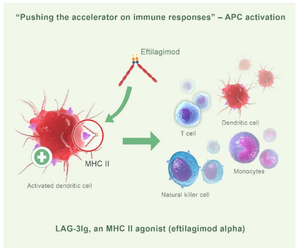
Primary efficacy results from AIPAC: A double-blinded, placebo controlled, randomized multinational phase IIb trial comparing weekly paclitaxel plus eftilagimod alpha (soluble LAG-3 protein) vs. weekly paclitaxel plus placebo in HR-positive metastatic breast cancer patients

Abstract # 132

Hans Wildiers[1], Anne Armstrong[2], Eveline Cuypere[3], Florence Dalenc[4], Luc Dirix[5], Steve Chan[6], Frederik Marme[7], Carolina Pia Schröder[8], Jens Huober[9], Jill Wagemans[10], , Peter Vuylsteke[11], Jean-Philippe Jacquin[12], Etienne Brain[13], Sherko Kümmel[14], Zsuzsanna Pápai[15], Luca Perjesi[16], Christian Mueller[17], Chrystelle Brignone[18] and Frederic Triebel[18]

[1]Department of General Medical Oncology and Multidisciplinary Breast Centre, Leuven, Belgium, [2]The Christie NHS Foundation Trust, Manchester, UK, [3]AZ Sint-Jan Burgge-Oostende AV, Ruddershove, Belgium, [4]Institut Claudius Regaud, Toulouse, France,[5]GZA ziekenhuizen campus Sint-Augustinus, Oosterveldlaan, Belgium, [6]Nottingham Cancer Clinical Trials Team (NCCTT), Nottingham, UK, [7]National Center for Tumor Diseases (NCT) Heidelberg, Heidelberg, DE, [8]University Medical Center Groningen, Groningen, Netherlands, [9]Universitätsfrauenklinik Ulm, Ulm, Germany [10]AZ Sint-Maarten, Mechelen, Belgium, [11]Clinique Sainte-Elisabeth, Uccle, Belgium, [12]Institut de Cancérologie de la Loire (ICO) Lucien Neuwirth, Saint Priest en Jarez, France, [13] Institut Curie -Hôpital René Huguenin, Saint-Cloud, France, [14]KEM | Evang. Kliniken Essen-Mitte, Essen, Germany, [15]MH Egészségügyi Központ Onkológiai Osztály, Budapest, Hungary, [16]Immutep, Budapest, Hungary, [17]Clinical Development, Immutep, Berlin, Germany, [18]Research & Development, Immutep, Paris, France

BACKGROUND



Eftilagimod alpha (efti) is a soluble LAG-3 protein (not an anti-LAG-3 antagonistic antibody) that binds to a subset of MHC class II molecules to mediate antigen presenting cells (APC) and CD8 T-cell activation. The stimulation of the dendritic cell network and subsequent T cell recruitment may lead to stronger anti-tumor responses in combination with paclitaxel than observed with paclitaxel alone. We report results from the randomized part of the AIPAC study (Active Immunotherapy PAClitaxel; NCT02614833) in metastatic breast carcinoma (MBC) patients.

TRIAL DESIGN

Multicentre, placebo-controlled, double-blind, 1:1 randomized Phase IIb study in female hormone receptor-positive metastatic breast cancer patients. The study comprises of two stages

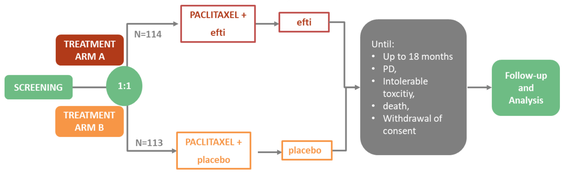
- **Safety run-in stage:** open-label, determining recommended Phase 2 dose of efti in combination with paclitaxel for randomized phase
- **Randomization stage:** placebo-controlled, double-blind, efti plus paclitaxel versus paclitaxel plus placebo

The results of the run-in phase were published in 2018 at ASCO. Here we report the results of the randomized double blinded phase IIb part of the study.

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 (12 months)



- *Treatment Arm A: 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*
- *Treatment Arm B: 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*

OBJECTIVES AND ENDPOINTS

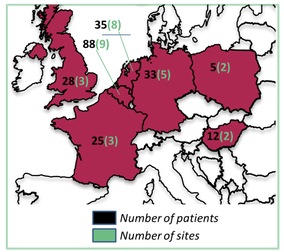
- **Primary Endpoint:** Progression Free Survival (PFS) per blinded independent central read (BICR)
- **Secondary Endpoints**: Overall survival (OS); Adverse events according to the current National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) and other safety parameters; other efficacy parameter (e.g. PFS according to local read, overall response rate (ORR), time to next treatment (TTNT), duration of response (DOR)), Quality of life (QoL) (e.g. EORTC QLQ-C30), to assess antidrug antibodies (ADA)
- **Exploratory Endpoints**: Blood immune cell phenotypes (CD8 T cells) and circulating Th1 biomarkers

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 (code for sponsor), 2015-002541-63 (EudraCT) and NCT02614833 (ClinicalTrials.gov).

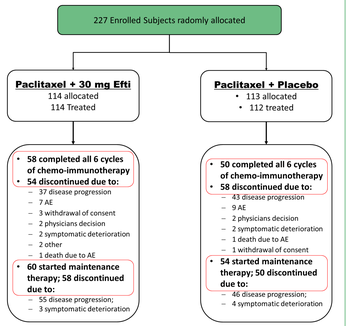
PATIENT DISPOSITION AND EXPOSURE

- In total, 227 patients were randomized to efti (n=114) and to placebo (n=113). All except one patient received at least 1 treatment and were included in the full analysis and safety population
- Dose intensity for paclitaxel and general exposure was similar between the groups

Baseline Characteristic	Efti + paclitaxel (N=114); N (%)	Placebo + paclitaxel (n=112); N(%)
Median age, years (range) < 65 years	58 (24-87) 76 (66.7)	61 (35-79) 71 (63.4)
ECOG 0	69 (60.5)	70 (62.5)
Visceral Disease	103 (90.4)	104 (92.9)
Prior therapy for met. disease *Containing CDK 4/6*	78 (68.4) *50 (43.9)*	80 (71.4) *48 (42.9)*
Luminal A / B / Other**	34.1 % / 48.8 % / 17.1 %	36.7 % / 49.4 % / 13.8 %
Monocytes <0.25/nl	25 (21.9)	22 (19.8)



- Patients were recruited across Europe (see figure above)
- 58 (50.8 %) pts (efti) and 50 (44.6%) pts (placebo) completed the chemo-immuno-phase→ details in the patient disposition chart

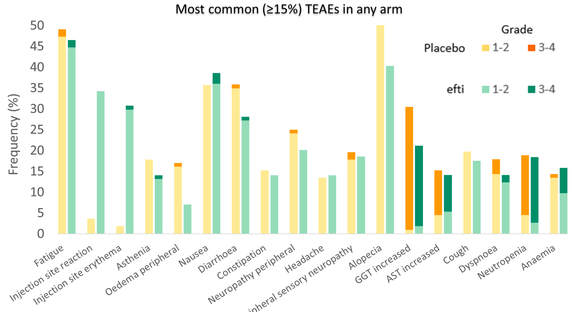


SAFETY

- 2 (1.8%) pts in the efti group and 3 (2.7%) pts in the placebo group had fatal treatment-emergent adverse events (TEAEs) – no fatal TEAE related to efti.
- 3 pts discontinued due to hypersenstivity reactions developing after efti injections and 4 pts due to paclitaxel-induced hypersensitivity, respectively
- Most common efti related adverse event was any kind of local injection site reaction up to grade 3 reported in 74 (64.9%) pts in the efti arm

Summary of treatment-emergent adverse events (TEAEs) ¶	Paclitaxel + efti N=114 n (%)	Paclitaxel + Placebo N=112 n (%)
At least one TEAE	113 (99.1)	112 (100)
At least one TEAE leading to death	2 (1.8)	3 (2.7)
At least one TEAE for which efti/placebo was discontinued	6 (5.3)	7 (6.3)
At least one Grade ≥3 TEAE	78 (68.4)	73 (65.2)
At least one Grade 1 or 2 TEAE as worst severity	35 (30.7)	39 (34.8)

Most common (≥15%) TEAEs in any arm



BIOMARKER

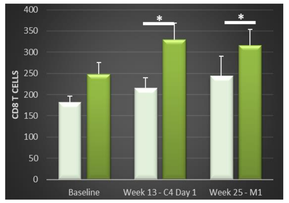
- Long-term, significant and sustained increase in number of circulating CD8 T cells in efti-treated group compared to placebo

Placebo
Efti

CD8 T cells

Mean ± SEM of Absolute Counts (million cells/L of blood)

* p<0.05 Wilcoxon



CONCLUSION

Overall Population

- **Efti did not prolong median PFS in women with HR+ MBC receiving paclitaxel, but ORR and OS trend favorably**
- **Efti shows statistically significant, sustained long-term increase in peripheral CD 8 T cells**
- **Efti in combination with weekly paclitaxel is well-tolerated**

Subgroups

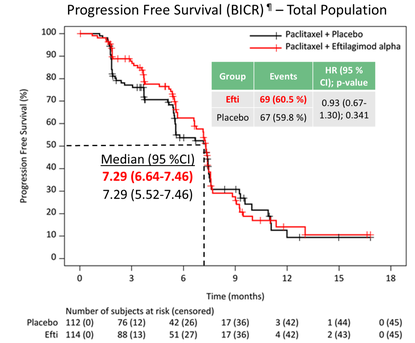
- **In pts with age < 65 yrs, low monocytes and luminal B, substantial and mostly statistically significant increases in all relevant efficacy parameters incl. OS were observed**

→ Multivariate analysis is ongoing and final OS data expected in 2021

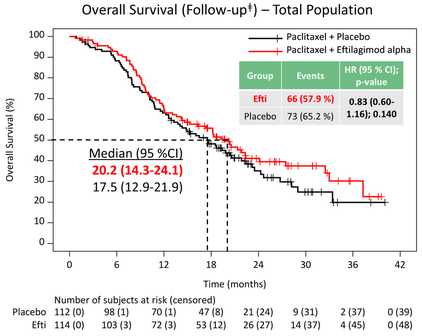
→ Efti in combination with weekly paclitaxel warrants further late-stage clinical development in HR+ MBC pts, especially in pts with age < 65 yrs

EFFICACY –OVERALL POPULATION

Progression Free Survival (BICR) ¶ – Total Population



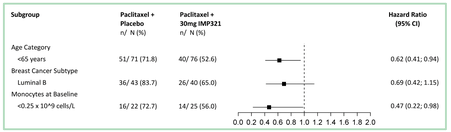
Overall Survival (Follow-up‡) – Total Population



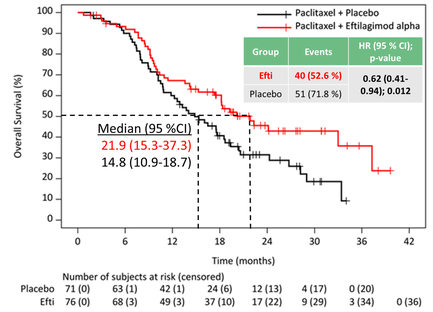
- Local assessment of PFS¶ (median 7.16 [95 % CI 5.65-7.39 in the efti group vs. median 6.70 [95 % CI 5.52-7.33] in the placebo group) concurs with BICR assessment¶
- ORR (BICR) ¶ was 48.3 % [95 CI 42-61] in efti group and 38.4 % [95 CI 31-51] in the placebo group (p-value= 0.118; CMH)
- DCR (BICR) ¶ in the efti group increased by the same magnitude from 75.9 % to 85.1 %
- Significant deterioration of Quality of Life¶ (QLQ-C30) in the placebo group at week 25, which was not observed in the efti group
- At second interim analysis‡ (~61 % events, cut-off 24th Sep 2020) for OS, HR improved from 0.88 to 0.83 for the overall group
- Post-study treatment was similar with 80.7 % (efti) and 83.9 % (placebo) receiving any post study systemic anticancer therapy. Vast majority received chemotherapy: 64.0 % (efti) vs. 69.6 % (placebo)

EFFICACY -SUBGROUPS

Forest Plot OS‡ – relevant subgroups



Overall Survival (Follow-up‡) – Age < 65 yrs



- In three pre-defined subgroups, clinically relevant and statistically significant differences (except for PFS < 65 yrs and OS luminal B) were reported for PFS and OS
- CDK-4/6 had negative impact on OS in placebo group (median reduced from 20.0 to 14.9 months), which is not the case in the efti group (median OS 20.9 vs. 20.4 months)

Subgroup	Treatment	Median PFS¶ (95 % CI)	Absolute PFS¶,Δ Gain◊; HR (95 % CI); p-value	Median OS‡ (95 % CI)	Absolute OS‡ Gain; HR (95 % CI); p-value
<65 yrs	Efti	7.2 (5.6-7.4)	+1.7 months; 0.77 (0.54-1.10); p=0.077	21.9 (15.3-37.3)	+7.1 months; HR 0.62 (0.41-0.94); p=0.012
	placebo	5.5 (5.1-7.2)		14.8 (10.9-18.7)	
Low monocytes (<0.25/nl)	Efti	7.5 (5.4-9.1)	+2.3 months; HR 0.44 (0.21-0.90); p=0.012	22.4 (18.2-37.3)	+9.4 months; HR 0.47 (0.22-0.98); p=0.02
	placebo	5.2 (3.3-7.3)		12.9 (7.5-20.4)	
Luminal B	Efti	7.2 (5.5-7.5)	+1.7 months; HR 0.72 (0.45-1.15); p=0.081	16.3 (9.9-21.4)	+3.8 months; HR 0.69 (0.42-1.15); p=0.077
	placebo	5.6 (3.7-7.2)		12.6 (10.2-17.5)	

APC... antigen-presenting cell
AST... aspartate aminotransferase
BICR... blinded independent central read
CI – Confidence interval
CMH ... Cochran Mantel-Haenszel
CTCAE...Criteria for Adverse Events
DCR ... Disease control rate
DOR... duration of response
ECOG... Eastern Cooperative Oncology Group
efti... Eftilagimod alpha
GGT... gamma-glutamyltransferase
HR+... Hormone receptor-positive
MBC...metatstatic breast cancer
ORR...Overall response
OS...Overall Survival
PFS... Progression Free Survival
QoL... Quality of life
TTNT... time to next treatment

* *Blood samples (selected pts) were collected prior to paclitaxel administration (i.e. 13 days after 6th/12th injection of placebo/efti) to monitor absolute counts of CD45+CD3+CD8+CD4- cytotoxic T cells by flow cytometry. Mean (+/- SEM, n=36/31 in placebo/efti group) is presented in the 2 arms at each timepoints. Difference between two groups was tested by Wilcoxon rank sum tests.*

** *performed in central laboratory restrospectively primary tumor and metastasis; not all pts had available samples → N=169*

¶ *Primary analysis used for safety and PFS cut-off: Jan 9th 2020*

‡ *Follow-up 2 used for OS cut off: 24th Sep 2020*

Δ *investigator assessment*

◊ *vs. Placebo in the same subgroup*