Final results from AIPAC: A phase IIb trial comparing eftilagimod alpha (soluble LAG-3 protein) in combination with weekly paclitaxel in HR+ HER2- MBC

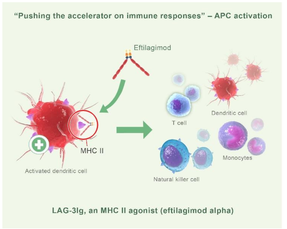
Abstract # 948

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], Christian Mueller[16], Chrystelle Brignone[17] and Frederic Triebel[17]

[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]Clinical Development, Immutep, Berlin, Germany, [17]Research & Development, Immutep, Paris, France

BACKGROUND

Figure 1. efti's mechanism of action



Eftilagimod alpha (efti) is a soluble LAG-3 protein targeting a subset of MHC class II molecules, thus mediating antigen presenting cell (APC) and CD8 T-cell activation (**Figure 1**). Such stimulation of the dendritic cell network and resulting T cell recruitment may lead to stronger anti-tumor responses in combination with paclitaxel than observed with paclitaxel alone. We report the final results from the randomized part of the AIPAC (Active Immunotherapy PAClitaxel *NCT02614833*) study in metastatic breast carcinoma (MBC) patients.

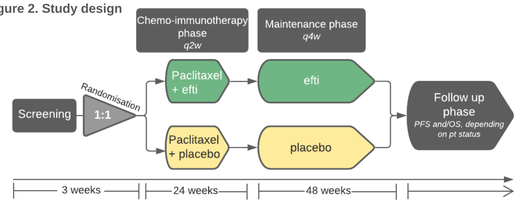
METHODS

Study Design and Patients

Multicenter, placebo-controlled, double-blind, 1:1 randomized Phase IIb study in female hormone receptor-positive metastatic breast cancer patients.

The randomized stage consisted of a chemo-immunotherapy phase followed by a maintenance phase. Patients received 80 mg/m^2 paclitaxel i.v. days 1, 8, 15 plus efti/placebo s.c. days 2 and 16 up to 24 weeks and then efti/placebo s.c. every 4 weeks (**Figure 2**).

Figure 2. Study design



Assessments and Statistical Analyses

- **Primary Endpoint:** Progression-free survival (PFS) based on blinded independent central review (BICR) – RECIST1.1.
- **Secondary Endpoints**: Overall survival (OS), safety and tolerability, PFS based on investigator review, overall response rate (ORR), time to next treatment (TTNT), duration of response (DOR), quality of life (QoL), presence of antidrug antibodies (ADAs).
- **Exploratory Endpoints**: Blood immune cell phenotypes (CD8 T cells) and circulating Th1 biomarkers.
- Safety was analyzed in all patients who received at least one dose of study medication.
- Efficacy was analyzed in all patients with measurable disease at baseline who received at least one dose of any study medication.
- Database cut-off date was May 14, 2021.

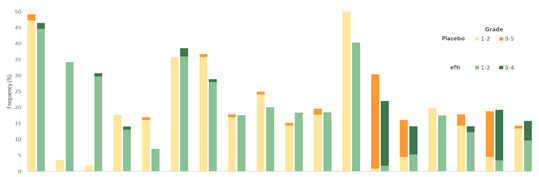
SAFETY

- 2 (1.8%) patients in the efti group and 3 (2.7%) patients in the placebo group had fatal TEAEs – no fatal TEAE related to efti (see **Table 2**).
- 3 patients discontinued due to hypersensitivity reactions developing after efti injections and 4 patients due to paclitaxel-induced hypersensitivity.
- Most common efti-related adverse event was any kind of local injection-related reaction (grade 1-3), reported in 75 (65.8%) patients in the efti arm compared to 13 (11.6%) in the placebo arm (**Figure 4**).

Table 2. Summary of treatment-emergent adverse events

Summary of treatment-emergent adverse events (TEAEs)	Efti + Paclitaxel (N=114); N (%)	Placebo + Paclitaxel (N=112); N (%)
≥1 TEAE	113 (99.1)	112 (100)
TEAE leading to death	2 (1.8)	3 (2.7)
≥1 TEAE leading to efti/placebo discontinuation	6 (5.3)	7 (6.3)
≥1 TEAE ≥3 Grade	78 (68.4)	73 (65.2)

Figure 4. Most common TEAEs (≥15%)



PATIENT DISPOSITION & EXPOSURE

- 227 patients were randomized to efti (N=114) or to placebo (N=113) between January 2017- July 2019. All except one patient received at least 1 dose of study medication and were included in the full analysis and safety populations.

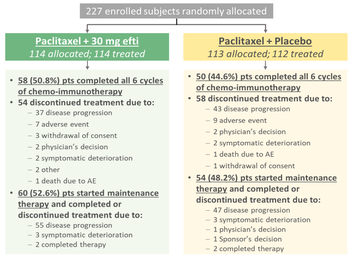
Table 1. Baseline disease characteristics and prior therapy

	Efti + Paclitaxel N=114	Placebo + Paclitaxel N=112	Overall N=226
Baseline characteristics, n (%)			
Age, median (range), years	58 (24-87)	61 (35-79)	60 (24-87)
<65 years	76 (66.7)	71 (63.4)	147 (65.1)
Body mass index, median (range)	24.7 (18.1-48.1)	24.9 (15.4-44.5)	24.7 (15.4-48.1)
ECOG 0	69 (60.5)	70 (62.5)	139 (61.5)
Visceral disease	103 (90.4)	104 (92.9)	207 (91.6)
Luminal A / B / Other¶, %	34.1 / 48.8 / 17.1	36.7 / 49.4 / 13.8	35.5 / 49.1 / 15.4
Monocytes <0.25/nl	25 (21.9)	22 (19.8)	47 (20.9)
Elevated (>250 U/L) LDH	74 (65.5)	81 (73.0)	155 (69.2)
Prior therapy, n (%)			
Prior surgery	92 (80.7)	94 (83.9)	186 (82.3)
Prior radiotherapy	87 (76.3)	84 (77.7)	174 (77.0)
Prior systemic therapy	106 (93.0)	108 (96.4)	214 (94.7)
Prior adjuvant therapy	85 (74.6)	81 (72.3)	166 (73.5)
Prior therapy for metastatic disease	78 (68.4)	80 (71.4)	158 (69.9)
Prior taxanes (adjuvant)	51 (44.7)	43 (38.4)	94 (41.6)
Prior CDK4/6	50 (44.6)	50 (43.9)	100 (44.2)
Prior endocrine therapy	103 (90.4)	104 (92.9)	207 (91.6)
*Endocrine resistant*Δ	*85 (82.5)*	*89 (85.6)*	*174 (84.1)*
Last therapy prior to inclusion, n (%)			
None	6 (5.3)	4 (3.6)	10 (4.4)
Adjuvant/curative	25 (21.9)	22 (19.6)	47 (20.8)
Palliative	83 (72.8)	86 (76.8)	169 (74.8)

¶ Central assessment performed on available and evaluable primary or metastatic tissues (n=169). Classified using PgR and Ki67 index according to St Gallen International Expert Consensus guidelines[1].
Δ Defined according to ESMO Internal Consensus Guidelines (Advanced Breast Cancer 4)[2].

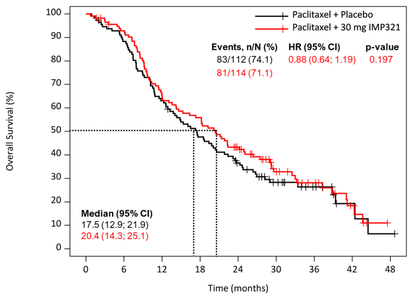
- All patients were HR+ and HER/neu- as per local assessment with majority as luminal B[1] (49.1%) and luminal A (35.5%) as per central assessment (**Table 1**).
- Subjects were heavily pre-treated with a median of 2 prior systemic anticancer regimens. Patients were predominantly endocrine resistant (84%), while 44.2% were pre-treated with CDK4/6 inhibitors and received prior palliative therapy (74.8%)
- Treatment exposure for paclitaxel was similar between arms with mean dose intensity of 93%. A total of 60 (52.6%) efti and 54 (48.2%) placebo patients completed the chemo-immunotherapy phase (**Figure 3**).

Figure 3. Subject disposition



EFFICACY – OVERALL POPULATION

Figure 5. Kaplan-Meier curve for OS in the overall population



Number of subjects at risk (censored)

Placebo	112 (0)	98 (1)	70 (1)	52 (2)	38 (4)	21 (13)	11 (22)	3 (28)	1 (28)
IMP321 30mg	114 (0)	103 (3)	72 (3)	62 (3)	45 (6)	24 (18)	15 (24)	6 (29)	0 (33)

Figure 6. Global Health Status/ QoL QLQC30-B23

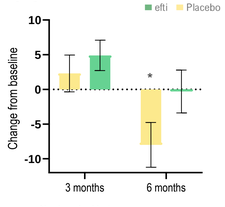


Figure 7. Mean ± SEM of absolute count of CD8 T cells* prior next dosing

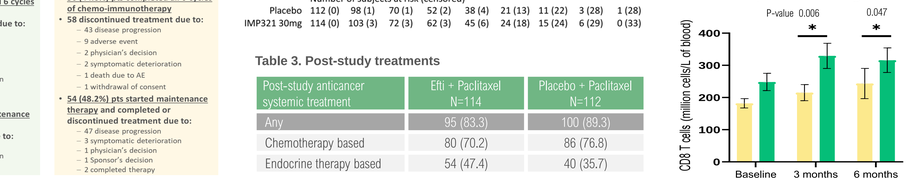


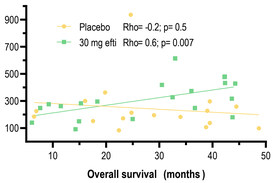
Table 3. Post-study treatments

Post-study anticancer systemic treatment	Efti + Paclitaxel N=114	Placebo + Paclitaxel N=112
Any	95 (83.3)	100 (89.3)
Chemotherapy based	80 (70.2)	86 (76.8)
Endocrine therapy based	54 (47.4)	40 (35.7)

At database cut-off (14 May 2021) for **final analysis** (73% events), minimum follow-up was 22 months:

- Numerical increase in OS: +2.9 months from median of 17.5 (95% CI: 12.9-21.9) in placebo to 20.4 (95% CI: 14.3 -25.1) in the efti group (**Figure 5**).
- HR 0.68 for OS overall (95% CI: 0.64-1.19; p=0.197).
- ORR and PFS by BICR was not updated during final analysis.
- Post-study treatment similar: patients received chemotherapy 70.2% (efti) vs. 76.8% (placebo) or endocrine therapy 47.4 % (efti) vs. 35.7 % (placebo) (**Table 3**)
- Significant deterioration of QoL (QLQ-C30-B23) observed in the placebo group at 6 months. No deterioration with efti (**Figure 6**).
- Efti significantly increased CD8 T cells compared to placebo (**Figure 7**). *(Note: Blood samples were taken 2 weeks after last dosing and prior to next dosing, showing the minimal residual effect.)*
- Increase in pre-dose CD8 T cells is significantly correlated to increased overall survival (**Figure 8**).

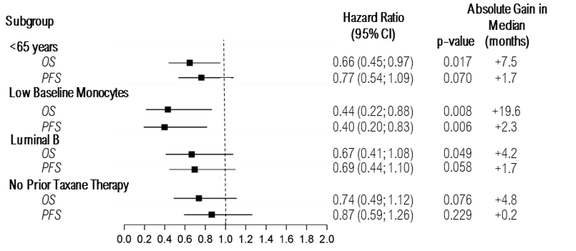
Figure 8. Correlation between cytotoxic CD8 T cells and OS



EFFICACY – UNIVARIATE/MULTIVARIATE ANALYSIS

- Through exploratory multivariate analyses, poor prognostic markers using baseline characteristics were analyzed in a Cox model using backward selection (p<0.15). Prior CDK4/6 and higher BMI at baseline were found to be independent significant poor prognostic markers for both PFS and OS. Other markers were found solely for PFS or OS.
- Median OS for patients pre-treated with CDK4/6 was reduced to 14.9 months in the placebo group and remained at 20.2 months for the efti group.

Figure 9. Forest plot for OS/PFS from univariate analysis (defined prior unblinding) significant for OS or significant predictive in multivariate analysis

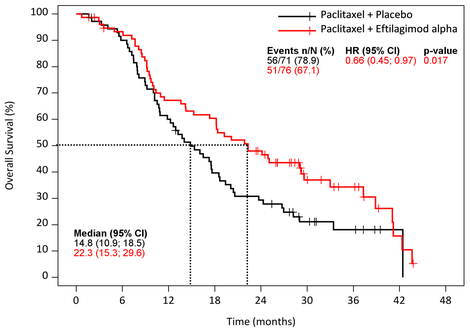


- Exploratory univariate analysis (analysis groups defined prior unblinding) showed that younger patients (<65 years), those with low baseline monocytes (<0.25/nL) or breast cancer subtype luminal B had significant and clinical meaningful improvement in median OS compared to placebo (**Figure 9**).
- No prior taxanes and low monocytes were found to be significant (p<0.15) in an exploratory multivariate analysis using the multivariate prognostic model.

EFFICACY – SUBGROUP <65 YEARS

- Cut off <65 years was defined prior to unblinding and showed significant (p=0.017, one-sided) improvement in OS with a HR of 0.66 (95% CI: 0.45-0.97) and median increase of 7.5 months (**Figure 10**). Within this subgroup, all poor prognostic markers from multivariate analyses were equally distributed between the placebo and efti groups.

Figure 10. Kaplan-Meier curve for OS in patients <65 years of age

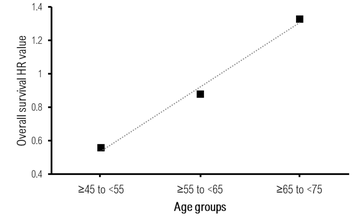


Number of subjects at risk (censored)

Placebo	71 (0)	63 (1)	42 (1)	27 (2)	20 (2)	11 (6)	6 (10)	1 (15)	0 (15)
Efti	76 (0)	68 (3)	49 (3)	44 (3)	33 (5)	16 (16)	11 (20)	3 (24)	0 (25)

- The effect of age upon survival was investigated through exploratory analysis in 10-year increments. Age had an almost linear effect on HR for OS. **Figure 11** displays HR point estimates for different age groups. Point estimate of HR for OS flips to >1 in the age group ≥65 and <75 years.

Figure 11. OS HR point estimates for different age groups



CONCLUSION

- Efti added to paclitaxel led to a non-significant 2.9 months median OS increase in predominantly endocrine-resistant HR+ HER2- MBC patients.
- Effects were significant and clinically-meaningful (median improved between 4.2 and 19.6 months) for OS in younger patients (<65 years), those with low monocytes (<0.25/nl) or more aggressive disease (luminal B).
- Efti significantly increased circulating CD8 T cells, further significantly correlating to improved OS.
- The overall safety profile remained consistent with previous results with no new safety signals.

→ Weekly paclitaxel + efti should be further investigated in a phase III HR+ MBC setting.

ADA…anti-drug antibodies
APC… antigen-presenting cell
AST… aspartate aminotransferase
BICR… blinded independent central review
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
i.v… intravenous
MBC…metastatic breast cancer
ORR…overall response
OS…overall survival
PgR… progesterone receptor
PFS… progression free survival
QoL… quality of life
s.c… subcutaneous
TEAE…treatment-emergent adverse event
TTNT… time to next treatment

1. Goldhirsch A, Winer EP, Coates AS, et al. 2013;24(9):2206–2223. doi:10.1093/annonc/mdt303
2. Cardoso F, et al. 2018;29(8):1634-1657. doi: 10.1093/annonc/mdy192.

¶Pre-dose blood samples (selected patients) 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.

The AIPAC trial protocol has been published, 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).