AIPAC-003: A randomized, double-blind, placebo-controlled phase 3 trial testing efiltiramod alpha (soluble LAG-3) in HER2-neg/low metastatic breast cancer patients receiving paclitaxel, following an open-label dose optimization

**BACKGROUND**

Metastatic Breast Cancer (MBC):
- As the worldwide most diagnosed cancer1 with four main molecular subtypes based on the degree of expression of HER2 and HR status, this trial aims to recruit patients with HR2 or HR- and HER2-neg/low MBC.
- **HR** HER2-neg/low: high unmet medical need with most patients eventually facing resistance to endocrine-based therapy (ET). Single agent chemotherapy (especially taxanes) are commonly used for this patient population (Figure 1).
- **Triple Negative Breast Cancer (TNBC)**: aggressive disease with poor outcome. Choice of therapy depends predominantly on PD-L1 expression (Figure 2). Limited choice of treatment for patients ineligible for anti-PD-X-based therapy and candidates for chemotherapy. No active immune-oncology (IO) treatment approved for this patient population.

**Eiltiramod alpha (efti):**
- **Mechanism of action:** as a soluble LAG-3 protein (LAG-3 domains fused to human IgG backbone), efti targets a subset of MHC class II molecules to mediate activation of antigen presenting cells (APCs: dendritic cells & monocytes), natural killer (NK) and T-cells (Figure 3).
- **Difference to anti-LAG-3 mAbs:** efti does not bind to LAG-3 on T cells like anti-LAG-3 antagonists; efti is an MHC class II agonist.
- **Synergistic effect with chemotherapy:** efti reinforces long-lasting T cell responses, leading to more durable effects and prolonged survival with minimal related side effects.

**Rationale for trial:**
- Data from predecessor randomized, phase 2b trial of paclitaxel plus either efti or placebo in HR+ HER2-MBC patients (AIPAC; NCT02614833) linked sustained pharmacodynamic activity to improved overall survival (OS) in the efti arm2.
- To address a high unmet medical need in HR+ HER2-neg/low MBC and metastatic TNBC patients eligible to receive chemotherapy after failure of previous standard of care therapies.

**TRIAL DESIGN**

Open-label dose optimization lead-in (DOL) component followed by a double-blinded, randomized, placebo-controlled phase 3 component (Figure 4).
- **Dose optimization lead-in:** determine optimal biological dose (OBD) based on final safety, tolerability, efficacy & pharmacodynamic data. Comprises a safety lead-in followed by a randomized dose optimization lead-in.
- **Phase 3:** randomized, double-blinded; to be further defined after completion of DOL.

Treatment for the DOL and Phase 3 components of the trial will consist of a chemo-immunotherapy (chemo-IO) phase followed by an immunotherapy (IO)-phase (Figure 5).

**DOSE OPTIMISATION LEAD-IN**

**PHASE 3**

**TRIAL SITES & RECRUITMENT**

**RECRUITMENT**

Recruitment is ongoing. For more info, please visit: https://www.clinicaltrials.gov/ct2/show/NCT05747794

**EUROPE: SPAIN & BELGIUM**

**Country** | **# of sites**
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Belgium | 4
Spain | 7
US | 5
**Total** | **16**

**KEY ELIGIBILITY CRITERIA**

**Key inclusion criteria**
- HR+ and HER2-neg/low MBC.
- HR+ MBC patients with proven resistance to endocrine-based therapy and are indicated to receive chemotherapy for metastatic disease.
- TNBC patients who are ineligible for anti-PD-X-based therapy and are indicated to receive paclitaxel for metastatic disease in 1st line setting.
- Measureable disease as defined by RECIST 1.1 for the dose optimization lead-in.
- ECOG performance status 0-1.
- Expected survival longer than 3 months.

**Key exclusion criteria**
- Prior chemotherapy for MBC.
- Disease-free interval less than 12 mo from last dose of adjuvant chemotherapy.

**PATIENT POPULATION FOR THE PHASE 3 WILL BE DEFINED ONCE OBD IS DEFINED.**

**TRIAL SITES**

Europe: Spain & Belgium

**PAACLITAXEL**

- 80 mg/m2 as I.V. infusion over 1-hr as part of a 4-week cycle.
- 6 planned cycles with extension possibility at discretion of investigator as per patient’s tolerability. If paclitaxel is stopped due to toxicity, patient may move on to efti/placebo alone if 4 cycles with paclitaxel were completed.

**EILTIRAMOD ALFA**

- 30 or 90 mg injected same day ±30 min after paclitaxel infusion as a s.c. injection in the anterior face of thigh.
- Maximum of 26 injections.

**REFERENCES**

1. N. K. Ibrahim1; K. Papadimitriou2; F. P. Duheux3; S. M. Marullo3; M. Oliveira4; B. Doger4; D. Houtsma5; A. Becker6; J. Peguero7; O. Marathe8; F. Triebel9
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3. AIPAC—Active Immunotherapy Paclitaxel
DOL—Dose optimization lead-in
ECOG—Eastern Cooperative Oncology Group
ET—Endocrine Therapy
MBC—Metastatic Breast Cancer
US—United States

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**DISCLOSURES**

First author: Dr. Michiel Oostrom
COI: This author has no potential conflicts of interest to disclose.