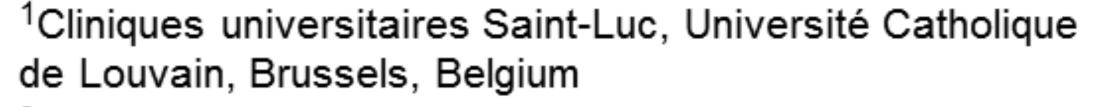
Combination of paclitaxel and a LAG-3 fusion protein (eftilagimod alpha), as a first-line chemoimmunotherapy in patients with metastatic breast carcinoma (MBC): final results from the run-in phase of a placebo-controlled randomized phase II.

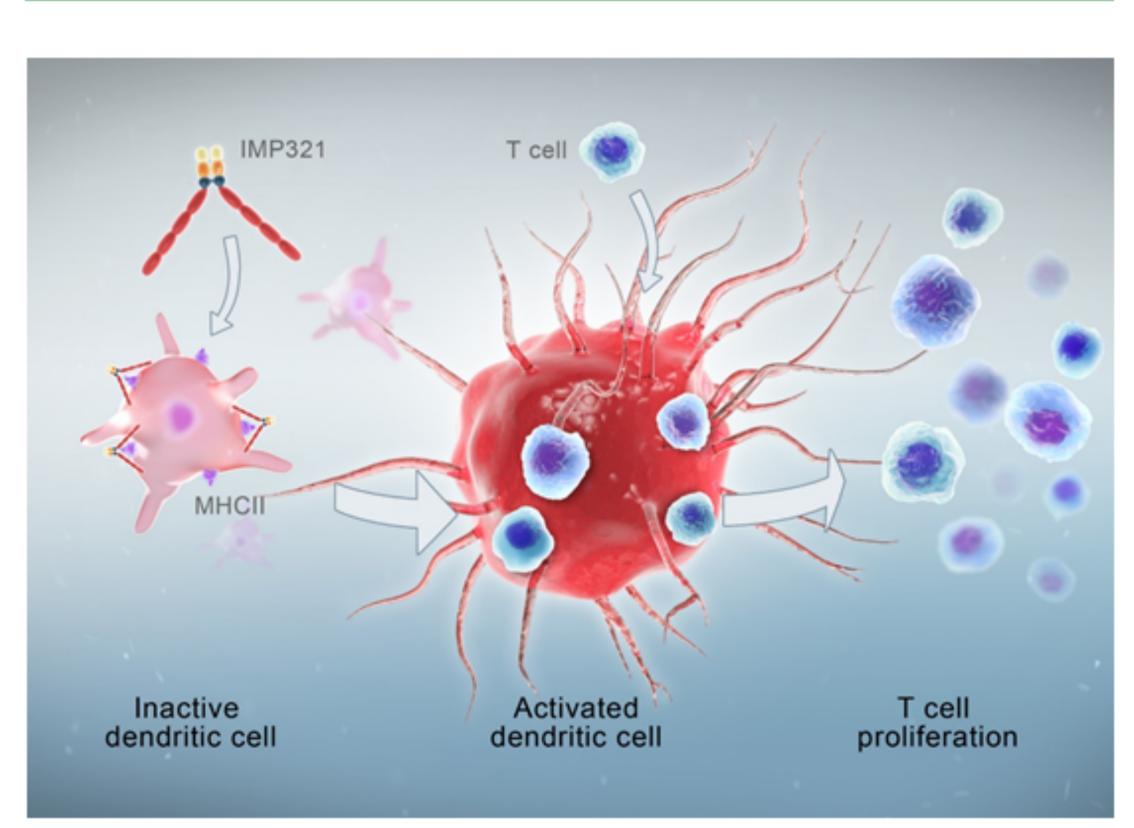


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Background



Eftilagimod alpha (efti, previously IMP321) is a recombinant LAG-3lg fusion protein that binds to MHC class II and mediates antigenpresenting cell (APC) activation followed by CD8 T-cell activation. The activation of the dendritic cell network with efti the day after chemotherapy may lead to stronger antitumor CD8 T cell responses. We report final results of the safety run-in of a phase IIb trial (NCT02614833) in patients (pts) with hormone receptor positive MBC receiving weekly paclitaxel as first line chemotherapy. The randomization stage is actively recruiting.

For more information, please visit:

://www.immutep.com/technology/lag-3n or go to the presentation section by using the QR code below:



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The trial identifiers are IMP321-P011 (sponsor code), 2015-002541-63 (EudraCT) and NCT02614833 (ClinicalTrials.gov). Corresponding author: Francois P Duhoux, francois.duhoux@uclouvain.be

Trial design

Multinational, multicenter, placebo-controlled, double blind, 1:1 randomized Phase IIb trial consisting of 2 stages:

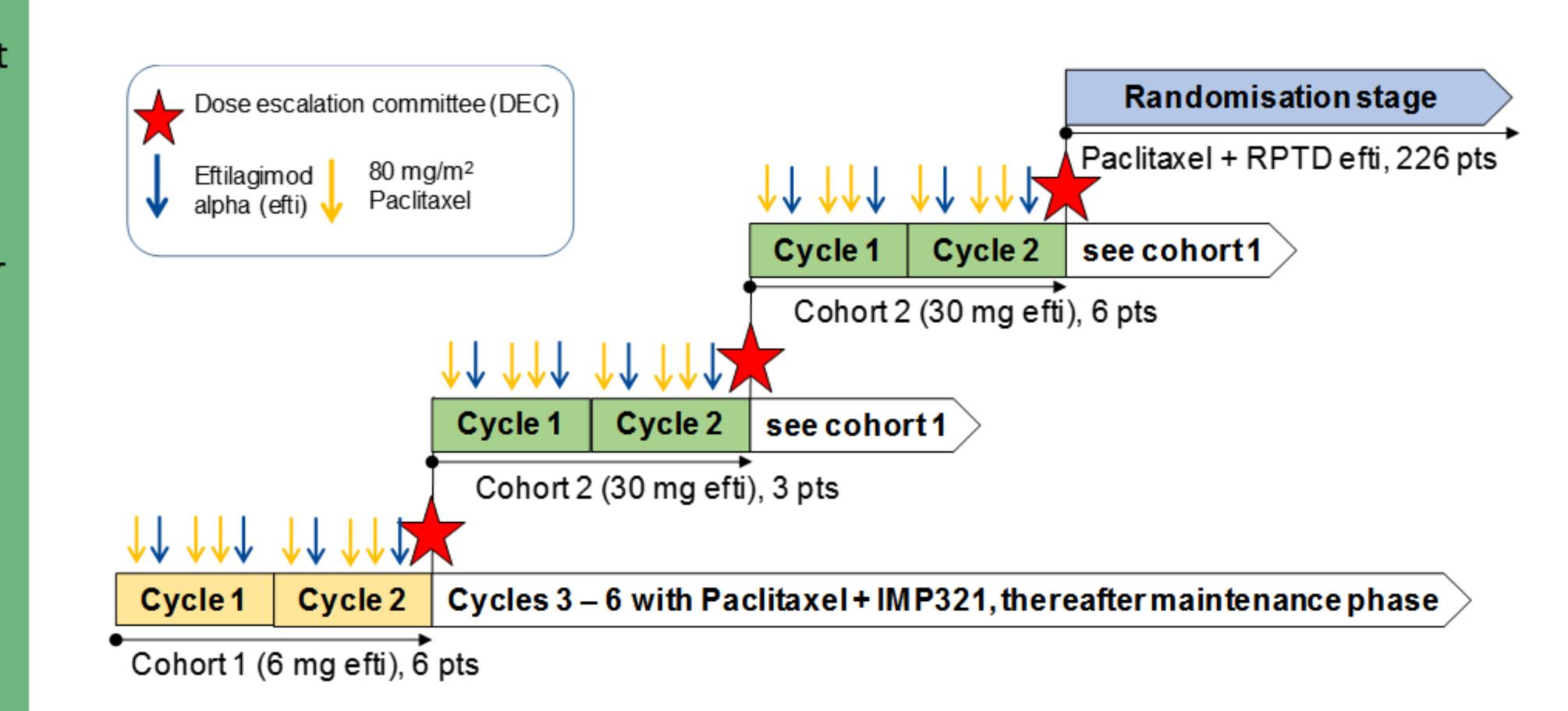
- Safety run-in stage (n = 15): open-label, determining recommended phase two dose (RPTD) of efti in combination with weekly paclitaxel for the randomized phase
- Randomization stage (n = 226)*: randomized (1:1), placebo-controlled, double-blind: paclitaxel + efti vs. paclitaxel + placebo

Treatment consists of a chemo-immunotherapy phase followed by a maintenance phase:

- chemo-immunotherapy phase: 6 cycles with weekly paclitaxel (80 mg/m²) at days 1, 8 and 15 + either efti or placebo, on Days 2 and 16 of each 4week cycle.
- maintenance phase: responding or stable patients will receive study agent (efti or placebo) every 4 weeks for additional 12 injections

Dose escalation process

Dose levels of 6 mg and 30 mg efti have been selected based on previous trials with efti in metastatic renal cell¹ and breast cancer².



Objectives (safety run-in stage)

Primary:

To determine the RPTD for the randomised stage

Secondary + Exploratory:

- To determine safety and tolerability
- To assess antitumor activity by best response (RECIST 1.1), PFS and OS
- To characterize the pharmacokinetic properties and immunogenic profile of efti
- To evaluate the immune response of patients in relation to the treatment with

Inclusion and exclusion criteria can be found on clinicaltrials.gov (NCT02614833).

*Information about the randomisation stage in progress can be found on poster #185b (abstract TPS1109).

Safety results

In total 15 pts received between 1-18+ efti injections. Cytokine release syndrome grade 1 was the only serious adverse event (SAE) related to efti.

Safety parameter	Paclitaxel + 6 mg efti (n=6)	Paclitaxel + 30 mg efti, (n=9)	Overall (n=15)
Pts with any AE	6 (100 %)	9 (100 %)	15 (100 %)
Pts with any SAE	5 (83 %)	4 (44 %)	9 (60 %)
No of SAEs	10	6	16
No of SAEs rel. to efti	0	1	1
No of SAEs rel. to paclitaxel	1	0	1
Pts with any grade 3/4 AE	5 (83 %)	7 (78 %)	12 (80 %)
Any grade 3/4 AE rel. to efti	0 (0 %)	4 (44 %)	4 (27 %)
Any grade 3/4 AE rel. to paclitaxel	1 (17 %)	3 (33 %)	4 (27 %)

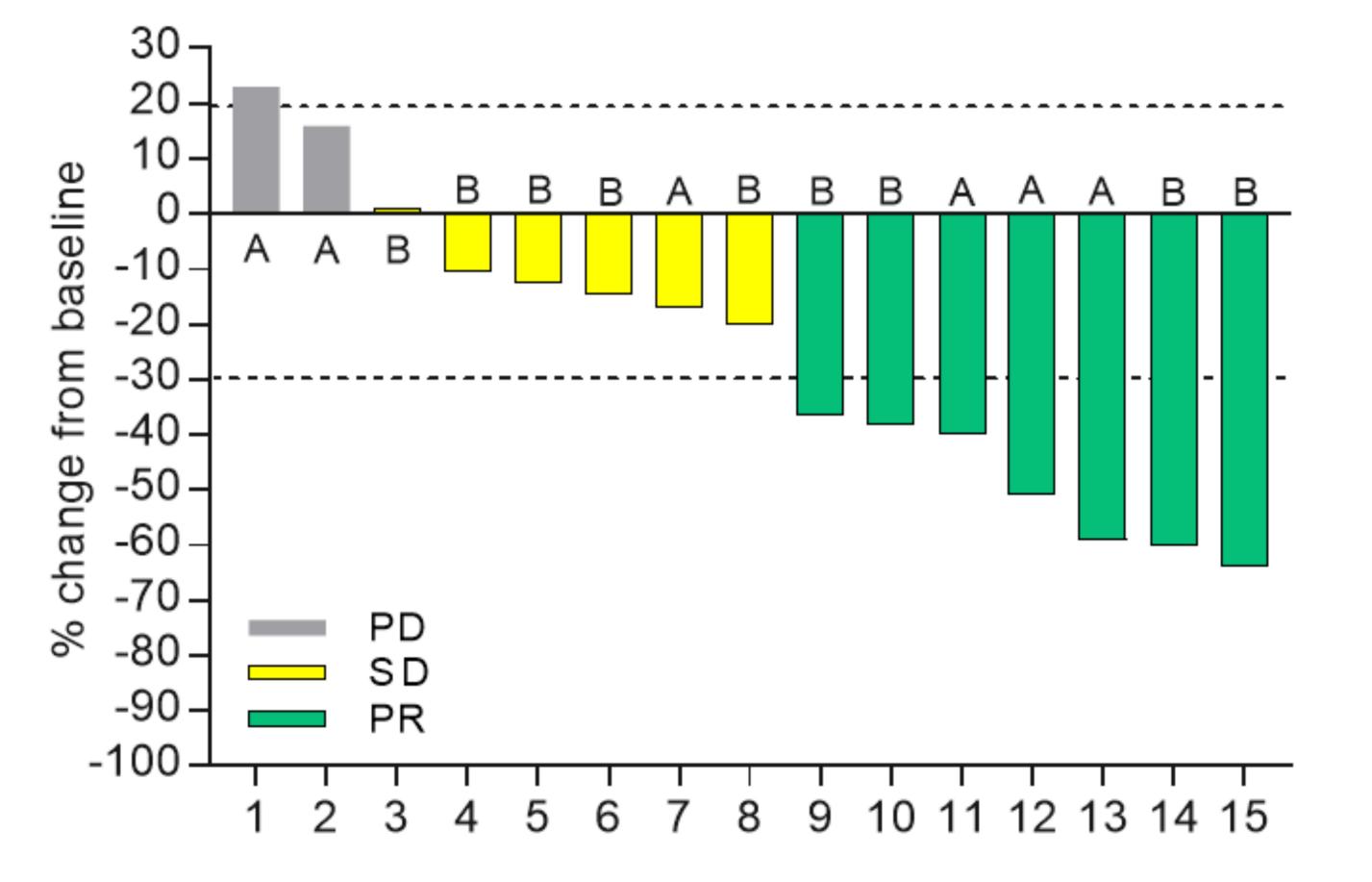
The grade 4 adverse event (AEs) was not related to paclitaxel or efti. The most common adverse events related to efti were injection site reactions grade 1 and 2 occurring in almost every patient. The dose escalation committee confirmed that 30 mg efti is the recommended phase 2 dose for combination with weekly paclitaxel.

Efficacy results

The ORR was 47 % accompanied by a DCR of 87 %. Two of the responses occurred relatively late (after ~6 months).

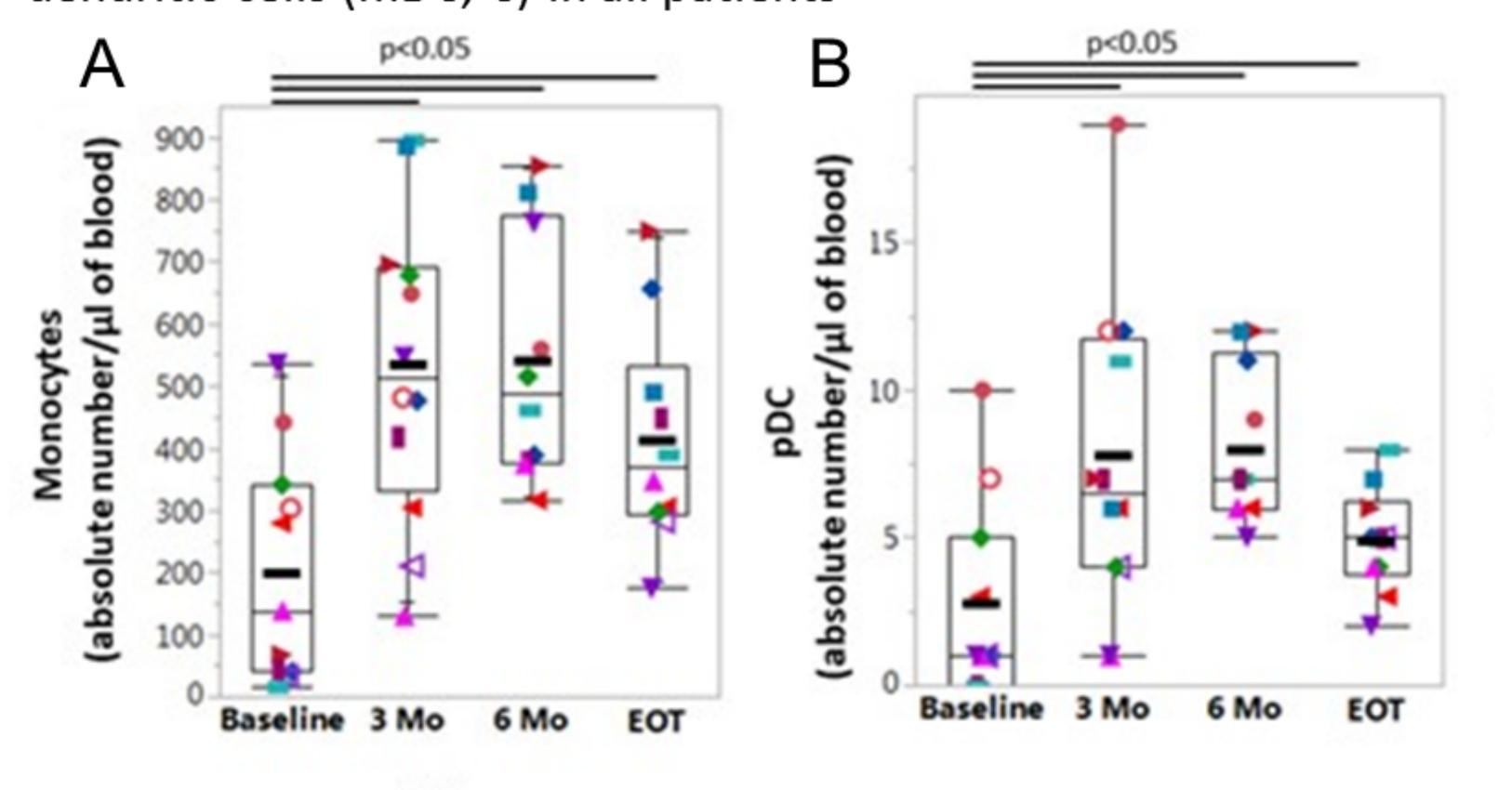
Response parameter	Paclitaxel + efti (n = 15)
Complete Response (CR)	0/15 (0 %)
Partial Response (PR)	7/15 (47 %)
Stable Disease (SD)	6/15 (40 %)
Progressive Disease (PD)	2/15 (13 %)
Overall Response Rate (ORR)	7/15 (47 %)
Disease Control Rate (DCR)	13/15 (87 %)

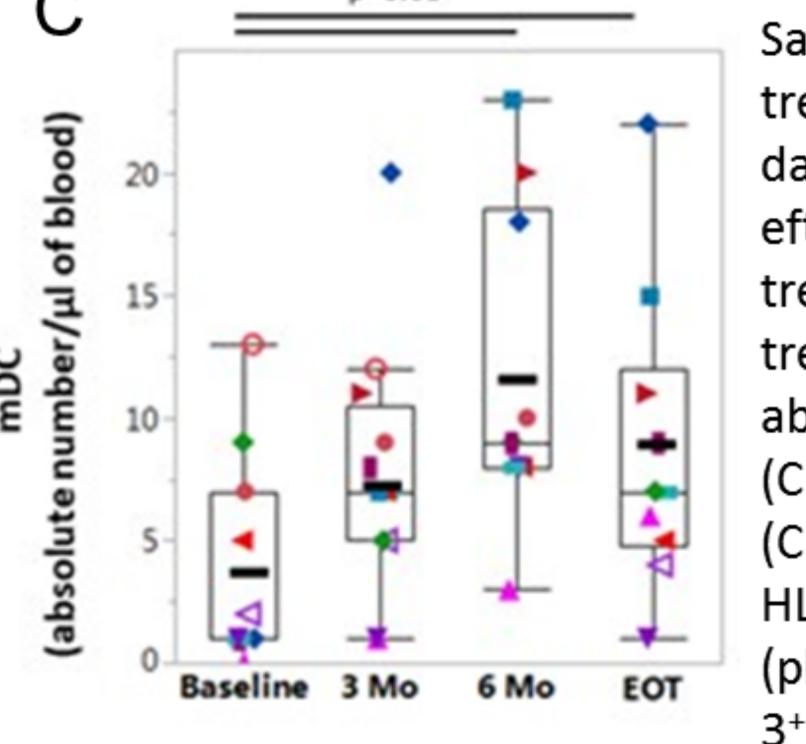
Waterfall plot for the analysis of response. Waterfall plot per treatment group and overall. A=6 mg group; B=30 mg group.



Pharmacodynamics

Pharmacodynamic effect on APC compartment: Treatmentinduced increase of circulating Antigen-Presenting Cells (APCs) like monocytes (A), peripheral dendritic cells (pDC, B) and myeloid dendritic cells (mDC, C) in all patients





Samples collected prior to any treatment in cycle 1 (baseline), 13 days after the 6th and 12th injection of efti (e.g. after 3 and 6 months of treatment) and at the end of treatment (EOT) to monitor the absolute counts of monocytes (CD45+CD14+) and dendritic cells (CD45+CD3-CD14-CD19-CD20-CD56-HLA-DR+) either BDCA-2+ (plasmacytoid DC) or BDCA-1+/BDCA-3+ (myeloid dendritic cells).

Left and right: Both doses levels (6 and 30 mg efti) are analyzed together (blue-green colors = 6 mg; red-purple colors = 30 mg). The distribution of patients data are shown in box plots: the box indicating 25 % to 75 % quartiles, with the internal line for the median and the whiskers indicating the minimum and maximum values. When applicable, outlier data points are provided. The black thick line indicates the mean. P values were calculated using the paired non-parametric Wilcoxon signed rank test (p < 0.05).

Conclusions

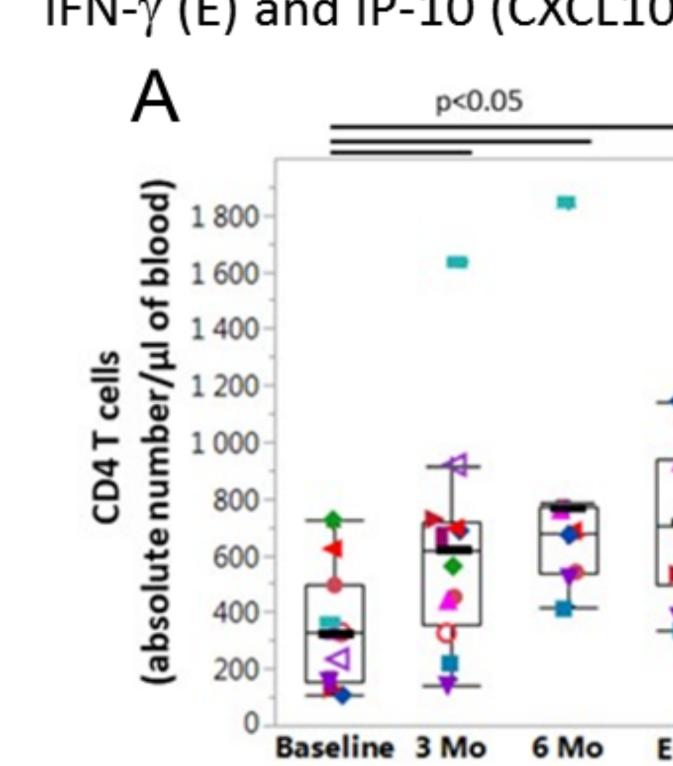
- 30 mg efti is the RPTD in combination with weekly paclitaxel as a first line chemotherapy treatment of MBC
- 6 and 30 mg efti are safe and well tolerated in combination with weekly paclitaxel
- Efti in combination with paclitaxel shows encouraging DCR (87 %) and ORR of 47 %
- Efti leads to sustainable (> 6 months) increase and activation of APCs
- Efti leads to sustainable (> 6 months) increase in T cell numbers, together with an improved Th1 status

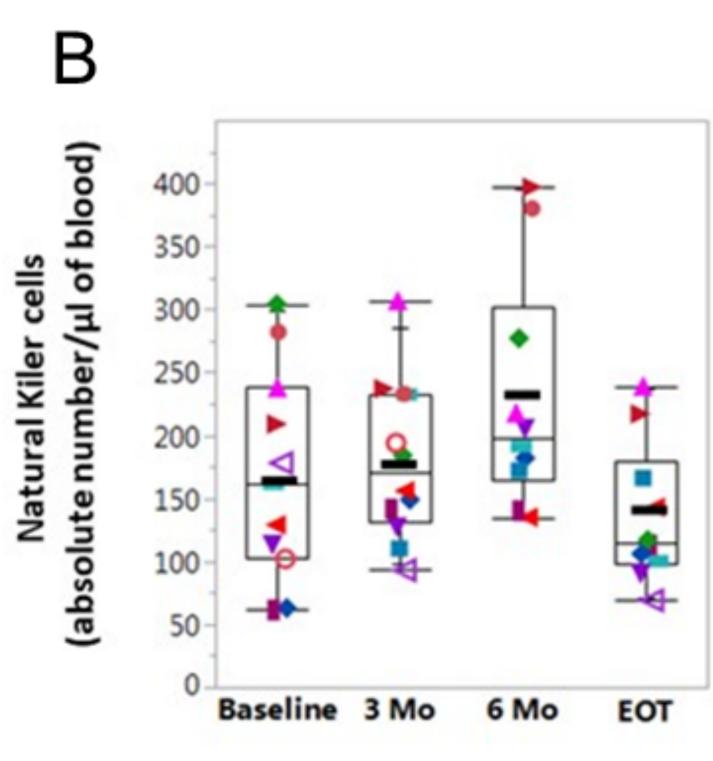
Pharmacodynamic effect on effector cell compartment:

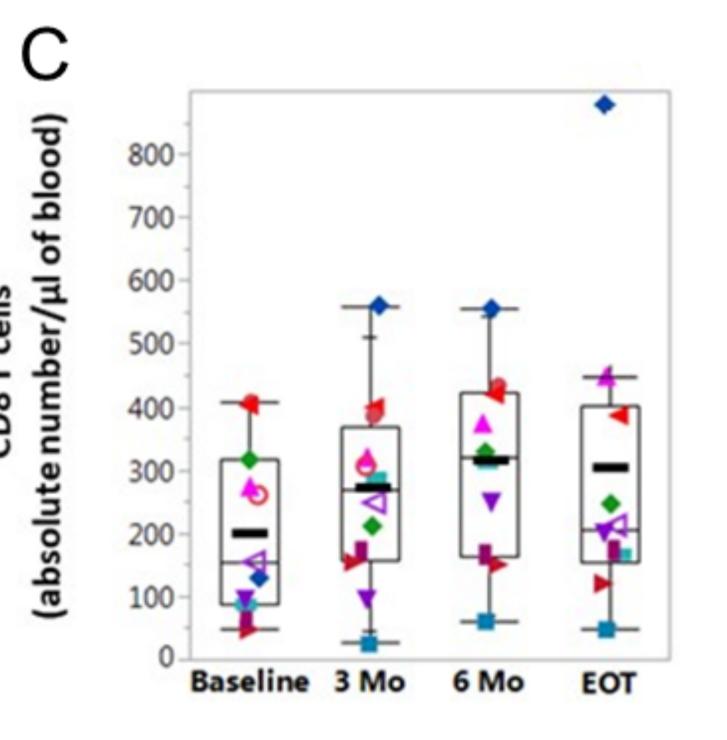
Treatment-induced increase in absolute numbers of effector cells in CD4 (A) and CD8 (C) T cells, natural killer cells (B), activated T cells (CD8 shown in D) in most of the patients. Eftiinduced early and sustainable increase of Th1 biomarkers like IFN-γ (E) and IP-10 (CXCL10, F).

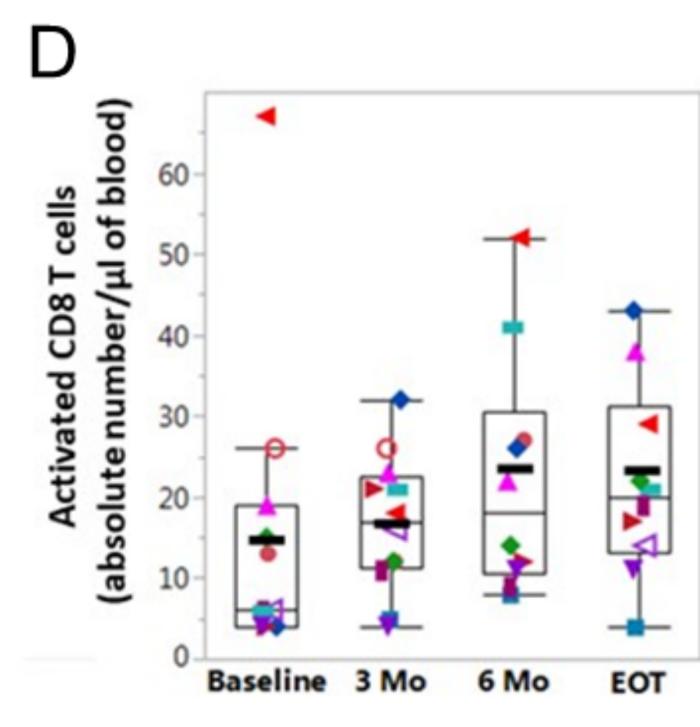
Immuted

LAG-3 IMMUNOTHERAPY

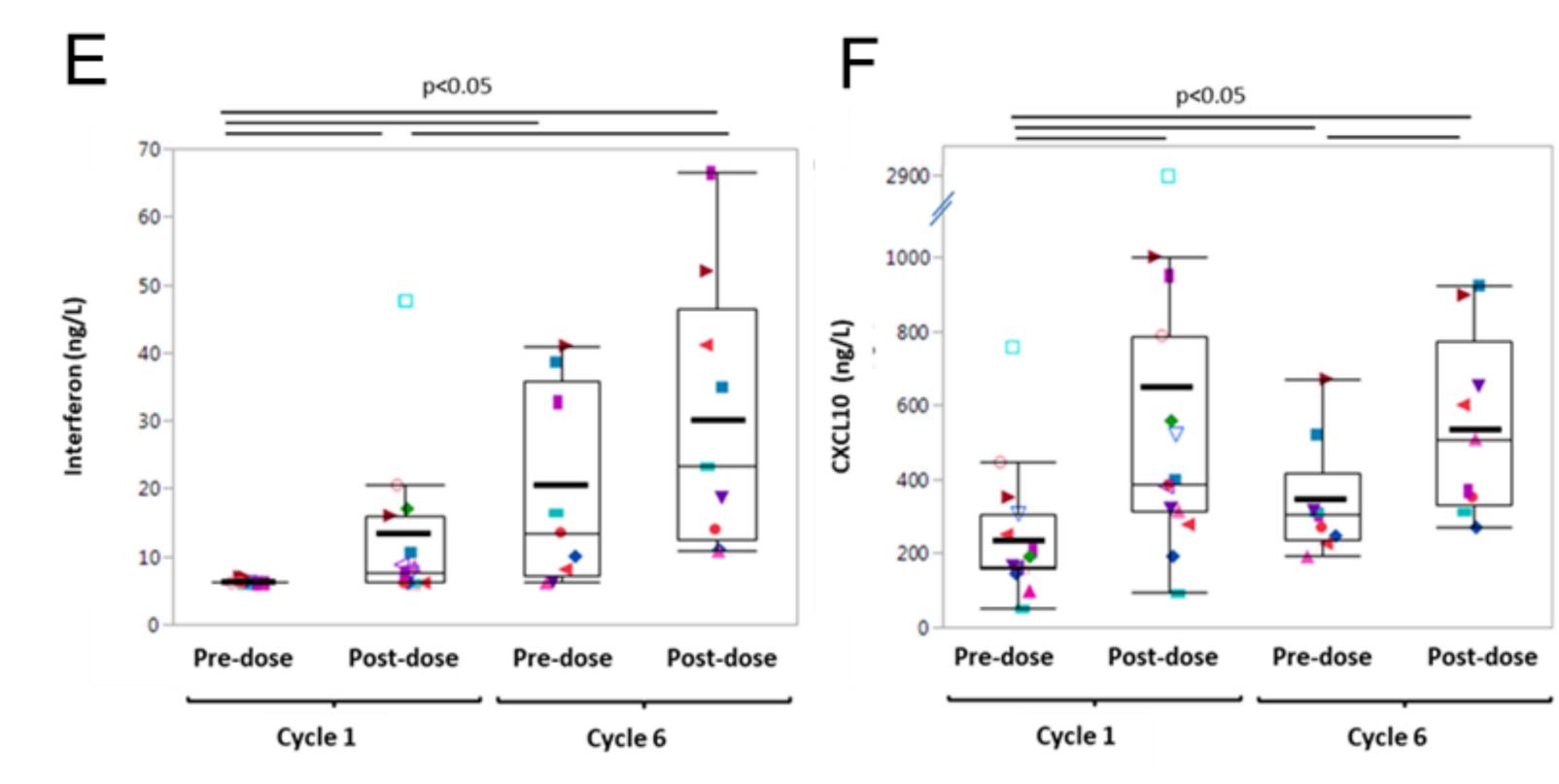








Samples were collected prior treatment (baseline) in cycle 1, 13 days after 6th efti inj. (e.g. 3 months) and 13 days after the 12th efti inj. (e.g. 6 months) to monitor the absolute counts of CD45+CD3+CD4+CD8- helper T cells (A), CD45+CD3-CD16/56+Natural Killer cells (B) CD45+CD3+CD4-CD8+ cytotoxic T cells (C) and activated cytotoxic T cells (coexpressing CD38 and HLA-DR, D).



Samples were collected prior to and up to 48 hours post 1st inj. in cycle 1 and prior to (i.e. 14 days after the 11th efti inj.) and after the 12th inj. in cycle 6 to monitor circulating levels of IFN-γ (E) and IP-10 (CXCL10,

CR...Complete response DCR...Disease Control Rate efti...Eftilagimod alpha

ORR...Overall response rate PD...Progressive disease PK...Pharmacokinetic

PFS...Progression-free survival PR...Partial response RPTD...Recommended phase 2 dose SD...Stable disease