Optimal biological dose of eftilagimod alpha, a soluble LAG-3 protein, in metastatic breast cancer patients receiving weekly paclitaxel in AIPAC-003

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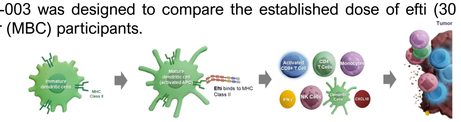
BACKGROUND

- **Eftilagimod alpha (eftilagimod alfa; efti):** an antigen presenting cell (APC) activator that binds to a subset of major histocompatibility complex (MHC) class II molecules. Activating APCs (e.g., dendritic cells) 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[1,2] (**Figure 1**). The established approach to administer efti is as a 30 mg subcutaneous (s.c.) injection in the thigh every 2 weeks for at least 6 months. Efti is always administered in combination with standard-of-care treatments including chemotherapy, immunotherapy, radiotherapy, or as a combination of these approaches.
- In line with the FDA's Project Optimus, AIPAC-003 was designed to compare the established dose of efti (30 mg) to a higher dose (90 mg) in metastatic breast cancer (MBC) participants.

Figure 1: Mechanism of action of efti

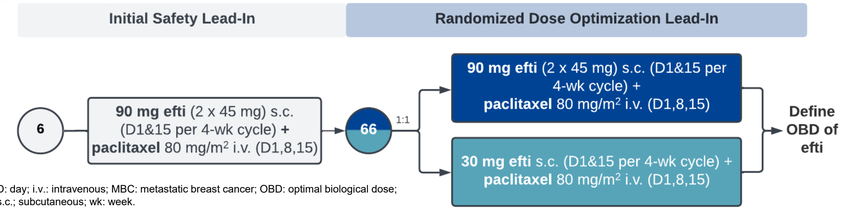


METHODS

Study Design

- AIPAC-003 enrolled heavily pretreated female participants with HR$^+$ and HER2-negative/HER2-low MBC resistant to endocrine-based therapy (ET) or with metastatic triple-negative breast cancer (mTNBC) not eligible for PD-(L)1-based therapy in two stages (**Figure 2**):
  1. An initial open-label **safety lead-in** (N=6) where the safety of a higher dose of efti (90 mg) was evaluated by an independent data monitoring committee.
  2. A Phase 2 **randomized dose optimization lead-in** (N=66) where participants were randomized 1:1 to receive efti at both doses (30 mg versus 90 mg).

Figure 2: Trial design



D: day; i.v.: intravenous; MBC: metastatic breast cancer; OBD: optimal biological dose; s.c.; subcutaneous; wk: week.

- The primary objectives of the study were to evaluate safety and tolerability of 30 mg versus 90 mg efti and to define the optimal biological dose (OBD) of efti as per an agreed pre-defined algorithm with the FDA.

Assessments and Statistical Analysis

- Absolute lymphocyte count (ALC) was assessed pre-dose at each cycle. Interferon-gamma (IFN-gamma) was assessed before the 7th, 13th and 19th doses of efti.
- Safety results are presented for the safety population (participants who received at least one dose of study treatment; N=72). Data cut-off date for safety results was January 31, 2025.
- Efficacy results are presented for the evaluable population (who had at least 1 evaluable post-baseline radiological scan; N=64) from the randomized dose optimization lead-in. Data cut-off date for efficacy results was September 15, 2025. Efficacy results from the safety lead-in were presented at ESMO Breast 2024[3].

RESULTS

Baseline Characteristics (N=64)

- Between May 2023 – Sep 2024, 66 participants were randomized; 64 were considered evaluable.
- 18.8% of participants had mTNBC. All HR$^+$ participants were previously treated with ET. 84.4% of the overall population was treated with CDK4/6 inhibitors (84.4%) and were considered ET-resistant (81.3%), as presented in **Table 1**.
- The 30 mg arm had fewer participants whose initial diagnosis was <5 years before informed consent (29.0%) compared to the 90 mg arm (51.5%).
- More participants had prior adjuvant taxanes in the 30 mg arm compared to 90 mg arm (64.5% versus 45.5%).

Table 1: Baseline characteristics (N=64)

Baseline characteristics	30 mg efti + paclitaxel N=31	90 mg efti + paclitaxel N=33	Overall N=64
Age, median (range), years	60 (34–80)	58 (43–85)	58.5 (34–85)
<65 years, n (%)	23 (74.2)	23 (69.7)	46 (71.9)
ECOG PS 0 / 1, n (%)	20 (64.5) / 11 (35.5)	21 (63.6) / 12 (36.4)	41 (64.1) / 23 (35.9)
HR$^+$ HER2 low, n (%)	18 (58.1)	6 (18.2)	24 (37.5)
HR$^+$ HER2 neg, n (%)	8 (25.8)	20 (60.6)	28 (43.8)
TNBC, n (%)	5 (16.1)	7 (21.2)	12 (18.8)
Pre- / Post-menopausal, n (%)	5 (16.1) / 26 (83.9)	3 (9.1) / 30 (90.9)	8 (12.5) / 56 (87.5)
Cancer stage at initial diagnosis, n (%) I / II / III / IV	4 (12.9) / 12 (38.7) / 11 (35.5) / 4 (12.9)	4 (12.1) / 12 (36.4) / 9 (27.3) / 8 (24.2)	8 (12.5) / 24 (37.5) / 20 (31.3) / 12 (18.8)
Time from initial diagnosis to informed consent, n (%) <5 years	9 (29.0)	17 (51.5)	26 (40.6)
(Neo)adjuvant therapy, n (%)	3 (9.7)	2 (6.1)	5 (7.8)
Endocrine-based therapy	29 (93.5)	28 (84.8)	57 (89.1)
Taxanes	20 (64.5)	15 (45.5)	35 (54.7)
CDK4/6i	26 (83.9)	28 (84.8)	54 (84.4)
Endocrine resistance, n (%)	26 (83.9)	26 (78.8)	52 (81.3)

CDK4/6i: cyclin-dependent kinase 4/6 inhibitors; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; TNBC: triple negative breast cancer.

Safety (N=72)

- Adverse reactions leading to treatment discontinuation occurred in 15.2% (30 mg) versus 17.9% (90 mg arm).
- 3 DLTs* occurred, all hypersensitivity reactions in the 90 mg arm.
- Local injection site reactions (LISRs) which were considered long-lasting (≥5 days) occurred in 18.2% (30 mg) versus 30.8% (90 mg). No LISR led to treatment discontinuation.

*Acute respiratory distress syndrome (G4); allergy (G4); immediate hypersensitivity reaction (G3).

Efficacy (N=64)

- Objective response rate (ORR) was 41.9% (30 mg) versus 48.5% (90 mg). Disease control rate (DCR) was 87.1% (30 mg) versus 78.8% (90 mg), as presented in **Table 2**. Details of best overall responses are depicted by best percentage change in **Figure 3**.
- Both doses elicited the desired pharmacodynamic (PD) response. There was no clinically meaningful difference in any PD parameter between the two dose levels (**Figure 4**).
- Time to onset of response (TTR) was 2.0 months (30 mg) versus 1.9 months (90 mg).

Figure 3: Waterfall plot (N=64)

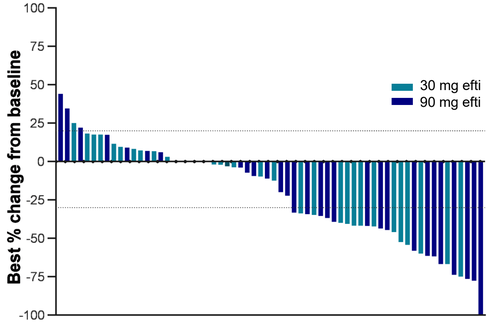
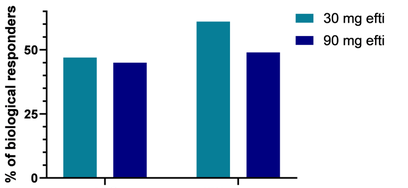


Table 2: Objective response rate and disease control rate (N=64)

Best overall response[1]	30 mg efti + paclitaxel N=31	90 mg efti + paclitaxel N=33
Complete Response, n (%)	0	0
Partial Response, n (%)	13 (41.9)	16 (48.5)
Stable Disease, n (%)	14 (45.2)	10 (30.3)
Progression, n (%)	4 (12.9)	7 (21.2)
ORR[1,2], n (%) [95% CI][3]	13 (41.9) [24.6-60.9]	16 (48.5) [30.8-66.5]
DCR[1], n (%) [95% CI][3]	27 (87.1) [70.2-96.4]	26 (78.8) [61.1-91.0]

[1] Per RECIST 1.1
[2] Unconfirmed.
[3] 95% CIs were calculated using the Clopper-Pearson method.
CI: confidence interval; DCR: disease control rate; ORR: objective response rate.

Figure 4: Proportion of biological responders per pharmacodynamic marker



Note: for ALC, a maximum change from baseline of ≥0.2 x 10^9/L within 8 weeks was considered indicative of a biological response and for IFN-gamma, the cut-off was ≥1.4-fold at pre-dose timepoints (i.e., two weeks after subcutaneous injection).
ALC: absolute lymphocyte count; IFN: interferon.

CONCLUSIONS

- **Both efti dose levels (30 and 90 mg) on top of weekly paclitaxel led to strong ORR and strong biological responses in heavily-pretreated MBC patients with no clinically-meaningful or significant differences between the doses as per the pre-defined algorithm.**
- **Other efficacy parameters, such as DCR & TTR, were also comparable between the two efti dose levels.**
- **Both efti dose levels (30 and 90 mg) are considered generally safe, however, tolerability at 90 mg was suboptimal including DLTs and a higher proportion of LISRs.**
- **In line with FDA guidance/advice (i.e., Project Optimus), 30 mg of efti administered subcutaneously is defined as the OBD.**

References
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Nuhad Ibrahim reports no conflicts of interest.

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