Cancer Immunology, Immunotherapy (2026) 75:17
https://doi.org/10.1007/s00262-025-04242-6

RESEARCH

Th7R predicts chemo-immunotherapy response and survival in small cell lung cancer

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Received: 29 August 2025 / Accepted: 16 November 2025

Abstract

Th7R is a novel Th1-like $CD4^+$ T cell lineage characterized by TCF7 and IL-7 receptor expression, exhibiting distinct transcriptional and epigenetic profiles compared with classical Th1 cells. The clinical significance of Th7R, including the efficacy of immune checkpoint inhibitors and the prediction of postoperative disease-free survival, has been demonstrated in non–small cell lung cancer (NSCLC) but not in small cell lung cancer (SCLC). In this study, we investigated Th7R expression as a predictive marker in patients with extensive-stage SCLC (ES-SCLC) who received chemotherapy or chemo-immunotherapy (n = 47). Results showed that Th7R was positively correlated with progression-free survival (PFS) after treatment and that long-term PFS was observed only in patients with $Th7R^{high}$ who were treated with anti-programmed cell death-1 ligand 1 (PD-L1) antibody combination therapy. Furthermore, high Th7R levels were associated with significantly better overall survival. Th7R showed a positive correlation with $GZMB^-GZMK^+$ precursor exhausted $CD8^+$ T cells (Tpex), which are known target cells for PD-1 blockade therapy. These findings suggest the presence of the Th7R–Tpex axis. Th7R, which reflects antitumor T-cell immunity, is a useful predictive marker for treatment efficacy in ES-SCLC.

Keywords Th7R · $CD4^+$ T cell · Small cell lung cancer · Immune checkpoint blockade · Precursor exhausted T cells (Tpex) · Tumor microenvironment

Introduction

Small cell lung cancer (SCLC) is relatively sensitive to cytotoxic anticancer agents, and combination therapy with platinum agents and etoposide has long been considered the standard treatment. Cytotoxic anticancer agent therapy can achieve tumor shrinkage, but not long-term survival in patients with extensive-stage SCLC (ES-SCLC) [1]. By contrast, the IMpower133 and CASPIAN trials demonstrated that the combination of anti-programmed cell death-1 ligand 1 (PD-L1) antibody therapy extended survival and resulted in long-term survival, as indicated by the long tail of overall survival (OS) curves [2, 3]. This suggests that long-term survival in SCLC is mediated by T cell immunity [4].

In non-SCLC (NSCLC), the pre-treatment PD-L1 tumor proportional score (TPS) has been used as a biomarker for programmed cell death-1 (PD-1) blockade therapy [5, 6]. PD-L1 expression in tumor cells reflects IFNγ in the tumor microenvironment (TME), and PD-L1 TPS is considered an indirect surrogate marker for the presence of IFNγ- producing T cells in TME [7]. However, PD-L1 expression is very low and often negative in SCLC cells, thus making PD-L1 unsuitable as a biomarker for patients with SCLC [8].

This is thought to be mainly attributable to two mechanisms: (1) the low expression of MHC class I molecules in cancer cells, which impairs antigen presentation to T cells and thereby reduces cytokine production [9]; and (2) the genetic mutations in the IFNγ signaling pathway, which result in decreased IFNγ levels within the TME and consequently the absence of PD-L1 expression. Tumor mutation

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Published online: 19 December 2025

burden is another candidate predictive biomarkers; however, its clinical reliability remains unconfirmed [10]. The lack of biomarkers indicating the immune status of the host T-cell hinders the selection of appropriate therapies for SCLC. Immunological biomarkers are essential not only for predicting the efficacy of anti-PD-L1 antibody therapy but also for predicting the efficacy of bispecific antibody therapy that binds cancer cells and T cells in the TME [11].

Precursor-exhausted $CD8^+$ T cells (Tpex) have gained attention as the origin of the proliferative burst of $CD8^+$ T cells induced by PD-1 blockade therapy [12]. Tpex have been identified as self-renewing competent cells, that express TCF7 and IL-7 receptors, despite expressing PD-1 through clonal proliferation and repeated antigen stimulation after priming [13]. Although Tpex do not express GZMB, they undergo asymmetric cell division, producing $CD8^+$ T cells that express GZMB while self-renewing, thereby sustaining a supply of cytotoxic $CD8^+$ T cells. Upon PD-1 blockade treatment, Tpex proliferate and serve as a reservoir for the production of large numbers of cytotoxic $CD8^+$ T cells. Therefore, Tpex are considered one of the most critical targets of PD-1 blockade [12]. Studies have shown that $CD4^+$ T cells are also essential for the generation and maintenance of Tpex [14, 15]. $CD4^+$ T cells play a crucial role in the formation of ectopic high endothelial venules (HEVs), which serve as entry points for Tpex into the TME [16].

We identified a novel Th1-like effector $CD4^+$ T-cell lineage that is abundant in the peripheral blood of pembrolizumab responders on the basis of trajectory analysis using single-cell RNA sequencing (scRNA-seq) data [17]. Th7R expresses TBX21 and IFN-γ but exhibits transcriptomic and epigenetic profiles that are distinct from classical Th1 cells [17]. On the basis of their high TCF7 expression and the IL-7 receptor, we designated this population as "Th7R." Furthermore, in patients with early-stage NSCLC, Th7R cells are present in both the TME and draining lymph nodes; however, only Th7R cells, —not classical Th1 cells—, are associated with postoperative disease-free survival [18]. The clinical relevance of the Th7R subset has been elucidated in NSCLC; however, its significance in small cell lung cancer remains unclear.

In this study, we analyzed peripheral blood samples from patients with ES-SCLC to investigate the association between T cell clusters including Th7R and clinical outcomes. We also examined the relationship among these T cell subsets, Tpex, and the long term survival achieved with anti-PD-L1 Ab therapy.

Table 1A Patient's characteristics

Baseline characteristics (n = 47)	
Age	
≤ 75 or > 75 years	17 (36.2%) / 30 (63.8%)
ECOG performance status	
0–1 or 2–4	42 (89.4%) / 5 (10.6%)
Sex	
Male / Female	40 (85.1%) / 7 (14.9%)
Smoking index	
Yes / No	47 (100%) / 0 (0%)
Staging status	
III / IV / Recurrence	4 (4.1%) / 41 (87.2%) / 2 (4.2%)
Histology	
SCLC / combined SCLC	45 (95.7%) / 2 (4.3%)
Metastasis (Yes / No)	
Brain	11 (23.4%) / 36 (76.6%)
Liver	15 (31.9%) / 31 (68.1%)
Bone	16 (34.0%) / 36 (66.0%)

ECOG Eastern Cooperative Oncology Group, *PR* Partial response, *SD* Stable disease, *RECIST* Response Evaluation Criteria in Solid Tumors, *SCLC* small cell carcinoma, *SCC* Squamous cell carcinoma

Table 1B Treatment and response

Total patients (n = 47)	
Treatment regimen	
CBDCA + ETP + Atezolizumab	20 (42.6%)
CBDCA + ETP	20 (40.4%)
CDDP + ETP	6 (12.8%)
CBDCA + PTX	1 (2.1%)
CDDP + CPT-11	1 (2.1%)
Response by RECIST	
PR / SD / PD	32 (68.1%) / 6 (12.8%) / 9 (19.1%)

Materials and methods

Patients and treatment

Between April 2017 and November 2020, a total of 99 patients were diagnosed with ES-SCLC at Saitama Medical University International Medical Center. To evaluate the association between T-cell immune cluster profiles and clinical outcomes, we analyzed peripheral blood samples from 47 patients who received first-line chemotherapy or chemoimmunotherapy and provided informed consent before treatment. Tables 1A and 1B show the detailed patient characteristics, treatments and responses. The final follow-up date

was June 30, 2024. Treatment response was evaluated using the Response Evaluation Criteria in Solid Tumors version 1.1. Progression-free survival (PFS) was defined as the time from the start of first-line treatment until the occurrence of progressive disease or death from any cause. Overall survival (OS) was defined as the time from the start of first-line treatment until death from any cause. All samples were collected after obtaining written informed consent, and the study protocol was approved by the Institutional Review Board of Saitama Medical University International Medical Center in accordance with the Declaration of Helsinki (approval number: 16–281).

Analysis of peripheral blood samples

Peripheral blood mononuclear cells (PBMCs) were collected at two time points, namely, before treatment initiation and at two or three weeks after initiation, by using heparinized CPT vacutainer tubes (Becton Dickinson Vacutainer Systems) as described previously [19]. The samples were cryopreserved using a Cellbanker2 (Nippon Zenyaku Kogyo Co.) and stored in a liquid nitrogen tank. For T-cell subset analysis, thawed PBMCs were cultured for 32–48 h in RPMI 1640 medium supplemented with 10% fetal calf serum, followed by cell staining for cytometric analysis.

Mass cytometry analysis

Supplementary Table S1 shows the list of monoclonal antibodies used for Helios mass cytometry (CyTOF) analysis. For targets without commercially available metal-conjugated antibodies, carrier-free purified IgG was selected and in-house conjugation was performed using the Maxpar® X8 Antibody Labeling Kit (Standard BioTools) according to the manufacturer's protocol. Sample preparation was performed and acquisition using the Helios system according to the manufacturer's protocol (Standard BioTools). Up to 3.0×10^6 cells were stained with metal-conjugated antibodies for CyTOF. For intracellular antigen staining, the cells were prepared using MaxPar Nuclear Antigen Staining Buffer and subsequently stained. After two washes with MaxPar Cell Staining Buffer, the cells were fixed in Maxpar Fix and Perm Buffer containing 125 nM iridium nucleic acid intercalator (Standard BioTools). The fixed cells were washed once with Maxpar Cell Staining Buffer, twice with Maxpar water, and finally resuspended in Maxpar water. At least 200,000 cells per sample were acquired on the Helios system. Data analysis was performed using Cytobank (https://www.cytobank.org) and FlowJo software. Supplementary Fig. 1 shows the gating strategy.

Statistical analysis

Statistical analyses were performed using GraphPad Prism 10 software (GraphPad Software). Unless otherwise indicated, data are presented as mean ± SEM. Correlations between T-cell subset percentages and between each subset and clinical outcomes (PFS and OS) were assessed using Pearson's correlation coefficients. Survival curves were generated using the Kaplan–Meier method, and group comparisons and hazard ratios (HRs) were evaluated using the log-rank (Mantel–Cox) test. All P values were calculated using two-sided tests, and P values < 0.05 were considered statistically significant.

Results

The peripheral Th7R subset is the second most abundant $CD4^+$ T-cell subset in patients with ES-SCLC

Among the 99 patients with ES-SCLC who received treatment, the median PFS and median OS were 152 and 364 days, respectively, which were generally consistent with previously reported data (Supplementary Fig. 2). Peripheral blood samples from 47 patients with ES-SCLC who provided informed consent were analyzed using mass spectrometry to assess immune cell phenotypes. In the 47 analyzed cases, the median PFS was 155 days, and the median OS was 364 days, showing no significant difference compared with the entire cohort (Supplementary Fig. 2B). First, we examined the effect of each $CD4^+$ T-cell subset at baseline on PFS and OS. $CD4^+$ helper T (Th) cell subsets were annotated on the basis of chemokine receptor expression: $CXCR3^+CCR4^-CCR6^-$ (Th1), $CXCR3^-CCR4^+CCR6^+$ (Th17), $CD45RA^-$ $Foxp3^{high}$ (Regulatory T cells [Tregs]), and $CD45RA^-Foxp3^-$ $CD62L^{high}$ $CXCR3^-CCR4^-CCR6^-CD4^+$ T cells (undifferentiated $CD4^+$ T cells). The Th7R lineage includes both $CXCR3^+$ and $CXCR3^-$ subpopulations and expresses CCR6 but not CCR4. Therefore, non-Treg $CD4^+$ T cells that possess $CXCR3^{\pm}CCR4^-CCR6^+$ pattern is considered as Th7R. Among the subsets, $CXCR3^+CCR4^-CCR6^-$ Th1 were the most abundant ($15.97 \pm 1.53\%$), followed by $CXCR3^{\pm}CCR4^-CCR6^+$ Th7R ($9.45 \pm 0.74\%$) (Supplementary Fig. 3A); this result is consistent with findings in both advanced and early-stage NSCLC [17, 18].

The peripheral blood Th7R subset predicts PFS and OS in patients with ES-SCLC

We investigated the effect of each T-cell subset on treatment response and survival. Given that the reported mPFS

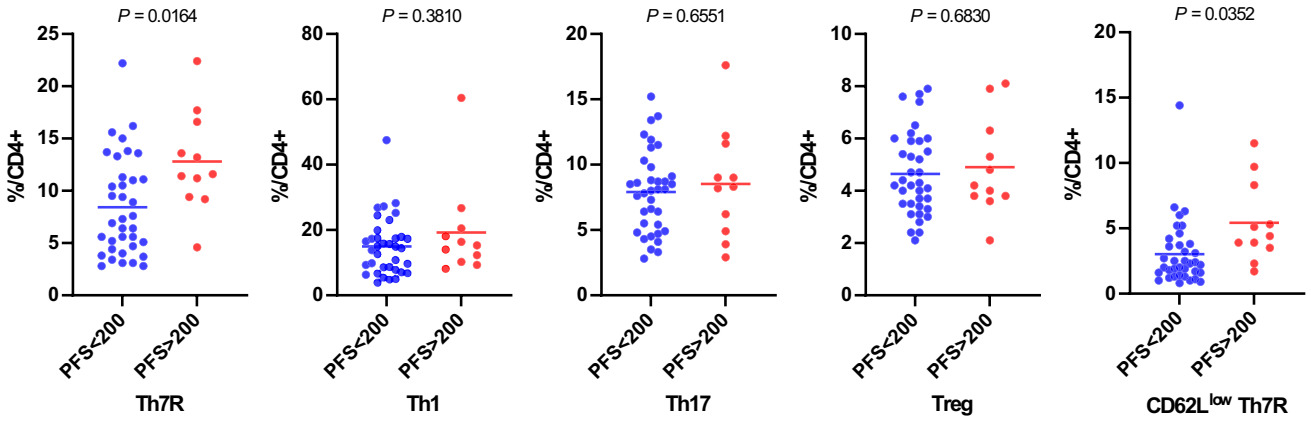

Fig. 1 Differential distribution of $CD4^+$ T-cell subsets According to treatment response. Patients with ES-SCLC were classified as responders or non-responders on the basis of PFS cutoff of 200 days, and the frequencies of $CD4^+$ T-cell subsets in the pre-treatment peripheral blood were compared. Th7R cells ($CXCR3^{\pm}CCR4^{-}CCR6^{+}$) were significantly more abundant in the responder group, whereas no significant differences were observed in Th1 ($CXCR3^{+}CCR4^{-}CCR6^{-}$), Th17 ($CXCR3^{-}CCR4^{+}CCR6^{+}$), or Treg ($CD45RA^{-}CD62L^{high}$ $Foxp3^{+}$) subsets. A similar trend was observed in $CD62L^{low}$ effector-type Th7R cells. Data are shown as mean ± SEM. Statistical comparisons were performed using an unpaired two-tailed t-tests

in patients with ES-SCLC receiving chemoimmunotherapy is approximately five to six months [2, 3], patients were classified as responders or non-responders on the basis of a PFS cutoff of 200 days. Strikingly, Th7R cells were the only subset that was significantly increased in the responder group, whereas no significant differences were observed in Th1 cells, Th17 cells, or Tregs (Fig. 1). In responders, undifferentiated $CD4^+$ T cells tended to decrease, suggesting that a greater proportion of $CD4^+$ T cells had undergone priming and activation (Supplementary Fig. S3B). Th7R cells were originally identified within the $CD62L^{low}$ $CD4^+$ T-cell population; therefore, we also analyzed $CD62L^{low}$ $CD4^+$ T cells subset. A similar trend was observed for the effector phenotype of $CD62L^{low}$ Th7R cells (Fig. 1).

Patients were stratified into high and low groups on the basis of the median proportion of each $CD4^+$ T-cell subset. Kaplan–Meier curves for PFS and OS were generated. The median interquartile range values for each subset were as follows: Th7R, 9.4% (5.1–13.3); Th1, 14.9% (8.7–18.1); Th17, 8.1% (4.9–9.8); and Treg, 4.2% (3.5–5.9). No significant differences in PFS or OS were observed between high and low Th1 or Th17 subsets (Fig. 2). Similarly, no significant differences were observed in Treg subsets (Supplementary Fig. 4). Notably, the $Th7R^{high}$ group showed significantly better PFS than the low group (174 vs. 150 days, $P = .0224$; HR, 0.5367; 95% confidence interval [CI], 0.2949–0.9767) (Fig. 2). In addition to PFS, OS was significantly longer in the $Th7R^{high}$ group (445 vs. 241 days, $P = .0274$; HR, 0.5119; 95% CI, 0.2737–0.9573) (Fig. 2). A similar analysis was performed in effector $CD4^+$ T cells with low CD62L expression ($CD62L^{low}$ $CD4^+$ T cells). In the $CD62L^{low}$ Th7R subset, the high group showed a trend toward better PFS and OS (Supplementary Fig. 5). When comparing patient characteristics between the $Th7R^{high}$ and $Th7R^{low}$ groups, no significant differences were observed in clinicopathological factors such as performance status or the presence of distant metastasis (Table 2).

We evaluated the association between the proportion of each T-cell subset and PFS and OS by using Pearson's correlation coefficient. No significant correlations were observed between the Th1, Th17, or Treg subsets and PFS. However, the Th7R subset showed a significant positive correlation with PFS ($P = .0124$, $r = 0.3620$) (Fig. 3). A similar trend was observed for OS, with a higher Th7R proportion associated with a longer OS ($P = .0557$, $r = 0.2810$).

These findings suggest that the peripheral Th7R subset ratio before treatment may serve as a predictive and prognostic biomarker in small-cell lung cancer.

Th7R may serve as a predictive marker for the therapeutic efficacy of chemoimmunotherapy

Among patients with ES-SCLC, 33 received first-line chemotherapy alone, and 66 received chemoimmunotherapy. PFS was significantly longer in the chemoimmunotherapy group than in the chemotherapy-only group (167 days vs. 136 days; $P = .0451$; HR, 0.6519; 95% CI, 0.4108–1.034) (Supplementary Fig. 6). Although the difference in OS was not statistically significant, a trend toward long-term survival was observed in the subset of patients receiving chemoimmunotherapy (445 vs. 241 days, P = .3349; HR 0.6519; 95%

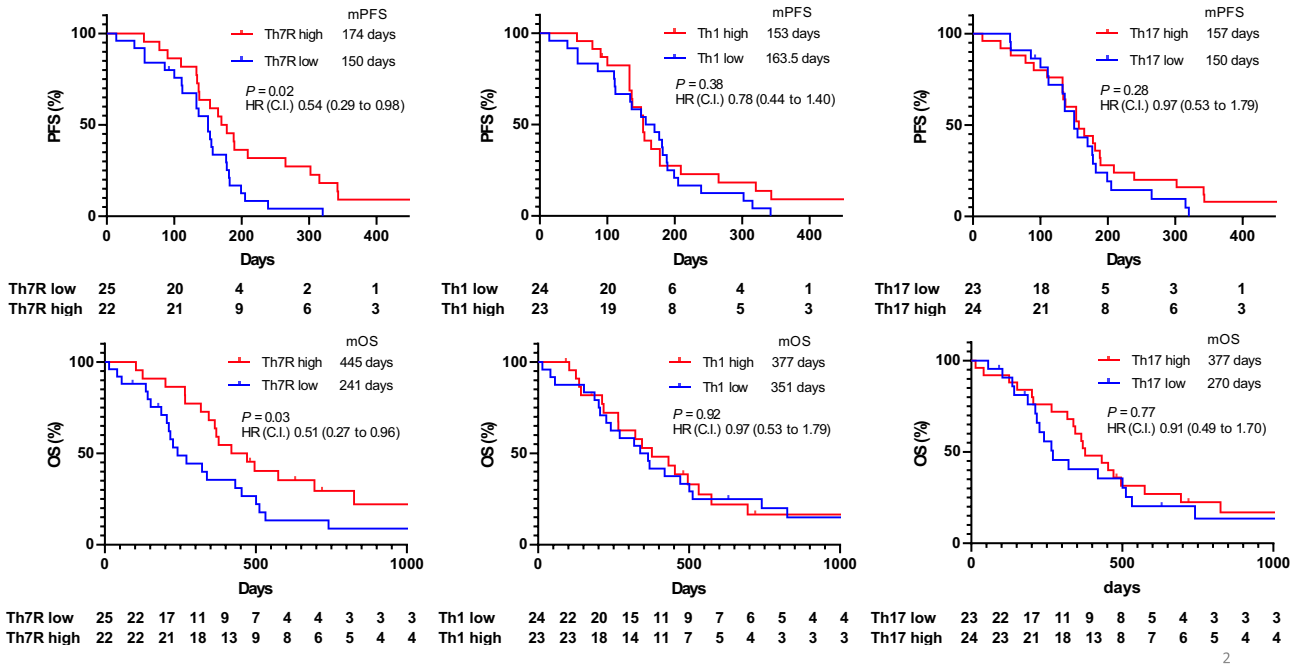

Fig. 2 Kaplan–Meier analysis of PFS and OS stratified by $CD4^+$ T-cell subsets in patients with ES-SCLC. Patients were divided into high- and low-frequency groups on the basis of the median frequencies of Th1, Th17, and Th7R subsets. Among these, only the $Th7R^{high}$ group showed a significantly longer PFS and OS than the $Th7R^{low}$ group

Table 2 Patient's characteristics according to Th7R levels

Different variables		Th7R / $CD4^+$ T cell		
		Low (≤9.4%) n = 25 (%)	High (9.4% <) n = 22 (%)	*p*-value
Age	< 75	16 (64.0)	14 (29.8)	> 0.999
	≥ 75 yrs	9 (36.0)	8 (17.0)	
Sex	Male	23 (92.0)	17 (77.3)	0.228
	Female	2 (8.0)	5 (22.7)	
ECOG PS	0–1	22 (88.0)	20 (90.9)	> 0.999
	2–3	3 (12.0)	2 (9.1)	
Smoking Index	Yes	25 (100.0)	22 (100.0)	> 0.999
	No	0 (0.0)	0 (0.0)	
Histology	SCLC	24 (96.0)	21 (95.5)	> 0.999
	Combined	1 (4.0)	1 (4.6)	
Liver meta	Yes	10 (40.0)	5 (22.7)	0.23
	No	15 (60.0)	17 (77.3)	
Brain meta	Yes	7 (28.0)	4 (18.2)	0.50
	No	18 (72.0)	21 (81.8)	
Bone meta	Yes	10 (40.0)	6 (27.3)	0.54
	No	15 (60.0)	16 (72.7)	
Response	PR	14 (56.0)	18 (81.8)	0.07
	Non-PR	11 (44.0)	4 (18.2)	

yrs years, *ECOG* Eastern cooperative oncology group, *PS* Performance status, *SCLC* Small cell lung carcinoma, *PR,* Partial response, *meta* Metastasis

CI 0.4106–1.034). We previously reported that Th7R, rather than Th1 or Th17, predicted the response to pembrolizumab in advanced NSCLC [17]. Therefore, we sought to determine whether Th7R was involved in the therapeutic efficacy of chemoimmunotherapy for ES-SCLC.

Pre-treatment blood samples were available for 27 patients who received chemotherapy alone and for 20 patients who received chemoimmunotherapy. The patient characteristics in each group are shown in Table 3. We assessed the effect of baseline peripheral blood Th7R subsets in each treatment group. In the chemotherapy group, there was no significant difference in PFS between the $Th7R^{high}$ and $Th7R^{low}$ groups; however, OS tended to be longer in the $Th7R^{high}$ group (574 vs. 322 days, P =.1219; HR 0.5267; 95% CI 0.2282–1.216), thus suggesting the potential contribution of Th7R to long-term survival rather than short-term treatment response (Fig. 4). By contrast, in the chemoimmunotherapy group, the $Th7R^{high}$ group showed a significantly prolonged PFS (240 vs. 164 days, P = 0.0382; HR 0.4418; 95% CI 0.1707–1.143) (Fig. 4). Although OS was also more favorable in the $Th7R^{high}$ group, the difference was not statistically significant (419 vs. 241 days, P =.2091; HR 0.5740; 95% CI 0.2223–1.482) (Supplementary Fig. 7. These findings suggest that Th7R may contribute to the efficacy of immune checkpoint blockade (ICB) therapy.

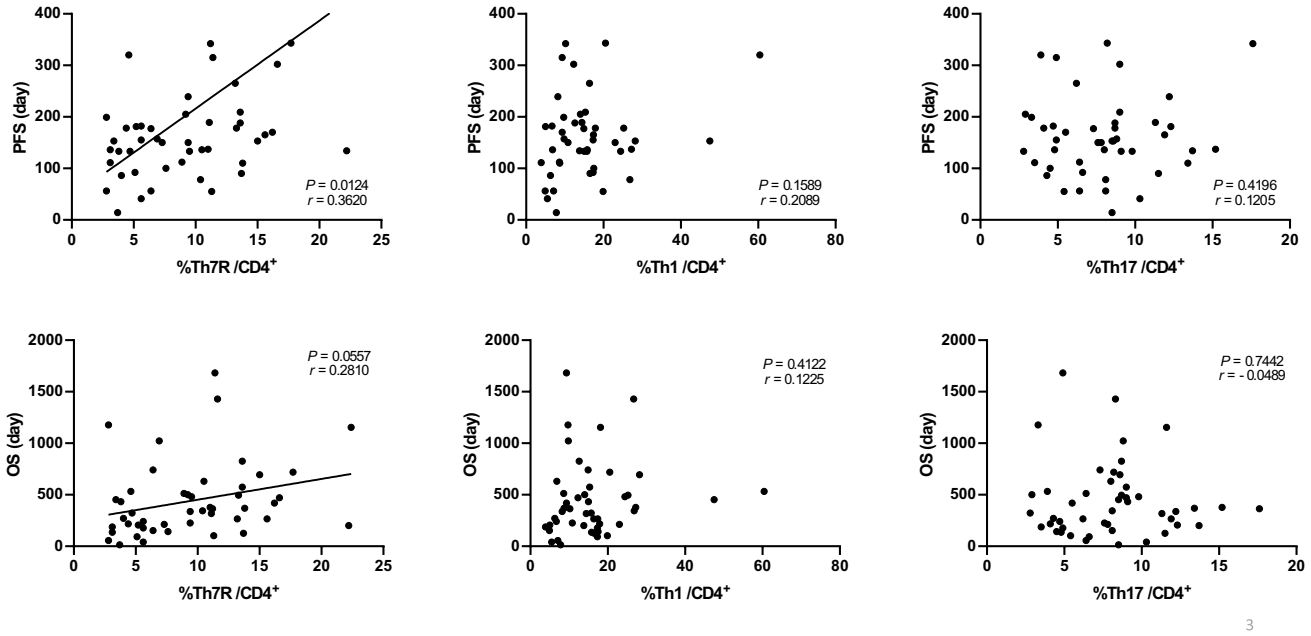

Fig. 3 Correlation between $CD4^+$ T-cell subset frequencies and clinical outcomes in patients with ES-SCLC. Pearson correlation analysis between the proportions of Th1, Th17, Th7R, and Treg subsets and survival duration. Only the Th7R subset showed a significant positive correlation with PFS and a trend toward a correlation with OS

Table 3 Patient's characteristics according to Treatment

		Treatment		
		Chemotherapy n = 27 (%)	Chemoimmunotherapy n = 20 (%)	*p*-value
Age	< 75 ≥ 75 yrs	15 (55.6) 12 (44.4)	15 (75.0) 5 (25.0)	0.226
Sex	Male Female	24 (88.9) 3 (11.1)	16 (80.0) 4 (20.0)	0.438
ECOG PS	0-1 2-3	25 (88.0) 2 (12.0)	17 (90.9) 3 (9.1)	> 0.999
Smoking Index	Yes No	27 (100.0) 0 (0.0)	17 (100.0) 0 (0.0)	> 0.999
Histology	SCLC Combined	25 (92.6) 2 (7.4)	20 (100.0) 0 (0)	0.50
Liver meta	Yes No	12 (40.0) 15 (60.0)	3 (22.7) 17 (77.3)	0.06
Brain meta	Yes No	7 (28.0) 20 (72.0)	4 (18.2) 16 (81.8)	0.737
Bone meta	Yes No	8 (40.0) 19 (60.0)	8 (27.3) 12 (72.7)	0.54
Response	PR Non-PR	16 (56.0) 11 (44.0)	18 (81.8) 2 (18.2)	0.02

yrs years, *ECOG* Eastern cooperative oncology group, *PS* Performance status, *SCLC* Small cell lung carcinoma, *PR* partial response *BI* Brinkman index, *meta* metastasis

Th7R cells are numerically correlated with $GZMK^+$ $GZMB^-$ $CD8^+$ T cells

The priming, clonal expansion, migration, and cytotoxic functions of antitumor $CD8^+$ T cells depend on $CD4^+$ T-cell assistance via dendritic cells, as exemplified by the interaction between Th1 cells and CTLs. Recently, a subset of tumor-infiltrating T cells expressing the TCF-7 and IL-7 receptors (i.e., Tpex) was identified using scRNA-seq. These cells retain their self-renewal capacity after priming and expansion and have been shown to exert critical antitumor effects alongside CTLs. In this study, we examined the numerical relationships between $CD4^+$ and $CD8^+$ T-cell subsets regardless of treatment timing.

$CD8^+$ Tpex have been reported in multiple analyses to exhibit a distinct molecular profile characterized by the expression of GZMK and absence of GZMB. By contrast, classical CTLs express GZMB but not GZMK, thus displaying a complementary expression pattern. On the basis of this differential expression of the proteases GZMB and GZMK, $CD8^+$ T cells were classified into two clusters: $GZMB^+GZMK^-$ (CTLs) and $GZMB^-GZMK^+$ (Tpex). The Th1 subset showed a significant positive correlation with $GZMB^+$ CTLs ($P = .0036$, $r = 0.3217$), but not with $GZMK^+$ Tpex, instead exhibiting a trend toward a negative correlation ($P = 0.3609$, $r = -01035$) (Fig. 5). Consistent with previous reports, Th1 cells supported CTLs during acute infection. Interestingly, in contrast to Th1, the Th7R subset showed a negative correlation with $GZMB^+$ CTLs ($P =$

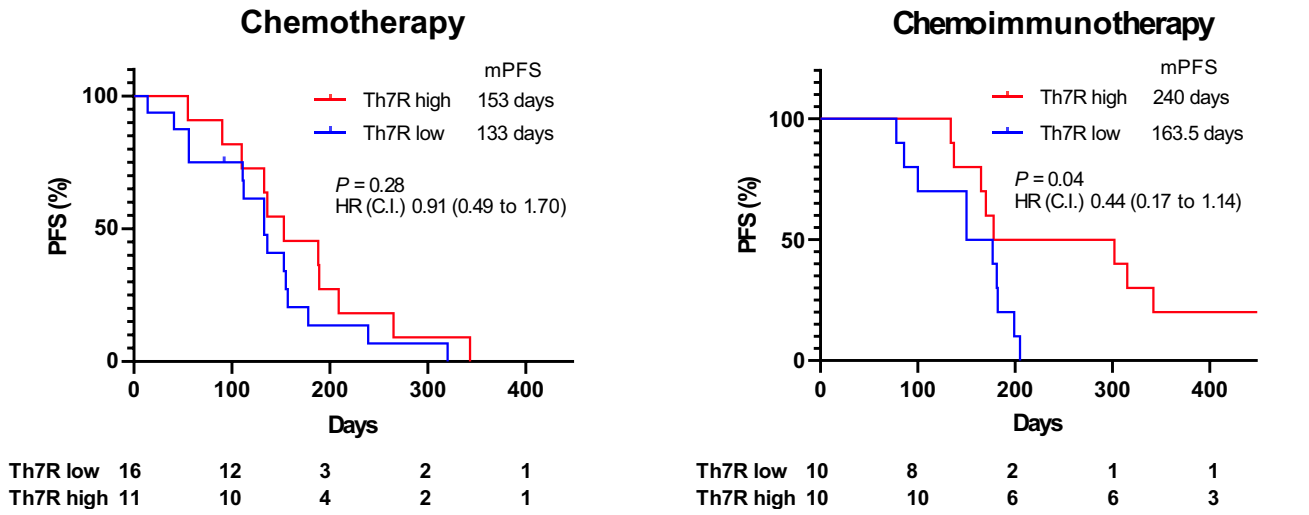

Fig. 4 Effect of baseline Th7R frequency on survival outcomes by treatment group in patients with ES-SCLC. The Kaplan–Meier curves of PFS stratified into Th7R^{high} and Th7R^{low} groups in the chemotherapy and chemoimmunotherapy cohorts. Th7R^{high} status was associated with significantly longer PFS in the chemoimmunotherapy group

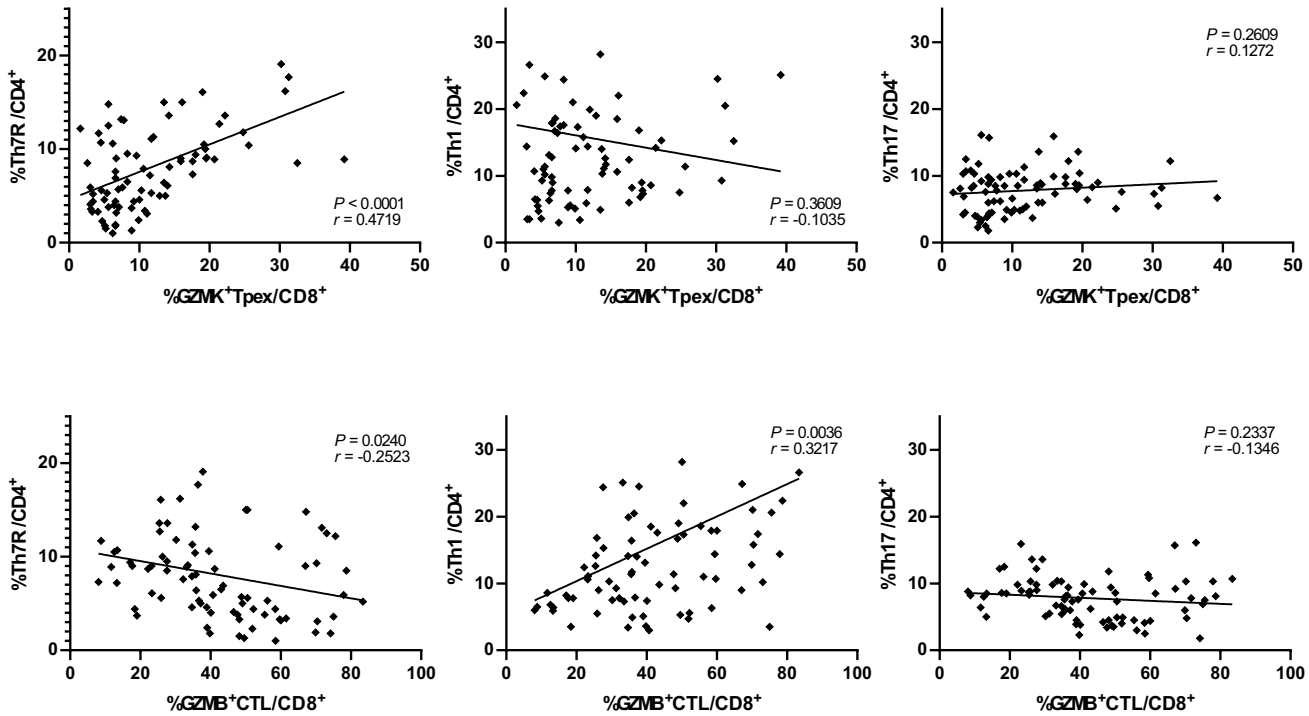

Fig. 5 Correlation between CD4$^+$ T-cell subsets and CD8$^+$ T-cell subsets defined by GZMB and GZMK expression. Pearson correlation analysis between Th1, Th7R, and Th17 subsets and CD8$^+$ T-cell clusters classified as GZMB$^+$CD8$^+$ T cells (CTLs) and GZMK$^+$CD8$^+$ T cells (Tpex). Th1 cells correlated positively with CTLs, whereas Th7R cells correlated positively with Tpex and negatively with CTLs.

0.0240, r = − 02523) and was the only subset that exhibited a significant positive correlation with GZMK$^+$ $^+$pex (P = 0.0001, r = 0.4719) (Fig. 5). Th17 cells did not show a significant correlation with either GZMB$^+$ CTLs or GZMK$^+$ Tpex.

CTLs are effector T cells that downregulate CD62L expression. To explore their association with CD4$^+$ T-cell subsets, we examined their correlation with CD62L^{low} CD8$^+$ T cells. Among the subsets, only Th1 cells showed a trend

toward a positive correlation ($P = 0.1115$, r = 0.2352) (Supplementary Fig. 8). These findings suggest the presence of a Th7R–Tpex axis in addition to the conventional Th1–CTL axis.

Discussion

We demonstrated that Th7R in the peripheral blood of SCLC patients showed a positive correlation with GZMK$^+$ Tpex and a negative correlation with GZMB$^+$ CTLs. On the other hand, classical Th1 showed a strong positive correlation with GZMB$^+$ CTLs but had no correlation with GZMK$^+$ Tpex. These results suggest that two distinct partner relationships exist between Th1–CTL and Th7R–Tpex. Tpex are CD8$^+$ T cells that have been primed by antigen and undergo clonal proliferation. However, unlike CTLs, Tpex express receptors and transcription factors such as IL-7R, TCF7, and LEF1, which confer self-renewal capacity, and express GZMK, which is an effector molecule [20]. Similarly, Th7R cells express IL-7R, TCF7, and LEF1, which are not expressed in classical Th1 cells [17]. Therefore, Th7R cells and Tpex not only correlated in terms of frequency but also share significant similarities in gene expression profiles. This finding suggests the existence of a Th7R–Tpex axis that is specialized for long-term sustained immune responses and is distinct from the Th1–CTL axis, which is adept at short-term immune responses.

Additionally, we reported that Th7R cells express CXCL13 and lymphotoxinβ, which are not found in Th1 cells, within the lung cancer microenvironment [18]. These genes are involved in the formation of HEVs and tertiary lymphoid structures (TLSs) [21, 22]. Unlike CTLs, Tpex express CD62L to recognize perinode addressins, invade TMEs via HEVs as entry gates, and reside within TLSs. This suggests that Th7R plays a role in establishing the entry gateway and residence site for Tpex [23, 24]. To support this hypothesis, future mechanistic studies involving genetic modification of chemokine receptors in Th7R cells or inhibition of chemokine signaling pathways will be required.

Th7R is the only CD4$^+$ T cell subset in the pre-treatment peripheral blood of ES-SCLC that predicts both PFS and OS, and its frequency is significantly associated with the duration of PFS. However, when stratified by treatment type, this association was observed only in the chemo-immunotherapy group. Therefore, Th7R does not substantially contribute to the response to cytotoxic chemotherapy but may play a role in the efficacy of ICB. Tpex are considered the origin of the CD8$^+$ T-cell proliferation burst induced by PD-1 blockade therapy, and because Th7R cells are numerically correlated with Tpex, Th7R may function as an indirect marker for predicting ICB responsiveness. Conversely, increasing Th7R levels through external interventions may promote the induction and expansion of Tpex, thereby enhancing ICB efficacy. Regarding OS, an improvement in survival rates was observed in the Th7Rhigh group, particularly in patients receiving concurrent chemotherapy.

This study has a few limitations. First, all analyses in this study were performed using PBMCs, which represent a clinically practical approach but may not necessarily reflect immune responses within TMEs with full accuracy. This is because TMEs represents a highly complex concept composed not only of malignant cells but also of diverse non-malignant components, including immune cells, blood vessels, lymphoid tissues and lymph nodes, nerves, extracellular matrix, and metabolites. Diverse intercellular mediators, such as cytokines, chemokines, and extracellular vesicles, are intricately involved in regulating its formation and dynamics [25]. To characterize this complexity with higher resolution, recent studies have increasingly employed advanced analytical approaches, including single-cell transcriptomics and spatial transcriptomics [26]. However, accumulating evidence in cancer immunotherapy highlights the importance of systemic immune responses in addition to local immune activity [27]. We previously reported that the CD62L^{low} Th7R cluster in peripheral blood shows a significant numerical correlation with CD4$^+$ T cells in the tumor stroma, and that effector CD4$^+$ T cells within TMEs consist predominantly of CD62L^{low} Th7R and Th1 subsets [18]. These findings suggest a potential continuity between the peripheral immune response and the immune landscape within TMEs. However, a more precise understanding requires assessment of clonal overlap between these immune compartments using single-cell TCR sequencing.

Recent studies have reported that SCLC can be divided into several subtypes on the basis of gene expression information, and that the immunological environment differs among these subtypes [28]. However, recent studies reported that the number of T cells infiltrating the TME, rather than gene-based subtypes, was associated with treatment response and prognosis in SCLC; this finding is controversial [29]. The current study is a retrospective observational study with a relatively small number of cases at a single institution; therefore, it was not possible to perform subtype-specific analyses on the basis of the genetic mutation information of cancer cells. We plan to conduct a prospective study to analyze both tumor genetic mutation patterns and host immunity using by Th7R.

In summary, Th7R, which is a Th1-like CD4$^+$ T-cell subset, may contribute to sustained antitumor immunity and the efficacy of ICB not only in NSCLC but also in SCLC. While the existence of a Th7R–Tpex axis remains hypothetical, our findings suggest a potential link between these populations, implying that Th7R could serve as an indirect biomarker for predicting ICB responsiveness.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00262-025-04242-6.

Acknowledgements The authors thank all the patients and their families. We thank Mrs. Koko Kodaira, Mrs. Kozue Watanabe, Mrs. Hiroko Noguchi, Mr. Jyoji Shiotani, and Mrs. Chieko Ono for their technical assistance in this study.

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Funding KAKENHI program of the Japan Society for the Promotion of Science grant 17H04184, Japan Agency for Medical Research and Development grant 19ae0101074h0001. KAKENHI program of the Japan Society for the Promotion of Science grant,Japan Agency for Medical Research and Development grant. We thank Mrs. Koko Kodaira, Mrs. Kozue Watanabe, Mrs. Hiroko Noguchi, Mr. Jyoji Shiotani, and Mrs. Chieko Ono for their technical assistance in this study.

Data availability All raw data are available upon request from the author.

Declarations

Conflict of interest OY reports personal fees from Ono Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Bristol Myers Squibb, Eli Lilly and Company, AstraZeneca, Takeda Pharmaceutical Company Limited, Nippon Kayaku, Daiichi Sankyo, MSD, Novartis Pharma K.K., Kyowa Kirin Co., Ltd., Amgen K.K., and Janssen Pharmaceutical K.K. KK reports personal fees from Ono Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., and AstraZeneca and research grants from AstraZeneca. HK reports personal fees from Ono Pharmaceutical Co., Ltd., Bristol Myers Squibb, Chugai Pharmaceutical Co., AstraZeneca, MSD, and research grants from Boehringer Ingelheim, Chugai Pharmaceutical Co., Nippon Kayaku. No disclosures were reported by the other authors.

Ethics approval The study protocol was approved by the Institutional Review Board of Saitama Medical University International Medical Center in accordance with the Declaration of Helsinki (approval number: 16–281).

Consent to participate All participants provided written informed consent.

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