BRIEF REPORT

Brief Report: Comprehensive Clinicogenomic Profiling of Small Cell Transformation From *EGFR*-Mutant NSCLC Informs Potential Therapeutic Targets

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ABSTRACT

Introduction: NSCLC transformation to SCLC has been best characterized with *EGFR*-mutant NSCLC, with emerging case reports seen in *ALK*, *RET*, and *KRAS*-altered NSCLC. Previous reports revealed transformed SCLC from *EGFR*-mutant NSCLC portends very poor prognosis and lack effective treatment. Genomic analyses revealed *TP53* and *RB1* loss of function increase the risk of SCLC transformation. Little has been reported on the detailed clinicogenomic characteristics and potential therapeutic targets for this patient population.

Methods: In this study, we conducted a single-center retrospective analysis of clinical and genomic characteristics of patients with *EGFR*-mutant NSCLC transformed to SCLC. Demographic data, treatment course, and clinical molecular testing reports were extracted from electronic medical records. Kaplan-Meier analyses were used to estimate survival outcomes. Next generation sequencing-based assays was used to identify *EGFR* and co-occurring genetic alterations in tissue or plasma before and after SCLC transformation. Single-cell RNA sequencing (scRNA-seq) was performed on a patient-derived-xenograft model generated from a patient with EGFR-NSCLC transformed SCLC tumor.

Results: A total of 34 patients were identified in our study. Median age at initial diagnosis was 58, and median time to SCLC transformation was 24.2 months. 68% were female and 82% were never smokers. 79% of patients were diagnosed as stage IV disease, and over half had brain metastases at baseline. Median overall survival of the entire cohort was 38.3 months from initial diagnoses and 12.4 months from time of SCLC transformation. Most patients harbored *EGFR* exon19 deletions as opposed to exon21 L858R alteration. Continuing EGFR tyrosine kinase inhibitor post-transformation did not improve overall survival compared with those patients where tyrosine kinase inhibitor was stopped in our cohort. In the 20 paired pre-transformed and post-transformed patient samples, statistically significant enrichment was seen with *PIK3CA* alterations ($p = 0.04$) post-transformation. Profiling of longitudinal liquid biopsy samples suggest emergence of SCLC genetic alterations before biopsy-proven SCLC, as shown by increasing variant allele frequency of *TP53, RB1, PIK3CA* alterations. ScRNA-seq revealed potential therapeutic targets including DLL3, CD276 (B7-H3) and PTK7 were widely expressed in transformed SCLC.

Conclusions: SCLC transformation is a potential treatment resistance mechanism in driver-mutant NSCLC. In our cohort of 34 *EGFR*-mutant NSCLC, poor prognosis was observed after SCLC transformation. Clinicogenomic analyses of paired and longitudinal samples identified genomic alterations emerging post-transformation and scRNA-seq reveal potential therapeutic targets in this population. Further studies are needed to rigorously validate biomarkers and therapeutic targets for this patient population.

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Keywords: Histologic transformation; SCLC; NSCLC; Resistance mechanism; Osimertinib; Cell surface target

Introduction

NSCLC can undergo histologic transformation to SCLC. This phenomenon is best characterized in *EGFR*-mutant NSCLC,[1–3] but has been increasingly observed in NSCLC with other driver mutations such as *ALK*, *RET*, and *KRAS*.[4–6] *EGFR*-mutant NSCLC accounts for 10% to 15% of NSCLC in Western populations, and up to 50% in Asian populations.[7] It has been reported that 3-14% patients with *EGFR*-mutant NSCLC undergo histologic transformation to SCLC as a resistance mechanism to EGFR inhibition; and the presence of *TP53* and *RB1* mutations at initial diagnosis increase the risk of this transformation.[1–3,8] It is therefore imperative to better understand features of *EGFR*-mutant NSCLC to SCLC transformation and identify therapeutic vulnerabilities, to develop effective therapeutics for this highly aggressive and plastic disease.

In this study, we report a single-center retrospective analysis of clinical and genomic characteristics of 34 patients with *EGFR*-mutant NSCLC transformed to SCLC. We also provide perspectives on future investigation and potential therapeutic avenues in transformed SCLC.

Materials and Methods

Patient Population

We reviewed the Genomic Marker-Guided Therapy Initiative database of patients with lung cancer treated at The University of Texas, MD Anderson Cancer Center from March 2014 to June 2023 to identify patients who have *EGFR*-mutant NSCLC with histologic transformation

to SCLC. Additional demographic data, detailed treatment course, and clinical molecular testing reports were extracted and reviewed from electronic medical records. This study was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. The project was performed under The University of Texas, MD Anderson Cancer Center Institutional Review Board approved protocol PA13-0589, PA14-0276 and PA16-0661 with informed consents.

Clinical Molecular Profiling

Molecular testing reports were obtained through electronic medical record as part of standard of care. Next-generation sequencing (NGS) was used to evaluate *EGFR* alterations and co-occurring alterations in tissue or plasma before and after SCLC transformation. The NGS platforms varied depending on the year and type of tests, which included the Clinical Laboratory Improvement Amendments-certified MD Anderson in-house tumor 50 gene (2018-before) or 146 gene panel (2018-current), MD Anderson in-house liquid biopsy test (MDA LB-70 gene panel), and commercial tests (FoundationOne CDx and Guardant360).

Single-Cell RNA Sequencing Analyses

Single-cell RNA sequencing (scRNA-seq) was performed at the MD Anderson core facility. Detailed scRNA-seq methods were described previously.[9] Briefly, transformed SCLC tumors were harvested from patient-derived xenograft (PDX) model generated from MDA-TS14 under institutional review board protocol PA14-0276, processed and sorted to select only live, human cells for downstream single-cell transcriptomic analyses. Fastq reads were processed using the Cell Ranger v3.1.0 (10X Genomics) pipeline to obtain the unique molecular identifier data matrix. Cells with less than 300 detectable genes were filtered out. Samples sequenced in different batches were normalized and integrated after the sample integration pipeline in SEURAT v3. SEURAT (https://github.com/satijalab/seurat) was used to select relevant principal components for dimensionality reduction, uniform manifold approximation and projection conversion, data visualization, and density-based clustering for subpopulation discovery. Cell subpopulations were identified and annotated using SingleR package (https://github.com/dviraran/SingleR) with additional manual curation. Gene expression levels were visualized in uniform manifold approximation and projection space using SEURAT.

Statistical Analyses

Descriptive statistics were used to analyze the clinical data. Kaplan-meier curves were used to estimate survival outcomes and generated using R (https://www.r-project.org/). McNemar tests were used to analyze statistical significance of genomic alterations in paired pre- and post- SCLC transformation samples.

Table 1. Patient Baseline Characteristics

Patient Characteristics	N = 34
Age	
Median (range)	58 (32-77)
Sex	
Female	23 (67.6%)
Male	11 (33.4%)
Smoking status	
Never smoker	28 (82.4%)
Previous smoker	6 (17.6%)
Initial stage	
I-III	7 (20.6%)
IV	27 (79.4%)
Brain metastases	14 (51.9%)
EGFR mutation	
Exon 19 del	26 (76%)
Exon 21 L858R: 5	5 (14.7%)
Atypical	3 (8.8%)
Time to transformation (month)	
Median (range)	24.2 (3.5-194.8)
Transformed SCLC stage	
Limited stage - SCLC	7 (20.6%)
Extensive stage - SCLC	27 (79.4%)
Tx prior to SCLC transformation	
Median no. of lines (range)	2 (1-4)
TKI	34 (100%)
Chemo	13 (38.2%)
IO	8 (23.5%)
Tx after SCLC transformation	
Median no. of lines (range)	2 (1-5)
TKI	25 (73.5%)
Chemo	34 (100%)
IO	19 (56%)

Results

Patient Characteristics and Clinical Outcome

At the data cutoff on June 30, 2023, 34 patients were identified in LUNG Genomic Marker-Guided Therapy Initiative database that had initial *EGFR*-mutant NSCLC that subsequently transformed to SCLC, with patient characteristics summarized in Table 1. The median age at initial diagnosis was 58 (range: 32–77), with 68% female and 82% never smokers, reflecting the demographic characteristics of *EGFR*-mutant NSCLC.[7] At diagnosis, 79% (27 of 34) of patients had stage IV disease, and over half of them (14 of 27) had brain metastases. Median time to transformation was 24.2 months. All patients received EGFR-targeting tyrosine kinase inhibitor (TKI) with median two lines of treatment before SCLC transformation, and 26.5% (nine of 34) patients received three or four lines. Post transformation, 100% of patients received

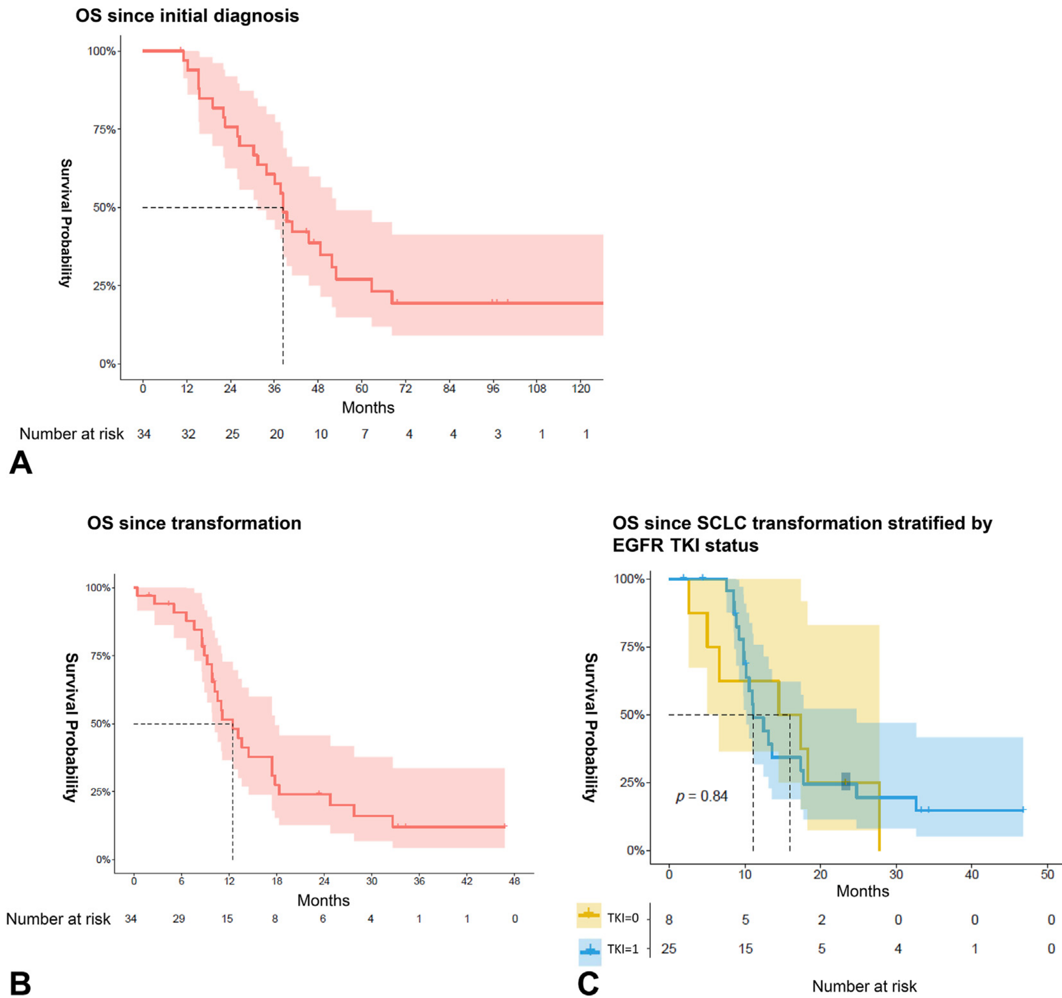


Figure 1. Kaplan-Meier survival curves. (*A*) OS since initial diagnosis; (*B*) OS since SCLC transformation; (*C*) OS since SCLC stratified by whether EGFR TKI was continued after SCLC transformation. OS, overall survival; TKI, tyrosine kinase inhibitor; TKI=0: TKI stopped after transformation; TKI=1: TKI continued after transformation.

chemotherapy, while EGFR TKI (majority received osimertinib) was continued in 76% (25 of 33, one patient with unknown status) with median two lines of treatment (Table 1). 56% (19 of 34) received immunotherapy (anti–programmed cell death protein-1 and anti–CTLA4, or anti–programmed death-ligand 1) as part of their treatment regimen post SCLC transformation. Detailed individual treatment course and TKI exposure pre- and post-transformation are summarized in Supplementary Table 1. Median overall survival of the entire cohort was 38.3 months from initial diagnoses and 12.4 months from time of transformation (Fig. 1*A* and *B*). Intriguingly, when survival curves were stratified by whether EGFR TKI was continued or not after transformation, we found no statistically relevant difference in OS after transformation. Median OS after transformation was 11.1 months in TKI-continued group (TKI = 1) and 15.9 months in TKI-discontinued (TKI = 0) group, $p = 0.95$ (Fig. 1*C*).

Clinical Molecular Characteristics Pre- and Post-SCLC Transformation

Genomic alterations were extracted from NGS-based clinical molecular panel testing on patients' tumor or liquid biopsies. 76% (26) of *EGFR* mutations in this cohort was exon19 deletions (Table 1). A total of 31 of the 34 patients had broad NGS testing either before or after SCLC transformation, among those 20 patients had paired pre- and post-tumor or liquid profiling. Common co-occurring alterations in the tumors before transformation include *TP53* (88.5%), *RB1* (34.6%), *PIK3CA* (23.1%), *CCNE1* (15.4%), *MET* (11.5%), *BRAF* (7.7%), and *MYC* (7.7%) (Fig. 2). When compared with published large datasets of *EGFR*-mutant NSCLC and *de novo* SCLC, numerically higher frequencies of *PIK3CA*, *CCNE1*, *MET*, *BRAF*, *MYC*, and several other gene alterations were observed (Supplementary Table 2). In the paired samples, statistically significant enrichment was seen with

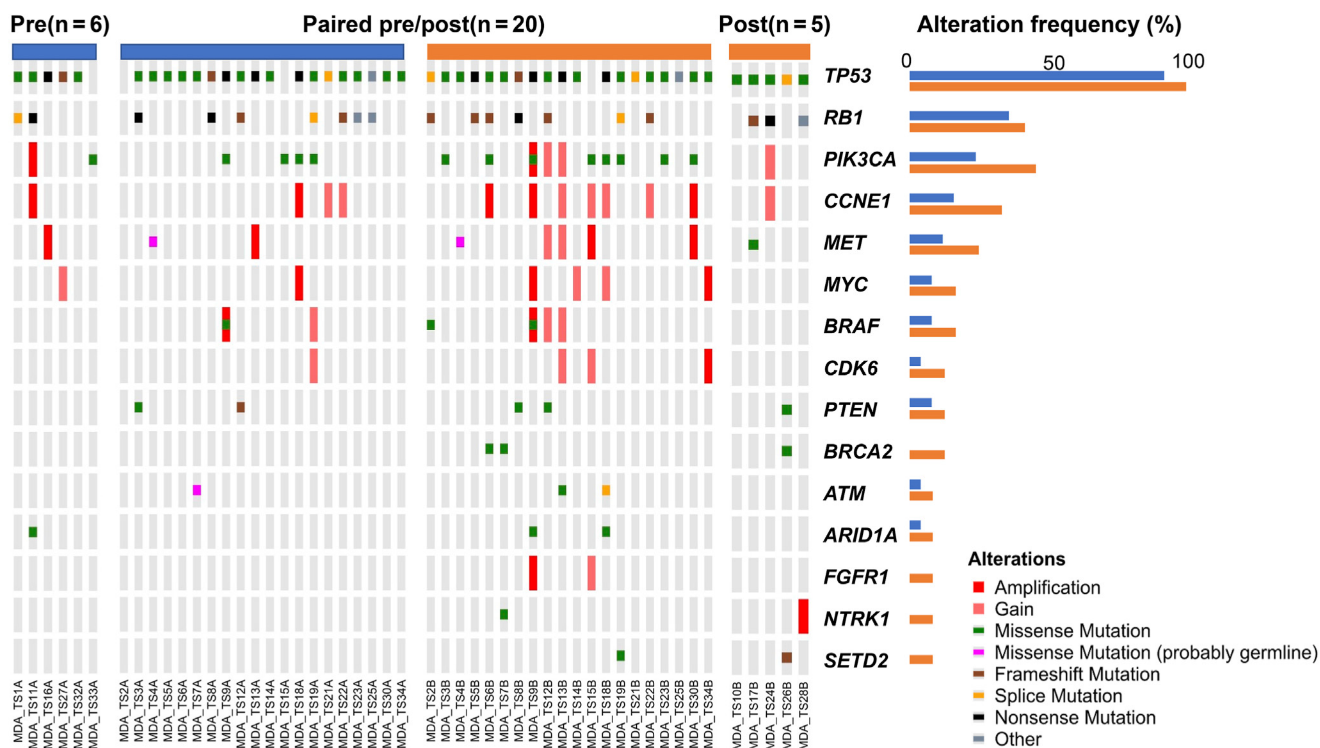


Figure 2. Genomic characteristics of patients in this cohort. (*A*) OncoPrint of 15 most frequently altered genes in this patient cohort. 20 patients had paired pre- and post- SCLC transformation samples. (*B*) Longitudinal liquid biopsies correlated with clinical status of patients. Upper panel: Liquid biopsy results for four patients before- and at the time of SCLC transformation (denoted with a red star). Lower panel. Case details of patient MDA-TS18, including treatment and corresponding radiographic and pathologic characteristics. Time on therapy is not drawn to scale.

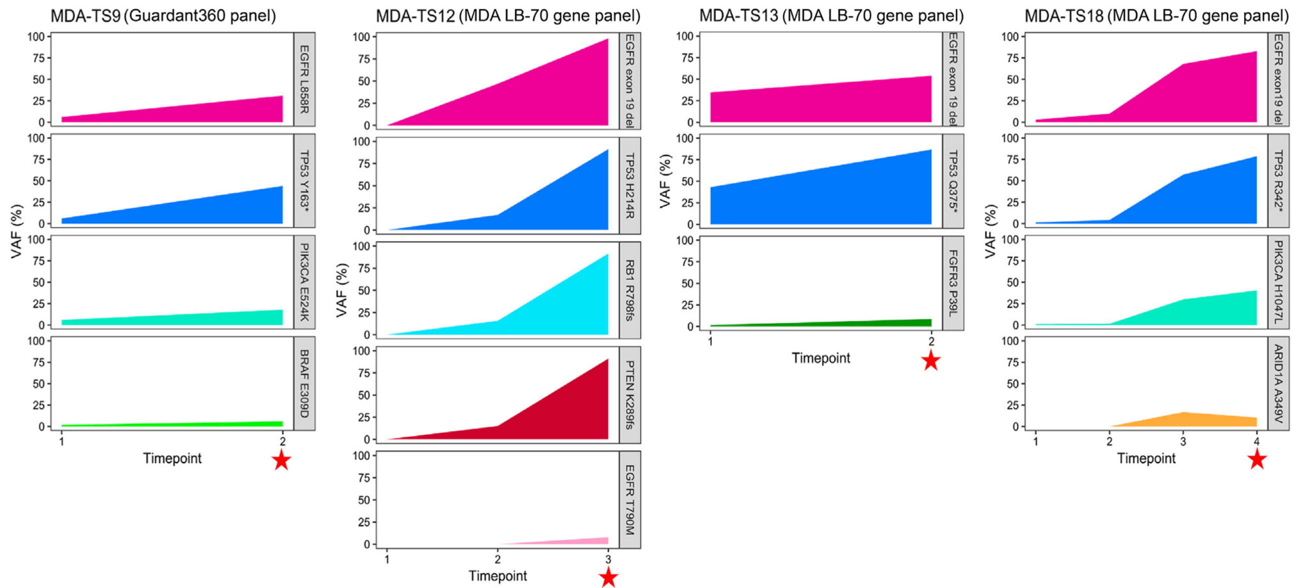
PIK3CA alterations post-transformation ($p = 0.04$, McNemar test), while several other alterations are numerically higher but not statistically significant (*BRAF* [7.7%-pre, versus 16.0%-post], *CDK6* [3.8% versus 12.0%], *PTEN* [7.7% versus 12.0%], and *BRCA2* [0% versus12.0%]). (Fig. 2*A*). Detailed genomic profiling of patients in this cohort pre- and post-SCLC transformation is reported in Supplementary Table 3.

Longitudinal Circulating Tumor DNA Analyses Reveal Genomic Level Changes Preceding Biopsy-Confirmed SCLC

Four patients in our cohort had several longitudinal liquid biopsy samples (MDA-TS9, MDA-TS12, MDA-TS13, and MDA-TS18) with variant allele frequency (VAF) of frequently altered genes plotted (VAF $>5\%$) (Fig. 2*B*). For each patient, the same type of panel testing was used to compare longitudinal samples, and the last time point (time point 4) represented the transformed-SCLC time point (denoted with a red star). One patient (MDA-TS18) had four serial liquid biopsies taken at various times of progression, with the last one taken a month before the biopsy-proven SCLC transformation. Detailed clinical time course and representative radiographic and pathologic images were described in Figure 2*B*. At progression (time point 2 and 3), tumor burden did not change drastically, as noted by mild increase in lung nodule and abdominal lymphadenopathy (time point 2) and a pathologic rib fracture (time point 3). However, molecular profiling of liquid biopsies revealed a relevant increase in VAF of *TP53* and *PIK3CA* mutations and *EGFR* exon 19 deletion at time point 3. Gains in *CCNE1*, *EGFR* and *MYC* also emerged during time point 3 and 4 (data not shown). This data suggests underlying cell state changes and an emerging SCLC-transformed tumor cell population as opposed to increased VAF merely a reflection of overall disease burden.

scRNA-Seq Analyses Reveal Subtype and Therapeutic Target in Transformed SCLC

A PDX model was generated from transformed-SCLC from patient MDA-TS14. The patient had stage IV *EGFR* exon19 deletion - NSCLC and progressed after 10 months of osimertinib treatment with a liver biopsy that



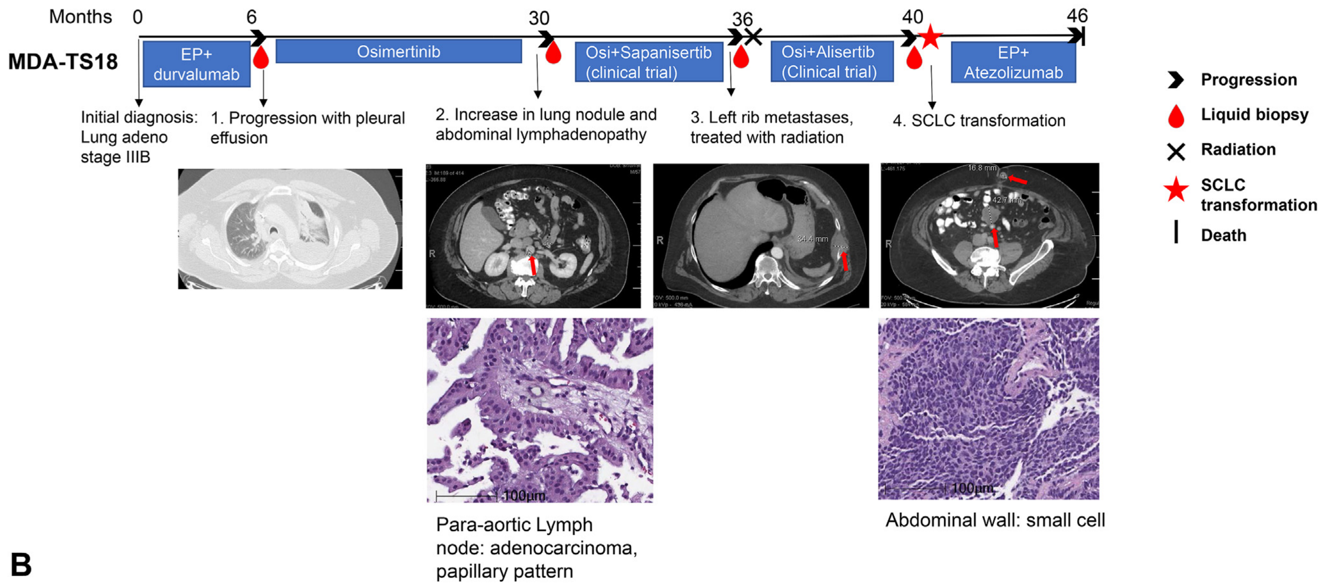


Figure 2. Continued.

confirmed SCLC. Single-cell RNA sequencing of the PDX tumor revealed 80% cells express ASCL1, the defining transcriptional factor for the ASCL1 subtype of SCLC.[9] SCLC surface target DLL3, a Notch inhibitory ligand and downstream target of ASCL1, was expressed in over 40% of cells. Other SCLC/NSCLC surface targets such as PTK7 and CD276 (B7-H3) were also abundantly expressed (Supplementary Fig.1).

Discussion

Consistent with previously published case series,[1,10] our cohort of 34 patients with EGFR-mutant NSCLC to SCLC transformation revealed poor prognosis, with OS after transformation (∼1 y) identical to *de novo* extensive-stage SCLC patients.[11] Previous case series have revealed that SCLC transformation portends a poor prognosis and transformed tumors do not respond to immunotherapy (0 responses out of 17 patients treated with immunotherapy in this reported case series),[10] which is perhaps not surprising given the aggressive and generally "immune-cold" phenotype of SCLC. In addition, we found that continuing TKI post-transformation did not significantly improve overall survival in this cohort.

Clinical molecular panel tests revealed that most patients with SCLC transformation had *EGFR* exon 19 deletions, in keeping with prior observations.[10,12]

However, little is known about the mechanistic underpinning of this predominance, as co-mutation rates with *TP53* are roughly the same with *EGFR* exon 19 deletion and L858R.[13] As expected, *TP53* and *RB1* mutations were most prevalent in pre-SCLC-transformed tumors. Here the rate RB1 loss was lower than previously reported, which may be owing to decreased detection sensitivity of NGS testing for RB1 loss (owing to its large protein size).[3] Analyzing paired samples pre- and post-SCLC transformation, we observed statistically relevant enrichment of *PIK3CA* gene alteration, and numerically increased frequency of several other alterations in RTK pathways (*MET*, *BRAF*, *PTEN*) and cyclin (*CCNE1*, *CDK6*) pathways, compared with those in either EGFR-NSCLC or de novo SCLC.

Tissue biopsy remains definitive standard to detect SCLC transformation as a potential treatment resistance mechanism in *EGFR*-mutant NSCLC and other driver-mutant NSCLC (e.g., ALK, RET, and KRAS alterations), however liquid biopsy may offer complimentary and earlier insights on emerging SCLC transformation before tissue biopsy can be obtained, as revealed with relevant uprising TP53, RB1 or PIK3CA VAF out-of-proportion to tumor growth in our longitudinal samples. An important limitation of the genomic analyses in this study is the heterogeneity of NGS platforms used in the study population, as the platforms evolved over the years and had expanding genes included in later years of the data set.

Many important questions remain. Because of the retrospective nature and limited patient numbers, our TKI data post-transformation is hypothesize-generating, as one may hypothesize that although post-transformed tumors are mixed adenocarcinoma and SCLC, the remaining adenocarcinoma may have also lost EGFR dependency and no longer respond to EGFR TKI.

The utility of continuing EGFR TKI after SCLC transformation is a matter of debate given case report suggesting efficacy of osimertinib in this setting,[14] more definitive study is needed to answer this question. In addition, it is currently unknown why more patients with *EGFR* exon19 deletion were seen in the SCLC-transformed cohort. Lastly, SCLC transformation is not restricted to *EGFR*-mutant NSCLC and likely represents a larger pathway-indifference resistance mechanism in a permissive genetic background under the selective treatment pressure.[15] There is no established effective treatment for transformed SCLC and immunotherapy did not seem to add benefit particularly in this population.[10] Our data suggests one potential strategy is to target the cell surface of transformed SCLC such as DLL3, B7-H3 and PTK7, all of which are promising lung cancer cell surface targets with therapeutics in clinical trials (e.g., NCT03319940, NCT05280470, NCT04189614). Including patients with transformed SCLC in relevant clinical trials would be essential to develop better treatment options for these patients.

CRediT Authorship Contribution Statement

Bingnan Zhang: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Validation, Visualization, Roles/Writing - original draft, Writing - review & editing.

Whitney Lewis: Conceptualization, Data curation, Investigation.

C. Allison Stewart: Conceptualization, Data curation, Methodology, Resources, Writing - review & editing.

Benjamin B. Morris: Formal analysis, Visualization, Writing - review & editing.

Luisa Solis Soto: Conceptualization, Data curation, Visualization.

Alejandra Serrano: Conceptualization, Data curation, Visualization.

Yuanxin Xi: Formal analysis, Visualization.

Qi Wang: Formal analysis, Visualization.

Elyse R. Lopez: Data curation, Investigation.

Kyle Concannon: Data curation, Investigation.

Simon Heeke: Visualization, Writing - review & editing.

Ximing Tang: Data curation, Investigation.

Gabriela Raso: Data curation, Investigation.

Robert J. Cardnell: Project administration, Resources.

Natalie Vokes: Project administration, Resources.

George Blumenschein: Project administration, Resources.

Yasir Elamin: Investigation, Resources.

Frank Fosella: Investigation, Resources.

Anne Tsao: Investigation, Resources.

Ferdinandos Skoulidis: Investigation, Resources.

Celyne Bueno Hume: Investigation, Resources.

Koji Sasaki: Investigation, Resources.

Jeff Lewis: Project administration, Resources, Software.

Waree Rinsurongkawong: Project administration, Resources, Software.

Vadeerat Rinsurongkawong: Project administration, Resources, Software.

Jack Lee: Project administration, Resources, Software.

Hai Tran: Project administration, Resources, Software.

Jianjun Zhang: Project administration, Resources, Software.

Don Gibbons: Project administration, Resources, Software.

Ara Vaporciyan: Project administration, Resources, Software.

Jing Wang: Methodology, Supervision.

Keunchil Park: Investigation, Resources.

John V. Heymach: Conceptualization, Funding acquisition, Investigation, Resources, Supervision.

Lauren A. Byers: Conceptualization, Funding acquisition, Investigation, Resources, Supervision, Writing - review & editing.

Carl M. Gay: Conceptualization, Funding acquisition, Investigation, Resources, Supervision, Writing - review & editing.

Xiuning Le: Conceptualization, Funding acquisition, Investigation, Resources, Supervision, Writing - review & editing.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2023.100623.

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