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INTERNATIONAL BREAST CANCER STUDY GROUP

IBCSG 55-17
TOUCH

Phase II open-label, multicenter, randomized trial of neoadjuvant palbociclib in combination with hormonal therapy and HER2 blockade versus paclitaxel in combination with HER2 blockade for postmenopausal patients with hormone receptor positive/HER2 positive early breast cancer

To reduce the use of Chemotherapy in postmenopausal patients with ER-positive and HER2-positive breast cancer: the TOUCH trial

EudraCT number:	**2017-005067-40**
Pfizer number:	[redacted]
Roche number:	[redacted]
Sponsor:	**International Breast Cancer Study Group (IBCSG)**

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Amendment 2
Protocol Version 2.1, 12 June 2020

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If the retreatment parameters are met within 3 weeks of treatment interruption or cycle delay, palbociclib may be resumed. Please refer to Dose Reductions Section 10.3.2 for adverse events requiring dose reduction at the time of treatment resumption.

Within 1 treatment cycle, if these parameters have not been met after 3 weeks of dose interruption (including the scheduled 1 week off treatment and/or up to 14 days of cycle delay), the patient should permanently discontinue palbociclib treatment. Treatment resumption for patients recovering from treatment-related toxicity after >3 weeks of treatment interruption (corresponding to 1 week rest plus 2 weeks delay), or cycle delay but deemed to be suitable for lower dosing, may be considered and needs to be discussed with IBCSG beforehand by contacting ibcsg55_touch@frontierscience.org.

10.3.2. Dose reductions

Palbociclib dose modifications may occur in three ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;
- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

No specific dose adjustments are recommended for Grade 1 or short lasting grade 2 (<3 weeks) treatment-related toxicity. However, Investigators should always manage their patients according to their medical judgment based on the particular clinical circumstances.

In case of a grade 2 toxicity lasting for >3 weeks or a grade 3 toxicity (both assessed in the presence of maximum supportive care as judged by the Investigator), dose reduction is recommended for the subsequent cycles (exception: alopecia grade 2 does not require dose reduction). Dose reduction of palbociclib by one, and, if needed, by two dose levels (Table 3 below) is recommended depending on type and severity of the toxicity. Patients requiring more than two dose reductions will be allowed to receive 75 mg/day for 2 weeks after 2 weeks off trial treatment (if, per the Investigator's judgment, such a schedule is manageable and preferred; this must be discussed with IBCSG beforehand by contacting ibcsg55_touch@frontierscience.org). Taking palbociclib according to recommendation (i.e., with food) should be reinforced and confirmed. The Investigator should discuss with IBCSG (see email address above) if the patient appears to be unable or unwilling to comply with this recommendation. All dose modifications/adjustments must be clearly documented in the patient's source notes and the Form 55-PALBO.

Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Dose re-escalation is not allowed.

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Patients discontinuing palbociclib treatment due to treatment-related toxicity may continue on the active treatment phase of the trial receiving letrozole and anti-HER2 therapy at the Investigator's discretion.

Table 3. Available dose levels for palbociclib

Dose Level	Palbociclib for 3 out of 4 weeks
Starting dose	125 mg/d
-1	100 mg/d
-2	75 mg/d*
-3 (for selected cases only)	Discontinue palbociclib treatment or consider schedule of 75mg/d 2 weeks on / 2 weeks off. This must be discussed with IBCSG beforehand by contacting ibcsg55_touch@frontierscience.org. If 2 weeks on/2 weeks off is not tolerated, then discontinue palbociclib.

* Palbociclib dose de-escalation below 75 mg/d is not allowed but if considered appropriate the schedule may move to 75 mg/day two weeks on followed by two weeks off.

Palbociclib recommended dose modifications for treatment related toxicities requiring treatment interruption/delay despite optimal medical treatment are described in Table 4 taken from tables 2 and 3 of the SPC.

Table 4. Palbociclib dose modification and management

CTCAE grade	Dose modifications
Hematological toxicities Applies to all hematological adverse reactions except lymphopenia (unless associated with clinical events, e.g., opportunistic infections). Complete blood count should be monitored prior to the start of palbociclib therapy, and at the beginning of each cycle, as well as on day 14 of the first 2 cycles, and as clinically indicated.	
Grade 1 or 2	No dose adjustment

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CTCAE grade	**Dose modifications**
Grade 3	Day 1 of cycle: Withhold palbociclib, repeat complete blood count monitoring within 1 week. When recovered to grade ≤2, start next cycle at same dose Day 14 of first 2 cycles: Continue palbociclib at current dose to complete cycle, repeat complete blood count on day 21. Consider dose reduction in cases of prolonged (>1 week) recovery from grade 3 neutropenia or recurrent grade 3 neutropenia in subsequent cycles
Grade 3 ANC (absolute neutrophil count) <1000 to 500/mm^3 + fever ≥38°C and/or infection	Withhold palbociclib until recovery to grade ≤2. Resume at next lower dose.
Grade 4	Withhold palbociclib until recovery to grade ≤2. Resume at next lower dose.

Non-hematological toxicities	
Grade 1 or 2	No dose adjustment is required
Grade ≥3 non-hematological toxicity (if persisting despite medical treatment)	Withhold until symptoms resolve to: - Grade ≤1; - Grade ≤2 (if not considered a safety risk for the patient) Resume at the next lower dose.

Permanently discontinue palbociclib in patients with severe interstitial lung disease (ILD)/pneumonitis

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10.4. Dose modifications and delays for trastuzumab and pertuzumab

Refer to standard of care guidance or current clinical practice or currently approved trastuzumab and pertuzumab European SPCs, as well as the following table. There are no dose modifications for trastuzumab or pertuzumab. Administration may be delayed to assess or treat adverse events, such as cardiac adverse events or other non-hematological adverse events as shown in Table 5:

In the case of overlapping toxicities, doses of anti-HER2-therapy should be delayed only if toxicity persists after paclitaxel (Arm A) or palbociclib (Arm B) dose has been modified or delayed, according to Section 10.3 and Section 10.5, respectively.

Table 5. Actions to be taken in case of trastuzumab and/or pertuzumab (anti-HER2 therapy) related adverse events

Adverse event (AE)	Action
Non-hematological grade 1 or 2 (excluding cardiac)	Continue anti-HER2 therapy
Non-hematological grade 3 or 4 (excluding cardiac), and AE resolves to grade ≤2 within a maximum of 5 weeks from last dose	Hold anti-HER2 therapy until recovery to grade ≤2
Non-hematological grade 3 or 4 (excluding cardiac), and ARE NOT resolved to grade ≤2 within a maximum of 5 weeks from last dose	Please contact ibcsg55_touch@frontierscience.org for advice
Non-hematological grade 3 or 4 (excluding cardiac), upon rechallenge with anti-HER2 therapy	Discontinue anti-HER2 therapy permanently
Cardiac: asymptomatic drop in LVEF or symptomatic congestive heart failure	Use algorithm in figure 1 discontinue anti-HER2 therapy permanently in case of symptomatic CHF
Other cardiac toxicities not covered in figure 1	Follow rules for non-hematological toxicities above

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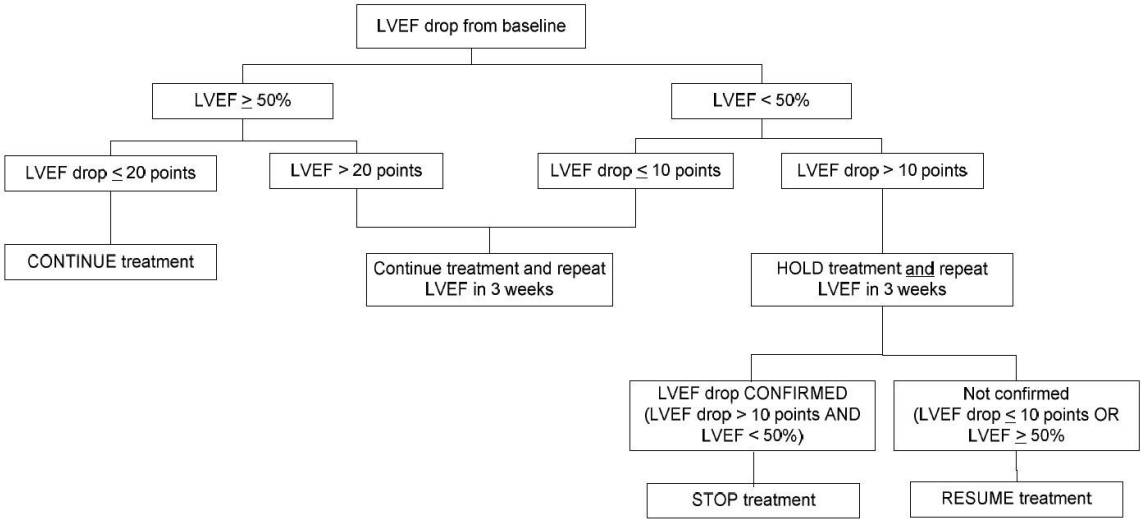
Adverse event (AE)	Action
Hematological (neutropenia grade 3)	If toxicity persists after paclitaxel (Arm A) or palbociclib (Arm B) dose has been modified or delayed according to Section 10.3 and Section 10.5, hold anti-HER2-therapy until recovery to grade ≤2.

Figure 1: Algorithm for continuation and discontinuation of anti-HER2 treatment based on interval LVEF assessments, for patients with NYHA class I or II congestive heart failure. LVEF drop >10 points: Temporarily discontinue anti-HER2 treatment and repeat LVEF in 3 weeks. If LVEF drop >10 points not confirmed, then resume treatment.



Note: If pertuzumab has to be stopped, continue with trastuzumab alone; if trastuzumab has to be stopped, stop pertuzumab as well.

10.5. Dose modifications and delays for paclitaxel

Refer to standard of care guidance or current clinical practice or currently approved paclitaxel European SPC for patients receiving paclitaxel treatment, and to Table 6.

In case of paclitaxel related adverse effects, doses should be reduced rather than delayed. The total cumulative delay across all 4 cycles should not exceed 4 weeks. If the delay is >4 weeks, paclitaxel should be stopped and treatment should continue with anti-HER2 drugs.

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Table 6. Actions to be taken in case of paclitaxel related adverse events

Adverse event	Action
Non-hematological grade 1 or 2	Continue paclitaxel
Non-hematological grade 3 or 4	Hold paclitaxel until recovery to grade ≤1 then decrease paclitaxel dose by 20%
Non-hematological, grade 3 or 4, and adverse events NOT resolved to grade ≤2 within a maximum of 3 weeks from last planned administration	Discontinue paclitaxel
Hematological adverse events: - ANC <1.0 × 10^9/L - Platelets <75 × 10^9/L - Hemoglobin <9.0 g/dL (after transfusion if needed)	Hold paclitaxel therapy until recovery to ANC ≥1.0 × 10^9/L and/or platelets ≥100 × 10^9/L. If ANC recovers to 1.0 × 10^9/L within 7 days, then continue at the same dose. If recovery to 1.0 × 10^9/L requires >7 days, then decrease paclitaxel dose by 20% Dose modifications for thrombocytopenia: same as for neutropenia above. Next cycle should not begin until platelet count has recovered to ≥ 100 × 10^9/L.
Biochemistry: - unresolved grade 3 or 4 (except bilirubin) - bilirubin ≥2 × ULN	Hold paclitaxel therapy until recovery to grade ≤1
Serum creatinine ≥2 × ULN or calculated clearance ≤40mL/min	Hold paclitaxel therapy until recovery to grade ≤1

10.6. Dose modifications and delays for letrozole

Refer to standard of care guidance or current clinical practice or currently approved letrozole European SPC for patients receiving letrozole treatment. No dose modifications are allowed. Compliance with the protocol endocrine treatment should be strictly observed.

Interruptions in the administration of letrozole should not exceed 2 days.

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In the case of adverse event(s) grade ≥3, judged by the Investigator to be at least possibly related to letrozole, letrozole treatment will be stopped and patient will continue with the other trial drugs or undergo surgical intervention.

10.7. Concomitant therapy

The following rules should be followed for both treatment arms:

- **Anti-cancer** (cytotoxic or endocrine therapy, other than letrozole and paclitaxel provided within the trial protocol) **or any other investigational therapy** is not permitted while patients are on trial therapy.
- **Radiotherapy** is not permitted while patients are on trial therapy.

The use of other concomitant medication/therapy judged by the Investigator to be necessary for the care of the patient is permitted. The Investigator should instruct the patient to notify the trial site about any new medications she takes after the start of the trial drug.

Concomitant medications need to be recorded as follows:

- At baseline, prior to start of treatment, medications or treatments for comorbidities should be recorded on the History form 55-H.
- In case of an SAE, all concomitant medication used to treat the SAE must be reported on the SAE form (55-SAE-B).

10.7.1. CYP3A inhibitors/inducers

Palbociclib is a weak, time-dependent inhibitor of CYP3A. Strong inhibitors of CYP3A4 administered concomitantly to palbociclib may lead to increased toxicity. Concomitant use of strong CYP3A inhibitors during treatment with palbociclib should be avoided. Co-administration should only be considered after careful evaluation of the potential benefits and risks. If co-administration with a strong CYP3A inhibitor is unavoidable, reduce the palbociclib dose to 75 mg once daily. When the strong inhibitor is discontinued, increase the palbociclib dose (after 3-5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor.

Co-administration of *CYP3A inducers* with palbociclib may lead to decreased palbociclib exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of palbociclib with strong CYP3A4 inducers should be avoided. No dose adjustments are required for co-administration of palbociclib with moderate CYP3A inducers.

10.7.2. Medications not recommended

The following treatments are not recommended throughout the duration of the active treatment phase. Alternative therapies should be considered whenever possible.

- Chronic immunosuppressive therapies should be avoided, including systemic corticosteroids. Steroids given for physiological replacement, as anti-emetics or as premedication of paclitaxel treatment, or inhaled as well as short course of oral/topical

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steroids given for allergic reactions or asthma flares are allowed. Steroids given for the pre-medication of patients treated with paclitaxel in the chemotherapy arm are allowed.

- The use of herbal medicine is not recommended during the active treatment phase.

10.8. Stop of trial treatment

Duration of protocol neoadjuvant therapy is planned as 16 weeks, and will depend on tolerance.

In case one or more trial medications have to be stopped early, treatment with the other trial drugs of the respective arm should be continued if deemed appropriate by the local Investigator. Stop of trial treatment is defined as stop of all trial medications assigned by the randomization. Patients are not allowed to cross over from the randomly assigned arm to the other arm.

If pertuzumab has to be stopped, continue with trastuzumab alone; if trastuzumab has to be stopped, stop pertuzumab as well.

All trial medication of the individual patient has to stop in case of:

- Disease progression as defined in Section 13.
- Unacceptable adverse event(s).
- Intercurrent illness that prevents further administration of trial treatment.
- Patient demonstrates an inability or unwillingness to comply with the treatment regimen and/or trial requirements.
- General or specific changes in the patient's condition which render her unacceptable for further trial treatment in the opinion of the treating Investigator.
- Patient withdraws consent to continue trial treatment.

Patients who discontinue all trial medications early for any reason should proceed to surgery.

After the discontinuation of all trial medications, future therapeutic decisions are at the discretion of the Investigator, with no restrictions.

The End of Treatment (EoT) is defined as the breast cancer surgery. If the patient does not undergo surgery, the EoT occurs when all trial medication is stopped. The EoT visit is to be done within 30 days after EoT.

10.9. Removal from the trial

After a patient has been randomized, she becomes part of the clinical trial population and cannot be removed from the trial for any reason other than a decision by the patient to decline any further participation with the trial requirements and/or to decline further collection of data and tissue (see Section 18.2.2). If the patient discontinues treatment for any of the reasons listed in the prior subsection, she should continue to be followed according to the protocol and eCRFs should be completed as described in Section 16.1.

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Patients who have been randomized but never received any trial treatment for whatever reason (refusal, medical condition etc.) will be followed until surgery and will have to be documented with an End of Treatment visit (see Section 14.5).

11. Safety

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: very common ≥10%, common ≥1% to <10%, uncommon ≥0.1% to <1%, rare ≥0.01% to <0.1%, very rare <0.01%, not known (cannot be estimated from the available data).

11.1. Adverse reactions to palbociclib

Table 7, taken from the SPC, reports the adverse reactions from the pooled dataset of 3 randomized studies. The median duration of palbociclib treatment across the pooled dataset was 12.7 months. The adverse reactions are listed by system organ class and frequency category.

The effect of palbociclib on the QT interval corrected for heart rate (QTc) interval was evaluated using time matched electrocardiogram (ECG) change from baseline and pharmacokinetic data in 77 patients with breast cancer. At the recommended dose, no palbociclib relevant effects on QT have been observed.

Table 7. Adverse reactions to palbociclib based on pooled dataset from 3 randomized studies (N=872)

System Organ Class *Frequency* Preferred Term[a]	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Infections and infestations			
Very common			
Infections[b]	516 (59.2)	49 (5.6)	8 (0.9)
Blood and lymphatic system disorders			
Very common			
Neutropenia[c]	716 (82.1)	500 (57.3)	97 (11.1)
Leukopenia[d]	424 (48.6)	254 (29.1)	7 (0.8)
Anaemia[e]	258 (29.6)	45 (5.2)	2 (0.2)
Thrombocytopenia[f]	194 (22.2)	16 (1.8)	4 (0.5)
Common			
Febrile neutropenia	12 (1.4)	10 (1.1)	2 (0.2)
Metabolism and nutrition disorders			
Very common			
Decreased appetite	152 (17.4)	8 (0.9)	0 (0.0)
Nervous system disorders			
Common			
Dysgeusia	79 (9.1)	0 (0.0)	0 (0.0)
Eye disorders			
Common			
Vision blurred	48 (5.5)	1 (0.1)	0 (0.0)
Lacrimation increased	59 (6.8)	0 (0.0)	0 (0.0)
Dry eye	36 (4.1)	0 (0.0)	0 (0.0)

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System Organ Class *Frequency* Preferred Term[a]	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Respiratory, thoracic and mediastinal disorders			
Common			
Epistaxis	77 (8.8)	0 (0.0)	0 (0.0)
ILD/pneumonitis[*,i]	12(1.4)	1 (0.1)	0 (0.0)
Gastrointestinal disorders			
Very common			
Stomatitis[g]	264 (30.3)	8 (0.9)	0 (0.0)
Nausea	314 (36.0)	5 (0.6)	0 (0.0)
Diarrhoea	238 (27.3)	9 (1.0)	0 (0.0)
Vomiting	165 (18.9)	6 (0.7)	0 (0.0)
Skin and subcutaneous tissue disorders			
Very common			
Rash[h]	158 (18.1)	7 (0.8)	0 (0.0)
Alopecia	234 (26.8)	N/A	N/A
Dry skin	93 (10.7)	0 (0.0)	0 (0.0)
General disorders and administration site conditions			
Very common			
Fatigue	362 (41.5)	23 (2.6)	2 (0.2)
Asthenia	118 (13.5)	14 (1.6)	1 (0.1)
Pyrexia	115 (13.2)	1 (0.1)	0 (0.0)
Investigations			
Very common			
ALT increased	92 (10.6)	18 (2.1)	1 (0.1)
AST Increased	99 (11.4)	25 (2.9)	0 (0.0)

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ILD=interstitial lung disease; N/n=number of patients; N/A=not applicable.

* Adverse Drug Reaction (ADR) identified post-marketing.

[a] Preferred Terms (PTs) are listed according to MedDRA 17.1.

[b] Infections includes all PTs that are part of the System Organ Class Infections and infestations.

[c] Neutropenia includes the following PTs: Neutropenia, Neutrophil count decreased.

[d] Leukopenia includes the following PTs: Leukopenia, White blood cell count decreased.

[e] Anaemia includes the following PTs: Anaemia, Haemoglobin decreased, Haematocrit decreased.

[f] Thrombocytopenia includes the following PTs: Thrombocytopenia, Platelet count decreased.

[g] Stomatitis includes the following PTs: Aphthous stomatitis, Cheilitis, Glossitis, Glossodynia, Mouth ulceration, Mucosal inflammation, Oral pain, Oropharyngeal discomfort, Oropharyngeal pain, Stomatitis.

[h] Rash includes the following PTs: Rash, Rash maculo-papular, Rash pruritic, Rash erythematous, Rash papular, Dermatitis, Dermatitis acneiform, Toxic skin eruption.

[i] ILD/pneumonitis includes any reported PTs that are part of the Standardised MedDRA Query Interstitial Lung Disease (narrow).

Interstitial lung disease/pneumonitis

Severe, life-threatening, or fatal ILD and/or pneumonitis can occur in patients treated with palbociclib when taken in combination with endocrine therapy.

Across clinical trials (PALOMA-1, PALOMA-2, PALOMA-3), 1.4% of palbociclib-treated patients had ILD/pneumonitis of any grade, 0.1% had Grade 3, and no Grade 4 or fatal cases were reported. Additional cases of ILD/pneumonitis have been observed in the post-marketing setting, with fatalities reported. For dose modifications in case of signs or symptoms, see section 10.3.

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11.2. Adverse reactions to trastuzumab

Patients treated with trastuzumab are at increased risk for developing CHF (New York Heart Association [NYHA] Class II-IV) or asymptomatic cardiac dysfunction. These events have been observed in patients receiving trastuzumab therapy alone or in combination with paclitaxel, particularly following anthracycline (doxorubicin or epirubicin) containing chemotherapy. These may be moderate to severe and have been associated with death. In addition, caution should be exercised in treating patients with increased cardiac risk, e.g. hypertension, documented coronary artery disease, CHF, LVEF of <55%, older age. The following table has been taken from the European SPC:

Table 8. Undesirable effects reported with intravenous trastuzumab monotherapy or in combination with chemotherapy in pivotal clinical trials (N = 8386) and in post-marketing

System organ class	Frequency	Adverse reaction
Infections and infestations	Very common	Infection, nasopharyngitis
	Common	Neutropenic sepsis, cystitis, herpes zoster, influenza, sinusitis, skin infection, rhinitis, upper respiratory tract infection, urinary tract infection, erysipelas, cellulitis, pharyngitis
	Uncommon	Sepsis
	Not known	
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Not known	Malignant neoplasm progression, neoplasm progression
Blood and lymphatic system disorders	Very common	Febrile neutropenia, anemia, neutropenia, white blood cell count decreased/leukopenia, thrombocytopenia
	Not known	Hypoprothrombinemia, immune thrombocytopenia
Immune system disorders	Common	Hypersensitivity
	Not known	[+]Anaphylactic reaction, [+]anaphylactic shock
Metabolism and nutrition disorders	Very common	Weight decreased/weight loss, anorexia
	Not known	Hyperkalemia
Psychiatric disorders	Very common	Insomnia
	Common	Anxiety, depression, thinking abnormal
Nervous system disorders	Very common	[1]Tremor, dizziness, headache, paresthesia, dysgeusia
	Common	Peripheral neuropathy, hypertonia, somnolence, ataxia
	Rare	Paresis
	Not known	Brain edema
Eye disorders	Very common	Conjunctivitis, lacrimation increased
	Common	Dry eye
	Not known	Papilledema, retinal hemorrhage
Ear and labyrinth disorders	Uncommon	Deafness
Cardiac disorders	Very common	[1]Blood pressure decreased, [1]blood pressure increased, [1]heart beat irregular, [1]palpitation, [1]cardiac flutter, ejection fraction decreased*
	Common	[+]Cardiac failure (congestive), [+1]supraventricular tachyarrhythmia, cardiomyopathy
	Uncommon	Pericardial effusion
	Not known	Cardiogenic shock, pericarditis, bradycardia, gallop rhythm present

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System organ class	Frequency	Adverse reaction
Vascular disorders	Very common	Hot flush
	Common	[+1]Hypotension, vasodilatation
Respiratory, thoracic and mediastinal disorders	Very common	[+1]Wheezing, [+]dyspnea, cough, epistaxis, rhinorrhea
	Common	[+]Pneumonia, asthma, lung disorder, [+]pleural effusion
	Rare	Pneumonitis
	Not known	[+]Pulmonary fibrosis, [+]respiratory distress, [+]respiratory failure, [+]lung infiltration, [+]acute pulmonary edema, [+]acute respiratory distress syndrome, [+]bronchospasm, [+]hypoxia, [+]oxygen saturation decreased, laryngeal edema, orthopnea, pulmonary edema, interstitial lung disease
Gastrointestinal disorders	Very common	Diarrhea, vomiting, nausea, [1]lip swelling, abdominal pain, dyspepsia, constipation, stomatitis
	Common	Pancreatitis, hemorrhoids, dry mouth
Hepatobiliary disorders	Common	Hepatocellular injury, hepatitis, liver tenderness
	Rare	Jaundice
	Not known	Hepatic failure
Skin and subcutaneous tissue disorders	Very common	Erythema, rash, [1]swelling face, alopecia, nail disorder, palmar-plantar erythrodysesthesia syndrome
	Common	Acne, dry skin, ecchymosis, hyperhydrosis, maculopapular rash, pruritus, onychoclasis, dermatitis
	Uncommon	Urticaria
	Not known	Angioedema
Musculoskeletal and connective tissue disorders	Very common	Arthralgia, [1]muscle tightness, myalgia
	Common	Arthritis, back pain, bone pain, muscle spasms, neck pain, pain in extremity
Renal and urinary disorders	Common	Renal disorder
	Not known	Glomerulonephritis membranous, glomerulonephropathy, renal failure
Pregnancy, puerperium and perinatal conditions	Not known	Oligohydramnios, renal hypoplasia, pulmonary hypoplasia
Reproductive system and breast disorders	Common	Breast inflammation/mastitis
General disorders and administration site conditions	Very common	Asthenia, chest pain, chills, fatigue, influenza-like symptoms, infusion related reaction, pain, pyrexia, mucosal inflammation, peripheral edema
	Common	Malaise, edema
Injury, poisoning and procedural complications	Common	Contusion

[+]Denotes adverse reactions that have been reported in association with a fatal outcome.
[1]Denotes adverse reactions that are reported largely in association with infusion-related reactions. Specific percentages for these are not available.
*Observed with combination therapy following anthracyclines and combined with taxanes.

11.3. Adverse reactions to pertuzumab

Pertuzumab has been administered in the adjuvant and neoadjuvant setting in combination with trastuzumab, anthracyclines and taxanes. The most common adverse reactions were neutropenia, febrile neutropenia, leukopenia, diarrhea, nausea and alopecia.

Table 9 has been taken from the European SPC (Table 1)

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Table 9. Summary of ADRs in patients treated with pertuzumab in the metastatic and neoadjuvant setting

System organ class	Very common	Common	Uncommon
Infections and infestations	Upper respiratory tract infection Nasopharyngitis	Paronychia	
Blood and lymphatic system disorders	Febrile neutropenia* Neutropenia Leucopenia Anemia		
Immune system disorders	Hypersensitivity/ anaphylactic reaction° Infusion reaction/cytokine release syndrome°°		
Metabolism and nutrition disorders	Decreased appetite †		
Psychiatric disorders	Insomnia		
Nervous system disorders	Neuropathy peripheral Headache † Dysgeusia	Peripheral sensory neuropathy Dizziness	
Eye disorders		Lacrimation increased	
Cardiac disorders		Left ventricular dysfunction † (including congestive heart failure)**	
Respiratory, thoracic and mediastinal disorders	Cough †	Pleural effusion Dyspnea †	Interstitial lung disease
Gastrointestinal disorders	Diarrhea † Vomiting † Stomatitis Nausea † Constipation † Dyspepsia		
Skin and subcutaneous tissue disorders	Alopecia Rash † Nail disorder	Pruritus Dry skin	
Musculoskeletal and connective tissue disorders	Myalgia Arthralgia		
General disorders and administration site conditions	Mucositis/mucosal inflammation Pain † Edema † Pyrexia Fatigue † Asthenia †	Chills	

* Including adverse reactions with a fatal outcome.
** For the overall treatment period across the 3 studies.
† Except for febrile neutropenia, neutropenia, leukopenia, lacrimation increased, interstitial lung disease, paronychia, and alopecia, all events in this table were also reported in at least 1% of patients participating in

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pertuzumab monotherapy trials, although not necessarily considered causally related to pertuzumab by the Investigator. Very common events (reported in ≥ 10% of pertuzumab monotherapy-treated patients) are marked in the Table with a †.
° Hypersensitivity/anaphylactic reaction is based on a group of terms.
°° Infusion reaction/cytokine release syndrome includes a range of different terms within a time window

11.4. Adverse reactions to paclitaxel

Table 10 has been taken from the electronic Medicines Compendium (eMC) (www.medicines.org.uk). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 10. Summary of ADRs in patients treated with paclitaxel in the metastatic and post marketing surveillance setting

System organ class	Frequency and adverse reactions
Infections and infestations:	Very common: infection (mainly urinary tract and upper respiratory tract infections), with reported cases of fatal outcome Uncommon: septic shock Rare*: sepsis, peritonitis, pneumonia
Blood and the lymphatic system disorders:	Very common: myelosuppression, neutropenia, anemia, thrombocytopenia, leucopenia, bleeding Rare*: febrile neutropenia Very rare*: acute myeloid leukemia, myelodysplastic syndrome
Immune system disorders:	Very common: minor hypersensitivity reactions (mainly excessive flushing and rash) Uncommon: significant hypersensitivity reactions requiring therapy (e.g., hypotension, angioneurotic oedema, respiratory distress, generalised urticaria, chills, back pain, chest pain, tachycardia, abdominal pain, pain in limbs, pain in extremities, diaphoresis and hypertension) Rare*: anaphylactic reactions Very rare*: anaphylactic shock
Metabolism and nutrition disorders:	Very rare*: anorexia Not known*: tumor lysis syndrome
Psychiatric disorders:	Very rare*: confusional state
Nervous system disorders:	Very common: neurotoxicity (mainly: peripheral neuropathy) Rare*: motor neuropathy (with resultant minor distal weakness) Very rare*: grand mal seizures, autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), encephalopathy, convulsions, dizziness, ataxia, headache
Eye disorders:	Very rare*: optic nerve and/or visual disturbances (scintillating scotomata), particularly in patients who have received higher doses than recommended Not known*: macular oedema, photopsia, vitreous floaters
Ear and labyrinth disorders:	Very rare*: hearing loss, ototoxicity, tinnitus, vertigo
Cardiac disorders:	Common: bradycardia Uncommon: myocardial infarction, AV block and syncope, cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy Rare: heart failure Very rare*: atrial fibrillation, supraventricular tachycardia
Vascular disorders:	Very common: hypotension Uncommon: thrombosis, hypertension, thrombophlebitis Very rare*: shock Not known*: phlebitis

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System organ class	Frequency and adverse reactions
Respiratory, thoracic and mediastinal disorders:	Rare*: respiratory failure, pulmonary embolism, lung fibrosis, interstitial pneumonia, dyspnoea, pleural effusion Very rare*: cough
Gastrointestinal disorders:	Very common: diarrhoea, vomiting, nausea, mucosal inflammation Rare*: bowel obstruction, bowel perforation, ischaemic colitis, pancreatitis Very rare*: mesenteric thrombosis, pseudomembranous colitis, neutropenic colitis, ascites, oesophagitis, constipation
Hepatobiliary disorders:	Very rare*: hepatic necrosis, hepatic encephalopathy (both with reported cases of fatal outcome)
Skin and subcutaneous tissue disorders:	Very common: alopecia Common: transient and mild nail and skin changes Rare*: pruritus, rash, erythema Very rare*: Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, onycholysis (patients on therapy should wear sun protection on hands and feet) Not known*: scleroderma
Musculoskeletal and connective tissue disorders:	Very common: arthralgia, myalgia Not known*: systemic lupus erythematosus
General disorders and administration site conditions:	Common: injection site reactions (including localised oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis, skin fibrosis and skin necrosis) Rare*: pyrexia, dehydration, asthenia, oedema, malaise
Investigations:	Common: severe elevation in AST (SGOT), severe elevation in alkaline phosphatase Uncommon: severe elevation in bilirubin Rare*: increase in blood creatinine

* Reported in post marketing surveillance setting

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11.5. Adverse reactions to letrozole

Table 11 has been taken from the European SPC (Table 1):

Table 11. Adverse reactions to letrozole by system organ class and frequency

System organ class	Frequency	Adverse reaction
Infections and infestations	Uncommon	Urinary tract infection
Neoplasms, benign, malignant and unspecified (including cysts and polyps)	Uncommon	Tumor pain [1]
Blood and the lymphatic system disorders	Uncommon	Leukopenia
Immune system disorders	Not known	Anaphylactic reaction
Metabolism and nutrition disorders	Very common	Hypercholesterolemia
	Common	Anorexia, appetite increase
Psychiatric disorders	Common	Depression
	Uncommon	Anxiety (including nervousness), irritability
Nervous system disorders	Common	Headache, dizziness
	Uncommon	Somnolence, insomnia, memory impairment, dysesthesia (including paresthesia, hypoesthesia), taste disturbance, cerebrovascular accident
Eye disorders	Uncommon	Cataract, eye irritation, blurred vision
Cardiac disorders	Uncommon	Palpitations[1], tachycardia, ischemic cardiac events(including new or worsening angina, angina requiring surgery, myocardial infarction and myocardial ischemia)
Vascular disorders	Very common	Hot flushes
	Common	Hypertension
	Uncommon	Thrombophlebitis (including superficial and deep vein thrombophlebitis)
	Rare	Pulmonary embolism, arterial thrombosis, cerebrovascular infarction
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnea, cough
Gastrointestinal disorders	Common	Nausea, dyspepsia[1], constipation, abdominal pain, diarrhea, vomiting
	Uncommon	Dry mouth, stomatitis[1]
Hepatobiliary disorders	Uncommon	Increased hepatic enzymes
	Not known	Hepatitis
Skin and subcutaneous tissue disorders	Very common	Increased sweating
	Common	Alopecia, rash (including erythematous, maculopapular, psoriaform, and vesicular rash), dry skin
	Uncommon	Pruritus, urticaria
	Not known	Angioedema, toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
	Common	Myalgia, bone pain[1], osteoporosis, bone fractures
	Uncommon	Arthritis
Renal and urinary disorders	Uncommon	Increased urinary frequency
Reproductive system and breast disorders	Common	Vaginal bleeding

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System organ class	Frequency	Adverse reaction
	Uncommon	Vaginal discharge, vaginal dryness, breast pain
General disorders and administration site conditions	Very common	Fatigue (including asthenia, malaise)
	Common	Peripheral edema
	Uncommon	General edema, mucosal dryness, thirst, pyrexia
Investigations	Common	Weight increase
	Uncommon	Weight loss

[1] Adverse drug reactions reported only in the metastatic setting

11.6. Potential drug induced liver injury

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold for laboratory abnormalities in the case of potential drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin **baseline values within the normal range**
  - who subsequently present with AST or ALT ≥3 × ULN

  concurrent with
  - a total bilirubin ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase ≤2 × ULN or not available.
- Patients with pre-existing AST or ALT **baseline values above the normal range**:
  - AST or ALT ≥2 × the baseline values and ≥3 × ULN, or ≥8 × ULN (whichever is smaller)

  concurrent with
  - total bilirubin ≥2 × ULN and increased by 1 × ULN over baseline or ≥3 × ULN (whichever is smaller) with no evidence of hemolysis and an alkaline phosphatase ≤2 × ULN or not available

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, prothrombin time (PT)/INR, and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced subject, 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

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warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal liver function tests. **Such potential Hy's Law cases must be reported as SAEs**.

11.7. Drug-drug interactions

Drug interaction studies for palbociclib have not been conducted in humans. Palbociclib is metabolized *in vitro* primarily via CYP3A4. See Sections 10.7.1 and 10.7.2 for medications that are not recommended.

Palbociclib is metabolized to multiple metabolites in a qualitatively similar manner in rat, dog and human liver microsomes. In vitro, palbociclib is primarily metabolized by Cytochrome P-450 (CYP) 3A4 enzymes.

12. Adverse event and serious adverse event reporting

12.1. Adverse event reporting

The main criterion for tolerability is the occurrence of toxicities and adverse events. The severity and causality will be classified according to the NCI CTCAE Version 5. The CTCAE is available for downloading on the internet at http://evs.nci.nih.gov/ftp1/CTCAE/About.html.

An adverse event is defined as any untoward medical occurrence that occurs from the first dose of trial medication until 30 days after all discontinuation of trial medication, regardless of whether it is considered related to a medication.

Adverse events should be reported on the Adverse Event Form (55-AE) in DFexplore. See Section 12.1.1 for requirements of reporting. Symptoms of the targeted cancer (if applicable) should not be reported as adverse events.

12.1.1. Severity / intensity

The adverse event severity grade provides a qualitative assessment of the extent or intensity of an adverse event, as determined by the Investigator or as reported by the patient. The severity grade does not reflect the clinical seriousness of the event, only the degree or extent of the affliction or occurrence (e.g., severe nausea, mild seizure), and does not reflect the relationship to trial drug.

Severity grade for other adverse events not covered in the toxicity grading scale:

Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required

Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required

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Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible

Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

Grade 5 = Death – the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on patient/event *outcome* or *action* criteria associated with events that pose a threat to a patient's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

Note:

- Report the highest grade observed in a cycle.
- Targeted AEs of any grade will have to be documented on the 55-AE Form.
- Any other AEs grade ≥3 as well as other AEs grade 2 requiring relevant medical intervention will have to be documented on the 55-AE Form.
- Abnormal laboratory values will have to be documented on the treatment forms 55-PALBO or 55-PAC, respectively, and not on the 55-AE Form. For non-targeted adverse events caused by an abnormal lab value, grades ≥3 should be reported in the 55-AE Form.
- Non-targeted AEs should not be reported in a narrative description, but rather by using the applicable CTCAE v5.0 term.

12.2. Targeted adverse events

The presence of any grade of the following AEs must be indicated on the Adverse Event Form 55-AE:

- Neutrophil count decreased
- Febrile neutropenia
- Anemia
- Platelet count decreased
- Nausea
- Diarrhea
- Thromboembolic event
- Infections
- Skin and cutaneous disorders
- Left ventricular systolic dysfunction
- Hypertension
- Ejection fraction decreased

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- Hepatobilliary disorder
- ILD/pneumonitis

12.3. Adverse events of special interest (AESIs)

Potential cases of drug-induced liver injury (see Section 11.6) are considered AESIs and need to be notified to IBCSG immediately (i.e., within 24h), following the SAE reporting instructions described in Section 0, even if not fulfilling a seriousness criterion.

12.4. Otherwise reportable events

Certain types of events, as identified below, are reportable to IBCSG under the reporting processes and requirements for SAEs, even if there is no associated adverse event. These are considered "otherwise reportable events" and generally reflect circumstances that could lead to an increased risk of an adverse event. Like an SAE, an otherwise reportable event is to be reported to IBCSG within 24 hours of awareness and followed up to determine outcome, including the later occurrence of an associated SAE.

12.4.1. Relevant overdose of IMP

An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as the intake of

- more than 23 capsules of palbociclib during a cycle (e.g.. two capsules on more than two days of a cycle, or more than two capsules during the week of break), or
- more than 2 capsules of palbociclib on the same day.

The overdose has to be reported within 24h on the 55–SAE–A Form.

12.5. Serious adverse event (SAE)

12.5.1. Definition

An SAE is defined in general as any undesirable medical occurrence/adverse drug experience that occurs from signature of Informed Consent until 30 days after stopping all trial treatment that, at any dose, results in any of the following:

- fatal (any cause)
- life-threatening
- requires or prolongs inpatient hospitalization
- persistent or significant disability/incapacity
- secondary (non-breast) malignancy
- constitutes an important medical event

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the patient or require medical or surgical intervention to prevent one of the other outcomes listed above.

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Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Report all SAEs up to 30 days after completion of trial treatments (for EoT definition see Section 10.8).

A suspected unexpected serious adverse reaction (SUSAR) is an adverse event that is serious, related to the investigational drug and not listed as a known toxicity of the investigational drug in the Investigator's brochure. All suspected unexpected serious adverse reactions judged by either the Investigator or IBCSG as the sponsor will be reported in accordance with applicable local regulations.

12.5.2. Exceptions to the definition

Hospitalizations occurring under the following circumstances are not considered to be serious adverse events:

- elective surgery
- occur on an outpatient basis and do not result in admission (hospitalization <24h)
- are part of the normal treatment or monitoring of the studied treatment

12.5.3. Causality assessment

The Investigator needs to assess the relationship between protocol treatment and the occurrence of each SAE following the definitions in this table:

Relationship to the protocol treatment	**Description**
Suspected	The possibility that the protocol treatment caused the event is deemed definite or probable or possible
Not suspected	The possibility that the protocol treatment caused the event is deemed unlikely or unrelated

The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, medical history, concurrent conditions, concomitant therapy, other risk factors, and the temporal relationship of the event to the protocol treatment will be considered and investigated.

The decision will be recorded on the SAE Form and if necessary the reason for the decision will also be recorded.

12.5.4. Expectedness assessment

The expectedness assessment is the responsibility of the sponsor of the trial. The expectedness assessment will be performed against the SPCs of the respective drugs.

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12.6. Reporting SAEs

Any SAE and any AESI or other reportable event (Sections 12.3 and 12.4) occurring in a patient after providing Informed Consent must be reported, including death due to any cause , which occurs within 30 days following cessation of treatment or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the investigational product. Information about all such events will be collected and recorded on the IBCSG Serious Adverse Event eCRFs (55–SAE–A and 55–SAE–B).

To ensure patient safety, the IBCSG must be informed of each SAE using the procedures described below:

- The Investigator/MD responsible for the patient must complete a Serious Adverse Event (SAE-A) eCRF in English within 24 hours of awareness via DFexplore. A copy is automatically forwarded to the IBCSG Safety Office for medical review.
- Queries may be issued by the IBCSG Safety Office via email; a timely response by the Investigator to all SAE-related queries is crucial.
- Follow-up information should be completed, via DFexplore, on the Serious Adverse Event (SAE-B) eCRF as soon as available and not later than 15 days of the initial report, even if the event reported in the SAE-A eCRF is not yet resolved. If the event is not resolved within 15 days, revise the original Serious Adverse Event (SAE-B) eCRF in DFexplore to report the final resolution.
- All SAEs that have not resolved upon discontinuation of the patient's participation in the trial must be followed until recovered, recovered with sequelae, not recovered (death due to another cause) or death (due to the SAE).
- If a non-serious adverse event becomes serious, this and other relevant follow-up information must also be provided within 24 hours.
- If submitting photocopies of SAE examinations, please send via DFSend (preferred) or fax. Care should be taken to ensure that the patient's identity is protected and the Patient ID number is properly included on ALL pages of any reports. For laboratory results, include the laboratory normal ranges. Please also note on each page that the information is "SAE related" so it can be properly categorized in DFexplore.
- In the event the eCRF system is not working, the SAE Forms can be found in the Trial Site File or downloaded from the IBCSG trial webpage and sent via fax or DFSend into the DFexplore system.

If an SAE (SAE-A and SAE-B Forms) was submitted by fax or DFSend, the original forms and the fax confirmation sheet(s) must be kept at the Participating Center.

The IBCSG will inform Pfizer Pharmacovigilance and other appropriate persons about all SAEs within 24 hours of receipt at the IBCSG.

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The IBCSG will record the SAE and prepare a monthly SAE report. Principal Investigators will receive the summary report on a monthly basis, and these reports can be found on the IBCSG web site (www.ibcsg.org).

12.7. Occupational exposure

If any patient-care or other personnel comes into contact with the content of palbociclib capsules then this needs to be reported to IBCSG via email to ibcsg55_touch@frontierscience.org.

13. Disease assessment, response and progression

Objective response prior to surgery will be assessed using the **WHO tumor measurement and response criteria.**

13.1. Tumor measurements

Bilateral mammography and breast/axilla ultrasound are required at baseline and prior to surgery. A physical tumor evaluation (by palpation, measured by caliper) should be done after 2 cycles.

The technique(s) used for measurement of the tumor (breast and axilla) should include physical and imaging and, for each patient the same technique(s) should be used throughout the study treatment period. Whenever possible, measurements should be made by the same clinician for all assessments for each patient.

All measurements (bi-dimensional) should be recorded in metric notations (centimeters and tenths of centimeters) using a ruler or calipers.

Primary tumor diameters as well as nodal status must be reported in the appropriate sections of the eCRF.

In case of multifocal or multicentric disease, only the lesion with the largest dimensions will be considered.

All measurable lesions with diameter(s) that decrease to <0.5 cm will continue to be recorded as having a diameter of 0.5 cm until the lesion is completely resolved or until the diameter increases to >0.5 cm. When the diameter increases to >0.5 cm, the actual measured diameter will again be recorded. When the lesion is completely resolved, record as: 0.0 × 0.0 cm.

13.2. Response criteria

To determine response, changes in tumor size from baseline to the assessments after 2 cycles will be measured physically by caliper (palpation). Prior to surgery, changes in tumor size from baseline will be measured physically by caliper and by breast tumor imaging using a ruler. The response will be determined using WHO criteria.

No confirmatory assessment will be required.

13.2.1. Complete response (CR)

The disappearance of all known disease.

13.2.2. Partial response (PR)

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A 50% or more decrease in total tumor size, i.e., the sum of the products of the maximal diameter (MD) and the corresponding largest perpendicular diameter (LPD) of the lesions which have been measured to determine the effect of therapy. In addition, there can be no appearance of new lesions or progression of any lesion.

13.2.3. Stable disease (SD)

Neither a 50% decrease in total tumor size (i.e., the sum of the products MD*LPD of lesions), nor a 25% increase in the size of one or more measurable lesions has been determined.

13.2.4. Progressive disease (PD)

An increase of least 25% in total tumor size relative to the smallest size measured during the trial (i.e., the sum of the products MD*LPD of lesions), and/or the appearance of one or more new lesions.

13.3. Best overall response

Best overall response is defined as best response recorded from the start of treatment across all time points until disease progression or surgery. Confirmation of partial or complete response by additional imaging is not requested in this trial. Best overall response will be reviewed by the Head of Medical Affairs.

13.4. Treatment in case of progression

Patients with evidence of complete response, partial response, or no change will remain on treatment for the full protocol-defined neoadjuvant treatment.

Patients with progressive disease confirmed by imaging will stop all trial medication and will undergo surgery, if clinically appropriate.

13.5. Pathological complete response

pCR (ypT0N0 or ypTisN0, see also Section 5.2) will be determined from the local histopathologic evaluation according to the American Joint Committee on Cancer Staging Manual, and is defined by the absence of invasive carcinoma in the breast and lymph nodes. The presence of *in situ* cancer after trial treatment in the absence of residual invasive disease constitutes a pCR.

The presence of tumor within lymphatic and / or vascular spaces in the breast (lymphatic vascular invasion – LVI) with or without other residual invasive cancer precludes classification as a complete pathological response.

Patients who do not proceed to surgery will be considered as not having pCR.

14. Clinical and laboratory evaluations and follow-up

14.1. Screening

The following examinations should be done within a maximum of 4 weeks before randomization (hematology and blood chemistry: within 14 days before randomization). If examinations were done prior to 28 days before randomization, they have to be repeated.

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14.1.1. Obtain informed consent for screening evaluations and trial participation. (Informed consent may be obtained earlier than within 28 days before randomization.)

14.1.2. Confirm that primary tumor is ER-positive (ER ≥ 10%) and HER2-positive by IHC and/or ISH.

14.1.3. Confirm with local pathologist that one FFPE block from the diagnostic biopsy is available exclusively for the purposes of this trial. This block will have to be sent to the IBCSG Central Pathology Office within 4 weeks after randomization.

14.1.4. Medical history including details of malignancy: date of diagnosis, primary tumor type characteristics.

14.1.5. Physical (breast and axilla palpation) and radiological (by mammography and ultrasound) tumor assessments.

14.1.6. Chest X-ray or CT scan, if medically indicated; not required in patients who have undergone a PET scan.

14.1.7. Abdominal ultrasound or CT if medically indicated; not required in patients who have undergone a PET scan.

14.1.8. Bone scan if medically indicated. Required if the patient has unexplained bone pain; not required in patients who have undergone a PET scan.

14.1.9. Feasibility of surgery and type of planned breast cancer surgery.

14.1.10. Cardiac evaluation: Electrocardiogram (ECG) and Echocardiogram.

14.1.11. Physical examination according to local standards, ECOG Performance Status, height, weight.

14.1.12. Hematology, within 14 days prior to randomization: Hemoglobin, platelet count, white blood cell count including differential (absolute neutrophil count).

14.1.13. Biochemistry, within 14 days prior to randomization: creatinine, alkaline phosphatase, AST or ALT, total bilirubin.

14.1.14. Geriatric assessment (for patients aged ≥65 years): all three questionnaires are available in the local language. Complete all three questionnaires by reading the questions to the patient and if necessary explain them further.

- G8: complete and then calculate the score, which is needed for the stratification (see Section 8.1.3; patient cannot be randomized without entering the score in the randomization system)
- Instrumental Activity of Daily Living (IADL)
- Charlson Comorbidity Index (CCI)

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14.1.15. Baseline comorbidities (record on 55-H Form, and add medication to treat the corresponding comorbidity).

14.2. During treatment

The following should be done prior to the start of the next treatment cycle.

Investigations marked with * need to be repeated on day 1 of the cycle prior to start of treatment if not done within 3 days prior to this day.

14.2.1. Physical examination according to local standards, ECOG Performance Status and weight.

14.2.2. * Hematology: Hemoglobin, platelet count, white blood cell count including differential (absolute neutrophil count).

Note: Hematology needs to be done

- prior to every paclitaxel dose (Arm A only)
- on day 1 and 14 for the first two palbociclib cycles, and on day 1 of cycles 3 and 4 (Arm B only).

Note: Generally, frequency of hematology needs to be adapted to the treatment and the condition of the patient throughout the 4 treatment cycles

14.2.3. * Biochemistry: creatinine, alkaline phosphatase, AST or ALT, total bilirubin.

14.2.4. Echocardiogram or MUGA must be repeated 3 months into the trial treatment (at week 7, plus/minus 1 weeks and before surgery).

14.2.5. For adverse events observed in the previous cycle, record all grades for any targeted adverse event (see Section 12.2). Record all grade ≥3 non-targeted events. Record grade 2 non-targeted events *if they require relevant medical intervention*. Assign the appropriate adverse events grade according to the NCI CTCAE Version 5.0. Record medication used to treat the AEs.

14.2.6. Arm B: Compliance assessment; check patient diary; hand out new patient diary for next cycle.

14.2.7. Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (e.g. hypoxia, cough, dyspnea). In patients who have new or worsening respiratory symptoms and are suspected to have developed ILD/pneumonitis, interrupt palbociclib immediately and evaluate the patient.

14.3. Tumor assessments

Tumor measurements have to be done at baseline, and before surgery:

14.3.1. Baseline: Physical (breast and axilla palpation and caliper) and radiological (mammography and ultrasound, and ruler) tumor assessments.

Chest X-ray or CT scan, if clinically indicated: not required in patients who have

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undergone a PET scan.

14.3.2. A physical tumor evaluation (by caliper) should be done after 2 paclitaxel cycles (Arm A) or 2 palbociclib cycles (Arm B).

14.3.3. Before surgery: tumor assessment by breast and axilla palpation (and caliper) and by mammography and ultrasound (and ruler).

14.3.4. Bone scan, if medically indicated; Required if the patient has unexplained bone pain; not required in patients who have undergone a PET scan.

14.4. Before surgery

After the end of trial treatment and before surgery:

14.4.1. Physical examination according to local standards, weight and ECOG Performance Status.

14.4.2. For adverse events observed in the last cycle before surgery, record all grades for any targeted adverse event (see Section 12.2). Record all grade ≥3 non-targeted events. Record grade 2 non-targeted events *if they require relevant medical intervention*. Assign the appropriate adverse events grade according to the NCI CTCAE Version 5.0. Record medication used to treat the AEs.

14.4.3. Hematology: Hemoglobin, platelet count, white blood cell count including differential (absolute neutrophil count).

14.4.4. Biochemistry: creatinine, alkaline phosphatase, AST or ALT, total bilirubin.

14.4.5. If not done in the 30 days prior to this visit, determination of response through physical and radiological tumor assessments by breast and axilla palpation (caliper) and ultrasound and mammography (ruler; see Section 13).

14.4.6. Electrocardiogram (ECG) and echocardiogram.

14.5. After surgery

Immediately after surgery, if there is residual invasive tumor, secure FFPE tumor specimen for central review and translational research.

The end of treatment visit has to be done within 30 days after EoT as defined in Section 10.8. (time of breast cancer surgery; if not operated, date of stop of all trial medication). The following should be documented:

14.5.1. Physical examination according to local standards, weight and ECOG Performance Status.

14.5.2. Serious adverse events up to 30 days after EoT (for EoT definition see Section 10.8).

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15. Biological evaluations

15.1. Tumor tissue

Tumor tissue from the biopsy taken prior to start of treatment will be sent to the IBCSG Central Pathology Office (CPO) in Milan, Italy, and biobanked.

A tumor tissue specimen from definitive surgery must also be sent to the CPO. If there is no residual invasive tumor, please inform IBCSG.

All biological material will be logged in the IBCSG Pathology Material Tracking System and banked in the IBCSG Biobank.

15.2. Submitting pathology material to IBCSG

Both FFPE blocks and copies of Pathology Reports must be marked with the IBCSG Patient ID number. Please erase or black out any other identifiers like name or date of birth. Refer to the IBCSG website for additional FFPE specimen shipping recommendations.

Both FFPE blocks should be submitted within 4 weeks after being taken:

- Tumor tissue from the biopsy taken prior to start of treatment
- Tumor tissue specimen from definitive surgery

Mailing address for the FFPE blocks and Pathology Reports:

IBCSG Central Pathology Office
European Institute of Oncology, EIO
Division of Pathology
Via Ripamonti 435
20141 Milano, Italy
Email: pathology.ibcsg@ieo.it

NOTE: Pathology Reports must also be submitted to DFexplore via fax or DFSend.

15.3. Translational research

15.3.1. Integral translational research

Pre-treatment biopsy will be analyzed by gene-expression profiling to assess RBsig status.

15.3.2. Further translational research

Pre-treatment biopsy gene-expression profiling may also be utilized to explore potential biomarkers in the randomized arms. Surgical tumor tissue samples may be analyzed by gene-expression profiling to assess changes in RBsig status between baseline and surgery and explore potential biomarkers of resistance to treatment.

Additionally, studies on proteins and genes involved in the ER and RB1 pathway may be conducted using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) on both pre-treatment and surgical samples.

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15.3.3. Not yet specified translational research

The use of the biological material for future research not outlined in this protocol will be under the guardianship of the Steering Committee. As part of the trial Informed Consent process, patients are asked to indicate whether they agree to donate their sample for not yet specified future research. The patient's decision is recorded on the trial Consent Form.

Translational research proposals not outlined in this protocol will be assessed by IBCSG's Biological Protocol Working Party (BPWG) for merit and feasibility.

Biomarkers that are published in the future and considered to be of relevance may also be assessed in the context of this trial.

16. Data submission

We will conduct the trial according to the ICH Good Clinical Practice (GCP) guidelines. Keeping accurate and consistent records is essential to a cooperative trial. The following forms are to be submitted at the indicated times by the participating institutions for each patient:

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16.1. Case report forms schedule

Forms	***Description/Name***	***Forms Submission*** ***ALL data should be completed in DFexplore (unless otherwise specified)***
Informed Consent Form	Consent to participation in clinical trial and biologic material submission	Obtain before registration and keep with patient records as documentation (hard copy only).
Registration and Randomization		
Geriatric assessment (only for patients aged ≥65 years)	Geriatric Assessment G8 questionnaire (55-G8) Lawton Instrumental Activities of Daily Living Scale (55-IADL) Charlson Comorbidity Index (55-CCI)	Complete questionnaires in local language on paper with the patient; note that the G8 score is needed in order to randomize the patient. After randomization, complete eCRF within 1 week.
55-A	Confirmation of Randomization Form	Complete eCRF after you have randomized the patient in the IBCSG Registration/ Randomization System and to confirm eligibility. Patient will be available eCRF **within 24 hours** of successful randomization.
Baseline		
55-H	History Form	Complete eCRF within 1 week of randomization.
55-TEV-B	Tumor Evaluation Baseline Form	Complete eCRF within 1 week of randomization.
55-Pathology Report		
During neoadjuvant treatment		
55-TP	Arms A and B Trastuzumab / Pertuzumab Log	Complete at Baseline and update every 3 weeks with each injection (and at Week 7 with Echo/MUGA result)
55-PAC	Arm A Paclitaxel Form	For patients on Arm A, complete eCRF at the end of each 28 day cycle until treatment stops.
55-PALBO	Arm B Palbociclib Form	For patients on Arm B, complete eCRF at the end of each 28 day cycle until treatment stops.
55-LET	Arm B Letrozole Form	For patients on Arm B, complete eCRF at the end of letrozole treatment.
55-AE	Adverse Events Form	Complete eCRF at the end of each 28 day cycle (on day 1 of the next cycle).
55-TEV-Phys	Tumor Evaluation Physical Exam Form	Complete after 2 cycles of Arm A paclitaxel or Arm B palbociclib.
After completion of trial medication, prior to Surgery		
55-TEV-PRESX	Tumor Evaluation Pre-Surgery Form	Complete eCRF within 4 weeks after trial treatment stops but prior to surgery.
55-AE	Adverse Events Form	Complete eCRF after all trial medication is complete up to 4 weeks prior to surgery.
55-TMC	Trial Medication Completion Form	Complete eCRF after all trial medication is complete up to 4 weeks prior to surgery.
Surgery		
55-C	Surgery form	Complete eCRF within 2 weeks after surgery.

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Forms	***Description/Name***	***Forms Submission*** ***ALL data should be completed in DFexplore (unless otherwise specified)***
55-P	Pathology form	Complete eCRF within 2 weeks after surgery.
Pathology report		Pathology report for definitive surgery.
Follow Up (after discontinuation of trial treatment and after surgery)		
55-EoT	End of Treatment Form	Complete eCRF 30 days after surgery or, if no surgery, after **ALL** protocol treatment stops.
Event Driven		
55-SAE-A	Serious Adverse Event/Adverse Event of Special Interest Form A - Initial report	Complete eCRF within 24 hours of the SAE awareness. If eCRF is not available, submit the form within 24 hours to IBCSG DMC.
55-SAE-B	Serious Adverse Event/Adverse Event of Special Interest Form B - Follow-up report	Complete eCRF as soon as follow-up information available, and not later than 15 days of the initial report (55-SAE-A). If event is not resolved in 15 days, update 55-SAE-B again at the time of resolution.
55-COC	Change of Consent Form	Complete eCRF if there is any change in patient's consent to participate in the trial, see Section 18.2.2.
55-E-Death	Death Form	Complete eCRF if a patient dies, if patient is still in active follow-up.

The DFexplore User Manual and the Data Managers' Manual for this trial contain instructions for completing and submitting forms using the DFexplore system.

16.2. Signing and submitting forms

An Authorization Log (see Section 16.5) should be completed at each Participating Center to identify the persons who are authorized to complete CRFs.

CRFs should be completed on-line in DFexplore. Reports (lab, pathology, etc.) and any other non-CRF data will need to be sent to the DFexplore system via fax or DFSend. Full instructions on submitting forms will be available on the IBCSG website (www.ibcsg.org). Also available on the website is a list of fax numbers that are available for faxing CRFs.

16.3. Data management

Data collected in this trial will be submitted to the IBCSG Data Management Center in Amherst, NY, USA. The Data Management Center will process the data and will generate queries and forms requests. The Data Quality Control Office will oversee overall data submission and query resolution. The IBCSG Coordinating Center in Bern, Switzerland will provide medical review and summary of SAEs. The IBCSG Statistical Center in Boston, MA, USA will perform the data analysis.

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16.4. Investigator Site File

Each Participating Center should keep documentation about this trial in an Investigator Site File (ISF). Please arrange the documentation in the order foreseen in the ISF index which will be provided by IBCSG. The following documents should be included (list is not complete):

- Protocol and appendices
- Activation letter
- Accrual reports
- Amendments
- Copy of signed Protocol Signature Pages
- Sample CRFs including blank SAE Forms
- For patients aged ≥65 years: geriatric assessment sheets (G8, IADL, Charlson Comorbidity Index) in local languages
- Patient diary for treatment with letrozole and palbociclib (Arm B)
- Data Managers' Manual
- Obvious Corrections Document and Signature Page
- Randomization Manual
- DFexplore Manual
- Drug Supply Manual
- Patient information and Informed Consent templates approved by Ethics Committee
- Palbociclib SPC
- Letrozole SPC
- Trastuzumab SPC
- Pertuzumab SPC
- Paclitaxel SPC
- Ethics Committee (and Health Authority, if applicable) approval of protocol, Patient Information Sheet and Informed Consent, amendments
- Ethics Committee review of SAE, Investigators' alert, and other documents
- Correspondence with Ethics Committee and Health Authority (if applicable)
- Certificate of clinical trial insurance
- Agreement with IBCSG

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- Center Activation email(s) from IBCSG Data Management Center (protocol and amendments, if any)
- Correspondence with / Information issued by IBCSG Coordinating Center, Data Management Center
- SAE Reports sent from IBCSG Data Management Center
- Normal laboratory values/reference ranges
- Laboratory Certifications
- CV of Principal Investigator and Co-Investigators, GCP certificates
- Trial Training Certificates issued by IBCSG Center Training Office
- Documentation of any training done internally (e.g. by use of IBCSG Training Confirmation Log)
- Authorization Log
- Center Information Sheet
- Patient screening log
- Patient identification log (see Section 16.6)
- Drug shipment records
- Drug accountability log (including certificates of destruction if applicable)
- Temperature logs
- Weblink to ICH GCP guidelines/Declaration of Helsinki and updates
- Audit certificates / monitoring follow-up letters

16.5. Authorization log

The Principal Investigator (PI) should identify the other members of the Clinical Trial Team who are supervised by the PI and approved to provide information in CRFs, queries, etc. Instructions for completing the Authorization Log can be found in the Authorization Log Manual, posted on the IBCSG website. All changes need to be communicated to IBCSG by updating and emailing the authorization log.

16.6. Patient identification log

No patients' names should be used in CRFs or any other documentation transmitted to IBCSG central offices. The only item used to identify a patient is the Patient ID (Randomization Number). It is therefore imperative that the local data manager keep an identification log for all patients entered in this trial including:

- Patient's name

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- Patient ID issued by the Registration/Randomization System
- Date of birth
- Date of randomization

17. Statistical considerations

17.1. Design

This is an international, multi-center, randomized phase II trial that will randomize women with ER+/HER2+ primary breast cancer, in a 1:1 ratio, to receive the combination of: (A) paclitaxel + trastuzumab + pertuzumab versus (B) palbociclib + letrozole + trastuzumab + pertuzumab. Tumor RBsig status (high vs. low) by gene expression profiling will be assessed after the recruitment period in a central laboratory from a pre-treatment biopsy FFPE specimen.

17.2. Sample size determination

The primary efficacy endpoint is pathological complete remission pCR, as defined in Section 5.2. The trial hypothesis is that, in patients with RBsig LOW, palbociclib plus letrozole plus trastuzumab + pertuzumab will be more active than paclitaxel plus trastuzumab +pertuzumab, while in patients with RBsig HIGH, paclitaxel plus trastuzumab + pertuzumab will be more active than palbociclib plus letrozole plus trastuzumab + pertuzumab.

The overall pCR rate is expected to be 26%, on the basis of patients with HR+ tumors treated with docetaxel-trastuzumab-pertuzumab in the NeoSphere trial [25] and those treated with palbociclib-fulvestrant-trastuzumab-pertuzumab in the NA-PHER2 [75]. The assumed pCR rates in the 4 subgroups defined by randomized treatment assignment and RBsig status are summarized in Table 12, on the basis of the retrospective in-silico study of RBsig (see Section 4.9) and ongoing analyses of other clinical trial cohorts (Malorni, personal communication). It is assumed that 50% of pre-biopsy samples are RBsig-high and 50% RBsig-low, which was the cutpoint in the in-silico study and ongoing studies but not yet adequately confirmed as the optimal cutpoint; as sensitivity analysis, a distribution of 25%/75% was also assessed, which has been a secondary cutpoint evaluated in the in-silico and ongoing studies. Sample size was determined on the basis of simulations of exact logistic regression test for treatment-by-RBsig interaction. An asymptotic method, such as that of Demidenko [76] was not used because the number of patients per subgroup will be relatively small and the pCR rates relatively low, and the appropriateness of an asymptotic method was uncertain. On the basis of simulations, an assessable sample size of 120 patients with successful RBsig results was determined to provide 86% power for the test of treatment-by-RBsig interaction (two-sided α=0.05; Table 13). The enrolled sample size is inflated by 20% to 144 patients to account for non-assessable RBsig status (which is determined after randomization).

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Table 12. Hypothesized pCR rates in subgroups defined by treatment and RBsig status for sample size determination.

	RBsig Prevalence	A: Paclitaxel + trastuzumab + pertuzumab	B: Palbociclib + letrozole + trastuzumab + pertuzumab	Odds Ratio (B:A)	Rate Ratio (B/A)
		pCR rate			
RBsig LOW	50%	15%	30%	2.429	2.0
RBsig HIGH	50%	50%	10%	0.111	0.2

Table 13. Statistical power for test of treatment-by-RBsig interaction in exact logistic regression model (two-sided α=0.05) on the basis of simulations.

	N=100	N=110	N=120
RBsig LOW / HIGH			
50% / 50%	75%	80%	86%
*Freq. questionable fit**	*(9%)*	*(7%)*	*(5%)*
25% / 75%	52%	60%	68%
*Freq. questionable fit**	*(17%)*	*(13%)*	*(11%)*

* *Frequency that simulation resulted in a 0% pCR rate in one subgroup and the fit of the model was questionable*

17.3. Definitions of Trial Populations

Randomized Population: Will include all patients who are randomized, according to treatment assignment.

Assessable Population: Will include the subset of the randomized population with RBsig status successfully determined who received at least 1 dose of trial medication.

Treated Population: Will include the subset of the randomized population who receive at least 1 dose of trial medication.

17.4. Primary Objective

The primary objective will be tested in the assessable population.

The primary endpoint is pCR, as defined in Section 5.2. pCR rate will be estimated as the number of patients with pCR documented, divided by the number of patients in the assessable population. Patients whose disease progresses and do not undergo surgery will be considered as not having pCR documented; patients who otherwise do not have available surgery results (e.g., stop study participation early) will be considered as not having pCR documented. Sensitivity analyses will be included in the statistical analysis plan, e.g., excluding the latter patients.

pCR rates will be summarized as N (%) with two-sided 95% CIs, by treatment and RBsig status. The primary objective will be tested using exact logistic regression analysis with pCR as the dependent variable, by testing treatment-by-RBsig interaction and estimating the odds ratios (95% CIs) for Arm A versus B according to RBsig. Rate ratios and rate differences will also be

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estimated (with 95% CIs). As noted in Section 17.2, the cutpoint of RBsig as high and low for the primary objective is presumed to be the median, and the cutpoint will be confirmed and pre-specified in the statistical analysis plan. Further, treatment-by-RBsig interaction with RBsig as a continuous value will be explored using STEPP methodology [77, 78] on both the relative and absolute treatment effects.

pCR rates and odds ratios may also be estimated by subgroups defined by the stratification factors (see Section 8.3).

The pCR rates will also be summarized according to treatment on the basis of the treated population.

17.5. Secondary Objectives

Among patients in the assessable population, the rate of pCR in breast only will be estimated as the number of patients with absence of invasive tumor cells in the breast at the time of surgery (ypT0/ypTis), divided by the number of patients in the assessable population. Rates will be summarized as N (%) with two-sided 95% CIs, by treatment and RBsig status. The rates will also be summarized according to treatment on the basis of the treated population.

Among patients in the assessable population, the rate of objective response (as defined in Section 13) will be estimated as the number of patients with best overall response of complete response or partial response, divided by the number of patients in the assessable population. Rates will be summarized as N (%) with two-sided 95% CIs, by treatment and RBsig status. The rates will also be summarized according to treatment on the basis of the treated population.

Among patients in the treated population, treatment tolerability will be assessed according to treatment on the basis of adverse events (AEs). For each AE, the frequency (N, %) of patients by worst grade of the AE will be summarized and tabulated by treatment. Two-sided 95% CI for the between-treatment difference in proportion of patients with each type of grade 3 or higher targeted AE will be estimated.

Among patients in the assessable population, the breast-conserving surgery (BCS) rate will be estimated as the number of patients undergoing BCS, divided by the number of patients in the assessable population. In addition, the rates will be recalculated with the denominator considering only those patients reported at baseline not to be candidates for BCS. Rates will be summarized as N (%) with two-sided 95% CIs, by treatment and RBsig status. The rates will also be summarized according to treatment on the basis of the treated population.

17.6. Interim Analyses

Interim analyses are not planned.

17.7. Accrual

Enrollment of 144 patients is anticipated over approximately 24 months, after a start-up period of 6 months as the trial is being activated by Participating Centers and enrollment will be slow.

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17.8. Data and Safety Monitoring

Accrual, treatment and surgery completion, and AEs will be reviewed by the IBCSG Data and Safety Monitoring Committee (DSMC) twice per year. Successful assessment of RBsig status will be reviewed after the recruitment period.

17.9. Correlative Objectives

Among patients in the treated population that do not experience pCR, the tumor Ki67 proliferation marker changes between pre-treatment biopsy and residual disease of surgery sample will be calculated. Absolute and relative changes in Ki67 will be summarized descriptively and graphically, by treatment and by RBsig status (including unknown status).

Exact logistic regression will be used to identify features of pre-treatment tumor samples associated with pathologic response to treatment, and to explore the predictive value of such features for differential responsiveness to trial treatments.

Logistic regression will also be used to explore whether features in baseline geriatric assessments (for the subgroup of women aged ≥65 years) are associated with adverse events experienced on trial treatments.

18. Criteria for termination of the trial

18.1. General criteria for termination of the trial

The trial may be discontinued early in parts or completely if the information on the trial treatments leads to doubt as to the benefit/risk ratio, by decision of the IBCSG Foundation Council upon recommendation of the IBCSG 55-17 TOUCH Steering Committee and DSMC.

The trial can be terminated at any time if the authorization and approval to conduct the trial is withdrawn by ethics committee or regulatory authority decision, insufficient accrual, emerging new data impacting the scientific value of the trial or ethical grounds.

18.2. Patient-specific criteria for termination and withdrawal

18.2.1. Cessation of trial treatment

Patients have the right to refuse further trial treatment at any time during the trial. Patients may also be withdrawn from trial treatment at any time at the discretion of the Investigator due to an adverse event, or based on any other relevant medical condition. Such patients will remain in the trial. The patient will continue to be documented according to protocol. See Section 10.8 for details on stop of trial treatment.

18.2.2. Withdrawal of consent

Patients have the right to withdraw consent for further trial participation at any time without having to specify the reason. The data recorded up to the time point of withdrawal will continue

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to be evaluated in the trial. The Investigator should ask the patient for consent to continue to collect information on her disease up to surgery.

Withdrawal of consent should be documented in both the medical records and in the eCRF (Form 55-COC). For the patient's safety, an end of treatment visit should be performed and documented in the eCRF.

19. Ethical aspects, regulatory approval, and patient informed consent

The Investigator will ensure that this trial is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The trial must fully adhere to the principles outlined in "Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice (November 2016)" or with local law if it affords greater protection to the patient. For trials conducted in the EU/EEA countries, the Investigator will ensure compliance with the current EU legislation.

19.1. Ethical Review Board/Ethics Committee

All protocols and the patient Informed Consent forms must have the approval of a properly constituted committee or committees responsible for approving clinical trials. The Ethics Committee (EC) / Ethics Review Board (ERB) / Institution Review Board (IRB) written, signed approval letter/form must contain approval of the designated Investigator, the protocol (identifying protocol title and version number), and of the Patient Information Sheet and Informed Consent (PIS/IC). Documentation of Ethics Committee approval(s) must be sent to the IBCSG Data Management Center prior to enrollment of the first patient. The IBCSG Ethics Committee also approves the protocol and reviews it annually.

Any modifications made to the protocol will be reviewed by the IBCSG Ethics Committee and must also be submitted to the appropriate EC/ERB/IRB for information or approval in accordance with local procedures and regulatory requirements and to Health Authorities if required.

Once approved or acknowledged by the appropriate EC/ERB/IRB and by the Health Authorities (if required), the Investigator shall implement the protocol modifications. Protocol modifications for urgent safety matters may be directly implemented following the instructions of IBCSG.

19.2. Regulatory approval procedures

If applicable, in addition to the approval of the Ethics Committee according to national legislation, the protocol, other protocol-related documents including patient information and Informed Consent and other documents as required locally must be submitted to and be approved by the health authority. Documentation of health authority approval must be sent to the IBCSG Data Management Center prior to Participating Center activation.

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19.3. Protection of human patients

The IBCSG has an Office for Human Research Protection (OHRP) Federal Wide Assurance (FWA00009439) and follows all of the policies and procedures that are part of that assurance. All potential patients for this trial will receive a Patient Information Sheet with a full explanation of the trial, its purpose, treatments, risks, benefits, and all of the other items listed in Section 19.4. Additional institution-specific sections should be added to Appendix 1 as needed.

The medical record must be available for review by the IBCSG monitors and audit team and regulatory authorities as described in Section 20.7.

Serious Adverse Event (SAE) Reports are distributed monthly. In addition they are available on the IBCSG website (www.ibcsg.org) for participating Centers.

19.4. Informed Consent

Informed Consent for each patient will be obtained prior to initiating any trial procedures in accordance with the “IBCSG Patient Information Sheet and Informed Consent" (See Appendix 1). One signed and dated copy of the Informed Consent must be given to each patient and the original copy must be retained in the Investigator's trial records. The Informed Consent form must be available in the case of data audits. Verification of signed Informed Consent and the date signed are required for randomization to this trial.

The "Declaration of Helsinki" recommends that consent be obtained from each potential patient in biomedical research trials after the aims, methods, anticipated benefits, and potential hazards of the trial, and discomfort it may entail, are explained to the individual by the physician (http://www.wma.net/en/30publications/10policies/b3/index.html). The potential patient should also be informed of her right to not participate or to withdraw from the trial at any time. The patient should be told that material from her tumor will be stored and potentially used for additional studies not described in this protocol.

If the patient is in a dependent relationship to the physician or gives consent under duress, the Informed Consent should be obtained by an independent physician. By signing this protocol, the Investigator agrees to conduct the trial in accordance with GCP and the "Declaration of Helsinki."

The IBCSG recognizes that each institution has its own local, national, and international guidelines to follow with regard to Informed Consent. Therefore, we provide a template information sheet and Informed Consent form (Appendix 1), which can be downloaded and edited to incorporate information specific to your institution (see www.ibcsg.org). The template Patient Information Sheet and Informed Consent (PIS/IC) has been written according to ICH guidelines which state the Informed Consent should adhere to GCP and to the ethical principles that have origin in the “Declaration of Helsinki”. The final version should receive the Institutional Review Board/ Local Ethics Committee approval in advance of its use. Centers should send their locally modified PIS/IC to the IBCSG Data Management Center for review and approval before submitting to their Ethics Committee.

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20. Governance and Administrative Considerations

20.1. Final report

A final clinical trial report will be written and distributed to health authorities as required by applicable regulatory requirements

20.2. Clinical trial insurance

IBCSG will contract the appropriate liability insurance for this trial. Patients who suffer injuries due to the trial should report them immediately to their physician. The local Center should report all alleged claims immediately to the IBCSG.

20.3. Steering Committee

A Steering Committee will be constituted for this trial. The primary responsibilities of the Steering Committee are twofold. First, the Steering Committee is responsible for maintaining the scientific integrity of the trial, for example, by recommending changes to the protocol in light of emerging clinical or scientific data from other trials. Second, the Steering Committee is responsible for the translation of recommendations of the IBCSG Data and Safety Monitoring Committee into decisions. Membership will include IBCSG officials, trial chairs and co-chairs, trial statisticians, representatives from some Participating Centers.

General partition of responsibilities:

The Steering Committee has the authority to make and implement any final decisions, such as substudies of the trial or amendments to the trial protocol, and may recommend the termination/early termination of the trial.

The IBCSG Foundation Council decides on the termination/early termination of the trial.

20.4. Data and Safety Monitoring Committee (DSMC)

The trial will be presented for review to the IBCSG Data and Safety Monitoring Committee (DSMC) at each of their semi-annual meetings. Accrual, safety and accumulation of PFS events will be monitored.

20.5. Publication of trial results

IBCSG will publish the results of the trial based on the final trial report.

20.6. Premature discontinuation of the trial

The trial may be discontinued early in parts or completely if the information on the trial treatment leads to doubt as to the benefit/risk ratio.

The trial can be terminated at any time if the authorization and approval to conduct the Study is withdrawn by ethics committee or regulatory authority decision, insufficient accrual, emerging new data impacting the scientific value of the trial or ethical grounds.

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20.7. Quality Assurance

The IBCSG conducts trials according to the ICH GCP guidelines. The Trial IBCSG Data Manager reviews each CRF. In addition, the IBCSG Medical Reviewer reviews each case at specific time points. The IBCSG conducts periodic audit visits to ensure proper trial conduct, verify compliance with GCP, and perform source data verification.

The Investigator should ensure that source documents are made available to appropriately qualified personnel from IBCSG or its designees, or to health authority inspectors after appropriate notification.

At regular intervals during the clinical trial, the Center will be contacted, through monitoring visits, letters or telephone calls, by a representative of the Monitoring Team to review trial progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient Informed Consent, patient recruitment and follow-up, SAE documentation and reporting, AEs with pre-specified monitoring documentation and reporting, AE documentation, trial treatment administration, patient compliance with the regimens, drug accountability, concomitant therapy use and quality of data.

20.8. Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the Investigator contact IBCSG or personnel monitoring the trial to request approval of a protocol deviation, as no deviations are permitted. The Investigator should document and explain any deviations from the approved protocol and promptly report them to IBCSG and to the EC concerned in accordance with the applicable EC policies and procedures. If the Investigator feels a protocol deviation would improve the conduct of the trial this must be considered a protocol amendment, and unless such an amendment is developed and activated by IBCSG and approved by the EC/ERB/IRB it cannot be implemented. All protocol deviations will be documented.

20.9. Data protection

The samples and data collected will be coded to protect patient confidentiality. A unique Patient Identification (ID)/Randomization Number will be assigned by the IBCSG Registration/ Randomization System to each patient registered into the trial. The names of the patients will not be disclosed to the IBCSG.

Only the Patient ID will be used to identify a patient on the eCRF. Identification of patients must be guaranteed at the Participating Center. In order to avoid identification errors, Centers should keep a Patient Identification Log containing the patients' name, year of birth, and the Patient ID allocated by IBCSG.

Biological material will be assigned the same unique identifier. No identifiable / personal data will be stored in the trial database or the tissue repository in the central lab.

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Biological material will be transferred outside the treating institution for central review and for determination of RRsig and translational research. Results of the assays will be coded only by the patient identifier.

Regulatory authorities and the pertinent Ethics Committee (EC/ERB/IRB) may have access to patient data on-site. IBCSG audit or monitoring personnel will also have access to such data on-site.

20.10. Record Retention

The Center must retain all essential documents according to ICH GCP. This includes copies of the patient trial records, which are considered as source data, patient Informed Consent statement, laboratory printouts, drug inventory and destruction logs, and all other information collected during the trial. These documents are to be stored until at least 15 years after the termination of the trial. IBCSG guarantees access and availability of the data entered into DFexplore for at least 15 years after the termination of the trial.

Longer retention may be required for Participating Centers according to national regulations.

In the event that the Principal Investigator retires or changes employment, custody of the records may be transferred to another competent person who will accept responsibility for those records. Written notice of such transfer has to be given to IBCSG and the local Ethics Committee at least one month in advance.

21. Confidentiality

The protocol, CRFs and other protocol-related documents are confidential and are the property of the IBCSG.

22. References

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