SYNOPSIS – PROTOCOL N° UC-0140/1606 – BIG 16-01

A) TRIAL IDENTIFICATION

**SPONSOR – PROTOCOL CODE NUMBER:** UC-0140/1606 – UCBG 105 - BIG 16-01

**VERSION (NR & DATE):** 1.0, OCTOBER 6th, 2016

**TRIAL TITLE:** A phase II trial testing durvalumab combined with endocrine therapy in patients with ER+/her2- breast cancer eligible for neoadjuvant endocrine therapy and who present CD8+ T cell infiltration after 4-6 weeks exposure to immune-attractant.

**ABBREVIATED TITLE:** ULTIMATE

**INTERNATIONAL COORDINATING INVESTIGATOR:** Pr. Fabrice ANDRE

**NUMBER OF PARTICIPATING CENTERS (ESTIMATE):** 40

**NUMBER OF PATIENTS:**
- SCREENING PHASE: 240
- PHASE II: 56

B) SPONSOR IDENTIFICATION

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C) TRIAL GENERAL INFORMATION

**INDICATION:** Patients with ER+ and HER2- primary non-metastatic breast cancer who are eligible to neoadjuvant endocrine therapy.

**METHODOLOGY:** This is an open-label, multicentric, international, phase II trial testing aromatase inhibitors in combination with durvalumab in patients with CD8+ T cell infiltration (>10% CD8+ T cells in the tumor). The trial includes two sequences: The first part of the treatment will consist in 4-6 weeks treatment with immune-attractants; in the second part, CD8+ patients will receive 6 months of durvalumab combined with exemestane.

**PRIMARY OBJECTIVE:** To assess the efficacy of durvalumab combined with exemestane in patients with CD8+ T cells on pathological response at surgery after a lymphocyte attraction phase.
SECONDARY OBJECTIVE(S):

**Efficacy:**
- To evaluate the capacity of several “immune-attractants” approaches to increase CD8+ T cells in the tumor site and to determine the best “immune-attractant”. The ability to attract CD8+ T cells in the tumor will be assessed by comparing the rate of CD8+ T cells after part 1 treatment with rate of CD8+ T cells at baseline.
- To assess the efficacy of six months durvalumab + exemestane combination therapy in ER+/Her2- BC presenting CD8+ T cells after 4-6 weeks exposure to immune-attractants on secondary endpoints
- To evaluate whether durvalumab expands intratumor lymphocytes.

**Safety**
- To assess the safety of each treatment (part 1 and part 2).

**Molecular and Exploratory**
- To assess the predictive value of mutational load, PDL1 expression on the efficacy of durvalumab / endocrine therapy
- To identify predictive biomarkers as measured by mutation, expression and copy number data for the efficacy of durvalumab / endocrine therapy
- To explore the pCR after six months durvalumab + exemestane according to the lymphocyte attraction treatment
- To assess CD8+ cells in surgical specimens of non-pCR patients
- To correlate immune infiltrate intensity with the proportion of tumor cells expressing PD-L1.

**INCLUSION CRITERIA:**

1. Age ≥18 years post-menopausal according to one of the following criteria:
   - Age > 60 years
   - Bilateral ovariectomy
   - Or Age ≤ 60, with an uterus and presenting an amenorrhea of more than 12 months and FSH and estradiol in the postmenopausal range
   - Or Age ≤ 60, without an uterus and FSH and estradiol in the postmenopausal range

2. Histologically proven invasive breast cancer eligible to neoadjuvant endocrine therapy according to multidisciplinary tumor board;
   - **Note:** Multicentric/multifocal tumors are allowed if all share the same characteristics.

3. cT2-T4, any N; cT2 are eligible only if the clinical tumor size is > 3cm

4. Non metastatic, M0 (according to clinical staging);

5. Luminal A patients ER-positive by IHC according to the following criteria (local assessment): Grade I or II AND ER-positive (≥ 60%) AND Ki67 <20%;

6. Her2-negative by IHC (score 0 or 1+) and/or FISH/CISH negative according to local assessment;

7. CD8+ T Cell infiltration defined as >10% cells stained with anti-CD8 mAB by IHC at the 3-week biopsy (applicable for inclusion in part 2 only);

8. Available tumor samples from baseline biopsy;

9. World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at enrolment;

10. Adequate organ and marrow function as defined below:
    - Hemoglobin ≥9.0 g/dL
    - Absolute neutrophil count ≥1.5 × 10⁹ /L
    - Platelet count ≥100 × 10⁹ /L
11. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures;

12. Written informed consent obtained prior to performing any protocol-related procedures, including screening evaluations.

**NON-INCLUSION CRITERIA (PART 1 AND 2):**

1. Inflammatory breast cancer

2. No prior exposure to immune-mediated therapy including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti-programmed cell death ligand 2 (anti-PD-L2) antibodies, excluding therapeutic anticancer vaccines;

3. Any concurrent chemotherapy, investigational product (IP), biologic therapy for cancer treatment;

4. Previous Radiotherapy treatment to more than 30% of the bone marrow;

5. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose;

6. History of allogenic organ transplantation;

7. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn’s disease], diverticulitis with the exception of diverticulosis, celiac disease or other serious gastrointestinal chronic conditions associated with diarrhea), systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome (granulomatosis with polyangiitis), Graves’ disease, rheumatoid arthritis, hypophysitis, uveitis, etc within the past 3 years prior to the start of treatment. The following are exceptions to this criterion:
   - Patients with vitiligo or alopecia
   - Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement or psoriasis not requiring systemic treatment;

8. Any condition that, in the opinion of the Investigator, would interfere with the evaluation of investigational product or interpretation of patient safety or study results, including ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring adverse events from investigational products, or compromise the ability of the patient to give written informed consent;

9. Mean QT interval corrected for heart rate using Fridericia’s formula (QTcF) ≥470 ms;

10. History of active primary immunodeficiency;

11. Known history of active tuberculosis;

12. Active infection including hepatitis B, hepatitis C, or human immunodeficiency virus (HIV).
13. Current or prior use of immunosuppressive medication within 14 days before the first dose. The following are exceptions to this criterion:
   - Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection).
   - Systemic corticosteroids at physiologic doses not exceeding 10 mg/day of prednisone or its equivalent
   - Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)

14. Receipt of live, attenuated vaccine within 30 days prior to the first dose of IP.
   Note: Patients, if enrolled, should not receive live vaccine during the study and up to 30 days after the last dose of IP.

15. Known allergy or hypersensitivity to any medicinal product used in the trial or any excipient

**PRIMARY ENDPOINT:**
Rate of pathological complete response on the surgical specimen.

**SECONDARY ENDPOINT(S):**

**EFFICACY CRITERIA**
- Number of CD8+ T cells
- Clinical response after 6 months therapy. Clinical response is determined by tumor assessments performed by palpation
- Assessment of Ki67 on the surgical specimen according to the recommendations from the International Ki67 in Breast cancer Working Group.
- Measurement of TILs according to the recommendations published by the international TILs working group 2014

**SAFETY**
According to the CTC-AE v4.03.

**TRANSLATIONAL RESEARCH (EXPLORATORY ENDPOINTS):**
Predictive value of Mutational load for the efficacy of durvalumab will be assessed by whole exome sequencing on baseline samples
Predictive value of PDL1 expression for the efficacy of durvalumab will be assessed both on baseline samples and at 3 weeks biopsy (Ventana SP263 assay)
Other biomarker research will be defined by the study steering committee at the end of the trial to ensure the optimal use of update technologies and hypotheses

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**D) INVESTIGATIONAL MEDICINAL PRODUCTS**

<table>
<thead>
<tr>
<th>Product names and administration:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug name (INN)</td>
</tr>
<tr>
<td>Lymphocyte activation</td>
</tr>
<tr>
<td>Durvalumab</td>
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<tr>
<td>Lymphocyte attraction: will be defined by the steering committee during the course of the trial</td>
</tr>
<tr>
<td>1st Cohort: Tremelimumab</td>
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<tr>
<td>Other cohorts: to be defined</td>
</tr>
</tbody>
</table>
**NON INVESTIGATIONAL MEDICINAL PRODUCTS (background treatment)**

<table>
<thead>
<tr>
<th>Exemestane</th>
<th>Aromasin® Tablet</th>
<th>Per os 25 mg/day</th>
</tr>
</thead>
</table>

**THERAPEUTIC REGIMENS:**
The study is conducted in 2 parts:

**Part 1: lymphocyte attraction.**
After the screening phase, the patient will receive immune-attractant combined with exemestane for six weeks.
As immune-attractants are added over the course of the study, they will appear as subsequent appendices in the full protocol.
Up to 4 cohorts may be tested sequentially in this design until up to 240 evaluable patients have been treated.
The first cohort patients will receive tremelimumab (3 mg/kg, single infusion) combined with exemestane (25 mg daily). In each cohort, an interim analysis will be performed after 30 patients in order to potentially stop the cohort (if less than 25% of patients present >10% CD8+ cells in the tumor after 3 weeks). If all 4 cohorts are closed and the target number of 56 patients for part 2 has not been reached, additional patients will be recruited and treated with the best performing immune-attractant treatment based on the part 1 results. From the moment 56 patients are included in part 2, no more patients will be entered in part 1.

After three weeks (+/- 3 days), a tumor biopsy will be done. Patients who present >10% CD8+ cells in the tumor after 3 weeks and remain eligible will be included in the second part of the trial (patients who do not present CD8+ T cells on the 3-weeks biopsy will be treated at the investigator’s choice).

**Part 2: lymphocyte activation (anti-PD1 treatment)**
Four to six weeks after immune-attractant start, patients having >10% CD8+ cells in the tumor will receive durvalumab 1500 mg Q4W (equivalent to 20 mg/kg Q4W) IV, combined with exemestane (25 mg daily), for six months.
Part 2 will include two steps. In the first step, we will include 23 patients. If 2 or more pathological complete responses are observed in these 23 patients, the part 2 will move to step 2. 33 additional patients will be included in the step 2.

**TREATMENT DURATION: 7 – 8 months**
E) STATISTICAL ANALYSIS PLAN

**PRIMARY OBJECTIVE:** Simon’s optimal two-stage design will be used. The null hypothesis that the true response rate is 5% will be tested against a one-sided alternative. In the first stage, 23 patients will be accrued. If there is 1 or fewer pCRs in these 23 patients, the study will be stopped. Otherwise, 33 additional patients will be accrued for a total of 56 (no matter what treatment was used for the lymphocyte attraction phase). The null hypothesis will be rejected if 6 or more pCRs are observed in 56 patients. This design yields a type I error rate of 5% and power of 80% when the true pCR rate is 15%.

**LYMPHOCYTE ATTRACTION PHASE:** We expect each drug in the window cohort to generate 25% of patients with CD8+ lymphocytes in the tumor. We assume from historical data that for endocrine therapy alone 10% of cells are CD8+ after the window phase. If 4 experimental arms are compared separately against the historical control, each comparison will be made at a 5%/4 = 1.25% α-level. A number of 60 patients by arm will allow to reject the null hypothesis of 10% or less CD8+ cells with 82% power, when the true CD8+ rate is 25% and when one interim analysis is performed after 30 patients. Early stopping for futility uses the Pocock-type spending function and early stopping for efficacy the Haybittle-Peto method.

F) SAMPLES COLLECTED FOR TRANSLATIONAL RESEARCH

**SAMPLE TYPES:**
- Paraffin blocks:
  - 1 formalin fixed paraffin embedded block (FFPE) from baseline
  - 2 FFPE core biopsies must be performed 3 weeks after the start of part 1
  - 1 FFPE tumor block at surgery if residual disease
- Blood samples (Total blood and plasma)
  - 20 ml (before lymphocyte attraction, before starting durvalumab, before surgery)

G) TRIAL DURATIONS

**INCLUSION PERIOD:** 2 YEARS

**TREATMENT PERIOD:** 7-8 MONTHS

**FOLLOW-UP:** 1 YEAR

**OVERALL TRIAL DURATION (INCLUDING FOLLOW-UP):** 4 YEARS

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**UNICANCER Tumor Group: UCBG**
**Protocol n°: UC-0140/1606 – BIG 16-01**
**EudraCT n°: 2016-000764-42**

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**TRANSLATIONAL RESEARCH**
### H) TRIAL FLOW-CHART

#### VISITS

<table>
<thead>
<tr>
<th></th>
<th>Inclusion</th>
<th>Treatment Part 1°</th>
<th>Treatment Part 2°</th>
<th>pre-operatory assessment (end of treatment)</th>
<th>Surgery</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Week 0</td>
<td>Week 3 (+/- 3 days)</td>
<td>Every 4 weeks (during 6 months)</td>
<td>30 days after end of treatment</td>
<td>At 1 month, 6 and 12 months after surgery</td>
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<tr>
<td>Written informed consent</td>
<td>X</td>
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<tr>
<td>Verification of eligibility criteria</td>
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<tr>
<td>Medical history</td>
<td>X</td>
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<tr>
<td>Biopsy collection (FFPE block)</td>
<td>X°</td>
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#### CLINICAL EXAMINATION

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<tbody>
<tr>
<td>Clinical examination and vital signs, PS (WHO)</td>
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<tr>
<td>Safety assessment*</td>
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<td>X</td>
<td>X</td>
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#### PARACLINICAL EXAMINATION

| | | | | | |
|---|---|---|---|---|
| Mammogram | X | X | | | X² |
| Mammary Ultrasound | X | X | | | |
| ECG | X | | | | |
| LVEF | X | | | | |
| Bone densitometry | X | | | | X³ |
| Optional: MRI, PET-Scan | X | | | | |

#### BIOLOGICAL TESTS

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<tr>
<td>Hematology, Blood chemistry</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>Renal, Liver evaluation, thyroid function tests, amylase, lipase</td>
<td>X</td>
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#### TRANSLATIONAL RESEARCH

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<tbody>
<tr>
<td>Blood sample (total and plasma)*</td>
<td>X°</td>
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#### TREATMENT

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<tbody>
<tr>
<td>Exemestane</td>
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<tr>
<td>Immune-attractant</td>
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<tr>
<td>Durvalumab*</td>
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a. Only for patients who present > 10% CD8+ T cells in the tumor; b. Two mandatory cores biopsies to be performed at week 3, to assess CD8+ cells in the tumor; c. At 12 months according to local practice; d. Should be assessed at each clinical visit; e. 20 ml total blood and plasma to be collected before the first administration of immune attractant treatment, before starting durvalumab, before surgery; f. one FFPE tumor block from baseline and one at surgery if residual disease; g. schedule of visit will depend on the treatment tested (please refer to appendix 1); h. Every 6 weeks according to standard practice; i. eligibility criteria will be checked only before starting treatment part 2.