Brief Report

Sex-based differences in CEACAM5 expression in lung cancer

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Abstract: Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) is expressed in 20–25% of non-small cell lung cancer (NSCLC) and there is interest in CEACAM5 as a biomarker given its potential for blood-based detection and investigational study as a drug target. Increased expression of CEACAM5 has been observed in semi-solid lung adenocarcinoma lesions, which have an increased prevalence in women and never smokers. Given this association, sex-based differences in CEACAM5 were evaluated. The Cancer Genome Atlas (TCGA) data on CEACAM5 expression in NSCLC tumors (n=994) in women (n=398) and men (n=596) were analyzed for differences in expression of CEACAM5 based on sex and histologic subtypes of adenocarcinoma and for correlations with overall survival (OS). Among all stages of NSCLC, mean expression of CEACAM5 was 143.3 fragments per kilobase of transcript per million (FPKM) with differences observed between female and male patients (194.5 *vs.* 109.2 FPKM, P<0.0001) and between adenocarcinoma and squamous cell carcinoma (239.3 *vs.* 46.2 FPKM, P<0.0001). Differences persisted among combined sex and histology subgroups. High CEACAM5 was not predictive of survival in NSCLC or adenocarcinoma overall, but was associated with worse survival among stage I female patients with adenocarcinoma (5-year OS CEACAM5 high =33% *vs.* low =64%, log-rank P=0.008). Higher levels of CEACAM5 expression are observed in NSCLC tumors in female patients and adenocarcinoma histology. High CEACAM5 expression in lung adenocarcinoma is associated with worse survival among female patients. The biologic impact of sex on CEACAM5 as a biomarker warrants further study.

Keywords: Biomarkers; sex-based differences; carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5); lung cancer; adenocarcinoma

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Introduction

The carcinoembryonic antigen-related cell adhesion molecules (CEACAM) family comprises 12 cell surface molecules with functions in cell adhesion, signaling, and cancer progression. CEACAM5 is recognized as a tumor marker and therapeutic target in lung, colorectal, pancreatic cancer, and melanoma (1). As a blood marker of malignancy, the serum CEACAM5 glycoprotein (CEA) is the most well-known tumor marker for epithelial derived cancers and is clinically used in the treatment of colorectal cancer for postoperative surveillance in patients who have undergone surgical resection (2).

In non-small cell lung cancer (NSCLC), plasma levels of CEA as a marker of prognosis have been studied since the 1970's (3). CEACAM5 expression in NSCLC has been shown to correlate with increased risk of lymph node involvement, higher histologic grade, and stimulation of NSCLC progression via p38-Smad2/3 signaling (4).

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CEACAM5 expression is more likely to be high among NSCLC with a Kirsten rat sarcoma viral oncogene (*KRAS*) driver mutation and tumors without programmed death-ligand 1 (PD-L1) expression (5).

More recently, there is interest in using CEA as a marker to distinguish benign and malignant pulmonary nodules. Blood levels of CEA used in combination with radiomic signatures have been shown to help differentiate benign from malignant pulmonary nodules found on chest computed tomography (CT) scan (6,7). Furthermore, among many blood-based biomarkers studied for use in lung cancer, CEA has been repeatedly shown to be the most accurate with the highest area under the curve sensitivity and specificity (7,8). Serum CEA levels have also been studied as a potential predictor of risk of recurrence following surgical resection of stage I lung cancer. Various smaller studies reported mixed results, with some showing that elevated CEA levels predicted recurrence (9,10) and other studies showing no correlation (11,12). Circulating CEA levels can be elevated by a variety of factors including age, smoking, inflammatory bowel disease, pancreatitis, cirrhosis, renal dysfunction, hypothyroidism, uncontrolled diabetes, and peripheral artery disease, which have limited its clinical use as a diagnostic marker in lung cancer (13).

CEACAM5 also has promise as a therapeutic target in NSCLC, with the development of antibody drug conjugates, specifically the CEACAM5-targeted drug tusamitamab ravtansine (Sanofi, SAR408701). Tusamitamab ravtansine showed promise in early trials (14), but the phase 3 CARMEN-LC03 trial was recently concluded due to lack of benefit in progression-free survival compared to docetaxel alone among non-squamous stage IV NSCLC patients (15). CEACAM5 is also currently being explored use as a target for intraoperative molecular imaging. These studies use an anti-CEACAM5 targeted near-infrared fluorochrome to illuminate CEACAM5-positive tumors during pulmonary resection to assist in localizing small lesions, ensuring negative margins, and identifying neighboring synchronous cancers (16). This strategy has been used in clinical trials for colorectal cancer metastasectomy pulmonary resections, and there is preclinical data to support the feasibility of this approach in primary lung cancer (17,18). Thus, CEACAM5 remains a promising and interesting biomarker in NSCLC tumors, however the impact of patient sex on CEACAM5 expression has not been studied.

Semi-solid lung adenocarcinoma (LUAD) is a subset of NSCLC that is frequently found incidentally as a semi-solid lung nodule on chest CT. It is known to be a slower growing, more indolent form of NSCLC that poses a treatment challenge given its slow growth but potential to transform into more invasive cancer. We have previously demonstrated that CEACAM5 is the most upregulated gene within the solid, invasive portion of this subtype of NSCLC and may be a potential biomarker for invasive potential in these tumors (19). Semi-solid adenocarcinoma is increasingly identified on chest CTs with a growing number of patients found to have semi-solid lung nodules each year and the percentage of CT scans with semi-solid nodule findings increasing over the past decade (20). In multiple studies, CEACAM5 gene expression has been shown to be elevated within semi-solid LUAD and premalignant ground glass nodules (19,21).

Given the known sex-based female predominance of semi-solid LUAD, differences in outcome and CEACAM5 expression warrant further study in a larger data set. The impact of sex on CEACAM5 expression in lung cancer has not previously been evaluated. Here, the impact of sex, histologic subtype, and tumor stage on CEACAM5 expression in NSCLC is studied and differences in survival are evaluated. We present this article in accordance with the REMARK reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-983/rc).

Methods

Data source

The Cancer Genome Atlas (TCGA) gene expression data from the Human Protein Atlas (www.proteinatlas.org, accessed on March 30, 2024) database was used to obtain a dataset of CEACAM5 expression levels in n=500 LUAD and n=494 lung squamous cell carcinoma (LUSC) tumors as well as information on patient sex, tumor stage, and survival. TCGA is a joint effort between the National Cancer Institute and the National Human Genomics Research Institute which has collected genomic, epigenomic, transcriptomic, and proteomic data from over 20,000 cancer and matched normal samples. RNA-sequencing (RNA-Seq) gene expression data is available for 994 NSCLC samples, all of which were included in this analysis. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical analysis

GraphPad Prism version 10.2.2. was used for statistical

analyses. Demographic characteristics between LUAD and LUSC patients were compared using a Chi-squared test for categorical variables test for sex, race (white *vs.* other), stage (stage I *vs.* other), and an unpaired *t*-test of equal variance for continuous variables.

Gene expression data sets downloaded from TCGA were analyzed as mean and *t*-tests of unmatched samples with equal variance for two sample comparisons and analysis of variance (ANOVA) for comparison of multiple groups. For survival estimates, optimal cut-off value for CEACAM5 fragments per kilobase of transcript per million mapped reads (FPKM) in LUAD was calculated as 57.15 FPKM. This FPKM cut-off value for high *vs.* low CEACAM5 expression was calculated as the optimal point which maximized survival differences with the lowest long-rank P value for the adenocarcinoma (n=500) data set overall. Notably, the chosen FPKM cut-off point in the adenocarcinoma (n=500) data is not statistically significant in this group overall. This "high expression" FPKM cut-off point was then held constant throughout all of the subsequent subgroup survival analysis and analysis of NSCLC tumors overall. Prognostic differences in overall survival (OS) based on high or low CEACAM5 expression was calculated samples using the Kaplan-Meier method and log-rank test with P<0.05 considered statistically significant. The impact of CEACAM5 expression level on survival based on sex, tumor histology and stage subgroups were then studied individually.

The correlation of CEACAM5 expression with expression levels of other frequently mutated genes in NSCLC was performed on the Lung Cancer Explorer portal (22) with the most common driver mutations in lung cancer including epidermal growth factor receptor (*EGFR*), Kirsten rat sarcoma virus oncogene (*KRAS*), v-raf murine sarcoma viral oncogene homolog B (*BRAF*), MET proto-oncogene (*MET*), and anaplastic lymphoma kinase (*ALK*). Heatmap of these correlations performed in GraphPad Prism version 10.2.2.

Results

A total of 994 patients with NSCLC have TCGA gene expression data available from The Protein Atlas, of which 60.0% are male (n=596) and 40.0% are female (n=398) and 50.3% represent adenocarcinoma NSCLC (n=500) and 49.7% represent squamous cell NSCLC (n=494). Demographic characteristics of the TCGA NSCLC cohort and the differences between the LUAD cohort and the LUSC cohort were compared with more women in the LUAD group compared to the squamous cell carcinoma group (54% *vs.* 26%, P<0.001). Patients with LUAD were slightly younger (65.2 *vs.* 67.2 years, P<0.001) and had a higher percentage of white race patients (76.4% *vs.* 68.2%, P=0.004) compared to lung squamous cell patients. Stage distributions between LUAD and squamous cell tumors in the TCGA data set were similar (*Table 1*).

Overall expression of CEACAM5 ranged from 0 to 4,077.7 with a mean of 143.3 FPKM. Significant differences in CEACAM5 expression existed between tumors from male and female patients with females having higher CEACAM5 expression (194.5 *vs.* 109.2 FPKM, *t*-test P<0.0001). Adenocarcinoma tumors had significantly higher expression of CEACAM5 than squamous cell carcinoma (239.3 *vs.* 46.2 FPKM, *t*-test P<0.0001). These differences persisted among subgroups that combined sex and histology: male adenocarcinoma (n=230) mean 218.3 FPKM; female adenocarcinoma (n=270) mean 257.3 FPKM; male squamous cell (n=366) mean 40.6 FPKM; and female squamous cell (n=128) mean 62.2 FPKM (ANOVA P<0.0001). Significant differences were found by ANOVA as well as by individual *t*-tests between subgroups (*Figure 1*).

CEACAM5 expression was then evaluated as a biomarker to predict OS among the dataset overall and within each histology. High expression was defined as CEACAM5 expression >57 FPKM for all survival analyses. High CEACAM5 expression was not associated with any significant differences in survival for NSCLC patients overall or in men or women specifically among all types of NSCLC. Additionally, no significant differences in survival were observed among adenocarcinoma histology NSCLC. However, in female adenocarcinoma patients specifically, high CEACAM5 expression was associated with worse survival outcomes among all stages combined (5-year OS high =28% *vs.* low =47%, log-rank P=0.07). These differences were significant among stage I (5-year OS high =33% *vs.* low =64%, log-rank P=0.008) and stage IA (5-year OS high =36% *vs.* low =93%, log-rank P=0.004). No similar survival correlations were observed among all patients combined or male patients specifically (*Figure 2*).

To explore the relationship of CEACAM5 with common lung cancer driver mutations expression of CEACAM5 was correlated with *EGFR*, *KRAS*, *BRAF*, *MET*, and *ALK* expression among LUAD tumors in TCGA gene expression data. Overall there were no strong correlations between CEACAM5 and the expression of the most common lung cancer driver mutation genes. There was a

Table 1 Demographics of TCGA lung cancer data set

Clinical variables	All TCGA lung cancer (n=994)	LUAD (n=500)	LUSC (n=494)	P value*
Sex, n (%)				<0.001
Male	596 (60.0)	230 (46.0)	366 (74.1)	
Female	398 (40.0)	270 (54.0)	128 (25.9)	
Age (years), mean	66.2	65.2	67.2	<0.001
Race, n (%)				0.004
White	719 (72.3)	382 (76.4)	337 (68.2)	
Black	81 (8.1)	52 (10.4)	29 (5.9)	
Asian	16 (1.6)	7 (1.4)	9 (1.8)	
American Indian or Alaskan Native	1 (0.1)	1 (0.2)	0	
Other or N/A	177 (17.8)	58 (11.6)	119 (24.1)	
Stage, n (%)				0.18
Stage IA	219 (22.0)	129 (25.8)	90 (18.2)	
Stage IB	283 (28.5)	134 (26.8)	149 (30.2)	
Stage I (no substage)	8 (0.8)	5 (1.0)	3 (0.6)	
Stage II	277 (27.9)	119 (23.8)	158 (32.0)	
Stage III	160 (16.1)	80 (16.0)	80 (16.2)	
Stage IV	32 (3.2)	25 (5.0)	7 (1.4)	
N/A	15 (1.5)	8 (1.6)	7 (1.4)	
CEACAM5 (FPKM), mean				
Overall	143.3	239.3	46.2	<0.001
Male	109.2	218.3	40.6	<0.001
Female	194.5	257.3	62.2	<0.001

*, P values for Chi-squared test for sex, race (white *vs.* other), stage (stage I *vs.* other), and P values for unpaired t-test of equal variance for continuous variable of age and CEACAM5 expression between TCGA LUAD and LUSC. TCGA, The Cancer Genome Atlas; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; N/A, not applicable; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; FPKM, fragments per kilobase of transcript per million.

slight positive correlation of 0.14 with *KRAS* expression and slight negative correlation with *EGFR* (–0.11) and *MET* (–0.15), but overall no significant relationships were observed (*Figure 3*).

Discussion

This is the first study to report sex-based differences in CEACAM5 expression and a correlation with survival in female patients with LUAD. CEACAM5 expression may play a different role among NSCLC tumors in male and female patients and thus may be underrecognized as an important biomarker in NSCLC. Here, in a large public dataset, we observe significant differences in CEACAM5 expression by sex and histologic subtype of NSCLC with higher expression seen in female patients with LUAD. Higher expression of CEACAM5 in this group was associated with significantly worse survival among stage I female LUAD patients.

Sex-based differences in lung cancer are increasingly recognized, as is demonstrated by the higher incidence of LUAD among young, never smoking females (23,24).

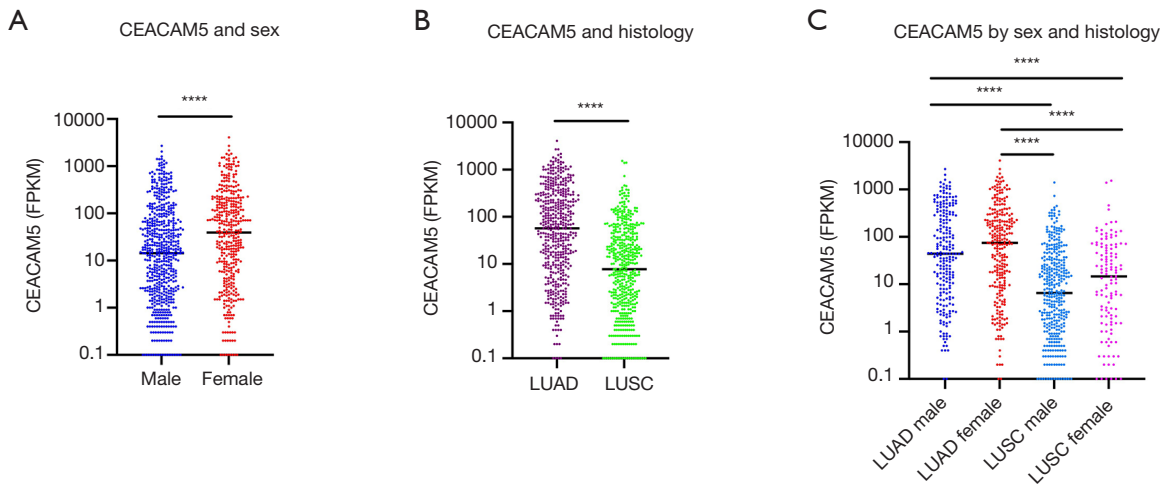

Figure 1 CEACAM5 expression. CEACAM5 expression in NSCLC stratified by sex (A), histologic subtype (B) and combined sex and histology (C). CEACAM5 expression in NSCLC from female patients is significantly higher than male patients (P<0.0001) and significantly higher in LUAD types than LUSC (P<0.0001). ****, P<0.0001. CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; FPKM, fragments per kilobase of transcript per million; NSCLC, non-small cell lung cancer.

The lung tumors that develop in never smokers have distinct clinical, histologic, and molecular features and are associated with lower mortality than smoking-related lung cancer (25,26). The higher CEACAM5 expression in female patients with adenocarcinoma that we observed likely reflects the underlying differences in tumor biology and subtype that affect this demographic.

Higher levels of CEACAM5 expression correlated with worse outcomes among female patients with LUAD. It is unclear if estrogen exposure provides a mechanism to explain this observation. Previous studies of the role of estrogen in lung cancer incidence, progression, and mortality have shown no clear relationship of estrogen on lung cancer progression (27,28). Use of hormone replacement therapy does not increase risk of developing lung cancer, but is associated with increased mortality among women with NSCLC (29,30). Females with lung cancer have better OS rates than men, even when controlling for age, stage, smoking history, therapies, and mutation status (31). There are likely different biologic subtypes of lung tumors that are more common among female patients that explain both the differences in CEACAM5 expression and survival.

Our data demonstrating worse survival with elevated CEACAM5 is concordant with several small studies which have shown elevated serum CEA levels to be a poor prognostic factor in EGFR mutated LUAD and in NSCLC overall (32,33). In the TCGA data, CEACAM5 expression was not correlated with EGFR expression, or expression of other common lung cancer driver mutations. Prior research evaluating the role of CEACAM5 may underestimate its impact on outcomes as potential sex-based differences remain unexplored.

The major limitation of this study is the use of a single large gene expression data set to demonstrate these findings without external validation. TCGA is the largest publicly available data set with well-annotated RNA-Seq data linked to demographic information and survival outcomes. These observations require additional validation in other large data sets.

This is the first study to describe the correlation of sex with CEACAM5 expression in NSCLC and CEACAM5 as a poor prognostic biomarker among female patients with LUAD. These findings suggest that when evaluating the potential role of CEACAM5 in lung cancer, patient sex should be considered as an important variable as CEACAM5 likely has a different role and potential as a biomarker in female patients than in male patients.

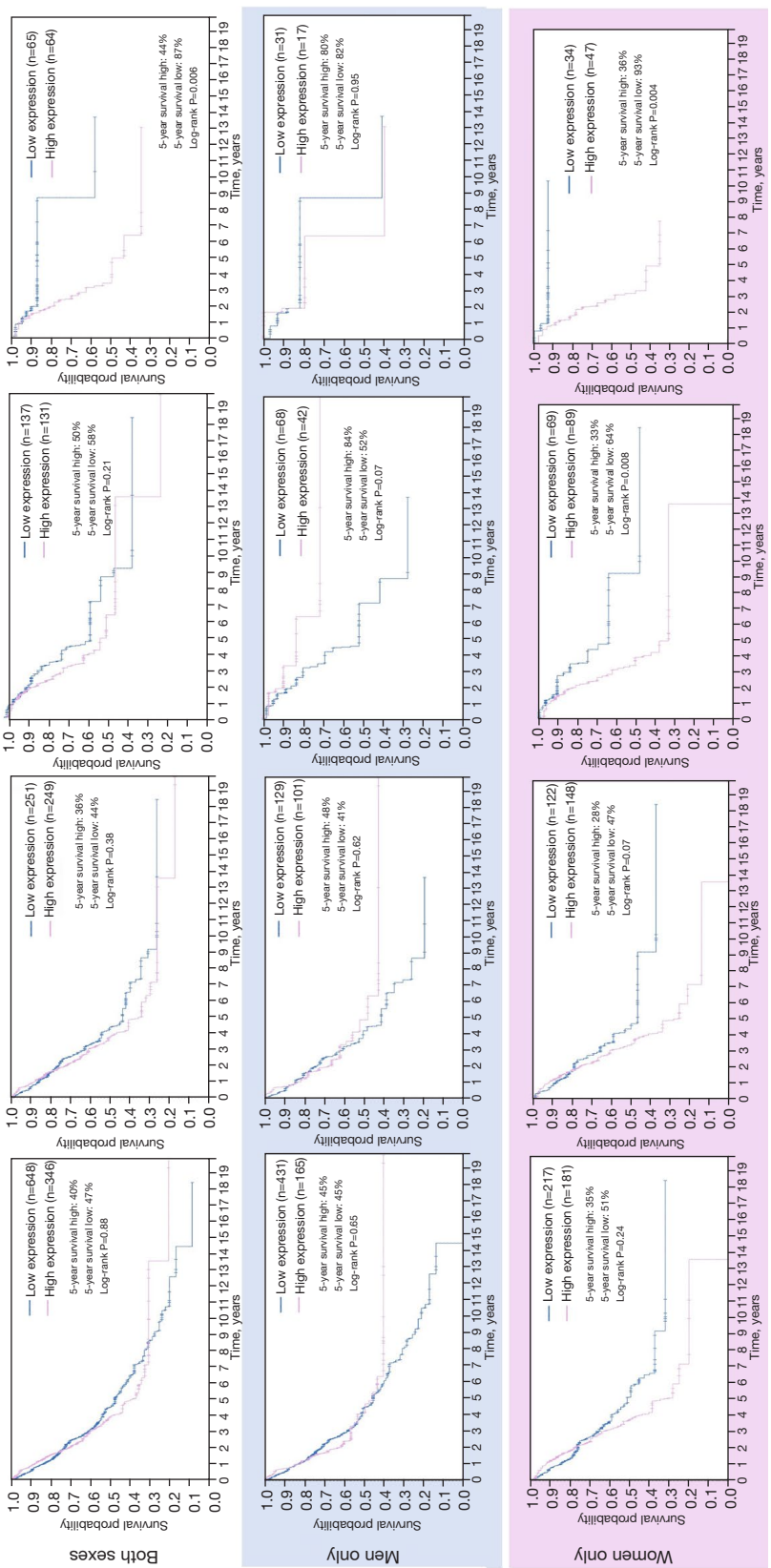

Figure 2 CEACAM5 and survival. High CEACAM5 expression (>57 FPKM) is not associated with survival in NSCLC patients overall. However, in women with adenocarcinoma, high CEACAM5 is a marker of poor prognosis and is significantly associated with worse survival outcomes in stage I (log-rank P=0.008) and stage IA (log-rank P=0.004) lung adenocarcinoma. NSCLC, non-small cell lung cancer; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; FPKM, fragments per kilobase of transcript per million.

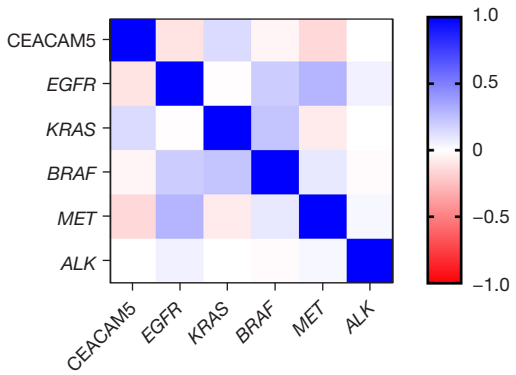

Figure 3 CEACAM5 correlation with lung cancer driver mutations. CEACAM5 expression was correlated with gene expression for common lung cancer driver mutations among lung adenocarcinoma tumors in TCGA. *EGFR*, *KRAS*, *BRAF*, *MET*, and *ALK* expression are shown with positively correlated genes (blue) and negatively correlated genes (red) without any significant expression correlations. CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; *EGFR*, epidermal growth factor receptor; *KRAS*, Kirsten rat sarcoma virus oncogene; *BRAF*, v-raf murine sarcoma viral oncogene homolog; *MET*, MET proto-oncogene; *ALK*, anaplastic lymphoma kinase; TCGA, The Cancer Genome Atlas.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-983/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-983/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-983/coif). Unrelated to this work, G.A.W. reports participation in advisory boards for AstraZeneca. S.D. reports being a consultant to AstraZeneca. Unrelated to this work, L.C. has been a consultant/board member for NextCure, Junshi, Zai Lab, Tcelltech, Vcanbio, DynamiCure, OncoC4, Normunity and GenomiCare; is a founder of NextCure, Tcelltech, Normunity, and Tayu; and has sponsored research agreements with NextCure, Normunity, and DynamiCure. 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).

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