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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
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In collaboration with Pfizer Italy (supply of palbociclib and trial support) and Roche (supply of trastuzumab and pertuzumab).

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Protocol Signature Page Amendment 2

IBCSG 55-17 TOUCH

Approved by:

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Principal Investigator Protocol Signature Page Amendment 2

IBCSG 55-17

TOUCH

I have read the protocol and agree that it contains all necessary details for conducting this trial. I will conduct the trial as outlined in the following protocol and in compliance with GCP, and will apply due diligence to avoid protocol deviations. I will provide copies of the protocol and all drug information relating to preclinical and prior clinical experience furnished to me by IBCSG, **to all physicians responsible to me who participate in this trial. I will discuss this material with them to assure that they are fully informed** regarding the drugs and the conduct of the trial. I agree to keep records on all patient information (Case Report Forms and patient's Informed Consent statement), drug-shipment and return forms, and all other information collected during the trial for a minimum period of 15 years.

Name of Principal Investigator: _____

_____ _____
Signature Date

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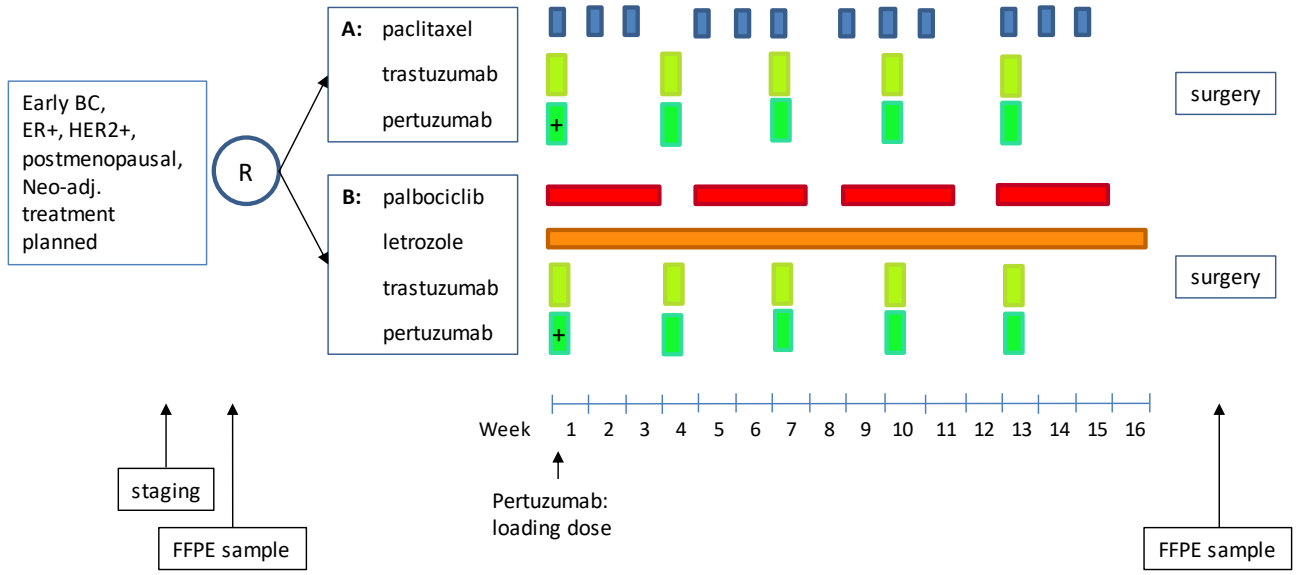
1. Protocol Summary

Title	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
Sponsor	International Breast Cancer Study Group IBCSG
Pharma Partner	Pfizer and Roche
Clinical Phase	Randomized Phase II
Patient population	Postmenopausal patients with histologically confirmed estrogen receptor positive, HER2 positive primary breast cancer
Treatment	Patients will be randomized in a 1:1 fashion to: • Arm A → **Paclitaxel** 80 mg/m^2 i.v. on day 1, 8, 15 every 28 days for 4 cycles **Trastuzumab** 600 mg s.c. every 3 weeks for a total of 5 doses **Pertuzumab** 840 mg i.v. loading dose followed by 420 mg i.v. every 3 weeks for a total of 5 doses • Arm B → **Palbociclib** 125 mg/day orally for 21 days followed by 7 days' rest, for four 28-day cycles **Letrozole** 2.5 mg/day orally for 16 weeks **Trastuzumab** 600 mg s.c. every 3 weeks for a total of 5 doses **Pertuzumab** 840 mg i.v. loading dose followed by 420 mg i.v. every 3 weeks for a total of 5 doses Patients will then proceed to surgery



Background and rationale	Human epidermal growth factor receptor-2 (HER2) is overexpressed and/or amplified in about 10-20% of breast tumors. HER2+ breast cancer (BC) is usually treated with regimens containing anti-HER2 agents and chemotherapy. Clinically approved anti-HER2 agents include monoclonal antibodies (trastuzumab and pertuzumab), tyrosine kinase inhibitors (lapatinib) or antibody–drug conjugates (T-DM1).

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	Around 50% of HER2+ tumors co-express estrogen receptors (ERs), dividing HER2+ patients into hormone receptor (HR) negative and positive subgroups (HRneg/HER2+ and HR+/HER2+). Clinical data have increasingly demonstrated that these two subgroups of HER2+ patients show different prognosis when treated with anti-HER2 targeted agents and chemotherapy [Prat et al., 2014]. However, patients with HR+/HER2+ BC receive chemotherapy in combination with anti-HER2 agents as first choice treatment and only secondly endocrine treatment (ET). Extensive preclinical evidence indicates that ER and HER2 pathways are strictly interdependent and that targeting both pathways in ER- and HER2- co-expressing tumors might be an effective therapeutic strategy [Osborne et al., 2011]. Few trials investigated the addition of ET to anti-HER2 in patients with HR+/HER2+ advanced disease indicating that a proportion of patients with HR+/HER2+ advanced BC benefit from the combination of hormonal and anti-HER2 therapy with manageable side effects [Johnston et al., 2009; Kaufman et al., 2009]. However, whether the combination of anti-HER2 and ET would be superior to the approved combination of anti-HER2 and chemotherapy in patients with advanced HR+/HER2+ BC remains an open question since there is no direct comparison between these two strategies. Additionally, a recent phase II pre-operative trial of trastuzumab + lapatinib + the endocrine agent letrozole showed that the combination yielded a pCR rate of only 21% in a cohort of 39 ER+/HER2+ patients [Rimawi et al, 2013]. These considerations highlight that the current paradigm for the treatment of HER2+ patients (chemotherapy + anti-HER2 agents) does not necessarily fit the subgroup of patients co-expressing ER, and that current endocrine treatments alone might not be a sufficient partner for anti-HER2 agents in HR+/HER2+ disease. Cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors are bringing great improvements in the management of patients with HR+/HER2neg advanced BC. Three different CDK4/6 inhibitors (palbociclib, abemaciclib and ribociclib) are in clinical development in this patient subgroup, mostly in combination with endocrine therapy. Palbociclib has been granted FDA approval in the U.S. for the treatment of HR+/HER2neg advanced BC in combination with the hormonal treatments letrozole and fulvestrant given the unprecedented results in terms of efficacy of two pivotal clinical trials (PALOMA-2 and PALOMA-3) [Finn et al. 2016; Cristofanilli et al., 2016]. Palbociclib and other CDK4/6 inhibitors have also shown a good toxicity profile and therefore are ideal candidates for combination with hormonal therapy. CDK4 and 6 control the transition from the G1 to the S phase in the cell cycle by binding to D-type cyclins. A primary target of CDK action is the retinoblastoma susceptibility gene product (RB), which mediates G1 arrest through sequestration of transcriptional factors of the E2F family. Phosphorylation of RR (pRB) by active cyclin-CDK complexes leads to release of E2F transcription factors and the transcription of genes required for S-phase entry. CDK4/6 inhibitors, by inhibiting RB phosphorylation, induce a cell cycle arrest in RB proficient cancer cells. CyclinD1-CDK4/6-Rb pathway is critical for the development and maintenance not only of ER+ but also of HER2+ tumors [Migliaccio et al., 2014] and molecular alterations involving the RB pathway frequently occur both in ER+ and in HER2+ BC [Cancer Genome Atlas, 2012]. Indeed, preclinical studies demonstrated that ER+ or HER2+ cell lines are the most sensitive to inhibition by CDK4/6 inhibitors and that combination of CDK4/6 inhibitors and ET or CDK4/6 inhibitors and anti-HER2 agents are synergistic in ER+ or HER2+ BC models, respectively [Finn et al., 2009]. CDK4/6 pathway activation is a well-known mechanism of resistance to endocrine therapy [Migliaccio et al., 2014], indeed CDK4/6 inhibitors have shown activity in cellular models of acquired resistance to endocrine therapies [Wardell et al., 2015]. Also, palbociclib showed activity in cellular models of acquired resistance to lapatinib indicating that activation of the pathway might be implicated in resistance to such agents [Witkiewicz et al., 2014]. These data collectively indicate that CDK4/6 are therapeutic targets that function downstream of both ER and HER2 pathways. Therefore tumors co-expressing ER and HER2 might be the most sensitive to CDK4/6 inhibition.

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	Genetic loss of *RB1* is a marker of primary resistance to CDK4/6 inhibitors but it is uncommon in HR+ or HER2+ subtypes. Recent studies have shown that functional loss of the CyclinD1/CDK4-6/RB pathway can be measured by gene-expression studies. Several gene-signatures of RB-loss have been developed which have shown to be prognostic in breast cancer subtypes as well as predictive of response to neoadjuvant chemotherapy [Witkiewicz et al., 2012; Herschkowitz et al., 2008]. A recently developed gene-signature of functional loss of RB (RBsig) that is prognostic in luminal breast cancer subtypes can predict response to the CDK4/6 inhibitor palbociclib in cell line models of breast cancer [Malorni et al., 2016]. In particular, cell lines with increased levels of RBsig (RBsig HIGH) are among the most resistant to palbociclib treatment. Additionally, preliminary data suggest that the RBsig might be also predictive of response to chemotherapy + trastuzumab in ER+/HER2+ breast cancer patients. Indeed, we performed a retrospective in-silico study using publicly available datasets of gene-expression data (10 studies) obtained from a total of 514 HER2+ BC patients treated with neoadjuvant chemotherapy +/- anti-HER2 therapy. For these patients, we computed the RBsig and correlated the RBsig expression with clinical outcome. The pCR rate to neoadjuvant CT + anti-HER2 for patients with RBsig LOW expression was significantly lower than the pCR rate for patients with RBsig HIGH expression. Results were similar for patients receiving neoadjuvant CT alone. Of note, the relationship between RBsig and pCR was observed only in HER2+/ER+, and not in HER2+/ER-negative tumors, suggesting that, as expected, RBsig seems to be relevant only in tumors with a luminal phenotype. These data suggest that RBsig identifies a subset of HR+/HER2+ patients (RBsig LOW) who derive little benefit from chemotherapy. Taken together, our data suggest that, among patients with ER+/HER2+ BC, those with RBsig HIGH derive benefit from chemotherapy and might be resistant to CDK4/6 inhibitors. Conversely, patients with RBsig LOW BC who derive little benefit from chemotherapy may benefit from CDK4/6 inhibitors. Based on this rationale, we hypothesize that the CDK4/6 inhibitor palbociclib in combination with the anti-HER2 trastuzumab + pertuzumab and the endocrine therapy letrozole may be effective neoadjuvant therapy in patients with ER+/HER2+ BC, especially in the subset of RBsig LOW patients. We also hypothesize that patients with RBsig HIGH ER+/HER2+ BC might be particularly sensitive to neoadjuvant chemotherapy with paclitaxel and trastuzumab + pertuzumab. In 2019, it is estimated that of 260,600 newly diagnosed cases of invasive breast cancer in the United States, 82% occurred in women aged 50 or over. Furthermore, of the 41,760 breast cancer-related deaths in the same year, 90% occurred in this predominantly post-menopausal age group [American Cancer Society, 2019]. Around 40% of breast cancers occur in women aged 65 and older. Of these, 10-15% have tumors that overexpress HER2 [Musgrove et al., 2011; Turner et al., 2015]. Jenkins et al. recently showed that among patients with HR+/HER2+ tumors, BC subtypes vary with age with luminal B tumors ranging from 20% in patients aged <60 years to 50% in patients over 60 [Jenkins et al., 2014]. Elderly patients are generally underrepresented in clinical trials; subgroup analyses have shown that they benefit from anti-HER2 agents as much as the younger population [Biganzoli et al., 2012; Miles et al., 2013; Syed et al., 2014]. Overall a higher incidence of adverse events has been observed in the elderly, mainly related to the chemotherapy backbone of the treatment [Miles et al., 2013]. For this trial, we have therefore chosen 4 cycles of weekly paclitaxel with a 3 out of 4 weeks schedule [Biganzoli et al., 2016]. Palbociclib can be safely and effectively administered to older patients without requiring dose adjustment based solely on age [Rugo et al., 2017]. De-escalation of chemotherapy is of particular appeal in the older population. Recruitment of older women and prospective use of geriatric assessment instruments in those aged ≥65 will produce valuable safety and efficacy data within this under-represented subgroup.

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Primary Objective and Endpoint	The primary objective is to explore the interaction between the RBsig status (HIGH or LOW) and treatment activity, assessed by pathological complete response (pCR), of palbociclib + letrozole versus paclitaxel when given with trastuzumab + pertuzumab) for ER+/HER2+ primary BC. The study hypothesis is that, - in patients with RBsig LOW, trastuzumab + pertuzumab + palbociclib + letrozole will be more active than trastuzumab + pertuzumab + paclitaxel, - while in patients with RBsig HIGH, trastuzumab + pertuzumab + paclitaxel will be more active than trastuzumab + pertuzumab + palbociclib + letrozole. Primary endpoint: Pathological complete response pCR, defined as absence of invasive tumor cells in the breast and in the axillary lymph nodes at the time of surgery (ypT0/ypTis ypN0).
Secondary Endpoints	• pCR in breast only • Objective response prior to surgery, defined as partial or complete response assessed clinically and by ultrasound and/or mammography • Tolerability, as defined by adverse events according to CTCAE version 5 • Rate of breast-conserving surgery
Number of patients	Randomization of 144 patients during approximately 24 months, after a start-up period of 6 months as the trial is being activated by participating Centers. Patients will be followed and documented until End of Treatment visit to be done within 30 days after surgery.
Trial duration	With a start-up period of 6 months during which the sites will be activated, 24 months of recruitment, approximately 5 months after the inclusion of the last patient until End of Treatment visit, and 6 months for completion of the documentation and writing the trial report, the total duration of the trial is estimated to be 41 months after the randomization of the first patient.
Inclusion criteria	• Histologically confirmed invasive breast cancer, with the following characteristics: - Early breast cancer with tumor size >1 cm (as measured by at least one of the required examination methods of clinical examination, mammography and ultrasonography) - No clinical evidence of regional lymph node metastasis (via physical and/or radiological exam) (cN0), OR clinical evidence of cN1 status, defined by nodal involvement limited to clinically detectable metastasis to movable ipsilateral level I, II axillary lymph node(s)) - No evidence of metastasis (M0) • Postmenopausal, defined as women with: - Prior bilateral surgical oophorectomy; OR - Amenorrhea and age ≥60 years; OR - Age <60 years and amenorrhea for 12 or more consecutive months in the absence of alternative pathological or physiological cause (including chemotherapy, tamoxifen, toremifene, ovarian suppression, or hormonally-based contraception) plus FSH and serum estradiol levels within the laboratory's reference ranges for post-menopausal women • Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 • Primary tumor must have positive estrogen receptor (ER) ≥10% • Primary tumor must be HER2-positive (by IHC and/or ISH) • Baseline LVEF ≥55% measured by Echocardiography (preferred) or MUGA scan

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	• Normal hematologic status, - Absolute neutrophil count ≥1500/mm^3 (1.5 × 10^9/L) - Platelets ≥100 × 10^9/L - Hemoglobin ≥9 g/dL (≥90 g/L) • Normal renal function: serum creatinine ≤1.5 ULN • Normal liver function: - Serum total bilirubin ≤1.5 × upper limit of normal (ULN). In the case of known Gilbert's syndrome, a higher serum total bilirubin (<2 × ULN) is allowed - AST or ALT ≤2.5 × ULN - Alkaline phosphatase ≤2.5 × ULN • Written Informed Consent (IC) must be signed and dated by the patient and the Investigator prior to randomization. • The patient has been informed of and agrees to data transfer and handling, in accordance with national data protection guidelines. • The patient agrees in writing to make tumor (**mandatory** diagnostic core biopsy and surgical specimen) available for submission for central pathology review and to conduct translational studies as part of this protocol. **NOTE**: Central Pathology Review on the primary tumor is mandatory for this trial, but patients will be evaluated for eligibility according to tumor characteristics as determined by the local pathologist. Both the diagnostic breast core biopsy specimen and the final breast surgical specimen (unless no residual invasive tumor is found at surgery) must be submitted for Central Pathology Review which will be done by the IBCSG Central Pathology Office in Milan, Italy.
Exclusion criteria	• Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules) (T4 according to AJCC 8th edition cancer staging TNM) • Inflammatory breast cancer • Bilateral invasive breast cancer • Received any prior treatment for primary invasive breast cancer • Any active tumor of non-breast-cancer histology • Any of the following in the previous 6 months: myocardial infarction, severe/unstable angina pectoris, ongoing cardiac dysrhythmias of NCI CTCAE grade ≥2, atrial fibrillation of any grade, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (NYHA functional classification ≥II), cerebrovascular accident including transient ischemic attack, or symptomatic pulmonary embolism • Concurrent disease or condition that would make the subject inappropriate for study participation or any serious medical disorder that would interfere with the subject's safety • Contraindications or known hypersensitivity to any of the trial medications or excipients • Treatment with any investigational agents within 30 days prior to expected start of trial treatment • Any GI disorder that may affect absorption of oral medications, such as malabsorption syndrome or status post major bowel resection • Evidence via physical and/or radiological exam of cN2 or cN3 nodal involvement defined by: metastasis to ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted, OR involvement of ipsilateral infraclavicular, internal mammary and/or supraclavicular lymph node(s) • History of extensive disseminated/bilateral or known presence of interstitial fibrosis or interstitial lung disease, including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, obliterative bronchiolitis, and pulmonary fibrosis. History of prior radiation pneumonitis is not an exclusion criterion.
Assessments	Efficacy: • Breast disease assessment with clinical examination by caliper and bilateral breast ultrasound and mammography will be performed at baseline and before surgery. • A physical tumor examination by caliper should be done after 2 treatment cycles

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	• Evaluation of tumor response will be the task of the Investigator. Scans will not be centrally reviewed. Safety: • Complete blood count will be performed as required by treatment schedule • Blood chemistry will be checked every 4 weeks, prior to the next treatment cycle • Adverse events will be graded according to CTCAE version 5; worst grade of adverse events will be recorded at beginning of next cycle • All Serious Adverse Events must be notified to IBCSG within 24h • End of treatment visit within 30 days after surgery For patients aged ≥65 years: geriatric assessment at baseline: • G8 • Instrumental Activity of Daily Living (IADL) • Charlson Comorbidity Index
Documentation	Electronic Case Report Forms (eCRFs) must be completed in DFexplore
Integral translational research	Pre-treatment biopsy will be analyzed by gene-expression profiling to assess RBsig status.
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. 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 be assessed in the context of this trial.
Randomization and Stratification	Stratification will be performed according to: • Age and G8 score (<65 years vs. ≥65y and G8 score >14 vs ≥65y and G8 score ≤14) • No clinical evidence of regional lymph nodes metastasis (cN0) vs nodal involvement limited to clinically detectable metastasis to movable ipsilateral level I, II axillary lymph node(s) (cN1) Randomization will be in a 1:1 ratio to: Arm A: paclitaxel + trastuzumab + pertuzumab Arm B: palbociclib + letrozole + trastuzumab + pertuzumab
Statistical considerations	For the primary objective, pCR rates are assumed to be:

	A: Paclitaxel + trastuzumab + pertuzumab	B: Palbociclib + letrozole + trastuzumab + pertuzumab	Odds Ratio (B:A)
RBsig LOW	15%	30%	2.429
RBsig HIGH	50%	10%	0.111

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Statistical power for RBsig-by-treatment interaction is summarized below for varied sample sizes and for two-sided alpha error of 0.05, under two assumptions of RBsig prevalence:

Prevalence	**N=100**	**N=110**	**N=120**
RBsig low / high	α=0.05	α=0.05	α=0.05
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 a questionable model*

Power was estimated on the basis of simulations of exact logistic regression test for RBsig-by-treatment interaction, as with the two low expected pCR rates, the appropriateness of an asymptotic method such as that of Demidenko et al., 2008 was uncertain. On the basis of simulations, taking into consideration the frequency with which 0 pCRs occurred in one of the subgroups, we propose an analyzable sample size of 120 patients with successful RBsig results. The enrolled sample size is inflated by 20% to 144 to account for non-assessable RBsig status (which is determined after randomization).

The primary analysis will use exact logistic regression to test RBsig-by-treatment interaction and estimate the odds ratios for Arm B vs. A according to RBsig (rate ratios and rate differences will also be estimated; all with alpha-level confidence intervals).

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2. Trial schedule

2.1. Arm A (paclitaxel, trastuzumab, pertuzumab)

	≤4 weeks prior to rando	week																Up to 4 weeks prior to surgery	30 days after surgery
week		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16		
Informed consent	x																		
History	x																		
Physical examination, ECOG PS	x	Day 1 of every paclitaxel cycle																x	x
Baseline comorbidities	x																		
Adverse events		At the end of every cycle: all grades for targeted events, all grade 3/4 non-targeted events; record grade 2 non-targeted events only if they require relevant medical intervention																	SAEs only
Geriatric assessment (for patients aged ≥65 years)	x																		
Neoadjuvant Treatment																			
Paclitaxel 80 mg/m^2 [1]		x	x	x		x	x	x		x	x	x		x	x	x			
Trastuzumab 600 mg [2]		x			x			x			x			x					
Pertuzumab 420 mg [3]		x			x			x			x			x					
Laboratory tests																			
Hematology[4]	x	Prior to every dose of paclitaxel																x	
Blood chemistry[5]	x	Prior to every paclitaxel cycle																x	
Tumor Evaluation																			
Caliper/ruler	x								x*									x	
Mammography[6]	x																	x	
Breast Ultrasound[6]	x																	x	
Chest x-ray or CT[7]	√																		
Abdominal US or CT [8]	√																		
Bone scan[9]	√																		

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	≤4 weeks prior to rando	week																Up to 4 weeks prior to surgery	30 days after surgery
week		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16		
Other tests																			
Electrocardiogram (ECG)	x																	x	
Echocardiography (preferred) or MUGA scan	x							x*										x	
Pathology eval. (local)	x																		x
FFPE sample[10]	x																		x

x = mandatory √ = if medically indicated * = ±1 week # only SAEs

Legend for trial schedule:

Neoadjuvant treatment: 4 cycles of 28 days each

1. Paclitaxel 80 mg/m^2 i.v. on day 1,8,15 for four cycles of 28 days
2. Trastuzumab 600 mg s.c. every 3 weeks for a total of 5 doses
3. Pertuzumab 840 mg i.v. loading dose followed by 420 mg i.v. every 3 weeks for a total of 5 doses.

Laboratory tests

4. Hematology (Hemoglobin, platelet count, white blood cell count including differential (absolute neutrophil count) must be done within 14 days prior to randomization, on day 1 or within 3 days prior to every paclitaxel dose, and at the visit prior to surgery.
5. Blood chemistry (creatinine, alkaline phosphatase, AST or ALT, total bilirubin) must be done within 14 days prior to randomization, on day 1 or within 3 days prior to every 28 day paclitaxel cycle, and at the visit prior to surgery.

Tumor evaluation

6. Bilateral mammography, and tumor assessments by breast/axilla palpation and ultrasound (caliper/ruler measurement) must be done prior to randomization, and prior to surgery. A tumor assessment (breast/axilla palpation and caliper measurement) should be done after 2 paclitaxel cycles.
7. Chest X-ray or CT scan, if medically indicated; not required in patients who have undergone a PET scan.
8. Abdominal ultrasound or CT scan, if medically indicated not required in patients who have undergone a PET scan.
9. Bone scan if medically indicated. Requiredif the patient has unexplained bone pain; not required in patients who have undergone a PET scan.

Biological material

10. A formalin-fixed, paraffin-embedded (FFPE) tumor block from core biopsy at diagnosis and from surgery (if not pCR) must be submitted for central pathology review and for gene-expression profiling to assess RBsig status and future translational research studies.

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2.2. Arm B (palbociclib, letrozole, trastuzumab, pertuzumab)

	≤4 weeks prior to rando	week																Up to 4 weeks prior to surgery	30 days after surgery
week		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16		
Informed consent	x																		
History	x																		
Physical examination, ECOG PS	x	Day 1 of every palbociclib cycle																x	x
Baseline comorbidities	x																		
Adverse events		At the end of every cycle: all grades for targeted events, all grade 3 and 4 non-targeted events; record grade 2 non-targeted events only if they require relevant medical intervention																	SAEs only
Geriatric assessment (for patients aged ≥65 years)	x																		
Neoadjuvant Treatment																			
Palbociclib 125 mg/day [1]		.....daily ♯.....				.....daily ♯.....				.....daily ♯.....				.....daily ♯.....					
Letrozole 2.5 mg/day [2]		.....daily.....																	
Trastuzumab 600 mg [3]		x			x			x			x			x					
Pertuzumab 420 mg [4]		x			x			x			x			x					
Laboratory tests																			
Hematology[5]	x	Day 1 and 14 during the first two palbociclib cycles, then on day 1 of cycles 3 and 4																x	
Blood chemistry[6]	x	Prior to every palbociclib cycle																x	
Tumor Evaluation																			
Caliper/ruler	x								x*									x	
Mammography[7]	x																	x	
Breast Ultrasound[7]	x																	x	
Chest x-ray or CT[8]	√																		
Abdominal US or CT[9]	√																		
Bone scan[10]	√																		
Other tests																			

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	≤4 weeks prior to rando	week																Up to 4 weeks prior to surgery	30 days after surgery
week		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16		
Electrocardiogram (ECG)	x																	x	
Echocardiography (preferred) or MUGA scan	x							x*										x	
Pathology eval. (local)	x																		x
FFPE sample[11]	x																		x

x = mandatory √ = if medically indicated * = ±1 week ♯ = check patient diary; hand out new patient diary for next cycle

Legend for trial schedule:

Neoadjuvant treatment: 4 cycles of 28 days each

1. Palbociclib 125 mg/day orally for 21 days followed by 7 days rest, for 4 cycles.
2. Letrozole 2.5 mg/day orally, continuously for 16 weeks
3. Trastuzumab 600 mg s.c. every 3 weeks for a total of 5 doses
4. Pertuzumab 840 mg i.v. loading dose followed by 420 mg i.v. every 3 weeks for a total of 5 doses

Laboratory tests

5. Hematology (Hemoglobin, platelet count, white blood cell count including differential (absolute neutrophil count)) must be done within 14 days prior to randomization, on day 1 (or within 3 days prior) and day 14 during the first two palbociclib cycles, then on day 1 (or within 3 days prior) of cycles 3 and 4, and at the visit prior to surgery.
6. Blood chemistry (creatinine, alkaline phosphatase, AST or ALT, total bilirubin) must be done within 14 days prior to randomization, prior to every palbociclib cycle, and at the visit prior to surgery.

Tumor evaluation

7. Bilateral mammography, and tumor assessments by breast/axilla palpation and ultrasound (caliper/ruler measurement) must be done prior to randomization and prior to surgery. A tumor assessment (breast/axilla palpation and caliper measurement) should be done after 2 palbociclib cycles.
8. Chest X-ray or CT scan, if medically indicated; not required in patients who have undergone a PET scan.
9. Abdominal ultrasound or CT scan, if medically indicated; not required in patients who have undergone a PET scan.
10. Bone scan if medically indicated. Required if the patient has unexplained bone pain; not required in patients who have undergone a PET scan.

Biological material

11. A formalin-fixed, paraffin-embedded (FFPE) tumor block from core biopsy at diagnosis and from surgery (if not pCR) must be submitted for central pathology review and for gene-expression profiling to assess RBsig status and future translational research studies.

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3. List of abbreviations

AE	Adverse event
AESI	Adverse event of special interest
AI	Aromatase Inhibitor
AJCC	American Joint Committee on Cancer
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute Neutrophil Count
AST	Aspartate transaminase
BC	Breast Cancer
BIG	Breast International Group
BSC	Breast-Conserving Surgery
CBR	Clinical Benefit Rate
CDK	Cyclin Dependent Kinase
CHF	Congestive Heart Failure
CI	Confidence interval
CNS	Central Nervous System
CPO	Central Pathology Office
CR	Complete Response
CRF	Case Report Form
CT	Computed tomography
CTCAE	Common toxicity criteria for adverse events
CYP3A	Cytochrom P450 3A4
DC	Disease control
DMC	Data Management Center
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EEA	European Economic Area
ET	Endocrine Treatment
EoT	End of Treatment
ER	Estrogen receptor
ERB	Ethical Review Board
FDG	Fluoro-D-Glucose
FFPE	Formalin-fixed paraffin-embedded
FISH	Fluorescence in situ hybridization
FLT	Fluorothymidine
FSTRF	Frontier Science and Technology Research Foundation
GCP	Good clinical practice
GGT	Gamma-Glutamyl Transferase
HER2	Human Epidermal Growth Factor Receptor 2
HIV	Human Immunodeficiency Virus
HR	Hormone Receptors
IADL	Instrumental Activities of Daily Living
IB	Investigator's Brochure
IBCSG	International Breast Cancer Study Group

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IC	Informed consent
IC50	Half Maximal Inhibitory Concentration
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
INR	International Normalized Ratio
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISH	In Situ Hybridization
LHRH	Luteinizing Hormone-Releasing Hormone
LPD	Largest Perpendicular Diameter
MBC	Metastatic breast cancer
MD	Maximal Diameter
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTOR	Mechanistic Target of Rapamycin
NAT	Neoadjuvant Treatment
NCI	National Cancer Institute
NE	Not Evaluable
NIMP	Non-Investigational Medicinal Product
NYHA	New York Heart Association
OHRP	Office for Human Research Protection
ORR	Overall response rate
pCR	Pathological Complete Response
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression free survival
PgR	Progesterone receptor
PI	Principal Investigator
PIS/IC	Patient information sheet / informed consent
PR	Partial response
pRb	Phosphorylated Retinoblastoma
PS	Performance status
PT	Prothrombin Time
QD	Once daily (Quaque Die)
QTc	Corrected QT Interval
Rb	Retinoblastoma
RR	Response Rate
SAE	Serious adverse event
SD	Stable disease
SPC	Summary of Product Characteristics
SPIM	Standard Procedures Imaging Manual
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEV	Tumor Evaluation Form
TNM	Tumor-Node-Metastasis
ULN	Upper limit of normal

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4. Background and scientific rationale

4.1. Introduction

About 70% of all invasive breast cancers (BC) express hormone receptors (HR) (Estrogen Receptor – ER and Progesterone Receptor – PgR) and are therefore treated with endocrine therapy (ET). The human epidermal growth factor receptor-2 (HER2) is overexpressed and/or amplified in about 10-20% of BC. Until recently, HER2 positive (HER2+) BC has been considered as a single entity, yet studies are increasingly demonstrating that HER2+ BCs are clinically and biologically heterogeneous. Around 50% of the HER2+ tumors co-express ER, dividing HER2+ patients in two main subgroups (HR-neg/HER2+ and HR+/HER2+).

Patients with HR+/HER2+ BC represent a unique group of patients with an unmet clinical need. This population is the focus of this trial.

4.2. Neoadjuvant treatment in HR+ and HER2+ BC

Neoadjuvant therapy (NAT) (also called preoperative or primary systemic therapy) is delivered before surgical treatment and has historically been used mainly for locally advanced or inflammatory BC, because of its ability to downstage the disease and to favor operability in primary inoperable breast tumors.

More recently, NAT use has become increasingly common also for patients with operable disease for a number of reasons including: a) tumor downsizing with a subsequent increased chance to achieve breast conserving surgery b) early treatment of distant micro-metastases c) selection of individualized therapy by early detection of treatment failures. NAT also offers a unique platform in clinical research to rapidly evaluate new drugs or treatment modalities to be further studied in other clinical settings.

One of the main therapeutic goals of NAT is pathological complete response (pCR). The frequency of pCR following NAT varies among, and also within, BC subtypes.

Triple negative and HER2+ BCs have the highest pCR rates after NAT, while HR+ tumors achieve lower pCR rates. Within HR+ tumors, pCR rates are particularly low for patients with low-grade tumors, while they are more than doubled for patients with high-grade tumors. Within HER2+ tumors, HR status also affects the pCR rates after neoadjuvant chemotherapy, pCR being less common for HR+ compared to HR negative BCs [1].

Several studies revealed an association between pCR and improved survival. However, pCR rate has a clear prognostic value only in particular BC subgroups. A recent meta-analysis from von Minckwitz and colleagues [2] including more than 6000 patients showed that, among HER2+ patients, pCR after NAT is prognostic for survival in HR negative BC but not in HR+ BC, irrespective of trastuzumab treatment.

Bhargava and colleagues divided HER2+ BC into three subgroups based on the levels of expression of ER and PgR [3]. These authors reported that the pCR rate and the level of ER expression are inversely correlated.

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Recently, clinical trials of NAT in HER2+ disease (NeoALTTO, NeoSphere, CALGB40601, see below) also showed different response rates to anti-HER2 agents in HR+ vs HR- tumors.

Available current data in the NAT setting suggest that HR+/HER2+ BC behaves differently from HR negative/HER2+ BC, achieving lower pCR rates after neoadjuvant chemotherapy with or without anti-HER2 agents; pCR may not be predictive of outcome in this subtype of BC.

4.3. Endocrine treatment

Endocrine treatment (ET) with aromatase inhibitors (AI), tamoxifen or fulvestrant represents the mainstay of HR+ BC treatment given its efficacy and very limited toxicity. HER2 is a major and well-recognized factor of primary resistance to ET and therefore HR+/HER2+ BC patients are seldom treated with ET alone.

Extensive preclinical and clinical data have shown a complex bi-directional cross talk between ER and HER2 signaling pathways that may have important implication in resistance of HR+/HER2+ tumors to endocrine therapy and anti-HER2 agents [4]. HER2 overexpression or amplification affects endocrine therapy responsiveness; indeed, HR+/HER2+ BC patients treated with letrozole or tamoxifen, showed less Ki67 suppression when compared to HR+/HER2 negative patients, despite similar short-term clinical efficacy [5].

Combining targeted treatments that simultaneously block both signaling pathways is a promising approach to prevent or overcome either endocrine or anti-HER2 therapy resistance in some HR+/HER2+ tumors.

Indeed, several clinical trials have explored this concept both in the metastatic and in the NAT setting. A small phase II trial of trastuzumab and letrozole enrolled 31 evaluable post-menopausal patients with HR+/HER2+ metastatic BC. More than 80% of included patients had received prior tamoxifen [6]. This trial showed an objective response rate of 26% and a clinical benefit rate (CBR) of 52%. The median time to progression was 5.8 months and the median duration of response was 20.6 months, suggesting that durable responses can be seen with combined ET and anti-HER2 therapy.

In the randomized phase II TAnDEM trial, 207 patients with ER+/HER2+ metastatic breast cancer (MBC) were treated with either anastrozole alone or in combination with trastuzumab as first-line therapy. This trial demonstrated that the 2-year progression-free survival (PFS) rate was about 15% with anastrozole plus trastuzumab and only 5% with anastrozole alone. No difference in overall survival was seen. Clinical Benefit Rate (CBR) was about 43% with trastuzumab plus anastrozole compared to about 28% with anastrozole alone. Combination treatment was well tolerated with mostly mild to moderate side effects including fatigue (21%), diarrhea (20%), vomiting (21%), and pyrexia (17.5%) [7].

The eLEcTRA trial, compared letrozole alone or with trastuzumab as first line therapy and showed a non-significant trend toward longer PFS with combination therapy. CBR was 65% in the combination arm and 39% in the letrozole alone arm. Also in this trial, the more commonly

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reported symptoms included fatigue (27%), diarrhea (19%), vomiting (19%) and peripheral edema (19%) [8].

The dual HER1/2 (EGFR/HER2) kinase inhibitor lapatinib has also been investigated in combination with hormonal therapy. The EGF30008 trial randomized 1286 patients with ER+ MBC to receive letrozole in combination with lapatinib or placebo as first line therapy. Of these, 219 patients had HER2+ tumors. In the ER+/HER2+ population, there was a large and statistically significant improvement in PFS and the CBR was significantly improved from 29 to 48% with the combination [9].

All these trials in the MBC setting have confirmed that ET and anti-HER2 therapy can be safely and effectively combined.

Only two published trials in early disease setting tested the combination of ET and anti-HER2 agents in HR+/HER2+ BC. In the phase II TBCRC006 study [10], 64 patients with stages I–III HER2+ BC, received lapatinib plus trastuzumab for 12 weeks in the NAT setting. The 39 women with HR+ disease also received letrozole (plus luteinizing hormone-releasing hormone (LHRH) agonist if premenopausal). HR+/HER2+ patients achieved a pCR rate of 21% which was remarkable, given the absence of chemotherapy in the study regimen.

The TBCRC023 trial compared lapatinib plus trastuzumab, adding letrozole (along with ovarian suppression if premenopausal) in HR+ patients, for 12 weeks vs 24 weeks. Longer treatment duration of endocrine therapy and anti-HER2 therapy (without chemotherapy) led to a meaningful increase in pCR rate in HR+/HER2+ BC (33% with 24 weeks vs 9% with 12 weeks of therapy) while pCR rates were quite similar for the ER negative patients, independently from treatment duration [11].

Regarding the choice of ET agent in ER+/HER2+ BC, data suggest a superiority of AI over tamoxifen. The advantage of the AI letrozole over tamoxifen in HR+/HER2+ BC, was shown in a phase III study including 330 postmenopausal women; the difference in response rate (RR) between the two treatment arms, was more evident in HER2+ patients (RR= 88% vs 21%), than in HER2- patients (RR=54% vs 42%) [12].

These results were confirmed in the IMPACT trial, comparing the AI anastrozole vs tamoxifen vs the combination of the two agents; patients with HER2 overexpressing tumors presented a higher response rate with the AI when compared with tamoxifen although the difference was not statistically significant (58% vs 22% vs 31% with anastrozole, tamoxifen, and combination therapy, respectively) [13].

4.4. Chemotherapy

Chemotherapy in combination with anti-HER2 agents remains the most frequently used treatment for HR+/HER2+ BC patients.

pCR rates and outcomes of patients treated with chemotherapy and anti-HER2 agents vary between trials according to the type of chemotherapy and the anti-HER2 agent under study.

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The addition of trastuzumab to primary chemotherapy has significantly improved the pCR rate in HER2+ BC. The first randomized trial was reported by Buzdar and colleagues in 2005 [14]. Patients were randomized to receive taxane and anthracycline-based chemotherapy with or without weekly trastuzumab for a total of 24 weeks. The results were strongly in favor of trastuzumab combination therapy in both the whole population (pCR rate=65.2% versus 26%), and in patients selected by HR status. The updated safety and efficacy data from this trial [15] confirmed the initial findings and showed an improved disease-free survival among trastuzumab-treated patients without clinical cardiac dysfunctions or other relevant toxicities.

In the NOAH trial, neoadjuvant chemotherapy with doxorubicin, paclitaxel, cyclophosphamide, methotrexate and fluorouracil, was administered alone or in combination with trastuzumab. The study included 235 patients with HER2+ BC, 151 of whom had HR+ status. In the overall population, the pCR rate was higher in patients receiving trastuzumab, but the difference between the two treatment arms was more evident in HR negative tumors compared to HR+ tumors (Hazard ratios= 0,46 vs 0,87 in HR- and HR+ respectively). Equally, in terms of event free survival, HR negative patients had a more pronounced benefit from trastuzumab than HR+ patients [16, 17].

The GeparQuattro study [18] evaluated the incorporation of capecitabine into an anthracycline/taxane-based regimen and the concurrent use of trastuzumab in HER2+ patients. Also in this case, HR status was the only factor independently associated with pCR in a univariate and multivariate analysis (pCR rate= 43.5% in HR negative vs 23.4% in HR+).

The phase III ACOSOG Z1041 trial [19] randomized patients to paclitaxel and trastuzumab followed by concurrent 5-fluorouracil + epirubicin + cyclophosphamide (FEC) and trastuzumab compared with FEC alone followed by concurrent paclitaxel and trastuzumab. No difference in pCR rate was found between the two arms, irrespective of hormone receptor status, and pCR rates were lower in those patients with HR+ status (pCR rate=70.4% and 77.6% in HR negative vs. 47.6% and 38.1% in HR+).

Collectively, these data show that, among patients with HER2 + disease, those with HR+ BC derive less benefit from combination of chemotherapy and anti-HER2 agents, compared to patients with HR negative disease.

4.5. Anti-HER2 treatment

Clinically approved anti-HER2 agents include monoclonal antibodies (trastuzumab and pertuzumab), tyrosine kinase inhibitors (lapatinib) or antibody–drug conjugates (T-DM1).

Trastuzumab was the first anti-HER2 agent used as chemotherapy partner in HR+/HER2+ tumors. However, preclinical data have suggested that a more complete inhibition of the HER2 pathway by means of dual blockade with trastuzumab and lapatinib could be a more efficacious treatment strategy.

The dual combination of the anti-HER2 agents lapatinib and trastuzumab with chemotherapy was used in the in the NSABP B-41 [20], NeoALTTO trial [21], CALGB 40601 trial [22], and CHER-

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LOB trial [23], and was associated with higher pCR rates compared with single-agent anti-HER2 treatments independent of the receptor status.

Regarding toxicity, all the trials including a lapatinib + trastuzumab arm showed consistently that the addition of lapatinib increases the incidence of class-specific side effects such as diarrhea, rash and liver toxicity.

The positive results in the NAT setting in terms of activity of the dual blockade with trastuzumab and lapatinib were not replicated in the post-operative adjuvant setting. In the phase III ALTTO trial, a total of 8,331 patients with operable HER2+ BC were randomized to receive either lapatinib concurrently with trastuzumab, trastuzumab followed by lapatinib, lapatinib alone, or trastuzumab alone. The lapatinib-alone arm was closed early due to demonstrated superiority of trastuzumab over lapatinib alone. No significant difference between the lapatinib plus trastuzumab and the trastuzumab alone arms was observed in terms of the primary endpoint disease free survival (DFS) [24].

Given these unexpected results, along with the tolerability data from the NAT studies, the dual blockade with trastuzumab and lapatinib is not clinically indicated in the NAT setting.

Trastuzumab has also been evaluated in combination with pertuzumab in the NAT setting.

In the phase II NeoSphere trial 417 patients with HER2+ BC were randomized to one of the four following treatment arms: 1) trastuzumab + docetaxel; 2) pertuzumab + docetaxel; 3) trastuzumab and pertuzumab + docetaxel; or 4) trastuzumab and pertuzumab without chemotherapy prior to breast surgery. After surgery, all groups received additional chemotherapy + trastuzumab. This study showed that patients who were given the dual blockade of pertuzumab and trastuzumab plus docetaxel had a significantly improved pCR (45.8%) compared with those given trastuzumab with docetaxel (29%) or pertuzumab with docetaxel (24%). In this study, pCR rates in the docetaxel-trastuzumab-pertuzumab arm were higher in patients with HR negative (63.2%) compared to HR+ (26%) tumors. This was also observed in the chemo-free dual HER2 blockade arm (27.3% vs 5.9%) [25].

In the phase II TRYPHAENA study, pertuzumab and trastuzumab were combined with different chemotherapy regimens. Patients randomized to arms A and B received three cycles of FEC followed by three cycles of docetaxel and were randomized to start the combination of pertuzumab and trastuzumab with cycle 1 of FEC (Arm A) or with cycle 1 of docetaxel (Arm B). Patients randomized in Arm C received six cycles of concurrent docetaxel, carboplatin and pertuzumab plus trastuzumab [26].

All three treatment regimens were highly active; indeed a pCR was seen in 50.7% (Arm A), 45.3% (Arm B) and 51.9% (Arm C). Higher pCR rates were observed in patients with HR negative disease (79.4%, 65% and 83.8% for arms A, B and C, respectively) than in patients with HR+ disease (46.1 %, 48.6% and 50% for Arm A,B and C, respectively). TRYPHAENA was not intended to evaluate superiority of any arm, with all three arms being experimental. However this study showed that pertuzumab does not increase the rate of cardiac dysfunction observed with the combination of trastuzumab plus standard chemotherapy.

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The results from the NeoSphere trial drove the FDA approval of pertuzumab for neoadjuvant treatment of HER2+ BC.

The combination of trastuzumab and pertuzumab was also tested in the APHINITY trial, a randomized, double-blind, placebo controlled study, evaluating adjuvant pertuzumab plus trastuzumab plus chemotherapy vs trastuzumab plus placebo plus chemotherapy [27]. The study met the primary objective, indeed the addition of pertuzumab to trastuzumab was shown to lower the chance of developing recurrent invasive BC by 19% compared to trastuzumab alone. However the absolute benefit from adding pertuzumab was lower than 1% against increased toxicity and costs. A bigger benefit was observed only in high risk patients with node positive or ER-negative disease.

Since August 2013, a subcutaneous formulation of trastuzumab has been available for patients with HER2-positive early and MBC. The subcutaneous formulation is administered as a fixed dose of 600 mg over a period of up to 5 minutes. The efficacy of subcutaneous versus intravenous trastuzumab as neoadjuvant/adjuvant therapy in patients with HER2-positive BC was evaluated in the HannaH study [28, 29]. This phase III, open-label, multinational study compared subcutaneous with intravenous administration and found comparable pharmacokinetics, efficacy and tolerability for both administration forms of trastuzumab. Furthermore, in the randomized, open-label, multinational, crossover study PrefHer, neoadjuvant/adjuvant or adjuvant subcutaneous administration of trastuzumab was preferred over intravenous administration by patients, mainly because it was time saving and induced less pain and discomfort [30, 31].

In the recent Phase III KATHERINE study, 1486 patients with HER2-positive early breast cancer who were found to have residual disease in the breast or axilla at surgery after neoadjuvant taxane-containing chemotherapy were randomized to receive adjuvant trastuzumab emtansine (T-DM1) or trastuzumab for 14 cycles. T-DM1 reduced the risk of recurrence of invasive breast cancer or death by 50% compared to adjuvant trastuzumab alone (95% CI, 0.39-0.64, $p<0.001$), with a 3-year invasive disease-free survival rate of 88.3% in the T-DM1 group, versus 77% in the trastuzumab group [32].

4.6. CDK inhibition

Cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors are bringing great improvements in the management of patients with HR+/HER2neg advanced BC. Three different CDK4/6 inhibitors (palbociclib, abemaciclib and ribociclib) are in clinical development in this patient subgroup, mostly in combination with endocrine therapy.

CDK4 and 6 control transition from the G1 to the S phase of the cell cycle by binding to D-type cyclins. A primary target of CDK action is the retinoblastoma susceptibility gene product (Rb), which mediates G1 arrest through sequestration of transcriptional factors of the E2F family. Phosphorylation of Rb (pRb) by active cyclin-CDK complexes leads to release of E2F transcription factors and transcription of requisite genes for S-phase entry. CDK4/6 inhibitors, by inhibiting Rb phosphorylation, induce a cell cycle arrest in Rb proficient cancer cells [33]. CyclinD1-CDK4/6-Rb pathway is critical for the development and maintenance not only of ER+

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but also of HER2+ tumors [34] and molecular alterations involving the Rb pathway frequently occur both in ER+ and in HER2+ BC [35]. Indeed, preclinical studies demonstrated that ER+ or HER2+ cell lines are the most sensitive to inhibition by CDK4/6 inhibitors and that combination of CDK4/6 inhibitors and ET or CDK4/6 inhibitors and anti-HER2 agents are synergistic in ER+ or HER2+ BC models, respectively [36]. CDK4/6 pathway activation is a well-known mechanism of resistance to endocrine therapy [37], indeed CDK4/6 inhibitors have shown activity in cellular models of acquired resistance to endocrine therapies [38]. Little is known about the role of CDK4/6 pathways in anti-HER2-targeted therapies resistance. However palbociclib showed activity in cellular models of acquired resistance to lapatinib indicating that activation of the pathway might be implicated in resistance to such agents [39]. These data collectively indicate that CDK4/6 is a therapeutic target that functions downstream of both ER and HER2 pathways. Therefore tumors co-expressing ER and HER2 might be more sensitive to CDK4/6 inhibition.

Notwithstanding this rationale, to date there is a lack of data on the effect of the addition of CDK4/6 inhibitors to the combination of endocrine and HER2-targeted therapies in tumors co-expressing ER and HER2 and there are only very few clinical trials assessing the combination in patients with ER+/HER2+ BC.

4.7. Palbociclib

Palbociclib has been granted approval both in the U.S. and more recently in Europe for the treatment of HR+/HER2neg advanced BC in combination with the hormonal treatments letrozole and fulvestrant given the unprecedented results in terms of efficacy of two pivotal clinical trials (PALOMA-2 and PALOMA-3) [40, 41]. Palbociclib and other CDK4/6 inhibitors, have also shown a good toxicity profile.

Palbociclib is a selective ATP-competitive, orally-administered inhibitor of CDK4 and CDK6 and was the first compound of this class to be developed and tested in clinical trials. Palbociclib is highly specific for CDK4 (IC50, 0.011 μmol/L) and CDK6 (IC50, 0.016 μmol/L). It exerts G1 arrest with consequent anti-proliferative activity in vitro and prevents tumor growth in vivo in an array of Rb-positive tumor cells [42, 43]. Palbociclib was first studied in two phase I dose escalation trials in patients with advanced solid tumor or non-Hodgkin's lymphoma with histologically proven Rb tumor expression [44, 45]. These studies revealed that hematological toxicity in general is common with this agent. Grade 3 or 4 hematological adverse events consisted of lymphopenia (36%), neutropenia (24%), leucopenia (21%), thrombocytopenia (9%) and anemia seen in a single patient (3%). The most common non-hematological adverse events were fatigue, nausea and diarrhea. However, treatment was generally well tolerated and no patient discontinued treatment permanently because of treatment-related adverse events [44]. Tumor responses were observed in non-seminomatous germ cell testicular tumor, liposarcomas, thyroid tumor, melanoma, cholangiosarcoma and angiomyxoma. The recommended phase II dose of palbociclib was 125 mg once daily. Palbociclib subsequently moved into Phase II and III clinical trials in different tumor types, including BC.

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Clinical data from several trials confirmed the activity of CDK4/6 inhibitors in patients with HR positive BC. Although palbociclib showed modest activity (CBR of 21%) when used as a single-agent in a phase II trial (NCT01037790) in heavily pre-treated advanced BC patients, partial responses and stable disease were observed in patients with ER positive tumors [46].

Additional clinical data for palbociclib in combination with endocrine therapy in the metastatic setting come from the seminal randomized phase II PALOMA-1/TRIO-18 trial where the combination of palbociclib plus letrozole was compared to single-agent letrozole in the first line treatment setting for post-menopausal patients with ER-positive/HER2 negative MBC. The study was composed of two parts: Part 1 enrolled patients with ER+/HER2 negative disease with no further biomarker assessment, while Part 2 enrolled patients with tumor harboring Cyclin D1 gene amplification and/or loss of p16. The primary endpoint was Investigator-assessed PFS. A total of 165 patients were randomized in this study (66 patients in Part 1 and 99 patients in Part 2).

The final analysis of primary endpoint showed a statistically significant improvement in PFS for the combination arm (20.2 months) compared to the letrozole (10.2 months) with hazard ratio 0.488 (95% CI: 0.319 to 0.748, 1-sided p=0.0004). Significant improvements in PFS were also seen in both Part 1 and Part 2 when analyzed separately (hazard ratio=0.299 [95% CI: 0.156, 0.572]; 1-sided p=0.0001 for Part 1 and hazard ratio =0.508 [95% CI: 0.303, 0.853]; 1-sided p=0.0046 for Part 2) [47].

These results were further confirmed in a larger phase III, double-blind, registration trial with the same design, namely the PALOMA-2 trial. In this trial, 666 postmenopausal women with ER-positive, HER2-negative BC, who had not received prior treatment for advanced disease, were randomized in a 2:1 fashion to receive palbociclib plus letrozole or placebo plus letrozole. The primary end point was PFS, as assessed by the Investigators. Results showed that the median PFS was 24.8 months (95% confidence interval [CI], 22.1 to not estimable) in the palbociclib–letrozole group, as compared with 14.5 months (95% CI, 12.9 to 17.1) in the placebo–letrozole group (hazard ratio, 0.58; 95% CI, 0.46 to 0.72; P<0.001). Subgroup analysis did not reveal any subset of patients who received benefit from the combination [41].

In the setting of endocrine pre-treated MBC, results from the phase III PALOMA-3 trial have recently been published [48]. This trial involved patients with ER-positive/HER2-negative MBC that had relapsed or progressed during prior ET. Patients were randomized in a 2:1 ratio favoring the combination arm, to receive palbociclib and fulvestrant or placebo and fulvestrant. Premenopausal or perimenopausal women were eligible and also received the LHRH agonist goserelin. Patients who had received one line of prior chemotherapy for the treatment of metastatic disease were eligible for this trial. A total of 521 patients were randomized in this study, 347 in the palbociclib and fulvestrant arm and 174 in the palbociclib and placebo arm. The majority of the patients were post-menopausal (79.3% in both arms) and had received one or more prior lines of therapy for metastatic disease (patients who had received no prior treatment for metastatic disease represented 24.2% and 25.9% of the trial population in the palbociclib + fulvestrant and the placebo + fulvestrant arms, respectively). The study met its primary objective,

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showing improved median PFS of 9.2 months with palbociclib and fulvestrant and 3.8 months with placebo and fulvestrant, corresponding to a hazard ratio 0.42 (95% CI, 0.32 to 0.56, p<0.001) [48].

Overall survival analysis of the phase II PALOMA 1 ([49] Finn R.S. ASCO 2017) showed a numerical but not statistically significant superiority of the combination treatment versus the single agent arm. However, it must be noted that this study was not powered to detect a significant difference in overall survival. PALOMA-3 demonstrated a statistically insignificant improvement in median overall survival of 34.9 months for palbociclib plus fulvestrant, versus 28.0 months for fulvestrant plus placebo (hazard ratio for death, 0.81; 95% CI 0.64-1.03; p=0.09) [50]. Overall survival data from the first-line PALOMA-2 study are not yet mature.

The toxicity profile of palbociclib appears very favorable. In the above-mentioned single agent trial [46], side effects were mainly hematological, in line with data from the phase 1 trials. Grade 3 and 4 toxicities were limited to transient neutropenia (50%) and thrombocytopenia (21%), and all other toxicities were grade 1/2. Similarly, in the PALOMA-1 study, the most common adverse events in the combination arm were neutropenia, leucopenia, fatigue and anemia [47]. In particular, grade 3-4 neutropenia was reported in 54% of the patients in the combination arm versus 1% of the patients in the letrozole arm. Of note, no cases of febrile neutropenia or neutropenia-related infections were reported and discontinuation rates due to adverse events were 13% in the combination arm versus 2% in the letrozole arm. This was further confirmed in the larger PALOMA -2 trial where the most common grade 3 or 4 adverse events were neutropenia (occurring in 66.4% of the patients in the palbociclib– letrozole group vs. 1.4% in the placebo–letrozole group), leukopenia (24.8% vs. 0%), anemia (5.4% vs. 1.8%), and fatigue (1.8% vs. 0.5%). Febrile neutropenia was reported in 1.8% of patients in the palbociclib–letrozole group and in none of the patients in the placebo–letrozole group. Permanent discontinuation of any trial treatment as a result of adverse events occurred in 43 patients (9.7%) in the palbociclib–letrozole group and in 13 patients (5.9%) in the placebo–letrozole group [41]. Also in PALOMA-3, similar figures were observed in terms of adverse events with toxicities being in line with previous data. The rate of discontinuation due to adverse events was 2.6% with palbociclib and 1.7% with placebo. Hematological toxicities, especially neutropenia, are the most frequently reported adverse events for palbociclib [48]. A recent work investigated the mechanism of palbociclib-induced bone marrow suppression and compared it to that induced by cytotoxic chemotherapeutic agents [51]. The authors demonstrated that, in contrast to chemotherapeutic agents which caused DNA damage and apoptotic cell death in human bone marrow mononuclear cells (hBMNCs), palbociclib did not induce senescence, with hBMNCs resuming proliferation following palbociclib withdrawal. These data, along with clinical data, confirm that the hematological toxicity induced by palbociclib is intrinsically different from the one observed with chemotherapy and is more clinically manageable, inducing less morbidity and complications.

Severe, life-threatening, or fatal interstitial lung disease (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

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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.

4.8. Elderly patients

Around 40% of BCs occur in women aged 65 and older and 20% in women over 75. Older patients have tumors with more favorable biological characteristics when compared with younger postmenopausal patients, i.e., a higher degree of ER and PgR expression, less peritumoral vascular invasion, less HER2 expression, lower proliferative rates, diploidy, and normal p53 [52]. However, some studies suggest that BC in the elderly is not more indolent. In a single-institution analysis by Sigh et al. in a subgroup of elderly patients (>70 years of age) with lymph node-negative disease, BC appeared to be more aggressive, with a greater risk of developing distant metastases compared with younger patients [53]. Similarly, in another single-institution analysis smaller tumors seemed to be associated with increased axillary lymph node involvement [54]. The hypothesis made by the authors was that small BCs in older patients have different behavior because of decreased immune defense mechanisms related to aging. Overexpression of HER2 is reported in 10-15% of older BC patients [33, 40]. Jenkins et al. recently showed that among patients with HR+/HER2+ tumors, BC subtypes vary with age with luminal B tumors ranging from 20% in patients aged <60 years to 50% in patients over 60 [55].

HER2 directed therapy in combination with chemotherapy is the standard of care for HER2 overexpressing BC. Elderly patients are generally underrepresented in clinical trials; only 16% of patients in the key studies of adjuvant trastuzumab were 60 and above [56, 57]. Subgroup analyses have shown that they benefit from anti-HER2 agents as much as the younger population [58-60]. However, in elderly populations, there is a concern for increasing toxicity, especially cardiotoxicity, when these patients also receive anthracycline-based chemotherapy regimens. In a large and recent meta-analysis of randomized and cohort studies including 29,000 women, cardiotoxicity increased from 2.3% in individuals <50 years to 3.5% and 4.9% in those 50-59 years and >60 years of age [61]. In a single-arm study, patients with HER2+ node-negative BC received weekly paclitaxel × 12 and trastuzumab. This regimen has not been evaluated in older cancer patients specifically but, given its safety profile, is an attractive option [62]. Elderly patients are almost unrepresented in neoadjuvant trials. In Geparquinto, for example, only five of 307 patients in the trastuzumab arm were older than 70 [63]. Due to the limited participation of older patients in neoadjuvant trials subgroup analyses by age are not performed.

Limited data are available on the safety and efficacy of pertuzumab in patients ≥65 years of age. NeoSPHERE randomized patients up to the age of 80; no subgroup analysis by age was performed in this study in which patients' median age was 50 [25]. In the Cleopatra trial no significant differences in efficacy of pertuzumab were observed between elderly patients aged 65 to 75 years and adult patients aged <65 years. Diarrhea, fatigue, asthenia, decreased appetite, vomiting, and dysgeusia were reported more frequently in patients 65 years of age or older compared with younger patients. The safety profile of a Cleopatra-like regimen can be improved

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by substituting docetaxel with paclitaxel. No febrile neutropenia or symptomatic left ventricular systolic dysfunction were reported in a phase II study that evaluated paclitaxel in combination with trastuzumab and pertuzumab as first-line treatment for advanced BC (patients median age 53, range 26-84) [64]. No dose adjustment is necessary when pertuzumab is used in the elderly population ≥65 years of age [59].

Subgroup analyses looking at the efficacy and the safety profile of the combination of CDK 4/6 inhibitors with ET have been conducted and recently published [65, 66]. Focusing on palbociclib, Rugo and colleagues have conducted a pooled analysis of data from elderly patients enrolled in randomized phase 2 and 3 trials of palbociclib (PALOMA studies). Overall, among 872 patients treated with palbociclib plus ET, 221 patients (25%) were aged ≥65-74 years while 83 (10%) were aged ≥75 years. Amongst patients aged ≥65 years, 218 (of whom 56 were 75 years old or older) were treated with palbociclib plus letrozole (PL) as first-line therapy, while 86 (of whom 27 were aged ≥75 years) were treated with palbociclib plus fulvestrant. In patients treated with PL, median PFS was significantly improved with the addition of palbociclib to the AI in all age groups. No new safety concerns were identified for palbociclib in elderly patients. Hematologic toxicities were the most frequently registered AEs during palbociclib treatment across all age groups. Most events were of grade 1 or 2 severity, with the exception of neutropenia and leukopenia: neutropenia was reported in 81% of patients treated with palbociclib vs 5% of patients in control group, with similar incidence among patients aged 65-74 years (77% vs 1%) and higher incidence in the ≥75 years-old subgroup (90% vs 3%). Febrile neutropenia was reported in 11 patients receiving palbociclib, including 2 (1%) aged 65-74 years and 2 (1%) aged ≥75 years. Treatment discontinuation due to AE occurred in 77 (9%) in the palbociclib group vs 22 (5%) in the control group. Among patients aged ≥65-74 years, 28 (13%) in the palbociclib group and 8 (6%) in the control group discontinued because of AEs, compared with 16 patients (19%) and 4 (13%) aged ≥75 years. The most common AE leading to permanent discontinuation across all age groups was neutropenia. The authors presented also pharmacokinetics data indicating that no dose adjustment of palbociclib based solely on age is required in elderly patients.

Elderly patients are under-represented in clinical trials and as such, inclusion of older women and the prospective utilization of geriatric assessment instruments in those ≥65 years will produce valuable safety and efficacy data within this subpopulation.

4.9. Biomarkers for CDK4/6 inhibitor activity

Currently, there is a lack of biomarkers to identify patients more likely to achieve a response to CDK4/6 inhibitors. Efforts have been made towards the identification of single biomarkers in the CyclinD1/CDK4-6/RB1 pathway itself or in other co-activating pathways such as the PI3K pathway, but have proven unsuccessful so far. This suggests that single biomarkers may not capture the complex biology of resistance to CDK4/6 inhibitors and that a more thorough evaluation of the pathway activity may be necessary.

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Genetic loss of RB1 is a marker of primary resistance to CDK4/6 inhibitors but it is uncommon in HR+ or HER2+ subtypes. Recent studies have shown that functional loss of the CyclinD1/CDK4-6/Rb pathway can be measured by gene-expression studies [67]. Several gene-signatures of RB-loss have been developed which have shown to be prognostic in BC subtypes as well as predictive of response to neoadjuvant chemotherapy [68, 69].

A recently developed gene signature of functional loss of Rb (RBsig) that is prognostic in luminal BC subtypes can predict response to the CDK4/6 inhibitor palbociclib in cell line models of BC [70]. In particular, cell lines with increased levels of RBsig (RBsig HIGH) are among the most resistant to palbociclib treatment.

Additionally, preliminary data suggest that the RBsig might be also predictive of response to chemotherapy + trastuzumab in ER+/HER2+ BC patients. Indeed, we performed a retrospective in-silico study using publicly available datasets of gene-expression data (10 studies) obtained from a total of 514 HER2+ BC patients treated with neo-adjuvant chemotherapy +/- anti-HER2 therapy. For these patients, we computed the RBsig and correlated the RBsig expression with clinical outcome. The pCR rate to neoadjuvant CT + anti-HER2 for patients with RBsig LOW expression was significantly lower than the pCR rate for patients with RBsig HIGH expression. Results were similar for patients receiving neoadjuvant CT alone. Of note, the relationship between RBsig and pCR was observed only in HER2+/ER+, and not in HER2+/ER− tumors, suggesting that, as expected, RBsig seems to be relevant only in tumors with a luminal phenotype. These data suggest that RBsig identifies a subset of HR+/HER2+ patients (RBsig LOW) who derive little benefit from chemotherapy.

Further validation of RBsig has been shown within the phase III NeoALTTO study, a neoadjuvant trial involving women with HER2+ primary breast cancer, which originally showed that pathological complete response (pCR) rates were significantly improved in patients receiving paclitaxel plus dual HER2 blockade in the form of trastuzumab and lapatinib compared with paclitaxel given with either of the two anti-HER2 agents alone[21]. RNA sequencing data from pre-treatment biopsies derived from NeoALTTO were collected, with RBsig status subsequently correlated with pCR. Overall, the pCR rate was significantly higher in patients with RBsig HIGH tumours than those with RBsig LOW (35% versus 18% respectively; p=0.01). In the subset of patients with HR+/HER2+ disease, a remarkably low pCR rate was observed in those with RBsig LOW status (11%), versus those with RBsig HIGH status (28%) [71].

Taken together, our data suggest that, among patients with ER+/HER2+ BC, those with RBsig HIGH derive benefit from chemotherapy and might be resistant to CDK4/6 inhibitors. On the other end, patients with RBsig LOW who derive little benefit from chemotherapy may benefit from CDK4/6 inhibitors.

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4.10. Trial hypothesis

Based on this rationale, we hypothesize that the CDK4/6 inhibitor palbociclib in combination with the anti-HER2 trastuzumab and the ET letrozole may be active as neoadjuvant therapy in patients with ER+/HER2+ BC, especially in the subset of RBsig LOW patients.

We also hypothesize that patients with RBsig HIGH ER+/HER2+ BC might be particularly sensitive to neoadjuvant chemotherapy with paclitaxel and trastuzumab.

4.11. Overall risk-benefit assessment

Patients with operable HR+/HER2+ BC represent a population for whom standard treatment options include either surgery, most of the time followed by adjuvant chemotherapy + anti-HER2 agents, or NAT. In patients considered fit for chemotherapy, the latter would consist of chemotherapy plus anti-HER2 agents in most cases, as per current recommendations.

We hypothesize that chemotherapy could be safely avoided in this population by using a combination of ET, trastuzumab plus pertuzumab and palbociclib. This regimen would be substantially less toxic compared to standard chemotherapy.

The setting of the NAT is particularly suitable to test our hypothesis because it supports easy monitoring of the effects of therapy therefore minimizing the risk of offering a sub-optimal treatment in the experimental arm. Also, tissue biopsies for the evaluation of the RBsig from each patient may be acquired as part of routine clinical practice, therefore limiting the need for invasive procedures to obtain tissue samples.

The available data provide scientific rationale for the combination of palbociclib, letrozole and trastuzumab plus pertuzumab in this patient population.

4.12. Rationale for the trial design

This is an open label, international, phase II neoadjuvant trial with the primary objective to explore the interaction between the RBsig status (HIGH or LOW, as determined centrally on the mandatory pre-treatment biopsy collected as FFPE specimen) and treatment activity, assessed by pathological complete response (pCR), of palbociclib + letrozole versus paclitaxel when administered in combination with trastuzumab plus pertuzumab for ER+/HER2+ primary BC. The neo-adjuvant setting was chosen to evaluate these therapy combinations in a short time-frame and to provide access to biomaterial both at baseline and after the end of the treatment, at surgery.

Palbociclib is a potent, highly selective, reversible, orally active, inhibitor of CDK 4/6. This compound prevents progression of the cell cycle from G1 into the S phase, therefore inhibiting cell growth. CDK4/6 is a key downstream effector of both the ER and HER2 pathways, representing a major driver of the proliferation and growth of HR+/HER2+ BC cells. In preclinical experiments, palbociclib synergizes with anti-estrogens and also with trastuzumab to cause tumor regression in ER + and HER2+ BC cell lines.

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Clinical data from the HR+/HER2 negative setting show that combinations of palbociclib and letrozole are safe and effective. These combinations have not yet been tested in the HR+/HER2+ population that we include in this trial. However, combinations of trastuzumab and ET, including letrozole have shown to be safe and to have some additional activity compared to ET alone in the HR+/HER2+ population. Therefore, the role of palbociclib in addition to letrozole and trastuzumab plus pertuzumab needs to be further studied. Of note the combination of trastuzumab, pertuzumab, palbociclib and fulvestrant has been recently evaluated in the context of a neoadjuvant trial. The four drug regimen was well tolerated and led to a 30% pCR in breast and 27% in breast and axilla and to a 97% clinical response rate. The authors concluded that overall the data support further evaluation of the approach of multi-signaling block including CDK4/6 inhibition in HER2+ and ER+ BC [72].

Current standard of care for treatment of HER2+ BC incorporates chemotherapy and anti-HER2 agents, with chemotherapy regimens of sequential anthracyclines and taxanes, used as single agents or in combination with other chemotherapy drugs. Trastuzumab is often administered concurrently with a single agent taxane to avoid the possible additive cardiac toxicity of combinations of anthracycline containing regimens and trastuzumab. Additional chemotherapy, depending on the schedule used pre-operatively, can be administered following surgery. Combinations of chemotherapy and anti-HER2 therapy may result in excessive toxicity in patients with ER+ and HER2+ disease, and a non-chemotherapy-based treatment may provide a less toxic treatment without compromising efficacy. However, endocrine therapy alone may not be a sufficient partner for anti-HER2 agents.

A regimen of weekly paclitaxel and trastuzumab plus pertuzumab was chosen as the comparator arm in this trial. This was based on a twofold rationale: i) the particular features of patients included (patients with ER+ and HER2+ BC of limited stage), representing a population where more aggressive chemotherapy may not be justified, and ii) considering that patients participating in the trial may receive additional treatment after surgery, at the discretion of the Investigator. As outlined in the background section, previous trials in this setting have used different schedules of paclitaxel and trastuzumab, and there is no currently defined standard schedule. Duration of the preoperative trastuzumab + paclitaxel treatment varies among clinical trials, ranging from 12 (neoALTTO) to 16 weeks (CALGB40601) of continuous treatment.

Preclinical and clinical rationale exists to support the proposal that palbociclib may represent a valuable option for increasing the activity of ET and anti-HER2 agents, such that a triple combination with these agents could prove superior to a standard treatment with chemotherapy and anti-HER2 agents.

Additionally, further data suggest that the substantial heterogeneity in response observed within the HR+/HER2+ population may be in part resolved by classifying these tumors by means of the RBsig status. This marker may represent a tool to identify the patients who are more likely to benefit from a chemotherapy-free regimen in this population

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The optimal duration of endocrine + anti-HER2 therapy in the pre-operative setting has not been finally determined, with studies suggesting that extending the duration of the combination treatment from 12 to 24 weeks led to improved outcomes (TBCR-023). We hypothesize that the combination of palbociclib, letrozole and trastuzumab plus pertuzumab proposed in this trial will be more efficacious compared to the combinations of anti-HER2 agents and ET reported in other trials. Therefore, we set the duration of treatment in the experimental arm to 16 weeks, consisting of 4 cycles of palbociclib.

The choice of administering paclitaxel in 12 weekly doses over a 16 week period (day 1,8,15 every 28 days) was chosen to match the minimum number of weekly paclitaxel administrations with the total duration of 16 weeks of treatment in the experimental arm. It also matches the paclitaxel + trastuzumab schedule used in the NSABP B-41 trial.

Around 40% of BCs occur in women aged 65 and older. Of these, 10-15% have tumors that overexpress HER2 [33, 40]. Jenkins et al. recently showed that among patients with HR+/HER2+ tumors, BC subtypes vary with age with luminal B tumors ranging from 20% in patients aged <60 years to 50% in patients over 60 [55]. Elderly patients are generally underrepresented in clinical trials; subgroup analyses have shown that they benefit from anti-HER2 agents as much as the younger population [58, 59, 73]. Overall a higher incidence of adverse events has been observed in the elderly mainly related to the chemotherapy backbone of the treatment [59]. For this trial, we have therefore chosen 4 cycles of weekly paclitaxel with a 3 out of 4 weeks schedule [74]. Palbociclib can be safely and effectively administered to older patients without need for dose adjustment based solely on age [66]. Treatment de-escalation, namely harnessing and taking maximum advantage of targeted therapies vs conventional treatment (chemotherapy) in order to limit side effects, is particularly appealing in the older population. Active enrollment of older women and prospective utilization of geriatric assessment instruments in all participating women aged ≥65 will provide much-needed safety and efficacy data in this under-represented population.

5. Trial objectives and endpoints

5.1. Primary objective

The primary objective is to explore the interaction between the RBsig status (HIGH or LOW, as determined centrally on the mandatory pre-treatment biopsy collected as an FFPE specimen) and treatment activity, assessed by pathological complete response (pCR), of palbociclib + letrozole versus paclitaxel when given with trastuzumab plus pertuzumab for ER+/HER2+ primary BC. The pre-treatment biopsy will be analyzed at the end of the trial by gene-expression profiling to assess RBsig status.

5.2. Primary endpoint

Pathological complete response pCR, defined as absence of invasive tumor cells in the breast and in the axillary lymph nodes at the time of surgery (ypT0/ypTis ypN0).

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5.3. Secondary objectives

To evaluate:

- pCR in breast only (ypT0/ypTis)
- Objective response prior to surgery, defined as partial or complete response assessed physically and by ultrasound and mammography
- Tolerability, as defined by adverse events according to CTCAE version 5
- Rate of breast-conserving surgery

5.4. Correlative objectives

Evaluations may be done to identify:

- molecular characteristics of responding tumors by immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), gene expression
- factors at baseline and prior to surgery predictive of response to randomized treatments
- Ki67 proliferation marker changes between baseline and residual invasive tumor at surgery
- For subgroup of women aged ≥65 years, features in geriatric assessments which correlate with (lack of) tolerability of trial treatment

6. Trial design, duration and termination

6.1. Trial design

This is an international, multi-center, randomized phase II trial that will randomize postmenopausal women with histologically confirmed ER+, HER2+ primary breast cancer to receive the combination of palbociclib plus letrozole plus trastuzumab plus pertuzumab or paclitaxel plus trastuzumab plus pertuzumab during a treatment period of 16 weeks prior to surgery. Patients will be randomized in a ratio of 1:1.

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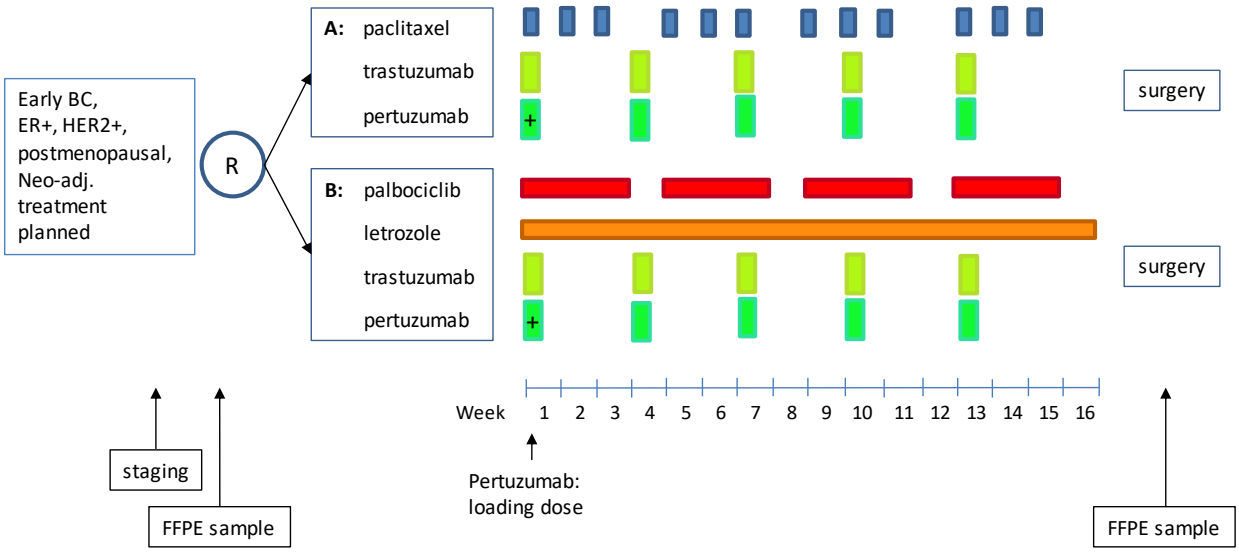
6.2. Trial schema



6.3. Treatment

Patients will be randomized in a 1:1 fashion to:

Arm A: Paclitaxel 80 mg/m^2 i.v. on day 1, 8, 15 every 28 days for 4 cycles

Trastuzumab 600 mg s.c. every 3 weeks for a total of 5 doses

Pertuzumab 840 mg i.v. loading dose followed by 420 mg i.v. every 3 weeks for a total of 5 doses

Arm B: **Palbociclib** 125 mg/day orally for 21 days followed by 7 days' rest, for four 28-day cycles

Letrozole 2.5 mg/day orally for 16 weeks

Trastuzumab 600 mg s.c. every 3 weeks for a total of 5 doses

Pertuzumab 840 mg i.v. **loading** dose followed by 420 mg i.v. every 3 weeks for a total of 5 doses

Definitive surgery should be performed not later than 4 weeks after the final dose of any of the drugs in the combinations described above.

6.4. Clinical evaluations

Tumor assessments will be performed by ultrasound and mammography at screening (prior to start of protocol therapy), and before surgery. Tumor measurements by caliper will be assessed at the same time points and after 2 cycles (8 weeks) of therapy. All patients who are discontinued from the protocol therapy for any reason will be documented within 30 days after surgery. If a patient does not undergo surgery, the end of treatment visit should take place within 30 days after her last dose of trial treatment.

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6.5. Biological evaluations

An FFPE tumor specimen of the pre-treatment biopsy must be submitted for all patients. At surgery, one FFPE tumor specimen for central review and translational research has to be retained, unless no residual invasive tumor is found at surgery. Both specimens will be submitted to the IBCSG Central Pathology Office in Milan, Italy, and will be analyzed by gene-expression profiling to assess RBsig status. The laboratory analyzing RBsig will be defined and carefully selected closer to the time of the analysis, based on their scientific track record.

Gene-expression profiling will also be utilized to explore potential biomarkers of response or resistance to treatment.

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

6.6. Sample size and trial duration

A total of 144 patients will be randomized by approximately 30 sites in Belgium, Italy, France and Switzerland.

The enrollment is expected to occur over a period of 24 months after a start-up period of 6 months as the trial is being activated by participating Centers. Individual patient's trial participation ends with the End of Treatment visit to be done within 30 days after surgery. The final trial analysis is expected 41 months after the randomization of the first patient.

7. Patient selection

7.1. Inclusion criteria

7.1.1. Histologically confirmed invasive breast cancer, with the following characteristics:

- Early breast cancer with tumor size >1 cm (as measured by at least one of the required examination methods of clinical examination, mammography and ultrasonography)
- No clinical evidence of regional lymph node metastasis (via physical and/or radiological exam) (cN0) OR
- Clinical evidence of cN1 status, defined by nodal involvement limited to clinically or radiologically detectable metastasis to movable ipsilateral level I, II axillary lymph node(s)
- No evidence of metastasis (M0)

7.1.2. Postmenopausal, defined by women with:

- Prior bilateral surgical oophorectomy; OR
- Amenorrhea and age ≥60 years; OR
- Age <60 years and amenorrhea for 12 or more consecutive months in the absence of

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alternative pathological or physiological cause (including chemotherapy, tamoxifen, toremifene, ovarian suppression, or hormonally-based contraception) plus FSH and serum estradiol levels within the laboratory's reference ranges for postmenopausal women

7.1.3. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (see Table 1)

7.1.4. Primary tumor must have positive estrogen receptor (ER) ≥10%

7.1.5. Primary tumor must be HER2-positive (by IHC and/or ISH)

7.1.6. Baseline LVEF ≥55% measured by Echocardiography (preferred) or MUGA scan

7.1.7. Normal hematologic status:

- Absolute neutrophil count ≥1500/mm^3 (1.5 × 10^9/L)
- Platelets ≥100 × 10^9/L
- Hemoglobin ≥9 g/dL (≥90 g/L).

7.1.8. Normal renal function: serum creatinine ≤1.5 upper limit of normal (ULN).

7.1.9. Normal liver function:

- Serum total bilirubin ≤1.5 × ULN. In the case of known Gilbert's syndrome, a higher serum total bilirubin (<2 × ULN) is allowed
- AST or ALT ≤2.5 × ULN
- Alkaline phosphatase ≤2.5 × ULN

7.1.10. Written Informed Consent (IC) must be signed and dated by the patient and the Investigator prior to randomization.

7.1.11. The patient has been informed of and agrees to data transfer and handling, in accordance with national data protection guidelines.

7.1.12. The patient agrees in writing to make tumor samples (**mandatory** diagnostic core biopsy and surgical specimen) available for submission for central pathology review and to conduct translational studies as part of this protocol.

NOTE: Central Pathology Review on the primary tumor is mandatory for this trial, but patients will be evaluated for eligibility according to tumor characteristics as determined by the local pathologist. **Both the diagnostic breast core biopsy specimen and the final breast surgical specimen** (unless no residual invasive tumor is found at surgery) **must be submitted** for Central Pathology Review which will be done by the IBCSG Central Pathology Office in Milan, Italy.

7.2. Exclusion criteria

7.2.1. Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration

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or skin nodules) (T4 according to AJCC 8th edition cancer staging TNM)

7.2.2. Inflammatory breast cancer

7.2.3. Bilateral invasive breast cancer

7.2.4. Received any prior treatment for primary invasive breast cancer

7.2.5. Any active tumor of non-breast-cancer histology

7.2.6. Any of the following in the previous 6 months: myocardial infarction, severe/unstable angina pectoris, ongoing cardiac dysrhythmias of NCI CTCAE grade ≥2, atrial fibrillation of any grade, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (NYHA functional classification ≥II, see Table 2 below), cerebrovascular accident including transient ischemic attack, or symptomatic pulmonary embolism.

7.2.7. Concurrent disease or condition that would make the subject inappropriate for study participation or any serious medical disorder that would interfere with the subject's safety.

7.2.8. Contraindications or known hypersensitivity to any of the trial medications or excipients.

7.2.9. Treatment with any investigational agents within 30 days prior to expected start of trial treatment.

7.2.10. Any GI disorder that may affect absorption of oral medications, such as malabsorption syndrome or status post major bowel resection.

7.2.11. Evidence via physical and/or radiological exam of cN2 or cN3 nodal involvement defined by: metastasis to ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted, OR involvement of ipsilateral infraclavicular, internal mammary and/or supraclavicular lymph node(s)

7.2.12. History of extensive disseminated/bilateral or known presence of interstitial fibrosis or interstitial lung disease, including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, obliterative bronchiolitis, and pulmonary fibrosis. A history of prior radiation pneumonitis is not considered an exclusion criterion.

Table 1. ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction.
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.

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PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Table 2. NYHA functional classification

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity.
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

8. Randomization and stratification

This trial will use a web-based randomization system. Specific details for randomization are in the "IBCSG Registration/Randomization Procedures Manual" which is available on the IBCSG website (www.ibcsg.org).

8.1. Randomization

8.1.1. Patient needs to give informed consent to trial participation, screening procedures and biomaterial submission.

8.1.2. Verify eligibility (see Section 7). Screening procedures need to be done within 28 days (hematology within 14 days) before randomization.

8.1.3. For subgroup of women aged ≥65 years: Complete the Geriatric Assessment G8 questionnaire (Form 55-G8) and calculate the total score needed for the stratification.

8.1.4. Access the IBCSG Registration/Randomization System (Registration: Step 1) and provide the requested information as indicated on the Confirmation of Randomization (55-A) Form. The date the Informed Consent Form was signed by the patient and the

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date signed by the Investigator are both required to complete randomization.

The IBCSG Registration/Randomization System will provide the Patient ID (randomization number) and treatment assignment via email.

8.1.5. Submit the Confirmation of Randomization (55-A) electronic case report form (eCRF) via DFexplore.

8.2. Randomization Help Desk

The IBCSG Data Management Center (located at Frontier Science and Technology Research Foundation (FSTRF)) is responsible for developing and maintaining the IBCSG Registration/Randomization System. The Help Desk includes technical personnel and administrators of the registration programs at the Data Management Center in Amherst, NY, USA.

The Help Desk is available round the clock 7 days per week, except for New Year's Eve, Memorial Day, Independence Day, Thanksgiving Day, Christmas Day.

FSTRF Randomization Help Desk
Frontier Science & Technology Research Foundation (FSTRF)
4033 Maple Rd, Amherst, NY 14226 USA
Phone: +1 716 834 0900 Extension 7301
Fax: +1 716 832-8437
Email: bc.helpdesk@frontierscience.org

8.3. Stratification

For randomization, patients will be stratified by

- Age and G8 score (<65 years vs ≥65y and G8 score >14 vs ≥65y and G8 score ≤14), see 14.1.14
- No clinical evidence of regional lymph nodes metastasis (cN0) vs nodal involvement limited to clinically detectable metastasis to movable ipsilateral level I, II axillary lymph node(s) (cN1)

Dynamic institution balancing will be used in order to balance randomized assignments within institutions.

9. Trial drugs formulation and handling

Palbociclib is the Investigational Medicinal Product (IMP) used in this trial; IMP will be supplied.

Trastuzumab and pertuzumab are Non-Investigational Medicinal Products (NIMPs) and used as background treatment in both arms. Both will be supplied.

Letrozole and paclitaxel are part of standard neoadjuvant treatment and will be sourced locally.

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Complete details of the trial drug logistics, distribution, packaging, labeling, storage and handling as well as accountability are described in a separate ***Drug Supply Manual***. This document is available for reference by the pharmacist and trial personnel.

9.1. Palbociclib

9.1.1. Formulation

Refer to the current version of the palbociclib SPC (Summary of Product Characteristics) for pharmaceutical formulation information.

9.1.2. Packaging and labeling

IMP will be affixed with a clinical label in accordance with regulatory requirements.

9.1.3. Storage and handling

Supplies must be stored at 15°C to 30°C in a secure, limited-access location under the storage conditions specified on the label. The Investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

9.2. Trastuzumab

Trastuzumab is used in accordance with the currently approved SPC (Summary of Product Characteristics), and with the applicable EU legislation and current guidelines.

9.2.1. Packaging and labeling

Supplies will be packaged and labeled in accordance with regulatory requirements.

9.2.2. Storage and handling

Supplies must be stored at 2°C to 8°C in a secure, limited-access location under the storage conditions specified on the label.

9.3. Pertuzumab

Pertuzumab is used in accordance with the currently approved SPC (Summary of Product Characteristics), and with the applicable EU legislation and current guidelines. Supplies will be packaged and labelled in accordance with regulatory requirements.

9.3.1. Packaging and labeling

Supplies will be packaged and labelled in accordance with regulatory requirements.

9.3.2. Storage and handling

Supplies must be stored at 2°C to 8°C in a secure, limited-access location under the storage conditions specified on the label.

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9.4. Paclitaxel

Paclitaxel is used in accordance with the currently approved SPC (Summary of Product Characteristics), and with the applicable EU legislation and current guidelines.

9.5. Letrozole

Letrozole is used in accordance with the currently approved SPC (Summary of Product Characteristics), and with the applicable EU legislation.

10. Treatment

10.1. Trial treatments

Trial treatment should start within one week after randomization. Trial treatments will be administered in four 28-day cycles, or until protocol treatment is discontinued (see Section 10.8).

Treatment administration should comply with the protocol; compliance will be monitored by the Monitoring Team and Data Management Center. Complete details of dispensation and dosing are recorded on the eCRF.

10.2. Treatment Administration

10.2.1. Palbociclib administration

Palbociclib will be administered orally at a dose of 125 mg per day continuously dosed for 21 days followed by 7 days rest; repeated at each subsequent cycle. The duration of a cycle of treatment is 28 days. A deviation of 1-3 days from this schedule is permitted. On treatment day 1, patients will be provided with trial treatment for self-administration at home. Sufficient capsules should be provided to cover administration until next scheduled visit. The patients will be instructed to take the trial treatment exactly as prescribed, promoting compliance.

Palbociclib intake should be documented by the patient on the patient diary which will be dispensed for each cycle.

Patients should be instructed to take the palbociclib with food. Concomitant intake of proton pump inhibitors does not significantly affect the overall exposure to palbociclib when taken with food. Patients should be instructed to swallow palbociclib capsules whole and not to chew them prior to swallowing. No capsule should be ingested if it is broken, cracked, or otherwise not intact. Patients should be encouraged to take their dose at approximately the same time each day. Patients should be instructed to record daily administration of the trial drug in the patient diary, and to bring the diary to the clinic at each visit. The Investigator should keep a copy in the patient file.

10.2.2. Trastuzumab administration

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Trastuzumab will be administered at a dose of 600 mg, irrespectively of the patient body weight for a total of 5 doses. Trastuzumab will be administered by s.c. injection according to local guidelines.

10.2.3. Pertuzumab administration

Pertuzumab will be administered at a loading dose of 840 mg on day 1 of cycle 1, and then every 3 weeks at a dose of 420 mg for a total of 5 doses. Pertuzumab will be administered over 30-60 minutes (60 minutes for 840 mg/kg loading dose) by i.v. infusion according to local guidelines.

10.2.4. Paclitaxel administration

Paclitaxel will be administered at a dose of 80 mg/m^2 on days 1, 8, and 15 of every cycle. The administration is by i.v. infusion according to local guidelines.

10.2.5. Letrozole administration

Letrozole will be taken as one tablet of 2.5 mg/day orally continuously during four cycles of 28 days each for a total of 16 weeks. On day 1 of each cycle, one bottle of letrozole tablets will be dispensed to the patient.

Letrozole intake should be documented by the patient on the patient diary which will be dispensed for each cycle.

10.3. Dose delays and modifications for palbociclib

In the event of significant treatment-related toxicity, palbociclib dosing may be interrupted or delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse sign or symptom.

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.

Permanently discontinue palbociclib in patients with severe ILD or pneumonitis.

10.3.1. Dose delays

Patients experiencing the following adverse events should have their treatment of palbociclib interrupted/delayed until criteria for retreatment (see below) are met:

- Grade 3 or 4 neutropenia (ANC<1000/mm^3) associated with a documented infection or fever ≥38.5°C;
- Grade 3 or 4 thrombocytopenia (Platelet count <50,000/mm^3);
- Non-hematologic toxicity persisting <u>despite optimal medical treatment</u> if either grade 2 lasting more than 3 weeks, or grade ≥3 (including nausea, vomiting, diarrhea, and hypertension). Patients should not hold or discontinue palbociclib for non-

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hematological side effects potentially or likely related to concomitant antihormonal therapy (e.g., grade 3 or long lasting grade 2 joint pain) as per the Investigator's judgment;

- In case of concurrent >3×ULN ALT and 2×ULN total bilirubin, the dose needs to be held while the cause is being investigated.

Appropriate follow up assessments should be done until adequate recovery occurs as assessed by the Investigator. Criteria required before treatment can resume are described in the Retreatment Criteria Section (see below).

Doses may be held as needed until toxicity resolution. Depending on when the adverse event resolved, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle or delayed initiation of the subsequent cycle.

If the adverse event that led to the treatment interruption recovers within the same cycle, then resuming treatment in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in the Section 10.3.2, unless expressly agreed otherwise following discussion between the Investigator and IBCSG (please contact ibcsg55_touch@frontierscience.org). If a dose reduction is applied in the same cycle, the patient will need to return to the clinic to receive new drug supply.

In the event of a treatment interruption due to toxicity and for reasons other than treatment-related toxicity (e.g., non-cancer related surgery) lasting >3 weeks, treatment resumption will be decided in consultation with IBCSG (please contact ibcsg55_touch@frontierscience.org).

In the event of palbociclib 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 total delay is >4 weeks, palbociclib should be stopped and treatment should continue with the other drugs.

Retreatment Criteria

Retreatment with palbociclib following treatment interruption for treatment related toxicity or at the start of any new cycle may not occur until all of the following parameters have been met:

- Platelet count ≥50'000/mm^3;
- ANC ≥1000/mm^3 and no fever;
- Grade 3 or higher treatment-related non-hematologic AEs considered related to palbociclib (including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment), have recovered to grade ≤1 or baseline.

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