Biomarker results from the 1st line non-small cell lung cancer cohort of TACTI-002: pharmacodynamic effects of combining eftilagimod alpha (soluble LAG-3) and pembrolizumab

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Forster M[1], Felip E[2], Majem M[3], Doger B[4], Clay T[5], Carcereny E[6], Bondarenko I[7], Peguero J[8], Cobo Dols M[9], Ursol G[10], Kalinka E[11], Garcia Ledo G[12], Vila Martinez L[13], Krebs M.G[14], Iams W[15], Mueller C[16], Brignone C[17] and Triebel F[17]

[1]UCL Cancer Institute / University College London Hospitals NHS Foundation, London, UK; [2]Vall d'Hebron University Hospital, Barcelona, Spain; [3]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [4]START Madrid- Fundación Jiménez Diaz, Madrid, Spain; [5]St John of God Subiaco Hospital, Perth, Australia; [6]Catalan Institute of Oncology Badalona-Hospital Germans Trias i Pujol, B-ARGO group, Badalona, Spain; [7]Dnipro Medical University, City Clinical Hospital № 4" of Dnipro Regional Council, Dnipro, Ukraine; [8]Oncology Consultants, P.A., Houston, USA; [9]Hospital Regional Universitario de Málaga - Hospital General, Malaga, Spain; [10]St. Luke's Hospital - Medical and Diagnostic Center "Acinus", Kropyvnytskyi, Ukraine; [11]Instytut Centrum Zdrowia Matki Polki, Lodz, Poland; [12]HM Universitario Sanchinarro, Madrid, Spain; [13]Parc Tauli Sabadell Hospital Universitari, Barcelona, Spain; [14]Division of Cancer Sciences, The University of Manchester and The Christie NHS Foundation Trust, Manchester, UK; [15]Vanderbilt Ingram Cancer Center Division of Hematology/Oncology, Nashville, USA; [16]Clinical Development, Immutep, Berlin, Germany; [17]Research & Development, Immutep S.A.S., Orsay, France.
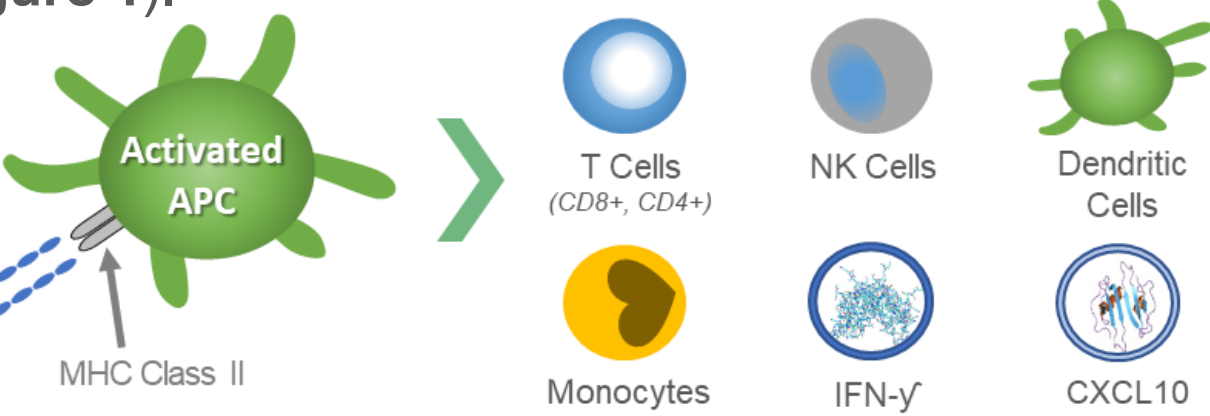
BACKGROUND

Mechanism of action: eftilagimod alpha (efti) is soluble LAG-3 protein (LAG-3 domains fused to human IgG backbone). Activating antigen presenting cells (APCs) with efti leads to a broader immune response to fight cancer, including increases in activated T cells (CD4/CD8) (**Figure 1**).

Figure 1. Mechanism of action of efti

Distinct from anti-LAG-3: efti targets MHC Class II on APCs, unlike LAG-3 antagonists that target T cells.

Rationale: efti activates APCs, leading to an increase in activated T cells, augmenting responses and disease control when combined with PD-1/PD-L1 antagonists. After combining efti with weekly paclitaxel (in HR+ MBC patients in the AIPAC study), an early and sustained increase of Th1 biomarkers (IFN-gamma, CXCL-10) was observed together with absolute lymphocyte count (ALC) increase (≥0.2) which was significantly correlated with improved overall survival (ESMO breast poster 2022; NCT02614833). AIPAC showed that ALC is a potential on-treatment predictive biomarker for efti. We present our biomarker findings from Part A of TACTI-002.

STUDY DESIGN AND METHODS

Study design:
- TACTI-002: multinational, open-label, trial for **1st line advanced/metastatic NSCLC** patients **unselected for PD-L1 expression.**
- 114 patients recruited at 18 sites across 6 countries between Mar 2019-Nov 2021.
- Efti was administered as a 30 mg subcutaneous and pembrolizumab (pembro) was administered at a standard dose of 200 mg intravenous (**Figure 2**).
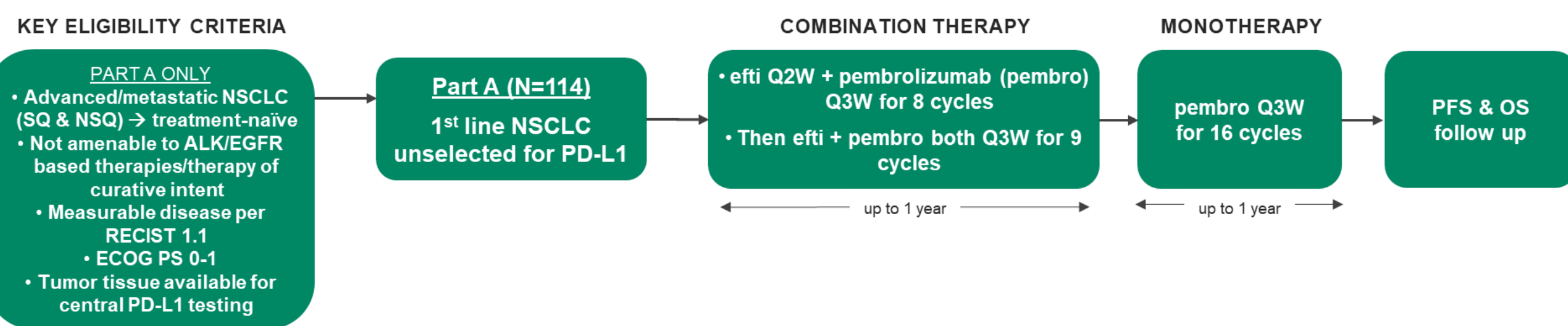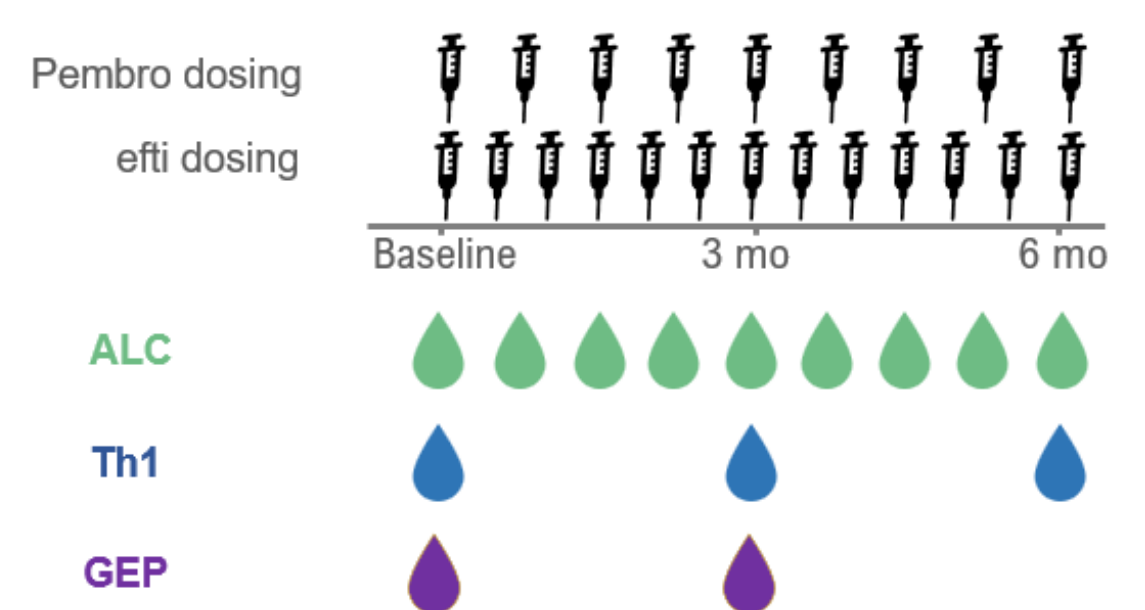
Endpoints:
- **Primary endpoint:** ORR by iRECIST.
- **Secondary endpoints:** ORR by RECIST 1.1, DoR, safety, PFS & OS.
- **Exploratory endpoint:** identify and characterize relevant biomarkers.

Assessments (Biomarkers):
- Plasma concentration of Th1 biomarkers (IFN-γ/CXCL10) was assessed in a central lab.
- Blood samples were collected in PAXgene tubes at screening (baseline, n=108) and after 4 complete cycles (on-treatment, Cycle 5 Day 1 pre-dose, n=69) and were centrally assessed for gene expression profiling (GEP) analyses (**Figure 3**).
- Absolute lymphocyte count (ALC) was measured locally at clinical sites (**Figure 3**).
- Database cut-off: August 15th, 2023.

Figure 2. Study design

Figure 3. Blood sampling schedule
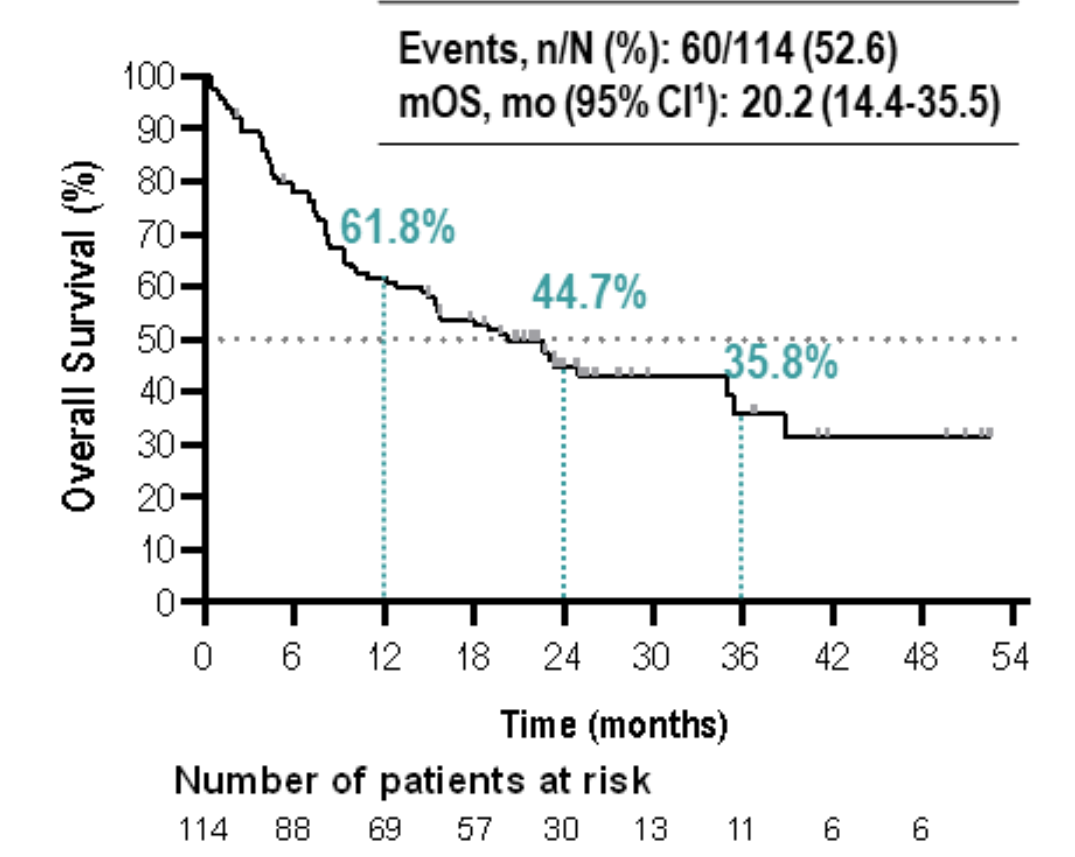

RESULTS

EFFICACY

- ITT: Median (m) DoR of 21.6 mo and mOS of 20.2 mo (**Table 1; Figure 4**) although 75% had PD-L1 TPS <50% (including 35% with PD-L1 TPS <1%).
- For TPS ≥1%: ORR of 48.3%, median PFS of 11.2 mo and mOS of 35.5 mo (**Table 1**).
- Promising efficacy (ORR, PFS, OS, DoR) visible across all PD-L1 groups especially in patients with TPS <1% or TPS 1-49% as depicted in **Table 1**.

Table 1. Tumor Response[1] by PD-L1[2] (N=90) and in ITT (N=114)

Efficacy parameter, n (%)	<1%[2], N=32	1-49%[2], N=38	≥50%[2], N=20	≥1%[2], N=58	ITT, N=114
ORR[3,4], % (95% CI)[5]	31.3 (16.1-50.0)	44.7 (28.6-61.7)	55.0 (31.5-76.9)	48.3 (35.0-61.8)	40.4 (31.3-50.0)
mPFS[3], mo (% events)	4.2 (90.6)	9.3 (71.1)	16.5 (70.0)	11.2 (70.7)	6.6 (76.3)
mDoR[3], mo (% events)	20.7 (57.1)	NR (35.7)	18.7 (63.6)	24.2 (48.0)	21.6 (50.0)
mOS, mo (% events)	15.5 (71.9)	23.4 (52.6)	NR (40.0)	35.5 (48.3)	20.2 (56.1)

[1] Presented at ESMO congress 2023
[2] Central assessment of PD-L1 TPS using Dako IHC 22C3 pharmDx; [3] per iRECIST;
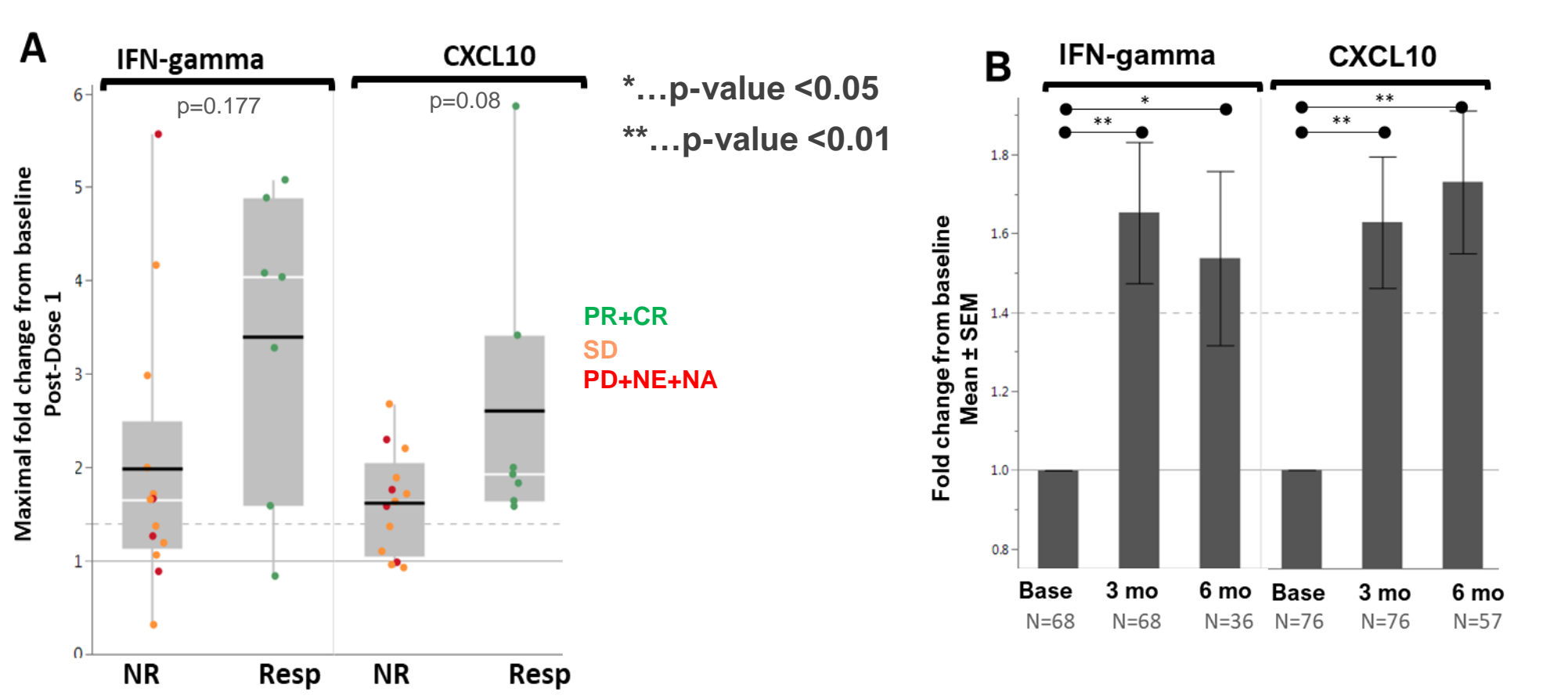[4] unconfirmed; [5] calculated using Clopper Pearson method; NR: not reached.

Figure 4. Overall survival, ITT (N=114)

Events, n/N (%): 60/114 (52.6)
mOS, mo (95% CI[1]): 20.2 (14.4-35.5)

[1] 95% CIs calculated using Kaplan-Meier survival analysis method.

BIOMARKER

Th1 results (IFN-Gamma, CXCL10)

Figure 5. Th1 biomarker in blood fold change from baseline

*…p-value <0.05
**…p-value <0.01

A) Early (within 96 hours of 1st efti dose) Th1 biomarker change from baseline by BOR (iRECIST) for patients with PK sampling; *NR= Non-Responder (SD+UPD+NE+NA, n=13); Resp= Responder (CR+PR, n=7).*
B) Th1 biomarker change from baseline in all patients with samples.
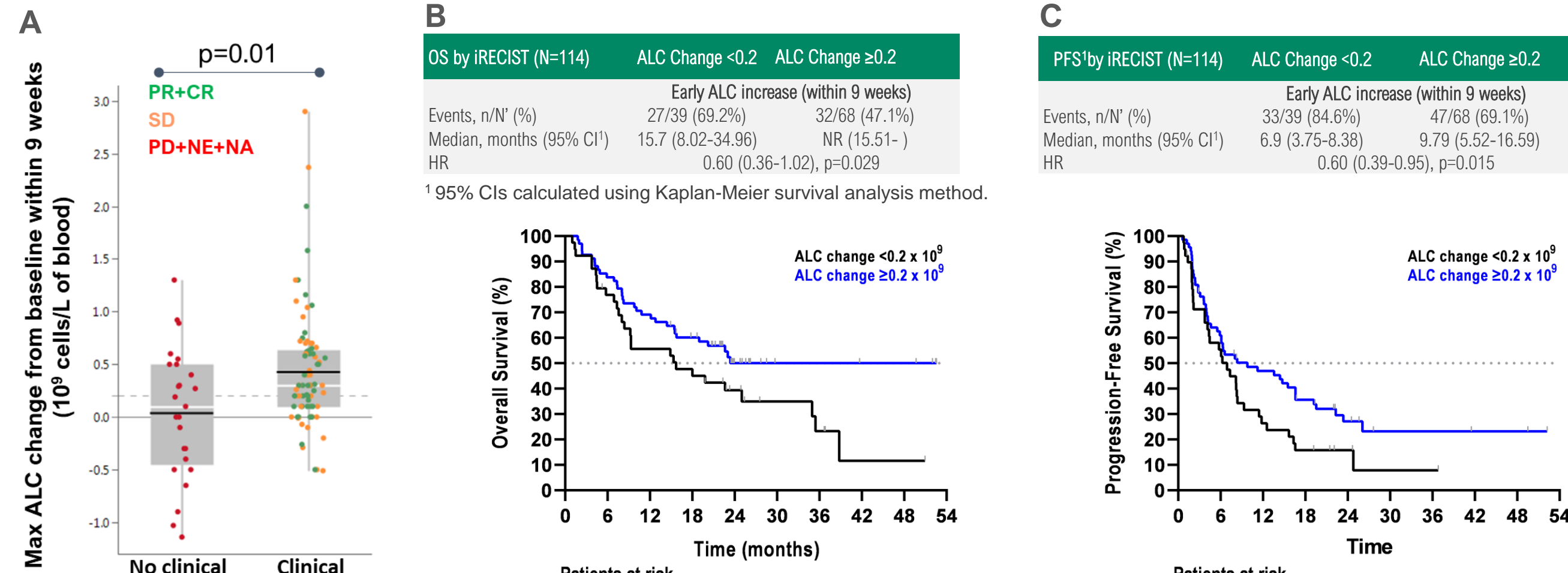
- Early kinetics showed rapid (within few hours [N=20]; data not shown) increase of IFNγ/CXCL10 which was non-significantly greater in responders (**Figure 5A**).
- Sustained and significant increase of minimal residual effects of IFN-γ and CXCL10 at 3- and 6-mo on-therapy (**Figure 5B**), substantiates efti's unique stimulation of the immune system, also seen in the AIPAC study.
- 86% (6/7) and 100% (5/5) of subjects with <1.4-fold change of IFN-γ and CXCL10 after first efti dosing did not respond to treatment (BOR= SD, PD, NE, NA)[1] and 86% (6/7), 100% (7/7), of responders (BOR= PR, CR)[1] showed a ≥1.4-fold change of IFN-γ and CXCL10 after 1st efti dosing, respectively.

[1] Per iRECIST

ALC results and correlation with survival

Figure 6. Early ALC change from baseline per clinical outcome

OS by iRECIST (N=114)	ALC Change <0.2	ALC Change ≥0.2
	Early ALC increase (within 9 weeks)	
Events, n/N (%)	27/39 (69.2%)	32/68 (47.1%)
Median, months (95% CI)[1]	15.7 (8.02-34.96)	NR (15.51-)
HR	0.60 (0.36-1.02), p=0.029	

[1] 95% CIs calculated using Kaplan-Meier survival analysis method.

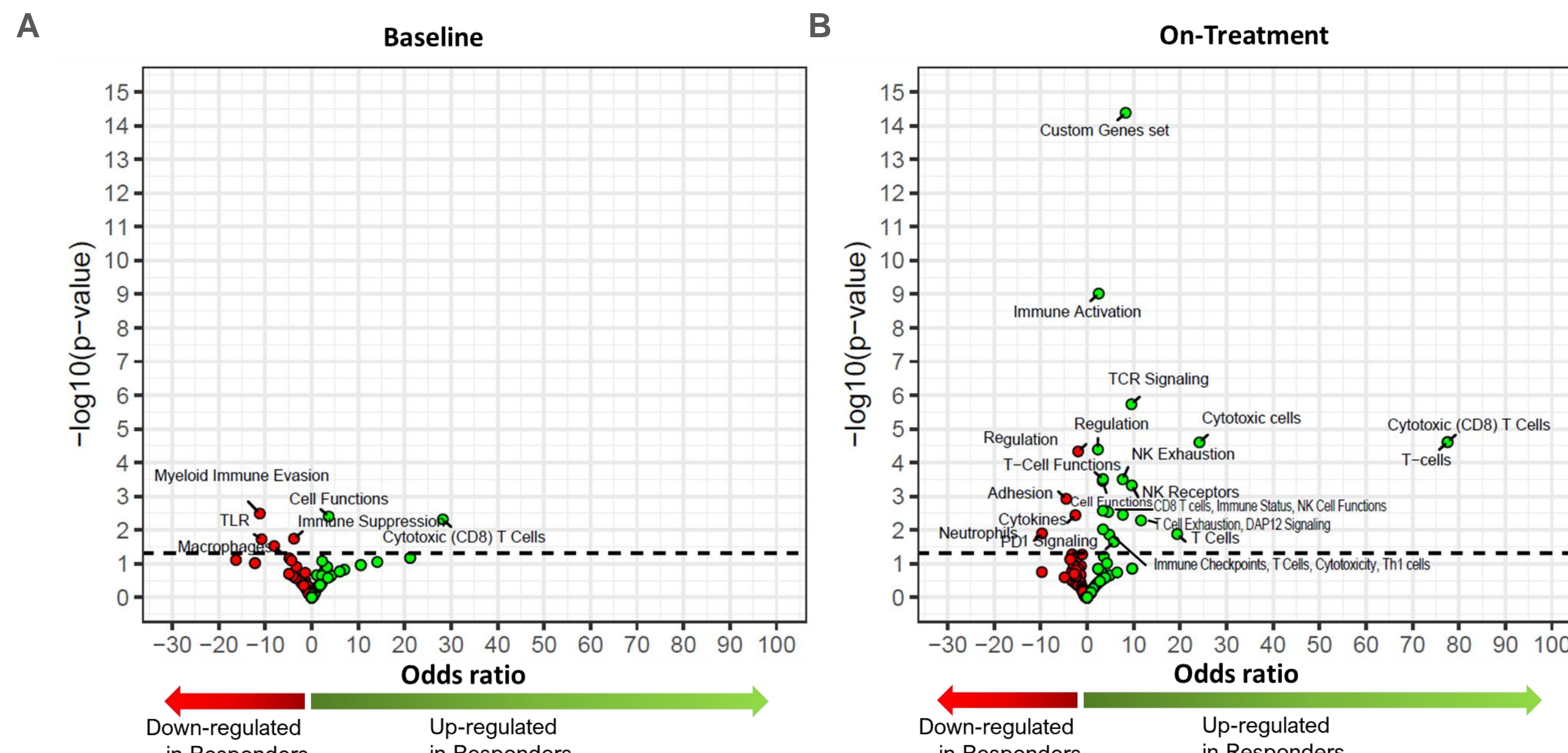| PFS[1]by iRECIST (N=114)	ALC Change <0.2	ALC Change ≥0.2
	Early ALC increase (within 9 weeks)	
Events, n/N (%)	33/39 (84.6%)	47/68 (69.1%)
Median, months (95% CI)[1]	6.9 (3.75-8.38)	9.79 (5.52-16.59)
HR	0.60 (0.39-0.95), p=0.015	

A) Maximal Absolute Lymphocyte Counts change from baseline within the first 9 weeks (before the 4th cycle) is shown in patients with no clinical benefit (UPD+NE+NA, n=25) and clinical benefit (CR+PR+SD, n=82); per iRECIST
B-C) Kaplan Meyer survival curves for OS (B) and PFS (C) per subgroups of patients with ALC change within the first 9 week < or ≥ 0.2. 10⁹/L

Early (<9 weeks) ALC change from baseline is associated with the clinical outcome[1] :
- Increase of ALC was significantly greater in patients with clinical benefit (SD+PR+CR) compared to no clinical benefit (**Figure 6A**).
- PFS (median of 6.9-9.9 mo; HR 0.6; p=0.015) and OS (median 15.7-NR mo; HR 0.6; p=0.029) were significantly improved in subjects displaying an increase of ALC within 9 weeks (**Figure 6B** and **C**).

[1] Per iRECIST

GEP in liquid biopsies

- Significant differences at baseline by response were minimal (**Figure 7A**).
- Functions related to immune activation functions and cytotoxicity functions were highly linked to favourable responses (CR+PR as BOR).
- Genes involved in the definition of the following cell types were significantly enriched in Responder: Cytotoxic CD8 T cells, T cells. NK cells, Th1 cells, Gamma Delta T Cells (**Figure 7B**).

Figure 7. Volcano plot of pathways and cell types at (A) Baseline and (B) On-treatment comparing Responders vs Non-Responders

CONCLUSION

- Sustained significant increase in circulating Th1 biomarker (IFN-γ; CXCL10) was found at 3- and 6-mo.
- Early (<96 h) increase was linked to clinical response.
- ALC increase at a similar cut-off as in AIPAC was significantly associated with improved clinical outcome in terms of clinical benefit, PFS and OS.
- Blood-based GEP analyses revealed significant enrichment of genes involved in immune activation and cytotoxicity (including CD8 T cells) in patients with a favourable tumor response.
- ALC is a potential on treatment biomarker for response to this combination therapy and liquid biopsies should be conducted in future randomized studies.
- Biomarker findings from AIPAC (efti plus paclitaxel in MBC) confirmed in this study (TACTI-002 Efti plus pembro in NSCLC)