PALLET

A phase II randomised study evaluating the biological and clinical effects of the combination of palbociclib with letrozole as neoadjuvant therapy in post-menopausal women with ER+ primary breast cancer

UK PROTOCOL

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Funder:	Pfizer
UK Coordinating Trials Unit:	ICR Clinical Trials and Statistics Unit (ICR-CTSU) The Institute of Cancer Research
North America Coordinating Trials Unit:	National Surgical Breast and Bowel Project (NSABP)

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The PALLET trial has been endorsed
by Cancer Research UK's Clinical Trials Awards & Advisory Committee (CTAAC)

The PALLET trial is part of the National Institute for
Health Research Clinical Research Network Trial Portfolio

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ICR-CTSU (a CRUK funded, UKCRC registered and NCRI accredited clinical trials unit) is responsible for the central coordination of the trial on behalf of the co-sponsors.

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The UK Trial Management Group (TMG) will be constituted from UK members of the Protocol Development Group and will include the Chief Investigator, Biological Lead, key ICR-CTSU staff, Co-investigators and identified collaborators and a lay representative. Principal Investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of sites and professional groups. A copy of the current membership of the TMG can be obtained from the PALLET Trial Manager at ICR-CTSU.

Protocol Authorised by:

Name & Role	Signature	Date
Prof Stephen Johnston (Chief Investigator)		24/11/2015

The PALLET trial represents an international collaboration between investigators in the UK (NCRI Breast Clinical Studies Group working with ICR-CTSU) and North America (led by NSABP). This protocol describes the UK PALLET trial and provides information about procedures for entering participants into this trial in the UK. A parallel protocol exists for North American participation in PALLET. For governance purposes two separate country specific protocols exist to document the requirements for treating patients within the respective health systems. Both protocols describe the same treatment regimen and contain the same statistical considerations, including overall target sample size and plans for interim and final analysis. The primary analysis will include all UK and North America randomised patients.

The protocol should not be used as a guide for the treatment of patients outside of this trial.

Every care was taken in the preparation of this protocol, but corrections or amendments may be necessary. Protocol amendments will be circulated to participating sites as they occur, but sites entering patients for the first time are advised to contact ICR-CTSU to confirm they have the most recent version.

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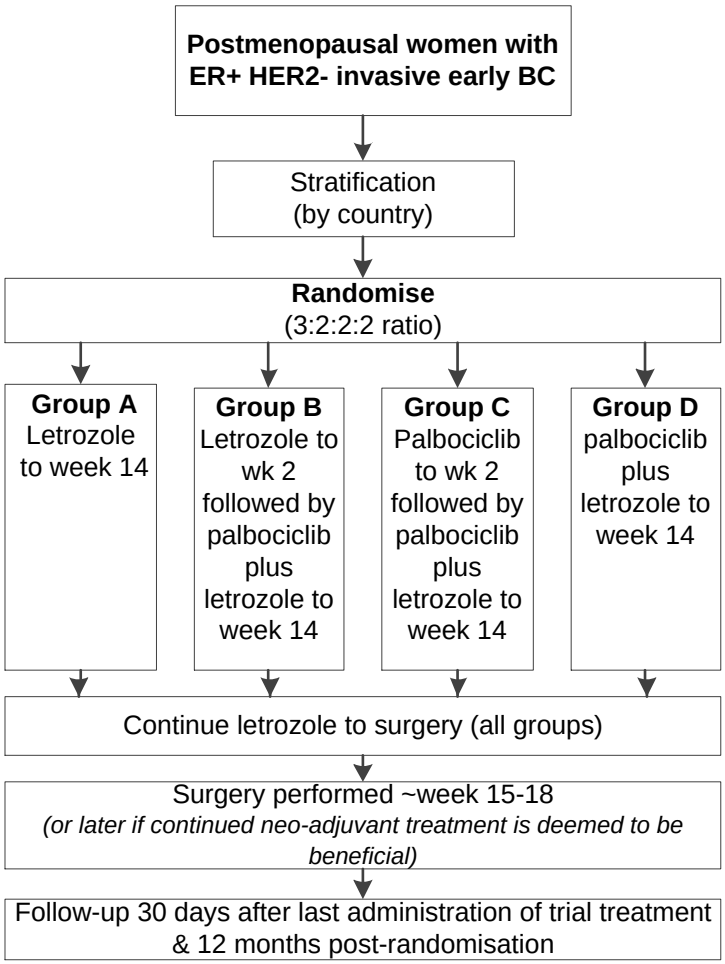
PALLET TRIAL SUMMARY

PROTOCOL TITLE	A phase II randomised study evaluating the biological and clinical effects of the combination of palbociclib with letrozole as neoadjuvant therapy in post-menopausal women with ER+ primary breast cancer.
STUDY OBJECTIVES	1. To compare the changes in the proliferation marker Ki67 after 14 weeks treatment with letrozole with or without palbociclib. 2. To compare clinical response after 14 weeks treatment with letrozole with or without palbociclib.
STUDY DESIGN	Phase II randomised multicentre trial with parallel UK and North American protocols.
TRIAL POPULATION	Post-menopausal patients with ER+ primary breast cancer.
RECRUITMENT TARGET	306 patients (global), 100-200 patients (UK target).
TREATMENT REGIMEN	Patients will be randomised to one of four treatment groups (3:2:2:2 ratio): Group A: Letrozole alone for 14 weeks Group B: Letrozole for 2 weeks followed by letrozole + palbociclib to 14 weeks Group C: Palbociclib for 2 weeks followed by letrozole + palbociclib to 14 weeks Group D: Letrozole + palbociclib for 14 weeks. Beyond week 14 letrozole (the standard therapy) will continue until surgery in all treatment groups. In all groups, letrozole will be administered as 2.5mg daily PO. Palbociclib will be administered as 125 mg daily PO on a schedule of 21 days on, 7 days off (21/7). Post-surgical treatment will be at discretion of treating clinician.
CO-PRIMARY ENDPOINTS	• Change in the proliferation marker Ki67 (% positive tumour cells) as tested by IHC from baseline to after 14 weeks treatment with letrozole with or without palbociclib; • Clinical response as measured by ultrasound according to ECOG criteria after 14 weeks treatment with letrozole with or without palbociclib.
SECONDARY ENDPOINTS	• Effect of palbociclib on Ki67 after 2 weeks and the added effect of letrozole from weeks 2-14 (within group) • Effect of letrozole on Ki67 after 2 weeks and the added effect of palbociclib from weeks 2-14 (within group) • pCR rates after letrozole with or without 14 weeks palbociclib • PEPI score after letrozole with or without 14 weeks palbociclib

	• Assessment of safety and tolerability • Changes between surgical intent at baseline, surgical intent after 14 weeks and actual surgery received after treatment with letrozole with or without palbociclib
EXPLORATORY ENDPOINTS	• Explore whether subgroups with greater or lesser Ki67 response or clinical response to added palbociclib can be identified in molecular profiles conducted in pre-treatment samples. • Characterisation of the molecular effects of palbociclib with and without letrozole and assessment of whether these vary according to pre-treatment tumour characteristics.
FOLLOW UP	Patients will be followed up approximately 30 days after last administration of trial treatment and at 12 months post-randomisation.

TRIAL SCHEMA

Figure 1:



1. INTRODUCTION

1.1. Background

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

Aromatase inhibitors (AIs) are the most effective endocrine treatment for ER-positive (ER+) 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+ breast cancer. Letrozole is also licensed in the neo-adjuvant setting for ER+ postmenopausal 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+/HER2- advanced breast cancer patients. Preclinical evidence that palbociclib is highly active in ER+ cell lines and encouraging early safety and PK results led to a randomised 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+/HER2- advanced breast cancer (NCT00721409). A phase II dose of 125mg QD on a schedule of 21/7 (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 tumour CCND1 amplification and/or p16 loss. 165 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) [4]. 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 [5]. No biomarkers have yet been identified as indicating populations with greater or lesser response to the additional palbociclib. The response of tumours with gain of CCND1 and/or loss of p16 appears to be no different from that of tumours without these characteristics despite encouraging preclinical evidence [6]. 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.

The randomised phase II PALOMA-1 trial (palbociclib in combination with letrozole vs. letrozole alone as first-line treatment of ER+/HER2- advanced breast cancer) reported a median PFS of 10.2 months (95% CI 5.7–12.6) for the letrozole group compared to 20.2 months (13.8–27.5) for the palbociclib + letrozole group (HR 0.488, 95% CI 0.319–0.748; one-sided p=0·0004) [7]. A recent phase III trial of 521 patients with advanced HR+/HER2-breast cancer that had relapsed or progressed during prior endocrine therapy assessed the efficacy of palbociclib in combination with fulvestrant (NCT01942135, PALOMA-3). The trial reported median PFS of 9.2 months (95% CI, 7.5 to not estimable) with palbociclib–fulvestrant and 3.8 months (95% CI, 3.5 to 5.5) with placebo–fulvestrant (HR for disease progression or death, 0.42; 95% CI, 0.32 to 0.56; P<0.001) [8]. A phase III study (NCT01864746, PENELOPE-B) evaluating palbociclib in patients with HR+/HER2- primary breast cancer with high relapse risk after neoadjuvant chemotherapy is currently recruiting internationally; the trial is led by the German Breast Group under the auspices of the Breast International Group with UK participation.

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

1.2. Known Risks and Benefits of Palbociclib

Clinical studies to date suggest that toxicity associated with palbociclib is largely limited to uncomplicated neutropenia, fatigue, diarrhoea and anaemia, 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 similar to those seen with either palbociclib or letrozole alone (NCT00721409).

Data from in vitro and in vivo pre-clinical studies has indicated that palbociclib has the potential to delay cardiac repolarization as measured by prolongation of the QT interval on ECG. Of 385 patients treated with palbociclib in clinical trials to date, one patient experienced an incidence of a QTc increasing by 67msec, with a QTc interval <500msec. However, the patient's medical history and concomitant medications may have been implicated in this event. No patient has experienced a QTcF interval >500 msec in clinical studies to date. 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). Monitoring of patients enrolled in clinical studies of palbociclib, including clinical examinations, vital signs measurements, routine ECGs and AE monitoring, is therefore recommended.

1.3. Study Rationale

The use of AI therapy in the neoadjuvant treatment of women with ER+ breast cancer has been established as a safe and effective treatment option allowing down-staging of tumours 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+ 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 [9].

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. PALLET is a randomised trial to examine the biological and clinical effect of neoadjuvant letrozole +/- 14 weeks palbociclib in the first-line treatment of ER+/HER2- early invasive breast cancer.

Pre-treatment samples will be collected and used to identify subgroups of patients who may derive most clinical benefit, and 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+ breast cancer may be warranted to see if an improved standard of care can be established.

In this phase II PALLET trial 306 patients will be recruited from sites in the UK and North America.

2. TRIAL OBJECTIVES

2.1. Primary Objective

The co-primary objectives of the PALLET trial are:

- To compare the changes in the proliferation marker Ki67 after 14 weeks treatment with letrozole with or without palbociclib.
- To compare clinical response after 14 weeks treatment with letrozole with or without palbociclib.

2.2. Secondary Objectives

- To determine the effect of palbociclib on Ki67 after 2 weeks and the added effect of subsequent treatment with palbociclib and letrozole from weeks 2-14.
- To determine the effect of letrozole on Ki67 after 2 weeks and the added effect of subsequent treatment with palbociclib and letrozole from weeks 2-14.
- To compare the pathological complete response (pCR) rate after letrozole +/- 14 weeks of palbociclib.
- To compare the preoperative endocrine prognostic index (PEPI) score after letrozole +/- 14 weeks of palbociclib.
- Assessment of safety and tolerability
- 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.

2.3. Exploratory Objectives

- To explore whether subgroups with greater or lesser Ki67 response or clinical response to added palbociclib can be identified in molecular profiles conducted in pre-treatment samples.
- To characterize the molecular effects of palbociclib with and without letrozole and assess whether these vary according to pre-treatment tumour.

3. TRIAL DESIGN

The PALLET Trial initiative is a joint partnership between UK investigators and the US NSABP group. Parallel protocols will be conducted in the UK and North America with joint analysis of interim and final data. Each collaborative group will recruit at least 1/3 and no more than 2/3 of the target accrual (N=306).

PALLET is a 4 group parallel open label randomised phase II trial with clinical response, fall in proliferation markers (Ki67), PEPI score and pCR as endpoints. Postmenopausal women, newly diagnosed with ER+/HER2- early breast cancer, who are suitable candidates for neoadjuvant endocrine therapy will be invited to join the PALLET trial.

Patients will be randomised to one of four treatment groups (3:2:2:2 ratio). Treatment in the first 14 weeks of neoadjuvant therapy will be:

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

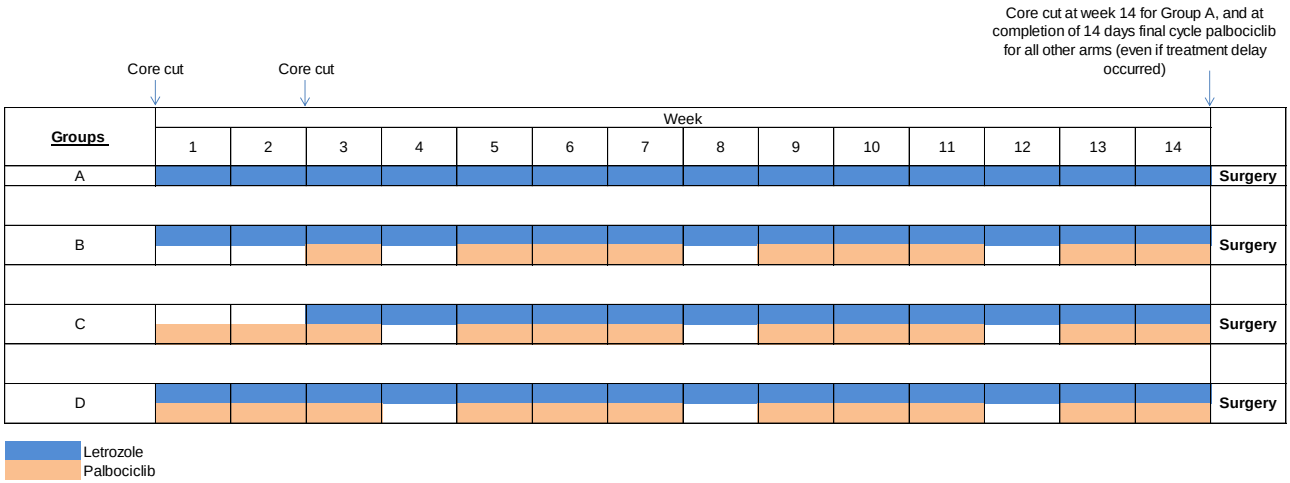
Beyond week 14 letrozole (the standard therapy) should continue until surgery in all treatment groups.

Ultrasound imaging of the tumour will be performed pre-biopsy at baseline and at week 14 and clinical response assessed according to ECOG criteria (see appendix 1).

Up to a maximum of four core-cut biopsies will be collected at baseline, after two weeks of trial treatment and at the time of last trial treatment (usually week 14).

The treatment schedule for the four groups is illustrated in Figure 2.

Figure 2: PALLET treatment schedule



Palbociclib will be administered orally as 125mg daily on a schedule of 3 weeks on, 1 week off (3/1).

Letrozole will be administered orally as a 2.5mg daily tablet.

Patients in groups B, C and D will continue treatment until they have completed 14 days of palbociclib in the final treatment cycle.

The end of trial treatment for patients in Group A will be completion of week 14. Patients in Groups B, C and D will complete trial treatment following 14 days of palbociclib in the final treatment cycle.

All patients should continue letrozole until surgery. Letrozole is not considered trial treatment beyond completion of week 14 for patients in Group A or after 14 days of palbociclib in the final treatment cycle for patients in Groups B, C and D.

Surgery may be scheduled for 15-18 weeks post-randomisation. Post-surgical treatment will be at the discretion of the treating clinician, following local protocols, and not influenced by allocation of treatment within PALLET. Access to samples routinely collected at surgery will be requested from all patients.

Beyond the end of trial treatment, all patients will be followed up at 30 days from last administration of trial treatment and again at 12 months post-randomisation, including those who prematurely withdrew from trial treatment (unless patient withdraws consent). Post-treatment follow-up will be in line with standard practice but will include collection of data on disease-related outcomes.

4. STUDY ENDPOINTS

4.1. Co-primary Endpoints

- Change in the proliferation marker Ki67 (% positive tumour cells) as tested by IHC from baseline to after 14 weeks treatment with letrozole with or without palbociclib
- Clinical response as measured by ultrasound according to ECOG criteria after 14 weeks treatment with letrozole with or without palbociclib.

4.2. Secondary Endpoints

- Effect of palbociclib on Ki67 after 2 weeks and the added effect of letrozole from weeks 2-14 (within group)
- Effect of letrozole on Ki67 after 2 weeks and the added effect of palbociclib from weeks 2-14 (within group)
- pCR rates after letrozole with or without 14 weeks palbociclib
- PEPI score after letrozole with or without 14 weeks palbociclib
- Assessment of safety and tolerability
- Changes between surgical intent at baseline, surgical intent after 14 weeks and actual surgery received after treatment with letrozole with or without palbociclib.

4.3. Exploratory Endpoints

- Pre-treatment molecular subgroups with greater or lesser Ki67 response or clinical response to added palbociclib
- Molecular effects of palbociclib with and without letrozole and assessment of whether these vary according to pre-treatment tumour characteristics.

5. PATIENT SELECTION & ELIGIBILITY

5.1. Number of Participants

The aim is to recruit a combined total of 306 participants from the UK and North America. The UK will recruit at least 100 and no more than 200 from the target accrual.

5.2. Source of Participants

5.2.1. UK Participants

Participants will be recruited from approximately 25 participating sites in the UK. Potential participants will be identified by surgical clinics and in oncology clinics and discussed at Multi-Disciplinary Team (MDT) meetings.

5.2.2. North American Participants

In North America, participants will be recruited from approximately 19 participating sites. Potential participants will be identified in oncology clinics and discussed at Multi-Disciplinary Team (MDT) meetings.

5.3. Inclusion Criteria

1. Postmenopausal women defined as:
   i. Age 56 or older with no spontaneous menses for at least 12 months prior to study entry; **or**

ii. 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 oestradiol level in the postmenopausal range according to local institutional/laboratory standard; **or**
iii. Age ≥16 with documented bilateral oophorectomy

2. Operable ER+ HER2- invasive early breast cancer suitable for neoadjuvant AI treatment. ER positivity is defined as an Allred score of 3 (or equivalent). HER2 negativity will be defined as per the 2013 ASCO/CAP guidelines as follows:
   i. IHC 1+ as defined by incomplete membrane staining that is faint/barely perceptible and within >10% of the invasive tumour cells; **or**
   ii. IHC 0 as defined by no staining observed or membrane staining that is incomplete and is faint/barely perceptible and within ≤10% of the invasive tumour cells; **or**
   iii. ISH negative based on:
      - Single-probe average HER2 copy number <4.0 signals/cell
      - Dual-probe HER2/CEP17 ratio <2.0 with an average HER2 copy number <4.0 signals/cell
3. No medical contraindication to palbociclib (as defined according to latest version of Investigator Brochure)
4. A tumour with an ultrasound size of at least 2.0cm
5. No evidence of metastatic spread by standard assessment according to local guidelines
6. ECOG performance status of 0 or 1 (see appendix 2)
7. Adequate organ function including:
   a) haemoglobin ≥10g/dL (100g/L)
   b) ANC ≥1,500/mm³ (>1.5 x 10^9/L)
   c) platelets ≥100,000/mm³ (>100 x 10^9/L)
   d) AST and/or ALT ≤1.5 x upper normal limits (ULN)
   e) alkaline phosphatase ≤1.5 x ULN
   f) total serum bilirubin ≤ ULN 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
   g) serum creatinine ≤1.25 x ULN or estimated creatinine clearance >60 mL/min (as calculated using the method standard for the institution)
   h) no severe and relevant co-morbidity that would affect a patient's participation in the study
   i) INR must be within normal limits of the local laboratory ranges
8. Written informed consent to participate in the trial and to donation of tissue and blood samples
9. Patients must have the ability to swallow oral medication

5.4. Exclusion Criteria

1. Premenopausal or peri-menopausal women
2. Inflammatory/inoperable breast cancer
3. HER2 positive
4. Concurrent use (defined as use within 4 weeks prior to baseline tissue sample being taken) of HRT or any other oestrogen-containing medication (including vaginal oestrogens)
5. Prior endocrine therapy for breast cancer
6. Any invasive malignancy within previous 5 years (other than basal cell carcinoma or cervical carcinoma in situ)
7. Bilateral invasive disease
8. Any severe coincident medical disease, including seizure disorder requiring medication
9. Diagnosis by FNA alone or excisional biopsy or lumpectomy performed prior to study entry

10. Surgical axillary staging procedure prior to study procedure (with the exception of FNA or core biopsy)
11. Definitive clinical or radiologic evidence of metastatic disease
12. History of ipsilateral invasive breast cancer regardless of treatment or ipsilateral DCIS treated with radiotherapy or contralateral invasive breast cancer at any time
13. New York Heart Association classification of level III or IV heart disease (see Appendix 3)
14. Any treatment, including radiotherapy, chemotherapy, and/or targeted therapy, administered for the currently diagnosed breast cancer prior to study entry
15. Patients on established CYP3A inhibitors/inducers (see section 9.5)
16. QTc >480 msec or a family or personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation, or Torsade de Pointes (TdP)
17. Active hepatitis B or hepatitis C with abnormal liver function tests
18. HIV positive patients receiving antivirals

6. SCREENING

6.1. Screening Log

Participating sites will be requested to keep a log of all postmenopausal patients with ER+/HER2- invasive early breast cancer who are suitable for neoadjuvant endocrine therapy and potentially eligible for this study. The information collected on the log will include:

- Date patient identified
- Screening outcome (patient approached/accepted participation/declined participation)
- Reasons for not approaching / declining participation (if available)
- Trial ID (if applicable)

This information will be used by the TMG to monitor recruitment activity. No patient identifiable data (except Trial ID) should be sent to ICR-CTSU on the screening logs.

6.2. Procedure for obtaining Informed Consent

The Principal Investigator (or designated individual) must ensure that each trial patient is fully informed about the nature and objectives of the trial and possible risks associated with participation. Participants should be given the current ethics approved PALLET patient information sheet for their consideration. Patients should only be asked to consent to the study after they have had sufficient time to consider the trial, and the opportunity to ask any further questions.

No protocol required assessments should be conducted until the PALLET consent form has been signed and dated by both the patient and the Investigator, unless they are performed routinely as part of standard patient care.

Confirmation of the patient's consent and the informed consent process must be documented in the patient's medical notes. A copy of the signed consent form should be provided to the patient and the original retained in the investigator site file, which must be available for verification by ICR-CTSU study staff or for regulatory inspection at any time.

6.3. Participation in other Clinical Trials

PALLET patients will not be permitted to participate in any other trials of investigational medicinal products whilst they are being treated within PALLET or for 1 month afterwards.

7. RANDOMISATION

Patients recruited in the UK must be randomised centrally by the trials unit (ICR-CTSU) before trial treatment can commence.

UK patients should be randomised by telephoning ICR-CTSU on:
+44 (0)20 8643 7150
09.00-17.00 (UK time) Monday to Friday

Randomisation should take place as close to the planned start date of treatment as possible. An eligibility and randomisation checklist must be completed prior to randomisation.

The following information will be required at randomisation:

- Name of hospital, consultant and person registering patient
- Confirmation that patient has given written informed consent for trial
- Confirmation that patient is eligible for the trial by completion of the eligibility checklist
- Patient's full name, hospital number, date of birth and NHS/CHI number (or equivalent for international participants)

The caller will be given the patient's unique randomisation number (Trial ID) and treatment allocation.

ICR-CTSU will send confirmation to the trial contact at the recruiting site to confirm a patient's entry into the trial.

8. TRIAL ASSESSMENTS

8.1. Screening Assessments

The following assessments should be conducted within 14 days prior to randomisation except for the radiological tumour assessment by ultrasound, which should be conducted within 28 days prior to randomisation. Any of the tests below which have been performed as part of standard clinical practice prior to randomisation may be used if conducted within the specified timeframe:

- Complete medical history
- Physical examination including height and weight
- ECOG performance status
- Vital signs including heart rate and blood pressure
- ECG
- Assessment of concomitant medications/treatments
- Haematology: haemoglobin, platelet counts, white blood cells with differential count (including absolute neutrophil count)
- Prothrombin time/INR
- Biochemistry: sodium, potassium, calcium, magnesium, alanine aminotransferase (ALAT, ALT), aspartate aminotransferase (ASAT, AST), bilirubin (total) albumin; alkaline phosphatase (total ALP), creatinine, urea, glucose, total protein
- Radiological tumour assessment (ultrasound)
- Tumour assessment by palpation

8.2. Pre-treatment Assessments

The following samples should be collected following randomisation and prior to first administration of trial treatment. Further details on sample collection in PALLET are in Section 18.

- Blood sample collection (1 x 10ml EDTA, 1 x 8.5ml PAXgene DNA)
- Core biopsy (at least 2 and up to 4 cores to be collected)

8.3. On-treatment Assessments

Trial treatment has a scheduled duration of 14 weeks. The following assessments should be conducted at the appropriate timepoints (+/-2 days).

8.3.1. Week 1

- Assessment of concomitant medications/treatments
- Assessment of compliance with trial treatment
- Symptom assessment (NCI CTCAE v4.0)
- Haematology: haemoglobin; platelet counts; white blood cells with differential count (including absolute neutrophil count)

8.3.2. Week 2

- ECOG performance status
- Vital signs including heart rate and blood pressure
- Assessment of concomitant medications/treatments
- Assessment of compliance with trial treatment
- Symptom assessment (NCI CTCAE v4.0)
- Haematology: haemoglobin; platelet counts; white blood cells with differential count (including absolute neutrophil count)
- Prothrombin time/INR
- Tumour assessment by palpation
- Blood sample collection (1 x 10ml EDTA)
- Core biopsy (at least 2 and up to 4 cores to be collected)

8.3.3. Week 3

- Assessment of concomitant medications/treatments
- Assessment of compliance with trial treatment
- Symptom assessment (NCI CTCAE v4.0)
- Haematology: haemoglobin; platelet counts; white blood cells with differential count (including absolute neutrophil count)

8.3.4. Week 4

- ECOG performance status
- Vital signs including heart rate and blood pressure
- Assessment of concomitant medications/treatments
- Assessment of compliance with trial treatment
- Symptom assessment (NCI CTCAE v4.0)

- Haematology: haemoglobin; platelet counts; white blood cells with differential count (including absolute neutrophil count)
- Biochemistry: sodium; potassium; calcium; magnesium, alanine aminotransferase (ALAT, ALT); aspartate aminotransferase (ASAT, AST), bilirubin (total); albumin; alkaline phosphatase (total ALP), creatinine, urea, glucose, total protein
- Tumour assessment by palpation

8.3.5. Week 6

- ECG
- Assessment of concomitant medications/treatments
- Assessment of compliance with trial treatment
- Symptom assessment (NCI CTCAE v4.0)
- Haematology: haemoglobin; platelet counts; white blood cells with differential count (including absolute neutrophil count).

8.3.6. Week 8

- ECOG performance status
- Vital signs including heart rate and blood pressure
- Assessment of concomitant medications/treatments
- Assessment of compliance with trial treatment
- Symptom assessment (NCI CTCAE v4.0)
- Haematology: haemoglobin; platelet counts; white blood cells with differential count (including absolute neutrophil count).
- Biochemistry: sodium; potassium; calcium; magnesium, alanine aminotransferase (ALAT, ALT); aspartate aminotransferase (ASAT, AST), bilirubin (total); albumin; alkaline phosphatase (total ALP), creatinine, urea, glucose, total protein
- Tumour assessment by palpation

8.3.7. Week 10

- Assessment of concomitant medications/treatments
- Assessment of compliance with trial treatment
- Symptom assessment (NCI CTCAE v4.0)
- Haematology: haemoglobin; platelet counts; white blood cells with differential count (including absolute neutrophil count).

8.3.8. Week 12

- ECOG performance status
- Vital signs including heart rate and blood pressure
- Assessment of concomitant medications/treatments
- Assessment of compliance with trial treatment
- Symptom assessment (NCI CTCAE v4.0)
- Haematology: haemoglobin; platelet counts; white blood cells with differential count (including absolute neutrophil count)

- Biochemistry: sodium; potassium; calcium; magnesium, alanine aminotransferase (ALAT, ALT); aspartate aminotransferase (ASAT, AST), bilirubin (total); albumin; alkaline phosphatase (total ALP), creatinine, urea, glucose, total protein
- Tumour assessment by palpation

8.3.9. Week 14

- ECG
- Assessment of concomitant medications/treatments
- Assessment of compliance with trial treatment
- Symptom assessment (NCI CTCAE v4.0)
- Haematology: haemoglobin; platelet counts; white blood cells with differential count (including absolute neutrophil count).
- Prothrombin time/INR
- Radiological tumour assessment (ultrasound)
- Blood sample collection (1 x 10ml EDTA)
- Core biopsy (at least 2 and up to 4 cores to be collected). The final biopsy should be performed within 48 hours of the last treatment administration

8.4. End of Trial Treatment Assessments

The following assessments should be performed at the end of trial treatment visit, 30 days (± 7 days) after last administration of trial treatment.

- ECOG performance status
- Vital signs including heart rate and blood pressure
- Assessment of concomitant medications/treatments
- Symptom assessment treatment (NCI CTCAE v4.0)
- Haematology: haemoglobin; platelet counts; white blood cells with differential count (including absolute neutrophil count).
- Biochemistry: sodium; potassium; calcium; magnesium, alanine aminotransferase (ALAT, ALT); aspartate aminotransferase (ASAT, AST), bilirubin (total); albumin; alkaline phosphatase (total ALP), creatinine, urea, glucose, total protein

8.5. Post- Trial Treatment Follow-up

All patients should be followed up at 12 months post-randomisation; assessment should be in line with standard practice and should include:

- ECOG performance status
- Vital signs including heart rate and blood pressure
- Symptom assessment treatment (NCI CTCAE v4.0)
- Haematology: haemoglobin; platelet counts; white blood cells with differential count (including absolute neutrophil count)

8.6. Discontinuation from Trial Treatment

Participants may discontinue from trial treatment at any time at their own request, or they may be discontinued at the discretion of the Principal Investigator. Reasons for discontinuation may include:

- Disease progression or recurrence

- Unacceptable toxicity
- Co-morbidities

Participants who discontinue treatment should continue to be followed up. Patients who prematurely discontinue trial treatment, and have received at least one cycle of trial treatment, should be asked to provide blood and tissue samples at that time for correlative study. Samples should be collected within 48 hours from last administration of trial treatment. Patients should also receive an ultrasound at that point.

8.7. Discontinuation from Follow-up

If a patient withdraws from further follow-up a trial deviation form should be submitted to ICR-CTSU stating whether the patient has withdrawn consent for information and routinely collected histological material to be sent to the ICR-CTSU or whether they simply no longer wish to attend trial follow up visits. In the very rare event that a patient requests that their data is removed from the study entirely, the implications of this should be discussed with the patient first to ensure that this is their intent and, if confirmed, ICR-CTSU should be notified in writing. Should a patient withdraw consent for their samples to be used in PALLET, these will be destroyed following receipt of written confirmation.

8.8. Schedule of Assessments

Visit/Assessment	Baseline	Randomisation	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Surgery	End of treatment (30 days after last administration)	Follow-up (12 months post-randomisation)
Informed consent	X													
Medical history	X													
Physical examination[a]	X													
ECOG performance status	X			X		X		X		X			X	X
Vital signs[b]	X			X		X		X		X			X	X
ECG	X						X				X			
Assessment of concomitant medications[c]	X		X	X	X	X	X	X	X	X	X		X	
Assessment of compliance with trial treatment			X	X	X	X	X	X	X	X	X			
Assessment of adverse events[d]			X	X	X	X	X	X	X	X	X		X	X
Haematology[e]	X		X	X	X	X	X	X	X	X	X		X	X
PT/INR[f]	X			X							X			
Biochemistry[g]	X					X		X		X			X	
Radiological tumour assessment by ultrasound scan	X										X			

Visit/Assessment	Baseline	Randomisation	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Surgery	End of treatment (30 days after last	Follow-up (12 months post-randomisation)
Tumour assessment by palpation	X			X		X		X		X				
Dispense trial medication		X		X[h]		X		X		X				
Collection of bloods for correlative study[i]		X[j,k]		X							X			
Core biopsy[l]		X[k]		X							X[m]			

Footnotes:

a) Including height and weight

b) Including heart rate and blood pressure

c) To be recorded at the baseline visit, from then on only changes to be recorded

d) Assess symptoms, report as necessary (refer to protocol section 10)

e) Haemoglobin, platelet counts, white blood cells with differential count (including absolute neutrophil count)

f) Prothrombin time/international normalised ratio

g) To include sodium, potassium, calcium, magnesium, alanine aminotransferase (ALAT, ALT), aspartate aminotransferase (ASAT, AST), bilirubin (total) albumin, alkaline phosphatase (total ALP), creatinine, urea, glucose, total protein

h) Groups B and C only

i) 1x 10ml EDTA to be collected at each of the three specified timepoints

j) Additional 1 x 8.5ml PAXgene blood sample to be collected at baseline (if missed at baseline, the PAXgene sample can be collected at any subsequent visit)

k) Collection of baseline blood samples and core biopsies must be performed following randomisation, and prior to commencement of trial treatment

l) A minimum of 2 and a maximum of 4 cores should be collected at the designated timepoints. Tissue collected via biopsy should be fixed in the following order of priority: 1) formalin fixed; 2) fresh frozen; 3) formalin fixed; 4) fresh frozen. Access to material routinely collected during surgery will also be requested

m) Core biopsy should be performed within 48 hours of administration of last trial treatment

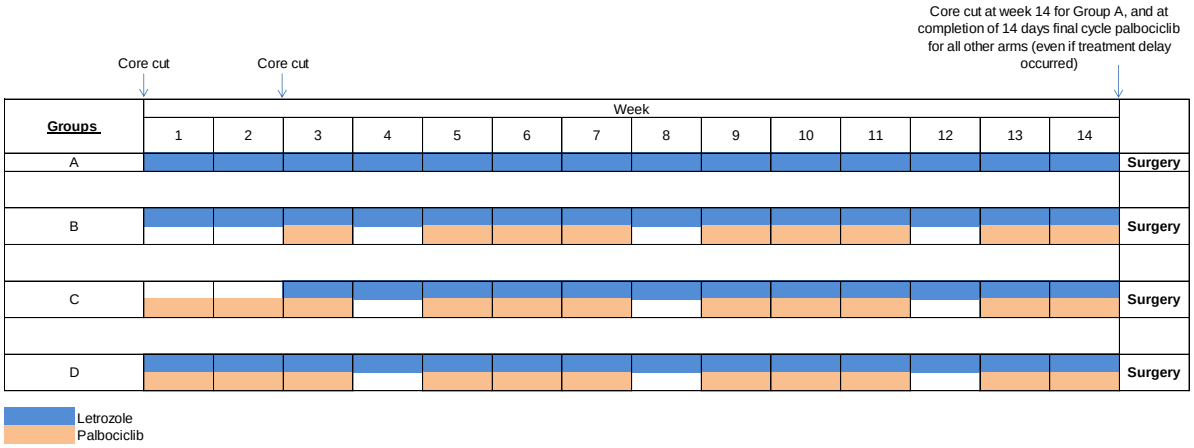
9. TRIAL TREATMENT

The trial treatments under investigation (IMPs) are palbociclib and letrozole. The end of trial treatment for patients in Group A will be at completion of week 14. Patients in groups B to D will complete trial treatment after they have received 14 days of palbociclib in the final treatment cycle. All patients should continue letrozole until surgery.

9.1. Dose and Schedule

Patients will be randomised to one of four treatment groups:

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



Letrozole should continue until surgery in all treatment groups.

Palbociclib will be administered orally at a dose of 125 mg once a day on a 28 day schedule of 21 days on, 7 days off (21/7).

Patients should be instructed to take palbociclib with food. Patients should be advised to swallow palbociclib capsules whole and not to chew them prior to swallowing. No capsule should be ingested if it is broken, cracked, or otherwise not intact. Patients should be encouraged to take their dose at approximately the same time each day.

Letrozole will be administered orally as a 2.5mg daily tablet (all groups). Patients should be instructed to swallow letrozole tablets whole (with or without food). Letrozole should be taken together with palbociclib (groups B, C and D).

Patients experiencing toxicities related to the trial treatment may have their dose modified according to section 9.6.

9.2. Prescription and Dispensing

Palbociclib will be provided in non-patient-specific bottles. The patient's trial ID number should be recorded on the bottle label prior to dispensing. Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container. Palbociclib capsules

must not be opened and/or emptied into any vehicle for oral ingestion; capsules must be swallowed intact.

All efforts should be made to ensure that patients clearly understand the directions for self-medication. Patients should be given a sufficient supply and unused drug and/or empty bottles should be returned at the appropriate time points. Returned unused medication must not be re-dispensed to a patient.

Only one capsule strength will be dispensed to the patient at any one time.

9.3. Patient Cards

Small wallet sized cards will be produced by ICR-CTSU on request by the participating site. Each card will state:

- the name of the participating site
- that the patient is participating in the PALLET trial
- that the patient is taking palbociclib
- an emergency contact number

9.4. Duration of Treatment

According to their randomised treatment group, patients allocated to palbociclib will start treatment either at the same time as starting letrozole or 2 weeks earlier or 2 weeks later. Patients will remain on palbociclib up to week 14 (or until they have completed 14 days of palbociclib in the final treatment cycle) and should continue letrozole to the time of surgery. Patients may withdraw from trial treatment early if they experience unacceptable toxicity or if the treating clinician believes further treatment is no longer appropriate.

9.5. Concomitant Therapy

Patients should be instructed not to take any additional medications (including over-the-counter products) during the study without prior consultation with the investigator as some herbal supplements or over the counter medications can impact pharmacokinetics of palbociclib. All medication considered necessary for the participants' welfare and which is not expected to interfere with the evaluation of the study drugs may be given at the discretion of the investigator.

All concomitant medications must be recorded in the patient's notes at baseline and any changes recorded at subsequent study visits.

9.5.1. Non-permissible Medications

The following medications are not permitted whilst on trial treatment:

- Anticancer agents: no additional anticancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy (other than letrozole) will be permitted whilst the patient is on trial treatment.
- Strong CYP3A inhibitors/inducers: palbociclib is metabolized to multiple metabolites. In vitro, palbociclib is primarily metabolized by CYP3A4 enzymes. Co-administration with drugs that are CYP3A inhibitors and inducers may change the plasma concentrations of palbociclib in humans. The concurrent use of CYP3A inhibitors including, but not limited to, amprenavir, atazanavir,

boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, voriconazole, and grapefruit, grapefruit juice or any product containing grapefruit, is not permitted. The concurrent use of CYP3A inducers, including carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's wort, is not permitted.

- Drugs known to cause QT interval prolongation are prohibited. This includes, but is not limited to, amiodarone, azithromycin, citalopram, clarithromycin, domperidone, erythromycin, methadone, sotalol.
- Hormone replacement therapy, topical oestrogens (including any intra-vaginal preparations), megestrol acetate and selective oestrogen-receptor modulators (e.g. raloxifene) are prohibited.
- Erythropoietin for the supportive treatment of anaemia is not permitted.
- Use of growth factors, e.g. G-CSF, is not permitted.

9.5.2. Medications Not Recommended

The following treatments are not recommended whilst the patient is receiving trial treatment. Alternative therapies should be considered whenever possible**.** If usage of the following treatments is deemed necessary, consultation with the Chief Investigator via ICR-CTSU is required prior to treatment initiation.

- Moderate CYP3A inducers: the concurrent use of moderate CYP3A inducers such as dexamethasone is not recommended.
- CYP3A substrates: caution should be exercised in patients receiving palbociclib in combination with drugs that are predominantly metabolized by CYP3A. In particular, co-administration of palbociclib with CYP3A4 substrates with narrow therapeutic index including, but not limited to, alfentanil, aripiprazole, cyclosporine, ergotamine, fentanyl, halofantrine, pimozide, quinidine, sirolimus, tacrolimus, triazolam, astemizole*, cisapride*, and terfenadine* (*withdrawn from U.S. market) are not recommended. Alternative therapies should be used where possible.
- Chronic immunosuppressive therapies: should be avoided, including systemic corticosteroids. Steroids given for physiological replacement, as anti-emetics or inhaled as well as short course of oral/topical steroids given for allergic reactions or asthma flares are allowed.
- The use of herbal medicine is not recommended whilst on trial treatment.

9.5.3. Permitted Medications

All medication considered necessary for the participants' welfare and which is not expected to interfere with the evaluation of the study treatment may be given at the discretion of the investigator. This includes:

- Standard therapies for pre-existing medical conditions, medical and/or surgical complications. Any medication intended solely for supportive care (e.g. analgesics, antidiarrheals, antidepressants) may also be used at the investigator's discretion.
- Bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors for the treatment of osteoporosis.

All concomitant medications must be recorded in the patient's notes, as well as the appropriate pages of the eCRF.

9.6. Palbociclib Dose Modifications

Every effort should be made to administer palbociclib at the planned dose and schedule. However, patients experiencing toxicities related to the trial treatment may have their dose modified as outlined in this section.

Letrozole should always be taken, unless the local investigator deems it necessary to interrupt or discontinue the treatment.

9.6.1. Treatment interruptions

Patients experiencing the following adverse events within a treatment cycle should have their treatment with palbociclib interrupted (delayed) until criteria for re-commencement of treatment are met (see 9.6.2):

- Uncomplicated grade 3 or 4 neutropenia (ANC <1000/mm^3)
- Grade 3 neutropenia (ANC <1000/mm^3) associated with a documented infection or fever ≥38.5°C. Grade 4 life threatening febrile neutropenia (ANC <500/mm^3) associated with a documented infection or fever results in *immediate discontinuation* of trial treatment
- Grade 3 thrombocytopenia (platelet count <50,000/mm^3). Grade 4 thrombocytopenia (platelets <25,000/mm^3) results in *immediate discontinuation* of trial treatment
- Non-haematological toxicity persisting despite optimal medical treatment if either grade 2 and lasting more than 2 weeks or grade ≥3 (excluding adverse events that are likely to be related to endocrine treatment e.g. grade 3 joint pain)
- Grade 3 QTc prolongation (QTc ≥501 msec on at least two separate ECGs)
- If a patient experiences concurrent >3xULN ALT and 2xULN bilirubin treatment should be withheld while the cause is investigated.

The criteria a patient should meet before they can recommence palbociclib (following either the planned treatment break between cycles or a treatment interruption for a treatment-related toxicity) are described in Section 9.6.2. If these criteria are not met, appropriate follow up should be conducted until adequate recovery occurs.

Withholding doses until the adverse event resolves may lead to the patient missing some, or all, subsequent planned doses within that same cycle or delaying the initiation of the subsequent cycle. If the adverse event that led to the treatment interruption recovers within the same cycle, then recommencement of treatment in that cycle is permissible. Doses omitted for toxicity should not be replaced within the same cycle. Any surplus or unused drug should be returned to pharmacy.

The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in Section 9.6.3. If a patient has dysfunctional liver function tests, please also refer to section 10.8 (Hy's Law) to determine whether an SAE should be reported. If a dose reduction is applied in the same cycle, the patient will need to return to the clinic to receive new drug supply.

9.6.2. Criteria for recommencement of treatment

The following parameters should be met prior to recommencement of treatment: 1) at the start of every new cycle and; 2) following a treatment interruption for treatment related toxicity:

- Platelet count ≥ 75,000/mm^3 (≤grade 1 or baseline)
- ANC ≥ 1000/mm^3 and no fever (≤grade 2)

- ≥grade 3 treatment-related non-haematological AEs considered related to palbociclib (including, nausea, vomiting, diarrhoea, and hypertension only if persisting despite optimal medical treatment) have recovered to ≤grade 1 or baseline

If a treatment delay results from a decline in haematological parameters, the frequency of blood count assessments should be adjusted as clinically indicated.

If the re-treatment parameters are met within 3 weeks of treatment interruption, palbociclib may be resumed. If interruption occurred during a treatment cycle and the 3 week delay included the scheduled one week off, the next treatment cycle should be commenced and all doses of the previous cycle returned to pharmacy. Please refer to Section 9.6.3 for adverse events requiring dose reduction at the time of treatment resumption. If these parameters have not been met after 3 weeks of treatment interruption (including the scheduled 1 week off treatment), trial treatment should be permanently discontinued.

9.6.3. Dose reductions

The following criteria should be followed when considering dose reduction of palbociclib for patients with treatment related toxicities. A staged approach to dose reduction should be used upon recommencement of treatment following treatment interruption.

- No specific dose reductions are recommended for treatment related grade 1 toxicity (any duration) or grade 2 toxicity lasting <3 weeks.
- In the case of a grade 2 toxicity lasting for ≥3 weeks or grade 3 toxicity of any length (both assessed in the presence of maximum supportive care, and as judged by investigator to be associated with palbociclib) a dose reduction is recommended in the next treatment cycle. The dose should be reduced by 1 and, if needed, by 2 dose levels (see Table 1) depending on the type and severity of the toxicity.
- Patients requiring more than 2 dose reductions should be discontinued from trial treatment.

All dose modifications must be clearly documented in the patient's notes and on the eCRF. Once a dose has been reduced, re-escalation is not permitted.

Table 1: Dose reductions

Level	**Palbociclib dose (21/7 days schedule)**
Starting dose	125mg/day
Dose reduction 1	100mg/day
Dose reduction 2	75mg/day*

*Palbociclib dose reduction below 75 mg/day is not allowed.

9.6.4. Management of specific toxicities

Table 2: Recommended dose modifications for treatment related toxicities requiring treatment interruption or persisting despite optimal medical treatment

CTCAE v4.0 Adverse Event	CTCAE v4.0 Grade	Action to be Taken	
		Letrozole	**Palbociclib**
Blood and Lymphatic System Disorders and Investigations			
Neutropenic fever	**3** *ANC <1000 – 500mm^3 with infection or fever*	Maintain dose	Hold until clinically stable, then resume: *1st appearance:* ↓one dose level *2nd appearance:* ↓ one dose level *3rd appearance:* Discontinue
	4 *ANC <500mm^3 with infection or fever*	Maintain dose	Discontinue
Neutrophil count decreased	**3** *<1000 – 500mm^3*	Maintain dose	Hold until ≥ 1000/mm3 *1st appearance:*, if recovery takes: ≤ 14 days –maintain dose > 14-≤21 days– ↓ one dose level *2nd appearance:* Hold until ≥ 1000/mm3. If recovery takes: ≤ 14 days - ↓ one dose level >14 days: Discontinue
	4 *<500mm^3*	Maintain dose	Hold until ≥ 1000/mm3 *1st appearance, if recovery takes:* ≤ 21 days: ↓ one dose level *2nd appearance*, if recovery takes; ≤ 14 days: ↓ one dose level >14 days: Discontinue
Platelet count decreased	**2** *<75,000mm^3 – 50,000mm^3*	Maintain dose	Hold until ≥ 75,000/mm3 *1st appearance:* Maintain dose *2nd appearance:* Maintain dose *3rd appearance:* Discontinue

CTCAE v4.0 Adverse Event	CTCAE v4.0 Grade	Action to be Taken	
		Letrozole	**Palbociclib**
Platelet count decreased	**3** *<50,000mm^3 – 25,000mm^3*	Maintain dose	Hold until ≥ 75,000/mm3 *1st appearance:* ↓ one dose level *2nd appearance:* Discontinue
	4 *<25,000mm^3*	Maintain dose	Discontinue
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 at standard dose
	3	Maintain dose	Hold until clinically stable, then resume: *1st appearance:* Maintain dose *2nd appearance:* ↓ one dose level *3rd appearance:* Discontinue
	4	Maintain dose	Discontinue
Liver Function Test Investigations			
• **Alanine aminotransferase (ALT) increased** • **Alkaline phosphatase increased** • **Aspartate aminotransferase (AST) increased** • **Blood bilirubin increased** *(See Section 10.8 for information and reporting requirements related to Hy's Law cases.)*	**2** *ALT >3.0 – 5.0 x ULN* *Alk Phos >2.5 – 5.0 x ULN* *AST >3.0 – 5.0 x ULN* *Bilirubin >1.5 – 3.0 x ULN*	Maintain dose	Hold until ≤ Grade 1 *1st appearance:* ↓ one dose level *2nd appearance:* Discontinue
	3 *ALT >5.0 – 20.0 x ULN* *Alk Phos >5.0 – 20.0 x ULN* *AST >5.0 – 20.0 x ULN* *Bilirubin >3.0 – 10.0 x ULN*	Maintain dose	Discontinue
	4 *ALT >20.0 x ULN* *Alk Phos >20.0 x ULN* *AST >20.0 x ULN* *Bilirubin >10.0 x ULN*	Maintain dose	Discontinue

CTCAE v4.0 Adverse Event	CTCAE v4.0 Grade	Action to be Taken	
		Letrozole	Palbociclib
Other			
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 level
	3/4	Maintain dose	Discontinue
If QTc ≤ 500 msec and potential reversible causes (e.g. electrolyte imbalance, concomitant medications known to prolong QTc) are corrected, study therapy may be resumed (Groups B, C, D ↓palbociclib one dose level). If QTc remains >480msec, a cardiologist should be consulted and ECG should be monitored more frequently until QTc ≤480 msec.			

**In the standard schedule (21 days on palbociclib/7 days off) recovery should be achieved by the end of the 7 day treatment break. If recovery is not achieved within this timeframe, commencement of the next cycle may be delayed by up to 2 weeks.*

9.7. Missed Doses

Patients should be encouraged to take their dose at approximately the same time each day. If a palbociclib dose is missed at the usual time, it should be taken as soon as possible and within 12 hours following the time the dose should have been taken. If it is >12 hours after the usual time, the dose should be missed for that day. Patients who miss a day's dose entirely should resume their usual schedule the following day. They should not be advised to take a higher dose the next day.

Patients who vomit any time after taking a dose should not repeat that dose. The patient should take the next dose at the scheduled time. If vomiting persists, the patient should be instructed to notify their local study team.

9.8. Overdoses

Patients who take more than the recommended dose should be advised to contact their local study team.

9.9. Discontinuation and Subsequent Therapy

Patients who prematurely discontinue from trial treatment should wait at least two weeks before undergoing surgery to allow for normalisation of neutrophil counts. An ultrasound scan and biological sample collection should be carried out within 48 hours of last trial treatment, where possible.

9.10. Compliance

Patients will be provided with a medication diary card that they will be asked to complete each day to record treatments taken or missed. At the end of each treatment cycle, patients should be asked to bring all their trial medication (palbociclib only) when they attend the clinic for the purposes of treatment compliance assessment and drug accountability. Every effort should be made to encourage participants to return the unused medication and empty bottles. The unused capsules should be collected by the investigator/study nurse and counted to ascertain patient compliance. Medication should then be returned to pharmacy for drug accountability prior to destruction according to local practices.

9.11. Supply and Distribution

Palbociclib is manufactured and provided free of charge by Pfizer to participating sites.

The drug distribution company (Fisher Clinical Services UK Ltd.) are responsible for distribution of palbociclib to participating sites.

No drug will be distributed to participating centres unless ICR-CTSU is satisfied that the required approvals and agreements and initiation procedures are complete.

Letrozole should be dispensed from standard hospital stock.

9.12. Formulation, Packaging and Storage Conditions

Palbociclib is presented as 125mg capsules. Capsules of sizes 75mg and 100mg will also be available for patients where a dose reduction is required as above. Palbociclib will be supplied in HDPE bottles each containing 23 capsules.

Palbociclib capsules should be stored at room temperature (15-30°C) in their original container. Returned medication should be stored separately from medication that needs to be dispensed.

Letrozole will be administered orally as a 2.5mg daily tablet.

The drug distribution company are responsible for labelling palbociclib in accordance with the MHRA approved PALLET label.

9.13. Drug Supplies, Labelling and Drug Accountability

9.13.1. Palbociclib

Palbociclib must not be used outside the context of the PALLET protocol.

Records must be kept of all deliveries, dispensing and destruction in accordance with the PALLET Pharmacy Guidance Notes. These records may be requested by ICR-CTSU during the trial to monitor supply and usage of stock. Account must be given of any discrepancies and certificates of delivery and return must be signed.

9.13.2. Letrozole

Letrozole should be prescribed by the investigator and dispensed by hospital pharmacy from hospital stock for the duration of the trial.

In addition to the local pharmacy label, the dispensed drug should be labelled in accordance with the MHRA approved PALLET label. Drug formulation, storage, accountability and destruction should be in accordance with local policy. ICR-CTSU should be provided with confirmation of the local pharmacy's clinical trial drug handling and destruction procedures.

10. PHARMACOVIGILANCE

10.1. Definitions

Adverse Event (AE)
An AE is any untoward medical occurrence in a patient or clinical trial subject administered an investigational medicinal product; the event does not necessarily have a causal relationship with the treatment or usage.

Serious Adverse Event (SAE)
An SAE is any untoward medical occurrence that occurs after the commencement of study treatment and within 30 days of the last administration and:

- results in death,
- is life-threatening
- requires hospitalisation or prolongation of existing inpatients´ hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect

Important adverse events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, may also be considered serious.

Progression of the indicated disease is not considered an SAE.

Pregnancy or aid in the conception of a child whilst participating in a trial is not itself considered an SAE but should be followed up for congenital anomalies or birth defects.

Serious Adverse Reaction (SAR)
A serious adverse reaction is an SAE that is suspected as having a causal relationship to the investigational medicinal product, as assessed by the investigator responsible for the care of the patient. A suspected causal relationship is defined as possibly, probably or definitely related (see definitions of causality table).

Definitions of causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship with the trial drug
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment)
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments)
Probable	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out

Relationship	Description
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

Suspected Unexpected Serious Adverse Reaction (SUSAR)
A serious adverse reaction, the nature or severity of which is not consistent with the safety information provided in the applicable Investigator's Brochure (IB) or Summary of Product Characteristics (SmPC), and is assessed as unexpected by the Chief Investigator.

10.2. Reporting Adverse Events to ICR-CTSU

Any toxicity, sign or symptom that occurs after commencement of study treatment and within 30 days of the last administration of study treatment, which is not unequivocally due to progression of disease, should be considered an AE.

All AEs must be reported on the relevant CRF and submitted to ICR-CTSU.

The severity of AEs should be graded according to the NCIC-CTC criteria. For each AE, the highest grade observed since the last visit should be reported.

Whenever one or more toxicity/sign/symptom corresponds to a disease or a well-defined syndrome only the main disease/syndrome should be reported.

10.3. Reporting of Serious Adverse Events to ICR-CTSU

Any SAE that occurs after the commencement of study treatment and up to 30 days following the end of trial treatment must be reported. The end of trial treatment in PALLET is defined as the end of week 14 for patients in Group A. The end of trial treatment for patients in Groups B, C and D is at completion of 14 days of palbociclib in the final treatment cycle.

All SAEs should be reported to ICR-CTSU within 24 hours of the Principal Investigator (or designated representative) becoming aware of the event, by completing the PALLET SAE form and faxing to:

The ICR-CTSU safety desk
Fax no: **+44 (0)208 722 4368**
For the attention of the PALLET Trial team

As much information as possible, including the Principal Investigator's assessment of causality, must be reported to ICR-CTSU in the first instance. Additional follow up information should be reported as soon as it is available.

All SAE forms must be completed, signed and dated by the Principal Investigator or designated representative.

All reported SAEs and follow up information will be forwarded to Pfizer upon receipt at ICR-CTSU.

10.4. Review of Serious Adverse Events

The Chief Investigator (or designated representative) will assess all reported SAEs for causality and expectedness (NB. The Chief Investigator cannot down-grade the Principal Investigator's assessment of causality.)

SAEs assessed as having a causal relationship to study drug and as being unexpected (SUSARs) will undergo expedited reporting to the relevant authorities and all other interested parties by ICR-CTSU (see 10.5).

Sites should respond as soon as possible to requests from the Chief Investigator or designated representative (via ICR-CTSU) for further information that may be required for final assessment of an SAE.

10.5. Expedited Reporting of SUSARs

If an SAE is identified as being a SUSAR by the Chief Investigator, and is fatal or life threatening, it will be reported by ICR-CTSU to the MHRA, the main REC, the Co-sponsors, Pfizer and all other interested parties within 7 days of being notified of the event.

If an SAE is identified as a SUSAR by the Chief Investigator, and is not fatal or life threatening, it will be reported by ICR-CTSU to the MHRA, the main REC, the Co-sponsors and Pfizer within 15 days of ICR-CTSU being notified of the event.

ICR-CTSU will report any additional relevant information to the MHRA, main REC, the Co-sponsors and Pfizer as soon as possible, or within 8 days of the initial report of a fatal/life threatening SUSAR.

The Principal Investigators at all actively recruiting sites will be informed of any SUSARs occurring within the trial at appropriate intervals.

The US coordinating group in will report SUSARs, as per their local requirements, to the national Competent Authority, IECs and local investigators, and to ICR-CTSU to facilitate EU reporting requirements.

10.6. Follow up of Serious Adverse Events

SAEs should be followed up until clinical recovery is complete or until disease has stabilised. SAE outcomes should be reported to ICR-CTSU using the relevant section of the SAE form as soon as the Principal Investigator or designee becomes aware of the outcome.

10.7. Annual Reporting of Serious Adverse Events

An annual report will be provided to the MHRA and the main REC by ICR-CTSU and copied to the Co-sponsors and the North America coordinating group at the end of the reporting year.

10.8. 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).

10.8.1. 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 aetiology of the abnormal laboratory values:

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

10.8.2. Evaluation of potential Hy's Law cases

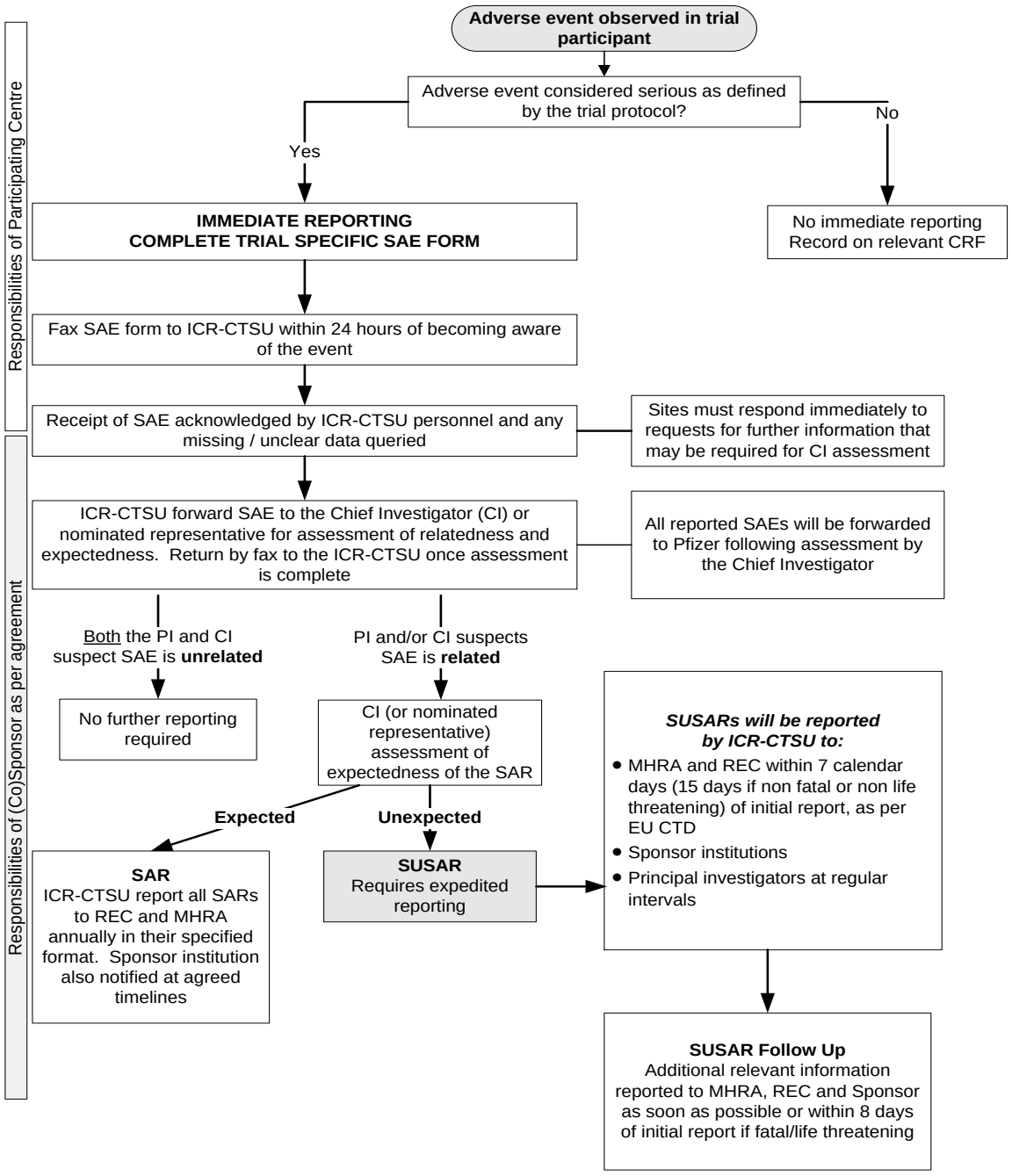
The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. In addition to repeating AST and ALT, laboratory tests 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 SAEs (see Section 10.3).

10.9. Reporting Pregnancies

If any trial patient becomes pregnant while receiving study drug or up to 90 days after receiving study drug, this should be reported to ICR-CTSU using the pregnancy reporting form. Participants who become pregnant should discontinue from trial treatment immediately. Pregnancies should be followed up until conclusion and all follow-up information should be reported to ICR-CTSU. If the outcome of the pregnancy meets the definition of serious (i.e. congenital abnormality) this should be reported to ICR-CTSU following the serious adverse event reporting procedures described above.

Figure 3: Flow diagram for SAE reporting, and action following report



NB. All SAEs should continue to be followed up as specified above

11. STATISTICAL CONSIDERATIONS

11.1. Statistical Design and Sample Size Justification

284 evaluable patients are required in PALLET. 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 PALLET is 306 patients.

PALLET 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 [10]. The sample size required is 284 (n=189:95).

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) [11].

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).

11.2. Treatment Allocation

PALLET is a randomised, four group study. Participants will be randomised 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 endpoints will compare group A with the combination of 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. Randomisation will be stratified by geographic location; one randomisation list produced for North America (the US/Canada) and another for the UK.

11.3. Endpoint Definitions

11.3.1. Primary endpoint

This study has two co-primary endpoints:

- Change in the proliferation marker Ki67 (% positive tumour cells) as tested by IHC from baseline to after 14 weeks treatment with letrozole with or without palbociclib
- Clinical response as measured by ultrasound according to ECOG criteria after 14 weeks treatment with letrozole with or without palbociclib.

11.3.2. Secondary endpoints

- Effect of palbociclib on Ki67 after 2 weeks and the added effect of letrozole from weeks 2-14 (within group)
- Effect of letrozole on Ki67 after 2 weeks and the added effect of palbociclib from weeks 2-14 (within group)
- pCR rates after letrozole with or without 14 weeks palbociclib
- PEPI score after letrozole with or without 14 weeks palbociclib
- Assessment of safety and tolerability
- Changes between surgical intent at baseline, surgical intent after 14 weeks and actual surgery received after treatment with letrozole with or without palbociclib

11.4. Statistical Analysis Plan

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 T-test (or non-parametric equivalent). Linear regression will be used to 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.

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 in appendix 5.

PEPI score after letrozole with or without 14 weeks palbociclib - PEPI score will be calculated for each patient and summarised within each randomised 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 randomised treatment group will also be produced.

Changes between surgical intent at baseline, surgical intent after 14 weeks and actual surgery received after 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.

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 logisitic 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.

North American and UK 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.

11.5. Interim Analyses and Stopping Rules

Final analysis is intended to occur once data on 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 terminate 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 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 favours palbociclib [12]. As this is a futility stopping rule and there is not 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).

12. TRIAL MANAGEMENT

12.1. Trial Management Group

A Trial Management Groups (TMG) will be set up in the UK and will include the UK Chief Investigator, UK Biological Lead, ICR-CTSU Scientific Lead, Co-investigators and identified collaborators. Principal Investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of sites and professional groups and membership will include a lay/consumer representative. The TMG will meet at regular intervals, and at least annually. Notwithstanding the legal obligations of the Co-sponsors and Chief Investigator, the TMG will have operational responsibility for the conduct of the trial in the UK including accrual, safety reporting and data collection. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU. A corresponding management group, coordinated by the NSABP, will oversee the day-to-day conduct of the trial in North America.

12.2. Global Operational Group

A Global Operational Group will be set up and will include operational, trial management and statistical personnel from ICR-CTSU, NSABP and IDDI (and Pfizer as required) to coordinate the operational aspects of the trial across the UK and North America. Specifically, the Global Operational Group will oversee database development, site initiations, data management, monitoring, audit and pharmacovigilance activities to ensure consistency of data collection and quality and to enable regulatory reporting requirements in each country to be met. The group will meet at regular intervals by teleconference and, where relevant, in person.

12.3. Global Trial Steering Committee

A Global Trial Steering Committee (GTSC) will be set up and will include the clinical leads from North America and the UK, operational leads from North America and UK, trial statisticians from IDDI (North America) and ICR-CTSU (UK), the North American and UK translational science leads, and Pfizer representatives. The GTSC will meet at regular intervals, and at least annually in person. The GTSC will provide global oversight of the trial in terms of accrual, toxicity, data collection, publication policy and procedures. The Committee will be defined by mutually agreed terms of reference.

12.4. Translational Science Working Group

The Translational Science Working Group will include translational science leads from the UK and North America. The group will provide global oversight of PALLET tissue in terms of collection, prioritisation of markers, distribution, analysis and policies on use of residual

tissue. The group will provide recommendations to the GTSC on the overall biomarker plan and review research proposals for residual tissues.

12.5. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be set up to monitor the progress of the trial and will include a Chairman and at least two further members with clinical or statistical expertise (at least one member must be a statistician) from the UK and North America. Membership of the IDMC will be approved by the GTSC.

The IDMC will meet in confidence at regular intervals, and at least annually. A summary of findings and any recommendations will be produced following each meeting. This summary will be submitted to the UK and North American Chief Investigators and GTSC and a resulting report for Pfizer will be produced. The IDMC will reserve the right to release any data on outcomes or side-effects through the GTSC to the UK and North American Chief Investigators (and corresponding trial management groups) if it determines at any stage that the combined evidence from this and other studies justifies it.

The Committee's terms of reference, roles and responsibilities will be defined in a charter approved by the GTSC.

13. RESEARCH GOVERNANCE

13.1. Sponsor Responsibilities

The Co-sponsors of the PALLET trial in the UK are The Institute of Cancer Research (ICR) and The Royal Marsden NHS Foundation Trust (RM), the Chief Investigator's host institution. Sponsor responsibilities, as defined by The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended, are allocated between ICR and RM, as set out in an agreement letter between ICR and RM.

13.2. Participating Site Responsibilities

Responsibilities delegated to participating sites are defined in an agreement between the Co-sponsors and the individual site.

13.3. Pfizer Responsibilities

Pfizer is responsible on behalf of the Co-sponsors for the manufacture of study drug in accordance with Good Manufacturing Practice and all applicable local legislation. Responsibilities are defined in an agreement between Pfizer and the Co-sponsors.

13.4. Drug Distribution Company Responsibilities

The drug distribution company (Fisher Clinical Services Ltd.) is responsible on behalf of the Co-sponsors for the packing, labelling and distributing of study drug to site in accordance with Good Manufacturing Practice and all applicable local legislation. Responsibilities are defined in an agreement between the drug distribution company and the Co-sponsors.

14. TRIAL ADMINISTRATION & LOGISTICS

14.1. Site activation

Before recruitment can commence at a site, the site agreement must have been signed by all required signatories, the required trial documentation (as specified by ICR-CTSU) must be in place and a site initiation must have taken place. Site initiation may be by teleconference or as a site visit if requested by the Principal Investigator or if deemed appropriate by ICR-CTSU. ICR-CTSU will provide the final confirmation that recruitment can commence at a site.

14.2. Data Acquisition

Electronic (e) Case Report Forms (CRF) will be used for the collection of trial data. ICR-CTSU will provide guidance to sites to aid the completion of the eCRFs. The Trial Management Group reserves the right to amend or add to the eCRF template as appropriate. Such changes do not constitute a protocol amendment, and revised or additional forms should be used by sites in accordance with the guidelines provided by ICR-CTSU.

14.3. Central Data Monitoring

Once data has been entered on the eCRF by the site personnel, ICR-CTSU will review it for compliance with the protocol, and for inconsistent or missing data. Should any missing data or data anomalies be found, queries will be raised for resolution by the site.

Any systematic inconsistencies identified through central data monitoring may trigger an on-site monitoring visit.

14.4. On-Site Monitoring

If a monitoring visit is required, ICR-CTSU will contact the site to arrange the visit. Once a date has been confirmed, the site should ensure that full patient notes of participants selected for source data verification are available for monitoring.

ICR-CTSU staff conducting on-site monitoring will review essential documentation and carry out source data verification to confirm compliance with the protocol. If any problems are detected during the course of the monitoring visit, ICR-CTSU will work with the Principal Investigator or delegated individual to resolve issues and determine appropriate action.

14.5. Completion of the Study and Definition of Study End Date

The study end date is deemed to be the date of last data capture.

14.6. Archiving

Essential trial documents should be retained according to local policy and for a sufficient period for possible inspection by the regulatory authorities (at least 5 years after the date of last data capture). Documents should be securely stored and access restricted to authorised personnel.

15. PATIENT PROTECTION AND ETHICAL CONSIDERATIONS

15.1. Trial Approvals

This trial has been formally assessed for risk by the Co-sponsors.

ICR-CTSU, on behalf of the UK Co-sponsors, will ensure that the trial has received ethics approval from a research ethics committee for multi-centre trials, regulatory approval from the MHRA and global R&D approval via the NIHR Coordinated System for gaining NHS Permission. Before recruiting patients, the Principal Investigator at each site is responsible for submitting Site Specific Information and gaining local Research and Development approval of this protocol.

15.2. Trial Conduct

This trial should be conducted in the UK according to the approved protocol and its amendments, supplementary guidance and manuals supplied by the Co-sponsors and in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended, the Research Governance Framework for Health and Social Care and the principles of GCP.

15.3. Informed Consent

Patients should be asked to sign the current ethics approved PALLET consent form at trial entry after receiving both verbal and written information about the trial, having been given sufficient time to consider this information. All consent forms must be countersigned by the Principal Investigator or a designated individual. A signature log of delegated responsibilities, listing the designated individuals and the circumstances under which they may countersign consent forms, must be maintained at the participating site. This log, together with original copies of all signed patient consent forms, should be retained in the Site Investigator File and must be available for inspection. The current ethics approved PALLET patient information sheets should be provided in addition to any standard patient information sheets that are provided by the site and used in routine practice.

15.4. Patient Confidentiality

Patients should be asked to consent to their full name being collected at trial entry in addition to their date of birth, hospital number and NHS number or equivalent to allow linkage with routinely collected NHS data and ensure accuracy in handling biological samples.

Each investigator should keep a separate log of all participants' Trial IDs, names, addresses and hospital numbers. The investigator must retain trial documents (e.g. participants' written consent forms) in strict confidence. The investigator must ensure the participants' confidentiality is maintained at all times.

Representatives of ICR-CTSU and the regulatory authorities will require access to participants' hospital notes for quality assurance purposes. ICR-CTSU will maintain the confidentiality of participants at all times and will not reproduce or disclose any information by which participants could be identified.

15.5. Data Protection

ICR-CTSU will comply with all applicable data protection laws.

15.6. Insurance and Liability

Indemnity to meet the potential legal liability of UK investigators participating in this trial is provided by the usual NHS indemnity arrangements.

16. FINANCIAL MATTERS

This trial is investigator designed and led, has been endorsed by Clinical Trials Awards & Advisory Committee (CTAAC) of Cancer Research UK, and meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England.

The trial is part of the National Institute for Health Research Clinical Research Network (NCRN) portfolio by virtue of its endorsement by CTAAC. NCRN resources should therefore be made available for the trial to cover UK specific research costs in line with normal DH funding arrangements for non-commercial research.

The Co-sponsors have received an Investigator Initiated Research grant (IIR) from Pfizer to conduct the PALLET trial.

17. PUBLICATION POLICY

The primary publication will be based on the joint analysis. The manuscript will be prepared by a writing group, consisting of members of the GTSC and key collaborators. Authorship will be on the basis of contribution (including intellectual input and patient enrolment). All participating clinicians will be acknowledged in the publication.

Authorship of any secondary publications (e.g. those relating to secondary analyses and sub-studies) will reflect contribution.

Any presentations and publications relating to the trial must be authorised by the GTSC.

No investigator may present or attempt to publish data relating to the PALLET trial without prior permission from the GTSC.

18. TRANSLATIONAL/CORRELATIVE STUDY

All PALLET trial samples should be collected, processed, stored and shipped as detailed in the PALLET Investigator Laboratory Manual.

18.1. Core Biopsies

A minimum of two and a maximum of four core-cut biopsies should be collected from each patient at baseline, 2 weeks and 14 weeks (or at completion of 14 days palbociclib treatment in the final cycle). At least one core should be fixed in formalin and processed into paraffin

wax and one should be frozen. Depending on the number of cores taken, any third sample should be fixed in formalin and a fourth frozen.

In all patients the final biopsy should be performed within 48 hours of last treatment administration. If a patient discontinues trial treatment prematurely, and has completed at least one treatment cycle, core biopsy should be performed.

Diagnostic blocks should be made available for PALLET if baseline core/s cannot be taken, or are unusable.

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

- Ki67, ER (H-score), PgR, apoptosis markers (will be assessed in Professor Dowsett's lab for UK and North American patients)
- Senescence marker, $p16^{INK4a}$, cyclinD1 amplification and expression, pRb, extended panel of cell cycle markers
- 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
- Reverse phase protein arrays

The tissue collected in PALLET will form an integral part of the primary analyses so all core biopsies in this trial will be mandated for patients. A prioritisation list will be drawn up to ensure that the most important markers are evaluable from the maximum number of samples.

Access to tumour material collected during surgery will also be requested from all patients. Surgical samples may be requested by ICR-CTSU for use in PALLET translational analyses.

18.2. Blood samples

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

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

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A1. ECOG RESPONSE CRITERIA

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 tumour 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

A2. ECOG PERFORMANCE STATUS

Score	Activity Performance Description
0	Fully active, able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

A3. NEW YORK HEART ASSOCIATION (NYHA) SCALE

Class I: Patients with cardiac disease but without resulting limitation of physical activity; ordinary physical activity does not cause undue dyspnoea (or fatigue, palpitation or anginal pain).

Class II: Patients with cardiac disease resulting in slight limitation of physical activity; they are comfortable at rest; ordinary physical activity results in dyspnoea (or fatigue, palpitation or anginal pain).

Class III: Patients with cardiac disease resulting in marked limitations of physical activity; they are comfortable at rest; less than ordinary physical activity causes dyspnoea (or fatigue, palpitation or anginal pain).

Class IV: Patients with cardiac disease resulting in inability to carry out physical activity without discomfort; symptoms of dyspnoea (or of angina) may be present even at rest; if any physical activity is undertaken, discomfort is increased.

A4. pCR EVALUATION CRITERIA

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.

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 tumour cells in the surgical breast specimen, axillary nodes, or SNs identified after neoadjuvant treatment.
- *Pathologic complete response in the breast (pCR breast)*
  No histologic evidence of invasive tumour cells in the surgical breast specimen.

A5. GLOSSARY

AE	Adverse Event
AI	Aromatase Inhibitor
ALT	Alanine Aminotransferase
ALAT	Alanine Transaminase
ALP	Alkaline Phosphatase
ANC	Absolute Neutrophil Count
ASCO/CAP	The American Society of Clinical Oncology and the College of American Pathologists
ASAT	Aspartate Transaminase
AST	Aspartate Aminotransferase
BC	Breast Cancer
CI	Chief Investigator
CR/PR/SD/PD	Complete Response/ Partial Response/ Stable Disease/ Progressive Disease
CRF	Case Report Form
CTAAC	Clinical Trials Awards and Advisory Committee
DCIS	Ductal Carcinoma In Situ
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ER	Oestrogen Receptor
FNA	Fine Needle Aspiration
GCP	Good Clinical Practice
GTSC	Global Trial Steering Committee
HDPE	High-Density Polyethylene
HER2	Human Epidermal Growth Factor 2
HR	Hazard Ratio
IB	Investigator's Brochure
ICR	The Institute Of Cancer Research
ICR-CTSU	The Institute Of Cancer Research- Clinical Trials and Statistics Unit
IDDI	International Drug Development Institute
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
MDT	Multi-Disciplinary Team
MHRA	Medicines and Healthcare Products Regulatory Authority
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCRN	NIHR (National Institute for Health Research) Cancer Research Network
NSABP	National Surgical Breast and Bowel Project
pCR	Pathological Complete Response
PEPI	Preoperative Endocrine Prognostic Index
PFS	Progression Free Survival
PI	Principal Investigator
PIS	Patient Information Sheet
PO	Per Oral - dose taken by mouth
PT	Prothrombin Ratio
QD	Daily
QTc/QTcF	QT interval (as measured by ultrasound)
R&D	Research and Development
REC	Research Ethics Committee

RCT	Randomised Controlled trial
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
US	United States of America
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organisation