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

Poster # 336b

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2023 ASCO ANNUAL MEETING

BACKGROUND

Metastatic Breast Cancer (MBC):

- As the worldwide most diagnosed cancer[1] with four main molecular subtypes based on the degree of expression of HER2 and HR status, this trial aims to recruit patients with HR$^+$ 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.

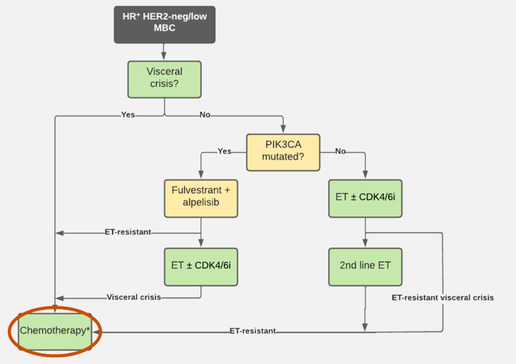
Eftilagimod alpha (efti):

- **Mechanism of action:** as a soluble LAG-3 protein (LAG-3 domains fused to human IgG backbone[2]), 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 arm[3].
- 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.

Figure 1: HR$^+$ HER2-neg/low MBC treatment algorithm adapted from ASCO[4]



MBC: metastatic breast cancer; HR: hormone receptor; HER2: human epidermal growth factor receptor 2; PIK3CA: phosphatidylinositol 3-kinase; ET: endocrine therapy; CDK4/6i: CDK4/6 inhibitors; *combination chemotherapy for patients with visceral crisis

Figure 2: Summarized algorithm for treatment of mTNBC based on ESMO guidelines

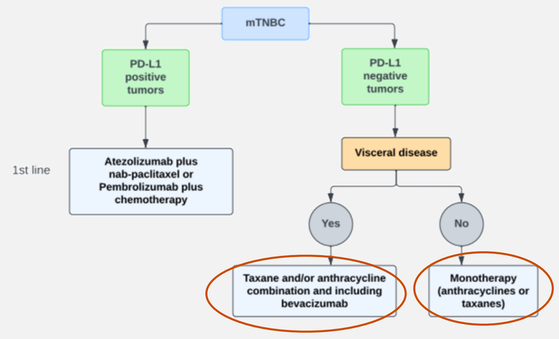
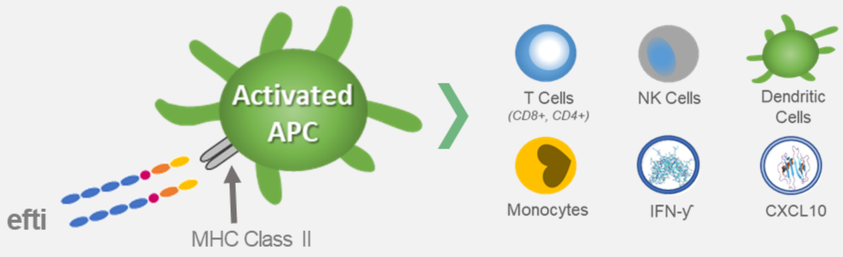


Figure 3: MoA of efti



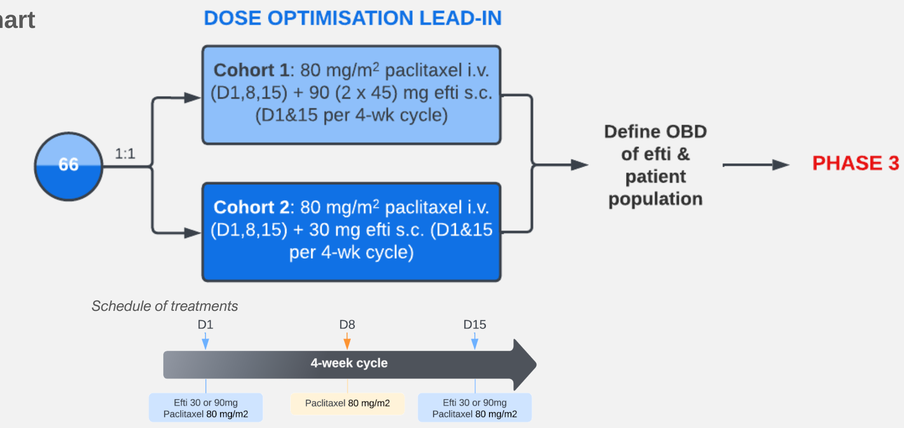
TRIAL DESIGN

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**).

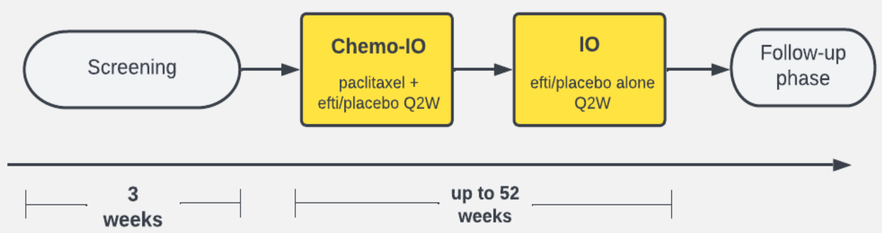
Figure 4: Trial flow chart



Dose optimization lead-in

PRIMARY OBJECTIVES	SECONDARY OBJECTIVES
• Safety and tolerability of 90 mg efti plus paclitaxel, compared to 30 mg efti plus paclitaxel. • Define OBD of efti when combined with weekly paclitaxel for the Phase 3 component of the trial.	• ORR by RECIST 1.1; PFS and OS of 30 and 90 mg efti plus paclitaxel. • Quality of life (QoL) at both doses. • Pharmacokinetic (PK) profile of efti at 30 and 90 mg.

Figure 5: Schematic overview of AIPAC-003 trial



For more details on duration of drug treatments see further details in Drug Administration section.

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.
- Measurable disease as defined by RECIST 1.1 for the dose optimization lead-in.
- ECOG performance status 0-1.
- Expected survival longer than 3 months.

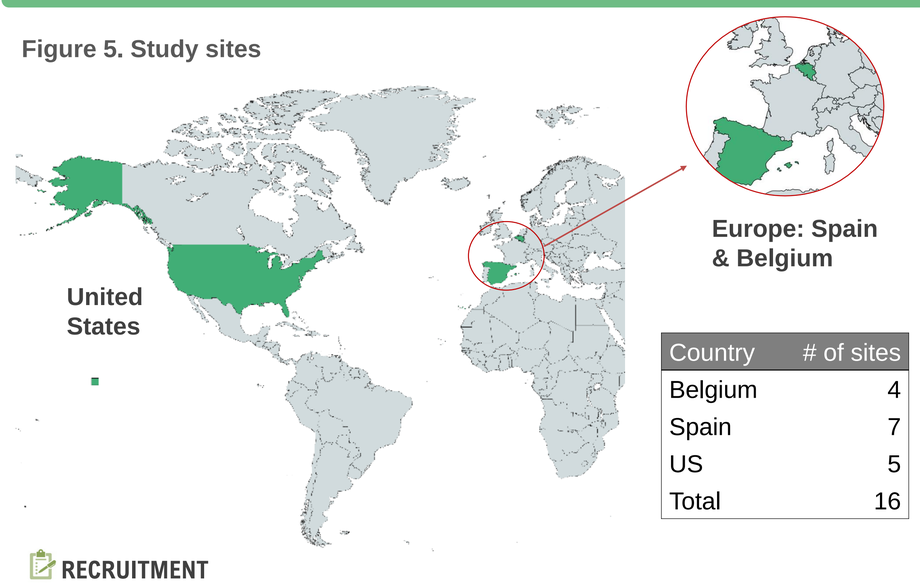
Key exclusion criteria

- 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 & RECRUITMENT

Figure 5. Study sites



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

RECRUITMENT

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

DRUG ADMINISTRATION

Paclitaxel:

80 mg/m^2 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.

Eftilagimod alpha:

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.

ABBREVIATIONS

AIPAC… Active Immunotherapy PAClitaxel
DOL… Dose optimization lead-in
ECOG… Eastern Cooperative Oncology Group
ET… Endocrine-based Therapy (ET)
HR... hormone receptor
IO... immuno-oncology therapy
(i)RECIST… (Immune) Response Evaluation Criteria In Solid Tumors
I.V.… intravenous
LAG-3... Lymphocyte Activation gene-3
MHC… Major Histocompatibility Complex
NK… natural killer
OBD… Optimal biological dose
ORR… objective response rate
OS… overall survival
PD-L1...Programmed death-ligand 1
PD-1... Programmed cell death protein 1
PFS… progression-free survival
PK… Pharmacokinetic
QoL… Quality of life
s.c… Subcutaneous
Th1… T helper type 1

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DISCLOSURES

First author: *Dr. Nuhad Ibrahim*
COI: This author has no relationships to disclose.

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