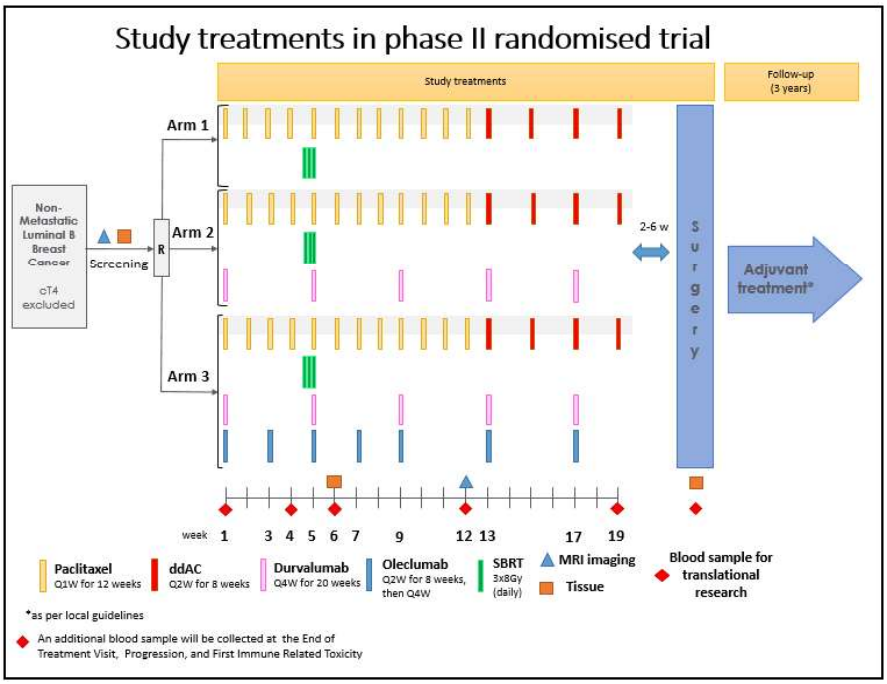
SYNOPSIS

STUDY TITLE	Neo-adjuvant chemotherapy combined with SBRT to the primary tumour +/- durvalumab (MEDI4736), +/- oleclumab (MEDI9447) in luminal B breast cancer: a phase II randomized trial
SHORT TITLE	Neo-CheckRay
SPONSOR	Institut Jules Bordet (IJB) - Brussels, Belgium
INDICATION(S)	Luminal B Breast Cancer
TARGET STUDY POPULATION	Pre or post-menopausal female subjects with luminal B primary breast cancer who are candidates for neo-adjuvant chemotherapy
PHASE	Phase II with a safety run-in for the first 6 subjects
STUDY DESIGN	 NEO-CHECKRAY is a multicenter, open-label phase II study that randomises luminal B breast cancer subjects candidate for neo-adjuvant chemotherapy in a 1:1:1 ratio in 3 arms: 1. Arm1: the combination of weekly paclitaxel followed by dose-dense doxorubicin-cyclophosphamide (ddAC) and pre-operative radiation therapy (boost dose) on the primary tumour 2. Arm 2: arm 1 with the addition of the anti-PD-L1 antibody durvalumab 3. Arm 3: arm 2 with the addition of the anti-CD73 antibody oleclumab The primary tumour will be excised 2-6 weeks after completion of ddAC. A safety run-in is planned for the 6 first subjects before starting

	the randomised phase II trial. Those 6 subjects will receive the treatment given in Arm 3.
STUDY RATIONALE	Luminal breast cancer is characterised by a positive estrogen receptor (ER) status and categorised into two subclasses, A and B [1]. Breast cancer-specific mortality rate is twice as high in luminal B subjects relative to luminal A subjects. The rates of pathological complete response (pCR) with chemotherapy, a surrogate marker for long-term benefit of neo-adjuvant treatment, compares poorly between luminal B and other types: 15% in luminal B versus 45.8% in HER2 positive and 44.5% in triple negative breast cancer (TNBC) [2–4]. Luminal B breast cancer subjects who cannot achieve a pCR after neo-adjuvant treatment have a significant diminished event-free survival, revealing a need to focus innovative research on effective neo-adjuvant treatments for luminal B breast cancer [5]. More recently, important developments in immuno-oncology permit classification of tumours according to their immunological susceptibility: inflamed cancer types are characterised by the presence of tumour infiltrating lymphocytes (TILs), programmed cell death receptor ligand 1 (PD-L1) positivity of tumours or immune cells and high CD8+ T-cell density. They attain overall better long term outcomes with systemic therapy, greatly due to this immune susceptibility [6]. Non-inflamed cancers, such as luminal B breast cancer, are also known as 'immune cold tumours'. An area of active research is how to turn 'immune cold tumours' into inflamed cancers, leveraging the effects of systemic treatment and increasing pCR rates after treatment by immunotherapy. Although immunotherapy has a major role for the treatment of inflamed cancers, such as melanomas and lung cancer, with a considerable fraction of subjects attaining long lasting benefits of it, it has been shown that isolated PD1 and PD-L1 blockade are disappointing in the setting of an immune cold tumour, hence priming immunologic response to increase its effects are important [7–9]. Priming of immunotherapy responses could be attained with a myriad of strategies: by combining it with chemotherapy, with blockade of the adenosine pathway and with radiation. Positive clinical data for the *first strategy* is already available: it was demonstrated in the I-SPY 2 trial that the addition of pembrolizumab, an anti-PD1, to standard neo-adjuvant chemotherapy (paclitaxel followed by doxorubicin and cyclophosphamide) for luminal B breast cancer subjects, increased pCR rates (30% vs 13%) compared to standard chemotherapy alone[10]. Regarding the *second strategy*, there are three phase I trials ongoing with immunotherapy and adenosine pathway blockade in subjects with solid tumours. Extracellular adenosine promotes tumour cell metastasis, angiogenesis and has multiple immunosuppressive functions [11]. Within the *third strategy*, radiosensitising immunotherapy is considered a potential curative therapeutic modality, akin to radiosensitising chemotherapy [12]. Radiation induces changes to

	the tumour cell immunophenotype by a variety of mechanisms and enhances cross-presentation of tumour antigens that can induce abscopal effects outside of the radiation field, radiation thereby acting as an in situ anti-tumour vaccine [13]. Currently, a phase I trial is ongoing to demonstrate safety and tolerability of pembrolizumab combined with radiation therapy on the primary tumour for TNBC and HR +/HER2 - breast cancer subjects. Furthermore, pre-clinical research demonstrated that adenosine regulates the ability of radiation therapy to induce anti-tumour immunity, by affecting dendritic cells maturation and T-cell activation [14]. These findings suggest that CD73 blockade is a promising strategy to improve the synergy between radiation therapy and immunotherapy. Considering all the synergistic effect and available safety data of chemotherapy with radiation, immunotherapy and blockade of the adenosine pathway, and the lack of efficacious treatment for luminal B breast cancer, we are thus proposing this trial of neo-adjuvant treatment with weekly paclitaxel followed by dose-dense doxorubicin-cyclophosphamide (ddAC-T) with pre-operative radiation to the primary tumour, durvalumab (anti-PD-L1) and oleclumab (anti-CD73) to enable capturing of a possible benefit with an easy-to-assess end-point (pCR) in the earliest and most susceptible stage available of the disease, allowing a rapid and thorough assessment of efficacy and safety, together with performance of translational research on the surgical specimen.
OBJECTIVES	**Safety Run-in** • To evaluate safety and toxicity of adding SBRT directed to the primary tumour to the combination durvalumab-oleclumab-paclitaxel. • To evaluate feasibility of performing surgery (breast conserving surgery or mastectomy) within 6 weeks after the end of neo-adjuvant treatment. **Phase II Primary objective** • To demonstrate improved tumour response of the primary tumour and nodal metastases in arms 2 or 3 versus arm 1. **Phase II Secondary objectives** • To evaluate the response to the primary tumour irrespective of the response to the pathological lymph nodes. • To evaluate the response to the pathological lymph nodes irrespective of the response to the primary tumour. • To evaluate the feasibility to perform breast-sparing surgery of the arms 2 and 3 versus arm 1.

	• To evaluate the ability to control invasive disease in arms 2 and 3 versus arm 1 during three years after surgery. • To evaluate the severity and duration of AEs of the arms 2 and 3 versus arm 1. • To evaluate the cosmetic changes to the breast of the arms 2 and 3 versus arm 1.
ENDPOINTS	**Safety run-in endpoints** • Occurrence of immune related or radiation therapy related toxicity of special interest • Feasibility of delivering a sufficient dose of paclitaxel and ddAC • Feasibility of performing surgery within a specified timeframe after the last neo-adjuvant treatment **Phase II Primary endpoint** • Residual cancer burden (**RCB 0-1 vs. RCB 2-3**) at time of surgery. RCB 0 is defined as pathological complete response (pCR) and RCB 1 is defined as minimal residual disease. RCB is calculated as a continuous index combining pathologic measurements of the primary tumour (size and cellularity) and nodal metastases (number and size) as defined by Symmans et al. [15]. **Phase II Secondary endpoints** • Complete pathologic response rate (pCR) of the primary tumour (ypT0), irrespective of the response rate of the resected nodal metastases. • Complete pathologic response rate (pCR) of the resected nodal metastases (ypN0), irrespective of the response rate of the primary tumour. • % of breast conservation surgery in arms 2 and 3 versus arm 1 • Invasive Disease-Free Survival (iDFS) 3 years after surgery. iDFS will be measured using regular follow-up investigations: lab work, clinical examination and annual breast ultrasound and mammography. Radiologic imaging will not be routinely performed, unless directed by abnormal blood results or clinical examination. • Duration and severity of AEs based on CTCAE 5.0. • Changes in breast appearance: breast fibrosis in whole breast, breast fibrosis in boost area, breast size, breast shape, nipple position, shape of the areola and nipple, skin color, appearance of surgical scar, evaluation of teleangiectasia and global cosmetic result .

NUMBER OF SUBJECTS	**Safety Run-in:** - Number of subjects to enrol: 6 **Phase II** - Estimated number of subjects to screen: 184 - Estimated number of subjects 18-64 y.o. : 110 - Estimated number of subjects >64 y.o. : 74 - Estimated number of subjects to randomise: 147 - Number of evaluable subjects: 132
INCLUSION CRITERIA	Subjects must meet all of the following criteria in order to be eligible for this study: 1. Age ≥ 18 years old 2. Female 3. ECOG performance status ≤ 1 4. Weight ≥ 35 kg 5. Histological diagnosis of invasive breast adenocarcinoma that is estrogen receptor-positive, and HER2- negative as per the updated American Society of Clinical Oncology (ASCO) - College of American Pathologists (CAP) guidelines according to local testing • ER-positive is defined as having an immunohistochemistry (IHC) of 1% or more and/or and Allred score of 3 or more • HER2 negative is defined as having an IHC of 0 or 1+ without ISH OR IHC 2+ and ISH non-amplified with ratio less than 2.0 and if reported, average HER2 copy number < 4 signals/cells OR ISH non-amplified with ratio less than 2.0 and if reported, average HER2 copy number < 4 signals/cells [without IHC]; note: a IHC of 3+ is always considered HER2 positive, independently of the ISH result. 6. Agreement to perform new study related biopsies to provide tissue samples. 7. Confirmed Mammaprint genomic high risk score according to central testing. Mammaprint will only be tested for luminal B breast tumours with either Proliferation Index Ki67 ≥ 15% or histology grade 3 tumours. (Testing to be done during screening period). In case the MammaPrint test returns an unevaluable result or is technically impossible, the sponsor should be contacted as soon as possible to discuss the inclusion of the concerned patient. Under some specific medical conditions and breast cancer disease caracteristics, the medical team of the sponsor can accept that the site continues the screening process of the patient. There will be maximum 5% of non-evaluable Mammaprint results among enrolled patients.

	8. Tumour size: • If subject is cN0: tumour size ≥ 2 cm, as determined by MRI imaging. • If subject is cN1,cN2 or cN3: tumour size: ≥ 1.5 cm, as determined by MRI imaging. 9. Multifocal, multicentric unilateral or bilateral breast adenocarcinoma tumours are allowed provided that all foci are ER+/HER2- according to local testing and all foci are able to receive SBRT treatment within the defined dosimetric constraints. For bilateral, multifocal or multicentric disease, the site selected for pre-treatment biopsy should correspond to the site of largest measurable disease meeting eligibility criteria. The location of tumour biopsy site (laterality, quadrant, position from the nipple and type of imaging modality to guide biopsy) should be collected. 10. Serum pregnancy test (for subjects of childbearing potential) negative within 2 weeks prior to first dose of study administration. 11. Women of childbearing potential must agree to use 1 highly effective method of contraception during the screening period, during the course of the study and at least 12 months after the last administration of study treatment. It is strongly recommended for the male partner of a female subject to also use male condom plus spermicide throughout this period. 12. Adequate bone marrow function as defined below: • Absolute neutrophil count ≥1500/μL, i.e. $1.5x10^9$/L • Hemoglobin ≥ 9.0 g/dL • Platelets ≥100000/μL, i.e. $100x10^9$/L 13. Adequate liver function as defined below: • Serum total bilirubin ≤ 1.5 x ULN. In case of known Gilbert's syndrome ≤ 3 x UNL is allowed • AST (SGOT) ≤ 3.0 x ULN • ALT (SGPT) ≤ 3.0 x ULN 14. Adequate renal function as defined below: • Creatinine ≤ 1.5 x UNL or eGFR≥40ml/min/$1.73m^2$ 15. Adequate coagulant function as defined below: • International Normalized Ratio (INR) ≤ 1.5 x ULN unless subject is receiving anticoagulant therapy as long as INR and activated partial thromboplastin time (aPTT) is within therapeutic range of intended use of anticoagulants 16. Completion of all necessary screening procedures within 21 days prior to randomisation. 17. Willingness to provide tissue and blood samples for immuno-monitoring and translational research activities

	18. Left ventricular ejection fraction (LVEF) ≥ 50%. LVEF performed in routine is accepted if done within 6 months prior to beginning of screening. 19. Signed Informed Consent form (ICF) obtained prior to any study related procedure. **Inclusion criterion for phase II only (all phase II subjects):** 20. Tumour sample provided for central PD-L1 IHC assessment (Testing done during screening period). **Inclusion criterion applicable to FRANCE only (Safety run-in and Phase II subjects)** 21. Affiliated to the French Social Security System (applicable only to subjects treated in France)
EXCLUSION CRITERIA	Subjects meeting one of the following criteria are not eligible for this study: 1. Pregnant and/or lactating women. 2. Subject with a significant medical, neuro-psychiatric, substance abuse or surgical condition, currently uncontrolled by treatment, which, in the principal investigator's opinion, may interfere with completion of the study. 3. TNM stage cT4 breast cancer including inflammatory breast cancer 4. Presence of any distant metastasis 5. Contra-indication for treatment by paclitaxel, doxorubicin or cyclophosphamide, or known allergy to any tested substance or excipients (e.g; chemotherapy or immunotherapy formulations). Contra-indication for subjects with known sensitivity to acetaminophen/paracetamol, diphenhydramine or equivalent antihistamine (this is a contra-indication for treatment with oleclumab). 6. Previously known contra-indication for treatment by radiation therapy such as rare genetic disorders associated with DNA repair disorders such as ataxia-telangiectasia (A-T), Nijmegen Breakage Syndrome (NBS) and Fanconi anemia. 7. Active or prior documented autoimmune disease (including inflammatory bowel disease, celiac disease, Wegener's granulomatosis) within the past 3 years. NOTE: Subjects with childhood atopy or asthma, vitiligo, alopecia, Grave's disease, Hashimoto's thyroiditis, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded 8. Prior malignancy active within the previous 5 years, except for localised cancers that are considered to have been cured and in the opinion of the investigator present a low risk for recurrence. Examples include basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast 9. Known history of, or any evidence of active, non-infectious pneumonitis.

	10. Active infection including: • Tuberculosis (TB) (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice) • Hepatitis B (known positive HBV surface antigen (HBsAg) result). Subjects with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. • Hepatitis C. Subjects positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA. 11. Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction transient ischemic attack, or stroke within the previous 3 months, unstable arrhythmias, and/or unstable angina 12. Medical condition requiring current systemic anticoagulation, or a history of congenital hypercoagulable condition. Subjects taking aspirin at doses < 325 mg per day are eligible provided that prothrombin time is within the institutional range of normal. Use of local anticoagulation for port maintenance is permitted. 13. Subjects with history of venous thrombosis in the past 12 months prior to the scheduled first dose of study treatment (oleclumab) 14. Diabetes mellitus Type 1 or poorly controlled Type 2 diabetes mellitus defined as a screening hemoglobin A1C ≥ 8 % or a fasting plasma glucose ≥ 160 mg/dL (or 8.8 mmol/L) 15. Any live (attenuated) vaccine within 30 days of planned start of study therapy 16. Prior systemic immunosuppressive medication (excluding corticosteroids) within 30 days of planned start of study therapy 17. Prior radiation therapy to the ipsilateral breast. 18. Prior immunotherapy, including tumour vaccine, cytokine, anti-CTLA4, PD-1/PD-L1, including durvalumab, blockade or similar agents 19. Concomitant use of other investigational drugs 20. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria. Subjects with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician. Subjects with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or oleclumab may be included only after consultation with the Study Physician. 21. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic

	gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the subject to give written informed consent. 22. 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. 23. Prior organ transplantation. 24. Subjects with urinary outflow obstruction. **Exclusion criterion applicable to FRANCE only (Safety run-in and Phase II subjects)** 25. Vulnerable persons according to the article L.1121-6 of the CSP, adults who are the subject of a measure of legal protection or unable to express their consent according to article L.1121-8 of the CSP
INVESTIGATIONAL MEDICINAL PRODUCT(S) DOSE/ROUTE/REGIMEN	• **Durvalumab** (MEDI4736) 1500 mg every 4 weeks (q4w) • **Oleclumab** (MEDI9447) 3000 mg every 2 weeks (q2w) for the first 4 administrations, then every 4 weeks (q4w) for the last 3 administrations. • **Paclitaxel** (80 mg/m^2) administered via IV infusion weekly for 12 weeks • Dose-dense **doxorubicin** (60 mg/m^2) IV + cyclophosphamide (600 mg/m^2) IV day 1, every 2 weeks for 4 doses.
NON-INVESTIGATIONAL MEDICINAL PRODUCT(S) DOSE/ROUTE/REGIMEN	• **G-CSF** (i.e., filgrastim or pegfilgrastim) G-CSF can be given to any subject at any time in fitting with the local site guidelines • Gadolinium-based contrast agents • Iodinated contrast agent • Chemotherapy pre- and post-medication including anti-emetics, antihistamines and steroids are administered according to local standard of care.

NON-MEDICINAL STUDY TREATMENT(S)	• **Stereotactic Body Radiotherapy (SBRT)** of the primary tumour in the breast.
	• Surgery
	  • mastectomy or tumourectomy
	  • sentinel node procedure or axillary lymph node clearance (according to local centre treatment protocol)

CONCOMITANT MEDICATIONS	**Not allowed:**

	Therapies for cancers including chemotherapy, immunotherapy and hormonal anticancer treatment are not allowed while the subjects are on study treatment. Inducers and strong inhibitors of CYP3A4 and CYP2B6 should be avoided if possible.
ASSESSMENT OF EFFICACY	The following efficacy parameters are assessed: • Residual cancer burden (RCB 0-1-2-3) at time of surgery • Complete pathologic response of the primary tumour (ypT0), irrespective of the response rate of the resected nodal metastases. • Complete pathologic response of the resected nodal metastases (ypN0), irrespective of the response rate of the resected nodal metastases. • Invasive Disease-Free Survival (iDFS) 3 years after surgery
ASSESSMENT OF SAFETY	Clinical and laboratory adverse events (AEs) and serious adverse events (SAEs) will be reported and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0
STATISTICAL ANALYSES	This analysis will be carried out on the eligible and randomised subjects who have been operated and in whom the residual cancer burden was measured. The observed proportions will be compared by a chi square test without continuity correction at an alpha two-sided level of 2.5%. Confidence intervals for the difference between proportions will be provided at the usual 95% level. The primary analyses will compare arm 1 and arm 2 as well as arm 1 and arm 3. As exploratory analysis, a confidence interval for the difference between proportions in arm 2 and arm 3 will be provided. **Secondary comparisons** : - Rates of subjects who have a two-fold increase in TIL levels in subjects with a baseline biopsy and operated and with TILs available using chi-square tests. - Rates of subjects with breast conservation surgery using chi square tests - Rates of subjects with pathological complete response on the positive axillary lymph nodes - Estimation using Kaplan-Meier method of disease-free survival and of invasive disease-free survival and comparison using log rank tests between arm 1 and arm 3 as well as arm 2 and arm 3. This analysis will be conducted on all subjects eligible and randomized. - Safety and toxicity will be descriptively analysed in all subjects eligible, randomized and having started treatment. **Exploratory analyses** :

	Exploratory analyses will be done to try to identify predictive factors of achievement of RCB0-1. The covariates that will be tested will include PDL1 status, TILs, TNM status. Modelling will be done using logistic regression models. Changes in prevalence of immune cell subpopulations will be descriptively analysed.
STRATIFICATION FACTORS	• PD-L1 status determined centrally • Centre
TRANSLATIONAL RESEARCH(ES)	• **Blood** samples will be drawn at baseline and during treatment in weeks 1, 4, 6, 12 and end of chemo (week 19 if no treatment interruptions), as well at surgery, end of treatment visit, first immune related toxicity and first progressive disease • Tissue **biopsies** will be obtained at baseline and a second time in week 6. An optional tissue sample could also be collected at disease progression, if that occurs. • Tissue from **surgical specimens** will be obtained in all eligible subjects.
LENGTH OF THE STUDY	**Safety Run-In** • Planned recruitment period : 2 months • Planned treatment period for a subject : 6 months • Planned follow-up period for a subject : up to 36 months **Phase II** • Planned recruitment period : 24 months • Planned treatment period for a subject : 6 months • Planned follow-up period for a subject : up to 36 months
END OF STUDY	• After last follow up visit of the last subject • The trial is mature for the analysis of the endpoints as defined in the protocol, if the trial reaches its endpoints • The database has been fully cleaned and frozen for all analyses