Eftilagimod alfa, an APC activator via MHC class II, induced lymphocyte activation linked to improved survival in metastatic cancer patients

Poster # 2569

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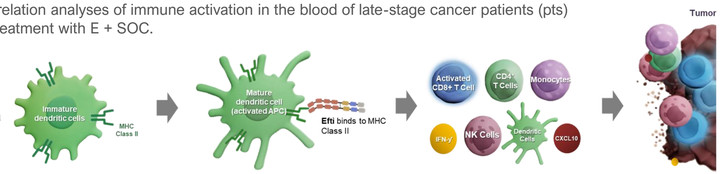
2026 ASCO ANNUAL MEETING

BACKGROUND

- Immune activation is important for survival in cancer. (1)
- Mechanism of action: Eftilagimod alfa (E) is an antigen-presenting cell (APC) activator that binds to a subset of MHC class II molecules on APCs (2) to mediate lymphocyte, e.g., T cell (CD4/CD8), recruitment and activation (**Figure 1**).
- Clinical studies of E in combination with different standard of care (SOC) treatments like PD-1 antagonist (P; pembrolizumab) or chemotherapy (C; paclitaxel) have shown promising results.(3)-(5)
- We present cumulative correlation analyses of immune activation in the blood of late-stage cancer patients (pts) with clinical efficacy after treatment with E + SOC.

Figure 1. Mechanism of action of Eftilagimod alfa



METHODS

Study Design and Patients

- 5 studies (AIPAC, NCT02614833; AIPAC-003, NCT05747794; TACTI-mel, NCT02676869; TACTI-002, NCT03625323; and TACTI-003, NCT04811027) with a total of 592 pts were included.
- 30 mg E in combination with SOC was administered SC biweekly for 6 months (mo), then every 2-3 weeks for another 6-18 mo (max 24 mo in total) in pts with metastatic non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), melanoma (MM), or breast cancer (MBC).
- SOC was either P (IV at 200 mg q3w or 400 mg q6w or 2 mg/kg q3w) or C (80 mg/m^2 day 1, 8, 15, q4w).

Assessments and Statistical Analyses:

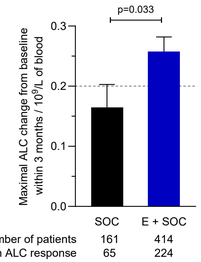
- Absolute lymphocyte count (ALC) was taken before dosing (on day 1 of each cycle). Subjects with a least one post-baseline assessment were included (N=575).
- As ALC was assessed immediately prior to dosing, i.e. two weeks after the preceding administration, the observed changes reflect sustained pharmacodynamic effects throughout the dosing interval.
- ALC response was pre-defined as a change of ≥0.2 x 10^9/L within 3 months on study (up to dose 7).
- Clinical efficacy was assessed locally by RECIST1.1 or iRECIST as per study protocol and overall survival (OS).
- For the correlation of ALC response with clinical response (N=574), patients with confirmed response (CR or PR) as best overall response (cBOR) were considered as responders.
- For the correlation of ALC response with OS (N=569), pts whose OS exceeded the arithmetic median were considered to have a survival benefit. The median OS for each cancer type and treatment line was calculated separately to categorize pts with or without a survival benefit.
- The TH1 biomarkers interferon gamma (IFN-γ) and C-X-C motif chemokine ligand 10 (CXCL10) were assessed in peripheral blood pre-dose and within 96 hours after 1st E administration in patients with PK sampling (N=79).
- Peripheral blood samples for gene expression profiles (GEP) were taken pre-treatment and after 3 mo (prior to E dose 7) in pts receiving E + SOC (N=111; pts with NSCLC treated in 1st line setting, TACTI-002), assessed using NanoString® nCounter® PanCancer Immune Profiling Panel and analyzed using nSolver software. Correlations between pathways/cell types and confirmed clinical response per iRECIST were investigated. Gene sets used to define pathways were per manufacturer (54-gene set for T-cell functions).

RESULTS

SIGNIFICANT INCREASE IN ABSOLUTE LYMPHOCYTE COUNTS (ALC) WITH E + SOC BUT NOT SOC ALONE

- Treatment with E + SOC led to a significant ALC gain compared to SOC (**Figure 2**).
- These substantial residual pharmacodynamic effects were observed at pre-dose, indicating a sustained effect throughout the dosing interval.
- These effects were evident from treatment initiation and sustained over the complete E treatment duration (data not shown).
- In the E + SOC group, 54.1% of pts were ALC responders and 40.4% in the SOC group (**Figure 2**). The combination partner did not affect the ALC response rate in the E + SOC group: 53.6% for E+P and 55.1% for E+C.

Figure 2. Maximal ALC change from baseline



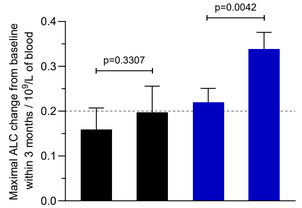
	SOC	E + SOC
Number of patients	161	414
Patients with ALC response	65	224

Mean and standard error of maximal ALC change from baseline within 3 months. The horizontal reference line indicates the cutoff value of 0.2 x 10^9/L. Wilcoxon rank-sum test p values are indicated.

POSITIVE CORRELATION OF ALC RESPONSE WITH CLINICAL RESPONSE WITH E + SOC BUT NOT SOC ALONE

- Clinical response correlated significantly with ALC response only in pts treated with E + SOC (p=0.0042) but not in pts treated with SOC (p=0.3307; **Figure 3**).
- Survival benefit correlated significantly with ALC response only in pts treated with E + SOC (p=0.0082) but not in pts treated with SOC (p=0.2389; **Figure 4**).

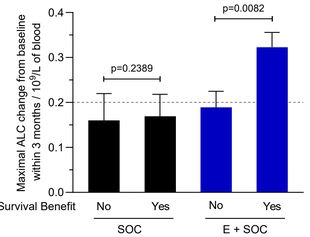
Figure 3. ALC change from baseline by clinical response



	SOC		E + SOC	
Number of patients	102	58	282	132
Patients with ALC response	38	27	140	84

Mean and standard error of maximal ALC change from baseline within 3 months. The horizontal reference line indicates the cutoff of 0.2 x 10^9/L. Wilcoxon rank-sum test p values are indicated.

Figure 4. ALC change from baseline by survival benefit



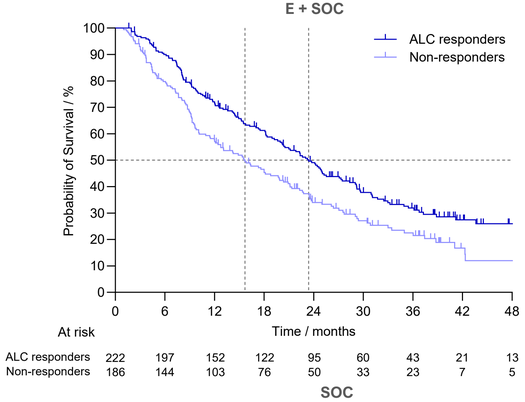
	SOC		E + SOC	
Number of patients	69	92	184	224
Patients with ALC response	24	41	87	135

Mean and standard error of maximal ALC change from baseline within 3 months. The horizontal reference line indicates the cutoff of 0.2 x 10^9/L. Wilcoxon rank-sum test p values are indicated.

PROLONGED OVERALL SURVIVAL IN ALC RESPONDERS TREATED WITH E + SOC BUT NOT SOC ALONE

- In the E + SOC group, OS in ALC responders was significantly prolonged compared to that in non-responders (median 23.4 vs. 15.7 mo; HR=0.69; p=0.0017; **Figure 5**).
- This effect was observed irrespective of the combination partner of E or the indication (data not shown).
- In the SOC group, there was no difference in OS between ALC responders and non-responders (median 17.5 vs. 20.4 mo; HR=0.98; p=0.93; **Figure 5**).

Figure 5. Overall survival by ALC response and by treatment

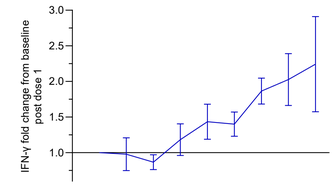


Kaplan-Meier plots for overall survival by ALC response and by treatment received.

RAPID INCREASE OF TH1 BIOMARKERS FOLLOWING TREATMENT WITH E + SOC

- The soluble TH1 biomarker IFN-γ increased rapidly in peripheral blood after 1st treatment with E + SOC (**Figure 6**).
- A comparable effect was observed for CXCL10 (data not shown).
- These effects were observed across indications and different combination partners and correlated with survival benefit (data not shown).

Figure 6. IFN-γ after 1st treatment with E + SOC



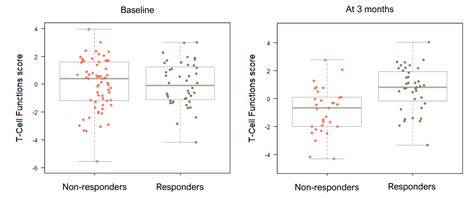
Time post dose 1	0h	1h	2h	4h	8h	24h	48h	72h	96h
Number of patients	79	77	75	71	66	76	74	56	56

Mean and standard error of relative fold changes of IFN-γ in peripheral blood of patients treated with E + SOC.

CLINICAL RESPONDERS TO E + SOC TREATMENT SHOW INCREASE IN T-CELL FUNCTIONS SCORE

- On-treatment score related to T-cell functions was increased in clinical responders to E + SOC compared to non-responders (**Figure 7**).
- A similar pattern was observed with other immune related pathways or cell types including cytotoxicity, NK cell functions, TH1 cells or CD8 T cells (data not shown).

Figure 7. T-cell functions score before and at 3 months of treatment with E + SOC



Values of a 54-gene T-cell functions score at baseline (left) and at 3 months (right), by clinical response to E + SOC.

SUMMARY & CONCLUSION

- In this meta-analysis, effect of Eftilagimod alfa (E) combined with different SOC treatments was analyzed in 592 late-stage cancer patients across 5 independent studies in 4 indications.
- Compared to SOC, E + SOC led to consistent ALC responses: early, significant and sustained increases throughout the dosing intervals and across cancer types, regardless of E's combination partner.
- ALC response was associated significantly with clinical response and significant OS improvement (ΔmOS +7.7mo; p= 0.0017) in the E + SOC group but not in the SOC group.
- Following treatment with E + SOC, circulating TH1 biomarkers showed a rapid increase which was associated with clinical response.
- Gene Expression Profiling indicated increases in T-cell functions score in responders to treatment with E + SOC.

Conclusion: E on top of different SOC treatments induced immune activation at different levels (number of circulating immune cells, cytokine and gene expression levels) which was associated with favorable clinical response (cBOR and OS) compared to SOC alone in late-stage cancer patients of different indications.

ABBREVIATIONS

ALC…absolute lymphocyte count
APC…antigen presenting cell
C…chemotherapy
cBOR…confirmed best overall response
(i)CR…(immune) complete response
CXCL10…C-X-C motif chemokine ligand 10
E…Eftilagimod alfa, efti
HNSCC…head and neck squamous cell carcinoma
HR…hazard ratio
(i)RECIST…(Immune) Response Evaluation Criteria In Solid Tumors
IFN-γ…interferon-gamma
IV…intravenously
LAG-3…Lymphocyte Activation Gene-3
MHC…Major Histocompatibility Complex
mo…months
NK…natural killer cell
NSCLC…non-small cell lung cancer
OS…overall survival
P…PD-1 antagonist
(i)PR…(immune) partial response
SC…subcutaneously
SOC…standard of care
TH1…T helper 1

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ACKNOWLEDGEMENTS

- We thank all the participating patients & their families.
- We thank the dedicated clinical trial investigators & their team members.
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