NSABP PROTOCOL FB-11

A Phase II Randomized Study Evaluating the Biological and Clinical Effects of the Combination of Palbociclib with Letrozole as Neoadjuvant Therapy in Post-Menopausal Women with Estrogen-Receptor Positive Primary Breast Cancer

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Protocol FB-11 IND #123239 (palbociclib), sponsored by the NSABP

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PROTOCOL REVISION RECORD

Original Version: August 12, 2014

Amendment #1: October 30, 2014

NSABP FB-11 Protocol and Consent amended prior to activation of study.

Amendment #2: April 21, 2015

Sections Changed/Added:

Cover Page

Protocol Revision Record

Information Resources Page

Section 1.0: 1.0 (Schema)

Section 3.0: 3.2.4 added (subsequent sections renumbered)

Section 4.0: 4.1

Section 5.0: 5.1 (Table 2)

Section 6.0: 6.1 (Table 3), 6.2, 6.3, 6.4.1

Section 7.0: 7.1 (Tables 5, 6, and 7), 7.3.6

Section 8.0: 8.1, 8.2, 8.2.1

Section 9.0: 9.2.3, 9.2.4

Section 10.0: 10.5

Section 12.0: 12.2

Section 14.0: 14.4.2, 14.5

Section 16.0: References have been updated; where references were deleted subsequent references were renumbered

Appendix C

Corresponding FB-11 consents are not a part of the protocol document.

- The study consent has been revised in the Cover page, pages, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 17, and Addendum #1 has been added.
- The Optional Tumor and Blood Sample Collection consent has been revised in the Cover page, pages 1, 2, 3, 5, and 6.

Amendment #3: July 18, 2017

Sections Changed/Added:

Cover Page

Protocol Revision Record

Section 4.0: 4.1.13

Section 5.0 Table 1

Corresponding FB-11 consents have been revised and Addendum #2 has been added.

TABLE OF CONTENTS

INFORMATION RESOURCES

NSABP Department of Site and Study Management [redacted]		
For questions regarding: • IRB review & informed consent • Submission of IRB approval • Study entry information • Eligibility • Treatment regimen • Dose modifications/delays • Other clinical aspects of the trial • Adverse event reporting including SAE reporting • eCRF completion • Palbociclib shipments	Department of Site and Study Management (DSSM)	[redacted]
For questions regarding data management	DSSM	[redacted]
Submission of data forms (including expedited AE reports)	DSSM	[redacted]
Requests for study drug (palbociclib)	DSSM	[redacted]
Questions and submission of tumor and blood samples for correlative science studies	NSABP Division of Pathology [redacted]	[redacted] *Refer to FB-11 Pathology and Correlative Science Instructions*

GLOSSARY OF ABBREVIATIONS AND ACRONYMS

ACOSOG	American College of Surgeons Oncology Group
ADCC	antibody dependent cytotoxicity
AE	adverse event
AI	aromatase inhibitor
ALT (SGPT)	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST (SGOT)	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
BCIRG	Breast Cancer International Research Group
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
CA	Canada
CAP	College of American Pathologists
CBC	complete blood count
CCND1	cyclin D1
CDK4,6	cyclin-dependent kinase 4,6
CHF	congestive heart failure
CI	confidence interval
CISH	chromogenic in situ hybridization
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE v4.0	Common Terminology Criteria for Adverse Events Version 4.0
CTEP	Cancer Therapy Evaluation Program
DLT	dose-limiting toxicity
DSMB	Data safety Monitoring Board
DSSM	Department of Site and Study Management
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment Center
ER	estrogen receptor
ErbB	epidermal growth factor receptor
FDA	Food and Drug Administration
FFPE	formalin fixed paraffin embedded
FISH	fluorescence in situ hybridization
FNA	fine needle aspiration
G-CSF	granulocyte colony stimulating factor
GM-CSF	granulocyte macrophage-colony stimulating factor
H&P	history and physical
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
HRT	hormone replacement therapy
IB	Investigator's Brochure

GLOSSARY OF ABBREVIATIONS AND ACRONYMS (Continued)

ICR	Institute of Cancer Research
ICR-CTSU	Institute of Cancer Research Clinical Trials Statistics Unit
IDDI	International Drug Development Institute
IDMC	Independent Data Monitoring Committee
IHC	immunohistochemistry
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IV	intravenous
LD	longest diameter
LFT	liver function test
LLN	lower limit of normal
MDT	Multi-disciplinary Team
Mg	milligram
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSABP	NSABP Foundation, Inc.
ORR	overall response rate
OTC	over-the-counter
p	probability
pCR	pathologic complete response
PEPI	preoperative endocrine prognostic index
PD	progressive disease
PFS	progression-free survival
PgR	progesterone receptor
PO	by mouth
PPI	proton pump inhibitor
PR	partial response
PT	prothrombin time
q	every
RT	radiation therapy
SAE	serious adverse event
SD	stable disease
SN	sentinel node
TDM	therapeutic drug monitoring
TdP	Torsade de Pointes
TUNEL	Terminal deoxynucleotidyl transferase mediated dUTP Nick End Labeling assay
ULN	upper limit of normal
UK	United Kingdom
US	United States of America
WOCBP	women of childbearing potential

1.0 OVERVIEW OF STUDY DESIGN

FB-11 is a phase II, randomized, open label, four arm study to examine the biological and clinical effect of neoadjuvant letrozole with or without palbociclib in the first-line treatment of estrogen-receptor (ER) positive, HER2-negative early invasive breast cancer. The co-primary aims of this study are to to compare the changes in the proliferation marker Ki67, and to compare clinical response after 14 weeks of therapy with letrozole with or without palbociclib.

The FB-11 study initiative is a joint partnership between the NSABP Foundation, Inc. (NSABP) Department of Site and Study Management (DSSM) and United Kingdom (UK) co-investigators at the Royal Marsden NHS Foundation Trust and the Institute of Cancer Research (ICR). Parallel protocols will be conducted in the US, Canada (FB-11), and the UK (PALLET) with joint analysis of interim and final data.

Postmenopausal women, newly diagnosed with ER-positive/HER2-negative early breast cancer, who are suitable candidates for neoadjuvant endocrine therapy will be invited to join the FB-11 trial. Approximately 306 patients will be accrued to this study. Each collaborative group will recruit at least 1/3 and no more than 2/3 of the target accrual.

Patients will be randomized to one of four treatment arms (3:2:2:2 ratio).

Treatment in the first 14 weeks of neoadjuvant therapy will be:

Arm A	Letrozole alone
Arm B	Letrozole for 2 weeks followed by letrozole + palbociclib to week 14
Arm C	Palbociclib for 2 weeks followed by letrozole + palbociclib to week 14
Arm D	Letrozole + palbociclib to week 14.

Letrozole will be administered orally as a 2.5mg daily tablet. Palbociclib will be administered orally as 125mg capsules, daily on a schedule of 3 weeks (21 days) on, 1 week (7 days) off of a 4 week [28 day] cycle.

The end of study therapy for patients in Arm A will be completion of week 14. Patients in Arms B, C, and D will complete study therapy following 14 days of palbociclib in the final treatment cycle past 14 weeks if treatment delays have occurred.

Note: After week 14 (end of study therapy) all patients should continue letrozole until surgery. Letrozole is not considered study therapy beyond completion of week 14 for Arm A or after 14 days of palbociclib in the final treatment cycle for patients in Arms B, C, and D.

Following completion of study therapy, surgery will be scheduled for 15-18 weeks post-randomization. Post-surgical treatment will be at discretion of treating clinician, following local protocols, and not influenced by allocation of treatment within the FB-11 study.

A minimum of 2 and a maximum of 4 core-cut biopsies will be collected from each patient at baseline, after 2 weeks of study therapy and upon completion of study therapy at 14 weeks. If gross residual disease ≥ 1.0 cm remains, tumor samples will be collected at the time of definitive surgery.

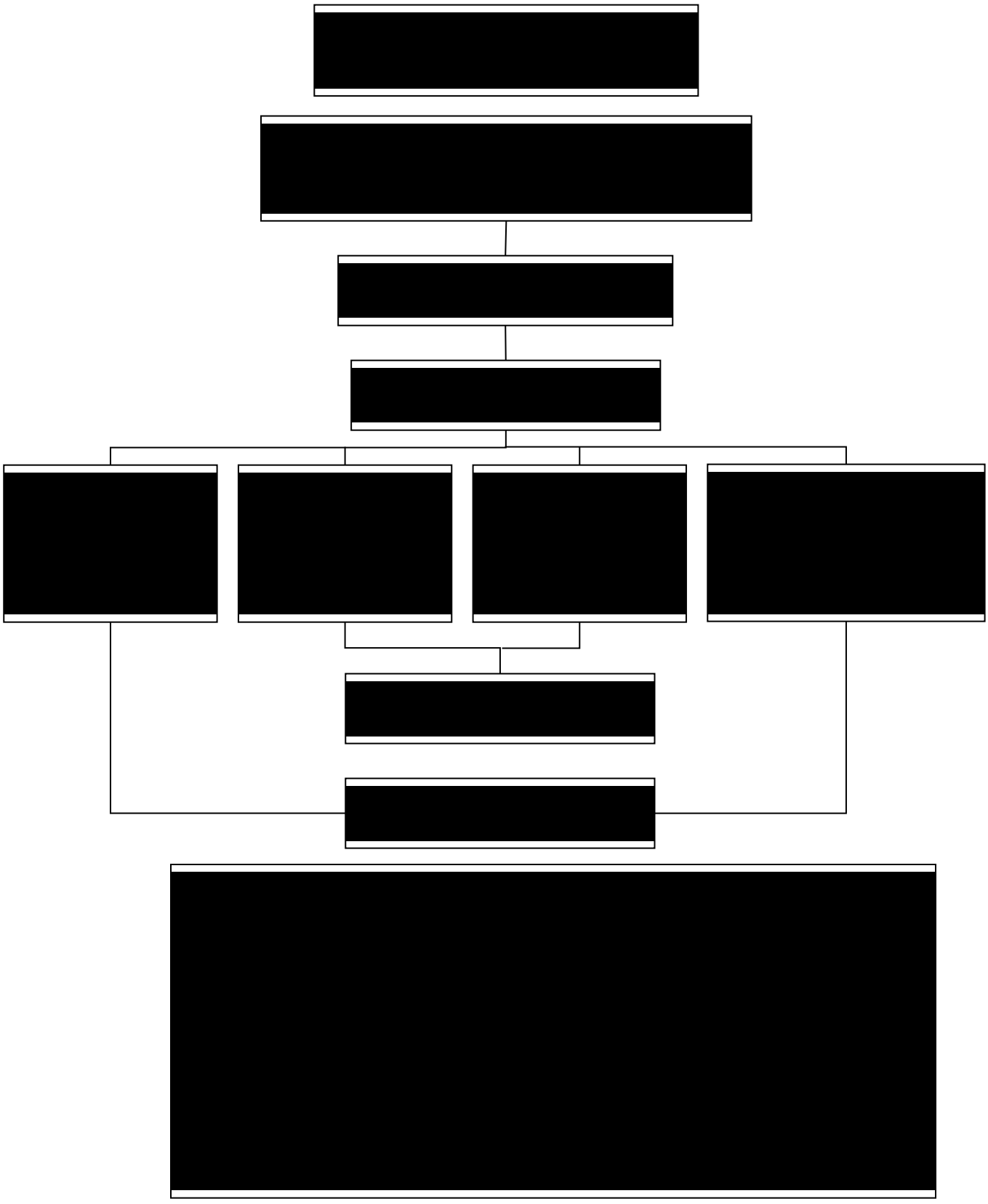
Toxicity will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0).

All patients will have a 12 months post-randomization follow-up, including those who prematurely withdrew from trial treatment (unless patient withdraws consent).

Pre-treatment samples and post-surgical samples (if residual disease ≥ 1.0 cm) will be collected and analysed to identify subgroups of patients who may derive the most clinical benefit. The results of the biological analyses may allow a target sensitive population to be selected for future trials. If the clinical response rate reported is clinically meaningful, then a definitive trial of palbociclib combined with letrozole as neoadjuvant or adjuvant treatment in certain subgroups of ER-positive breast cancer may be warranted to see if an improved standard of care can be established. Thus, the tissue collected in FB-11 will form an integral part of the primary analyses; so all core biopsies in this trial will be mandated for patients.

Collection of blood samples to be used in biomarker research is an essential part of FB-11 so these will be mandatory for all participants. Research blood samples will be collected at the time of each biopsy for germline DNA analyses and plasma estradiol analysis for confirmation of compliance with letrozole therapy and to study possible interaction of letrozole and palbociclib.

Patients who stop therapy prior to 14 weeks, who have received at least 1 cycle (4 weeks) of study therapy, will be asked permission for core biopsies and blood samples at that time. These tissue and blood samples will be optional (see optional tumor and blood sample collection consent).



2.0 BACKGROUND

2.1 Overview of Palbociclib

In 2010 there were 49,564 new cases and 11,633 deaths related to breast cancer in the UK; 209,005 new cases and 41,435 deaths related to breast cancer in the US.[1,2] Of all breast cancer diagnoses between 2008 and 2010, 80% occurred in women aged 50 and over.[3] Approximately 80% of incident breast cancers express the estrogen receptor (ER)[4] and are characterized by responsiveness to endocrine therapies.

Aromatase inhibitors (AIs) are the most effective endocrine treatment for ER-positive breast cancer in postmenopausal women. However, as with other treatments their effectiveness is limited in time as a result of escape pathways that are only partially defined. Letrozole, along with other third generation AIs, is standard of care for the first-line hormonal treatment of postmenopausal women with ER-positive breast cancer.

Palbociclib is an orally active potent and highly selective reversible inhibitor of CDK4 and CDK6. The compound prevents cellular DNA synthesis by prohibiting progression of the cell cycle from G1 into the S phase. Palbociclib has recently been used in conjunction with letrozole in first-line treatment of ER-positive/HER2-negative advanced breast cancer patients. Preclinical evidence that palbociclib is highly active in ER-positive cell lines and encouraging early safety and PK results led to a randomized phase II study evaluating the efficacy and safety of letrozole in combination with palbociclib when compared with letrozole alone in the first-line treatment of postmenopausal patients with ER-positive/HER2-negative advanced breast cancer (NCT00721409). A phase II dose of 125mg QD on a schedule of 3/1 (i.e. 21 days continuous treatment followed by 7 days off treatment) was used in combination with letrozole 2.5mg QD continuously. Later patients in the study were prospectively selected taking into account tumor CCND1 amplification and/or p16 loss. One hundred sixty-five patients were enrolled and the study demonstrated an improved clinical benefit rate (CR+PR+SD) of 59% v 36% and a prolongation of PFS from 7.5 to 26.1 months (HR 0.37 95%CI: 0.21, 0.63 P<0.001).[5] The shape of the survival curves suggests that patients who progress particularly quickly on letrozole alone may benefit markedly from the added palbociclib.

Palbociclib appears to act primarily as an anti-proliferative agent although there are some data that indicate this may be accompanied by a pro-apoptotic effect. Preclinical models have shown that lack of functional Rb precluded an anti-proliferative effect by palbociclib.[6] No biomarkers have yet been identified as indicating populations with greater or lesser response to the additional palbociclib. The response of tumors with gain of CCND1 and/or loss of p16 appears to be no different from that of tumors without these characteristics despite encouraging preclinical evidence.[7] Thus, identifying populations that are more or less responsive to palbociclib when added to letrozole is a priority for the drug's rational clinical application.

A phase III (NCT01864746) study evaluating palbociclib in patients with hormone receptor-positive/HER2-negative primary breast cancer with high relapse risk after neoadjuvant chemotherapy is currently being launched internationally by the German Breast Group under the auspices of the Breast International Group with possible future UK participation. Other phase III studies in advanced metastatic breast cancer with palbociclib are also in planning or underway: a phase III study with letrozole ± palbociclib in post menopausal women with ER-positive/HER2-negative disease (NCT017404271); a study with fulvestrant ± palbociclib in HR-positive/HER2-negative breast cancer (NCT01942135); and a study of exemestane + palbociclib vs. capecitabine (NCT02028507).

This proposed neoadjuvant study FB-11 will be important in identifying hypothesis generating potential biomarkers of sensitivity which could be validated in phase III metastatic trials.

2.2 Known Risks and Benefits of Palbociclib

Clinical studies to date suggest that toxicity associated with palbociclib is largely limited to uncomplicated neutropenia, fatigue, diarrhea, anemia, and nausea. The observed neutrophil nadir of 3 weeks will be managed by a 3 weeks on/1 week off schedule. The combination of palbociclib with letrozole has been shown to be well tolerated with adverse events (AEs) similar to those seen with either palbociclib or letrozole alone (NCT00721409).

Data from in vitro and in vivo non-clinical studies indicated that palbociclib has the potential to delay cardiac repolarization as measured by prolongation of the QT interval on ECG. [redacted]

No significant changes in blood pressure, pulse rate, and body weight have been observed in the two completed phase I clinical studies in advanced cancers (A5481001 and A5481002). It is recommended that the monitoring of patients enrolled in clinical studies of palbociclib include clinical examinations, vital sign measurements, routine ECGs and AE monitoring.[9]

2.3 Study Rationale

The use of AI therapy in the neoadjuvant treatment of women with ER-positive breast cancer has been established as a safe and effective treatment option allowing down-staging of tumors to enable less extensive surgery. The neoadjuvant setting is being increasingly used to provide early evidence of the clinical activity of novel agents and particularly to identify candidate markers of responsive populations and markers of resistance in residual disease. In ER-positive disease, change in the proliferation marker Ki67 has been validated as a marker of treatment benefit and 2 week residual levels as an indicator of risk of recurrence.[10]

Given the predominantly anti-proliferative effects of palbociclib, Ki67 is a rational end-point for estimating the added effectiveness of palbociclib in the neoadjuvant setting. The neoadjuvant design also allows a limited number of sequential biopsies to be taken for assessment of the effectiveness of single agents and subsequently the effect of a combination. FB-11 is a randomized trial to examine the biological and clinical effect of neoadjuvant letrozole with or without palbociclib for 14 weeks as a first-line treatment of ER-positive/HER2-negative early invasive breast cancer.

3.0 STUDY AIMS AND ENDPOINTS

3.1 Primary aims and endpoints

3.1.1 *Ki67 comparisons*

Aim: To compare the changes in the proliferation marker Ki67 (% positive tumor cells) as tested by immunohistochemistry (IHC) from baseline and following 14 weeks of treatment with letrozole with or without palbociclib.

Endpoint: Ki67 changes as tested by IHC

3.1.2 *Clinical Complete Response (cCR)*

Aim: To determine the clinical response by ultrasound according to ECOG criteria after 14 weeks of therapy with letrozole with or without palbociclib.

Endpoint: Clinical response of breast and axillary lesions as measured by ultrasound after 14 weeks of study therapy.

3.2 Secondary aims and endpoints

3.2.1 *Comparison of early and late drug effects on Ki67*

Aim: To compare Ki67 results after 2 weeks and 14 weeks of study therapy

Endpoint:

- Ki67 results after 2 weeks of palbociclib and subsequent therapy with letrozole from weeks 2 to 14; and
- Ki67 results after 2 weeks of letrozole and subsequent therapy with palbociclib from weeks 2 to 14.

3.2.2 *Pathological complete response (PCR)*

Aim: To compare the pCR rate after letrozole with or without 14 weeks of palbociclib.

Endpoint: pCR, breast

Endpoint: pCR, breast and axillary lymph nodes.

3.2.3 *Preoperative endocrine prognostic index (PEPI)*

Aim: To compare the PEPI score after letrozole with or without 14 weeks of palbociclib.

Endpoint: PEPI scores at 14 weeks of study therapy.

3.2.4 *Comparison of surgical intent (mastectomy; breast conservation)*

Aim: To compare changes between surgical intent at baseline; surgical intent after 14 weeks; and actual surgery received after treatment with letrozole with or without palbociclib.

Endpoint: Actual surgical procedure received after treatment.

3.2.5 ***Toxicity***

Aim: To evaluate the overall safety and tolerability for the combination of letrozole and palbociclib

Endpoint: Frequency and severity of adverse events categorized using the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0).

3.2.6 ***Correlative science***

Aim: To explore whether subgroups with greater or lesser Ki67 response or clinical response to added palbociclib can be identified in molecular and genetic profiles conducted on breast biopsies performed before initiating study therapy.

Aim: To examine the characterization of the molecular effects of palbociclib with and without letrozole and assess whether these vary according to assessment of breast tumor samples obtained before the initiation of study therapy.

4.0 PATIENT ELIGIBILITY AND INELIGIBILITY

Investigators should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for the FB-11 trial.

4.1 Conditions for patient eligibility

A patient cannot be considered eligible for this study unless all of the following conditions are met:

4.1.1 The patient must have consented to participate and, prior to study entry, must have signed and dated an appropriate IRB-approved consent form that conforms to federal and institutional guidelines (see FB-11 study therapy consent).

4.1.2 Patients must be female.

4.1.3 Patients must be ≥ 18 years old.

4.1.4 Patients must be postmenopausal women defined as:

- Age 56 or older with no spontaneous menses for at least 12 months prior to study entry; or
- Age 55 or younger with no menses for at least 12 months prior to study entry (e.g., spontaneous or secondary to hysterectomy) and with a documented estradiol level in the postmenopausal range according to local institutional/laboratory standard; or
- Age ≥ 18 with documented bilateral oophorectomy.

4.1.5 Operable ER-positive/HER2- negative, invasive early breast cancer, suitable for neoadjuvant AI treatment. HER2-negative as determined by ASCO-CAP guidelines.

4.1.6 No known severe hypersensitivity reactions to compounds similar to palbociclib or palbociclib excipients or to endocrine treatments.

4.1.7 A breast tumor with an ultrasound size of at least 2.0 cm.

4.1.8 Patients must have the ability to swallow oral medication.

4.1.9 ECOG performance status of 0 or 1.

4.1.10 At the time of randomization, blood counts performed within 4 weeks prior to randomization must meet the following criteria:

- ANC must be ≥ 1500/mm^3
- Platelet count must be ≥ 100,000/mm^3
- Hemoglobin must be ≥ 10 g/dL.

4.1.11 INR must be within normal limits of the local laboratory ranges.

4.1.12 The following criteria for evidence of adequate hepatic function performed within 4 weeks prior to study entry must be met:

- total bilirubin must be ≤ ULN for the lab unless the patient has a bilirubin elevation > ULN to 1.5 x ULN due to Gilbert's disease or similar syndrome involving slow conjugation of bilirubin; and
- alkaline phosphatase must be must be ≤ 1.5 x ULN for the lab; and
- AST and ALT must be ≤ 1.5 x ULN for the lab.

4.1.13 Serum creatinine performed within 4 weeks prior to study entry must be ≤ 1.25 x ULN or estimated creatinine clearance ≥ 60 mL/min (as calculated using the method standard for the institutions).

4.2 Conditions for patient ineligibility

Any patient with one or more of the following conditions will be ineligible for this study:

4.2.1 Active hepatitis B or hepatitis C with abnormal liver function tests.

4.2.2 HIV positive patients receiving antivirals.

4.2.3 Premenopausal or peri-menopausal women.

4.2.4 Inflammatory/inoperable breast cancer.

4.2.5 HER2-positive as determined using ASCO-CAP Guidelines.

4.2.6 Concurrent use (defined as use within 4 weeks prior to baseline tissue sample being taken) of hormone replacement therapy (HRT) or any other estrogen-containing medication (including vaginal estrogens)

4.2.7 Prior endocrine therapy for breast cancer.

4.2.8 Any invasive malignancy within previous 5 years (other than basal cell carcinoma or cervical carcinoma in situ).

4.2.9 Other nonmalignant systemic disease that would preclude the patient from receiving study treatment or would prevent required follow up such as:

- Active infection or chronic infection requiring chronic suppressive antibiotics;
- Malabsorption syndrome, ulcerative colitis, inflammatory bowel disease, resection of the stomach or small bowel, or other disease or condition significantly affecting gastrointestinal function;
- Chronic daily treatment with corticosteroids with a dose of ≥ 10 mg/day methylprednisolone equivalent (excluding inhaled steroids);
- Seizure disorders requiring medication.

4.2.10 Diagnosis by fine needle aspiration (FNA) alone or excisional biopsy or lumpectomy performed prior to study entry.

4.2.11 Surgical axillary staging procedure prior to study procedure (with *exception* of FNA or core biopsy).

4.2.12 Definitive clinical or radiologic evidence of metastatic disease.

4.2.13 History of ipsilateral invasive breast cancer regardless of treatment or ipsilateral DCIS treated with radiotherapy or contralateral invasive breast cancer at any time.

4.2.14 Any treatment, including radiotherapy, chemotherapy, and/or targeted therapy, administered for the currently diagnosed breast cancer prior to study entry.

4.2.15 Use of any medication or substances that are strong inhibitors or inducers of CYP3A isoenzymes (see Section 7.3.5).

4.2.16 Class III or Class IV myocardial disease as described by the New York Heart Association[11]; a recent history (within 6 months) of myocardial infarction, or symptomatic arrhythmia at the time of randomization.

Class III:	Patients with cardiac disease resulting in marked limitation of physical activity. Such patients are comfortable at rest. Less than ordinary physical activity that causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV:	Patients with cardiac disease resulting in inability to perform any physical activity without discomfort. Symptoms of cardiac insufficiency or anginal syndrome may be present even at rest.

4.2.17 QTc > 480 msec or a family or personal history of long or short QT syndrome, Brugada syndrome or know history of QTc prolongation, or Torsade de Pointes (TdP).

4.2.18 The investigator should assess the patient to determine if she has any psychiatric or addictive disorder or other condition that, in the opinion of the investigator, would preclude her from meeting the study requirements.

5.0 REQUIREMENTS FOR STUDY ENTRY, DURING TREATMENT, AND FOLLOW-UP

Tests, exams and other studies required prior to study entry are listed on Table 1. Requirements following study entry are outlined on Table 2.

TABLE 1. Tests, exams, and other requirements prior to study entry

Required Assessments	Prior to study entry	
Consent form signed by the patient	X	
Determination of hormone receptor status (Section 4.1.5)	X	
Determination of HER2 status (Section 4.1.5)	X	
History & physical exam[a]	X	Within 4 weeks
Performance status (Appendix A)	X	
Height & weight	X	
Assessment of concurrent therapies (Section 9.2.3 and Appendix B)	X	
Determination of measurable disease[b]	X	
CBC/differential/platelet count	X	
Total bilirubin/alk phos/AST/ALT/albumin/ total protein/ INR	X	
Serum chemistries: calcium/potassium/magnesium/sodium/chloride/bicarbonate or carbon dioxide/BUN or urea/glucose/ serum creatinine	X	
ECG	X	After consent is signed and eligibility screening completed
Submission of blood sample[c]	X	
Core biopsy to procure tumor samples for submission to the NSABP Division of Pathology[c]	X	

a Complete H&P by physician or other healthcare professional; including assessment of primary breast tumor and palpable regional lymph nodes (axilla, and supra- and infra-clavicular region).
b Radiologic tumor assessment by ultrasound.
c Submission of tumor and blood samples is a study requirement for all patients (see Section 6.1) See FB-11 Pathology and Correlative Science Instructions.

TABLE 2. Test, exams, and other requirements after study entry[a]

Required studies *(see footnote **a**)*	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	*End of study therapy (30 [+/-7] days after last dose of study therapy)*	Follow up *(12 months following study randomization)*
History & physical exam[b]								X	X	X	
Performance status		X		X		X		X		X	
Vital signs: including heart rate and blood pressure		X		X		X		X		X	
Assessment of concurrent therapies[c]	X	X	X	X	X	X		X	X	X	
Adverse event assessment[d]	X	X	X	X	X	X	X	X	X	X[d]	X[d]
Confirmation of study therapy compliance[e]	X	X	X	X	X	X	X	X	X		
CBC/differential/platelets	X	X	X	X	X[f]	X[f]	X[f]	X	X	X[f]	X
Sodium, potassium, calcium, magnesium, glucose, ALT, AST, total bilirubin, alkaline phosphatase, serum creatinine				X		X		X		X	
INR		X							X		
Tumor assessment by physical exam[g]		X		X		X		X	X		
Radiologic tumor assessment by ultrasound									X[h]		
ECG,					X				X		
Blood samples, [i,k]		X							X		
Core breast biopsy samples[j,k]		X							X	X[l]	
Vital status											X

a At the discretion of the investigator, additional exams, bloodwork, x-rays, scans, and other testing may be performed as clinically indicated.
b Updated H&P with exams (by physician or other healthcare professional on 1572) appropriate for assessments during therapy and follow-up.
c See section 7.3 and 9.2.3.
d Should the patient stop study therapy (e.g., due to disease/recurrence or second primary) and begin a new treatment prior to the 30 day assessment or following the 30 day assessment to 12 months, AE assessments should be collected *only* up to the date the new therapy begins.
e Verify assigned study therapy compliance with capsule/tablet count
f CBC/Diff *required* for Groups B, C, and D only.
g Assessment of the primary breast tumor and palpable regional lymph nodes. Required tumor assessment to determine the presence or absence of cCR.
h Should the patient stop study therapy after 1 cycle (4 weeks) and prior to Week 14, obtain ultrasound.
Perform surgery as soon as possible after final clinical tumor assessment and recovery from therapy.
i See Section 6.0 for required correlative study blood collection instructions.
j See Section 6.0 for core biopsy procurement study Week 2 and Week 14.
k Should patients stop study therapy prior to study completion (Week 14), see Section 6.0 and optional tumor and blood sample collection consent.
l If gross residual disease ≥ 1.0 cm remains, submission of tumor samples is required following definitive surgery.
(***Refer to the FB-11 Pathology and Correlative Science Instructions for tumor and blood sample submission instructions.)***

6.0 PATHOLOGY AND CORRELATIVE SCIENCE STUDIES

6.1 Overview of requirements

Collection and submission of all patient samples are listed below. By signing the FB-11 consent form, the patient has agreed to all required tumor and blood sample collections and submissions. (See Table 3, and FB-11 study treatment consent and optional tumor and blood sample collection consents.) Non-submission of required patient samples will be a protocol violation.

TABLE 3. Summary of FB-11 patient sample submission requirements

Study Requirements for ALL Patients *(unless indicated otherwise)*	**Prior to Study Therapy**	**Week 2**	**Week 14**	**Time of Surgery**
Required collection & submission of blood samples	Yes	Yes[a]	Yes[a]	N/A
Required collection and submission of biopsy tumor samples	Yes[a,b] *Samples should be submitted on the same day as procurement*	Yes *Samples should be submitted on the same day as procurement*[a,b]	Yes *Samples should be submitted on the same day as procurement*[b]	Yes *Samples should be submitted on the same day as procurement*[c]
Optional collection and submission of biopsy tumor and blood samples[d]	N/A	Samples should be submitted on the same day as procurement[d]		N/A

a See FB-11 Pathology and Correlative Science Instructions.

b Procurement of core biopsy specimens (2 to 4 cores) from an accessible tumor site prior to study entry, Week 2 and Week 14. (Patients must have at least 14 days of consecutive study therapy prior to the procurement of the Week 14 biopsy. See Section 8.2) **Note: The final biopsy (week 14) should be performed within 48 hours after the last dose of study therapy.**

c If gross residual disease ≥ 1.0 cm remains, collection and submission of tumor samples is required following definitive surgery.

d *Optional biopsy and blood samples:* If the patient decides to stop study therapy prior to completion of 14 weeks of therapy, procurement of optional core biopsy specimens from an accessible tumor site and blood samples should be requested and collected from consenting patients. (See the *Optional Tumor and Blood Sample Collection* consent.)

Note: Blood and biopsy samples should be collected within 48 hours from the last dose of study therapy.

NOTE: Refer to the FB-11 Pathology and Correlative Science Instructions for tumor and blood sample submission instructions.

6.2 Use of specimens

The blood and tumor samples collected in this study will be used for FB-11 studies as described in Section 6.0 and for analyses to be conducted in the future related to the purposes of the FB-11 study but not currently described in the protocol document. Additionally, the specimens procured may be used for future studies involving genes and protein conferring susceptibility to cancer or other diseases. If hereditary genetic studies (germline involving traits that are passed on or inherited) are conducted, an anonymization process will be used. Results of the correlative science studies, including raw sequencing data, will not be reported directly to the patient or the physician and will not have any bearing on patient treatment.

6.3 Tumor and blood sample submission procedures

The required ***blood samples are submitted to the NSABP Division of Pathology*** (see Information Resources on page iii) where the samples will be logged into the database and assigned a unique code number. The samples will be stripped of any remaining patient identifiers (except the NSABP FB-11 Patient ID numbers), processed, and stored. A portion of the samples may be shipped to collaborating laboratories. Refer to the FB-11 Pathology and Correlative Science Instructions for blood specimen collection and submission instructions.

The required tumor tissue samples are to be submitted to the NSABP Division of Pathology (see Information Resources on page iii) where the samples will be logged into the database and assigned a unique code number. The samples will be identified by the unique code number, processed, and stored. A portion of the samples may be shipped to collaborating laboratories. Refer to the FB-11 Pathology and Correlative Science Instructions for tumor tissue specimen collection and submission instructions.

6.4 Rationale for correlative science studies

6.4.1 *Tumor samples*

- **Core biopsies**

  A minimum of two and a maximum of four core-cut biopsies will be collected from each patient at baseline, 2 weeks of study therapy, and 14 weeks of study therapy. The final biopsy should be performed within 48 hours of the last dose of study therapy.

- **Surgical specimen**

  Representative cores of gross residual disease ≥ 1.0 cm must be submitted to NSABP following definitive surgery. These samples are required.

Biomarker end-points and potential predictive biomarker analyses performed on these samples may include:

- Ki67, ER (H-score), PgR, apoptosis markers;
- senescence marker, $p16^{INKa}$, Cyclin D1 amplification and expression, pRb, extended panel of cell cycle markers; and
- PIK3CA mutations (exon9 and 20).

Additional exploratory work is expected to include:

- targeted or whole exome sequencing, whole genome gene expression, to include evaluation of PI3K activation signature and E2F signature;
- extended mutational profile; and
- reverse phase protein arrays.

The tissue collected in FB-11 will form an integral part of the primary analyses so all core biopsies in this trial will be mandated for patients.

A prioritization list will be drawn up to ensure that the most important markers are evaluable of the maximum number of samples.

6.4.2 *Blood samples*

Collection of blood samples to be used in biomarker research is an essential part of FB-11 so these will be mandatory for all participants.

Research blood samples will be collected at the time of each biopsy for germline DNA analyses and plasma estradiol analysis for confirmation of compliance with letrozole therapy and to study possible interaction of letrozole and palbociclib.

7.0 STUDY TREATMENT

7.1 Treatment regimen

Study therapy should begin within 2 weeks following study entry. Patients will be assigned one of four study therapy Arms. (See Tables 4, 5, 6, 7, and Appendix C.)

TABLE 4. Treatment regimen – **ARM A**

Drug	Arm A	Dosing Interval	Planned Duration
Letrozole	2.5 mg PO	Daily	*Study therapy duration*: 14 weeks total
Use of a patient diary, calendar, or other tool for the patient to record letrozole doses should be strongly encouraged.			

TABLE 5. Treatment regimen – **ARM B**

Drug	Arm B	Dosing Interval	Planned Duration
Letrozole	2.5 mg PO	Daily	*Study therapy duration* 14 weeks total
Palbociclib	125 mg PO	*For Cycle 1 only* Beginning **two weeks** after starting letrozole: palbociclib daily x 7 days (Days 14-21) of the 28 day cycle (Days 22-28 off) *Cycles 2, 3, and 4:* Daily for 3 weeks (21 days) of a 4 week (28 day) cycle (i.e., 3 weeks [21 days] on/1 week [7 days] off)	

Other instructions:

- Instruct patients to take palbociclib capsules at the same time each day (preferably in the morning before noon), **with food and a full glass of water**. Patients should swallow capsules whole and not chew them. Instruct patients not to take capsules that are cracked or broken. Capsules which are cracked or broken should be returned to the study team.
- Patients should be instructed not to eat grapefruit or drink grapefruit juice while taking palbociclib.
- If a palbociclib dose is missed at the usual time, it should be taken as soon as possible ***within 12 hours*** following the time the dose should have been taken. If >12 hours, the dose will be missed for that day.
- If a patient vomits after taking study therapy, the patient should be instructed to not take another dose that day. The patient should resume taking study therapy at the next scheduled dose. If vomiting persists, the patient should be instructed to notify the investigator.

Use of a patient diary, calendar, or other tool for the patient to record palbociclib doses should be strongly encouraged.

TABLE 6. Treatment regimen – **ARM C**

Drug	Arm C	Dosing Interval	Planned Duration
Palbociclib	125 mg PO	Daily for 3 weeks (21 days) of a 4 week (28 day) cycle i.e.,3 weeks [21 days] on/1 week [7 days] off)	*Study therapy duration*: 14 weeks total
Letrozole	2.5 mg PO	*For Cycle 1 only* Begin **two weeks after** starting palbociclib daily x 12 weeks	

Other instructions:

- Instruct patients to take palbociclib capsules at the same time each day (preferably in the morning before noon), **with food and a full glass of water**. Patients should swallow capsules whole and not chew them. Instruct patients not to take capsules that are cracked or broken. Capsules which are cracked or broken should be returned to the study team.
- Patients should be instructed not to eat grapefruit or drink grapefruit juice while taking palbociclib.
- If a palbociclib dose is missed at the usual time, it should be taken as soon as possible ***within 12 hours*** following the time the dose should have been taken. If >12 hours, the dose will be missed for that day.
- If a patient vomits after taking study therapy, the patient should be instructed to not take another dose that day. The patient should resume taking study therapy at the next scheduled dose. If vomiting persists, the patient should be instructed to notify the investigator.

Use of a patient diary, calendar, or other tool for the patient to record palbociclib doses should be strongly encouraged.

TABLE 7. Treatment regimen – **Arm D**

Drug	Arm D	Dosing Interval	Planned Duration
Letrozole	2.5 mg PO	Daily	*Study therapy duration*: 14 weeks total
Palbociclib	125 mg PO	Daily for 3 weeks (21 days) of a 4 week (28 day) cycle (i.e., 3 weeks [21 days] on/1 week [7 days] off)	

Other instructions:

- Instruct patients to take palbociclib capsules at the same time each day (preferably in the morning before noon), **with food and a full glass of water**. Patients should swallow capsules whole and not chew them. Instruct patients not to take capsules that are cracked or broken. Capsules which are cracked or broken should be returned to the study team.
- Patients should be instructed not to eat grapefruit or drink grapefruit juice while taking palbociclib.
- If a palbociclib dose is missed at the usual time, it should be taken as soon as possible ***within 12 hours*** following the time the dose should have been taken. If >12 hours, the dose will be missed for that day.
- If a patient vomits after taking study therapy, the patient should be instructed to not take another dose that day. The patient should resume taking study therapy at the next scheduled dose. If vomiting persists, the patient should be instructed to notify the investigator.

Use of a patient diary, calendar, or other tool for the patient to record palbociclib doses should be strongly encouraged.

7.2 Supportive therapy

7.2.1 *G-CSF*

Use of growth factors, e.g., G-CSF, GM-CSF, is not permitted.

7.2.2 *Erythropoietin*

Use of an erythropoiesis-stimulating agent is not permitted.

7.3 Prohibited therapies

The following types of treatment, in addition to any cancer therapy other than the therapy specified in this protocol, are prohibited while on study therapy.

7.3.1 *Chemotherapy*

Administration of chemotherapy other than the chemotherapy specified in this protocol is prohibited.

7.3.2 *Targeted therapy*

Administration of targeted therapy for malignancy (other than the assigned targeted therapy regimen) is prohibited.

7.3.3 *Radiation therapy*

Radiation therapy (RT) to target lesions is prohibited.

7.3.4 *Hormone replacement therapy (HRT)*

Hormone replacement therapy (HRT), topical estrogens (including any intra-vaginal preparations, megestrol acetate and selective estrogen-receptor modulators (e.g., raloxifene) are prohibited.

7.3.5 *Concomitant CYP3A4/5 inhibitors or inducers*

Patients receiving any medications or substances that are strong inhibitors or inducers of CYP3A isoenzymes are ineligible. Lists including medications and substances known or with the potential to interact with the CYP3A isoenzymes are provided in Appendix B. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

7.3.6 *Potential QTc prolongation*

Medications which are known to cause QTc interval prolongation should be *avoided*. Use of these medications is at the investigator's discretion. QTc monitoring is recommended.

7.4 Participation in other clinical trials

If a patient participating in FB-11 considers participation in another clinical trial (including supportive therapy trials), contact DSSM (see Information Resources on page iii).

8.0 TREATMENT MANAGEMENT

8.1 General instructions

- The NCI CTCAE v4.0 must be used to report the term and grade the severity of AEs.
- All treatment decisions must be based on the AE requiring the greatest modification.
- Drug doses that have been reduced may not be escalated.

8.2 Treatment management for palbociclib and letrozole

The duration of the FB-11 study therapy is 14 weeks. Every effort should be taken to maintain study therapy schedule (14 weeks).

- The end of study therapy for patients in Arm A will be at the completion of week 14.
- Patients in Arms B, C, and D will complete study therapy following 14 days of palbociclib in the final treatment cycle (past 14 weeks if treatment delays have occurred in the final cycle).
- Withholding study therapy doses until an AE resolves may lead to the patient missing some or all subsequent doses *within* that same cycle or *delaying* the initiation of the subsequent cycle.
- After week 14 (or end of study therapy) all patients should continue letrozole until surgery. (Note: Letrozole will not be considered study therapy beyond completion of study therapy as noted above, for all patients [Arms A, B, C, and D].)

8.2.1 *Treatment decisions when therapy must be held*

- See Section 7.0 (Tables 5, 6, and 7) and Section 8.4 (Table 8) for palbociclib doses.
- See Table 9 for treatment management.
- If study therapy must be held for > 3 weeks of continuous delay, study therapy must be discontinued (see Section 8.2.2).

8.2.2 *Treatment decisions when therapy must be discontinued*

- If letrozole or palbociclib is discontinued, study therapy must be discontinued.
- If alternative (non-protocol) therapy is given at any time, study therapy must be discontinued.
- If study therapy is discontinued, further therapy is at the investigator's discretion; however, **continuance with letrozole is recommended** but will not be considered study therapy.
- Patients who prematurely discontinue study therapy should wait at least 2 weeks before undergoing surgery to allow normalization of neutrophil counts.

See Section 6.0 for required and optional correlative science sample collection.

8.3 Study therapy following tumor progression

If tumor progression occurs during study therapy, study therapy must be discontinued. Further therapy is at the investigator's discretion.

8.4 Dose modifications

There are no dose level changes or modifications for letrozole. Dose modifications for palbociclib are based on dose level changes outlined in Table 8.

8.4.1 *Dose modifications for palbociclib*

TABLE 8. Dose levels for palbociclib

	Dose Level 0 ***Starting Dose***	**Dose Level −1**	**Dose Level −2**	**Dose Level −3**
Palbociclib	125mg	100mg	75mg	Discontinue

8.4.2 ***Management of toxicities during letrozole and palbociclib study therapy***

The instructions for management of toxicities during letrozole and palbociclib are outlined in Table 9.

TABLE 9. Dose Modifications and Treatment management for **letrozole and palbociclib**

CTCAE v.4.0 Adverse Event	**CTCAE v.4.0 Grade**	**Action to be Taken**	
		Letrozole	**Palbociclib (991)**
Blood and lymphatic system disorders			
Neutropenic fever	3	Maintain dose	Hold until clinically stable, then resume: *1st appearance:* ↓one dose *2nd appearance:* ↓ one dose *3rd appearance:* Discontinue
	4	Discontinue (see Section 8.2.2)	
Infections and infestations			
Infection *(By site with normal ANC or grade 1 or 2 decrease in neutrophils)*	2	Maintain dose	Hold until clinically stable, then resume: Maintain dose
	3	*1st appearance:* Maintain dose *2nd appearance:* Maintain dose *3rd appearance* Discontinue	Hold until clinically stable, then resume: *1st appearance:* Maintain dose *2nd appearance:* ↓ one dose *3rd appearance:* Discontinue
	4	Discontinue (see Section 8.2.2)	
Investigations			
Alanine aminotransferase (ALT) increased **Alkaline phosphatase increased** **Aspartate aminotransferase (AST) increased**	2	Hold until ≤ Grade 1 *1st appearance:* Maintain dose *2nd appearance:* Discontinue	Hold until ≤ Grade 1 *1st appearance:* ↓ dose level *2nd appearance:* Discontinue
Blood bilirubin increased *(See Section 8.5 and 10.6.2 for information and reporting requirements related to Hy's Law cases.)*	3, 4	Discontinue (see Section 8.2.2)	

Table 9 continued on next page.

TABLE 9. Dose Modifications and Treatment management for **letrozole and palbociclib (continued*)***

CTCAE v.4.0 Adverse Event	**CTCAE v.4.0 Grade**	**Action to be Taken**	
		Letrozole	**Palbociclib (991)**
Electrocardiogram QT corrected interval prolonged	2	Maintain dose	*Reversible cause identified*: Maintain dose level 1. Treat reversible cause 2. Initiate more frequent ECG monitoring per investigator's discretion until QTc ≤ 480msec *No reversible cause identified:* Maintain dose level 3. Consult cardiologist 4. Initiate more frequent ECG monitoring until QTc ≤ 480msec *Note: If the QTc remains above 480 msec more than 2 cycles or if Grade 2 QTc prolongation recurs in the absence of other alternative causes or despite correction of alternative causes, dose adjustment and/or discontinuation should be considered in consultation with a cardiologist and with the investigator's best medical judgment.*
	3	Maintain dose	*Reversible cause identified*: *Hold until QTc ≤ 500msec;* resume at same dose level − Treat reversible cause − Monitor ECG more frequently per investigator's discretion until QTc ≤ 480msec *No reversible cause identified:* *Hold until QTc ≤ 500msec;* then resume at ↓ dose level − Consult cardiologist − Monitor ECG more frequently per investigator's discretion until QTc ≤ 480msec *Note: If the Grade 3 QTc prolongation occurs again after one dose reduction, further dose adjustment and/or discontinuation should be considered in consultation with a cardiologist and with the investigator's best medical judgment.*

Table 9 continued on next page.

TABLE 9. Dose Modifications and Treatment management for **letrozole and palbociclib (continued*)***

CTCAE v.4.0 Adverse Event	**CTCAE v.4.0 Grade**	**Action to be Taken**	
		Letrozole	**Palbociclib (991)**
Neutrophil count decreased *(Note: The use of growth factors is prohibited, see Section 7.2.1)*	3	Maintain dose	*Hold until ≥ 1000/mm^3.* *1st appearance*, if recovery takes: ≤ 14 days – Resume at same dose level > 14 days and ≤ 21 days – ↓ dose level *2nd appearance:* Hold until ≥ 1000/mm^3 If recovery takes ≤ 14 days: ↓ dose level > 14 days: Discontinue
	4	Maintain dose	*Hold until ≥ 1000/mm^3* *1st appearance, if recovery takes:* ≤ 21 days: ↓ dose level *2nd appearance, if recovery takes;* ≤ 14 days: ↓ additional dose level > 14 days: Discontinue
Platelet count decreased	2	*Hold until ≥ 75000/mm^3* *1st appearance:* Maintain dose *2nd appearance:* Maintain dose *3rd appearance:* Discontinue	*Hold until ≥ 75000/mm^3* *1st appearance:* Maintain dose *2nd appearance:* Maintain dose *3rd appearance:* Discontinue
	3	*Hold until ≥ 75000/mm^3* *1st appearance:* Maintain dose *2nd appearance:* Discontinue	*Hold until ≥ 75000/mm^3* *1st appearance:* ↓ dose level *2nd appearance:* Discontinue
	4	Discontinue (see Section 8.2.2)	
Other			
1. Other AEs requiring dose modification per investigator *(Note: Investigator must determine attribution of AE and only follow dose modifications for the **causal agent**.)*	2	Maintain dose	If lasting < 3 weeks: Hold until ≤ Grade 1 and maintain dose. If recurrent ↓ one dose
	3, 4	Discontinue (see Section 8.2.2)	

8.5 Liver dysfunction (Hy's Law)

Hy's Law is based on the observation that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. A diagnosis of potential drug-induced liver injury caused by a study drug can only be determined/inferred by excluding other potential causes of liver injury (e.g., other drugs or viral hepatitis) and by ruling out an obstructive cause for the elevated bilirubin (e.g., alkaline phosphatase should not be substantially elevated).[12,13]

8.5.1 *Definition of cases potentially meeting Hy's Law criteria*

Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- *Patients with AST or ALT baseline values within the normal range* who subsequently present with AST or ALT ≥ 3 times the ULN concurrent with a total bilirubin ≥ 2 times the ULN with no evidence of hemolysis and an alkaline phosphatase ≤ 2 times the ULN or not available.
- *Patients with pre-existing AST or ALT baseline values above the normal range* who subsequently present with AST or ALT ≥ 2 times the baseline values and ≥ 3 times the ULN, or ≥ 8 times the ULN (whichever is smaller) concurrent with a total bilirubin of ≥ 2 times the ULN and increased by one ULN over baseline or > 3 times the ULN (whichever is smaller) with no evidence of hemolysis and an alkaline phosphatase ≤ 2 times the ULN or not available.

8.5.2 *Evaluation of potential Hy's Law cases*

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), international normalized ratio (INR) and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, recreational drug and supplement consumption, family history, sexual history, travel history, history of contact with a jaundiced patient, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g. biliary tract) may be warranted. The possibility of progressive disease should be considered.

Potential Hy's Law cases should be reported as serious adverse events (see Sections 10.4.3 and 10.6.2).

9.0 DRUG INFORMATION

9.1 Letrozole

Letrozole is available as commercial supply, and will be administered orally as a 2.5 mg tablet.

For further details regarding the study drug, see the letrozole U.S. Package Insert as well as local prescribing information.

(Note: Postsurgical treatment (e.g. letrozole) will be at the discretion of the treating physician, and will not be considered study therapy.)

9.2 Palbociclib (PD-0332991)

9.2.1 *Description*

Palbociclib is an orally administered highly selective reversible inhibitor of cycline-dependent kinases (CDK) 4 and 6.

Palbociclib 125 mg capsules will be provided for the FB-11 study. Palbociclib will be available in 100mg and 75mg doses as study therapy where a dose reduction is required (see Section 8.4 and Table 8). The open label palbociclib will be packaged with 23 capsules per bottle.

9.2.2 *Toxicity*

Refer to the current palbociclib IB for toxicity information.

9.2.3 *Concomitant medications and other substances*

- Patients should be instructed to avoid agents known to be strong cytochrome P450 (CYP) 3A4 inducers or inhibitors (e.g., ketoconazole) for the duration of the study therapy. Patients should also avoid grapefruit and herbal remedies, including St John's Wort. Refer to Appendix B for a list of selected inhibitors and inducers of the cytochrome P450 CYP3A4, 5, 7 isoenzymes.
- Chronic immunosuppressive therapies should be avoided, including systemic corticosteroids. Steroids given for physiological replacement, as premedication for palbociclib, as anti-emetics or inhaled as well as short course of oral/topical steroids given for allergic reactions or asthma flares are allowed.
- Patients taking concomitant anticoagulant therapy (e.g., warfarin or its derivatives, low molecular weight heparin, unfractionated heparin) should be monitored regularly for changes in relevant coagulation parameters as clinically indicated, as well as for any clinical bleeding episodes. The dose of anticoagulant should be adjusted as needed.
- Patients taking concomitant digoxin should have digoxin levels monitored closely and their digoxin dose adjusted as needed.

9.2.4 ***Administration***

- Palbociclib doses are found in Section 7.0 and Section 8.4.
- Refer to Section 7.1 (Tables 5, 6, and 7) for palbociclib administration instructions. Patients must be carefully instructed by study staff as to how to take palbociclib. *Note:* Studies suggest that the administration of palbociclib with food results in a more consistent drug uptake and exposure than administration of palbociclib in a fasted state. Therefore, patients should be instructed to take palbociclib with food.[14]
- Patients should be strongly encouraged to use a patient diary, treatment calendar, or other tool to record palbociclib and letrozole doses.
- Instruct patients to bring all unused palbociclib and empty bottles to the treating site. Local site personnel must count and record the number of palbociclib capsules at the first study visit for each of the treatment cycles. Drug accountability records must be maintained.

9.2.5 ***Procurement of palbociclib***

Palbociclib will be supplied free of charge by Pfizer, and distributed via an external vendor. Palbociclib must be requested by the principal investigator (or his/her authorized designee) at each participating institution (see Information Resources on page iii for the e-mail address to be used for ordering study drug). The initial supply of palbociclib may be requested at the time the first patient signs the FB-11 consent form. Palbociclib will be shipped directly to the investigator whose sites are participating in FB-11.

9.2.6 ***Shipping***

Bottles of palbociclib are shipped at room temperature by overnight express delivery Monday through Thursday excluding holidays.

9.2.7 ***Storage/stability***

Palbociclib should be stored at room temperature (15-30°C [59-86°F]) in the study therapy containers. Unopened bottles of palbociclib are stable until the date indicated on the package label when stored at room temperature (up to 30°C [86°F]).

9.2.8 ***Transfer of palbociclib***

Palbociclib may not be used outside the scope of FB-11, nor can palbociclib be transferred or licensed to any party not participating in this clinical trial.

9.2.9 ***Destruction of palbociclib***

- All unopened, partially used, or empty bottles of palbociclib shall be destroyed by study sites in accordance with the local institution standard operating procedures after the approval of DSSM.
- Written documentation of destruction must contain the following:
  - identity (batch numbers) of palbociclib destroyed;
  - quantity of palbociclib destroyed;
  - date of destruction (date discarded in designated hazardous container for destruction); and
  - name and signature of the person who discarded the palbociclib in a hazardous container for destruction.

9.2.10 ***Drug accountability***

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drug received through the FB-11 study using an investigational agent accountability record form.

10.0 ADVERSE EVENT REPORTING

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or a serious adverse event (SAE), as provided in this protocol. Routine and expedited adverse event report forms and their supporting documentation must be submitted to DSSM according to the instructions in Section 10.0.

10.1 Definition of an AE

An AE is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, laboratory findings, or other physiologic observations occurring in a patient participating in FB-11. The event does not need to be causally related to study therapy or other requirements of the FB-11 trial to be considered an AE.

- Examples of an AE include, but are not limited to, the following:
  - Any toxicity related to study therapy.
  - Any clinically significant worsening of a pre-existing condition.
  - An AE occurring from a symptomatic overdose of any study therapy, whether accidental or intentional. Overdose is a dose greater than that specified in the protocol.
  - An AE occurring from abuse (e.g., use for non-clinical reasons) of any of the agents included in the study.
  - An AE that has been associated with the discontinuation of the use of any of the agents included in the study therapy.
  - An AE occurring during a clinical study that is not related to the study therapy, but is considered by the investigator or sponsor to be related to the study requirements, for example, an AE may be an untoward event related to a medical procedure required by the protocol.
- Examples of clinical events that should not be considered AEs:
  - Medical or surgical procedure (e.g., endoscopy, appendectomy). Note, the condition that leads to the procedure may be an AE, but the procedure itself is not.
  - Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2 Adverse Events and relationship to study therapy

The clinician's assessment of an AE's relationship to study therapy is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study therapy assessed using the terms 'related' or 'not related'. To help assess, the following guidelines are used:

Related

- *Definitely* – There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study therapy should be clinically plausible.
- *Probably* – There is evidence to suggest a causal relationship and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the study drug, is unlikely to be

attributed to concurrent disease or other drugs or chemicals and follows a clinically reasonable response on withdrawal.

- *Possibly* – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study therapy). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events).

Not Related

- *Unlikely*- A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study drug) and in which other drugs or chemicals or underlying disease provides plausible explanations.
- *Not related* –The AE is completely independent of study therapy administration, and/or evidence exists that the event is definitely related to another etiology.

10.3 Definition of an SAE

An SAE is any untoward medical occurrence that, at any dose causes one of the following:

- Results in death
- Is life-threatening

  The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which might have caused death, if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization

  Hospitalization is any inpatient admission to a health care facility even if for less than 24 hours. Hospitalization or prolongation of a hospitalization constitutes a criterion for an AE to be serious; however, it is not in itself considered an SAE. In the absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported as an SAE. For example, the following hospitalizations would not require expedited reporting for an SAE:
  - A hospitalization or prolongation of hospitalization needed for a procedure required by the protocol or as part of another routine procedure; or
  - A hospitalization for a pre-existing condition that has not worsened.

- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  - This is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect

Also, appropriate medical judgment should be exercised in deciding whether SAE reporting is required in other situations, such as important medical events that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition of an SAE (Section 10.3). Examples of such events are intensive treatment in an emergency room or at

home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or development of drug dependency or drug abuse.

10.4 Events requiring expedited reporting

All events listed in Section 10.4 must be reported in an expedited manner according to the instructions in Section 10.7.

10.4.1 *SAEs*

All events meeting the definition of an SAE (Section 10.3) require expedited reporting.

10.4.2 *Other events requiring expedited reporting*

Other events that must be recorded, reported, and followed up as indicated for an SAE (see Sections 10.4 and 10.6 for reporting procedures). This includes the following events:

- Inadvertent or accidental exposure to study therapy, with or without an AE
- Medication errors involving study therapy with an AE, including overdose, product confusion and potential product confusion. (A medication error is any preventable event that may cause or lead to inappropriate use or harm while the study therapy is in control of the healthcare professional or patient. Examples of reportable medication error include administration of unassigned treatment and administration of expired palbociclib, when associated with an AE/SAE.)
- Death, excluding death due to progression of breast cancer
- Potential Hy's Law cases (see Sections 8.5.2 and 10.6.2)

10.4.3 *Clinical laboratory abnormalities*

- Not every laboratory abnormality qualifies as an AE. A laboratory test results should be reported as an AE (and SAE) if it meets any of the following criteria:
  - Accompanied by clinical symptoms
  - Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
  - Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
  - Clinically significant in the investigator's judgment
- Special reporting requirements related to Hy’s Law: All cases confirmed on repeat testing as meeting one of the criteria described in Section 8.5.2 with no other cause for LFT abnormalities identified at the time should be considered potential Hy’s Law cases regardless of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy’s Law cases should be reported as serious adverse events (see Section 10.6.2).

10.4.4 *Disease-related events and/or disease-related outcomes not qualifying as SAEs*

An event which is part of the natural course of breast cancer does not need to be reported as an SAE. Progression and recurrence of breast cancer will be reported on the appropriate page of the eCRF.

10.5 Grading the severity of the AE

The NCI CTCAE v4.0 must be used to determine the event and the grade of the AE. The CTCAE provides descriptive terminology and a grading scale for each AE listed. Information regarding the CTCAE can be found on the CTEP homepage at http://ctep.info.nih.gov/reporting/ctc.html. If you need further assistance, contact DSSM (see Information Resources on page iii).

10.6 Expedited reporting instructions

10.6.1 *Time period for reporting SAEs and other events requiring expedited reporting*

- All SAEs and other events as noted in Sections 10.3 and 10.4 ***regardless of relationship to study therapy*** will be reported in an expedited manner as described in Section 10.6.2. Reporting SAEs (and other applicable events) regardless of relationship to study therapy begins with the first dose of study therapy and continues until 30 days after the last dose of study therapy.
- Any ***SAE assessed as related to study participation*** (e.g., protocol-mandated procedures) will be recorded ***from the time a patient consents to participate in the study up to and including the 30 day post study trial assessment***.
- Following the AE assessment 30 days after the last dose of study therapy, ***only SAEs determined to be related to study therapy*** will be reported in an expedited manner using FB-11 Form SAER.
- The investigator must follow up on all SAEs until the events have subsided, until values have returned to baseline, or until the condition has stabilized.

10.6.2 *Reporting instructions*

- All SAEs and other events requiring expedited reporting must be reported using FB-11 Form SAER and submitted to DSSM ***within 1 working day*** of the study site personnel's initial notification of the event (see Information Resources on page iii).
- When reporting potential Hy's Law cases, Form SAER should include the following:
  - Seriousness Criteria = Important Medical Event
  - Narrative: Include the term “Potential Hy’s Law case” in the narrative; the text should also detail what additional study results are available at the time of reporting and what other studies are planned or results pending to further investigate alternative causes of the abnormal ALT/AST or bilirubin that triggered the report. The timing of planned patient follow-up should also be noted.
- NSABP will forward expedited report forms and their supporting documentation for SAEs that meet reporting requirements to the FDA and also to Pfizer.
- Investigators are responsible for reporting AEs that meet specific criteria to their local IRBs.

10.7 Time period and frequency for routine reporting of AEs

- Patients will be monitored for the occurrence of AEs at each scheduled assessment and during any contact with the patient during the study.
- All AEs, including SAEs and other AEs that have been reported on FB-11 Form SAER, regardless of relationship to study therapy, will be recorded on Form AE of the eCRF from the first dose of study therapy until 30 days after the last dose of study therapy (up to the date that a new therapy begins after disease recurrence/progression or second primary).
- For routine reporting, **all ≥ grade 1 AEs** will be reported on Form AE of the eCRF.
- The investigator must follow up on all AEs until the events have subsided, until values have returned to baseline, or until the condition has stabilized.
- Following the AE assessment 30 days after the last dose of study therapy, routine reporting is no longer required. (See Section 10.6.1 for expedited reporting requirements.)

10.8 Documentation requested following death

For deaths that occur within 30 days of the last dose of study therapy:

- Autopsy reports should be secured whenever possible and should be submitted to the DSSM.
- A copy of the death certificate should be forwarded to DSSM if it is readily available or if it contains important cause-of-death information that is not documented elsewhere.
- Please submit the last clinic/office note made before the death or the investigator's note summarizing events resulting in death.

11.0 ASSESSMENT OF EFFECT

For the purposes of this study, all clinical response assessments will be performed by ultrasound and physical examination of the breast and the axilla using the ECOG response criteria.[15] (See Appendix D.)

11.1 Timing of clinical response assessments

Tumor measurement by ultrasound is required at baseline (prior to study entry) to determine eligibility. To document the presence or absence of cCR, protocol-required tumor assessments by ultrasound and physical exam must be performed after completion of study therapy, at 14 weeks.

11.1.1 *Definition of measurable lesions at baseline*

During the baseline assessment and before the start of protocol therapy, all lesions detected in the breast and the axilla are classified as measurable lesions if they meet the following criteria:

Lesions on baseline physical examination

- Breast tumors ≥ 2.0 cm
- Axillary nodes ≥ 2.0 cm

Lesions on baseline by ultrasound

- Breast tumors ≥ 2.0 cm
- Axillary nodes ≥ 1.5 cm

11.1.2 *Evaluation of cCR*

The following criteria will be employed at the time of the assessments for cCR at the end of study therapy:

- resolution of all measurable lesions identified at baseline, and
- no new lesions or other signs of disease progression.

11.1.3 *Progressive disease*

Criteria to be used for determination of progressive disease are at the investigator's discretion.

11.2 Pathologic assessment of effect

11.2.1 *Timing of evaluation*

The determination of pCR will be performed by the local pathologist following examination of tissue (breast and nodes) removed at the time of surgery.

11.2.2 *Criteria for evaluation of pathologic complete response*

- *Pathologic complete response in breast and axillary lymph nodes as well as non-axillary SN (pCR breast & nodes)*

  No histologic evidence of invasive tumor cells in the surgical breast specimen or axillary nodes after neoadjuvant treatment.

- *Pathologic complete response in the breast (pCR breast)*

  No histologic evidence of invasive tumor cells in the surgical breast specimen.

12.0 PATIENT ENTRY PROCEDURES

12.1 Patient consent form

Before study entry, the consent form including any addenda, must be signed and dated by the patient and the person obtaining informed consent. **In addition, before study entry, a copy of the signed and dated consent form must be forwarded to DSSM. All patient signatures (except initials of first, middle, and last names) should be expunged prior to submission.**

12.2 Study entry

DSSM will verify that the institution has current IRB approval for the study. Entry will not take place if the IRB approval is not current for the institution with IRB oversight responsibility.

All patients must be enrolled through DSSM. Once the entry eCRFs have been completed, submit the redacted signed consent form, and supporting source documents to [redacted].

The entry material must be received by DSSM staff no later than **4:00 p.m. Eastern Time, Monday through Friday, excluding holidays**. Once received the review process will begin. When the review is complete and approved, an enrollment confirmation will be sent. **This process could involve some unavoidable delays. Therefore, it is necessary to plan adequate time (at least 24 hours) between study entry and the initiation of the patient's study therapy.**

12.3 Patient study number and treatment assignment

After all the entry materials have been reviewed, the institution will receive the following via e-mail: 1) confirmation of registration and study entry; 2) the patient's study number; and 3) the study Arm assignment.

12.4 Investigator-initiated discontinuation of study therapy

In addition to the conditions outlined in the protocol, the investigator may require a patient to discontinue study therapy if one of the following occurs:

- the patient develops a serious side effect that cannot be tolerated or that cannot be controlled with other medications,
- the patient's health gets worse,
- the patient is unable to meet the study requirements, or
- new information about the study drugs or other treatments for breast cancer becomes available.

If study therapy is stopped, study data and other materials should be submitted according to the study schedule unless the patient withdraws from the study.

12.5 Patient-initiated discontinuation of study therapy

Even after a patient agrees to take part in this study, she may stop study therapy at any time. If study therapy is stopped but she still allows the study doctor to submit information, study data and other materials should be submitted according to the study schedule.

12.6 Patient-initiated withdrawal from the study

If a patient chooses to have no further interaction regarding the study, the investigator must document the patient's decision to fully withdraw from the study in writing and submit to DSSM. Any data collected up to the time of withdrawal from the study will continue to be used.

13.0 DATA HANDLING AND RECORDKEEPING

Please refer to the "FB-11 eCRF Completion Guidelines" for detailed instructions regarding data collection, AE reporting, and electronic case report form completion.

14.0 STATISTICAL CONSIDERATIONS

14.1 Statistical design and sample size justification

A total of 284 evaluable patients are required in FB-11. Allowing for a 5% non-evaluable rate for the co-primary endpoints and for the total sample size to be multiple of 9 for each stratification level (due to the 3:2:2:2 allocation ratio), the recruitment target for FB-11 is 306 patients.

FB-11 uses a conventional comparative design with alpha split between two endpoints (clinical response rate and Ki67).

Clinical response rate (ECOG): α=4% one-sided, β=10%

Allocation is 2:1, comparing combined outcome in the three combination groups (B+C+D on combination from 2 to 14 weeks) versus the control letrozole alone group (A). Improvement sought is from example scenario CR: 21%, PR: 54%, SD: 15%, PD 5% to CR: 31%, PR: 57%, SD: 5%, PD 2% (5% not evaluable for both). Analysis will treat response as an ordinal outcome by the Mann Whitney test corrected for ties. The sample size was estimated by simulation with sampling probabilities for each of the response categories as given. The letrozole alone response rates are based on results from ACOSOG Z1031.[16] The sample size required is 284 (n=189:9).

Ki67: α=1% one-sided, β=10%

The comparison groups will be as for clinical response. The sample size is determined based on the assumption that Ki67 reduction at the 14-week time-point compared to baseline for patients treated with letrozole alone is 80%, data from three studies of Ki67 fall in response to AI treatment gave an overall fall of 82% (95%CI: 78% to 85%, n=210).[17]

It has been assumed that Ki67 reduction is increased to 90% for patients treated with palbociclib combined with letrozole. The addition of palbociclib to letrozole has therefore been assumed to reduce residual Ki67 by 50% (i.e. 20% residual Ki67 for letrozole alone to 10% residual Ki67 for letrozole plus palbociclib) which equates to a log-fold change of -0.693 (ln(0.5)) under H1. The standard deviation of the log-fold change from baseline to week-14 Ki67 has been assumed to be 1.5 based on estimates of approximately 1.1 for baseline to two week change and 1.4 for baseline to 12 week change. Assuming a sample size calculation based on a one-sided T test, the number of evaluable patients required is 279 (n=186:93).

14.2 Treatment allocation

FB-11 is a randomized, four Arm study. Participants will be randomized to: A) letrozole alone; B) letrozole for 2 weeks followed by letrozole + palbociclib to week 14; C) palbociclib for 2 weeks followed by letrozole + palbociclib to week 14; D) letrozole + palbociclib to week 14.

Analysis of each co-primary end points will compare group A with the combination groups B, C, and D. A 1:2 ratio of the combined 3 groups treated with palbociclib compared with control gives a corresponding allocation ratio of (3:2:2:2) for the control compared with each of the individual palbociclib treatment groups.

Treatment allocation is by computer generated random permuted blocks. Randomization will be stratified by country; one randomization list produced for the USA and Canada and another for the UK.

14.3 Endpoint definition

14.3.1 *Primary endpoint*

This study has two co-primary endpoints: change in the proliferation marker Ki67 (% positive tumor cells) as tested by IHC after 14 weeks treatment with letrozole with or without palbociclib; and clinical response as measured by ultrasound according to ECOG criteria after 14 weeks treatment with letrozole with or without palbociclib.

14.3.2 *Secondary endpoints*

The secondary aims include looking at the effect of 2 weeks of palbociclib on Ki67, the effect of adding letrozole at 2 weeks (to 14 weeks) in this group and the effect of adding palbociclib (2 to 14 weeks) in the group which was initiated with 2 weeks of letrozole. Lastly, a major focus of this trial is the correlative science, one of the main goals being to determine whether it is possible to identify a pre-treatment marker or markers which are predictive of benefit from palbociclib. This will involve, for example, univariate Spearman rank correlation between pre-treatment biomarker levels and Ki67/clinical response. In addition, if multiple candidates emerge, multiple linear regression with dependent variables log Ki67 fold change (or logistic regression with a 50% fall in Ki67, or PR/CR vs none as the response variables) and biomarker levels, patient characteristics, the treatment given and interactions as independent variables.

14.4 Statistical Analysis Plan

14.4.1 *Change in Ki67*

The log fold change in Ki67 from baseline to 14 weeks will be compared between group A and groups B+C+D combined using a one-sided test (or non-parametric equivalent). Linear regression will be used investigate the relationship between treatment and other known prognostic factors on log fold change in Ki67. Consideration will also be given to the use of logistic regression with a 50% fall in Ki67 as the response variable.

14.4.2 *Clinical response*

A one-sided Mann-Whitney test (correcting for ties) will be used to compare ECOG clinical response between group A and groups B+C+D combined. Proportional odds modelling will also be used investigate relationship between treatment and other known prognostic factors on clinical response at 14 weeks. Consideration will also be given to the use of logistic regression with PR/CR vs. none as the response variable.

- *Effect of palbociclib on Ki67 after 2 weeks and the added effect of letrozole from weeks 2-14 (within group)* – descriptive analyses will be performed, with waterfall plots used to display changes in Ki67 from baseline to 2 weeks and from 2 to 14 weeks
- *Effect of letrozole on Ki67 after 2 weeks and the added effect of palbociclib from weeks 2-14 (within group)* – as above.
- *pCR rates after letrozole with or without 14 weeks palbociclib* – the proportion of patients with pCR will be compared between group A and the combination of groups B, C and D using a Chi-squared test (or Fisher's exact test as appropriate). Consideration will also be given to the use of logistic regression with pCR vs. not as the response variable. pCR will be evaluated using the criteria described Section 11.2.2.

- *Comparison of surgical intent at baseline, after 14 weeks, and actual surgery performed, following treatment with letrozole with or without palbociclib* – surgical intent at baseline and surgical intent at week 14 of peri-operative treatment will be cross-tabulated: first for all patients, and then separately for group A, and the combination of groups B, C, and D. The proportion of patients whose intended surgery at baseline was mastectomy for whom surgical intent has changed to breast conservation at week 14 will be presented separately for group A and the combination of groups B, C, and D along with associated 95% confidence intervals. Proportions will be compared between group A and the combination of groups B, C, and D using Fisher's exact test. In addition, the overall proportion of patients with breast conservation intended at week 14 will be calculated for each of these groups and compared using Fisher's exact test.

  The same approaches as above will be used to compare surgical intent at baseline and actual surgery received.
- *PEPI score after letrozole with or without 14 weeks palbociclib* - PEPI score will be calculated for each patient and summarized within each randomized treatment group.
- *Assessment of safety and tolerability* – The proportion of patients experiencing each toxicity (any grade) will be presented separately for group A and the combination of groups B, C and D. Groups will be compared by Chi-squared test (or Fisher's exact test as appropriate). The proportion of patients experiencing grade 3 or greater toxicity will also be presented. Listings of all dose delays/reductions by randomized treatment group will also be produced.

A major focus of this trial is the correlative science, one of the main goals being to determine whether it is possible to identify a pre-treatment marker or markers which are predictive of benefit from palbociclib. This will involve, for example, univariate Spearman rank correlation between pre-treatment biomarker levels and Ki67/clinical response. In addition, if multiple candidates emerge, multiple linear regression with dependent variables log Ki67 fold change (or logistic regression with a 50% fall in Ki67, or PR/CR vs none as the response variables) and biomarker levels, patient characteristics, the treatment given and interactions as independent variables.

US (FB-11) and UK (PALLET) data will be pooled centrally at ICR-CTSU and shared with IDDI for interim and final analyses. Further details of analysis methods will be specified in a Statistical Analysis Plan in accordance with ICR-CTSU Standard Operating Procedures and with the agreement of NSABP statisticians.

14.5 Interim analyses and stopping rules

Final analysis is intended to occur once data (284 evaluable patients) is available.

Interim analyses are planned at 25% and 50% of trial information (data available from 71 and 142 evaluable patients). Trial results will be reviewed by an Independent Data Monitoring Committee (IDMC) which will recommend termination of the trial if there is evidence that harm from palbociclib, outweighs any plausible therapeutic gain. The decision rules applied by the IDMC for the harm analysis (25% of information) are not formally documented but will incorporate information on toxicity and benefit available from FB-11 and PALLET and assessable from all contemporaneous palbociclib trials. The trial will be terminated for futility at the second interim analysis when 142 patients are evaluable (50% of information) if there is no evidence either of the primary endpoints favors palbociclib.[18] As this is a futility stopping rule and there is no scope for

concluding the efficacy of palbociclib at this stage, no adjustment to the overall alpha is required (i.e., the probability of a false positive is not increased.)

14.6 **Monitoring**

- A medical review team comprised of the Protocol Chair, Protocol Officer, NSABP Medical Director, study statistician, Director of DSSM, designated physician(s) of the DSSM Core Group, and designated DSSM staff will formally monitor the study on a monthly basis to identify accrual, toxicity, and any endpoint problems that might be developing.
- All grades for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns.

15.0 PUBLICATION INFORMATION

The publication or citation of study results will be made in accordance with the publication policy of the NSABP that is in effect at the time the information is to be made publicly available.

16.0 REFERENCES

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APPENDIX A

ASSESSMENT OF PERFORMANCE STATUS AND ACTIVITIES OF DAILY LIVING

1.0 DETERMINATION OF PERFORMANCE STATUS

ECOG or Zubrod Scale		Karnofsky Score
0	Fully active; able to carry on all pre-disease performance without restriction	90–100%
1	Restricted in physically strenuous activity but ambulatory	70–80%
2	Ambulatory and capable of self-care, but unable to carry out any work activities	50–60%
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours	30–40%
4	Completely disabled	10–20%

2.0 NCI DEFINITION FOR ACTIVITIES OF DAILY LIVING

Activities of daily living (ADL) are the tasks of everyday life. These activities include:

- eating
- dressing
- getting into or out of bed or chair
- taking a bath or shower
- using the toilet

APPENDIX B

CONCOMITANT MEDICATIONS AND OTHER SUBSTANCES PROHIBITED DURING STUDY THERAPY

TABLE B1. List of selected inhibitors and inducers of the Cytochrome P450 CYP3A4, 5, 7 isoenzymes

INHIBITORS*		**INDUCERS***	
3A4	**OTHER**	**34A**	**OTHER**
Clarithromycin	Amiodarone	**Carbamazepine**	Barbiturates
Erythromycin	Cannabinoids	Dexamethasone**	Cotrimoxazole
Fluvoxamine	Fluoxetine	Phenobarbital	Efavirenz
Grapefruit juice	Lopinavir	Phenytoin	Ethosuximide
Grapefruit-containing products	Metronidazole	Primidone	Methadone
Indinavir	**Quinine**	Rifabutin	Metyrapone
Ketoconazole	**Sertraline**	Rifampin	Mexiletine
Mibefradil	**Zafirlukast**	St John's Wort	**Nevirapine**
Miconazole			Oral contraceptives
Nefazodone			Troglitazone
Nelfinavir			
Norfloxacin			
Ritonavir			
Saquinavir			
Troleandomycin			
Voriconazole			

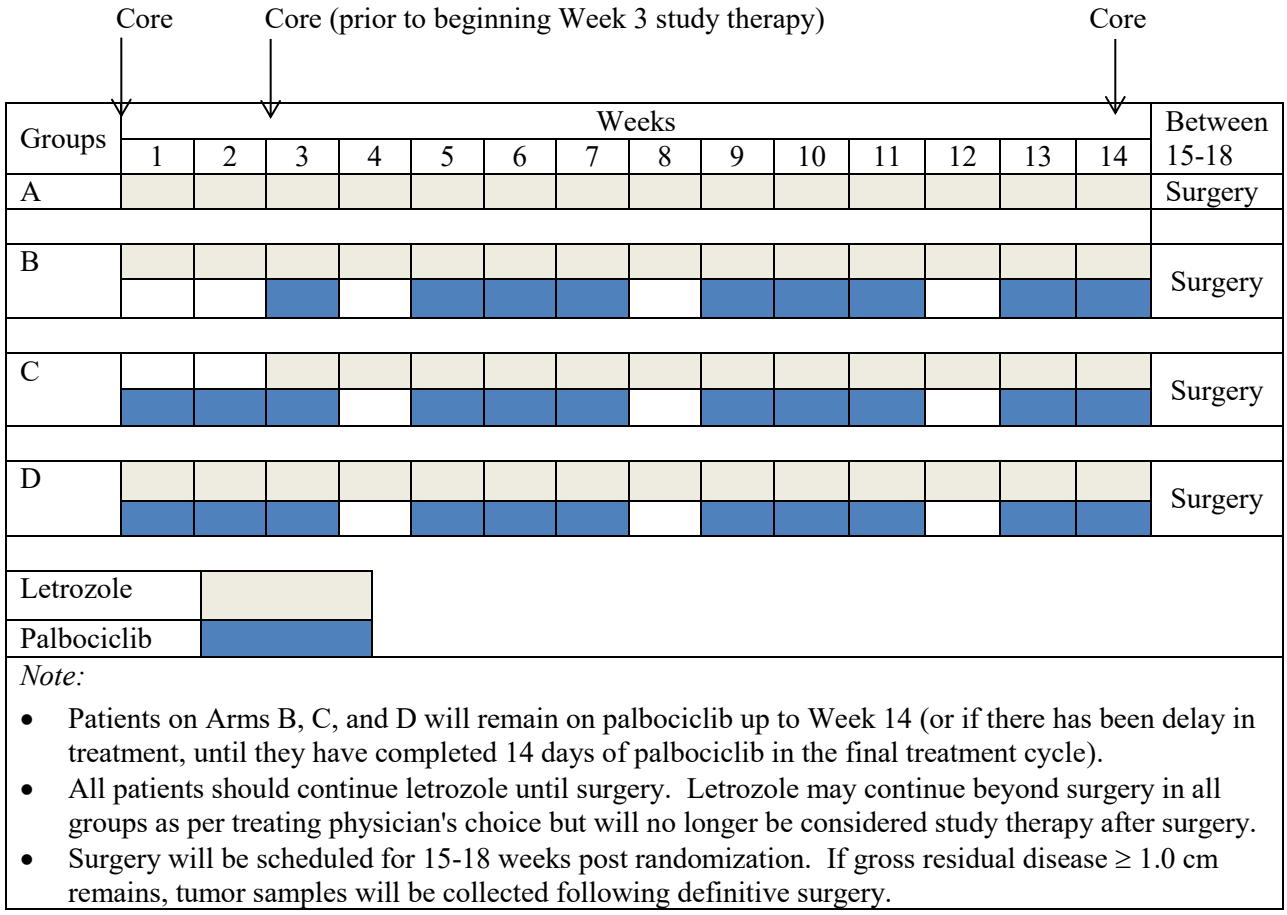
* In **boldface** are identified strong CYP3A4, 5, 7 inducers/inhibitors. This list is not meant to be considered all inclusive. From: Tatro BO. *Drug Interaction Facts 2003: The Authority on Drug Interactions, 2003*.

Consult updated lists such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx.

APPENDIX C

FB-11 TREATMENT SCHEDULE

TABLE C1 FB-11 treatment schedule



Note:

- Patients on Arms B, C, and D will remain on palbociclib up to Week 14 (or if there has been delay in treatment, until they have completed 14 days of palbociclib in the final treatment cycle).
- All patients should continue letrozole until surgery. Letrozole may continue beyond surgery in all groups as per treating physician's choice but will no longer be considered study therapy after surgery.
- Surgery will be scheduled for 15-18 weeks post randomization. If gross residual disease ≥ 1.0 cm remains, tumor samples will be collected following definitive surgery.

APPENDIX D

ECOG RESPONSE CRITERIA[18]

Complete Response	Clinical: • Complete disappearance of all clinically detectable malignant disease. Pathologic: • Pathologic proof of a clinically complete response after repeat biopsy of areas of known malignant disease.
Partial Response	≥ 50% decrease in tumor area, without increase in size of any area of known malignant disease of > 25% or appearance of new areas of malignant disease.
Stable Disease	No significant change in measurable or evaluable disease: • No increase in size of any known malignant disease • No appearance of new areas of malignant disease • This designation includes: – decrease in malignant disease of < 50% OR – decrease in uni-dimensional measurable disease of < 30% OR – increase in malignant disease of < 25% in any site – No deterioration in ECOG performance status of ≥ 1 level related to malignant disease
Progressive Disease	• Significant increase in size of lesions present at the start of therapy or after a response (> 25% in any site) OR • Appearance of new metastatic lesions known not to be present at the start of therapy OR • Stable objective disease associated with deterioration in ECOG performance status of ≥ 1 level related to malignancy