BREAST CANCER

Response to Induction Neoadjuvant Hormonal Therapy Using Upfront 21-Gene Breast Recurrence Score Assay—Results From the SAFIA Phase III Trial

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PURPOSE Luminal, human epidermal growth factor receptor 2–negative breast cancer represents the most common subtype of breast malignancies. Neoadjuvant strategies of operable breast cancer are mostly based on chemotherapy, whereas it is not completely understood which patients might benefit from neoadjuvant hormone therapy (NAHT).

MATERIALS AND METHODS The SAFIA trial is a prospective multicenter, international, double-blind, neoadjuvant phase III trial, using upfront 21-gene Oncotype DX Breast Recurrence Score assay (recurrence score [RS] < 31) to select operable luminal human epidermal growth factor receptor 2–negative patients, for induction hormonal therapy HT (fulvestrant 500 mg with or without goserelin) before randomly assigning responding patients to fulvestrant 500 mg (with or without goserelin) plus either palbociclib (cyclin-dependent kinase 4/6 inhibitor) or placebo. The objectives of this interim analysis were to assess the feasibility of upfront RS determination on core biopsies in the Middle-East and North Africa region and evaluate the efficacy of induction NAHT in patients with an RS < 31.

RESULTS At the time of this interim analysis, 258 patients with relative risk were accrued, including 202 patients (RS < 31% to 78.3%) treated with induction NAHT and 182 patients evaluable so far for response. The feasibility of performing the Oncotype DX assays on core biopsy specimens was optimal in 96.4% of cases. Overall, 93.4% of patients showed hormone sensitivity and no difference in NAHT efficacy was noticed between RS 0-10, 11-25, and 26-30. Interestingly, patients with high RS (26-30) showed a trend toward a higher major response rate ($P = .05$).

CONCLUSION The upfront 21-gene assay performed on biopsies is feasible in our population and has allowed us to select patients with high hormone sensitivity (RS < 31). This approach could be an alternative to upfront surgery without significant risk of progression, particularly during pandemic times.

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ASSOCIATED CONTENT

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Breast cancer (BC) is the leading cause of death in women according to the WHO, responsible for an estimated 626,679 deaths worldwide in 2018.[1,2] The heterogenous nature of BC leads to differential prognosis, treatment choices, and outcomes. Tumors with estrogen receptor (ER)-positive and human epidermal growth factor receptor 2 (HER2)-negative (luminal A and B) are the most common, comprising 65%-75% of all invasive BCs at time of diagnosis.[3,4] Multiple mechanisms can target ER signaling; either by inhibiting or downregulating the receptor or by modulating the downstream effectors, and the dual inhibition of cyclin-dependent kinase (CDK) 4/6 and ER signaling possess a highly synergistic anticancer and antiproliferative potential.[5,6]

Fulvestrant, a 17 β-estradiol analog, is an ER downregulator, was shown to be one of the most potent endocrine therapies for advanced breast when used at high dose (500 mg), and thus deserves to be evaluated in early BC management.[7,8] Palbociclib (PD 0332991), first-in-class CDK4/6 inhibitor, has significantly improved patients' outcome when combined with endocrine therapy in the metastatic setting.[9,10]

CONTEXT

Key Objective

The SAFIA trial is a first prospective phase III, multicenter, double-blind, third-generation neoadjuvant trial designed in the Middle-East and North Africa region and run in six countries using upfront 21-gene assay (Recurrence Score [RS] < 31) to select operable luminal human epidermal growth factor receptor 2–negative patients for induction hormone therapy (fulvestrant with or without goserelin) before randomly assigning responding patients to hormone therapy with or without palbociclib.

Knowledge Generated

This interim analysis reports on the feasibility of the 21-gene assay performed on core biopsies in our population and evaluates the efficacy of induction neoadjuvant hormone therapy (NAHT) in patients with an RS < 31 including the three groups RS 0-10, 11-25, and 26-30. We found that the use of upfront 21-gene assay on biopsies is feasible and has allowed us to select patients for NAHT without affecting their outcome.

Relevance

Our data support NAHT for patients with operable luminal estrogen receptor–positive, human epidermal growth factor receptor 2–negative breast cancer and an RS < 31 as an alternative to upfront surgery without significant loss of chance, in particular, during pandemic times.

The role of the combination of palbociclib and hormone therapy (HT) is presently investigated in early BC in either the adjuvant or neoadjuvant settings.[11,12]

In contrast to neoadjuvant chemotherapy (NACT), neoadjuvant endocrine therapy in luminal BC is not commonly used as standard of care in current practice. This situation arose mostly from the historical approach, basing therapeutic strategies upon a prognostic rather than a predictive approach. The problem resides in the assessment of chemosensitivity versus hormonal sensitivity, weighing the potential benefit of either intervention for early luminal BC. A significant fraction of those with luminal B, HER2– tumors and a limited number of those with luminal A tumors will benefit from NACT.

The 21-gene expression–based Oncotype DX Breast Recurrence Score test has been shown to be both prognostic in ER+ disease if treated with tamoxifen alone and predictive of benefit from adding chemotherapy (CT), particularly for those with Recurrence Score (RS) results > 30.[13,14] These conclusions came from retrospective analyses of prospective trials in which patients with high RS appeared to benefit significantly from the addition of standard CT to tamoxifen, whereas those with low RS results did not.[14-17] The results from the large-scale prospective trial TAILORx showed that patients with an RS < 11, treated with adjuvant HT alone, had at 5 years a very low rate of freedom from recurrence of BC at distant site (99.3%; 95% CI, 98.7 to 99.6), eliminating any role for CT in this context.[18,19] Patients with RS results between 11 and 25 (n = 6,711) HT alone had a similar efficacy compared with HT + CT with comparable disease-free survival at 9 years (risk ratio: 1.08; 95% CI, 0.94 to 1.24; P = .26). Freedom from distant recurrence was 94.5% and 95%, respectively.[18] A retrospective exploratory subgroup analysis suggested that some benefit from adding CT to HT could be seen in some young women (< 50 years) with the RS results between 16 and 25. Finally, for the group of patients with the RS results from 26 to 100, the estimated rate of freedom from recurrence at a distant site was 93% at 5 years, suggesting a better outcome than expected with HT alone. Overall, no benefit for CT was reported in the low-RS group (< 18), whereas the benefit was debatable for the intermediate-RS group of 18-30.[20] In terms of feasibility, the 21-gene assay can be confidently performed on core biopsies to support clinical treatment planning in ER+, HER2– invasive BCs, and the results can efficiently guide decisions about appropriate neoadjuvant therapy, including HT context.[21,22]

The SAFIA trial is a multicenter, neoadjuvant phase III study, performed in six countries of the Middle-East and North Africa (MENA) region, comparing in a double-blind manner HT plus placebo with HT plus palbociclib in patients with operable luminal BC, responding to induction HT. We report the first interim analysis of the feasibility of the upfront prospective use of the 21-gene assay to select patients for induction neoadjuvant HT (NAHT) and the related efficacy of HT before random assignment.

MATERIALS AND METHODS

SAFIA Study Design and Treatment Regimens

SAFIA trial is the first BC neoadjuvant phase III trial designed and performed in the MENA region (ClinicalTrials.gov identifier: NCT03447132).[23] This is a prospective multicenter, international, double-blind, randomized controlled, third-generation neoadjuvant phase III trial comparing fulvestrant 500 mg (with or without goserelin) plus palbociclib (CDK 4/6 inhibitor) with fulvestrant 500 mg (with or without goserelin) plus placebo in patients with

operable luminal BC responding to fulvestrant 500 mg (with or without goserelin).[23]

In terms of design (Fig 1), after signing the consent form, patients underwent upfront screening by the 21-gene assay, performed centrally on core biopsies, to select candidates for NAHT (RS < 31). Patients with an RS < 31 were treated with induction neoadjuvant fulvestrant (500 mg intramuscular at days 1, 14, and 28 and then every 4 weeks for 4 months) plus goserelin (3.6 mg subcutaneous every 4 weeks), for pre- and perimenopausal patients for 5 months, initiated 1 month before fulvestrant.

This treatment was followed by clinical and radiologic response assessment at both primary breast tumor and nodal disease, using mammography plus breast ultrasound and, when indicated, magnetic resonance imaging.[24,25] Radiologic responses were defined as per RECIST 1.1 criteria.[26] Additionally, to precisely assess the real response to HT and thus the hormone sensitivity, we divided stable disease in minor response (MR): 0%-50% reduction in cross-product and minor progression (MP): 1%-25% increase in cross-product or any new lesion.

Responding patients (complete response [CR], partial response [PR], and MR) to induction HT were then randomly assigned, in a double-blind manner, to fulvestrant 500 mg (with or without goserelin) with either palbociclib 125 mg orally once daily or placebo (3 weeks on/1 week off) every 4 weeks for 4 months.

Patient Population

The study population consisted of postmenopausal or pre- or perimenopausal patients with operable stage II and IIIA luminal BC (ER+, HER2–). Inclusion and exclusion criteria are tabulated in Table 1. This trial was performed in 24 centers and six countries of the MENA region (Saudi Arabia, Egypt, Jordan, Lebanon, Algeria, and Tunisia), after appropriate institutional approval through respective institutional review boards.

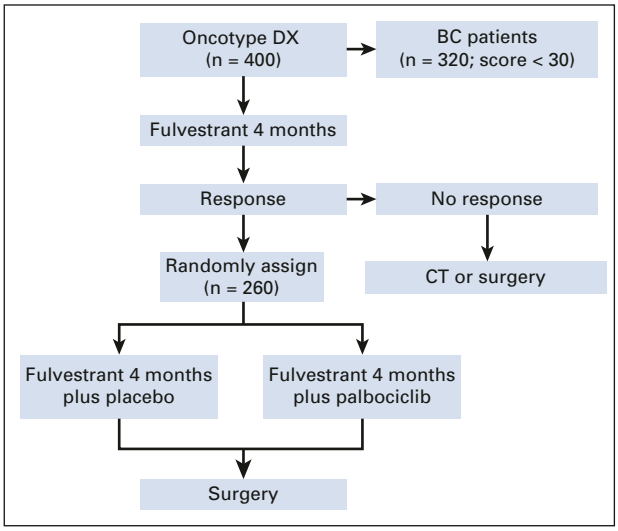

FIG 1. SAFIA trial design flow sheet. BC, breast cancer; CT, chemotherapy.

Objectives

The objectives of this interim analysis are (1) to report the response rates of induction NAHT with fulvestrant with or without goserelin given for 4-5 months in a patient population selected upfront by the 21-gene assay, (2) to assess the prediction of objective hormone sensitivity according to the levels of upfront RS levels, and (3) to analyze the feasibility of the 21-gene test performed on core biopsies in our Middle-East and Maghreb patient population.

Processing of the 21-Gene Assay

After obtaining the signature on the consent form and before initiating any neoadjuvant therapy, biopsy samples of eligible patients were immediately sent for upfront 21-gene assay at Genomic Health Inc (Redwood City, CA), following the established Standard Operating Procedures. Excluded from the trial were patients with insufficient tumor material in blocks or slides and unconfirmed diagnosis by Genomic Health pathologists.

Statistical Considerations

Sample size calculation. The sample size calculation of SAFIA trial was based on the assumption that the pathological complete response (pCR) rate will increase from 5% for fulvestrant (with or without goserelin) to 15% for the combination of fulvestrant–palbociclib. With an α value set at 5%, using one-sided significance tests and a β value at 20%, the sample size was conservatively set in 260 patients.

Considering that around 20% of patients will show de novo resistance to induction fulvestrant before random assignment, 60 additional patients were needed to identify 260 patients sensitive to induction therapy, bringing the sample size to 320.

Finally, assuming that around 20% of naïve patients with luminal tumors will be classified of high risk (RS $\geq$ 31), an additional 80 screened patients were considered necessary to identify the 320 patients with a score < 31. Therefore, the total sample size of the trial was estimated to be 400 patients (Fig 1).

Statistical methodology. The current analysis includes a description of the enrolled population with known RS results: patients with an RS < 31 (treated by NAHT) and an RS $\geq$ 31. Descriptive statistics (median and minimum-maximum) were used for continuous variables, and frequency or percentage for categorical variables. Correlations between the RS result and responses to NAHT were assessed by χ^2 or Fisher's exact tests. Data presented for this interim analysis were collected via an electronic observation booklet (eCRF) developed on a web-based MARVIN electronic system (XClinical, Munich, Germany), validated according to US Food and Drug Administration

TABLE 1. Patient Selection Criteria for SAFIA Trial

Inclusion Criteria	Exclusion Criteria
1. Written informed consent before beginning specific protocol procedures, including expected cooperation of the patients for the treatment and follow-up, must be obtained and documented according to the local regulatory requirements	1. Male patients
2. Age > 18	2. HER2+ tumors or unknown HR-HER2 status
3. Postmenopausal women or premenopausal	3. Pregnant or breastfeeding, or plan to become pregnant within 6 months post-treatment
4. Performance status < 2 (according to WHO criteria)	4. Pre- or perimenopausal women not willing to use highly effective methods of contraception (per institutional standard) during treatment and for 6 months post-treatment
5. Histologically confirmed, nonmetastatic BC (luminal A or B) • HR+ (estrogen or progesterone) > 1% • HER2– (score 0 or 1 by immunochemistry) • FISH-negative (if the IHC score is 2)	5. Any form of BC other than the inclusion criteria, particularly inflammatory and/or overlooked forms (stage IIIb or IV)
6. Clinical stages II and IIIA	6. Nonmeasurable tumor
7. No previous BC surgery, radiotherapy, HT, or CT	7. Bilateral BC
8. Measurable disease	8. Previous treatment for BC including surgery for their disease or have had primary axillary dissection, radiotherapy, and systemic therapy
9. Hematology • Neutrophil count ≥ 1.5 × 10^9/L • Platelet count ≥ 100 × 10^9/L • Leukocyte count > 3,000/mm • Hb > 9 g/dL	9. Patients with a history of other cancer, except in situ cervical cancer or basocellular skin cancer, considered cured
10. Hepatic function • Total bilirubin ≤ 1.5 × UNL • ASAT ≤ 2.5 × UNL • ALAT ≤ 2.5 × UNL • Alkaline phosphatase ≤ 2.5 × UNL	10. Patients have another disease, which is deemed incompatible with the inclusion in the protocol
11. Renal function • Creatinine clearance ≥ 40 mL/min in the case of MRI • Serum creatinine ≤ 1.5 × UNL (and if serum creatinine > 1.5 × UNL and creatinine clearance ≥ 50 mL/min)	11. Heart, kidney, medullary, respiratory, or liver failure • Clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure, and serious uncontrolled cardiac arrhythmia) < 1 year before enrollment in the study • History of interstitial lung disease, eg, pneumonitis or pulmonary fibrosis or evidence of interstitial lung disease at baseline • Acute urinary infection and ongoing hemorrhagic cystitis
12. Metabolic function • Serum calcium ≥ lower limit of normal • Serum magnesium ≥ lower limit of normal	12. Uncontrolled diabetes
13. No anthracycline contraindication and no progressive heart disease and (normal LFEV per institution guidelines)	13. A symptomatic or progressive disorder of the CNS or peripheral neuropathy > grade II
14. Negative pregnancy test (urine or serum) within 7 days before registration for all women of childbearing age. Patients of childbearing potential must implement adequate nonhormonal contraceptive measures during study treatment	14. Significant psychiatric abnormalities 15. History of hypersensitivity to studied treatment or excipients 16. Known previous or ongoing abuse narcotic drug, other medication, or alcohol 17. Any investigational agent within 30 days before initiation of study treatment 18. Major surgical procedure within 28 days of initiation of treatment 19. Subject unwilling or unable to comply with study requirement

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, chemotherapy; ET, endocrine therapy; HR+, hormone positive; HT, hormonal therapy; LVEF, left ventricular ejection fraction.

regulations (21CFR Part 11). The analyses were conducted on data extracted from the ongoing SAFIA database and were performed using the validated SAS 9.4, software.

RESULTS

Patient Disposition

At the time of this interim analysis of SAFIA trial (May 2020), a total of 331 patients were accrued in 24 centers and six countries of the MENA region (Saudi Arabia, Egypt, Jordan, Lebanon, Algeria, and Tunisia) (Fig 2). Owing to administrative barriers at the governmental level barring pathology samples to be shipped overseas, 53 patients from Egypt did not benefit from the determination of 21-gene test; four patients dropped out before sending the pathology material for testing; and one patient was deemed noneligible. Two hundred seventy-three 21-gene assays were performed: 10 patients had insufficient carcinoma material for RS result determination, and five patients dropped out after the results of the RS test and before NAHT. Among the remaining 258 patients, 202 patients with an RS of 0-30 (78.3%) were treated with induction NAHT.

Description of Patient Population With Known RS Results (n = 258)

Patient characteristics with known RS results are as follows: median age: 49 years (25-84); pre- or perimenopausal: 151 (58.5%) or postmenopausal: 107 (41.5%); invasive ductal carcinoma: 205 (79.5%), invasive lobular carcinoma: 30 (11.6%) and other carcinomas: 23 (8.9%); grade I: 27 (10.8%), grade II: 196 (78.7%), and grade III: 26 (10.5%); Ki-67 ≤ 14%: 98 (38%) and Ki-67 > 14%: 160 (62%); and clinical stage: IIA: 117 (45.3%), IIB: 103 (39.9%), and IIIA: 34 (13.2%) and missing: 4 (1.6%); Differential characteristics according to RS < 31 and ≥ 31 are shown in Table 2.

Distribution of RS Scores (n = 263)

Overall, the RS result determination showed a median of 18 (0-75) with 56 patients with an RS ≥ 31 (21.3%) and 207 with an RS < 31 (78.7%) distributed as follows: RS results 0-10: 35 (13.3%), 11-18: 88 (33.5%), 19-25: 59 (22.4%), and 26-30: 25 (9.5%).

Response to Induction Fulvestrant 500 mg (With or Without Goserelin)

At the time of this interim analysis, 182 patients were evaluable for response. Responses, according to the RS results, are displayed in Table 3 and Figure 3. Overall, the nonprogression (NP) rate (CR + PR + MR) was 93.4% with CR: 4.9% and PR: 67% for a major response rate (CR + PR) of 71.9% and a MR rate of 26.4%. Alternatively, six patients (3.3%) had a progression disease (PD), and six additional patients (3.3%) a MP (between 1% and 25%) for a total overall progression (PD + MP) of 6.6%.

Correlations Between Radiologic Response and RS Result

When considering NP rates between the RS groups 0-10, 11-25, and 26-30, no significant differences were observed with NP rates of 97%, 93%, and 95%, respectively, suggesting that all tumors in these subgroups are expressing a high hormone sensitivity. Interestingly, major response rates (CR + PR) were comparable for the two groups RS 0-10 (70%) and 11-25 (64%) but higher for the RS 26-30 group at 86% at the limit of the statistical significance ($P = .05$).

Feasibility of the 21-Gene Assay on Core Biopsies

At the time of the analysis, 273 core biopsies were sent and the RS results were available in a median time of 8 days. Two hundred sixty-three patients had a positive determination of RS results (96.3%), whereas 10 patients (3.7%) had insufficient carcinoma on the provided specimens.

DISCUSSION

Neoadjuvant therapy was initially used to treat inoperable inflammatory and locally advanced breast carcinoma.[27] First-generation neoadjuvant trials for operable disease showed that NACT was similar to adjuvant CT in terms of disease-free survival and overall survival, while increasing the rates of conservative surgery and pCR, which was shown to be correlated with improved survival. Second-generation

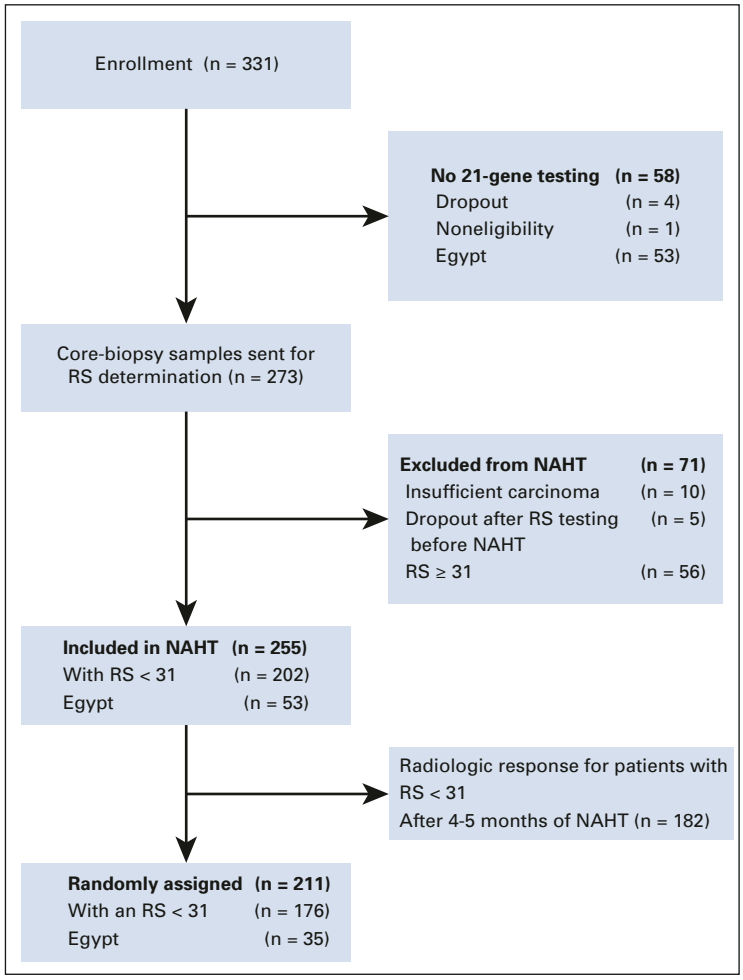

FIG 2. Patient disposition. NAHT, neoadjuvant hormone therapy; RS, recurrence score.

TABLE 2. Patient Characteristics (RS < 31 and RS ≥ 31)

	RS < 31 (n = 202), No. (%)	RS ≥ 31 (n = 56), No. (%)
Histologic type		
Ductal	154 (77)	51 (91)
Lobular	29 (14)	1 (2)
Mixed	2 (1)	1 (2)
Others	16 (8)	3 (5)
Histologic grade SBR		
I	27 (13.4)	0 (0)
II	155 (76.7)	41 (73.2)
III	13 (6.4)	13 (23.2)
NA	7 (3.6)	2 (3.6)
Ki67 value, %		
≤ 14	95 (47)	3 (5)
> 14	107 (53)	53 (95)
Clinical stage		
IIA	99 (49)	18 (32.1)
IIB	79 (39.1)	24 (42.9)
IIIA	21 (10.3)	13 (23.2)
NA	3 (1.6)	1 (1.8)
Luminal subtype by IHC		
A	111 (55)	9 (16)
B	90 (44.6)	47 (84)
NA	11 (5.4)	0 (0)

Abbreviations: IHC, immunohistochemistry; NA, not available; RS, recurrence score; SBR, Scarff Bloom Richardson.

neoadjuvant trials aimed at optimizing the pCR rates using various CT therapeutic strategies.[28] A meta-analysis of the three prospective studies that compared endocrine therapy (ET) with CT in the neoadjuvant setting of ER + BC showed that CT was comparable with ET.[29]

Third-generation neoadjuvant trials allow the prospective selection of in vivo patient subpopulations with secondary therapeutic adaptation on the basis of the individual patient sensitivity to induction therapy, representing a potential model for individual biologic developments.[30]

In our third-generation neoadjuvant trial, we used upfront 21-gene assay to select patients with a higher probability of hormone sensitivity (RS < 31) to prospectively assess in vivo the efficacy of induction fulvestrant 500 mg (with or without goserelin) before randomly assigning hormone-sensitive patients to fulvestrant 500 mg (with or without goserelin) plus palbociclib vs fulvestrant 500 mg (with or without goserelin) plus placebo. The characteristics of our cohort are in line with the literature on the BC population from the MENA region with a majority of pre- or peri-menopausal patients (58.5%) with relatively aggressive clinical-pathologic luminal characteristics such as Ki-67 ≥ 14% in 62% of cases.[31] Of note, the majority of patients presented with stage II (89.6%) tumors.

Our feasibility in performing the 21-gene assays on core biopsy specimens was optimal in 96.4% in our MENA population with insufficient carcinoma material in only 3.6% of cases. These results compare favorably with reports from the literature with failure rates ranging from 4.8% to 10.2%, further validating the feasibility of the 21-gene assay in a neoadjuvant setting.[32]

In terms of RS result distribution, Iwata et al[33] reported in the TransNEOS study on 275 patients with known RS: RS < 18: 53.2%, RS 18-30: 28.5%, and RS ≥ 31: 18.3%. Our results are comparable with 263 patients from the MENA region: RS < 18: 46.8%, RS 18-30: 31.9%, and RS ≥ 31: 21.3%.

Our responses to induction NAHT with fulvestrant with or without goserelin for patients with an RS < 31 confirm a high hormone sensitivity with a NP rate (CR + PR + MR) of 93.4%. We chose to divide stable disease into MR (response from 0% to 25%) and MP (from 1% to 25%), to assess more precisely the potential hormone sensitivity, in particular, for tumors with a low proliferative index such as the majority of luminal A subtypes. Alternatively, we consider that tumors with MP express an intrinsic hormone resistance. This approach was aimed at maximizing patients with in vivo hormone sensitivity before exposure to palbociclib versus placebo in the postrandomization stage. The low rate of progression (6.6%), combining MP (3.3%) and the classical PD (3.3%), suggests that the upfront determination of 21-gene assay RS < 31 has allowed us to

TABLE 3. Radiologic Response for Patients With an RS < 31

RS or Response	0-10, No. (%)	11-25, No. (%)	26-30, No. (%)	Total, No. (%)	*P*
CR	2 (6)	6 (5)	1 (5)	9 (5)	NS
PR	19 (64)	77 (59)	17 (81)	113 (62)	.05
CR + PR	21 (70)	83 (64)	18 (86)	122 (67)	.05
SD	29 (97)	121 (93)	20 (95)	170 (93.4)	NS
PD	1 (3)	10 (7)	1 (5)	12 (3.3)	NS
Total	30 (100)	131 (100)	21 (100)	182 (100)	NS

Abbreviations: CR, complete response; NS, nonsignificant; PD, progressive disease (> 25%); PR, partial response (response > 50%); RS, recurrence score; SD, stable disease.

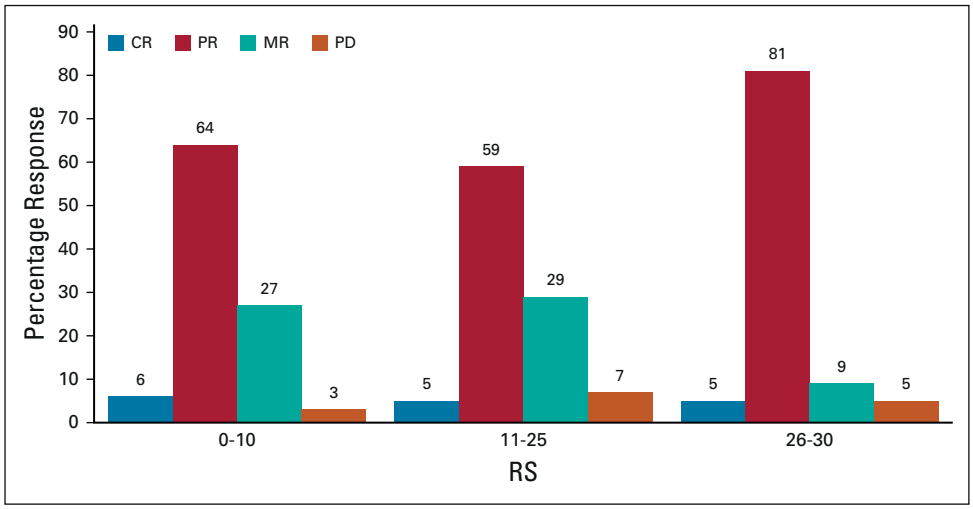

FIG 3. Bar chart depicting response rates (%) to induction fulvestrant with or without goserelin according to RS. CR, complete response; MR, minor response; PD, progressive disease; PR, partial response; RS, recurrence score.

eliminate the majority of potential de novo hormone-resistant tumors. Consequently, using induction fulvestrant 500 mg (with or without goserelin) in the RS < 31 group is not bearing a significant risk of progression for these patients. Of note is the fact that when evaluating the NP rates (CR + PR + MR) according to the RS (0-10, 11-25, and 26-30), we noticed that there was no significant difference in terms of hormone sensitivity between the three groups (NP rates 97%, 93%, and 95%, respectively). Interestingly, the major response rate (CR + PR) was superior in the RS 26-30 group compared with the RS 0-10 and 11-25 groups (respectively, 86% *v* 70%, 64%) at the limit of the statistical significance ($P = .05$). Alternatively, MR rates were lower in the RS 26-30 group compared with the RS 0-10 and 11-25 groups (respectively, 9% *v* 27%, 29%). These observations suggest that the tumor proliferation rate may play an important role in the kinetics of response to fulvestrant 500 mg (with or without goserelin) and thus could plead for a longer exposure to NAHT before drawing conclusions in terms of efficacy. This might be particularly true for tumors with low proliferation rates such as luminal A and low RS result tumors. These results, obtained by post hoc, exploratory analyses, are hypothesis-generating and deserve confirmation.

Our observations in selecting patients with potential hormone sensitivity with upfront 21-gene assay might be of value, especially during the COVID-19 outbreak during which many centers had to delay planned elective surgeries. Consequently, fulvestrant 500 mg (with or without goserelin) in patients with luminal ER+, HER2–, and an RS < 31 could be an alternative to upfront surgery without significant loss of chance in pandemic times. The COVID-19 Pandemic Breast Cancer Consortium has formulated preliminary guidelines regarding patients with ER+, HER2– tumors, that is, deferring surgery and receiving neoadjuvant endocrine therapy for 6-12 months without clinical compromise.[34]

In conclusion, the use of upfront 21-gene assay on biopsies is feasible and has allowed us to select in SAFIA neoadjuvant phase III study a large population of patients (78.7%) with an RS < 31 expressing a high hormone sensitivity. With an overall NP rate of 93.4%, no significant difference in fulvestrant (with or without goserelin) efficacy was noticed between RS results 0-10, 11-25, and 26-30. Interestingly, in exploratory analyses, patients with high RS results (26-30) showed a trend toward a higher major response rate, probably related to a higher tumor proliferation (Ki-67 > 14% in 95% of cases). Neoadjuvant fulvestrant with or without goserelin in patients with luminal ER+, HER2–, and an RS < 31 could be an alternative to upfront surgery without significant risk of progression, particularly in pandemic times.

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CLINICAL TRIAL INFORMATION

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DATA SHARING STATEMENT

Data are private as the study is still ongoing.

AUTHOR CONTRIBUTIONS

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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