# Testing a higher dose (90 mg s.c.) of eftilagimod alpha, a soluble LAG-3 protein, in metastatic breast cancer patients receiving weekly paclitaxel in AIPAC-003

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S. Morales Murillo[1]; F. Forget[2]; E. Segui[3]; N.K. Ibrahim[4]; B. Doger[5]; J. Canon[6]; P. Chalasani [7]; K. Papadamitriou[8]; M. Oliveira[9]; P. Sanchez Rovira[10]; F.D. Vogl[11]; C. Mueller[11]; F. Triebel[12]

[1]Hospital Universitario Arnau de Vilanova, IRB-Lleida, Lleida, Spain; [2]Centre Hospitalier de l'Ardenne, Libramont, Belgium; [3]Hospital Clinic de Barcelona, Barcelona, Spain; [4]The University of Texas MD Anderson Cancer Center, Houston, USA; [5]START Madrid: Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [6]Grand Hopital de Charleroi, Hopital Notre Dame, Charleroi, Belgium; [7]George Washington University, Washington, USA; [8]Antwerp University Hospital, Antwerp, Belgium; [9]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [10]Hospital Universitario de Jaen, Jaen, Spain; [11]Immutep GmbH, Berlin, Germany; [12]Immutep SAS, Saint-Aubin, France.

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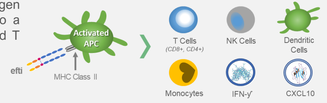
## BACKGROUND

### Eftilagimod alpha (efti):

- **Mechanism of action:** efti is a soluble LAG-3 protein (LAG-3 domains fused to human IgG backbone) and MHC Class II agonist. Activating antigen presenting cells (APCs: dendritic cells & monocytes) with efti leads to a broad immune response to fight cancer, including increases in activated T cells (CD4/CD8) and other important immune cells/cytokines **(Figure 1)**.
- **Synergistic effect with chemotherapy**: efti reinforces long-lasting T cell responses, leading to more durable effects & prolonged survival with minimal related side effects.

**Figure 1: MoA of efti**




### Trial Rationale:

- 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[1].
- 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.

## METHODS

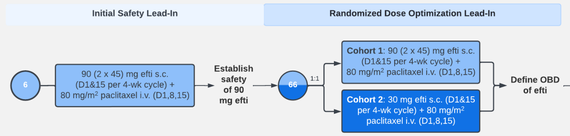
### Trial Design

AIPAC-003 has multiple components, including an **initial safety lead-in** component followed by a Phase 2 **open-label dose optimization lead-in** and final **Phase 3** component as described below and in **Figure 2**.

- **Initial safety lead-in (n=6):** evaluate safety of a higher dose of efti (90 mg).
- **Dose optimization lead-in (n=66):** randomized 1:1 to determine optimal biological dose (OBD) based on safety, tolerability, efficacy & pharmacodynamic/ pharmacokinetic (PK) data.
- **Phase 3:** randomized, double-blinded; to be further defined after determination of the OBD.

**Figure 2: Trial Design & Schedule of Treatments**

**A) Key trial components of AIPAC-003**




**B) Treatment phases & schedule of treatments**


### Key Inclusion/ Exclusion Criteria

- Female patients with MBC HR+ HER2-neg/low* or mTNBC.
- ECOG performance status 0-1.
- No prior chemo in the metastatic setting.
- Measurable disease.

### Assessments and Statistical Analysis

- Data cut-off date was April 3, 2024, for safety and efficacy analyses; and March 28, 2024 for immuno-monitoring & PK analyses.

*Estrogen and/or progesterone receptor positivity is defined as ≥1%, HER2 receptor negativity is defined in line with ASCO/CAP guidelines[2,3].

### Primary Objective:

- Safety & tolerability of 90 mg efti combined with paclitaxel.

### Secondary Objectives:

- ORR by RECIST 1.1, PFS, OS and PK profile.

## RESULTS

### BASELINE CHARACTERISTICS

- Between May–Sep 2023, 6 patients were enrolled into the safety lead-in with a minimum follow up of 4.0 months. Baseline characteristics are reported in **Table 1.**

**Table 1: Baseline characteristics**

| Baseline characteristics, n (%) | (N=6) |
|---|---|
| Age, median (range), years | 66.0 (35–78) |
| <65 years | 3 (50.0) |
| ECOG 0/1 | 5 (83.3) / 1 (16.7) |
| HR receptor positivity | |
| ER / PR | 6 (100) / 4 (66.7) |
| HER2 receptor status | |
| Negative / Low | 2 (33.3) / 4 (66.7) |
| Pre-menopausal / Post-menopausal | 1 (16.7) / 5 (83.3) |
| Cancer stage at initial diagnosis | |
| II / III / IV | 3 (50.0) / 2 (33.3) / 1 (16.7) |
| Time between initial diagnosis and first onset of metastasis, median (range), months | 77.5 (0.1–252.8) |
| (Neo)adjuvant therapy | 4 (66.6) |
| Endocrine therapy | 3 (50.0) |
| Chemotherapy* | 4 (66.6) |
| Duration of prior CDK 4/6i + ET for metastatic disease, median (range), months | 7.3 (0.6–82.1) |
| Endocrine resistance | 6 (100) |

CDK: cyclin-dependent kinase; ECOG: Eastern Cooperative Oncology Group; ER: estrogen receptor; HR: hormone receptor; PR: progesterone receptor.

*including 2 patients treated with taxanes.

### SAFETY

- No dose-limiting toxicities or treatment-emergent adverse events (TEAEs) of grade 3 or higher severity were recorded. Most frequent TEAEs are listed in **Table 2**.

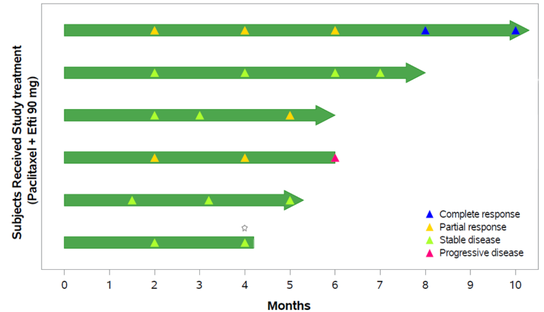
**Table 2: TEAEs with incidence ≥2 patients**

| Preferred term, n (%) | Grade 1-2 | Grade ≥3 |
|---|---|---|
| Anemia | 2 (33.3) | NA |
| Neutropenia | 2 (33.3) | NA |
| Polyneutropathy | 2 (33.3) | NA |
| Asthenia | 2 (33.3) | NA |

### EFFICACY

- All responses were confirmed, leading to a confirmed ORR per RECIST 1.1 of 50.0%, including one complete response (CR) (**Table 2** and **Figures 3-5**).
- DCR of 100% (**Table 3**).

**Figure 3: Swimmer plot**




Each bar represents one subject in the study (data cut-off =03-Apr-2024). Right arrow cap indicates patients ongoing treatment
☆ Discontinuation due to investigator´s decision

**Table 3: Confirmed best overall response**

| Response[1], n (%) | N=6 |
|---|---|
| Complete Response | 1 (16.7) |
| Partial Response | 2 (33.3) |
| Stable Disease | 3 (50.0) |
| Progression | 0 |
| ORR | 3 (50.0) |
| DCR | 6 (100) |

[1]Response was investigator-assessed per RECIST 1.1.

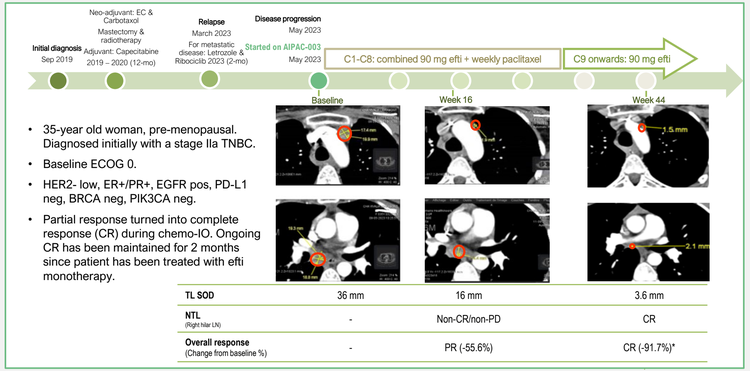
### IMMUNO-MONITORING

- Efti's 90 mg pharmacodynamic effects showed an increase of circulating levels of immune cells such as CD8 and CD4 T cells. Plasma TH1 biomarker levels were also increased (**Figure 5**).

### PHARMACOKINETICS

- 90 mg efti remains detectable at a pharmacologically-active dose (≥1 ng/mL) up to 96 hours after administration (**Figure 6**).

**Figure 4: Case study of a 35-year-old woman with confirmed CR on continued efti**

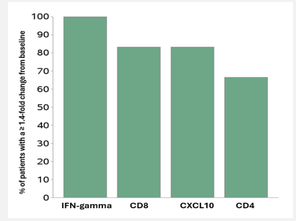



- 35-year old woman, pre-menopausal. Diagnosed initially with a stage IIa TNBC.
- Baseline ECOG 0.
- HER2- low, ER+/PR+, EGFR pos, PD-L1 neg, BRCA neg, PIK3CA neg.
- Partial response turned into complete response (CR) during chemo-IO. Ongoing CR has been maintained for 2 months since patient has been treated with efti monotherapy.

| | | | |
|---|---|---|---|
| **TL SOD** | 36 mm | 16 mm | 3.6 mm |
| **NTL** (Right hilar LN) | - | Non-CR/non-PD | CR |
| **Overall response** (Change from baseline %) | - | PR (-55.6%) | CR (-91.7%)* |

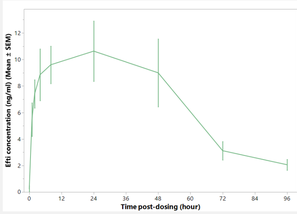
*Shrinkage of both lymph nodes target lesions to <10mm along short axis led to complete response of ~92%.

**Figure 5: Th1 biomarker ≥1.4* fold change from baseline**




*To detect a clinically-relevant change in biomarkers, the minimum fold change increase presented was at least ≥1.4.

**Figure 6: Efti PK profile**




## SUMMARY & CONCLUSION

- **Initial results from the safety lead-in of the AIPAC-003 study suggest 90 mg efti plus weekly paclitaxel can be safely combined & is well-tolerated in metastatic breast cancer patients.**
- **Encouraging confirmed ORR of 50% (including 1 confirmed CR) and DCR of 100%.**
- **The 90 mg dose of efti plus weekly paclitaxel is being evaluated further in the randomized OBD component (n=66), which will compare 90 mg vs 30 mg of efti to determine the optimal biological dose.**

Recruitment for this study is ongoing. For more info, please visit: Clinicaltrials.gov

**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*
*RECIST… 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*
*PD-L1…Programmed death-ligand 1*
*PD-1… Programmed cell death protein 1*
*s.c… Subcutaneous*
*Th1… T helper type 1*

**REFERENCES**

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**DISCLOSURES**

***First author:*** *Serafin Morales Murillo*
*COI: no COI to disclose.*

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