AIPAC (Active Immunotherapy PAClitaxel): A randomized, double blind, placebo-controlled, multinational Phase IIb trial evaluating the efficacy of eftilagimod alpha (a soluble LAG-3 fusion protein) in combination with paclitaxel in hormone receptor-positive metastatic breast cancer

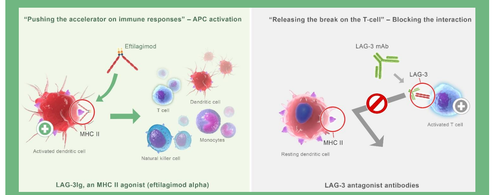
SABCS SAN ANTONIO BREAST CANCER SYMPOSIUM December 10-14, 2019 Henry B. Gonzalez Convention Center, San Antonio, Texas, USA

Dirix L[1], Wildiers H[2], Huizing M T[3], De Cuypere E[4], Schröder C P[5], Armstrong A C[6], Huober J[7], Marme F[8], Schneeweiss A[9], Khan S[10], Triebel F[11]

[1]GZA Hospitals Sint-Augustinus, Antwerp, Belgium
[2]Depatment of General Medical Oncology and Multidisciplinary Breast Centre, University Hospitals Leuven, Belgium
[3]Breast and Gynaecological Oncology Unit, UZA, Wilrijk, Belgium
[4]AZ Sint-Jan Brugge-Oostende AV, VZW Oncological Centre, Brugge, Belgium
[5]University Medical Centre Groningen, Groningen, The Netherlands
[6]The Christie NHS Foundation Trust/Clinic - Medical Oncology, Manchester, United Kingdom
[7]University Clinic for Women, Ulm, Germany
[8]Gynaecological Oncology, Heidelberg University, University Clinic Mannheim, Mannheim, Germany
[9]National Centre for Tumor Diseases, Heidelberg, Germany
[10]Nottingham University Hospitals NHS Trust, Clinical Oncology, Nottingham, United Kingdom
[11]Research & Development, Immutep S.A.S., Orsay, France

Poster No: OT1-01-05

Eftilagimod alpha (efti; previously IMP321) is a **soluble LAG-3 protein** that binds to a subset of MHC class II molecules to **mediate antigen presenting cell (APC) activation** and then **CD8 T-cell activation**.



Efti is a first-in-class APC activator

The activation of the dendritic cell network with efti injected s.c. the day after chemotherapy may lead to stronger anti-tumor CD8 T-cell responses at a time when these APCs are loaded with tumor antigens. This is tested in the present AIPAC trial (Active Immunotherapy PAClitaxel) in hormone receptor-positive (HR$^+$) stage IV metastatic breast carcinoma (MBC) patients receiving efti or placebo as adjunctive to weekly paclitaxel as a first-line chemotherapy.

Combining an APC activator like efti with chemotherapy is therefore **fundamentally different** from combining checkpoint inhibitors like an anti-LAG-3 mAb with chemotherapy. AIPAC is to our knowledge the first randomized trial in HR$^+$ metastatic breast cancer combining an active immunotherapy and chemotherapy.

Previous clinical trial experience with the same combination used in MBC suggests that the combination is safe and shows encouraging signs of efficacy. Primary analysis (PFS events) of this Phase IIb trial is expected in Q1 2020.

Trial design

A multicentre, placebo-controlled, double blind, 1:1 randomized Phase IIb clinical trial in 2 stages:

- **Safety run-in stage (n=15):** open-label, determining recommended Phase 2 dose of efti in combination with paclitaxel for randomized phase
- **Randomisation stage (n=227):** placebo-controlled, double-blind, treatment: efti plus paclitaxel versus paclitaxel plus placebo

Treatment design

The treatment consists of a chemo-immunotherapy phase followed by a maintenance phase:

- **Chemo-immunotherapy phase**: 6 cycles of 4 weeks with weekly paclitaxel (corticoid premedication allowed) at days 1, 8 and 15 plus either efti or placebo, on days 2 and 16 of each 4-week cycle
- **Maintenance phase**: responding or stable patients will afterwards receive study agent (efti or placebo) every 4 weeks for additional 12 injections

- Treatment **Arm A: 80 mg/m² paclitaxel i.v. days 1, 8, 15** plus **placebo s.c. days 2 and 16** until end of cycle 6 and then placebo s.c. every 4 weeks
- Treatment **Arm B**: **80 mg/m² paclitaxel i.v. days 1, 8, 15** plus **30 mg efti s.c. days 2 and 16** until end of cycle 6 and then 30 mg efti s.c. every 4 weeks
- Patients stay on treatment until disease progression, unacceptable toxicity, completion of the maintenance or discontinuation for any other reason
- Patients are staged according to RECIST 1.1 every 8 weeks until week 72 and every 12 weeks thereafter

Objectives (randomization stage)

- To determine efficacy of weekly paclitaxel combined with efti or placebo in HR$^+$ metastatic breast cancer patients
- To characterise anti-tumour activity of efti, safety, tolerability, immunogenic properties, quality of life, immune responses and biomarker of paclitaxel plus efti or placebo

Main Inclusion criteria

Patients are to be included in the study at the time of screening if all the following applies:

- Stage IV HR$^+$ breast adenocarcinoma (histologically proven estrogen receptor and/or progesterone receptor positive)
- Patients who are indicated to receive first line chemotherapy with weekly paclitaxel
- ECOG performance status 0-1
- Evidence of measurable disease as defined by RECIST 1.1

Main Exclusion criteria

Patients are to be excluded from the study at the time of screening for any of the following reasons:

- Prior chemotherapy for metastatic breast adenocarcinoma
- Disease-free interval of <12 months from the last dose of adjuvant chemotherapy
- Candidate for treatment with trastuzumab (or other Her2/neu targeted agents)
- Systemic chemotherapy, radiation therapy or any other investigational agent within 4 weeks, endocrine therapy within 1 week or CDK4/6 inhibitors within 5 times half-life prior to first dose of study treatment
- Known cerebral or leptomeningeal metastases
- Any condition requiring continuous systemic treatment with corticosteroids (>10 mg daily prednisone equivalents)

Primary Endpoint (randomization stage)

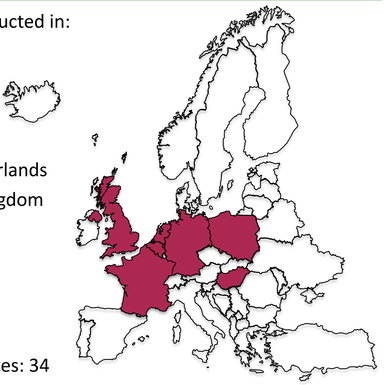
- Progression-free survival

Secondary Endpoints (randomization stage)

- Overall survival (gate keeping approach)
- Assessment of adverse events and other safety parameters
- Time to next treatment, objective response rate according to RECIST 1.1, time to and duration of response
- Development of anti-drug (efti) antibodies and assessment of Th1 biomarker

Involved countries

- AIPAC is conducted in:
  - Belgium
  - France
  - Hungary
  - Poland
  - The Netherlands
  - United Kingdom
  - Germany
- Number of sites: 34



Study status

- Stage 1 completed in 2017 → Poster at ASCO 2018
- Stage 2 fully recruited between January 2017 and June 2019 → Treatment and follow-up ongoing
- Primary analysis (after pre-determined number of PFS events) expected Q1 2020 → follow-up analyses including OS in 2021/2022

APC…antigen-presenting cell
ECOG…Eastern Cooperative Oncology Group
efti…Eftilagimod alpha
HR$^+$…hormone receptor-positive
mAb…monoclonal antibody
MBC…metastatic breast cancer
MHC…Major Histocompatibility Complex
OS…overall survival
PFS…progression-free survival
RECIST…Response Evaluation Criteria In Solid Tumors

The AIPAC trial protocol has been published, please see Dirix, L. & Triebel, F. Future Oncol. 2019 Jun;15(17):1963-1973. The trial identifiers are IMP321-P011 (sponsor code), 2015-002541-63 (EudraCT) and NCT02614833 (ClinicalTrials.gov).
Corresponding author: Frederic Triebel, frederic.triebel@immutep.com