at Baseline

Characteristic	All Patients	Standard Arm					CTC Arm				
		$Clin_{low}$ CTC_{low}	$Clin_{low}$ CTC^{high}	$Clin^{high}$ CTC_{low}	$Clin^{high}$ CTC^{high}	Total	$Clin_{low}$ CTC_{low}	$Clin_{low}$ CTC^{high}	$Clin^{high}$ CTC_{low}	$Clin^{high}$ CTC^{high}	Total
No. of patients	755	176	99	51	52	378	187	90	52	48	377
Age, years, median (range)	63 (30-88)	64 (31-83)	63 (36-87)	60 (42-83)	64 (34-83)	63 (31-87)	64 (36-85)	65 (30-87)	56 (32-81)	61 (33-88)	64 (30-88)
No. of CTCs/7.5 mL of blood, median (range)	2 (0-30,000)	0 (0-4)	14 (5-755)	1 (0-4)	34.5 (5-21,000)	2 (0-21,000)	0 (0-4)	17 (5-30,000)	1 (0-4)	30.5 (5-3040)	2 (0-30,000)
PS, No. (%)											
0	388 (53.7)	104 (61.9)	43 (44.8)	32 (68.1)	16 (32.0)	195 (54.0)	108 (60.0)	39 (45.4)	33 (67.4)	13 (28.3)	193 (53.5)
1	282 (39.1)	57 (33.9)	44 (45.8)	13 (27.7)	25 (50.0)	139 (38.5)	68 (37.8)	35 (40.7)	13 (26.5)	27 (58.7)	143 (39.6)
2/3	52 (7.2)	7 (4.2)	9 (9.4)	2 (4.3)	9 (18.0)	27 (7.5)	4 (2.2)	12 (13.9)	3 (6.1)	6 (13.0)	25 (6.9)
Missing[a]	33	8	3	4	2	17	7	4	3	2	16
Menopausal status, No. (%)											
Premenopausal or perimenopausal	86 (12.2)	20 (12.4)	9 (10.3)	9 (18.0)	5 (10.4)	43 (12.4)	17 (9.5)	6 (6.8)	13 (25.5)	7 (15.9)	43 (11.9)
Postmenopausal	587 (82.9)	136 (84.5)	76 (87.4)	36 (72.0)	40 (83.3)	288 (83.2)	152 (84.9)	79 (89.8)	33 (64.7)	35 (79.6)	299 (82.6)
Unknown	35 (4.9)	5 (3.1)	2 (2.3)	5 (10.0)	3 (6.3)	15 (4.3)	10 (5.6)	3 (3.4)	5 (9.8)	2 (4.5)	20 (5.5)
Missing	47	15	12	1	4	32	8	2	1	4	15
Bone metastases only, No. (%)											
No	555 (73.7)	121 (69.1)	62 (63.3)	40 (78.4)	46 (88.5)	269 (71.5)	137 (73.3)	58 (64.4)	47 (90.4)	44 (91.7)	286 (75.9)
Yes	198 (26.3)	54 (30.9)	36 (36.7)	11 (21.6)	6 (11.5)	107 (28.5)	50 (26.7)	32 (35.6)	5 (9.2)	4 (8.3)	91 (24.1)
Missing	2	1	1	0	0	2	0	0	0	0	0
Liver metastases, No. (%)											
No	600 (79.7)	157 (89.7)	76 (77.6)	40 (78.4)	32 (61.5)	305 (81.1)	162 (86.6)	74 (82.2)	34 (65.4)	25 (52.1)	295 (78.3)
Yes	153 (20.3)	18 (10.3)	22 (22.4)	11 (21.6)	20 (38.5)	71 (18.9)	25 (13.4)	16 (17.8)	18 (34.6)	23 (47.9)	82 (21.7)
Missing	2	1	1	0	0	2	0	0	0	0	0
Histology, No. (%)											
IC-NST	557 (74.6)	150 (86.2)	63 (63.6)	45 (88.2)	28 (54.9)	286 (76.3)	147 (79.4)	49 (55.1)	42 (82.3)	33 (70.2)	271 (72.8)
ILC	153 (20.5)	18 (10.3)	30 (30.3)	4 (7.9)	20 (39.2)	72 (19.2)	29 (15.7)	36 (40.4)	6 (11.8)	10 (21.3)	81 (21.8)
Mixed/others	37 (4.9)	6 (3.5)	6 (6.1)	2 (3.9)	3 (5.9)	17 (4.5)	9 (4.9)	4 (4.5)	3 (5.9)	4 (8.5)	20 (3.4)
Missing	8	2	0	0	1	3	2	1	1	1	5
Estrogen receptor, No. (%)											
Negative	26 (3.4)	7 (4.0)	4 (4.0)	0 (0.0)	2 (3.9)	13 (3.4)	7 (3.7)	2 (2.2)	2 (3.8)	2 (4.2)	13 (3.5)
Positive	681 (90.2)	151 (85.8)	88 (88.9)	49 (96.1)	49 (94.2)	337 (89.2)	169 (90.4)	85 (94.5)	47 (90.4)	43 (89.6)	344 (91.2)
Not done[b]	48 (6.4)	18 (10.2)	7 (7.1)	2 (3.9)	1 (1.9)	28 (7.4)	11 (5.9)	3 (3.3)	3 (5.8)	3 (6.2)	20 (5.3)
Progesterone receptor, No. (%)											
Negative	140 (18.5)	35 (19.9)	18 (18.2)	15 (23.4)	9 (17.3)	77 (20.4)	30 (16.0)	13 (14.4)	9 (17.3)	11 (22.9)	63 (16.7)

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TABLE 1. Patients' Characteristics at Baseline (continued)

Characteristic	All Patients	Standard Arm					CTC Arm				
		$Clin_{low}$ CTC_{low}	$Clin_{low}$ CTC^{high}	$Clin^{high}$ CTC_{low}	$Clin^{high}$ CTC^{high}	Total	$Clin_{low}$ CTC_{low}	$Clin_{low}$ CTC^{high}	$Clin^{high}$ CTC_{low}	$Clin^{high}$ CTC^{high}	Total
Positive	537 (71.1)	112 (63.6)	70 (70.7)	32 (62.8)	41 (78.9)	255 (67.5)	139 (74.3)	71 (78.9)	40 (76.9)	32 (66.7)	282 (74.8)
Not done[b]	78 (10.4)	29 (16.5)	11 (11.1)	4 (7.8)	2 (3.8)	46 (12.1)	18 (9.7)	6 (6.7)	3 (5.8)	5 (10.4)	32 (8.5)
Stage at diagnosis, No. (%)											
Synchronous metastasis[c]	45 (26.9)	39 (22.2)	24 (24.2)	8 (15.7)	25 (48.1)	96 (25.4)	56 (30.0)	21 (23.3)	18 (34.6)	12 (25.0)	107 (28.4)
Metachronous metastasis	552 (73.1)	137 (77.8)	75 (75.8)	43 (84.3)	27 (51.9)	282 (74.6)	131 (70.0)	69 (76.7)	34 (65.4)	36 (75.0)	270 (71.6)
Endocrine resistance,[d] No. (%)											
Endocrine-sensitive	539 (71.4)	128 (72.7)	76 (76.8)	27 (52.9)	37 (71.2)	268 (70.9)	141 (75.4)	68 (75.6)	29 (55.8)	33 (68.7)	271 (71.9)
Secondary endocrine resistance	199 (26.4)	45 (25.6)	22 (22.2)	21 (41.2)	15 (28.8)	103 (27.3)	43 (23.0)	21 (23.3)	19 (36.5)	13 (27.1)	96 (25.5)
Primary endocrine resistance	17 (2.2)	3 (1.7)	1 (1.0)	3 (5.9)	0 (0.0)	7 (1.8)	3 (1.6)	1 (1.1)	4 (7.7)	2 (4.2)	10 (2.6)

Abbreviations: CTC, circulating tumor cell; IC-NST, invasive carcinoma of no special type; ILC, invasive lobular carcinoma; PS, performance status.

[a]The information of whether patients were PS 0-1 or 2-3 was available for all participants as it was a stratification factor; however, the exact PS (0 or 1) was not available for all patients.

[b]Data from the latest tumor tissue sampling (for a few patients with a metastasis biopsy, estrogen receptor and progesterone receptor were not assessable, yet all these patients had an estrogen receptor–positive and/or progesterone receptor–positive primary tumor).

[c]If metastases had occurred within 6 months of diagnosis, they were considered as synchronous.

[d]Endocrine resistance status was obtained using the interval between the completion of any previous endocrine therapy and the diagnosis of the metastatic disease, following ABC-4 guidelines.[7]

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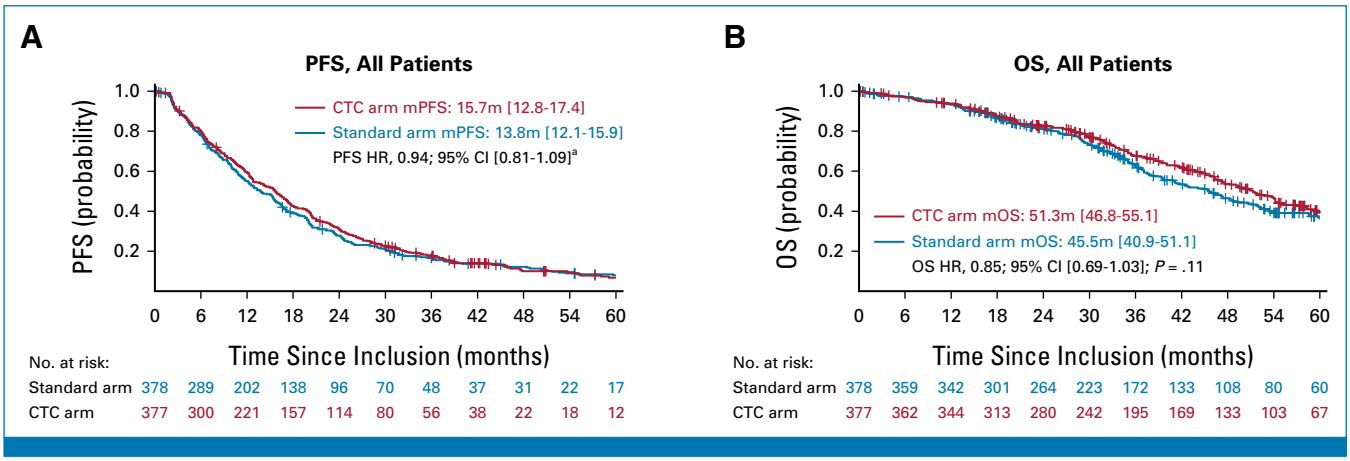

FIG 1. Patients' outcome in the whole population. (A) PFS, all patients. [a]Since the study previously reached its primary end point for PFS noninferiority, no *P* value was generated for this updated analysis. (B) OS, all patients. CTC, circulating tumor cell; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival.

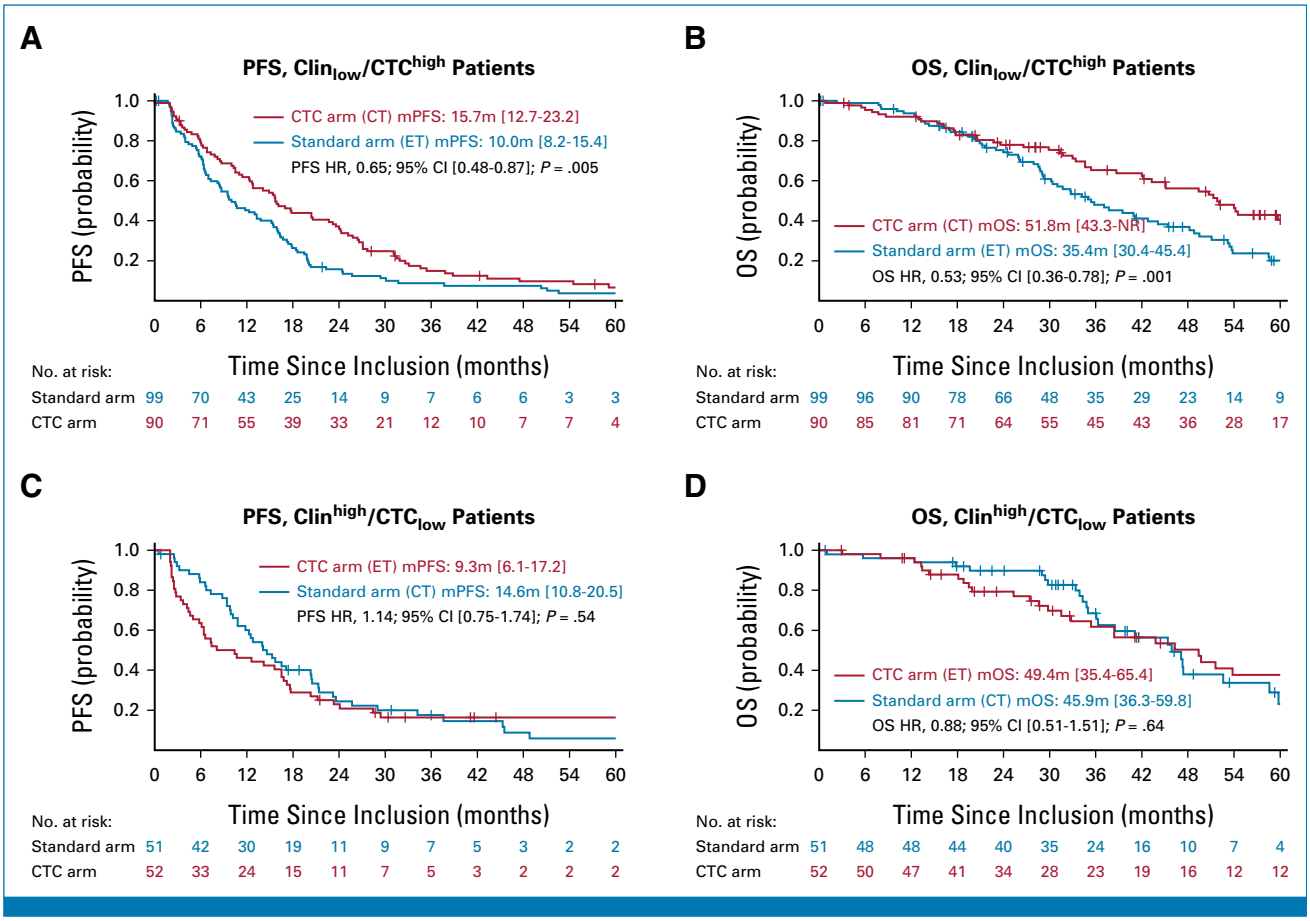

FIG 2. Patients' outcome in subgroups with discordant clinical and CTC estimates. (A) PFS, Clin$_{low}$/CTC^{high} patients. (B) OS, Clin$_{low}$/CTC^{high} patients. (C) PFS, Clin^{high}/CTC$_{low}$ patients. (D) OS, Clin^{high}/CTC$_{low}$ patients. CTC, circulating tumor cell; ET, endocrine therapy; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival.

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significantly prolonged PFS and—for ribociclib—OS.[9-11] Because of the significant survival benefit carried out by CDK4/6 inhibitors, we fully acknowledge that our trial results cannot be extrapolated to CDK4/6 inhibitor–naïve patients. However, the dilemma between ET and chemotherapy persists in patients who have received CDK4/6 inhibitor, either as first-line treatment for MBC or in the adjuvant setting. Our results suggest CTC count may be relevant as an aid to choose between the many ET-based treatment options or chemotherapy. Trials evaluating CTCs in the CDK4/6 inhibitor era are discussed in the Data Supplement.

In conclusion, the STIC trial established the overall safety of using the CTC count as a standalone biomarker, and despite a lack of significant survival benefit in the general population, it showed that patients with a high CTC count and a low clinical risk estimate may derive a significant OS benefit from chemotherapy.

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CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Overall Survival With Circulating Tumor Cell Count–Driven Choice of Therapy in Advanced Breast Cancer: A Randomized Trial

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