Statistical Analysis Plan

TRIAL FULL TITLE	ICON: a randomized phase IIb study evaluating immunogenic chemotherapy combined with ipilimumab and nivolumab in patients with metastatic hormone receptor positive breast cancer
SAP VERSION	v1.0
SAP VERSION DATE	05 APR 2022
TRIAL STATISTICIAN	Ragnhild Sørum Falk
Protocol Version (SAP associated with)	v4.3.1
TRIAL PRINCIPAL INVESTIGATOR	Jon Amund Kyte
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1 SAP Signatures

I give my approval for the attached SAP entitled "ICON: a randomized phase IIb study evaluating immunogenic chemotherapy combined with ipilimumab and nivolumab in patients with metastatic hormone receptor positive breast cancer" dated 05 APR 2022.

Statistician Reviewer

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Date: April 8, 2022

Principal Investigator

Name:

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Date: April 8, 2022

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3 Abbreviations and Definitions

AE	Adverse event
ANC	Absolute neutrophil count
BC	Breast cancer
CBR	Clinical benefit rate
CNS	Central nervous system
CR	Complete response by RECIST1.1
CTC	Circulating tumor cells
CTCAE	Common terminology criteria for adverse events
DR	Duration of response
DRR	Durable response rate
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ER	Estrogen Receptor
EPO	Erythropoietin
FQ	Fatigue questionnaire
FAS	Full analysis set
HR	Hormone receptor
HR	Hazard ratio
HER2	Human epidermal growth factor receptor 2
IMP	Investigational medical product
LVEF	Left ventricular ejection fraction
LLN	Lower level normal
MCID	Minimally clinically important difference
MedDRA	Medical dictionary for regulatory activities
MUGA	Multi gated acquisition scan
NYHA	New York Heart Association
NRS	Numerical rating scale
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD-1	Programmed death-ligand 1
PFS	Progression free survival

PLD	Pegylated liposomal doxorubicin
PP	Per protocol
PR	Partial response
RECIST	Response evaluation criteria in solid tumors
iRECIST	Immunotherapy response evaluation criteria in solid tumors
SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ class
TIS	Tumor inflammation signature
TTD	Time to deterioration
ULN	Upper Limit Normal

4 Introduction

4.1 Preface

Breast cancer (BC) is rarely curable after metastasis, and the therapeutic options are limited. Interestingly, the host immune response is strongly predictive for the effect of chemotherapy in subgroups of patients with breast cancer. In the present proposal, we aim at releasing the brake on the immune response by use of ipilimumab, which blocks CTLA-4 and may deplete regulatory T cells, combined with nivolumab (anti PD-1). Importantly, it is possible that non-responders to nivolumab/ipilimumab (nivo/ipi) can be turned responders by use of immunogenic chemotherapy. There is compelling evidence from animal studies, supported by data from humans, that some chemotherapeutic agents are immunogenic. Doxorubicin and cyclophosphamide have been shown to be particularly powerful inducers of immunogenic cell death. Both agents fulfil 5/5 criteria established for assessing the immunogenicity of different chemotherapeutic drugs (Table 1 in [2]). There is also strong evidence from humans, particularly in breast cancer, indicating that the clinical effect of doxorubicin and cyclophosphamide depends on the host immune response [3]. Further, these agents have been shown to induce a Type I interferon immune response in breast cancer [4, 5]. Taken together, there is a strong rationale for synergy between doxorubicin/cyclophosphamide and PD-1/CTLA-4 blockade [6].

In studies conducted at Oslo University Hospital and by a collaborator, we have observed that patients with hormone receptor positive breast cancer are highly diverse with regard to immune activation and up-regulation of inhibitory pathways, including PD1/PD-L1.

We will combine nivolumab and ipilimumab with established 1st choice chemotherapy in patients with metastatic hormone receptor (HR) positive breast cancer. We hypothesize that nivolumab/ipilimumab (nivo/ipi) may

i) potentiate the patient´s spontaneous anti-tumor immune response
ii) synergize with chemotherapeutic agents that induce immunological cell death

The prospect of clinical benefit from immunotherapy is probably best in patients that have not received multiple previous lines of chemotherapy, and we thus aim to bring the nivo/ipi combination into current early line regimes. Our chosen chemotherapeutic regime is a combination of antracyclin and cyclophosphamide, which is an acknowledged option. To facilitate rapid recruitment into the study, we suggest allowing for one previous line of chemotherapy, but with a requirement of good performance status (ECOG 0 or 1) and adequate organ function. Further, we suggest using the chemo drugs in a metronomic fashion (daily cyclophosphamide), rather than as high dose regimes administered every third week. We hypothesize that the metronomic regime will induce immunological cell death and counter T regulatory cells [7], while maintaining the leukocyte counts and the ability of the effector immune cells to respond. Indeed, a low-dose metronomic

cyclophosphamide regime has been used in several cancer vaccine studies, in order to counter regulatory T cells and myeloid suppressor cells . Finally, we will use liposomal doxorubicin (PLD; Caelyx), which minimizes the adverse effects of antracyclins on the heart and allows for continued treatment beyond the otherwise mandatory antracyclin limits. This is of particular importance for immunotherapy, where the aim is to induce long term disease remission. It is important to identify a chemo regime that can be continued for an extended period of time, in combination with nivo/ipi.

4.2 Scope of the analyses

These analyses will assess the safety and efficacy of combining nivolumab and ipilimumab in combination with immunogenic chemotherapy or alone in patients with metastatic hormone receptor (HR) positive/HER-2 negative breast cancer. These analyses will be presented in the final study report. Analyses of the main trial and the cross over part will be published as two separate reports.

5 Study Objectives and Endpoints

5.1 Study Objectives

Primary objectives
Assessment of toxicity of combined treatment with ipilimumab, nivolumab, pegylated liposomal doxorubicin and cyclophosphamide (ipi/nivo/chemo).

Assessment of progression-free survival (PFS) in ipi/nivo/chemo group compared to chemo only group

Secondary objectives
Assessment of clinical response in ipi/nivo/chemo group compared to chemo only group: Objective tumor response rate (ORR), duration of response (DR), durable tumor response rate (DRR; >6 months), clinical benefit rate (CBR), overall survival (OS).

Assessment of toxicity of ipi/nivo (without chemotherapy) in cross-over arm.

Assessment of ORR, DR, DRR, CBR, PFS and OS in cross-over arm receiving ipi/nivo (without chemotherapy).

Assessment of PD-L1 expression, mutation load and immune gene expression as biomarkers for clinical response

Comparison of clinical and biological response in molecular subtypes of breast cancer

Assessment of patient reported outcomes, as measured by the Chalder Fatigue Questionnaire (FQ), an 11 point Numerical Rating Scale (NRS) for pain intensity and EORTC QLQ-C15-PAL

5.2 Endpoints

Primary endpoints
The safety outcome measures will be evaluated in the Full Analysis Set (FAS) population, as follows:

i) Incidence, nature, and severity of adverse events graded according to NCI CTCAE v4.0
ii) Changes in vital signs, physical findings, and clinical laboratory results

The primary efficacy outcome measure is to be assessed in patients evaluable per protocol (PP), as follows:

i) PFS, defined as the time from randomization to the time of radiographic progression (as assessed by RECIST v1.1) or death from any cause during the study.

Secondary efficacy endpoints
The secondary efficacy outcome measures will be assessed in the *PP population, FAS population and in the PD-L1-positive subpopulation* as follows:

Overall survival (OS), defined as the time from the date of randomization to the date of death from any cause.

Objective tumor response rate (ORR), defined as the proportion of patients with an objective tumor response (either partial response (PR) or complete response (CR) using RECIST v1.1).

Durable response rate (DRR), defined as the proportion of patients with an objective tumor response lasting at least 6 months, according to RECIST v1.1.

Clinical benefit rate (CBR), defined as the proportion of patients with an objective tumor response or with stable disease lasting at least 6 months.

Duration of objective response (DOR) among patients with an objective response, according to RECIST v1.1.

PFS in the FAS population and PD-L1-positive subpopulation assessed by RECIST v1.1

PFS, ORR, DRR, CBR and DOR assessed by iRECIST.

PFS, ORR, DRR, CBR and DOR for patients after cross-over, assessed by RECIST v1.1.

PFS, ORR, DRR, CBR and DOR for patients after cross-over, assessed by iRECIST.

OS for patients in the cross-over part, defined as the time from cross over cycle 1 day 1 to death from any cause.

Other Secondary/Exploratory Outcome Measures
Assessment of immunological response

Identification of biomarkers for clinical response, toxicity and immune response, including assessment of PD-L1 expression, mutation load and immune gene expression

Characterization of tumor evolution and changes in immunological milieu induced by the immune/chemo combination therapy, as compared to chemo only, and by ipi/nivo (without chemo) in the cross-over arm

Development in FQ score. The analyses will include time to deterioration (TTD) in the FQ score, defined by a minimally clinically important difference (MCID) of ≥ 3 points. The maximum total FQ

score is 33 points. For mean score, a separate analysis will be performed for subjects with a baseline FQ score ≥ 21 points

Development in NRS pain intensity score. The analyses will include TTD in the pain intensity score, defined by a minimally clinically important difference (MCID) of ≥ 2 points (scale 0-10). For mean score, a separate analysis will be performed for subjects with a baseline score for ≥ 4 points.

Mean changes and TTD in in item 15 (quality of life score) of the EORTC QLQ-C15-PAL, defined by a MCID ≥ 20 points at patient individual level. A change of ≥10 points is considered to be of clinical importance at group level. The development of other scales and items of QLQ-C15-PAL will also be recorded.

6 Study Methods

6.1 General Study Design and Plan

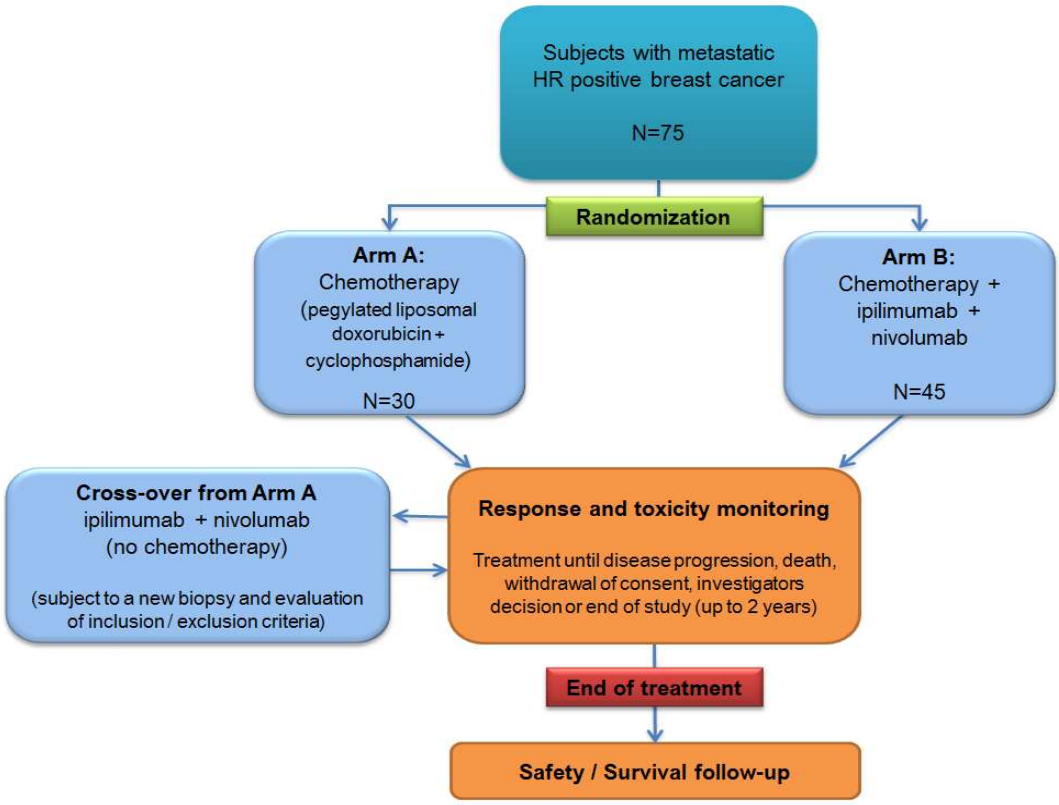
This is an open label randomized exploratory phase IIb study evaluating the safety and efficacy of combining nivolumab and ipilimumab with immunogenic chemotherapy in subjects with metastatic HR positive breast cancer. The Investigational Medicinal Products (IMPs) are nivolumab, ipilimumab, pegylated liposomal doxorubicin (PLD) and cyclophosphamide.

The trial will randomize 75 patients in to two arms (with randomization 2:3 in favour of arm B):

- Arm A: Chemotherapy only (pegylated liposomal doxorubicin + cyclophosphamide)
- Arm B: Chemotherapy + ipilimumab and nivolumab

Cross-over from arm A is allowed. The patients in arm A are offered ipilimumab + nivolumab (without chemotherapy) after disease progression, or treatment discontinuation due to toxicity, if considered not in need of immediate chemotherapy. Patients with aggressive and widespread disease, and acceptable tolerability for chemotherapy, should be recommended chemotherapy rather than cross-over to ipi/nivo therapy. Patients in arm A that have left the ICON study due to disease progression or treatment discontinuation due to toxicity, may be re-admitted to the cross over arm if they have received a maximum of one more line of chemotherapy after leaving the ICON study.

Study design:



6.2 Inclusion-Exclusion Criteria and General Study Population

(ICH E3;9.3. ICH E9;2.2.1)

7.2.1 Inclusion criteria

1. Metastatic hormone receptor positive breast cancer (primary or recurrent), defined as estrogen receptor (ER) positive >1% in metastatic biopsy (archival material or study biopsy) or cytology and HER2 negative in the last biopsy or cytology evaluable for HER2. HER2-analysis is to be perfomed according to national criteria.
2. Adequate core or excisional study biopsy of a tumor lesion. Lesions in previously irradiated areas may only be used for the biopsy if the lesion has appeared or progressed after radiation. No anti-tumor treatment is allowed between the time point for biopsy and study entry.
3. Measurable metastatic disease according to RECIST
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
5. Signed Informed Consent Form
6. Women or men aged ≥ 18 years
7. A minimum of 12 months from adjuvant/neoadjuvant chemotherapy with antracyclins to relapse of disease.
8. A maximum of one previous line with chemotherapy in the metastatic setting
9. Chemotherapy is considered as preferred treatment
10. Previous endocrine and targeted therapy is allowed
11. No use of systemic corticosteroids at study entry

12. Female subject of childbearing potential should have a negative urine or serum pregnancy within 7 days prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required
13. Female subjects of childbearing potential should agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year, during the treatment period and for at least 5 months after the last dose of study therapy.
14. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 7 months after the last dose of study therapy
15. Able to swallow and retain orally administered medication
16. Adequate organ function as defined in Table 1

Table 1 Adequate Organ Function Laboratory Values

System	**Laboratory Value**
Hematological	
Absolute neutrophil count (ANC)	≥1.00 x10^9/L
Lymphocyte count	≥0.50 x10^9/L
Platelets	≥75,000 / mcL
Hemoglobin	≥8 g/dL without transfusion or EPO dependency (within 10 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥40 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR** Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** **≤** 5 X ULN for subjects with liver metastases
Albumin	≥25 g/L
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

7.2.2 Exclusion criteria

The subject must be excluded from participating in the trial if the subject has/is:

1. Malignancies other than breast cancer within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death and treated with expected

curative outcome (such as adequately treated carcinoma in situ of the cervix or basal or squamous cell skin cancer)

2. Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for > 2 weeks prior to randomization
3. Known CNS disease, except for asymptomatic CNS metastases, provided all of the following criteria are met:
    a. Measurable disease outside the CNS
    b. Asymptomatic for CNS disease > 4 weeks
    c. No ongoing requirement for corticosteroids as therapy for CNS disease
    d. No radiation of brain lesions within 2 weeks prior to randomization
    e. No leptomeningeal disease
4. Uncontrolled pleural effusion, pericardial effusion, or ascites. Patients with indwelling catheters (e.g., PleurX®) are allowed
5. Uncontrolled tumor-related pain. Patients requiring narcotic pain medication must be on a stable regimen at study entry. Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to randomization. Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to randomization
6. Ionized calcium > 1.2 x UNL. The use of bisphosphonates is allowed
7. Pregnant or breastfeeding
8. Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome)
9. Significant cardiovascular disease, such as New York Heart Association (NYHA) cardiac disease (Class II or greater), myocardial infarction within 3 months prior to randomization, unstable arrhythmias, or unstable angina Patients with a known left ventricular ejection fraction (LVEF) < 40% will be excluded. Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF < 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate
10. Severe infection within 21 days prior to randomization, requiring hospitalization
11. Received oral or IV antibiotics within 1 week prior to Cycle 1, Day 1. Patients receiving routine antibiotic prophylaxis (e.g., to prevent chronic obstructive pulmonary disease exacerbation or for dental extraction) are eligible
12. Major surgical procedure within 21 days prior to randomization or anticipation of the need for a major surgical procedure during the course of the study other than for diagnosis. Placement of central venous access catheter(s) is not considered a major surgical procedure and is therefore permitted
13. A history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
14. Known hypersensitivity to any of the components of the investigational products
15. A history of autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxin, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Patients with eczema, psoriasis, lichen simplex chronicus or vitiligo with

dermatologic manifestations only (e.g., no psoriatic arthritis) are permitted provided that they meet all of the following conditions:

a. Rash must cover less than 10% of body surface area.
b. Disease is well controlled at baseline and only requiring low potency topical steroids
c. No acute exacerbations of underlying condition within the last 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids)

16. Undergone allogeneic stem cell or solid organ transplantation
17. A history of idiopathic pulmonary fibrosis or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted
18. A positive test for HIV
19. Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C. Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HbsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA
20. Active tuberculosis
21. Currently receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment
22. Received treatment with immune checkpoint modulators, including anti−CTLA-4, anti−PD-1, or anti−PD-L1 therapeutic antibodies
23. Received treatment with systemic immunostimulatory agents (including but not limited to interferons or IL-2) within 4 weeks or five half-lives of the drug (whichever is shorter) prior to randomization
24. Received treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti−tumor necrosis factor [TNF] agents) within 2 weeks prior to randomization, or anticipated requirement for systemic immunosuppressive medications during the trial
    a. Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study
    b. Patients with a history of allergic reaction to IV contrast requiring steroid pre-treatment should have baseline and subsequent tumor assessments performed using MRI
    c. The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed
25. Received anti-cancer therapy (medical agents or radiation) within 2 weeks prior to study Cycle 1, Day 1. Palliative radiotherapy for bone lesions is allowed up to 7 days before start of therapy.
26. A history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator
27. Known psychiatric or substance abuse disorders that would interfere with cooperation and the requirements of the trial

28. Received a live vaccine within 30 days of planned start of study therapy, or is expected to receive such a vaccine while on therapy
    a. *Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.*
29. Any reason why, in the opinion of the investigator, the patient should not participate

7.2.3 Cross-over criteria

Inclusion criteria 11-16 must be met at the time of cross-over. ECOG status of ≤2 is required. Maximum one line of chemotherapy after discontinuation of treatment in arm A. New tests for HIV/HCV/HBV, INR, aPTT and lipase are not required. Patients with anticipated requirement for systemic immunosuppressive medications during the trial are not eligible, with the exemptions listed under "exclusion criteria". If the patient has CNS disease, the following criteria must be met:

- No ongoing requirement for corticosteroids as therapy for CNS disease
- No radiation of brain lesions within 7 days prior to start of ipi/nivo therapy

6.3 Randomization and Blinding

Randomization is automated by the trials eCRF system (Viedoc). Patients are randomized in a ratio of 2:3 in favor of arm B. Randomization was stratified on tumor PD-L1 status (positive/negative) until protocol 4.0 was implemented January 2019, after this time point randomization was unstratified.

6.4 Study Assessments

Trial Period:	**Screening Phase**		**Treatment Phase**					**Post-Treatment**		
Treatment Cycle (C)/Title: (Each cycle is 2 weeks)	Informed consent (Visit 1)	Main Study Screening (Visit 2)	To be repeated (see footnotes for details) C1	 C2	 C3	 C4	Treatment discontinuation	Safety Follow-up	Patients not progressed during treatment Follow Up Visits	Patients progressed during treatment Follow Up Visit
Scheduling Window (Days)[a]:		-21 to -1	± 3	± 3	± 3	± 3	At time of discon	30 days[q] post discon ± 7 days	Every 12 weeks ± 7 days post discon for 12 months, or until disease progression	16 weeks ± 10 days post discon
Administrative Procedures										
Informed Consent[b]	x									
Inclusion/Exclusion Criteria		x								
Demographics and Medical History		x								
Prior and Concomitant Medication Review[c]		x	x	x	x	x	x	x		
Trial Treatment Administration			x	x	x	x				
Post-study anticancer therapy status									x	x
Clinical Procedures/Assessments										
Review Adverse Events[d,e]		x	x	x	x	x	x	x[e]	x[e]	x[e]
Full Physical Examination		x	x[f]					x		
Directed Physical Examination				x	x	x	x		x	x
Vital Signs and Weight		x	x	x	x	x	x	x	x	x
ECOG Performance Status		x	x	x	X	x	x	x	x	x
Electrocardiogram (ECG)		x	x[f]							
LVEF assessment		x[f]								
Laboratory Procedures										
Pregnancy Test – Urine or Ser–m-HCG[g]		x	x[g]		x		x	x		
INR and aPTT[h]		x								
CBC with Differential[i]		x	x	x	x	x	x	x	x	x
Comprehensive Serum Chemistry Panel[i]		x	x	x	x	x	x	x	x	x
Urine analysis[j]		x	x[f]				x	x		
FT4 and TSH, anti TPO[j]		x	x[f]				x	x	x	x
MUC-1, CA 125, CEA, amylase		x	x[f]		x		x		x	x
HIV/HCV/HBV-tests, lipase		x								
Efficacy Measurements										
Tumor Imaging[i, l]		x	x[f]				x		x	
Biobanking										
Tumor Biopsy[m]		x			x		x			
PBMC collection[n]		(x)[n]	x[n]	x			x		x[k]	x

Plasma and serum sample[o]			x[o]	x[o]	x[o]	x[o]	x		x[k]	x
Urine sample		x	x[f]				x			
Faeces sample		x	x[f]							
CTC collection (only if sufficient resources)			x[f]		x		x			
Patient Reported Outcomes										
FQ, NRS, EORTC QLQ-C15-PAL[p]			x				x		x	x

a. General, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 2 weeks; however the treatment cycle interval may be increased due to toxicity according to the dose modification guidelines provided in section 10.2.

b. Written consent must be obtained prior to performing any protocol specified procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame in the protocol. Subject number will be assigned when the study informed consent is signed.

c. Prior medications – Record all medications taken within 30 days of screening visit. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for AEs.

d. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.

e. After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. After this period, investigators should report any serious adverse events and adverse events of special interest that are believed to be related to prior treatment with study drug. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

f. The full clinical examination is to be replaced by a directed clinical examination at C1 day 1. FT4, TSH, anti-TPO and urin analyses are not to be performed at C1 day 1, but at screening and at day 1 of C5 and every 4th cycle thereafter. MUC-1, CA 125, CEA and amylase analyses are not to be performed at C1 day 1, but at screening and at day 1 of C3 and ever[y] 2nd cycle thereafter.Tumor assessment is not to be performed at C1 day 1, but at screening, and as indicated in footnote i and l. For cross-over patients the tumor assessment at the discontinuation visit will serve as screening assessment. Urine sampling for the biobank is only to be performed at screening, day 1 of C5 and at time of progression. CTC sampling is scheduled at day 1 of C1 (or screening), day 1 of C3 and ToP, with option for additional time points. ECG is to be performed at screening (not C1), C5 day 1 and every 4th cycle thereafter. Left ventricular ejection fraction is to be measured at screening, cyclus 9 and every 8th week thereafter, if administration of pegylated liposomal doxorubicin is continued. Faeces sampling is only to be performed at screening and at C5. LVEF may be measured by Multi Gated Acquisition Scan (MUGA) or echocardiography.

g. Women of childbearing potential must have a negative serum pregnancy test result ≤7 days prior to the first dose of nivolumab. A serum or urine pregnancy test (investigator's discretion) must be performed ≤3 days prior to Day 1 of every 2nd cycle thereafter during the treatment phase. A serum pregnancy test must be performed at the End of Treatment visit.

h. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.

i. Tumor assessments performed as standard of care prior to obtaining informed consent and within 21 days of Cycle 1, Day 1 may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at the screening visit. Radiologic imaging performed during the screening period should consist of 1) CT of the chest/abdomen/pelvis, alternatively MRI 2) bone scan (MRI, PET scan or scintigraphy), and 3) any other imaging studies (CT neck, plain films, etc.) as clinically indicated by the treating physician. No anti-tumor treatment is allowed between the time point for baseline radiological scans and start of study therapy. The same radiographic procedures and technique must be used throughout the study for each patient (e.g., if the patient had CT chest/abdomen/pelvis performed during screening, then she/he should subsequently undergo CT performed using the same radiologic protocol throughout the remainder of the study). Tumor assessments will be performed at baseline, every 8 weeks from C1 day1 (± 1 week) for the first 12 months following randomization, and every 12 weeks (± 10 days) thereafter, with additional scans as clinically indicated. A CT of the chest/abdomen/pelvis must be performed at every scheduled evaluation in all patients. In patients without bone lesions at screening, a bone scan must as a minimum be performed at every second scheduled evaluation. If iUPD is detected, a new radiological scan should be performed after 4-8 weeks, in accordance with iRECIST. Tumor response will be evaluated using both iRECIST criteria and RECIST v1.1. In the absence of disease progression per iRECIST,

tumor assessments should continue regardless of whether patients discontinue study treatment, unless they withdraw consent or the study is terminated by the Sponsor, whichever occurs first.

j. Unresolved abnormal labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.

k. For patients not progressed during treatment, plasma/serum and PBMC collection to be performed at first FU visit only (12 weeks after discontinuation). The Sponsor may ask for additional blood /PBMCs in selected cases.

l. In subjects who discontinue study therapy without confirmed disease progression, a radiologic evaluation should be performed at the time of treatment discontinuation (i.e., date of discontinuation ± 4 weeks). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. Radiological assessments performed as standard of care can replace the tumor scans at follow-up visits, if performed ± 4 weeks of the scheduled time point.

m. Fresh frozen and FFPE tumor biopsies before start of treatment (mandatory), 4 weeks from C1 day 1 (± 5 days), 6 months from C1 day 1 (± 10 days) and at time of treatment discontinuation (fine needle aspiration is not sufficient). The prestudy biopsy may be obtained any time after signed informed consent. Archival tumor tissue can be used instead of pretreatment biopsy, but must be obtained within three months of Cycle 1, Day 1. No anti-tumor treatment is allowed between the time point for biopsy and study entry. If the archival biopsy does not include fresh frozen tumor, a new pre-treatment biopsy for preservation as fresh-frozen material is mandatory.

n. PBMC; at day 1 of C1 (or screening) and day 1 of C2, C5, C9, C13, C25, time of progression and the FU visit 12/16 weeks after discontinuation. 100 ml ACD blood to be drawn at C1day1/screening. 70 ml ACD blood to be drawn at all later time points. Samples for PBMC collection should always be taken before infusion.

o. Plasma and serum to be collected at day 1 and day 2 of C1 and C5, and at the day of nivolumab injection (day 1) of C2, C3, C4, C6, C9, C13, C25,time of progression and the FU visit 12/16 weeks after discontinuation.

p. PRO forms to be completed at day 1 (+/- 7 days) of C1, C5, C9, C13, C25, C39 and at time of progression and the FU visit 12/16 weeks after discontinuation. The forms should be completed prior to the evaluation visit with the study doctor. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. The safety visit may be combined with the EOT-visit, if new anti-cancer therapy is started within 10 days of EOT. If a patient is not able to come to the study center for the safety visit or later follow-up visits, every effort should be made to conduct these visits by phone, combined with information from and tests at the local hospital.

7 Sample Size

The phase II study cannot be powered to demonstrate a statistically significant ($p<0.05$) clinical effect. If the study suggests acceptable toxicity and potential clinical benefit, a larger randomized study will be warranted. We plan to conduct a phase II study with 75 patients (45 patients in the nivo-chemo arm (arm B), 30 patients in the chemo-only arm (arm A)).

The number of 75 patients and the randomization ratio of 3:2 were based on the following considerations:

- A two sided hypothesis test with a 10% significance level
- Power of 80%
- Randomization 2:3 in favor of the experimental arm (arm B).
- Expected PFS in the control group (arm A) after 20 months 5%
- Hazard ratio between the treatment groups: 0.54, this corresponds to an expected PFS in the experimental arm of 20% after 20 months.

8 General Analysis Considerations

8.1 Timing of Analyses

The PFS-analysis will be performed when 70 PFS events have occurred in the PP population. If this time point is not met within 24 months after inclusion of the last patient, the PFS-analysis will be performed at this time point. The database locking process prior to analysis will be performed according to our internal SOP “Research Support Services SOP - DM 06 Database Lock”.

8.2 Analysis Populations

Participant Analysis Set	Description
Full analysis set (FAS)	The FAS is defined as a modified Intention To Treat population (ITT): all patients that have started therapy with at least one of the IMPs, and where data on the relevant endpoint is obtained. Safety will be evaluated in the FAS population.
Per protocol (PP) population	All randomized participants in arm A and B that where evaluated for tumor response, received ≥2 doses of PLD and total of ≥700 mg cyclophosphamide and in addition for arm B ≥1 dose of ipilimumab and ≥2 doses of nivolumab. The primary efficacy analysis will be performed in the PP population.
PD-L1 positive FAS population	Patients in the FAS population with PD-L1 positive tumors. PD-L1 positive tumors are defined as tumors that are assessed as positive by immunohistochemistry using the manufacturers specified cut off. If multiple tumor samples are available, patients with any PD-L1 positive tumor specimen will be categorized as PD-L1 positive.
PD-L1 positive PP population	Patients in the PP population with PD-L1 positive tumors. PD-L1 positive tumors are defined as tumors that are assessed as positive by immunohistochemistry using the manufacturers specified cut off. If multiple tumor samples are available, patients with any PD-L1 positive tumor specimen will be categorized as PD-L1 positive.
Full analysis set cross over (FAS-CO)	The FAS-CO is defined as a modified Intention To Treat population (ITT): all patients that have started therapy in the cross over part of the trial with at least one of the IMPs, and where data on the relevant endpoint is obtained. Safety will be evaluated in the FAS-CO population.
Per protocol population cross over (PP-CO)	Cross over patients that where evaluated for tumor response at any time point after start of nivolumab and ipilimumab and received ≥1 dose of ipilimumab and ≥ 2 doses of nivolumab
PD-L1 positive FAS-CO population	Patients in the FAS-CO population with PD-L1 positive tumors. PD-L1 positive tumors are defined as tumors that are assessed as positive by immunohistochemistry using the manufacturers specified cut off. If multiple tumor samples are available, patients with any PD-L1 positive tumor specimen will be categorized as PD-L1 positive.
PD-L1 positive PP-CO	Patients in the PP population with PD-L1 positive tumors.

population	PD-L1 positive tumors are defined as tumors that are assessed as positive by immunohistochemistry using the manufacturers specified cut off. If multiple tumor samples are available, patients with any PD-L1 positive tumor specimen will be categorized as PD-L1 positive.

8.3 Covariates and Subgroups

Exploratory efficacy analyses in the PP and PP-CO population will be performed using the following pre-defined factors:

- Tumor PD-L1 status (positive vs negative).
- Disease free interval between end of (neo)adjuvant chemotherapy or surgery, whichever was last, and relapse (less than 5 years vs ≥ 5 years).
- Time from diagnosis of metastatic disease to start of therapy in the ICON-study (less than 2 years vs ≥ 2 years).
- Prior chemotherapy against metastatic disease (no previous chemo vs. previous chemo). Chemotherapy given in the neoadjuvant/adjuvant setting is not to be considered in this analysis
- *Sites of metastases:*
  - «liver» (yes/no)
  - «bone» (yes/no)
  - «lung» (yes/no)
  - «lymph nodes» (yes/no)
  - «Central nervous system» (yes/no)
  - Number of metastatic sites (0-3 vs >3)
- *Molecular breast cancer profiles:*
  - Intrinsic breast cancer subtype by PAM50 subtype (luminal A, luminal B, HER-2 enriched and basal like). For patients with more than one sample analysed and discordant subtypes the latest sample will be used for the subgroup analysis.
  - Immune gene profile (e.g. Tumor Inflammation Signature)
  - Other gene expression-derived subgroups (not determined at the time of writing)

Additional variables and cut offs may be included in the analyses.

8.3.1 Multi-center Studies

The study is conducted in five centers Oslo university hospital (NOR), Stavanger university hospital (NOR), Kristiansand hospital (NOR), Institute Jules Bordet (BE) and CHU UCL Namur (BE). Data from the different centers will be combined and no comparative analyses between centers will be performed.

8.4 Missing Data

(ICH E3; 9.7.1, 11.4.2.2. ICH E9;5.3. EMA Guideline on Missing Data in Confirmatory Clinical Trials)

Progression and survival data:
Missing progression dates:

- Progression free survival (PFS) is defined as the time from randomization to progression or death from any cause, whichever occurs first. Patients without disease progression or death will be censored at the date of last tumor assessment.
- If no tumor assessment was performed after randomization, data will be censored at randomization date +1 day.
- Data for patients with a PFS event who missed two or more assessments scheduled immediately prior to the date of the PFS event will be censored at the last tumor assessment prior to the missed visits.

Missing survival follow up data:

- Patients with no recorded date of death will be censored at the latest survival follow up or if lost to follow up, the last visit registered in the eCRF.

Missing data for sub-grouping variables (section 8.3):

- Patients with missing PD-L1 data, breast cancer subtype (PAM50) or immune profile will be handled as a separate group "unknown" in the sub group analysis and baseline characteristics.
- Patients with missing date (day or month) of last (neo-)adjuvant treatment, primary diagnosis, local relapse or time of metastatic disease will be handled the following way: If only the month is known the 15th day of the month will be used, if only the year is known the date 01 JUL will be used. If the year is missing the data will be handled as missing and the number of missing data will be reported.
- Patients with confirmed stage IV disease within 3 months of initial diagnosis will be grouped as "Stage IV" from initial diagnosis.

Missing patient related outcome assessments:

Chalder Fatigue questionnaire (FQ) score, NRS pain intensity score and EORTC QLQ-C15-PAL is assessed at the following time points baseline, C5, C9, C13, C25, C39 and EOT.

- EORTC QLQ-C15-PAL assessments with a single missing item in the pain scale (item 5 and 12) will be imputed by "assuming that the missing items have values equal to the average of those items which are present for that respondent" if at least one item is completed, as suggested by the scoring manual. Other missing items will be treated as missing.
- Patients that have a missing baseline assessment (other than above) will be removed from the time to deterioration (TTD) and mean change analysis.
- For patients that are missing a single form, but have complete forms on the assessment before and after, the least favorable assessment of the two will be imputed at that time point.
- Patients that missed two consecutive assessments will be censored from the time to deterioration analysis at the last assessment registered.

8.5 Interim Analyses and Data Monitoring (as applicable)

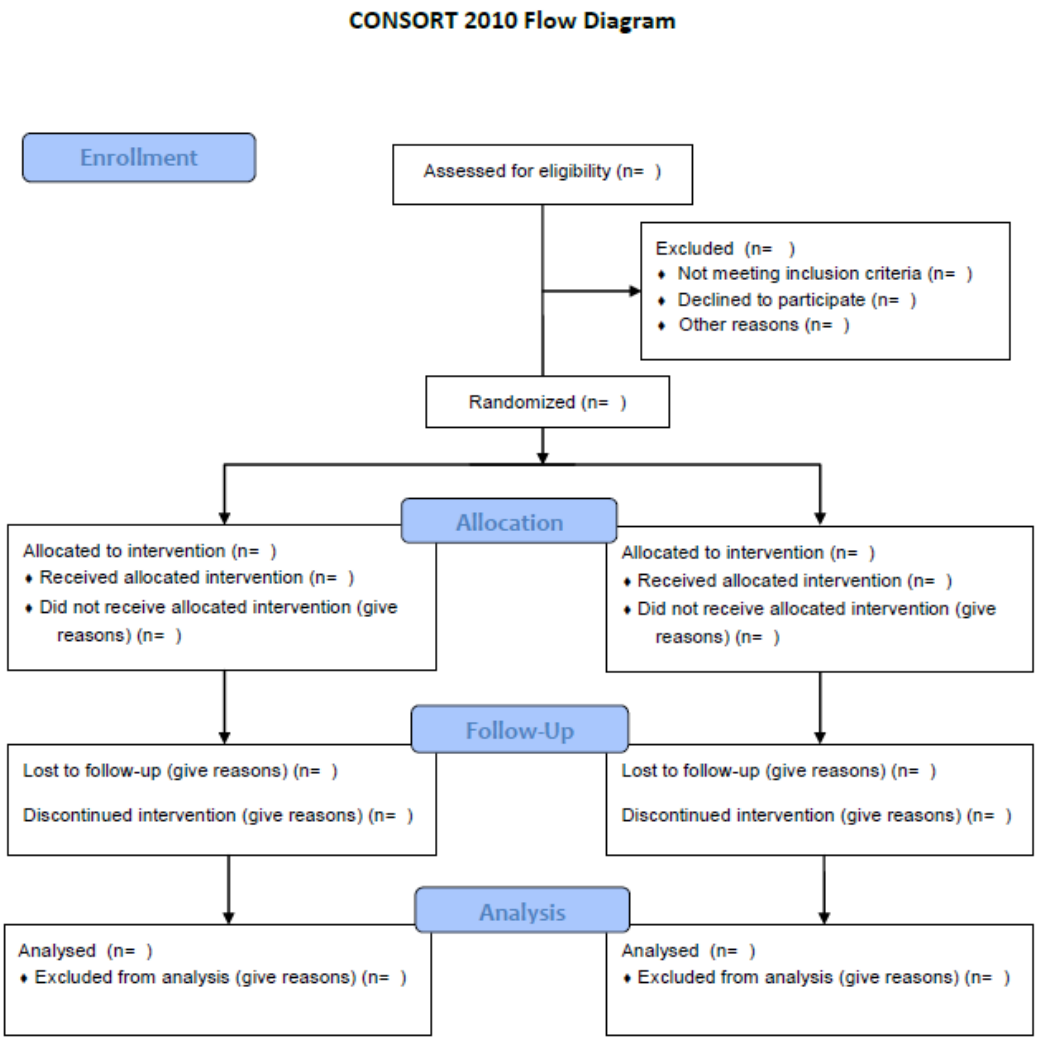
Not applicable

8.6 Multiple Testing

No formal hypothesis testing will be made in this data analysis, thus no adjustment for multiple testing will be performed.

9 Summary of Study Data

9.1 Subject Disposition



A consort diagram like above will be produced using the following variables from the eCRF:

- Subjects *assessed for eligibility* = patients that signed the ICF and started the screening process. These patients have all been given a trial ID in the eCRF and will be exported directly. Patients *assessed for eligibility* more than once, will be counted as a single subject.
- Patients *excluded* is the number of patients that were assessed for eligibility, but not randomized.

- The number of *randomized* subjects = patients that have completed the randomization module in the eCRF. All randomized patients have been *allocated to intervention*.
- Patients *lost to follow-up* = patients where survival data cannot be obtained.
- *Discontinued intervention* reason will be reported from "End of trial treatment" form in the eCRF.
- The number of patients *analyzed* = the number of patients analyzed in both the FAS and PP population.

9.2 Derived variables

Survival and response variables:

- Progression free survival: PFS = Date of progression or death from any cause (whichever comes first) - Randomization date
    - In the cross over part of the trial the start of the PFS interval is defined from cycle 1/day1:
      PFS = Date of progression or death from any cause (whichever comes first) – Date of Day 1/Cycle 1
    - Patients who discontinue follow up without progression will be censored at the date of the last registered radiological assessment.

- Overall survival: OS = Date of death – Randomization date
    - In the cross over part of the trial the start of the OS interval is defined as cycle 1/day 1:
      OS = Date of death – date of cycle 1/day 1
    - Patients alive at analysis will be censored at the date of the last registered survival follow up.

- Clinical benefit rate (CBR): the proportion of patients in the analyzed population with best overall response "PR" or "CR", or with stable disease (SD) lasting at least until the 6 month evaluation (performed at week 24 +/- 10 days). This means that patients where PD was first recorded at the 6 month evaluation will be considered to have clinical benefit.
  Duration of stable disease = Date of progression – Date of randomization
  Separate assessments will be done using both RECIST1.1 and iRECIST criteria.

- Duration of response (DOR): is defined as the interval from response was first documented (CR/iCR or PR/iPR) to either progression of disease or death from any cause, whichever comes first.
  DOR = Date of progression (or death) – Date response first documented
  Patients with an ongoing response at last follow up visit will be censored at this time point.

- Durable response rate (DRR): is the proportion of patients in the analyzed population with an objective response lasting at least 6 months.
  DRR = n with DOR ≥ 6 months/N

EORTC QLQ-C15-PAL scores:

- The EORTC QLQ-C15-PAL questionnaire score will be computed using the EORTC scoring manual.

9.3 Protocol Deviations

Protocol deviations that could affect the primary or secondary endpoints will be reported case by case.

9.4 Demographic and Baseline Variables

Baseline characteristics will be presented. A separate table for the single armed cross over part of the trial will be produced. For the cross over patients Cycle 1/day 1 will be defined as the baseline time point. Continuous variables will be presented with median and range, categorical variables presented as numbers with percentage in each group.

Potential variables to be described:

- Age, continous
- Sex
- Disease stage at initial diagnosis (Stage I-IV, patients with confirmed stage IV disease within 3 months of initial diagnosis will be grouped as “Stage IV”).
- ECOG score
- Metastatic sites: each organ grouped separately
- Number of metastatic sites: 0-3 vs >3
- Previous neoadjuvant or adjuvant chemotherapy, yes/no
- Previous adjuvant radiotherapy, yes/no
- Number of previous lines of chemotherapy in metastatic disease
- Type of prior metastatic chemotherapy
- Previous anthracyklin treatment in metastatic setting
- Prior CDK4/6 inhibitor therapy, yes/no
- The number of previous lines of endocrine therapy in metastatic setting presented as median with range and 0, 1, 2, ≥3.
- Ongoing bone resorption inhibitor treatment
- PD-L1 status: “positive”, “negative”, “unknown”
- Molecular subtype by PAM50
- Estrogen receptor expression 1-10% in metastasis, yes/no
- Time from initial diagnosis to randomization, continuous
- Time from diagnosis of advanced disease to randomization, continuous
- Time from last (neo)adjuvant treatment or surgery to randomization, continuous
- Time from last (neo)adjuvant antracycline/cyclophosphamide treatment or surgery to advanced diagnosis, continuous
- Study site

In addition for cross over patients:

- Objective response to treatment in Arm A, yes/no
- Clinical benefit to treatment in arm A, yes/no

Additional baseline variables may be presented.

9.5 Concurrent Illnesses and Medical Conditions

- Concurrent illnesses and medical conditions will be coded by MedDRA and listed by subject. This data will not be published.

- Previous (neo)adjuvant and metastatic breast cancer treatment, both will be summarized by treatment group and in the total patient population. The number and percentages of subjects that have received any previous treatment will be reported as well as the number and percentage of subjects that have received each drug class.

9.6 Treatment Compliance

Compliance for all IMPs are registered in the eCRF by study cycle under the treatment administration form. Administration of pegylated liposomal doxorubicin, nivolumab and ipilimumab are documented in hospital records and the administrated dose is registered in the eCRF. The compliance assessment for cyclophosphamide tablets is based on pill counts and is registered in the treatment administration form.

9.7 Adverse events

All adverse events and serious adverse events will be recorded from initiation of trial treatment until 30 days after the last dose of study drug or until the initiation of another anticancer therapy, whichever occurs first. After this period, investigators should report serious adverse events and adverse events of special interest that are believed to be related to prior treatment with study drug. Patients are actively followed for treatment related serious adverse events or adverse events of special interest until week 16 after treatment discontinuation. In addition serious adverse events that are related to any protocol specific intervention that occur prior to initiation of therapy will also be recorded.

Adverse events (AE) are coded using the Medical Dictionary for Regulatory Activities (MedDRA) and graded for severity using NCI Common Terminology Criteria for Adverse Events CTCAE 4.0.

Drug related AEs are those that are categorized in the eCRF as *possibly*, *probable* or *definite* related to the IMP by the investigator. For serious adverse events, relation to study drug is based on the causality assessment provided by the medical monitor.

Adverse events leading to drug discontinuation are: AEs where action taken due to AE is “Drug permanently discontinued” (serious adverse events or events of special interest) or where reason for treatment discontinuation is registered as an adverse event (non-serious events).

Adverse events recorded in arm A that are ongoing at cross over C1/D1 will be recorded as baseline symptoms in the cross over part of the trial.

Adverse events occurring after start of treatment in the cross over part are summarized separately. These events will not be counted in the summary for patients in arm A of the main trial, unless the event is considered related to previous treatment in arm A. Events that are considered possibly related to both arm A treatment and the cross over treatment will be included the adverse event summary for both of the groups.

Adverse events of special interest for this study include the following conditions which may be suggestive of an autoimmune disorder:

- Immune related Pneumonitis
- Immune related Colitis
- Immune related adrenal insufficiency

- Immune related Hepatitis
- Immune related Hypothyroidism
- Immune related Hyperthyroidism
- Immune related Pancreatitis
- Immune related Diabetes Mellitus
- Immune related Nephritis
- Severe treatment related cutaneous reactions
- Immune related Hypophysitis

10 Efficacy Analyses

10.1 Primary Efficacy Analysis

Analysis of PFS in the combination arm, compared to the control group in the PP population.

- Kaplan Meier curves will be produced.
- Comparison between the treatment arms will be given by HR for progression or death with 95% confidence intervals using the Cox proportional hazards model.
- Present the proportion of patients with progression or death within 20 months after randomization

10.2 Secondary Efficacy Analyses

10.2.1 Secondary Analyses of Primary Efficacy Endpoint

Stratification on the factors listed under 8.3. will be performed.

- A Forest plot for selected variables will be produced.

A comparison of PFS assessed by RECIST v1.1 in the

- FAS population
- PD-L1-positive PP population
- PD-L1 positive FAS population

In addition, the following PFS analysis will be performed on all populations

- PFS analysis without censoring at missing scans
- PFS analysis using iRECIST criteria

Kaplan Meier curves will be produced. Comparison between the treatment arms will be given by HR for progression or death with 95% confidence intervals using the Cox proportional hazards model.

10.2.2 Analyses of Secondary Endpoints

Comparison of OS between the treatment groups will be performed in the

- PP population
- FAS population
- PD-L1 positive PP population
- PD-L1 positive FAS population

Kaplan Meier curves will be produced. Comparison between the treatment arms will be given by HR for death with 95% confidence intervals using the Cox proportional hazards model.

Comparison of ORR between the treatment groups as assessed by RECIST v1.1 will be performed in the

- PP population
- FAS population
- PD-L1 positive PP population
- PD-L1 positive FAS population

The absolute number of patients with an objective response and the proportion with confidence intervals in each arm will be reported. A summary table of best objective response by treatment arm assessed by RECIST v1.1 will be produced.

Comparison of DRR between the treatment groups as assessed by RECIST v1.1 will be performed in the

- PP population
- FAS population
- PD-L1 positive PP population
- PD-L1 positive FAS population

The absolute number of patients with a durable response and the proportion with confidence intervals in each arm will be reported.

Comparison of CBR between the treatment groups as assessed by RECIST v1.1 will be performed in the

- PP population
- FAS population
- PD-L1 positive PP population
- PD-L1 positive FAS population

The absolute number of patients with clinical benefit and the proportion with confidence intervals in each arm will be reported.

Comparison of DOR between the treatment groups as assessed by RECIST v1.1 will be performed in the

- PP population
- FAS population
- PD-L1 positive PP population
- PD-L1 positive FAS population

Median duration of response, range and confidence intervals will be presented.

Comparison of ORR, DRR, CBR and DOR assessed *by iRECIST* will be performed in the

- PP population
- FAS population
- PD-L1 positive PP population
- PD-L1 positive FAS population

Data will be presented as above. A summary table of best overall response by arm assessed by iRECIST will be provided.

For the *cross over part* of the trial the following endpoints will be assessed by both RECIST v1.1 and iRECIST for the PP-CO, FAS-CO, PD-L1 positive PP-CO and PD-L1 positive FAS-CO population:

- PFS
    - Kaplan Meier curve will be produced.
- OS
    - Kaplan Meier curve will be produced

- ORR, DRR and CBR
    - The absolute number of patients and the proportion with confidence interval will be reported.
    - A summary table of best overall response and clinical benefit assessed by both RECIST v1.1 and iRECIST will be produced
- DOR
    - Median duration of response and range with confidence interval will be presented.

10.3 Handling repeated randomizations

In the case of a subject being randomized to both treatment arms, the subject will be included in the safety analyses of both arms. Regarding the efficacy assessment, the patient will be included in the FAS in both arms, and in the PP population in each arm if the PP criteria is fulfilled. The subject will be censored in the efficacy analyses for the first arm, as follows: PFS will be censored at the date of last tumor assessment, or at randomization +1 day if no tumor assessment is performed. OS will be censored at the date of the second randomization.

A sensitivity analysis will be performed to evaluate the effect of repeated randomizations on the primary efficacy endpoint, which is PFS in the PP population. In this analysis, the subjects will be censored for PFS as in the primary analysis above, but excluded from the PP population after the second randomization. Kaplan Meier curves will be produced and a comparison between the treatment arms will be given by HR for progression or death with 95% confidence intervals using the Cox proportional hazards model.

10.4 Exploratory Efficacy Analyses

Hazard ratio (HR) for death in arm B versus arm A with 95% confidence intervals will be calculated for each of the subgroups defined in section 8.3 using the Cox proportional hazard model. Forest plot of selected variables will be produced.

Kaplan-Meier curves will be produced for PFS and OS in the subgroups defined by selected variables defined in section 8.3.

Additional exploratory analyses may be performed. The statistical analyses will be dependent on the factors investigated and will be defined separately.

11 Safety Analyses

11.1 Extent of Exposure

The following parameters will be summarized for each IMP in the FAS population by each treatment arm and the cross over group:

- Mean dose intensity for each IMP, as a percentage of the full dose as defined in the protocol.
- Mean cumulative dose for each IMP
- Median duration of study therapy, defined as the date of the last treatment with IMP minus randomization date, including range

11.2 Adverse Events

When producing summary tables of adverse events repeated adverse events will be counted only once at the preferred term level for each subject with the worst CTCAE grade registered. Safety will be evaluated in the FAS population. Events are presented by preferred term and system organ class (SOC).

Adverse events

- The number of subjects with at least one grade ≥ 3 adverse event, by treatment group
- The number of subjects with at least one serious adverse event, by treatment group
- Overall summary of *all adverse events* by worst CTCAE grade (grade 1-5, total)
- Overall summary of *all adverse events* by worst CTCAE grade (any grade, grade 3-4, grade 5)
- Overall summary of *all treatment* related adverse events by worst CTCAE grade (any grade, grade 3-4, grade 5)
- Summary of *all adverse events* occurring *with a frequency ≥5%* within any arm by worst CTCAE grade (any grade, grade 3-4, grade 5)
- Summary of *all treatment related adverse events* occurring *with a frequency ≥5%* within any arm by worst CTCAE grade (any grade, grade 3-4, grade 5)
- Overall summary of all *non-serious adverse events* occurring *with a frequency ≥5%* within any arm by worst CTCAE grade (any grade, grade 3-4, grade 5)
- Other cutoffs may be used for producing summary tables

Adverse events of special interest

- Overall summary of all *adverse events of special interest* by worst CTCAE grade, by treatment group

Adverse events leading to discontinuation of study therapy

- Overall summary by worst CTCAE grade, by treatment group

Adverse events leading to dose modification of study therapy

- Overall summary by worst CTCAE grade, by treatment group

11.3 Deaths, Serious Adverse Events and other Significant Adverse Events

Deaths

All deaths will be summarized by treatment group. The following tables will be produced:

- All deaths, reason for death
- Deaths within 30 days of last dose of IMP, reason for death
- Deaths within 90 days of last dose of IMP, reason for death

Serious adverse events

- The number of subjects with at least one SAE, by treatment arm
- Overall summary of SAEs by worst CTCAE grade (grade 1-5, total)
- Overall summary of SAEs by worst CTCAE grade (any grade, grade 3-4, grade 5)
- Overall summary of treatment related SAEs by worst CTCAE grade (any grade, grade 3-4, grade 5)

11.4 Pregnancies (As applicable)

Pregnancy tests are performed regularly throughout the trial. Pregnancies occurring within the treatment phase or the 16 week follow up period will be reported.

11.5 Clinical Laboratory Evaluations

Specific normal limits for laboratory values on each site are registered in the CRF system. If laboratory values are to be presented, they will be presented in relation to the upper and lower limit of normal at each center. Only clinically significant laboratory abnormalities are recorded as adverse events.

11.6 Prior and Concurrent Medications (As applicable)

Prior and concurrent medications will be recorded in the CRF system and coded by ATC.

Summary of patients receiving immune modulating medication for management of immune mediated adverse events with oral or intravenous corticosteroids with a dose exceeding 20 mg prednisolone or equivalent for >1 week or other classes of immunosuppressant therapy (e.g., tumor necrosis factor alpha inhibitors, mycophenolate mofetil, tacrolimus or vedolizumab).

11.7 Other Safety Measures

NA

12 Pharmacokinetics (As Applicable)

NA

13 Other Analyses

13.1 Patient reported outcomes

Patient reported outcomes (FQ score, NRS pain intensity score and EORTC QLQ-C15-PAL) are assessed at C1, C5, C9, C13, C25, C39 and at the treatment discontinuation visit.

Time to deterioration analyses will be done using Kaplan-Meier methodology. Deterioration is defined as the time point where the change in score from baseline is equal to or greater than the MCID defined in chapter 6.2. Kaplan-Meier curves with deterioration-free survival will be produced. Comparison between the treatment arms will be given by HR for deterioration with 95% confidence intervals using the Cox proportional hazards model.

Mean score will be calculated at each time point and plotted with 95% confidence intervals for each treatment group. Separate FQ and NRS analyses will be performed for participants with a baseline

FQ score of ≥ 21 points or a baseline NRS score ≥ 4.

Change from baseline in the global health status of the EORTC QLQ-C15-PAL will be calculated at each assessment. A plot of mean change with 95% confidence intervals for each treatment group will presented.

Separate plots of patient related outcomes will be produced for the cross over part of the trial.

14 References

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We would like to acknowledge the Cambridge University Hospitals Clinical Trials Unit for the development of this SAP template (version CCTU/TPLV2), which has been modified by the Michigan Institute for Clinical & Health Research (MICHR).