

ARETTA: Assessing Response to Neoadjuvant Taxotere and Subcutaneous Trastuzumab in Nigerian Women With HER2-Positive Breast Cancer: A Study Protocol

Atara I. Ntekim, MD¹; Abiola Ibraheem, MD²; Adenike A. Sofoluwe, MB, BCh, MSc³; Olayinka Kotila, B Pharm, PhD⁴; Chinedum Babalola, B Pharm, PhD⁴; Theodore Karrison, PhD⁵; and Christopher O. Olopade, MD, MPH⁶

Human epidermal growth factor receptor 2 (HER2) subtype of breast cancer is aggressive, leading to a poor outcome. Targeted therapy with trastuzumab has been shown to be effective in the treatment of HER2-positive breast cancer. Cardiotoxicity is a specific adverse effect associated with trastuzumab. The initial formulation of trastuzumab was intravenous, but presently, a subcutaneous formulation (Herceptin SC) is available. Insufficient data on the response rate and cardiotoxic effects of trastuzumab among indigenous Black populations exist. In all studies evaluating the efficacy and toxicity of trastuzumab alone or in combination with chemotherapy, indigenous Black populations in Africa were not included, yet they are the ones most likely to benefit from highly effective cancer medicines. This is partly due to poor oncology clinical trial infrastructure in sub-Saharan Africa. The ARETTA study protocol (ClinicalTrials.gov identifier: [NCT03879577](https://clinicaltrials.gov/ct2/show/study/NCT03879577)) is a phase II multicenter feasibility study to evaluate the efficacy and toxicity of docetaxel given every 3 weeks for 4 cycles plus trastuzumab in 60 previously untreated women with nonmetastatic breast cancer. The primary endpoint is to assess the proportion of patients with complete pathologic response. Secondary endpoints include the number of patients who require dose delays in docetaxel and trastuzumab attributed to hematologic, GI, and cardiac toxicity. Pharmacokinetic profiles of subcutaneous trastuzumab will also be determined. The ARETTA study will provide important information on the clinical response and cardiac safety of subcutaneous trastuzumab in combination with docetaxel among indigenous African women with nonmetastatic breast cancer. It can also be used as a blueprint for conducting biomarker-driven oncology clinical trials in low-resource settings such as sub-Saharan Africa.

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INTRODUCTION

The incidence of cancer in sub-Saharan Africa (SSA) is increasing, with high mortality. Racial/ethnic disparities in cancer mortality continue to widen, and biomarker-intensive clinical trials rarely investigate patients with cancer in underserved populations of African ancestry. Few studies that describe differences in genomic characteristics of malignancies among people of African descent compared with Whites exist, implying the need for an individualized treatment approach.¹

Clinical trials through which evidence for effective therapies are obtained are scarce in SSA. Moreover, most cancer drugs currently in use in SSA were never tried in the region before approval. Among the study population, there is a scarcity of data on the response rate, toxicity, and quality of life (QoL) during treatment with any cancer therapy currently in use. Ethnic and population variations exist with respect to drug response and toxicity.² There is a need to bring oncology

clinical trials into SSA to provide evidence for treatment choice. Without optimal chemotherapy, cancer mortality, including breast cancer mortality in the Nigerian population, will remain high. In 2018, the estimated number of newly diagnosed patients with breast cancer in Nigeria was 26,310, constituting approximately 23% of all patients with cancer. Of these, 11,564 (45%) of patients with breast cancer died as a result of the disease.³ Ensuring the development of cancer research that meets the needs of people who live in low-resource settings is integral to alleviating the cancer burden. There is a view that a focus on phase II and III cancer clinical trials in SSA can give African researchers the opportunity to “learn by doing” to foster sustainable clinical research capacity through international collaboration between African partners and developed countries, and regional collaboration among African research institutes.⁴ Research collaborations between African and non-African partners hold the potential to have a significant impact on the development of clinical research capacity in SSA. This

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CONTEXT

Key Objective

Can more oncology clinical trials be conducted in sub-Saharan Africa? This study is an example of a simple, feasible, and suitable protocol that can be implemented in sub-Saharan Africa.

Knowledge Generated

The study protocol will determine the response and toxicity profile of docetaxel and subcutaneous Herceptin (trastuzumab) in Nigerian women with human epidermal growth factor receptor 2 (HER2)-positive breast cancer. The outcome of the study will provide local data that will guide oncologists in choice of chemotherapy for patients with HER2-positive breast cancer in Nigeria and sub-Saharan Africa.

Relevance

The implementation of this protocol will enable investigators in sub-Saharan Africa to build clinical trial teams and gain experience in oncology clinical trials.

study is a collaboration between the University of Chicago and 4 centers in Nigeria.

The lack of participation of Black patients in clinical trials prevents the application of clinical trial results to the global population.⁵ To ensure successful implementation of clinical trials in low-resource settings such as SSA, studies with a simple design should be started to provide a learning curve for conducting clinical trials in the region.² The ARETTA study is a good example of such a study. This study will provide for the first time, to our knowledge, efficacy data on oncology treatment of solid tumors among adults in the SSA population. Toxicity, pharmacokinetic, and QoL data will also be generated. Biosamples will be obtained for archiving for future correlative studies that will further assist in the discovery of other indices relevant to breast cancer in Nigeria. Lessons learned during the implementation of this clinical trial will be valuable toward improving clinical trial activities in SSA, and this information may also be applied to lower-resource settings in the United States.

This study will determine the efficacy and toxicity of 4 cycles of neoadjuvant docetaxel chemotherapy given every 3 weeks in conjunction with subcutaneous trastuzumab (Herceptin SC) followed by 1 year of subcutaneous trastuzumab in Nigerian women with HER2-positive breast cancer. The pharmacokinetic profiles of these drugs will also be determined. Currently, there is a scarcity of data on the response rate, toxicity, and pharmacokinetic profiles of these agents in the indigenous Black population. Of note is the fact that few people can afford HER2-targeted therapy in Nigeria or even standard chemotherapy without obtaining financial support from outside sources. The standard of chemotherapy care in Nigeria for HER2-positive breast cancer is anthracycline (doxorubicin-epirubicin with cyclophosphamide with or without fluorouracil [AC-EC-FEC]) for 4 courses, followed by a taxane with trastuzumab. This regimen is given in the adjuvant setting. In this study, neoadjuvant treatment will be given to assess

chemosensitivity of the systemic agents, namely, docetaxel and trastuzumab. FEC will be introduced if there is an unsatisfactory response to docetaxel and trastuzumab. Because such patients would already be receiving trastuzumab, it would be continued. A previous protocol using neoadjuvant paclitaxel given once per week plus trastuzumab followed by concurrent epirubicin (75 mg/m² once every 3 weeks plus trastuzumab) resulted in no patient developing drug-induced congestive cardiac failure.⁶ However, to minimize toxicity, only 3 courses of FEC instead of 4 will be given in this study to drastically reduce the cumulative dose of epirubicin, which is less cardiotoxic than doxorubicin.

Few patients in Nigeria have been able to afford a complete course of trastuzumab (18 cycles) so far. Most patients take a few courses and default because of lack of money.⁷ Patients with cancer in Nigeria pay for cancer treatment out of pocket. In most instances, because of the high cost of cancer treatment, most patients cannot afford treatment and therefore seek financial support from family members and philanthropists. If these are not forthcoming, they abandon the treatment. Health insurance in Nigeria, which covers approximately 5% of the population, provides limited support to patients with cancer.⁸ This often leads to suboptimal therapy. Under such conditions, retrospective data on the response rate and toxicity of chemotherapy agents are not reliable. In this study, optimal therapy will be provided. This will lead to the acquisition of complete data for analysis. The aim of this protocol is to study the effect of docetaxel and trastuzumab combination (response rate and toxicity) on the indigenous African population. The resulting data will be used to support advocacy activities to draw support from public and private sectors toward supporting effective treatment of patients with HER2-positive breast cancer in Nigeria.

ARETTA STUDY DESIGN

ARETTA (ClinicalTrials.gov identifier: [NCT03879577](https://clinicaltrials.gov/ct2/show/study/NCT03879577)) is a 1-stage, phase II, multicenter feasibility and suitability

study to evaluate the efficacy and toxicity of docetaxel given every 3 weeks for 4 cycles plus trastuzumab in 60 previously untreated women with nonmetastatic breast cancer. The primary endpoint is to assess the proportion of patients with complete pathologic response (pCR) at surgery. Secondary endpoints include the number of patients who required dose delays in docetaxel and trastuzumab attributed to hematologic, GI, and cardiac toxicity. Pharmacokinetic profiles of trastuzumab will also be described. The study has been approved by the institutional review boards of the 4 participating centers, as well as the National Agency for Food and Drug Administration, the body responsible for food and drug administration in Nigeria.

The study considers docetaxel given every 3 weeks for 4 cycles as recommended backbone to be combined with subcutaneous trastuzumab.⁹ This combination has been shown to be efficacious with manageable toxicities in other populations. One of the objectives for this biomarker-stratified phase II feasibility/suitability study is to establish a platform for clinical trials in Nigeria and identify genomic biomarkers of response and toxicity to protocol-driven and optimal HER2-targeted therapy in Nigerian women. The biomarker of interest in this study is HER2 protein. The expression of HER2 protein on breast cancer samples will be used to select patients with breast cancer for participation in this study because trastuzumab, an investigational medical product, is a targeted therapy against HER2-positive breast cancer. Taxane given once every 3 weeks has been reported to be well tolerated by elderly patients with breast cancer, and one of our objectives is to use this clinical trial to improve management of chemotherapy toxicities in patients undergoing treatment of cancer.¹⁰

Breast ultrasound will be performed at baseline and after every 2 cycles (every 6 weeks) during neoadjuvant chemotherapy. Patients with complete clinical response (CCR) after breast ultrasound assessment after 4 cycles of docetaxel plus subcutaneous trastuzumab will undergo surgery. At surgery, those with pCR will not have additional chemotherapy, and they will receive 1 year of subcutaneous trastuzumab to complete 18 cycles. Those with partial response (PR) or stable disease (SD; operable) based on RECIST criteria version 1.1 (using breast ultrasound measurements) will be switched to have FEC plus subcutaneous trastuzumab for an additional 3 cycles in the neoadjuvant setting. Breast ultrasound will be repeated, and those with clinical response (CCR- or PR-operable) will undergo surgery and continue to complete 18 cycles of subcutaneous trastuzumab after surgery within 1 year. Patients with SD (inoperable) after salvage FEC plus subcutaneous trastuzumab or patients with progressive disease (PD) before salvage FEC plus subcutaneous trastuzumab will go off study treatment and have additional therapy by the managing physician and will be followed for the survival endpoint. Adjuvant treatment will

include hormonal therapy for hormone receptor-positive disease. Radiation therapy will be administered per standard of care.

The primary endpoint is pCR in the 1-stage phase II design. All patients will have active follow-up every 3 months and have routine blood tests and physical examination for the first 2 years and every 6 months for 10 years. Computed tomography scans and bone scans will be performed as clinically indicated during the follow-up period to evaluate recurrence.

Treatment

All patients will commence per-protocol treatment within 2 weeks of diagnosis. We plan to treat patients with docetaxel plus subcutaneous trastuzumab given every 3 weeks for a total of 12 weeks per the schema in [Figure 1](#). Ultrasonography for response assessment will be performed every 6 weeks, and patients achieving CCR after 4 cycles of docetaxel plus subcutaneous trastuzumab will undergo surgery. Surgery will be performed in the fourth week after the last cycle of chemotherapy. Adjuvant hormone therapy is recommended for 5-10 years for all estrogen receptor-positive (ER+) or progesterone receptor-positive (PgR+) patients after the completion of surgery and chemotherapy (ER+/PgR+ defined as $\geq 1\%$ of stained nuclei/hpf). Hormone receptor status will be determined at initial core biopsy for assignment of targeted therapy with tamoxifen or aromatase inhibitor of choice, and it will be reassessed in resected tumors. Tamoxifen (20 mg orally once daily) or the aromatase inhibitor letrozole (2.5 mg orally once daily; for documented postmenopausal women only)¹¹ will be started within 12 weeks of completion of chemotherapy. This allows for the variable period needed for surgery to be completed. All premenopausal patients will receive the luteinizing hormone-releasing hormone (LHRH) agonist goserelin (Zoladex) 10.8 mg (subcutaneously) every 3 months for 2 years from the onset of study treatment. Addition of LHRH agonists to tamoxifen, chemotherapy, or both, has been reported to reduce disease recurrence and death after recurrence in premenopausal women with hormone receptor-positive breast cancer.¹² Furthermore, when fertility issues are a concern, the use of LHRH agonists has been recommended in young women with breast cancer when other more effective fertility preservation methods, such as unfertilized ova cryopreservation with in vitro fertilization, embryo cryopreservation, and ovarian tissue cryopreservation, are not feasible.¹³ In our setting, these methods are not available. QoL assessment using the European Organisation for Research and Treatment of Cancer QoL instrument (English or Yoruba language versions) will be administered for all participants before each chemotherapy session.

In this study, we consider docetaxel given every 3 weeks as recommended backbone to be combined with subcutaneous trastuzumab, with a manageable toxicity rate.

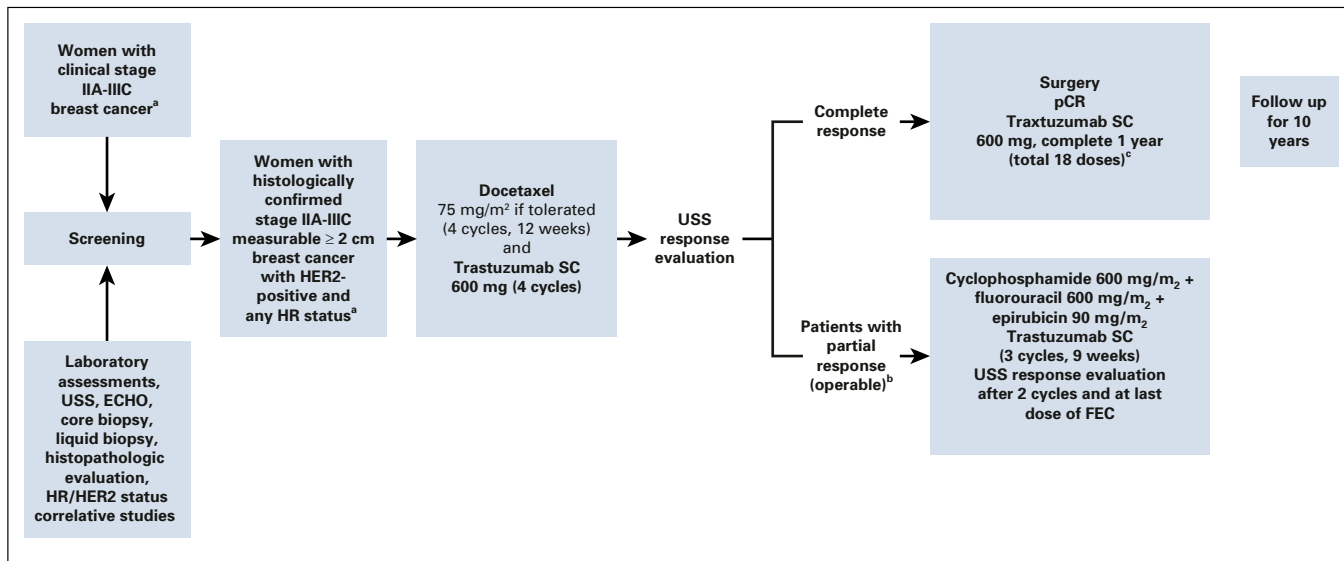


FIG 1. Schema showing the treatment schedule for patients in the ARETTA study. Docetaxel (T): given once every 3 weeks for a total of 4 cycles to be administered with trastuzumab. FEC: given once every 3 weeks for a total of 3 cycles to be administered for partial responders before surgery. Trastuzumab (Herceptin): given once every 3 weeks for a total of 4 cycles with docetaxel (or 7 doses for patients receiving FEC) preoperatively. Hormone receptor–positive patients will receive hormonal therapy. After surgery, all patients will continue trastuzumab to complete 1 year. ^(a) Women must also meet other inclusion criteria (listed in Key Inclusion Criteria). ^(b) Inoperable patients and patients with progressive disease will be taken off the study. ^(c) Patients with residual disease at surgery may receive additional chemotherapy at the discretion of the treating oncologists if hormone receptor negative. Hormone receptor positive patients will receive hormonal therapy. After surgery, all patients will continue trastuzumab to complete 1 year. ECHO, echocardiography; FEC, cyclophosphamide, fluorouracil, and epirubicin; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LHRH, luteinizing hormone-releasing hormone; pCR, complete pathologic response; SC, subcutaneous; USS, ultrasound scanning.

This combination has been shown to be efficacious with manageable toxicities in other populations and is also tolerated by elderly patients. Docetaxel is a highly effective agent in metastatic breast cancer. Response rates and duration of response and survival are improved when trastuzumab is combined with chemotherapy. Furthermore, preclinical reports demonstrate synergistic cytotoxic activity when docetaxel and trastuzumab are combined. Their different mechanisms of action and a nonoverlapping toxicity profile make this combination attractive for minimizing potential cardiotoxicity.¹⁴ Although many guidelines recommend the use of doxorubicin and cyclophosphamide for 4 cycles followed by docetaxel with subcutaneous trastuzumab, we chose to start with docetaxel and subcutaneous trastuzumab in the neoadjuvant setting. If there is a pCR, the patients will not need to continue with additional toxic regimen, which is one of the factors that most Nigerian women are afraid of while receiving chemotherapy. Docetaxel will be given at 75 mg/m², increasing to 100 mg/m² from cycle 2 onward if the 75-mg starting dose was well tolerated (by intravenous infusion and diluted in normal saline [NS] or 5% dextrose in water [D5W]) and given every 3 weeks for 4 cycles.¹⁵ Patients with CCR will have surgery within 4 weeks of the last dose of docetaxel plus trastuzumab. Patients with PR or SD will continue with 3 doses of FEC (3 cycles of intravenous FEC [fluorouracil 600 mg/m², epirubicin 90 mg/m², and cyclophosphamide 600 mg/m², diluted in NS or D5W]) plus trastuzumab every

3 weeks before surgery. Six courses of epirubicin have been combined with trastuzumab in metastatic breast cancer with a lower dose-limiting cardiotoxicity of 1.7% compared with the doxorubicin arm with a dose-limiting toxicity of 5%.¹⁶ In this study, we use a lesser dose (3 courses) to improve cardiotoxicity and to enlist the good response of breast cancer to an anthracycline-based regimen after poor response to first-line docetaxel.⁶ While receiving chemotherapy, patients with an absolute neutrophil count (ANC) between 1,000 and 1,500 will receive filgrastim with chemotherapy, whereas those with ANC < 1,000 will receive filgrastim and wait until ANC is ≥ 1,000 before additional chemotherapy.

All patients will receive anti-HER2 blockade trastuzumab. Trastuzumab therapy will be given at 600 mg subcutaneously (fixed dose irrespective of patients' weight/body surface area) on day 1 of each cycle and thereafter every 3 weeks. A total of 18 doses will be given (1 year). Trastuzumab dosing is not interrupted during surgery. The doses and treatments, as well as dose adjustment schedules, are presented in Tables 1 and 2.

Toxicity Assessment

Toxicity will be assessed using National Cancer Institute–Common Terminology Criteria for Adverse Events (version 5).

Toxicity due to docetaxel or FEC may be managed by symptomatic treatment, dose interruptions, and adjustment of docetaxel-FEC dose. Weekly reassessment of

toxicities will be performed to guide appropriate dose adjustments. The schedule for dose adjustments for the chemotherapy regimens is provided in Table 2. Doses of medications omitted for toxicity are not replaced or restored; instead, the patient should resume the planned treatment cycles. The omitted doses will be noted as treatment interruptions. Patients who miss their treatment doses for more than 2 consecutive weeks will be classified under treatment interruptions and will not be analyzed as per-protocol treatment. There is no dose modification for subcutaneous trastuzumab

Cardiomyopathy. We will assess for symptoms before each cycle and evaluate cardiac toxicity by echocardiography every 12 weeks during neoadjuvant treatment and every 12 weeks during adjuvant trastuzumab. Treatment with trastuzumab will be stopped for a minimum of 3 weeks (1 cycle) for any of the following: if left ventricular ejection fraction (LVEF) is < 50% with \geq 15% decrease from baseline; if LVEF returns to 50% or higher, treatment can be resumed; if a decrease in LVEF persists or has declined further, or if clinically significant congestive heart failure has developed, treatment with trastuzumab will be stopped; and if, after a repeat assessment within approximately 3-7 weeks (2 cycles), the LVEF has not improved or has declined further, trastuzumab will be discontinued.

Correlative studies. Tissue samples collected under this study will also be used by the University of Chicago with Nigerian investigators to generate additional biomarkers and molecular data on next-generation technology platforms and future studies on breast cancer in Nigerian

women. These molecular characteristics (biomarkers/pathways) will be used for better stratifying tumor type and to correlate with pathologic, imaging, or response to treatment measures. During the trial, standard and exploratory biomarkers will be tested for their ability to predict tumor response to specific classes of investigational targeted therapeutics.

Key Inclusion Criteria

Women ages 18 to 70 years who have biopsy-accessible breast tumor of significant size for core needle biopsy/ultrasound measurable (\geq 2 cm) and with histologically confirmed carcinoma of the female breast with 3+ positive HER2 status by immune histochemistry (IHC) are included. At present, there are no facilities for fluorescence in situ hybridization/in situ hybridization testing in Nigeria for the confirmation of equivocal HER2 status (2+ by IHC). Such samples are usually sent outside the country for confirmation if the individual can afford to pay for the services. Otherwise, additional treatment is usually at the discretion of the treating physician. However, if a participant with equivocal IHC result can afford FISH/ISH testing and the result is positive for HER2 overexpression, the patient will be eligible to participate in the study.

Participants should have clinical stages IIA-IIIC (American Joint Committee on Cancer 2009) and be chemotherapy naïve. They also should have Eastern Cooperative Group performance status 0-2; echocardiogram baseline LVEF \geq 55%; adequate bone marrow function defined as ANC \geq 1,000/mm³; platelets \geq 100,000/mm³; and hemoglobin \geq 10 g/dL or packed cell volume 30%.

TABLE 1. Dose and Treatment Schedule

Study Treatment	Pharmaceutical Form and Route of Administration	Dose	Frequency and/or Regimen
Docetaxel and trastuzumab			
Docetaxel	Intravenous infusion (1 hour)	75 mg/m ² , then 100 mg/m ² from dose cycle 2 onward, if tolerated	Day 1, 21 (once every 3 weeks), 4 doses
Trastuzumab	Subcutaneous injection (2-5 min)	600 mg	Day 1 (21-day cycle), 18 doses
FEC and trastuzumab			
Epirubicin	Intravenous infusion (1 hour)	90 mg/m ²	once-every-3-weeks cycle, 3 doses
Fluorouracil	Intravenous	600 mg/m ²	once-every-3-weeks cycle, 3 doses
Cyclophosphamide	Intravenous	600 mg/m ²	once-every-3-weeks cycle, 3 doses
Other medications			
Tamoxifen ^a	Oral tablets	20 mg	Daily (continuous) after surgery for 10 years
Letrozole ^a	Oral tablets	2.5 mg	Daily (continuous) after surgery for 10 years
LHRH agonist goserelin ^b	Subcutaneous injection	10.8 mg	Every 3 months for 2 years

Abbreviations: FEC, cyclophosphamide, fluorouracil, and epirubicin; LHRH, luteinizing hormone-releasing hormone.

^aTamoxifen/letrozole only for hormone receptor-positive patients.

^bLHRH agonist goserelin (Zoladex) only for premenopausal patients.

TABLE 2. Dose Adjustment Schedules After Toxicity

Adverse Drug Reaction	Grade 2	Grade 3	Grade 4
First appearance	Interrupt treatment until resolved to grade 0-1, then continue at 1 dose level ^a lower than the original docetaxel or FEC dose where possible	Interrupt treatment until resolved to grade 0-1, then continue at 1 dose level ^a lower than original docetaxel or FEC dose, with prophylaxis where possible	Interrupt treatment if investigator considers it to be in the best interest of the patient; continue at 2 dose levels lower for docetaxel or FEC dose, once toxicity has resolved to grade 0-1
Second appearance of the same toxicity	Interrupt treatment until resolved to grade 0-1, then continue at 2 dose levels ^b lower than the original docetaxel or FEC dose	Interrupt treatment until resolved to grade 0-1, then continue at 2 dose levels ^b lower than original docetaxel or FEC dose	
Third appearance of the same toxicity	Discontinue study treatment	Discontinue study treatment	

Abbreviation: FEC, cyclophosphamide, fluorouracil, and epirubicin.

^aOne dose level: docetaxel = 75 mg/m² if taking 100 mg/m² or 60 mg/m² if taking 75 mg/m²; FEC = decrease by 10% from normal dose.

^bTwo dose levels: docetaxel = 60 mg/m² if receiving 100 mg/m² or discontinuation if receiving 75 mg/m².

Key Exclusion Criteria

Pregnant or lactating women and those with distant metastasis (brain and/or visceral metastasis), with HER2-negative disease, or receiving treatment for other carcinomas within the last 5 years are excluded. Other exclusion factors include presence of other cardiac conditions that may increase the risk of cardiac compromise with trastuzumab. These include poorly controlled blood pressure (> 140/85 mmHg), significant valvular heart disease (presence of murmurs on auscultation), signs of heart failure (raised venous pressure, crepitations over the lung fields, or pedal edema), gross abnormalities in a 12-lead electrocardiogram such as arrhythmias (atrial fibrillation, atrial flutter, heart block), and evidence of previous myocardial infarction (Q waves, left bundle branch block).¹⁷

Statistical Considerations

All patients who signed consent and initiated neoadjuvant therapy will be included in the analysis. Demographics and baseline features will be presented using descriptive statistics. Based on a current review of the literature in other populations, for this study, we expect an inefficient treatment regimen of docetaxel plus subcutaneous trastuzumab to elicit 20% or fewer pCRs ($p_0 = 0.20$) and a successful treatment regimen to have at least 40% pCR at surgery ($p_1 = 0.40$; p_0 being the response proportion {pCR rate} that if true, clearly implies that the treatment does not warrant further study and p_1 being the response proportion that if true would imply that the treatment has sufficient efficacy to warrant further trials). The patients with SD or PR who attain pCR after an additional 3 courses of FEC will be counted as successes, whereas those who are declared inoperable or have PD will be considered failures. A 1-sided binomial test will be performed to test the null hypothesis of a 20% pCR rate versus a 40% alternative.

Secondary analyses will compare pCR rates by hormone receptor status, lymph node status, and breast cancer subtype using Fisher's exact test. Disease-free survival

(DFS) will be defined as the time from enrollment to first occurrence of any of the following events: recurrence of ipsilateral invasive breast tumor, recurrence of ipsilateral locoregional invasive disease, distant recurrence, contralateral invasive breast cancer, or death from any cause. DFS will be estimated by the Kaplan-Meier method; prognostic factors will be identified using Cox regression. The frequency of toxicity by type and grade will be summarized. Mixed effects regression models will be fit to analyze QoL.

PERSPECTIVES OF CANCER CLINICAL TRIALS IN SSA

The ARETTA protocol conforms with most of the considerations suggested on how to design trials toward increasing cancer clinical trials in SSA. A report by Gupta et al¹⁸ identified opportunities for clinical trials on cancer in developing countries, such as those in SSA. There are large numbers of patients who receive less intense treatments, thereby providing opportunities to try other agents, and trials using the neoadjuvant approach are particularly suitable. The ARETTA protocol will recruit treatment-naïve participants with nonmetastatic disease in the neoadjuvant setting. They also reported that clinical and translational research collaboration between centers in developed and developing countries is important for building capacity. The ARETTA protocol was developed by investigators from Nigeria but with guidance and input from collaborators from Novartis Institute for Biomedical Research, University of Chicago, and Roche, which are institutions from high-income countries. Specimens collected from the trial will be analyzed for collaborative studies at the University of Chicago. Gopal¹⁹ proposed key attributes of cancer clinical trials in SSA, as shown in Table 3.

Protocol Suitability

The concept of protocol suitability is different from feasibility. In contrast to "feasible," which is defined as achievable and possible, "suitable" means appropriate. Protocol suitability surpasses feasibility by addressing not only

TABLE 3. Ideal Attributes of a Cancer Treatment Trial in Sub-Saharan Africa and How ARETTA Study Meets These Attributes

Attributes	Features
The trial addresses local disease burden in an inclusive rather than exclusive manner.	The cancer is seen frequently in the region.
	The trial includes typical patients with this cancer in the region (eg, studies that include advanced-stage disease will generally be more valuable for most cancer types).
	The trial includes patients from urban and rural settings and from different tribal/ethnic groups. The trial makes a resource-appropriate standard of care available for all participants.
	This standard may not be exactly the same as that of HICs but, likewise, should not simply be what is usually available for routine care if this is not an acceptable standard.
The ARETTA study has the features for addressing local cancer disease burden in an inclusive manner.	
The trial provides new data for an intervention for which there is not sufficient published experience in the region.	The ARETTA study will provide data on docetaxel and trastuzumab for HER2-positive breast cancer among indigenous Black women. Such data are not currently available.
The intervention might be applied to patients in HICs if successful, although this is not essential to justify the trial.	Where these exist, opportunities to pursue a new global standard are important, rather than recurrently describing suboptimal or modestly effective treatment in challenging settings. The trial is designed and analyzed in a manner that maximizes time and cost efficiency.
	The anticipated cost-benefit ratio of the intervention is comparable to other established health interventions in the region.
	The ARETTA study outcome can be applied in the treatment of Blacks in HICs.
The trial's appropriateness and value are affirmed by local community representatives or patient groups before implementation.	Breast cancer survivors and support groups in Nigeria participated in the design of the ARETTA study.

NOTE. Adapted from Gopal.¹⁹

Abbreviations: HER2, human epidermal growth factor receptor 2; HICs, high-income countries.

technical aspects of the protocol but also considers study settings, environments, and culture, as well as effectiveness and efficiency of execution.²⁰ Protocol suitability can therefore be regarded as fit for purpose. This ensures minimal protocol deviation, which confers study integrity. Involvement of trial staff in protocol development has been stated as a key factor in ensuring protocol suitability. The ARETTA protocol development involved team members from the 4 participating institutions, thereby ensuring feasibility and suitability.

Indigenous Black women of SSA are under-represented in clinical trials. None of the current drugs used for breast cancer in the subregion were tested among SSA women

during the drug development processes. The design of a trial such as the ARETTA study, which takes into consideration the peculiarities of patient characteristics and available resources and infrastructure, will hopefully address barriers to participation of SSA women in global clinical trials and answer the question of the hematologic, neurologic, and cardiac safety of docetaxel and trastuzumab in indigenous Blacks from SSA. QoL issues as well as pharmacokinetic profiles of trastuzumab will also be described. The results of this novel trial will provide an important contribution toward narrowing the gap in cancer clinical trial disparities and further advance the goal of global personalized medicine.

AFFILIATIONS

¹Department of Radiation Oncology, College of Medicine, University of Ibadan, Ibadan, Nigeria

²Section of Hematology Oncology, University of Chicago, Chicago, IL

³Department of Radiology, College of Medicine, University of Ibadan, Ibadan, Nigeria

⁴Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Ibadan, Ibadan, Nigeria

⁵Department of Public Health Sciences, University of Chicago, Chicago, IL

⁶Center for Global Health, University of Chicago, Chicago, IL

CORRESPONDING AUTHOR

Atara I. Ntekim, MD, Department of Radiation Oncology, College of Medicine, University of Ibadan, Ibadan, Nigeria; Twitter: @tarantekim; e-mail: kimata2000@hotmail.com.

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AUTHOR CONTRIBUTIONS

Conception and design: Atara I. Ntekim, Abiola Ibraheem, Adenike A. Sofoluwe, Olayinka Kotila, Theodore Karrison, Christopher O. Olopade

Administrative support: Atara I. Ntekim, Olayinka Kotila, Chinedum Babalola

Provision of study materials or patients: Adenike A. Sofoluwe

Collection and assembly of data: Atara I. Ntekim, Abiola Ibraheem, Adenike A. Sofoluwe, Olayinka Kotila, Chinedum Babalola

Data analysis and interpretation: Abiola Ibraheem, Adenike A. Sofoluwe, Olayinka Kotila, Chinedum Babalola

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

- Pitt JJ, Riestler M, Zheng Y, et al: Characterization of Nigerian breast cancer reveals prevalent homologous recombination deficiency and aggressive molecular features. *Nat Commun* 9:4181, 2018 [Erratum: *Nat Commun* 10:288, 2019]
- Ramamoorthy A, Pacanowski MA, Bull J, et al: Racial/ethnic differences in drug disposition and response: Review of recently approved drugs. *Clin Pharmacol Ther* 97:263-273, 2015
- International Agency for Research on Cancer, WHO: Nigeria. Source: Globocan 2018. <https://gco.iarc.fr/today/data/factsheets/populations/566-nigeria-factsheets.pdf>
- Cochrane G, Manville C: Probing the barriers to conducting clinical research in sub-Saharan Africa. <https://www.rand.org/blog/2014/09/probing-the-barriers-to-conducting-clinical-research.html>
- Ibraheem A, Polite B: Improving the accrual of racial and ethnic minority patients in clinical trials: Time to raise the stakes. *Cancer* 123:4752-4756, 2017
- Watanabe N, Yuasa T, Shimada K: Concurrent administration of trastuzumab and anthracycline for breast cancer treatment: An unassailable contraindication? in Tan W (ed): *Cardiotoxicity*. Zagreb, Croatia, Intechopen, 2018, pp 110-125
- Egwuonwu OA, Anyanwu SN, Nwofor AM: Default from neoadjuvant chemotherapy in premenopausal female breast cancer patients: What is to blame? *Niger J Clin Pract* 15:265-269, 2012
- Uzochukwu BS, Ughasoro MD, Etiaba E, et al: Health care financing in Nigeria: Implications for achieving universal health coverage. *Niger J Clin Pract* 18:437-444, 2015
- Baselga J: Adjuvant trastuzumab: A milestone in the treatment of HER-2-positive early breast cancer. *Oncologist* 11:4-12, 2006 (suppl 1)
- Beuselink B, Wildiers H, Wynendaale W, et al: Weekly paclitaxel versus weekly docetaxel in elderly or frail patients with metastatic breast carcinoma: A randomized phase-II study of the Belgian Society of Medical Oncology. *Crit Rev Oncol Hematol* 75:70-77, 2010
- Schneider R, Barakat A, Pippen J, et al: Aromatase inhibitors in the treatment of breast cancer in post-menopausal female patients: An update. *Breast Cancer (Dove Med Press)* 3:113-125, 2011
- Cuzick J, Ambroisine L, Davidson N, et al: Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: A meta-analysis of individual patient data from randomised adjuvant trials. *Lancet* 369:1711-1723, 2007
- Abdel-Razeq H: Gonadotropin-releasing hormone agonists during chemotherapy for ovarian function and fertility preservation for patients with early-stage breast cancer. *Cancer Manag Res* 11:4273-4282, 2019
- Burris HA III: Docetaxel (Taxotere) plus trastuzumab (Herceptin) in breast cancer. *Semin Oncol* 28:38-44, 2001 (1; suppl 3)
- Cardoso F, Kyriakides S, Ohno S, et al: Early breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 30:1674, 2019
- Untch M, Muscholl M, Tjulandin S, et al: First-line trastuzumab plus epirubicin and cyclophosphamide therapy in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: Cardiac safety and efficacy data from the Herceptin, Cyclophosphamide, and Epirubicin (HERCULES) trial. *J Clin Oncol* 28:1473-1480, 2010
- Jones AL, Barlow M, Barrett-Lee PJ, et al: Management of cardiac health in trastuzumab-treated patients with breast cancer: Updated United Kingdom National Cancer Research Institute recommendations for monitoring. *Br J Cancer* 100:684-692, 2009
- Gupta S, Nag S, Dawood S: Challenges and opportunities in the design and implementation of breast cancer clinical trials in developing countries. *Clin Investig (Lond)* 2:579-587, 2012
- Gopal S: Cancer trials in sub-Saharan Africa: Aligning research and care. *PLoS Med* 14:e1002351, 2017
- Vischer N, Pfeiffer C, Kealy J, et al: Increasing protocol suitability for clinical trials in sub-Saharan Africa: A mixed methods study. *Glob Health Res Policy* 2:11, 2017

