Original Article

Peripheral T-cell receptor repertoire dynamics in small cell lung cancer

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Background: Identifying a circulating biomarker predictive of immune checkpoint inhibitor (ICI) benefit in patients with small cell lung cancer (SCLC) remains an unmet need. Characteristics of peripheral and intratumoral T-cell receptor (TCR) repertoires have been shown to predict clinical outcomes in non-small cell lung cancer (NSCLC). Recognizing a knowledge gap, we sought to characterize circulating TCR repertoires and their relationship with clinical outcomes in SCLC.

Methods: SCLC patients with limited (n=4) and extensive (n=10) stage disease were prospectively enrolled for blood collection and chart review. Targeted next-generation sequencing of TCR beta and alpha chains of peripheral blood samples was performed. Unique TCR clonotypes were defined by identical CDR3, V gene, and J gene nucleotide sequences of the beta chain and subsequently used to calculate TCR diversity indices.

Results: Patients with stable versus progressive and limited versus extensive stage disease did not demonstrate significant differences in V gene usage. Kaplan-Meier curve and log-rank analysis did not identify a statistical difference in progression-free survival (PFS) (P=0.900) or overall survival (OS) (P=0.200) between high and low on-treatment TCR diversity groups, although the high diversity group exhibited a trend toward increased OS.

Conclusions: We report the second study investigating peripheral TCR repertoire diversity in SCLC. With a limited sample size, no statistically significant associations between peripheral TCR diversity and clinical outcomes were observed, though further study is warranted.

Keywords: T-cell receptor repertoire (TCR repertoire); T-cell receptor (TCR); small cell lung cancer (SCLC); biomarker; immunogenomics

Submitted Sep 15, 2022. Accepted for publication Dec 21, 2022. Published online Feb 21, 2023.
doi: 10.21037/tlcr-22-666
View this article at: https://dx.doi.org/10.21037/tlcr-22-666

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Introduction

Although immune checkpoint inhibitors (ICIs) represent an opportunity to harness the immune system to target cancer cells in a variety of disease settings, only a subset of patients with small cell lung cancer (SCLC) achieve clinical benefit from ICIs (1). To date, no circulating predictive biomarkers to identify patients with SCLC who would benefit from ICIs have been identified; results using tumor programmed death-ligand 1 (PD-L1) and tumor mutational burden (TMB; both tumor and blood-based analyses) have been disappointing (2). The identification of reliable peripheral blood biomarkers offers a noninvasive opportunity to transform care.

Characteristics of tumor immune composition such as T cell infiltration and inflammatory gene expression correlate with clinical outcomes across multiple solid tumor histologies (3). This body of literature has demonstrated the importance of tissue-resident T cells in antitumor immunity across several tumor types (4). However, limited accessibility and tumor heterogeneity of tissue samples implores the need for peripheral blood immune biomarkers, particularly among patients with SCLC. Circulating T-cell receptor (TCR) repertoire dynamics represent one such biomarker.

Highlight box

Key findings

- No statistically significant association was observed between peripheral T-cell receptor (TCR) diversity and clinical outcomes in this limited cohort of 14 patients with small cell lung cancer (SCLC).
- Concordant with one previous report, we observed an exceptional responder with high TCR diversity.

What is known and what is new?

- Characteristics of intratumoral and circulating TCR repertoires predict clinical outcomes in non-small cell lung cancer patients treated with immune checkpoint inhibitors (ICIs). Limited data in SCLC demonstrates a cold and heterogeneous intratumoral TCR repertoire.
- We report the second study in SCLC characterizing peripheral TCR repertoires and investigating associations between TCR diversity and clinical outcomes.

What is the implication, and what should change now?

- A prospective, observational study investigating the peripheral TCR repertoire as a predictive biomarker in SCLC via collection of samples pre- and post-ICI administration in first-line extensive disease is warranted.

Targeted sequencing of the complementarity-determining region 3 (CDR3) of the TCR beta chain enables detection of unique T cell clonotypes and estimation of repertoire diversity (5).

Numerous recent studies characterize tissue-infiltrating and circulating TCR repertoires in non-small cell lung cancer (NSCLC) (5-7). Han *et al.* found that NSCLC patients with greater intratumoral PD1+ $CD8^+$ TCR repertoire diversity pre-treatment exhibit greater progression-free survival (PFS) with anti-PD-1/PDL-1 therapy, presumably due to an enhanced ability to amplify a tumor-reactive T cell clonotype in response to immunotherapy (8). This suggests utility of TCR repertoire diversity as a predictor of treatment response, particularly with ICI treatment. There is currently a paucity of peripheral TCR repertoire studies in patients with SCLC, with just one limited study demonstrating no change in diversity or clonality with ICI therapy except in one patient achieving complete response (9). The addition of ICIs (atezolizumab or durvalumab) to carboplatin-etoposide as first-line treatment in extensive stage SCLC and ongoing evaluation as adjuvant therapy in patients with limited stage SCLC prompted our investigation of potential circulating immune biomarkers in patients with SCLC (10). We aimed to (I) characterize peripheral TCR repertoires and (II) assess the relationship between circulating TCR repertoire diversity and outcomes in SCLC. We hypothesized that SCLC patients with higher TCR repertoire diversity would have improved clinical outcomes. We present the following article in accordance with the STROBE reporting checklist (11) (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-666/rc).

Methods

Study design & patient population

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Patients with a confirmed diagnosis of SCLC seen at Vanderbilt-Ingram Cancer Center were prospectively identified through chart screening and consented between October 2014 and January 2017 using an Institutional Review Board (IRB #030763)-approved protocol for collection of blood up to once per month with medical record review. Potential participants with SCLC were not excluded for any reason; the most comment reason patients cited for declining was desire to avoid additional blood draws. Follow-up occurred through routine clinical care appointments. Subsequent

analyses were performed for all additional blood draws of patients with limited (n=4) and extensive (n=10) stage SCLC, as defined at diagnosis, receiving then standard-of-care first-line chemotherapy (carboplatin or cisplatin with etoposide). Additional institutions were approached for participation to minimize selection bias, and as many patients were approached as were potentially eligible to maximize the patient cohort. Overall, we were able to complete a single institution study with a total cohort of 14 patients, with none having a pre-treatment collection, 6 with at least one sample collected during their first-line therapy, 2 with initial collections prior to second-line therapy, and 6 with initial collections during 2nd line or later therapy.

DNA isolation

Peripheral blood samples (10–20 mL) were collected in Streck™ tubes (Streck, Omaha, NE) at various time points. Following centrifugation at 1,200 ×g for 30 min, plasma was removed from buffy coat. DNA was isolated using a commercially available kit (DNeasy Blood and Tissue Kit, QIAGEN).

Next-generation TCRβ CDR3 sequencing

The CDR3 regions of the TCRα and TCRβ chains were amplified by multiplex PCR using the Resolution Bioscience hybridization target capture protocol with probes modified to target the V and J genes. Fragments were retrieved via Resolution Bioscience library method and paired-end sequenced using Illumina MiSeq.

Data analysis

Unique TCR clonotypes were defined by identical CDR3, V gene, and J gene nucleotide sequences. Frequencies of unique clonotypes for each sample were counted. Counts were subsequently used to calculate the Shannon diversity index, a commonly used parametric estimator of diversity dependent on number of unique clonotypes and relative abundances, as follows (12): $(H)=-\sum p_i \ln p_i$.

Statistical analysis

Analyses were performed using the immunarch (0.6.7) vegan (2.5-7), survival, precrec, and cutpointr packages in R (4.0.3) (13-17). The primary study endpoints were PFS and overall survival (OS), defined as the time from first treatment start date to the date of progression event (radiographic relapse, most recent follow-up without progression, or death) or date of all-cause death. Secondary endpoints included stable versus progressive disease, with the former defined as stable, partial, or complete response and no radiographic progression within 60 days of corresponding sample collection. The endpoints were selected based on their strength of reflection of clinical outcomes.

Student's *t* tests were used to compare group means. The optimal threshold for T-cell diversity was calculated using ROC and Youden index analysis. Kaplan-Meier curve and log-rank analysis were used to compare PFS and OS in high versus low pre-treatment diversity. For all analyses, $P<0.05$ was considered statistically significant. Code used to generate figures can be accessed at https://github.com/MLAxelrod/LungTCR. Appendix 1 for all sample sequencing data as .tsv files.

Results

Patient recruitment

Between October 2014 and January 2017, 4 limited and 10 extensive stage SCLC patients were prospectively enrolled from 28 patients screened and approached for consent. All patients received first-line carboplatin or cisplatin with etoposide. Those with progression (n=12) received second-line conventional chemotherapy (n=7) or immunotherapy (n=5). *Table 1* outlines patient demographics and clinical characteristics including treatment regimen and timing of sample collection. At the end of a 5-year observation window, 1 of 14 (7%) patients remained alive (see https://cdn.amegroups.cn/static/public/tlcr-22-666-1.xlsx).

V gene usage in variable disease states

Biased V and J gene usage can be indicative of a coordinated anti-tumor response, as well as other pathological states such as infection and post-organ transplant (18). As such, we hypothesized there may be a difference in usage of the V gene of the beta chain in patients who achieve disease control versus those who never experience SCLC control or those with limited versus extensive stage disease. However, there was no significant difference in the usage of any of 45 V genes between samples derived from patients with stable versus progressive (defined as disease trajectory within 60 days of sample collection) disease (*Figure 1A*).

Table 1 Demographic and clinical characteristics of enrolled patients

Patient ID	Stage of disease at initial Dx	Age at dx (years)	Race	Gender	BMI (kg/m^2)	1st line Tx	2nd line Tx	3rd line Tx
1	E	74	W	F	27.1	Carbo/Etopo	Nivolumab	
2	E	57	W	M	21.2	Cis/Etopo	Carbo/Etopo	Paclitaxel
3	L	54	W	F	19.4	Cis/Etopo	Carbo/Etopo	Rovalpituzumab tesirine
4	L	74	W	M	23.3	Carbo/Etopo	Paclitaxel	
5	L	39	W	F	31.6	Cis/Etopo		
6	L	61	W	M	29.6	Cis/Etopo	Paclitaxel	Carbo/paclitaxel
7	E	56	W	F	33.3	Carbo/Etopo	Nivolumab	
8	E	66	W	F	16.4	Carbo/Etopo	Etopo	
9	E	71	W	F	21.8	Carbo/Etopo	Paclitaxel ± alisertib	
10	E	69	W	M	25.8	Carbo/Etopo ± roniciclib	Nivolumab	Paclitaxel
11	E	72	W	F	27	Carbo/Etopo		
12	E	71	W	M	32.1	Carbo/Etopo	Nivolumab + ipilimumab	
13	E	61	W	M	30.5	Carbo/Etopo	Nivolumab	Paclitaxel
14	E	57	W	M	24.4	Carbo/Etopo	Carbo/Etopo	Rovalpituzumab tesirine

Blood droplet symbols represent individual blood samples collected. Dx, diagnosis; BMI, body mass index; Tx, treatment; E, extensive; L, limited; W, White; F, female; M, male; Carbo, carboplatin; Cis, cisplatin; Etopo, etoposide.

Similarly, there was no significant difference in usage between patients with limited versus extensive stage (defined at diagnosis) disease (*Figure 1B*).

TCR repertoire diversity and clinical outcomes

Given evidence of a positive correlation between TCR repertoire diversity and clinical outcomes in NSCLC, we next sought to examine this relationship in SCLC (8). Toward this aim, we first compared the Shannon diversity index in the first available sample for all patients with stable versus progressive disease (n=14), finding no statistically significant difference (P=0.94; *Figure 2*). Of note, however, these samples were derived from patients at various stages in their treatment regimens.

We next evaluated first-line on-treatment circulating TCR repertoire diversity as a predictive tool of clinical outcome in our limited cohort of patients with first-line on-treatment (platinum-based agent + etoposide) samples available (n=6) at a median of 51.5 days from treatment initiation. Patients with first available samples collected after completion of first-line treatment were excluded (n=8). Based on an optimal threshold of 7.7821 per ROC and Youden Index analysis of OS, TCR diversity was used to classify patients into high (n=3) and low (n=3) diversity subsets (*Figure 3A,3B*). Kaplan-Meier curve and log-rank analysis did not identify a statistical difference in PFS (P=0.900) or OS (P=0.200) between high and low on-treatment TCR diversity groups, although the high diversity group exhibited a trend toward improved OS (*Figure 3C,3D*).

Discussion

This report provides the second, albeit limited, characterization of peripheral TCR repertoires in SCLC.

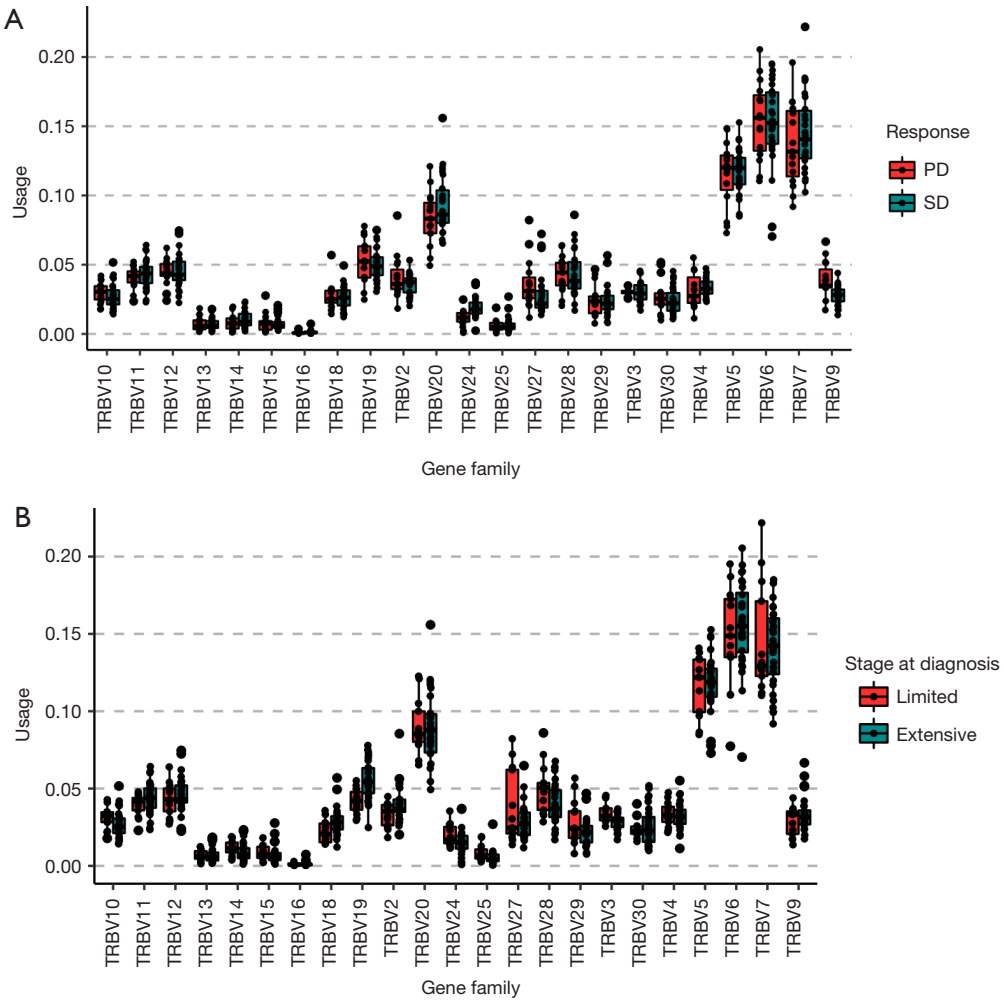

Figure 1 Samples derived from patients with variable disease characteristics demonstrate similar V gene usage frequencies. (A) Pooled gene usage frequencies in patients with SD (blue) versus PD (red) did not demonstrate significant differences in 45 V genes of the beta chain, with points representing individual gene frequencies (n=41). (B) Similarly, poled gene usage frequencies in patients with limited (red) versus progressive (blue) disease did not demonstrate significant differences in 45 V genes of the beta chain (n=41). PD, progressive disease; SD, stable disease; TRBV, T-cell receptor beta variable gene.

Intratumoral TCR repertoires in SCLC were recently found to be cold and heterogeneous relative to NSCLC, indicating a repertoire lacking strength and focus (19). Accordingly, we did not find evidence of biased V gene usage among patients with progressive disease, suggesting absence of a targeted anti-tumor response. While neither our study nor the aforementioned SCLC tumor analysis included patients on first-line ICI, these findings may provide a window of insight into the inferior response of SCLC to ICIs. Future work might concurrently evaluate intratumoral and peripheral TCR repertoires in SCLC to investigate the relationship between tissue-resident memory and circulating T cells, particularly in the setting of ICI therapy.

As a non-controlled, observational study, patients received treatment according to current National Comprehensive Cancer Network (NCCN) guidelines, resulting in variable regimens given varying disease characteristics. Few (n=5) of our patients received ICIs due to more limited indications at the time of enrollment. This limited our sample size of patients treated with ICIs compared to cytotoxic chemotherapy. While differences amongst TCR repertoires in patients with ICI versus cytotoxic chemotherapy would be interesting to study,

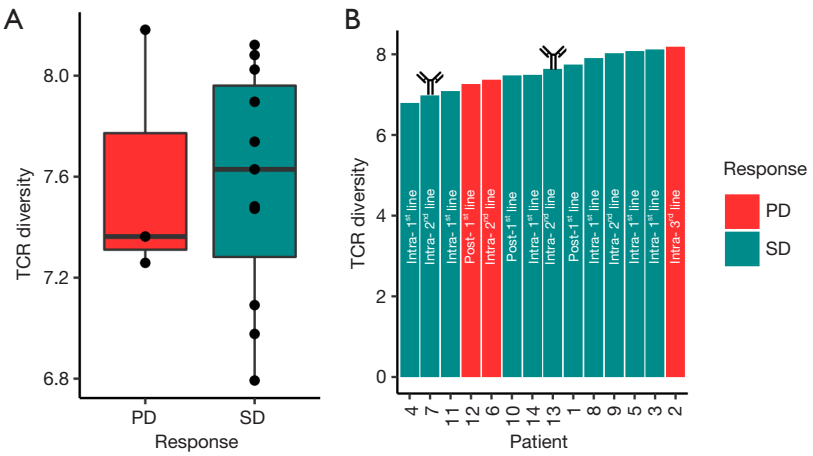

Figure 2 Patients with stable and progressive disease exhibit similar TCR repertoire diversity. (A) Comparison of TCR diversity in first available samples derived from patients with SD versus PD did not demonstrate a significant difference (P=0.351, n=14). (B) TCR repertoire diversity derived from Shannon Index for all samples with corresponding clinical response, SD (blue) or PD (red). TCR, T cell receptor; PD, progressive disease; SD, stable disease.

our limited sample size precluded meaningful analysis. In addition to non-standardized treatments and a small cohort, our study is limited by non-uniform collection timepoints. These limitations may contribute to the non-significant association between peripheral TCR repertoire diversity and clinical outcome, unlike prior studies in NSCLC. However, a trend (P=0.20) consistent with our hypothesis did emerge, with high TCR diversity patients demonstrating a trend toward better disease control and survival. This trend may be confounded by a "high diversity" exceptional responder with a PFS and OS >60 months. Interestingly, Roper *et al.* report a similar phenomenon in their limited cohort (n=20) study, with no evidence of changes in circulating TCR repertoire diversity and clonality except in one patient achieving complete response with ICI therapy (9). These findings, alongside a substantial body of evidence associating TCR repertoire diversity metrics with clinical outcome in other disease sites, suggest a need for larger studies to determine whether our exceptional responder is an outlier or representative of a subset of SCLC patients who benefit from ICIs, as well as the relationship between exceptional ICI responders with SCLC and the emerging immune-susceptible SCLC subtype (1,5,6,20).

While pre-treatment TCR repertoire diversity may act as a treatment-agnostic prognostic factor, other TCR repertoire metrics may serve as predictive factors while on ICIs. Intra and post-treatment TCR clonality may be posited as one such predictive biomarker on ICI therapy, as an increase in clonality may reflect expansion of a successful anti-tumoral clonotype. Indeed, Han *et al.* found that patients with NSCLC with greater increases in PD-1$^+$ CD8$^+$ TCR repertoire clonality post-ICI demonstrated greater PFS and OS (8). Similarly, correlation of improved OS in a subset of large cell neuroendocrine carcinoma (LCNEC) patients with normalization of TCR repertoire alterations after chemotherapy suggests utility of TCR dynamics as a predictive factor, particularly given the shared characteristics of LCNEC and SCLC (21). A prospective study investigating TCR repertoire clonality as a predictive biomarker in SCLC via collection of samples pre and post-ICI administration in first-line extensive disease is warranted. Such a study would eliminate confounding introduced by variable treatment regimens and collection timepoints while enabling exploration of additional TCR metrics in a more focused setting, that is, with ICI treatment.

Conclusions

We report the second study investigating peripheral TCR repertoire diversity in SCLC. With a limited sample size, no statistically significant associations between peripheral TCR diversity and clinical outcomes were observed, though further study is warranted, particularly exploring

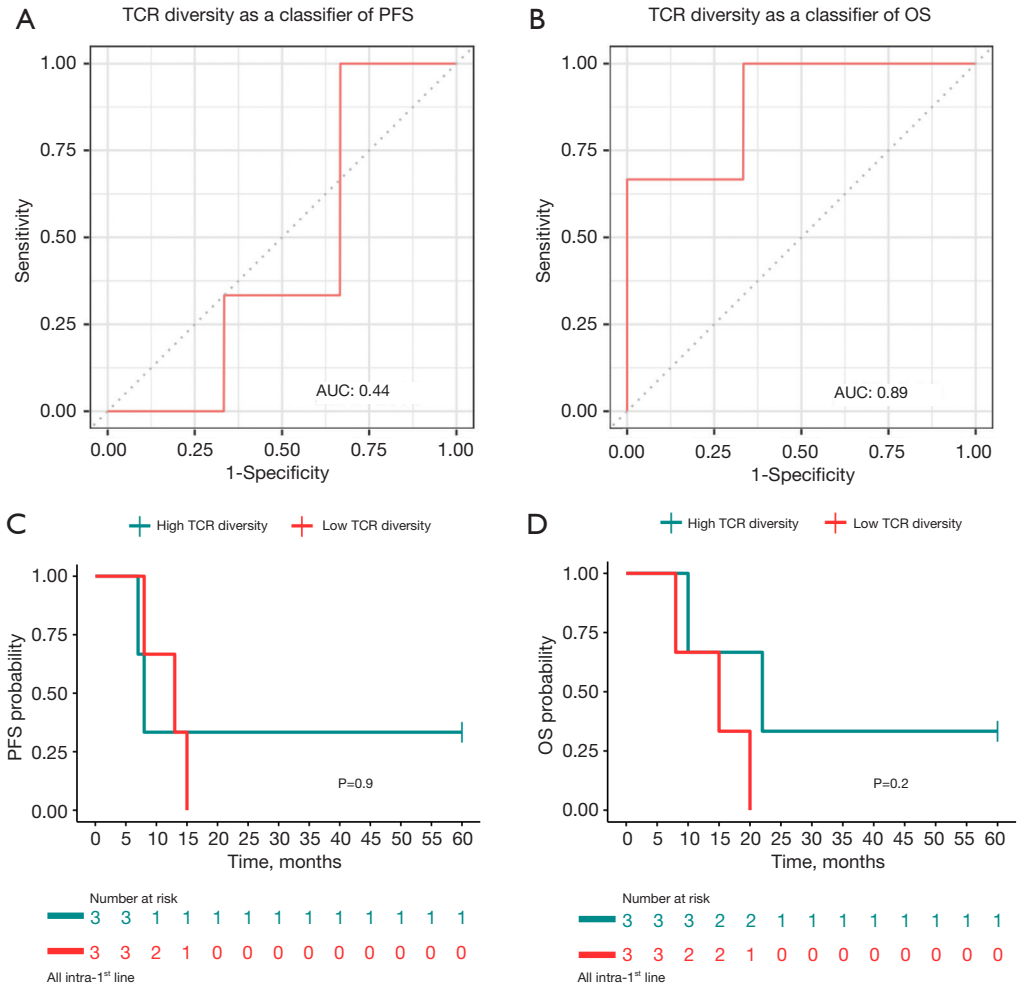

Figure 3 Clinical outcomes stratified by high and low TCR diversity. ROC analysis identified TCR diversity as a poor predictor of PFS (A) but a good predictor of OS (B), with an AUC of 0.89 and optimal Shannon diversity threshold of 7.7821 per Youden index analysis (n=6). (C) Using this threshold, TCR diversity was used to classify patients into high (n=3) and low (n=3) diversity subsets, finding no statistical difference (P=0.90) in PFS between the two groups. (D) Although differences in OS were insignificant (P=0.20), the high diversity group exhibited a trend toward improved OS. TCR, T cell receptor; PFS, progression-free survival; OS, overall survival; AUC, area under the curve; ROC, receiver operating characteristic.

relationships between circulating TCR diversity, tumor immune infiltrate, and SCLC subtype.

Acknowledgments

The authors thank participating patients who provided informed consent via Vanderbilt Institutional Review Board approved protocol #030763. Data derived from this work was presented at the North American Conference on Lung Cancer in Chicago, IL, USA on September 24th, 2022.

Funding: This work was supported by F30CA236157, T32GM007347 (MLA). WTI was supported by a National Comprehensive Cancer Network (NCCN) Young Investigator Award.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-666/rc

Data Sharing Statement: Available at https://tlcr.amegroups.

com/article/view/10.21037/tlcr-22-666/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-666/coif). MLA is listed as a coinventor on a provisional patent application for methods to predict therapeutic outcomes using blood-based gene expression patterns, that is owned by Vanderbilt University Medical Center, and is currently unlicensed. JMB receives research support from Genentech/Roche, Bristol Myers Squibb, and Incyte Corporation, has received consulting/expert witness fees from Novartis, and is an inventor on patents regarding immunotherapy targets and biomarkers in cancer. AB, TS, LL, JG, JH, and ML are current or former employees of Resolution Bioscience, a part of Agilent. WTI has served as a consultant for Bristol Myers Squibb, OncLive, Clinical Care Options, Chardan, Outcomes Insights, Cello Health, and Curio Science. He reports advisory board participation for Genentech, Jazz Pharma, G1 Therapeutics, Mirati, and Takeda. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Review Board (IRB00002125) of Vanderbilt University Medical Center with study number #030763. All patients provided informed consent at time of study enrollment.

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Cite this article as: Balbach ML, Axelrod ML, Balko JM, Bankhead A, Shaffer T, Lim L, Guo J, Hernandez J, Li M, Iams WT. Peripheral T-cell receptor repertoire dynamics in small cell lung cancer. Transl Lung Cancer Res 2023;12(2):257-265. doi: 10.21037/tlcr-22-666

Supplementary

Appendix 1 Table of Contents

Item	Description	File
Supplementary Dataset	Additional demographic, treatment, and response characteristics; sample groupings for individual analyses	Supplementary.Tablesxlsx
Sequencing Data	TCR clonotype sequences for each sample as .tsv files (within zip folder)	Supplementary Dataset 1.zip
R Analysis Code	Github link containing downloaded files with code used to perform analyses and generate figures	https://github.com/MLAxelrod/LungTCR

https://dx.doi.org/10.21037/tlcr-22-666