Paclitaxel plus Eftilagimod Alpha, a Soluble LAG-3 Protein, in Metastatic, HR$^+$ Breast Cancer: Results from AIPAC, a Randomized, Placebo Controlled Phase IIb Trial

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ABSTRACT

Purpose: Eftilagimod alpha (efti), a soluble lymphocyte activation gene (LAG-3) protein and MHC class II agonist, enhances innate and adaptive immunity. Active Immunotherapy PAClitaxel (AIPAC) evaluated safety and efficacy of efti plus paclitaxel in patients with predominantly endocrine-resistant, hormone receptor–positive, HER2-negative metastatic breast cancer (ET-resistant HR$^+$ HER2$^-$ MBC).

Patients and Methods: Women with HR$^+$ HER2$^-$ MBC were randomized 1:1 to weekly intravenous paclitaxel (80 mg/m^2) and subcutaneous efti (30 mg) or placebo every 2 weeks for six 4-week cycles, then monthly subcutaneous efti (30 mg) or placebo maintenance. Primary endpoint was progression-free survival (PFS) by blinded independent central review. Secondary endpoints included overall survival (OS), safety/tolerability, pharmacokinetics/pharmacodynamics, and quality of life. Exploratory endpoints included cellular biomarkers.

Results: 114 patients received efti and 112 patients received placebo. Median age was 60 years (91.6% visceral disease, 84.1% ET-resistant, 44.2% with previous CDK4/6 inhibitor treatment). Median PFS at 7.3 months was similar for efti and placebo. Median OS was not significantly improved for efti (20.4 vs. 17.5 months; HR, 0.88; $P = 0.197$) but became significant for predefined exploratory subgroups. EORTC QLQC30-B23 global health status was sustained for efti but deteriorated for placebo. Efti increased absolute lymphocyte, monocyte and secondary target cell (CD4, CD8) counts, plasma IFNγ and CXCL10 levels.

Conclusions: Although the primary endpoint, PFS, was not met, AIPAC confirmed expected pharmacodynamic effects and demonstrated excellent safety profile for efti. OS was not significantly improved globally (2.9-month difference), but was significantly improved in exploratory biomarker subgroups, warranting further studies to clarify efti's role in patients with ET-resistant HER2$^-$ MBC.

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Clin Cancer Res 2024;30:532–41

doi: 10.1158/1078-0432.CCR-23-1173

Introduction

Although most patients with breast cancer are diagnosed with early-stage disease, 6% to 10% initially present with metastatic breast cancer (MBC), and an additional 20% to 30% will later develop MBC (1). Of these, approximately two thirds have estrogen and/or progesterone receptor–positive, HER2-negative (HR$^+$ HER2$^-$) disease (2). The approval of cyclin-dependent kinase (CDK)4/6 inhibitors (CDK4/6i) in combination with endocrine therapy (ET) in 2015 set a new standard of care, eventually displacing ET alone or chemotherapy as the preferred first-line treatment option for most patients (3, 4). Although this extends survival, progression on CDK4/6i and ET almost inevitably occurs through a variety of resistance mechanisms (4, 5). Progression on CDK4/6i is frequently associated with a more aggressive phenotype, for which patients are often subsequently treated with chemotherapy (6, 7). In this post-CDK4/6i/ET treatment setting, chemotherapy benefits are limited, with a median treatment duration of 4 to 5 months and median overall survival (OS) of approximately 1 to 2 years (6, 7), and immunotherapeutic approaches have so far proven challenging (8). Most breast cancers, especially Luminal, are associated with low levels of T-cell infiltration, resulting in what has been termed an immunologically silent, or "cold," tumor (9), for which single-agent checkpoint inhibitors have generally proven ineffective (8). Thus, the paradigm shift induced by the introduction of first-line CDK4/6i/ET highlights the need for more effective and safe chemotherapy-based treatment approaches for patients with MBC.

Translational Relevance

Despite major advances in early breast cancer treatment the need for novel therapies for metastatic breast cancer (MBC) after failure of endocrine-based therapies (ET) remains high. Eftilagimod alpha (efti), a soluble lymphocyte activation gene protein, is a potent antigen-presenting cell activator. The activation of dendritic cells by efti could restore the deficient T-cell priming reported in poorly immunogenic HR^+ MBC tumors. The phase IIb, multicenter, randomized Active Immunotherapy PAClitaxel trial examined a chemo-immunotherapy approach using efti versus placebo in women with HR^+ MBC receiving weekly paclitaxel after failure of ET-based therapy. Median overall survival was significantly improved for efti in predefined subgroups. Levels of circulating monocytes, $CD4^+$, and $CD8^+$ T cells together with relevant Th1 biomarkers significantly increased in the efti arm, and $CD4^+$ and $CD8^+$ cell numbers were linked to improved overall survival. These findings support a further prospective investigation of efti in patients with ET-resistant HR^+ MBC.

The role of adaptive immune response in chemotherapy effectiveness is well established (10, 11). Priming $CD8^+$ T cells is a prerequisite for their tumor-killing property. Defects in T-cell priming, rather than T-cell exhaustion or lack of tumor penetration, may contribute to the low levels of T-cell infiltration observed in MBC (8, 9, 12). Thus, enhancing T-cell priming by activated and matured dendritic cells (DC) may help restore immunological response in the presence of tumor neoantigens. Chemotherapy-induced tumor cell apoptosis provides antigens used by antigen-presenting cells (APC) for $CD8^+$ T-cell priming. This ultimately leads to increased cytotoxic T-cell infiltration into tumors (Supplementary Fig. S1; ref. 13). The resulting immunoadjuvant effect suppresses tumor growth and is key to long-term survival (10, 14, 15). Lymphocyte activation gene-3 (LAG-3) protein is a dimeric cell surface receptor expressed on activated T cells that functions as an inhibitory checkpoint molecule in multiple cancers (16, 17). In addition, soluble LAG-3 levels in serum have been correlated with lower risk of relapse in patients with breast cancer (18). Eftilagimod alpha (efti; IMP321) is a unique recombinant soluble LAG-3 protein that mimics the structure of the dimeric LAG-3 receptor expressed on T-cell membranes (19). Efti acts as a MHC class II agonist, triggering activation of APCs and then secondary T-cell proliferation and activation, which results in a sustained immune response in preclinical and clinical studies (19–22).

The Active Immunotherapy PAClitaxel (AIPAC; NCT02614833) study was designed to investigate the efficacy and safety of efti plus paclitaxel versus placebo plus paclitaxel in patients with predominantly ET-resistant HR^+ $HER2^-$ MBC eligible to receive chemotherapy (23). Here, we report the final results from this randomized, double-blind, placebo-controlled phase IIb study.

Patients and Methods

Study design

Detailed methods for AIPAC and results of the run-in stage of the study have been described (23, 24). Briefly, this was a multicenter, placebo-controlled, double-blind randomized study comparing efti plus paclitaxel with placebo plus paclitaxel in women with HR^+ $HER2^-$ MBC. Patients were randomized 1:1 to receive intravenous paclitaxel (80 mg/m^2 on days 1, 8, and 15) followed by either subcutaneous efti at the recommended phase II dose of 30 mg or subcutaneous placebo on days 2 and 16 of each 4-week cycle for 6 cycles or until progression, withdrawal of consent, or death. Randomization was done using an interactive web-based response system stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1) via permutated blocks. Patients with a response or stable disease (SD) who completed ≥4 cycles were allowed to continue into the maintenance phase, thereupon receiving efti alone (30 mg subcutaneous) or placebo every 4 weeks for up to 12 cycles (Supplementary Fig. S2A). The trial was registered on clinicaltrials.gov (NCT02614833) and was conducted according to current Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol was reviewed by independent ethics committees at all participating institutions, and all patients provided written informed consent.

Patients

Eligible patients were females 18 years or older with HR^+ $HER2^-$ MBC who were indicated to receive chemotherapy with weekly paclitaxel. ECOG performance status of 0 or 1, and measurable disease per RECIST 1.1 were required. Individuals with prior MBC chemotherapy, inflammatory carcinoma, those requiring systemic corticosteroid or other immunosuppressive therapy, and candidates for trastuzumab or other HER2-targeted treatment were excluded. Prior endocrine-based therapy was allowed.

Outcomes

The primary objective was to determine the efficacy of efti plus weekly paclitaxel compared with placebo plus weekly paclitaxel. The primary endpoint was difference in progression-free survival (PFS) as determined by blinded independent central review (BICR) and by local assessment, both using RECIST 1.1 criteria. Secondary endpoints included OS, adverse events (AE) graded according to the NCI Common Terminology Criteria for Adverse Events V4.03, time to next treatment (TTNT), objective response rate (ORR), patient quality of life (QoL), and antidrug antibody (ADA) levels. Exploratory endpoints included blood immune cell phenotypes (e.g., monocyte numbers and activation, $CD8^+$ T-cell numbers), assessment of soluble T helper (Th)1 biomarkers, and tumor biomarkers. Whole blood and plasma samples were collected to monitor circulating immune cell subsets and Th1 biomarkers, respectively, before the start of the treatment on cycle 1 day 1, predose on cycle 4 day 1, at the maintenance start (i.e., 13 days after the previous efti injection to detect minimal residual effects) and at the end of treatment visit from a subset of patients in the randomized stage (67 and 49 patients for cellular and soluble biomarkers, respectively). Biomarkers were also monitored in patients in the run-in stage. Additional samples from run-in patients were collected to assess pharmacokinetics (PK) at early time points after 6 mg and 30 mg efti doses. *Ex vivo* absolute counts of blood cell subsets were determined in whole blood using a lyse-no-wash single-platform cytometry procedure and fluorescent staining antibody mixtures (see Supplementary Methods for details). Th1 biomarkers (IFNγ and CXCL10) were measured using an electrochemiluminescence assay. Absolute lymphocyte count (ALC), monocytes and neutrophils were obtained locally from whole blood samples collected predose over the treatment period.

Radiological assessments were conducted at 8-week intervals from date of randomization until week 73 and thereafter at 12-week intervals. Physical examinations were conducted on day 1 of each cycle. Patient QoL was measured using the European Organisation for Research and Treatment of Cancer QoL Cancer-Specific Version,

Breast Cancer Specific Version (EORTC QLQC30-BR23), and the EuroQol Research Foundation Health-Related Quality of Life at regular intervals (baseline, weeks 13, 25, 49, and at end of treatment). Retrospective central assessment of breast cancer subtypes was performed using PgR and Ki67 index according to St. Gallen International Expert Consensus guidelines (25).

Statistical analysis

Both the safety population and the full analysis set (FAS) consisted of all randomized patients who received ≥ 1 dose of study drug. Safety data, ADA data, and items on QoL scales were analyzed descriptively. The FAS population was the primary population for analyses of efficacy endpoints.

The null hypothesis of no PFS difference between treatment arms was tested using a log-rank test with a one-sided alpha of 0.05 stratified by ECOG performance status (0 vs. 1). Assuming PFS values of 12 months in the efti plus paclitaxel arm and 8 months in the placebo plus paclitaxel arm, 113 patients per arm would provide 80% power to detect a HR of 0.667. PFS and other time-to-event endpoints were estimated using the Kaplan–Meier method. Differences in ORR between randomized arms were tested using Cochran-Mantel-Haenszel testing at a two-sided alpha of 0.05, stratified by ECOG performance status (0 vs. 1). Poor prognostic markers using baseline characteristics were analyzed in a multivariate Cox model using backward selection. Biomarkers between group comparison was performed by nonparametric rank-sum two-sided Wilcoxon test. In-between group comparison of posttreatment values to baseline value was tested using matched-paired rank-signed Wilcoxon test. Spearman correlation coefficient was used to evaluate the relationship between biomarkers and clinical outcome parameters. SAS version 9.4 software (SAS software, Cary, NC) or SAS JMP version 12.0.1 software was used for the analyses.

Data availability statement

The data generated in this study are available from the corresponding author pursuant to reasonable request and approval from study sponsor (Immutep S.A.S) according to available guidelines at time of request. This access restriction is in place to safeguard patient privacy.

Results

Patient population

Results of the open-label safety run-in phase assessing the safety, tolerability, PK, and immune response of efti plus paclitaxel have been previously reported (24). The present report focuses on the randomization phase results. Between January 2017 and July 2019, AIPAC screened 277 patients at 32 sites in Belgium, the Netherlands, Germany, France, the United Kingdom, Hungary, and Poland. A total of 227 patients were enrolled, of which 114 were randomized to efti plus paclitaxel and 113 were randomized to placebo plus paclitaxel. One patient randomized to the latter received no study treatment and was excluded from analysis. Baseline characteristics were well-balanced between treatment groups (**Table 1**). The median age was 60 years (range, 24–87) and the majority of patients (61.5%) had ECOG performance status 0. Patients had late-stage disease (91.6% visceral, 69.2% elevated lactate dehydrogenase). Most patients (73.9%) had received 1 or 2 prior systemic therapies for MBC, and 84.1% were endocrine resistant (26). Notably, at the time the study began (January 2017), CDK4/6i (in combination with ET) were not routinely used. As a result, only 44% of patients had used prior CDK4/6i.

Table 1. Baseline patient and disease characteristics in the randomized patient population.

n, %	Efti + Paclitaxel *n* = 114	Placebo + Paclitaxel *n* = 112	Overall *N* = 226
Age, yrs			
Median (range)	58 (24–87)	61 (35–79)	60 (24–87)
<65	76 (66.7)	71 (63.4)	147 (65.1)
BMI, median (range)	24.7 (18.1–48.1)	24.9 (15.4–44.5)	24.7 (15.4–48.1)
ECOG PS 0	69 (60.5)	70 (62.5)	139 (61.5)
ECOG PS 1	44 (38.6)	42 (37.5)	86 (38.1)
Visceral disease	103 (90.4)	104 (92.9)	207 (91.6)
Luminal, %[a]			
A-like	34.1	36.7	35.5
B-like	48.8	49.4	49.1
Other	17.1	13.8	15.4
Monocytes <0.25/nL	25 (21.9)	22 (19.8)	47 (20.9)
LDH > 250 U/L	74 (65.5)	81 (73.0)	155 (69.2)
Prior surgery	92 (80.7)	94 (83.9)	186 (82.3)
Prior radiotherapy	87 (76.3)	84 (77.7)	174 (77.0)
Prior systemic therapies			
Any	106 (93.0)	108 (96.4)	214 (94.7)
≥3	19 (16.7)	28 (25.0)	47 (20.8)
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 CDK4/6i	50 (44.6)	50 (43.9)	100 (44.2)
Prior ET	103 (90.4)	104 (92.9)	207 (91.6)
Endocrine resistant[b]	85 (82.5)	89 (85.6)	174 (84.1)
Last therapy prior to inclusion			
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)

Note: Representativeness of study participants is provided in Supplementary Table S2.

Abbreviations: BMI, body mass index; CDKi, cyclin-dependent kinase inhibitor treatment; LDH, lactate dehydrogenase.

[a]Retrospective 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 (31).

[b]Defined according to the 4th ESO-ESMO International Consensus Guidelines (26).

Efficacy outcomes

In the efti and placebo arms, 60 (52.6%) and 54 (48.2%) patients, respectively, completed the six cycles of treatment (Supplementary Fig. S2B). At the cut-off date of May 14, 2021, the median follow-up time was 19.7 months (range, 0.7–47.6) in the efti arm and 16.9 months (range, 0.9–48.7) in the placebo arm. Median treatment duration was 6.2 months and 5.9 months, respectively, and the mean paclitaxel dose intensity during chemoimmunotherapy was 93.1% and 92.8%, respectively.

Median PFS by BICR, the primary endpoint, was 7.3 months [95% confidence interval (CI), 6.6–7.5] in the efti arm and 7.3 months (95%

CI, 5.5–7.5) in the placebo arm (HR, 0.93; 95% CI, 0.67–1.30; $P = 0.341$; **Fig. 1A**). PFS by investigator assessment provided similar results. Median OS was 20.4 months (95% CI, 14.3–25.1) in the efti arm and 17.5 months (95% CI, 12.9–21.8) in the placebo arm (HR, 0.88; 95% CI, 0.64–1.19; $P = 0.197$; **Fig. 1B**). At 12 and 24 months, the proportion of surviving patients was 65% (95% CI, 55–73) and 43% (95% CI, 34–52) for efti and 63% (95% CI, 53–71) and 37% (95% CI, 28–46) for placebo, respectively.

A total of 107 patients (93.9%) and 106 patients (94.6%), respectively, were evaluable for response. The ORR by BICR was 51.4% (95% CI, 42–61) in the efti arm and 40.6% (95% CI, 31–51; $P = 0.118$) in the placebo arm with disease control rates of 90.7% (efti) and 80.2% (placebo) (Supplementary Table S1).

Median TTNT was 7.7 months and 6.9 months for efti and placebo, respectively. The median time to objective response (based on BICR) for subjects in the efti group [2.1 months (95% CI, 1.87–3.58)] was lower than subjects in the Placebo group [3.6 months (95% CI, 1.94–3.71)]. Post-study treatment was similar in both arms, with 86% and 90.2% of patients in the efti and placebo groups, respectively, receiving any post-study systemic anticancer therapy. The majority of these patients (70.2% and 76.8%, respectively) received chemotherapy.

Preplanned univariate analysis identified four patient subgroups for which PFS, OS and/or ORR were significantly improved in the efti arm: younger than 65 years, low baseline monocytes (<0.25 × 10^9 cells/L), no prior taxane therapy, and Luminal B disease (**Fig. 2A** and **B**; Supplementary Figs. S3 and S4). In addition, an exploratory post hoc univariate analysis associated the subgroups high (>3.65; cutoff determined by its median) neutrophil to lymphocyte ratio at baseline and shorter time (<5 years, cutoff determined by its approximative median) since diagnosis with significantly improved OS (**Fig. 2B**; Supplementary Fig. S4). An exploratory multivariate analysis to identify independent poor prognostic markers regardless of the therapy received associated prior CDK4/6i therapy with decreased PFS (HR, 1.65; $P = 0.001$) and OS (HR, 1.37; $P = 0.072$) among all randomized patients. When analyzed by treatment arm, prior CDK4/6i treatment had a larger negative impact on OS in the placebo arm (median OS reduced from 20.4 to 14.9 months) than in the efti arm (median OS reduced from 21.9 to 20.2 months).

At 6 months, global health status per the EORTC QLQC30-B23 questionnaire had significantly deteriorated relative to baseline among patients in the placebo arm [mean change from baseline −8.0 (95% CI, −14.47 to −1.50)] but was maintained at a baseline level in the efti arm [mean change from baseline -0.3 (95% CI, −6.52 to 5.88); Supplementary Fig. S5].

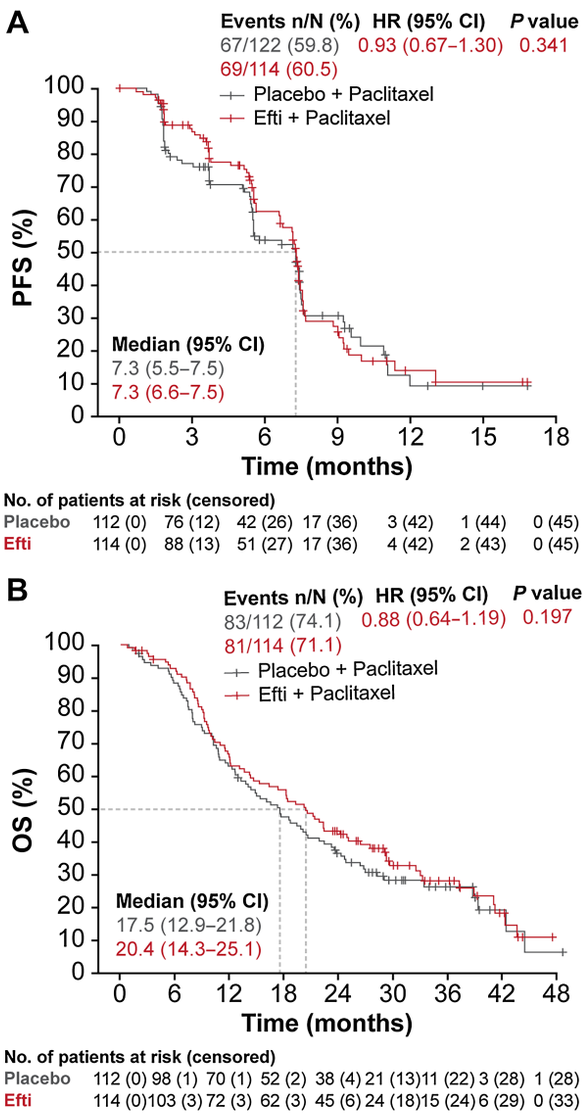

Figure 1.

A, PFS by BICR and (**B**) OS in the efficacy evaluable population by treatment arm.

Safety

Any treatment-emergent AEs (TEAE) grade ≥ 3 were reported in 68.4% and 65.2% of patients in the efti and placebo arm, respectively. The majority of TEAEs occurred at similar rates in both treatment arms (**Table 2**). Grade ≥ 3 anemia, though uncommon, was more frequent in the efti arm (6.1% vs. 0.9%). Grade ≥ 3 gamma-glutamyl transferase increase (20.2% vs. 29.5%), hypophosphatemia (0.9% vs. 8.0%) and any-grade peripheral edema (7.0% vs.17.0%) were more common in the placebo arm.

Discontinuations due to AEs during chemo-immunotherapy were infrequent and similar between arms (6.1% for efti; 8.0% for placebo), and no patient discontinued maintenance therapy due to an AE. TEAEs leading to discontinuation of efti or placebo (5.3% and 6.3% in the efti and placebo arms, respectively) or discontinuation of efti + paclitaxel or placebo + paclitaxel (7.0% and 10.7%, respectively) were infrequent and occurred at similar rates in both arms. TEAEs leading to death occurred at similar frequency in the efti and placebo arm (2.7% versus 1.8%) and were generally associated with progression of the underlying disease or paclitaxel toxicity.

Any kind of local injection-site reactions were notably more common in the efti arm (65.8% any grade) than in the placebo arm (11.6% any grade). None of them were serious, and none led to efti discontinuation. There were three (2.6%) immediate systemic hypersensitivity reactions to efti (2 of grade 4, 1 of grade 2) in the efti arm which occurred later in the treatment course (after 4, 5, and 9 efti injections).

Recurrent reactions indicating systemic inflammatory responses occurring shortly after efti injection were reported in 13 (11.4%) patients in the efti arm and 1 (0.9%) patient in the placebo arm and included, for example, chills, pyrexia, and influenza-like illness. All reactions were of mild or moderate severity.

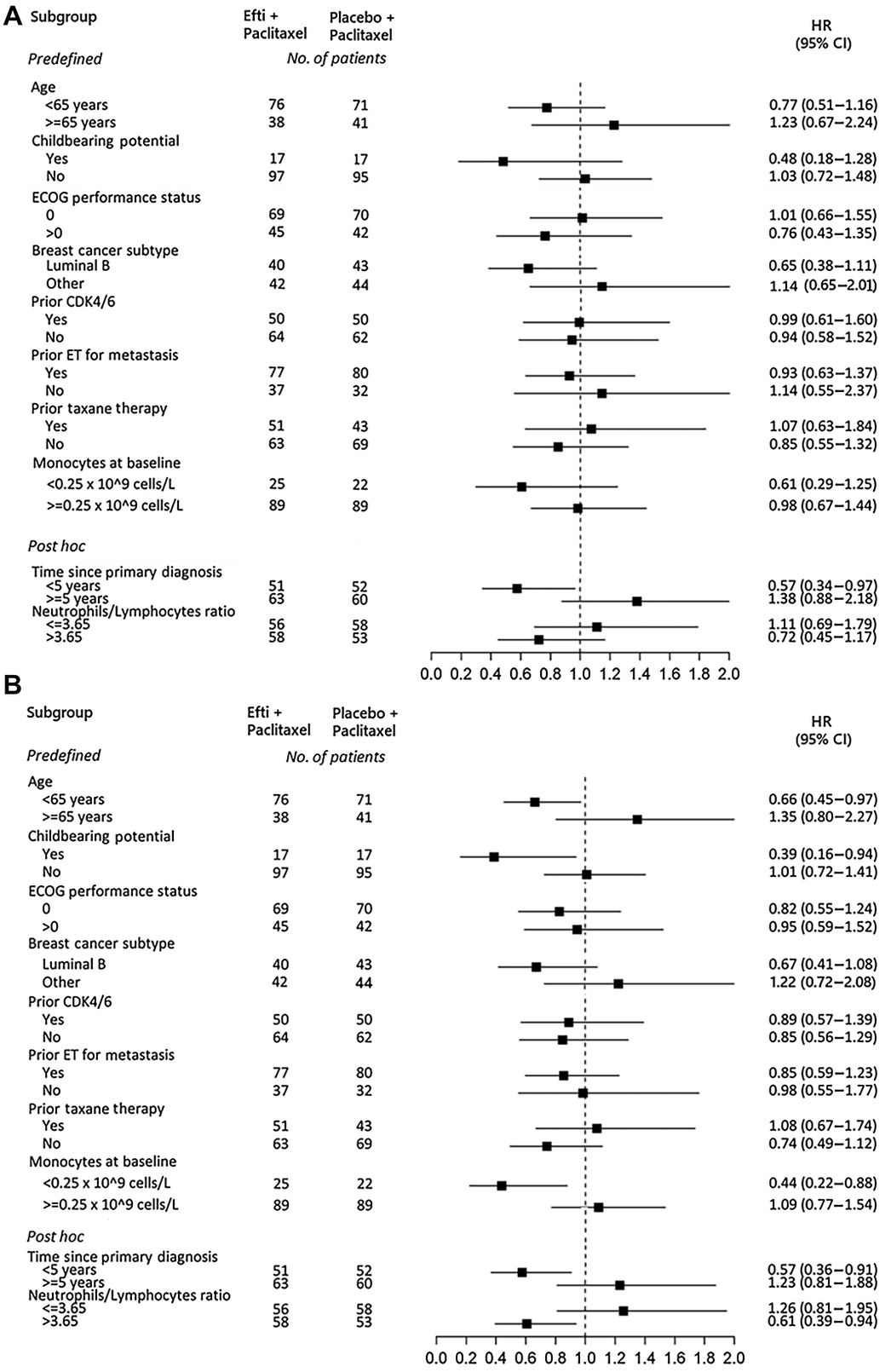

Figure 2.
Treatment effect by subgroup (**A**) PFS by BICR. **B,** OS.

Table 2. TEAEs of any grade in > 15% of patients and/or of grade ≥ 3 in > 5% of patients in either arm in the safety population.

	Efti + Paclitaxel ($n = 114$)		Placebo + Paclitaxel ($n = 112$)	
Event, *n* (%)	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Fatigue	53 (46.5)	2 (1.8)	55 (49.1)	2 (1.8)
Alopecia	46 (40.4)	0	56 (50.0)	0
Nausea	44 (38.6)	3 (2.6)	40 (35.7)	0
Diarrhea	33 (28.9)	1 (0.9)	41 (36.6)	1 (0.9)
GGT increased	25 (21.9)	23 (20.2)	34 (30.4)	33 (29.5)
Peripheral neuropathy	23 (20.2)	0	28 (25.0)	1 (0.9)
Injection site reaction	39 (34.2)	0	4 (3.6)	0
Peripheral sensory neuropathy	21 (18.4)	0	22 (19.6)	2 (1.8)
Neutropenia	22 (19.3)	18 (15.8)	21 (18.8)	16 (14.3)
Cough	20 (17.5)	0	22 (19.6)	0
Constipation	20 (17.5)	0	20 (17.9)	0
Headache	21 (18.4)	0	17 (15.2)	1 (0.9)
Injection site erythema	35 (30.7)	1 (0.9)	2 (1.8)	0
Asthenia	16 (14.0)	1 (0.9)	20 (17.9)	0
Dyspnea	16 (14.0)	2 (1.8)	20 (17.9)	4 (3.6)
AST increased	16 (14.0)	10 (8.8)	18 (16.1)	13 (11.6)
Anemia	18 (15.8)	7 (6.1)	16 (14.3)	1 (0.9)
Peripheral edema	8 (7.0)	0	19 (17.0)	1 (0.9)
Blood ALP increased	9 (7.9)	5 (4.4)	14 (12.5)	10 (8.9)
ALT increased	10 (8.8)	5 (4.4)	12 (10.7)	7 (6.3)
WBC count decreased	5 (4.4)	4 (3.5)	11 (9.8)	7 (6.3)
Lymphocyte count decreased	3 (2.6)	3 (2.6)	7 (6.3)	7 (6.3)
Neutrophil count decreased	2 (1.8)	2 (1.8)	6 (5.4)	6 (5.4)
Hypophosphatemia	2 (1.8)	1 (0.9)	9 (8.0)	9 (8.0)
Hypertension	14 (12.3)	7 (6.1)	11 (9.8)	3 (2.7)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl aminotransferase; WBC, white blood cell.

Pharmacokinetics, pharmacodynamics, and immunogenicity

Pharmacokinetic analyses conducted during the run-in phase (6-mg and 30-mg subcutaneous doses) indicated a dose-proportional increase in exposure parameters (C_{max}, AUC) with relatively high inter-subject variability, consistent with subcutaneous administration of a large protein (160 kDa) requiring lymphatic transport. At the 30-mg dose, T_{max} was found between 2 and 24 hours and decreased rapidly thereafter (Supplementary Fig. S6). No accumulation was observed after repeated dosing. Pharmacodynamic measurements at day 13 post-dose reflect the residual effect of efti on the immunological status, as efti is no longer present in blood at any detectable level. Thus, any immunostimulatory effect observed at that time would indicate a long-term sustainable innate and adaptive response and subsequent efti injection is expected to boost these responses again.

In the subset of patients ($n = 67$, baseline characteristics presented in Supplementary Table S3) participating in cellular biomarker assessment, significant increases in the number of circulating primary target cells [monocytes and myeloid DCs (mDCs)] relative to baseline were observed in the efti arm and, to a lesser extent, in the placebo arm at all postbaseline measured timepoints. Mean fold changes from baseline were higher in the efti arm compared with placebo at all visits, reaching significance at the final timepoint (3.55 vs. 2.07; $P = 0.04$ and 4.29 vs. 1.55; $P = 0.025$ for monocytes and mDC respectively). Increases in secondary target cells (T cells) were observed in the efti arm compared with placebo. $CD8^+$ T cell levels were significantly higher at all postbaseline timepoints ($P = 0.006$ at 3 months; $P = 0.047$, 6 months), whereas baseline values showed no significant difference ($P = 0.061$; **Fig. 3A**). The number of $CD8^+$ T cells at 6 months positively correlated with OS in patients treated with 30 mg efti (Rho = 0.58; $P = 0.007$), but not in those treated with placebo (Rho = −0.16; $P = 0.535$). A weaker but significant correlation was already noted at 3 months in efti group (Rho = 0.37; $P = 0.041$), but not in placebo group (Rho = −0.07; $P = 0.722$; **Fig. 3B**).

In available data sets compiled from all participants in immune monitoring, maximal postbaseline $CD8^+$ T-cell levels (obtained from sampling collected weeks after the previous efti or placebo dosing) were significantly ($P = 0.025$) higher in patients with median or above-median OS only in patients treated with efti (Supplementary Fig. S7A). $CD4^+$ T-cell levels were significantly higher in patients with OS at or above the median OS in patients treated with efti ($P = 0.002$) and with placebo ($P = 0.023$), and at baseline in the placebo arm ($P = 0.048$; Supplementary Fig. S7B).

Maximal postbaseline fold increases from baseline were higher in the efti arm for monocytes, mDC, and activated $CD4^+$ and $CD8^+$ T cells, reaching significant differences for monocytes ($P = 0.009$) and activated $CD8^+$ T cells ($P = 0.020$; Supplementary Fig. S7C). Higher maximal postbaseline fold change of activated $CD4^+$ T cells ($P = 0.013$) and activated $CD8^+$ T cells ($P = 0.013$) were significantly associated with median or above-median OS in the efti arm. Activated $CD4^+$ T cells correlated with this also in the placebo arm at the significance limit ($P = 0.052$; Supplementary Fig. S7D).

In the full randomization subject set, ALCs demonstrated early and sustained increases in the efti arm, with the effect being larger during maintenance with significant differences to placebo arm at two time periods (not shown). Increased ALCs were significantly associated with OS times at or above median in patients in the efti arm over the treatment period, but not the placebo arm (**Fig. 3C**). In the efti arm, the subgroup of patients displaying an early (within the first two cycles)

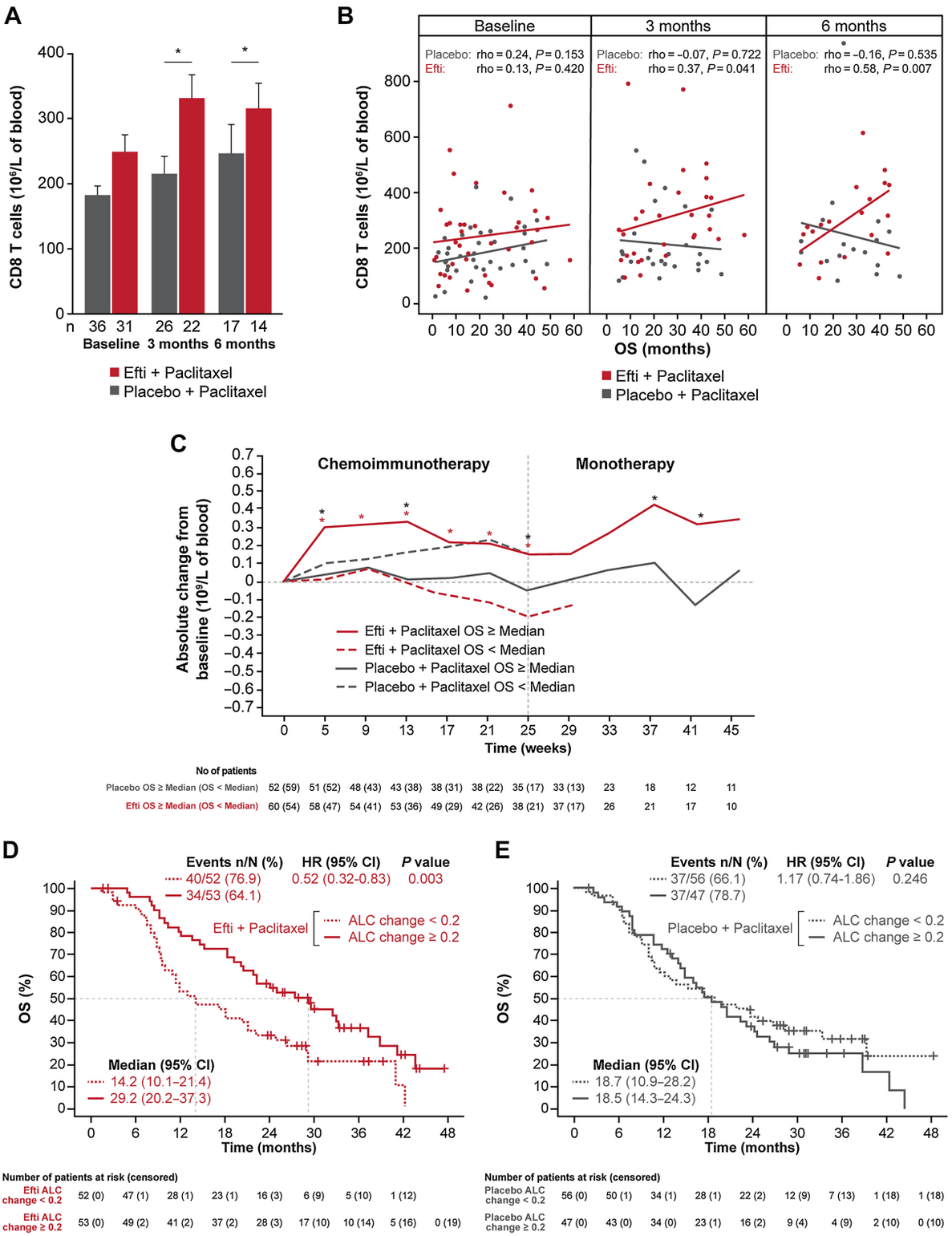

Figure 3.

A, Mean of peripheral blood CD8$^+$ T-cell count over time from randomization stage immuno-monitoring subject subset and (**B**) observed correlation between CD8$^+$ T-cell count at baseline, 3 and 6 months and OS among patients in the 30 mg efti plus paclitaxel and placebo plus paclitaxel treatment arms. **C,** Mean change from baseline in ALC over time by OS status and treatment arm in randomization stage. Timepoints with ≥ 8 patients per subgroup are displayed. **D** and **E,** Kaplan–Meier plot of OS of subgroup of efti (**D**) and placebo (**E**) treatment arms by ALC change from baseline (cutoff = 0.2×10^9/L of blood within 9 weeks of treatment). Median OS = 18.2 months. * indicates significant ($P < 0.05$) difference between treatment arms (black) and between OS status in eftilagimod arm (red).

ALC increase from baseline by 0.2 × 10^9/L of blood or more had a median OS of 29.2 months (95% CI, 20.2–37.3) while in the subgroup with lower increase or decrease in ALC, median OS was 14.2 months (95% CI, 10.1–21.4; HR 0.52; 95% CI, 0.32–0.83; $P = 0.003$; **Fig. 3D**). A gain of 15 months in OS was then observed between the ALC change subgroups in the efti arm. There was no difference in OS based on ALC change subgroups in the placebo arm (HR, 1.17; 95% CI, 0.74–1.86; $P = 0.246$; **Fig. 3E**).

IFNγ and CXCL10 levels increased significantly relative to baseline at 6 months in the efti group ($P = 0.014$ and $P = 0.02$), but not in the placebo group. At all timepoints, the fold changes from baseline of CXCL10 were higher in efti arm compared with placebo, reaching significant levels at the last timepoint (2.31 vs. 1.15; $P = 0.038$).

Non-neutralizing anti-efti ADAs were found in 85.5% of efti patients, with 64.2% developing ADAs within 4 weeks of the first dose. ADAs, however, were non-neutralizing and had no medically relevant effect on exposure, safety, or efficacy.

Discussion

In the AIPAC study, the efficacy and safety of efti versus placebo with weekly paclitaxel were evaluated in patients with ET-resistant HR^+ $HER2^-$ MBC eligible to receive chemotherapy. Consistent with its immunostimulatory mechanism of action, a 30-mg subcutaneous dose of efti was associated with a sustained significant increase of primary (monocytes and DCs) and secondary target cells (T cells) in addition to Th1 markers in peripheral blood. Levels of on-treatment $CD8^+$ T cells were linked to improved OS. Increased ALC levels in efti-treated patients were present during both the chemoimmunotherapy and maintenance phases and significantly correlated with improved OS among patients in that arm. Early increase in ALC correlated with a significantly longer OS in efti arm and a lower risk of death (HR, 0.54). Immunomonitoring of efti as a systemic APC activator can then be easily performed through repeated minimally invasive liquid biopsies (blood samplings).

Although the primary endpoint, median PFS was not met (both medians, 7.3 months; $P = 0.341$); the proportion of progression-free patients were numerically higher for the efti arm during the 6-month chemoimmunotherapy period (**Fig. 1A**; Supplementary Table S4A), the PFS advantage subsequently being lost during maintenance when chemotherapy was stopped. Mechanistically, these observations are consistent with the adjunctive effects of improved T-cell priming, for which efficacy is dependent upon the availability of tumor neoantigens supplied by chemotherapy-induced tumor cell killing. In this mechanism, chemotherapy cooperates with APC activation to transport tumor cell apoptotic debris-derived antigens to the lymph nodes for presentation to T cells. Conceivably, a longer course of chemotherapy could extend the efti PFS advantage observed during chemoimmunotherapy. It is also possible that the reduced efti dosing frequency during maintenance (every 4 weeks) may not have been sufficient for sustaining benefit because the duration of efti pharmacodynamic effects beyond 13 days was not examined in this study.

There was a non-statistically significant trend for improvement in OS in the overall efti arm (median 20.4 months vs. 17.5 months; $P = 0.197$). Exploratory subgroup analyses associated a significant efti efficacy benefit in patients <65 years, with low monocytes at baseline, with Luminal B disease, high neutrophil-lymphocyte ratio at baseline, no prior taxane therapy, and with <5 years since diagnosis. These findings are consistent with the mechanism of action of efti. Older patients with MBC are known to have a reduced number of $CD8^+$ T cells (27). In these patients, activation by efti would be expected to produce less of an effect. In patients with low monocytes at baseline, the ability of efti to boost numbers of primary and secondary target cells may also promote efficacy.

Prior CDK4/6i therapy, representing 44.2% of this patient population, was associated with a lower median OS in the placebo arm when compared with no prior treatment (20.4 to 14.9 months). Multivariate analysis showed that prior CDK4/6i therapy was associated with a higher risk of progression (HR, 1.65) and death (HR, 1.37) compared with patients without prior CDK4/6i. This is the first time to our knowledge that this poor prognostic effect of prior CDK4/6i on PFS of subsequent treatment and on survival, independent of factors such as time since diagnosis and number of metastatic sites at study entry, has been shown in a randomized setting. Interestingly, median OS was almost unchanged with efti in those patients previously treated with CDK4/6i (20.2 vs. 21.9 months), suggesting a possible protective effect of efti in this population. Approximately one-half of AIPAC patients were enrolled before CDK4/6i in combination with ET displaced chemotherapy as the standard of care in first-line HR^+ $HER2^-$ MBC. In the evolving treatment landscape, with chemotherapy reserved for later lines, a shorter survival benefit for chemotherapy than the approximately 25 to 26 months reported in older trials such as E2100 (28) and MERIDIAN (29), both of which had less heavily pretreated patient populations than AIPAC, is to be expected. Thus, the use of efti plus chemotherapy in later lines appears worthy of further study. For further development, it is noteworthy that QoL did not drop at 6 months as it did in the placebo arm. This is important as OS and QoL (the latter being better with efti compared with placebo) are considered as priority outcomes in the European Society of Medical Oncology Magnitude of Clinical Benefit Scale (30).

AEs for efti plus paclitaxel were dominated by the known toxicities associated with the latter in patients with breast cancer. Local injection site reactions (any grade, 65.8%) up to grade 2, immediate hypersensitivity reactions (any grade, 2.6%), and various mild-to-moderate severity systemic inflammatory responses (any grade, 11.4%) were the main TEAEs attributed to efti. Mechanistically, local injection site reactions may result from transitory high concentrations of efti in the dermis and the hypodermis after injection leading to strong activation of MHC II^+ Langerhans cells and subcutaneous DCs along with local inflammation.

This study had several limitations. As enrollment in AIPAC spanned a period in which there were two separate standards of care for ET-based therapies of HR^+ $HER2^-$ MBC—a situation that could not be foreseen when the study was designed—these results could be viewed as the collective analysis of two different patient populations, potentially confounding the interpretation of results. Sample size was also limited in this phase IIb trial, limiting the interpretation of final OS data.

In conclusion, results from AIPAC confirmed the expected pharmacodynamic effects of efti in sustainably stimulating the innate and adaptive immune response over long periods of time and demonstrated that it was well-tolerated in combination with paclitaxel in patients with HR^+ $HER2^-$ MBC. Although the primary endpoint of median PFS was not met, efti displayed a numerically, although not statistically significant, improvement in OS and significant clinical benefit in subgroups consistent with its mechanism of action. Efti was well tolerated and warrants further study to clarify its efficacy in combination with chemotherapy in this patient population. On the basis of the results of AIPAC, a follow-up study (AIPAC-003;

NCT04252768) was initiated with a couple of key adaptations: if tolerated, paclitaxel will not be stopped after 6 cycles, efti will be more frequently administered during in the maintenance phase (remaining at every 2 weeks). Most importantly, based on its excellent safety, the dose of efti will be increased to 90 mg. We saw in AIPAC a meaningful increase in many of the measured biomarkers within about 60% of efti-treated patients. We have reasonable belief that a higher dose can increase this proportion and thus increase efficacy as well. An extensive biomarker program is planned for AIPAC-003 in the potential phase III part of AIPAC-003.

Authors' Disclosures

H. Wildiers reports other support from university hospitals Leuven during the conduct of the study. A. Armstrong reports grants from research funding from AstraZeneca paid to institution; nonfinancial support from conference fees and travel expenses from Novartis; nonfinancial support from conference fees from MSD; and personal fees from Advisory Board Roche and Advisory Board AstraZeneca outside the submitted work. F. Marme reports personal fees from AstraZeneca, Clovis, GSK, Daiichi Sankyo, Gilead, Lilly, Pfizer, Novartis, Roche, Seagen, Myriad, MSD, Eisai, and PharmaMar outside the submitted work. J. Huober reports grants and personal fees from Lilly; personal fees from Novartis, Pfizer, Seagen and AstraZeneca; and personal fees and other support from Roche, Gilead, and Daiichi outside the submitted work. F.P. Duhoux reports other support from Immutep during the conduct of the study; grants from Fondation belge contre le cancer; and other support from Roche, Pfizer, AstraZeneca, Lilly, Novartis, Amgen, Daiichi Sankyo, Pierre Fabre, Gilead Sciences, Seagen, MSD, Amgen, Roche, Teva, Pfizer, Daiichi Sankyo/AstraZeneca, Gilead Sciences, and MSD outside the submitted work. P. Vuylsteke reports grants from Roche; grants and personal fees from MSD; and personal fees from Novartis outside the submitted work. S. Kuemmel reports personal fees from Roche, Exact Science, Lilly, Pfizer, Novartis, MSD, Hologic, Seagen, AstraZeneca, Daiichi Sankyo, Gilead, and Agendia and grants from Roche and Daiichi Sankyo outside the submitted work; as well as partial ownership WSG, uncompensated relationship. C.W. Menke-van der Houven van Oordt reports other support from ImmuTep during the conduct of the study. L. Perjesi reports other support from Immutep GmbH during the conduct of the study; as well as other support from Immutep GmbH outside the submitted work. C. Mueller reports personal fees and other support from Immutep S.A.S during the conduct of the study; personal fees and other support from Immutep S.A.S outside the submitted work; and is employed by Immutep, the sponsor of the discussed clinical research. F. Triebel reports a patent for Immutep pending and issued; is an employee of Immutep as well as owns stocks and is an inventor on some patents. No disclosures were reported by the other authors.

Authors' Contributions

H. Wildiers: Investigation, writing–review and editing. **A. Armstrong:** Investigation. **E. Cuypere:** Investigation. **F. Dalenc:** Investigation. **L. Dirix:** Investigation, project administration. **S. Chan:** Investigation. **F. Marme:** Investigation. **C.P. Schröder:** Investigation. **J. Huober:** Investigation. **F.P. Duhoux:** Investigation. **P. Vuylsteke:** Investigation. **A. Jager:** Investigation. **E. Brain:** Investigation. **S. Kuemmel:** Investigation. **Z. Pápai:** Investigation. **C.W. Menke-van der Houven van Oordt:** Investigation. **L. Perjesi:** Data curation, formal analysis, supervision, investigation, visualization, methodology. **C. Mueller:** Conceptualization, resources, data curation, formal analysis, supervision, funding acquisition, validation, investigation, visualization, methodology, project administration, writing–review and editing. **C. Brignone:** Conceptualization, data curation, software, formal analysis, supervision, investigation, visualization, methodology, writing–review and editing. **F. Triebel:** Conceptualization, resources, formal analysis, supervision, validation, investigation, visualization, methodology, writing–original draft, project administration, writing–review and editing.

Acknowledgments

We thank the patients, their supporters, and the investigators at the various study centers. We also thank Drs. Jean-Philippe Jacquin and Jill Wagemans for participating as investigators in this trial. Medical writing and editorial assistance were provided, under the direction of the authors, by Robert Rydzewski, MS, and Miriam Cohen, PhD, ISMPP CMPP, of Bio Connections, LLC (Chicago, IL), supported by Immutep.

This study was funded by Immutep S.A.S.

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Note

Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Received June 23, 2023; revised September 15, 2023; accepted November 3, 2023; published first November 8, 2023.

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