Fulvestrant Versus Anastrozole in Endocrine Therapy–Naïve Women With Hormone Receptor–Positive Advanced Breast Cancer: Final Overall Survival in the Phase III FALCON Trial

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ABSTRACT

The randomized phase III FALCON trial demonstrated significant improvement in progression-free survival (PFS) with fulvestrant versus anastrozole in postmenopausal women with endocrine therapy–naïve, hormone receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer. Herein, the prespecified final overall survival (OS) analysis is reported. After the primary PFS analysis, data were collected on survival, serious adverse events, and health-related quality of life. The final OS analysis was triggered at ≥65% maturity and ≥8 years since the last patient was enrolled. Analyses were descriptive with nominal *P* values (one-sided α threshold .01845). At the data cutoff (July 11, 2022), 314 (68.0%) of 462 patients had died (fulvestrant, 157/230 [68.3%], anastrozole, 157/232 [67.7%]). The final OS analysis of FALCON demonstrated no significant difference between fulvestrant and anastrozole (medians, 44.8 and 42.7 months, respectively; hazard ratio [HR], 0.97 [95% CI, 0.77 to 1.21]; *P* = .7579). Among patients with nonvisceral disease (n = 208), a trend showed a 15% reduction in the relative risk of death with fulvestrant versus anastrozole (median OS, 65.2 *v* 47.8 months; HR, 0.85 [95% CI, 0.60 to 1.20]). Data from FALCON are consistent with published evidence of long-term clinical benefit with fulvestrant and other endocrine therapies in the subset of patients with nonvisceral disease.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Protocol

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INTRODUCTION

Approval of the first-in-class selective estrogen receptor degrader (SERD) fulvestrant for endocrine therapy (ET)–naïve postmenopausal women with hormone receptor–positive patients with advanced breast cancer (ABC) was based on the phase III randomized clinical trial (RCT) FALCON (ClinicalTrials.gov identifier: NCT01602380).[1] In 2016, FALCON met its primary end point, demonstrating significant improvement in progression-free survival (PFS) with fulvestrant 500 mg versus the third-generation aromatase inhibitor (AI) anastrozole 1 mg.[1] PFS benefits with fulvestrant were largely consistent across predefined patient subgroups. Treatment was well tolerated, and health-related quality of life (HRQOL) was maintained in both arms.[1,2]

At the time of the primary PFS analysis, interim analysis of overall survival (OS) in FALCON showed no significant difference between arms.[1,3] Herein, we report the prespecified final OS analysis from FALCON and updated safety information.

METHODS

The FALCON study design and analysis methods have been reported previously[1,2] and are summarized in the Data Supplement (Methods, online only). The study protocol was amended following the primary analysis to trigger the final OS analysis at ≥65% maturity (300/462 events) and ≥8 years since the last patient was enrolled. This study was not formally powered to detect OS benefit, and analyses reported here are descriptive with nominal *P* values. A multiple testing procedure with an α-exhaustive recycling strategy controlled type I error at the overall α level.[4] The final OS analysis data cutoff was July 11, 2022, with a one-sided α threshold of .01845.

RESULTS

Patients

As reported previously and summarized in Table 1,[1] baseline characteristics of the intention-to-treat (ITT) population

TABLE 1. Patient Demographics and Baseline Disease Characteristics in the ITT Population

Patient Demographic/Characteristic	Fulvestrant 500 mg (n = 230)	Anastrozole 1 mg (n = 232)
Age, years, median (range)	64 (38-87)	62 (36-90)
≥65, No. (%)	108 (47)	91 (39)
Race, No. (%)		
White	175 (76)	174 (75)
Asian	36 (16)	34 (15)
Black or other	19 (8)	24 (10)
Time from diagnosis of breast cancer to randomization, No. (%)		
≤2 months	102 (44)	99 (43)
>2 months to ≤1 year	58 (25)	66 (28)
>1 year	70 (30)	67 (29)
Receptor status, No. (%)		
ER-positive/PgR-positive	175 (76)	179 (77)
ER-positive/PgR-negative	44 (19)	43 (19)
ER-positive/PgR unknown	10 (4)	7 (3)
ER-negative/PgR-positive	1 (<1)	3 (1)
ER-negative/PgR-negative	0	0
HER2 status, No. (%)		
HER2-positive	0	1 (<1)
HER2-negative	230 (100)	231 (100)
WHO performance status, No. (%)[a]		
0	117 (51)	115 (50)
1	106 (46)	105 (45)
2	7 (3)	12 (5)
Disease stage, No. (%)		
Locally advanced	28 (12)	32 (14)
Metastatic	202 (88)	200 (86)
Site of metastasis, No. (%)		
Visceral disease[b]	135 (59)	119 (51)
Bone or musculoskeletal only	24 (10)	24 (10)
Breast only	3 (1)	2 (1)
Skin or soft tissue only	8 (3)	6 (3)
Other nonvisceral	60 (26)	81 (35)
Measurable disease, No. (%)	193 (84)	196 (84)
Previous treatment, No. (%)[c]		
Chemotherapy		
Locally advanced or metastatic breast cancer[d]	36 (16)	43 (19)
Adjuvant	35 (15)	27 (12)
Neoadjuvant	11 (5)	16 (7)
Radiotherapy	53 (23)	50 (22)
Immunotherapy	0	0
Hormonal therapy	2 (1)	1 (<1)

NOTE. Reprinted from Robertson et al,[1] © 2016, with permission from Elsevier.
Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; ITT, intention-to-treat; PgR, progesterone receptor.
[a]WHO performance status: 0 represents normal activity, 1 represents restricted activity, and 2 represents being in bed ≤50% of the time.
[b]Includes patients with the site of baseline disease as any of the following: adrenal, bladder, CNS, esophagus, liver, lung, peritoneum, pleura, renal, small bowel, stomach, pancreas, thyroid, colon, rectal, ovary, biliary tract, ascites, pericardial effusion, spleen, or pleural effusion.
[c]Previous enrollment categories are not mutually exclusive.
[d]Includes first-line, second-line, third-line, metastatic, and palliative chemotherapies (two patients were reported as deviations for having received second-line chemotherapy and one patient was reported in error to have received three previous lines of chemotherapy).

TABLE 2. Survival Status in the ITT Population at the Time of OS Analysis Data Cutoff

Status	Fulvestrant 500 mg (n = 230)	Anastrozole 1 mg (n = 232)
Patients still in survival follow-up, No. (%)	25 (10.9)	31 (13.4)
Deaths, No. (%)	157 (68.3)	157 (67.7)
Terminated before death, No. (%)[a]	48 (20.9)	44 (19.0)
Voluntary discontinuation by the patient	33 (14.3)	32 (13.8)
Patient lost to follow-up	11 (4.8)	8 (3.4)
Other reason	4 (1.7)	4 (1.7)

Abbreviations: ITT, intention-to-treat; OS, overall survival.
[a]Patients who terminated before death were censored in the final OS analysis. Data cutoff: July 11, 2022.

were generally well balanced between the fulvestrant (n = 230) and anastrozole (n = 232) arms. Visceral disease was reported in 135 (58.7%) and 119 (51.3%) patients in the fulvestrant and anastrozole arms, respectively; nonvisceral disease was reported in 95 (41.3%) and 113 (48.7%) patients, respectively.

OS

Table 2 summarizes the survival status in the ITT population at the time of the final OS analysis. The median follow-up was 37.1 months (fulvestrant arm, 37.5 months; anastrozole arm, 36.5 months). Consistent with the interim analysis,[1] the final prespecified analysis of FALCON at 68% maturity demonstrated no differences in OS between fulvestrant and anastrozole (hazard ratio [HR], 0.97 [95% CI, 0.77 to 1.21]; $P = .7579$; Fig 1).[5]

Across most subgroups, OS HRs were consistent with the overall population. However, there was a trend for improved OS with fulvestrant versus anastrozole in patients with nonvisceral disease (Data Supplement, Fig S1). The OS HR in patients with nonvisceral disease with fulvestrant versus anastrozole was 0.85 (95% CI, 0.60 to 1.20; median OS, 65.2 months *v* 47.8 months, respectively; difference in median OS, 17.4 months; Fig 2A),[5] indicating a 15% reduction in the relative risk of death, although this was not statistically significant. Among patients with visceral disease, OS was comparable between the fulvestrant and anastrozole arms (HR, 1.06 [95% CI, 0.80 to 1.42]; median OS, 37.2 *v* 40.7 months, respectively; Fig 2B).[5]

In post hoc exploratory analyses, patients with nonvisceral versus visceral disease had greater OS improvements with fulvestrant (median OS, 65.2 *v* 37.2 months; difference, 28.0 months; HR, 0.62 [95% CI, 0.45 to 0.85]) compared with anastrozole (median OS, 47.8 months *v* 40.7 months; difference, 7.1 months; HR, 0.78 [95% CI, 0.57 to 1.07]; Figs 2C and 2D).[5]

An exploratory analysis evaluating the effect of the COVID-19 pandemic showed separation in OS between arms

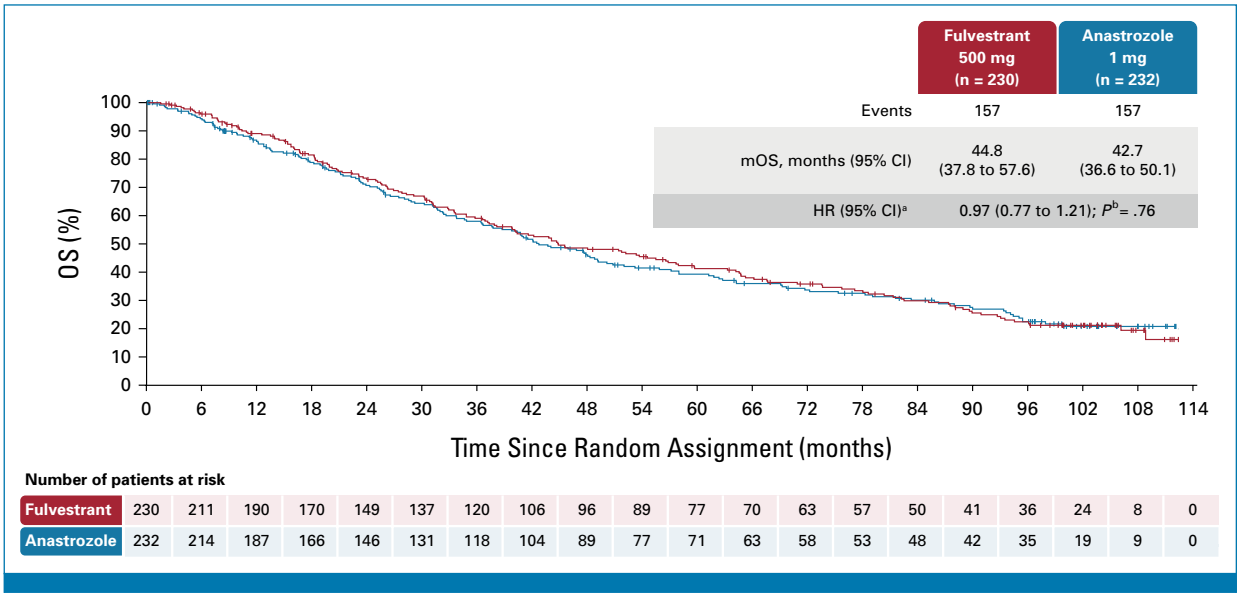

FIG 1. Kaplan-Meier curve for OS in the ITT population. [a]HR (fulvestrant:anastrozole) <1 favors fulvestrant. Crosses represent censored observations. HR, hazard ratio; ITT, intention-to-treat; mOS, median OS; OS, overall survival. [b]Two-sided *P* value.

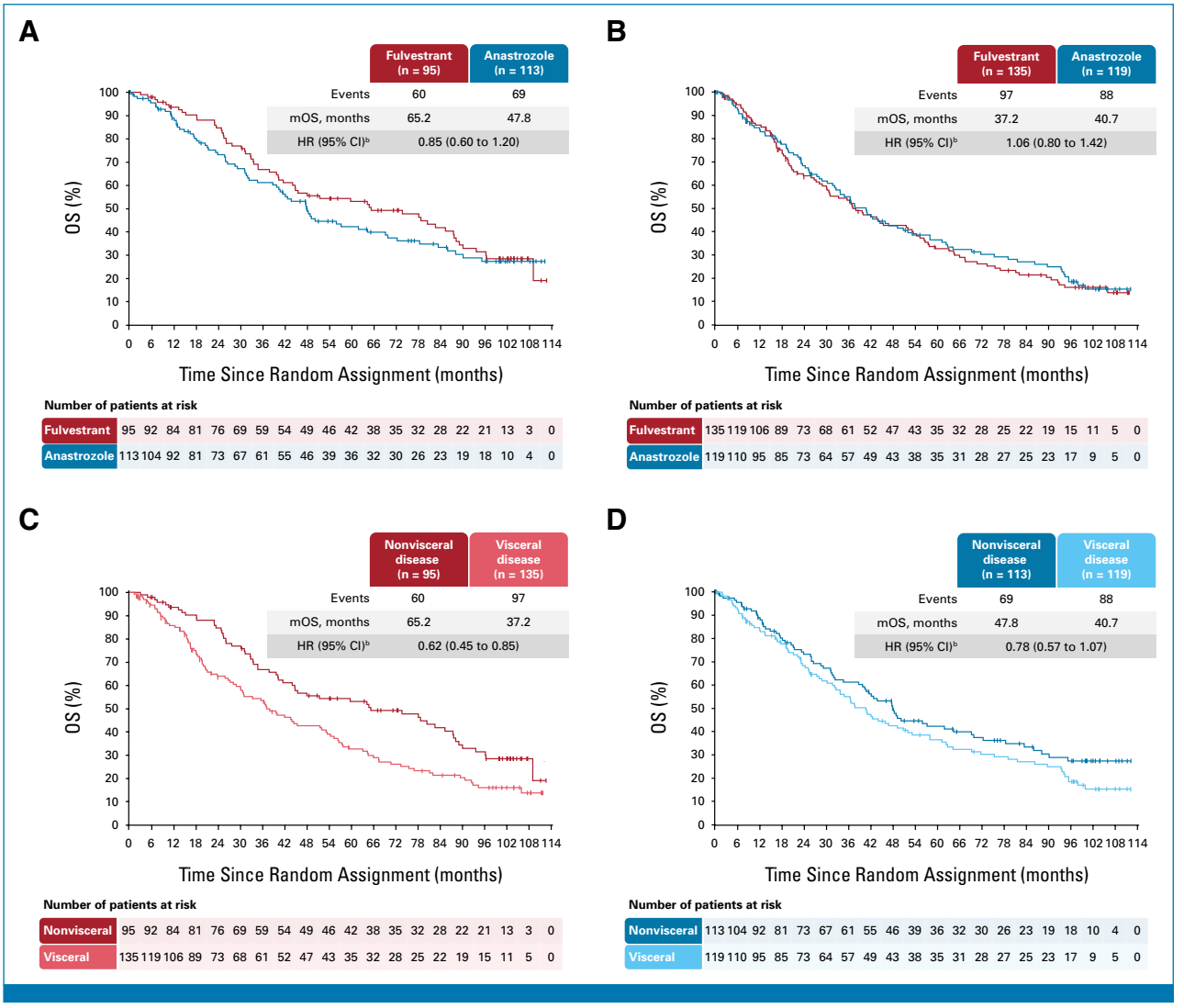

FIG 2. OS in patients with (A) nonvisceral or (B) visceral disease[a] and exploratory analysis in patients with nonvisceral and visceral disease[a] in the (C) fulvestrant and (D) anastrozole arms. [a]Visceral disease was defined by the presence of tumors in the adrenal glands, bladder, CNS, esophagus, liver, lung, peritoneum, pleura, kidney, small bowel, stomach, pancreas, thyroid, colon, rectum, ovary, biliary tract, or spleen or by the presence of ascites, or pericardial or pleural effusion. [b]HR (fulvestrant:anastrozole) <1 favors fulvestrant. Crosses represent censored observations. Data cutoff: July 11, 2022. HR, hazard ratio; mOS, median OS; OS, overall survival.

in patients with nonvisceral but not with visceral disease (Data Supplement, Fig S2).[5]

Subsequent Therapy

At the data cutoff, 216 patients (94.7%) in the fulvestrant arm and 222 (95.7%) in the anastrozole arm had discontinued study treatment for any reason, and 171 (75.0%) and 189 (81.5%), respectively, had discontinued due to worsening of the condition under investigation (including disease progression). Data on subsequent anticancer therapies were obtained for 49.1% of patients in each treatment arm of the ITT population. No clinically meaningful differences were observed in the use of any particular subsequent therapies (Table 3).

Serious Adverse Events

Despite longer treatment duration, the safety profile of fulvestrant remained consistent with earlier observations from this and other studies.[1,6,7] No new safety signals were identified, and most serious adverse events (SAEs) were considered unrelated to study treatment (Table 4; Data Supplement, Tables S1 and S2).

HRQOL

Overall, no meaningful differences in HRQOL outcomes were observed between the fulvestrant and anastrozole arms. There were no statistically significant differences in time to deterioration of Functional Assessment of Cancer Therapy-Breast

TABLE 3. Subsequent Therapy Use After Discontinuation in the Intention-to-Treat Population

Therapy	Fulvestrant 500 mg (n = 230)	Anastrozole 1 mg (n = 232)	Total (N = 462)
Any anticancer therapy, No. of patients (%)	113 (49.1)	114 (49.1)	227 (49.1)
Exemestane	34 (14.8)	50 (21.6)	84 (18.2)
Radiotherapy	31 (13.5)	29 (12.5)	60 (13.0)
Capecitabine	26 (11.3)	33 (14.2)	59 (12.8)
Paclitaxel	19 (8.3)	31 (13.4)	50 (10.8)
Letrozole	30 (13.0)	16 (6.9)	46 (10.0)
Tamoxifen	19 (8.3)	25 (10.8)	44 (9.5)
Fulvestrant	9 (3.9)	34 (14.7)	43 (9.3)
Cyclophosphamide	17 (7.4)	24 (10.3)	41 (8.9)
Doxorubicin	16 (7.0)	21 (9.1)	37 (8.0)
Anastrozole	20 (8.7)	11 (4.7)	31 (6.7)
Everolimus	8 (3.5)	18 (7.8)	26 (5.6)

NOTE. Table shows anticancer therapies after discontinuation of study treatment. Individual therapies with a frequency of ≥5% across all patients are shown. Not shown: Six patients (2.6%) in the fulvestrant arm and 10 patients (4.3%) in the anastrozole arm received subsequent CDK4/6 inhibitors.

total score (HR, 0.82 [95% CI, 0.66 to 1.03]; $P = .08$) or Trial Outcome Index (HR, 0.88 [95% CI, 0.70 to 1.11]; $P = .28$). However, these results should be interpreted with caution as questionnaire compliance varied over time.

DISCUSSION

The final analysis of FALCON showed no difference in OS between fulvestrant and anastrozole in ET-naïve postmenopausal women with hormone receptor–positive/human epidermal growth factor receptor 2 (HER2)–negative ABC. Although differences between populations limit cross-trial comparisons, the median OS with fulvestrant (44.8 months) was comparable with other studies with first-line fulvestrant for hormone receptor–positive/HER2-negative ABC, including FIRST (54.1 months), MONALEESA-3 (51.8 months), and MONARCH 2 (37.3 months).[8-10] The median OS with anastrozole (42.7 months) was consistent with FIRST (48.4 months) and the SWOG S0226 trial (42.0 months) and with first-line letrozole observed in MONALEESA-2 (51.4 months).[8,11,12]

Efficacy differences within treatment arms in patients with visceral versus nonvisceral disease emerged during the primary PFS analysis of FALCON and were consistent with other RCTs with fulvestrant. In FALCON, OS analysis within treatment arms in patients with visceral versus nonvisceral disease was post hoc, but further supported by similar results in RCTs with AIs and selective estrogen receptor modulators.[13] Accumulating evidence supports that nonvisceral metastases predict greater benefit with fulvestrant 500 mg. The trend favoring prolonged OS with fulvestrant versus anastrozole in the nonvisceral subgroup of FALCON was consistent with the main subgroup analyses of PFS and previous data from FIRST and CONFIRM.[1,3,8] A recent meta-analysis demonstrated improved outcomes with all first-line endocrine monotherapies in patients with nonvisceral versus visceral metastases, and the greatest survival improvements across all ET classes were with fulvestrant 500 mg.[13] Although the mechanistic basis of these differences is unclear, known biological differences between metastasis to nonvisceral and visceral sites, including hormone receptor, HER2, and Ki67

TABLE 4. SAEs in the Safety Population

Event	Fulvestrant 500 mg (n = 228)	Anastrozole 1 mg (n = 232)	Total (n = 460)
SAEs (including deaths), No. of patients (%)	39 (17.1)	36 (15.5)	75 (16.3)
SAEs leading to discontinuation of treatment	15 (6.6)	11 (4.7)	26 (5.7)
Deaths	7 (3.1)	9 (3.9)	16 (3.5)
Treatment-related SAEs, No. of patients (%)[a]	5 (2.2)	3 (1.3)	8 (1.7)
Treatment-related SAEs leading to discontinuation of treatment	2 (0.9)	1 (0.4)	3 (0.7)
Treatment-related deaths	0	0	0

NOTE. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each category.
Abbreviation: SAE, serious adverse event.
[a]As assessed by the investigator.

expression, as well as growth factor levels in the tumor environment, may have contributed to ET sensitivity.[14-17] It is unlikely that baseline *ESR1* mutations (*ESR1*m) accounted for the differences in the FALCON population as *ESR1*m occurs in <1% of ET-naïve patients.[18]

Recent data from the SONIA trial suggest that an optimal treatment sequence has not been reached for hormone receptor–positive/HER2-negative ABC,[19] which may prompt increasing use of first-line endocrine monotherapy. The significantly longer PFS with fulvestrant versus anastrozole and the notably long median OS (65.2 months) in patients with nonvisceral disease support the possibility of long-term benefit for select patients who receive fulvestrant monotherapy. Fulvestrant monotherapy, therefore, continues to be a relevant first-line treatment option, particularly for patients with highly sensitive breast cancers, patients for whom CDK4/6 inhibitors are unsuitable,[20] or for patients with limited life expectancy and/or a preference for better tolerability and HRQOL.

Although the final OS analysis was preplanned as a key secondary end point analysis using a multiple testing procedure, the study was not powered to demonstrate a significant OS difference. Other limitations include reduced data collection after the primary analysis, limited to survival follow-up, HRQOL, subsequent therapies, and SAEs. PFS to subsequent anticancer therapy was not a prespecified end point in FALCON, which started in 2012; data on subsequent therapies were collected from approximately half of the patients in each treatment arm.

There remains a high unmet need for a novel SERD that further improves convenience via oral dosing, addresses ET resistance, and provides broader efficacy across clinically relevant patient subgroups.[13,21] Several candidates have entered late-stage development with mixed results.[22-27] Elacestrant is approved for postmenopausal patients with estrogen receptor–positive/HER2-negative, *ESR1*m ABC that has progressed following ≥1 line of ET.[22] The safety and efficacy of giredestrant and imlunestrant treatment for estrogen receptor–positive/HER2-negative ABC are also under investigation.[24,25] Significantly improved PFS with camizestrant versus fulvestrant was demonstrated in the phase II SERENA-2 trial,[26] and the phase III SERENA-4 and SERENA-6 trials investigating camizestrant as an ET partner for CDK4/6 inhibitors versus AIs in the first-line setting are ongoing.[28,29]

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DISCLAIMER

M.J.E. was employed by AstraZeneca at the time the study analysis was conducted.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Stock and Other Ownership Interests: OncImmune, FaHRAS Ltd
Consulting or Advisory Role: AstraZeneca, Bayer, Novartis, OncImmune
Research Funding: AstraZeneca, Bayer, Novartis, OncImmune
Expert Testimony: AstraZeneca
Travel, Accommodations, Expenses: AstraZeneca

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Consulting or Advisory Role: AstraZeneca
Patents, Royalties, Other Intellectual Property: I hold joint patents not related to this study with Sysmex

Shankar Subramaniam
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Matthew J. Ellis
Patents, Royalties, Other Intellectual Property: Royalties from Veracyte from the PAM50 patent for Prosigna
Travel, Accommodations, Expenses: Veracyte

No other potential conflicts of interest were reported.