rapid communication

EGFR-Mutant Adenocarcinomas That Transform to Small-Cell Lung Cancer and Other Neuroendocrine Carcinomas: Clinical Outcomes

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abstract

PURPOSE Approximately 3% to 10% of *EGFR* (epidermal growth factor receptor) -mutant non–small cell lung cancers (NSCLCs) undergo transformation to small-cell lung cancer (SCLC), but their clinical course is poorly characterized.

METHODS We retrospectively identified patients with *EGFR*-mutant SCLC and other high-grade neuroendocrine carcinomas seen at our eight institutions. Demographics, disease features, and outcomes were analyzed.

RESULTS We included 67 patients—38 women and 29 men; *EGFR* mutations included exon 19 deletion (69%), L858R (25%), and other (6%). At the initial lung cancer diagnosis, 58 patients had NSCLC and nine had de novo SCLC or mixed histology. All but these nine patients received one or more EGFR tyrosine kinase inhibitor before SCLC transformation. Median time to transformation was 17.8 months (95% CI, 14.3 to 26.2 months). After transformation, both platinum-etoposide and taxanes yielded high response rates, but none of 17 patients who received immunotherapy experienced a response. Median overall survival since diagnosis was 31.5 months (95% CI, 24.8 to 41.3 months), whereas median survival since the time of SCLC transformation was 10.9 months (95% CI, 8.0 to 13.7 months). Fifty-nine patients had tissue genotyping at first evidence of SCLC. All maintained their founder *EGFR* mutation, and 15 of 19 with prior *EGFR* T790M positivity were T790 wild-type at transformation. Other recurrent mutations included *TP53*, *Rb1*, and *PIK3CA*. Re-emergence of NSCLC clones was identified in some cases. CNS metastases were frequent after transformation.

CONCLUSION There is a growing appreciation that *EGFR*-mutant NSCLCs can undergo SCLC transformation. We demonstrate that this occurs at an average of 17.8 months after diagnosis and cases are often characterized by *Rb1*, *TP53*, and *PIK3CA* mutations. Responses to platinum-etoposide and taxanes are frequent, but checkpoint inhibitors yielded no responses. Additional investigation is needed to better elucidate optimal strategies for this group.

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ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Performing repeat biopsies to study molecular mechanisms of acquired resistance to tyrosine kinase inhibitors (TKIs) in *EGFR* (epidermal growth factor receptor) -mutant non–small cell lung cancer (NSCLC) has been one of the cornerstones of developing next-generation treatment strategies, including the T790M-inhibitor osimertinib and combinations of EGFR and MET inhibitors.[1,2] Repeat biopsy cohorts have also elucidated that approximately 3% to 10% of acquired resistance to EGFR TKIs is associated with histologic transformation to small-cell lung cancer (SCLC).[3,4] Even more rarely, activating *EGFR* mutation can be identified among de novo SCLCs.[5]

Significant progress has been made in the past few years toward understanding the genetic mechanisms associated with such histologic transformation. For example, Niederst et al[6] demonstrated that whereas the founder *EGFR* mutation is still uniformly found at the DNA level in transformed cancers, expression of the EGFR protein is significantly diminished, thus rendering the transformed tumors unresponsive to EGFR TKIs. Work by Lee et al[7] suggests that the SCLC clone branches off from the founder clone early—in some cases even before initial clinical cancer diagnosis—and that cancers prone to transformation may show inactivation of both TP53 and Rb1 at initial NSCLC diagnosis.

Despite these advances, little is known about the clinical course of patients with *EGFR*-mutant cancer after SCLC transformation, which leads to uncertainty about appropriate treatments and prognostic implications for clinicians. Here, we describe clinical outcomes from a large retrospective cohort of patients with *EGFR*-mutant SCLC transformed cancers.

METHODS

We performed a retrospective chart review of patients with a history of *EGFR*-mutant SCLC or high-grade neuroendocrine carcinoma—henceforth collectively termed SCLC—who were seen at eight North American cancer centers. Institutional review board approval was obtained independently at each center.

Data that were collected included demographic information, tumor histology and molecular pathology, and clinical treatments and outcomes. Genotyping was performed with a variety of assays, including allele-specific polymerase chain reactions, next-generation sequencing (NGS), and whole-exome sequencing. For some cases with tissue available, older (narrower) genotyping results were expanded and updated using more modern assays for this project. Response and progression assessments were estimated to the best of the investigator's judgment using radiology reports and, when unavailable, physician's notes; formal Response Evaluation Criteria in Solid Tumors (RECIST) measurements or confirmation of response were not obtained. Nevertheless, the general principles that support the RECIST classification, including the magnitude of lesion size variation that defines response and progression, were used to guide the investigators.[8] In addition, as this cohort was analyzed retrospectively, there was no defined or standard time interval for obtaining response assessments.

Descriptive statistics were developed and time-to-event outcomes were analyzed using the Kaplan-Meier method.

RESULTS

Baseline Characteristics

A total of 67 patients with a history of *EGFR*-mutant SCLC who were treated between 2006 and 2018 were identified at eight cancer centers. The cohort included 38 women and 29 men with a median age at diagnosis of 56 years, a racial makeup of 49% white and 42% Asian, with 73% never smokers (Table 1). Fifty-eight patients (87%) had NSCLC histology at the time of the initial lung cancer diagnosis, predominantly adenocarcinoma, whereas nine patients (13%) had de novo SCLC or a mixed histology, including SCLC at diagnosis. All patients had *EGFR* mutations, including 46 (69%) with exon 19 deletion mutations and 17 (25%) with L858R. Genotyping platforms used historically at the time of diagnosis for this cohort rarely included the assessment of tumor suppressor genes associated with high-grade neuroendocrine cancers, such as *TP53* and *Rb1*, but the prevalence of mutations in these genes was high among the small subset of patients who were tested using NGS (*TP53*, 100% [n = 7]; *Rb1*, 50% [n = 4]; Appendix Table A1, online only).

Pretransformation Course

The 58 patients with NSCLC at diagnosis received a median of two lines of systemic therapy before SCLC transformation (range, one to six lines), including at least one EGFR TKI in all cases (Table 2). Of note, osimertinib was used as first-line therapy in only one patient. Seventeen patients (29%) acquired an *EGFR* T790M mutation and 23 (40%) received more than one EGFR TKI before transformation. Median total time on EGFR TKIs before transformation was 15.8 months (range, 1.3 to 53.4 months), and median time since diagnosis of advanced NSCLC to SCLC transformation was 17.8 months (95% CI, 14.3 to 26.2 months; Fig 1A). Nearly all patients (n = 53 [93%]) were receiving an EGFR TKI at the time of transformation.

SCLC Characteristics

At the time of transformation—for the 58 patients who started with NSCLC—or diagnosis—for the nine de novo SCLC cases—histology was reported as classic SCLC in 97% of cases and as large-cell neuroendocrine carcinoma in the remaining two cases. Additional pathology findings at the time of transformation are summarized in Appendix Table A2 (online only). The founder *EGFR* mutation was confirmed in all transformed cases that underwent genotyping (Appendix Table A3, online only). Only five SCLC transformed samples harbored an *EGFR* T790M mutation, including one patient who was known to have had de novo T790M since initial diagnosis, three with prior acquisition of T790M after TKI therapy, and one without any prior documentation of T790M. Mixed NSCLC-SCLC histology was noted in two SCLC cases with T790M. Conversely, at the time of transformation, T790M was not found in 15 (79%) of 19 patients with prior evidence of the mutation, including in one patient with de novo T790M at initial diagnosis.

The most common mutations identified in SCLC samples were *TP53* (38 [79%] of 48 patients), *Rb1* (18 [58%] of 31 patients), and *PIK3CA* (14 [27%] of 52 patients). Frequency of *TP53* mutations increased dramatically when considering only samples genotyped by NGS (32 [91%] of 35 patients), which highlights the low sensitivity of allele-specific polymerase chain reaction assays in detecting non–hot spot mutations in this tumor suppressor (Table 3). No other genes were mutated in a significant portion of cases, with *BRCA1* (n = 3) being the next most frequently mutated gene in the cohort (Appendix Table A3). Of note, none of the three observed *BRCA1* point mutations—Ile1568Met, Ser1294Gly, and Glu686Lys—are thought to be associated with a cancer predisposition syndrome.

TABLE 1. Demographics of the Study Population

Demographic	Total (N = 67)	NSCLC at Diagnosis (n = 58)	SCLC* at Diagnosis (n = 9)
Age, median (range)	56 (27-87)	51 (27-82)	56 (29-87)
Sex, No. (%)			
Female	38 (57)	33 (57)	5 (56)
Male	29 (43)	25 (43)	4 (44)
Race, No. (%)			
White	33 (49)	29 (50)	4 (44)
Asian	28 (42)	23 (40)	5 (56)
Other or not available	6 (9)	6 (10)	0
Smoking history, No. (%)			
Never smoker	49 (73)	40 (69)	9 (100)
< 5 pack-year smoker	7 (10)	7 (12)	0
≥ 5 and < 15 pack-year smoker	4 (6)	4 (7)	0
≥ 15 pack-year smoker	7 (10)	7 (12)	0
Histology at diagnosis of advanced lung cancer, No. (%)			
Adenocarcinoma	57 (85)	57 (98)	—
SCLC	5 (7)	—	5 (55)
Mixed histology, including SCLC	4 (6)	—	4 (44)
NSCLC not otherwise specified	1 (1)	1 (2)	—
Founder *EGFR* mutation, No. (%)			
Exon 19 deletion	45 (67)	42 (72)	3 (33)
L858R	16 (24)	13 (22)	3 (33)
S768I	1 (1)	0	1 (11)
L861Q	1 (1)	1 (2)	0
Exon 19 deletion + L833V	1 (1)	1(2)	0
A767V + L858R	1 (1)	0	1 (11)
E709A + G719X	1 (1)	1 (2)	0
G719X + S768I	1 (1)	0	1 (11)
De novo T790M, No. (%)	2 (3)	2 (3)	0

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non–small-cell lung cancer; SCLC, small-cell lung cancer.
*SCLC or mixed histology at diagnosis

Post-Transformation Course

After SCLC transformation—or after diagnosis for patients with de novo SCLC—patients received a median of two lines of systemic treatment (range, zero to six lines; Table 2). As expected, platinum-etoposide was the most commonly used regimen (n = 53, including 10 patients who previously received a platinum doublet regimen). Among patients with enough retrospective data for investigators to estimate a response to treatment (n = 46), the clinical response rate to platinum-etoposide was 54%. A high clinical response rate to the combination (eight [80%] of 10 patients) was achieved even in the subset of patients who had previously received platinum chemotherapy for adenocarcinoma. Median estimated progression-free survival on platinum-etoposide was 3.4 months (95% CI, 2.4 to 5.4 months; Fig 1B).

No responses were observed among 17 patients who received a checkpoint inhibitor, either a single-agent programmed death-1 or programmed death-ligand 1 inhibitor (n = 9) or as part of the combination ipilimumab-nivolumab regimen (n = 8). Indeed, none of the 17 patients even seemed to derive clinical benefit from these therapies, as the longest time to progression was only 9 weeks.

Taxanes were administered to 21 patients, generally late in the course—median of two prior lines of therapy after SCLC transformation—and as single-agent therapy (14 of 21 patients received taxane monotherapy). Among 20 patients with sufficient data to estimate response, clinical response rate to taxane-containing regimens was 50%, including some marked responses (Fig 2). Median estimated progression-free survival on taxanes was 2.7 months (95% CI, 1.3 to 3.4 months; Fig 1C). Additional analysis by type of

TABLE 2. Treatments Received

Therapy Received	No. (%)
Received before transformation to SCLC	n = 58
EGFR TKI	58 (100)
Erlotinib	49 (84)
Afatinib	13 (22)
Third-generation EGFR TKI	19 (33)
Osimertinib	18 (31)
Investigational	5 (9)
Checkpoint inhibitor	4 (7)
Cytotoxic chemotherapy	21 (36)
Platinum-doublet regimens	20 (34)
Bevacizumab	9 (16)
Received after SCLC transformation (or after diagnosis for de novo SCLC)	n = 65*
Cytotoxic chemotherapy	63 (97)
Platinum-etoposide	53 (82)
Other platinum-combination	7 (11)
Taxane	21 (32)
Campthotecin (topotecan, irinotecan)	12 (18)
Temozolamide	4 (6)
EGFR TKI	34 (52)
Checkpoint inhibitor	17 (26)
PD-1 or PD-L1 monotherapy	9 (14)
Ipilumumab plus nivolumab	8 (12)

NOTE. Only treatments received by at least four patients are listed and patients are listed more than once if they received more than one regimen.

Abbreviations: EGFR, epidermal growth factor receptor; PD-1, programmed death receptor 1; PD-L1, programmed death ligand; SCLC, small-cell lung cancer; TKI, tyrosine kinase inhibitor.

*Treatment histories were unavailable for two of the 67 patients in the cohort.

taxane revealed that both paclitaxel and nab-paclitaxel each elicited five responses among seven treated patients (clinical response rate, 71%), whereas no responses were observed among six patients who were treated with docetaxel.

Although EGFR TKIs were administered in 52% of patients after SCLC transformation, they were frequently used in combination with cytotoxic chemotherapy per the treatment-beyond-progression strategy or as maintenance therapy after the conclusion of cytotoxic chemotherapy.[9,10] Their varied pattern of use limits interpretation of clinical benefit, but a few responses were noted in cases in which concurrently active NSCLC clones were proven or highly suspected. Specifically, although serial biopsies after SCLC diagnosis were not performed in most cases, adenocarcinoma was identified in progressing lesions of at least four patients after SCLC transformation, which suggests more than one active clone concurrently in the same patient. In three of these patients, there seemed to be some degree of clinical benefit gained from EGFR TKI therapy.

As characteristically observed in de novo SCLC, there was a high rate of CNS involvement after SCLC transformation in our cohort. Thirty-eight (64%) of 59 patients with follow-up radiographic information after SCLC diagnosis experienced progression in the CNS at some point after SCLC diagnosis.

Median follow-up after transformation to SCLC was 8.1 months (range, 0 to 26.9 months) and 45 deaths (67%) have occurred. Median overall survival since the initial diagnosis of metastatic lung cancer was 31.5 months (95% CI, 24.8 to 41.3 months; Fig 1A), and median overall survival since the time of SCLC was 10.9 months (95% CI, 8.0 to 13.7 months; Fig 1D).

DISCUSSION

To our knowledge, this cohort represents the largest report to date of clinical outcomes for patients with *EGFR*-mutant lung cancers that either transform to or present initially as SCLC or large-cell neuroendocrine carcinoma. Whereas *EGFR*-mutated de novo SCLC cases are rare, they are likely part of the same biologic continuum as bona fide transformed tumors. Baseline demographic characteristics seem to be relatively similar among our cohort compared with the general population of patients with *EGFR*-mutant adenocarcinoma whose disease never undergoes such transformation. One characteristic that may distinguish patients with a higher chance of future transformation is the presence of baseline *TP53* and/or *RB1* mutations, as previously reported by Lee et al.[7] We observed that SCLC transformation can manifest at any time during the disease course, seen as early as 2 months and as late as 5 years after the diagnosis of metastatic lung cancer, but that the median time to transformation was 17.8 months. After transformation, clinical behavior mimics classic (*EGFR* wild-type) SCLC on many levels, with frequent but transient responses to platinum-etoposide, frequent CNS metastases, and median overall survival of 10.9 months.

Although the response rate to immune checkpoint inhibitors in pretreated SCLC is relatively modest, complete absence of clinical response in our *EGFR* cohort, including to anti–programmed death-1/anti–cytotoxic T-cell lymphocyte-4 combinations, is noteworthy and reminiscent of the poor activity of immunotherapy in more classic *EGFR*-mutant adenocarcinoma.[11-13] This suggests that these tumors are biologically more akin to the parental *EGFR*-mutant adenocarcinoma than to smoking-associated classic SCLC cases. As combination regimens with chemotherapy and immune checkpoint inhibitors have recently demonstrated more promise than single-agent checkpoint inhibitors in both *EGFR*-mutant adenocarcinoma and de novo SCLC, studying immunotherapy together with chemotherapy could be fruitful in *EGFR*-mutant transformed SCLC.[14,15]

Of equal interest was the relatively high clinical response rate to taxanes observed in *EGFR*-mutant transformed SCLC, notably to both paclitaxel and nab-paclitaxel (70% each), even among heavily pretreated patients. In classic

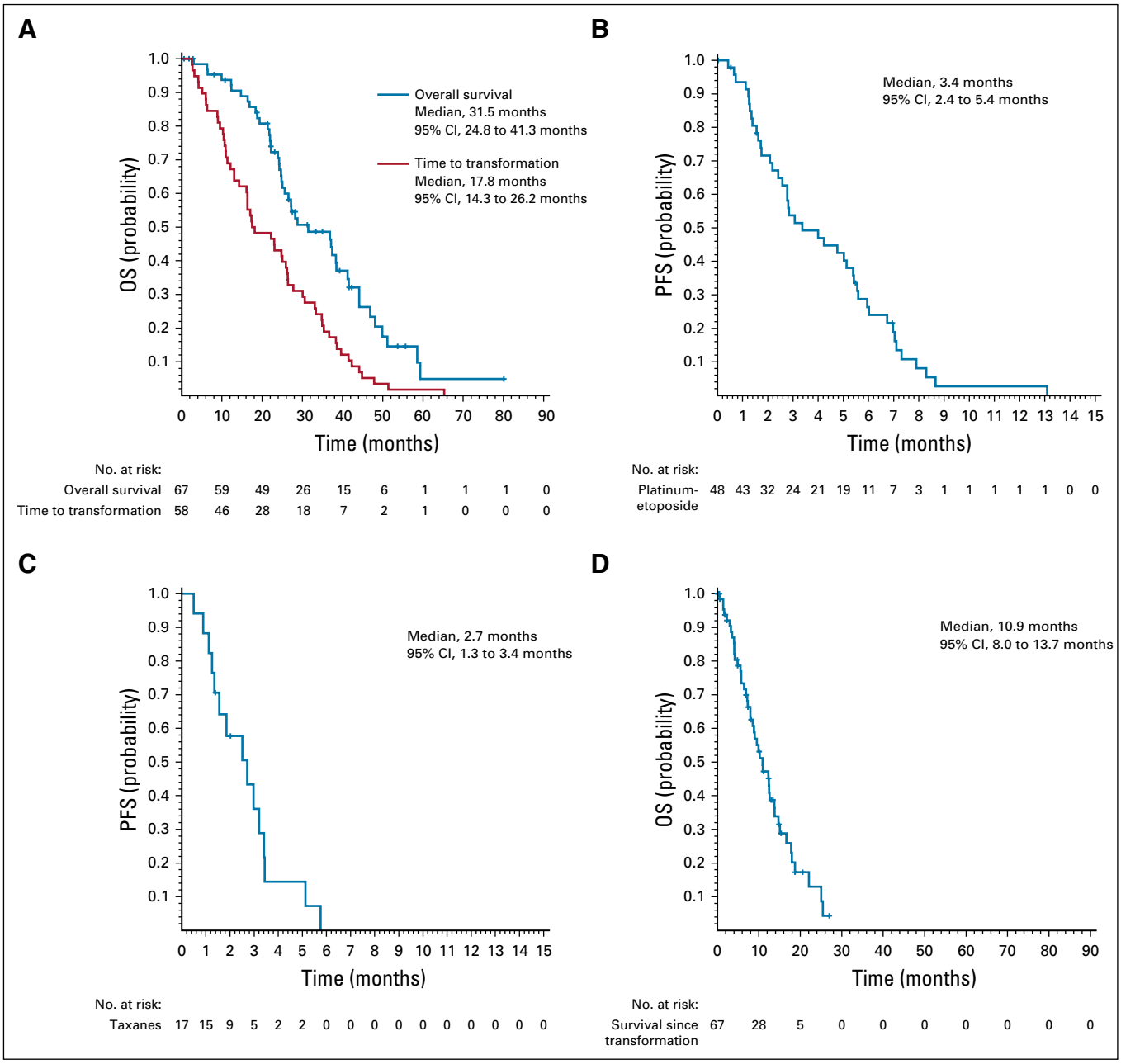

FIG 1. Time to event analyses. (A) Time since diagnosis to transformation to small-cell lung cancer (SCLC) and overall survival (OS) since the time of diagnosis. (B) Progression-free survival (PFS) of SCLC-transformed patients treated with platinum-etoposide. (C) PFS of SCLC-transformed patients treated with taxanes. (D) OS since the time of SCLC transformation.

SCLC, response rate to single-agent taxanes in pretreated patients is only 20% to 30%, albeit in small studies.[16-18] It is possible that taxanes are more active in *EGFR*-mutant transformed SCLC because of residual NSCLC clones that also are responding well to a taxane. Alternatively, *EGFR*-mutant transformed SCLC cells could have a biologic basis for increased sensitivity to taxanes compared with de novo SCLC cases. Nevertheless, despite the small sample size, frequent responses to taxanes were noteworthy and future prospective studies should be considered for this population.

Genotyping was restricted by the historical assays performed and the limited access to additional tissue, although some interesting observations were still possible. Despite few patients tested initially with platforms broad enough to assess *TP53* and *RB1*, high frequency of mutations in these tumor suppressors at diagnosis supports previously reported findings that alterations that affect both genes may strongly predispose to SCLC transformation.[7] It was rare for SCLC-transformed samples to harbor *EGFR* T790M, even if it had been previously detected in the patient's prior course, which suggests that the T790M gatekeeper mutation—the

TABLE 3. Frequency of Common Mutations Within Small-Cell Lung Cancer Cases, by Testing Method

Genotyping Platform	*TP53*	*RB1*	*PIK3CA*
All assays	38/48 (79)	18/31 (58)	14/52 (27)
Allele-specific PCR	2/8 (25)	—	3/8 (38)
NGS	32/35 (91)	15/26 (58)	11/39 (28)
Whole-exome sequencing	3/4 (75)	3/4 (75)	0/4 (0)
Unknown	1/1 (100)	0/1 (0)	0/1 (0)

NOTE. Data are given as No. (%). One case genotyped only by plasma cell-free DNA analysis is not included in this table (patient 53; Appendix Table A1).

Abbreviations: NGS, next-generation sequencing; PCR, polymerase chain reaction.

most common acquired resistance mutation to emerge after first and second-generation EGFR TKIs—tends to reside in a clone that is distinct from the SCLC transformed clone. In other words, the hypothesis of an early branching event between the SCLC clone and the initially predominant NSCLC clonal population,[7] from which *EGFR* T790M-positive clones emerge, is consistent with these clinical observations. Mutations that affect *TP53*, *Rb1*, and *PIK3CA* were frequent in the SCLC samples in our cohort, as in other reports.[3,4,7] Of importance, as a result of the high variability of assays and techniques used in this multicenter cohort, caution should be used when comparing the frequency of mutations with published studies.

Ferrer and colleagues[19] recently reported on a cohort of 48 *EGFR*-mutant SCLC transformed cases collected from centers in Europe. Although the cohort had fewer genotyping data available compared with our North American cohort, many similar clinical themes were observed, including a median time since diagnosis to SCLC transformation of 16 months and a median survival after transformation of 9 months.

Our study is limited by its retrospective nature and the fact that treatments and response assessments were not standardized across the cohort. Central review was not performed for pathology slides, nor for radiology scans; however, given the rarity of *EGFR*-mutant SCLC transformations, the size of the cohort we have collated is significant enough to draw conclusions and inform the treatment of patients in the absence of prospective data. Unfortunately, the current study cannot provide answers to some other relevant questions related to SCLC transformation, such as the impact of first-line use of osimertinib on its frequency or the absolute risk of transformation associated with *TP53* and *Rb1* mutations at the initial diagnosis of adenocarcinoma. Examining the closely related question of whether there is a signature mutational spectrum of adenocarcinomas that go on to transform to SCLC was limited by access to archival tissue, as many patients from this cohort were initially treated in a community setting and were

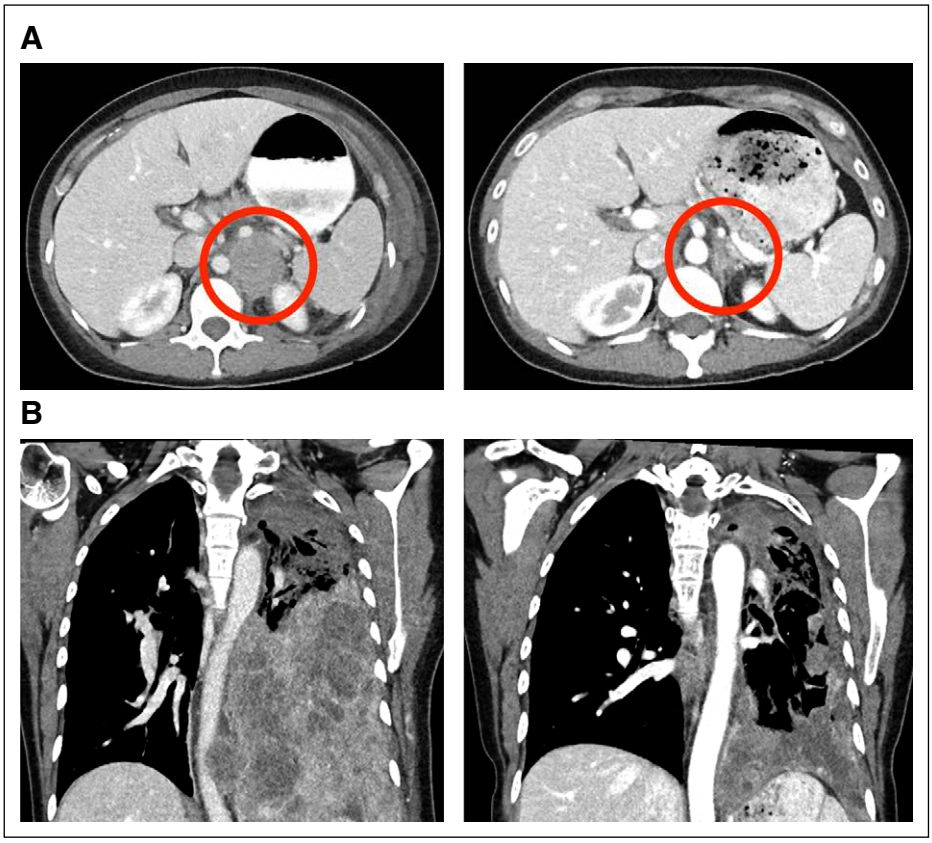

FIG 2. Example of a response to nab-paclitaxel in a SCLC-transformed cancer. (A and B) Significant response of an (A) adrenal metastastasis (red circle) and of (B) extensive thoracic involvement in a patient who had received eight prior lines of therapy for metastatic *EGFR* (epidermal growth factor receptor) -mutant lung cancer, including single-agent etoposide and a clinical trial of a BCL-2/BCL-XL inhibitor since SCLC transformation.

referred to participating centers later in the course of their disease.

In summary, *EGFR*-mutant lung cancers that transform to SCLC or that have high-grade neuroendocrine histology at the time of diagnosis exhibit high response rates to platinum-etoposide, which should be considered the first-line therapy of choice, and also exhibit high response rates to taxanes. Conversely, these tumors do not respond well to checkpoint inhibitors and the use of these therapies outside of a clinical trial should currently be discouraged. In cases that transformed from initial NSCLC, the founder *EGFR* mutation was universally maintained and the SCLC and *EGFR* T790M-positive clonal subpopulations seemed to be distinct from each other. *TP53*, *Rb1*, and *PIK3CA* mutations are common in SCLC transformations, with the former two also frequent at initial diagnosis among patients whose disease eventually undergoes transformation. Of importance, given the increasing use of cell-free DNA analysis at the time of acquired TKI resistance, our data emphasize the continued role of tissue biopsy at progression for histologic examination, especially in cases in which no genetic resistance mechanism is identified by noninvasive means. Additional investigation and ongoing multicenter collaborations are needed to better elucidate optimal strategies for this group.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

EGFR-Mutant Adenocarcinomas That Transform to Small-Cell Lung Cancer and Other Neuroendocrine Carcinomas: Clinical Outcomes

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APPENDIX

TABLE A1. Frequency of *TP53* and *Rb1* Mutations in Baseline Tissue, by Testing Method

Genotyping Platform	*TP53*	*RB1*
All assays	7/13	2/4
Allele-specific PCR	0/6	—
NGS	7/7	2/4

NOTE. Data are given as No.

Abbreviations: NGS, next-generation sequencing; PCR, polymerase chain reaction.

TABLE A2. Summary of Available Pathology Findings of All SCLC Cases

Patient No.	Report Available	Synaptophysin	Chromogranin	CD56	Ki-67, %	Morphologic Description
1	Yes	+	+		90	Small tumor cells with high nuclear/cytoplasmic ratios and speckled chromatin
2	Yes	+				Majority of cells consistent with small-cell carcinoma
3	Yes	+	+		80	Neuroendocrine features with solid growth, nuclear molding, no obvious mucin production, with nuclear rosettes present and conspicuous apoptotic debris
4	Yes	+	+			Consistent with small-cell transformation
5	Yes	+	+			Clearly distinct from prior adenocarcinoma
6	Yes	+	+			—
7	Yes	+	+			High-grade neoplasm consisting of solid nests of cohesive epithelioid cells with a moderate amount of amphophilic cytoplasm and finely dispersed chromatin without evident nucleoli; there is prominent apoptosis and brisk mitotic activity (> 20 mitoses/10 high-power fields); most features consistent with SCLC, but size of tumor cells and amount of cytoplasm greater than that observed in SCLC
8	Yes					Consistent with small-cell carcinoma
9	Yes	+				—
10	Yes	+	+			—
11	Yes	+	+	+		Consistent with small-cell carcinoma
12	Yes	+	+			Consistent with small-cell carcinoma
13	No					
14	Yes	+	—			Large bizarre cells consistent with large-cell neuroendocrine transformation
15	Yes		+			—
16	Yes	+	+	+	> 70	—
17	Yes	+	+	+	40	
18	Yes	+	+	+	85	Tumor cells have a high nuclear/cytoplasmic ratio, hyperchromatic nuclei, and frequent apoptotic bodies; larges areas have nuclear molding and focal areas of necrosis are observed
19	Yes	+	+			—
20	No					
21	Yes	—	—	+	100	Small cells with enlarged hyperchromatic nuclei with focal nuclear molding; consistent with small-cell carcinoma
22	Yes	+	+		> 95	Biphenotypic metastatic carcinoma with predominant cells with high nuclear/cytoplasmic ratios, nuclear molding, and abundant mitoses with focal areas of poorly differentiated adenocarcinoma
23	No					
24	Yes		+	+		
25	Yes	+	+		Very high	
26	Yes	+	+	+	> 90	
27	Yes	+	+	+	> 90	
28	Yes	+	+	+	90	
29	Yes					Consistent with small-cell carcinoma
30	Yes	+		+	100	
31	Yes	+	+			Consistent with small-cell carcinoma

(continued on following page)

TABLE A2. Summary of Available Pathology Findings of All SCLC Cases (continued)

Patient No.	Report Available	Synaptophysin	Chromogranin	CD56	Ki-67, %	Morphologic Description
32	Yes	+		+	> 90	Intermediate-sized cells containing scant to focally moderate amounts of cytoplasm, and ovoid to spindled nuclei containing finely dispersed chromatin, without prominent nucleoli; > 10 mitoses/1 high-power field; focal rosette-like structures
33	Yes		+	+	90	Tumor cells have round to ovoid pleomorphic hyperchromatic nuclei, inconspicuous nucleoli, scant/minimal faintly eosinophilic cytoplasm, and prominent nuclear molding; areas of necrosis are present; apoptotic bodies are readily identified; mitotic activity is brisk
34	Yes	+	+	+		Cells have small amounts of cytoplasm and finely dispersed nuclear chromatin; mitotic activity is brisk
35	Yes					Consistent with small-cell carcinoma
36	Yes	+	+	+	90	Many relatively small and highly pleomorphic cells with scanty cytoplasm, inconspicuous nucleoli, and the stippled chromatin pattern with molding; frequent mitoses, apoptotic bodies, and necrosis are noted; occasional cells show larger nuclei, distinct nucleoli, and a mild amount of cytoplasm
37	Yes	+	+	+	90	First component of moderately differentiated adenocarcinoma demonstrating acinar pattern; second component of small, round blue cell tumor infiltrating in solid sheets and possible trabeculae associated with necrosis; scanty cytoplasm and hyperchromatic nuclei with high nuclear/cytoplasmic ratio, indistinct nucleoli, and prominent nuclear molding
38	Yes	+	+	+	70	Solid nests of epithelioid cells with scant cytoplasm, high nuclear/cytoplasm ratio, and moderate nuclear pleomorphism
39	Yes	+	+	+	> 90	Sheets of malignant cells containing scant cytoplasm and hyperchromatic nuclei without prominent nucleoli; up to 8 mitoses/1 high-power field
40	Yes	+	—	+	100	Sheets of malignant small epithelial cells with scant cytoplasm, hyperchromatic nuclei, and inconspicuous nucleoli
41	Yes	+	+		90	Small neoplastic cells in densely crowded linear and rounded groups; scant cytoplasm and molded nuclei with neuroendocrine-type chromatin features; mitotic figures are readily identified
42	Yes	+	+	+	90	Sheets of tumor cells containing scanting cytoplasm and hyperchromatic nuclei with high nuclear/cytoplasmic ratio, indistinct nucleoli, and prominent nuclear molding; rare foci of larger cells with slightly more abundant cytoplasm and possible gland formation
43	Yes	+	+			Consistent with small-cell carcinoma
44	Yes	+		+		Increased mitosis and occasional single-cell necrosis
45	Yes	+	—	+		Cell block shows scattered aggregates and single atypical cells with elevated nuclear/cytoplasmic ratios and occasional single filing, irregular nuclear borders, and smudgy chromatin with conspicuous nucleoli; supports neuroendocrine differentiation, with features suggestive of small-cell carcinoma
46	Yes					Dark ink dot nuclei, scanty cytoplasm, and overlapping nuclei diagnostic of small-cell transformation

(continued on following page)

TABLE A2. Summary of Available Pathology Findings of All SCLC Cases (continued)

Patient No.	Report Available	Synaptophysin	Chromogranin	CD56	Ki-67, %	Morphologic Description
47	Yes	—	+			Clusters and sheets of malignant cells with crowded enlarged nuclei, irregular nuclear contours, nuclear molding, and scant cytoplasm; spectrum of changes with areas resembling large-cell neuroendocrine carcinoma and small-cell carcinoma
48	Yes	+	—			Consistent with small-cell carcinoma
49	Yes	+		+	90	Consistent with large-cell neuroendocrine carcinoma
50	Yes	+	+	+	90	
51	No					
52	Yes	+	+	+		Typical of small-cell carcinoma
53	Yes	+	+		80	Sheet-like growth of round to oval cells with minimal cytoplasm, nuclear molding, and salt and pepper chromatin
54	Yes			+		Small atypical cells with scanty cytoplasm, coarsely granular chromatin, and indistinct nucleoli
55	Yes	+	—	+	47	Consistent with small-cell carcinoma
56	Yes	+		+	40-50	Consistent with small-cell carcinoma
57	No					
58	No					
59	Yes	+	—		70-80	Consistent with small-cell carcinoma
60	Yes	+	+		90	Consistent with small-cell carcinoma
61	No					
62	Yes	+	+			—
63	Yes		—		High	Small round cells with minimal cytoplasm and oval molded nuclei
64	Yes	+	+		60-0	Consistent with small-cell transformation
65	Yes	+	—	+	90	Neoplasm composed of sheets of cells with high nuclear/cytoplasmic ratios, finely dispersed chromatin, and variably prominent nucleoli; there are numerous mitotic figures and areas of punctate necrosis
66	No					
67	Yes	+	—		85	—

Abbreviation: SCLC, small-cell lung cancer.

TABLE A3. Genetic Findings of All SCLC Cases

Patient No.	Histology at Diagnosis	Mutation Reported
1	Adenocarcinoma	*EGFR* exon 19 del
2	Adenocarcinoma	*EGFR* exon 19 del
		AKT1 Glu40Lys
		TP53 Gly154Val
		RB1 Leu343SerfsTer3
		PIK3CA Glu542_545GludelinsLysIleThrLys
3	Adenocarcinoma	*EGFR* exon 19 del
		RB1 splice donor variant
		NF1 Ile2746Met
		TP53 Arg333ValfsTer12
4	Adenocarcinoma	*EGFR* Leu858Arg
		DDR2 Met690Val
		TP53 Val197Gly
5	Adenocarcinoma	*EGFR* exon 19 del
		TP53 His193Arg
		PIK3CA Glu545Lys
		MYC Lys340Arg
6	Adenocarcinoma	*EGFR* exon 19 del
		TP53 Arg306Ter
		SMAD4 Cys363Phe
		ATM His231Arg
		RB1 splice region/intronic variant
7	Adenocarcinoma	*EGFR* exon 19 del
		TP53 Val173Leu
		PIK3CA Glu545Lys
		PIK3CA Gly726Leu
		HER3 Gly337Ala
		Biallelic *Rb1* loss
		FBXW7 Leu8Phe
8	Adenocarcinoma	*EGFR* Leu858Arg
9	Adenocarcinoma	*EGFR* exon 19 del
10	Adenocarcinoma	*EGFR* Leu858Arg
		PIK3CA His1047Arg
11	Adenocarcinoma	*EGFR* Leu858Arg
		PIK3CA Glu545Lys
12	Adenocarcinoma	*EGFR* exon 19 del
		TP53 Arg273Leu
13	Adenocarcinoma	*EGFR* exon 19 del
		RB1 Arg320Ter
		FBXW7 splice region variant
		BRCA1 Glu686Lys
		TP53 c.375G>C
		PIK3CA Gly545Lys

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TABLE A3. Genetic Findings of All SCLC Cases (continued)

Patient No.	Histology at Diagnosis	Mutation Reported
14	Adenocarcinoma	*EGFR* exon 19 del
15	Adenocarcinoma	*EGFR* exon 19 del
		EGFR amp
		TP53 pPhe109_Arg110del
16	SCLC	*EGFR* exon 19 del
		RB1 LOH + splice site mutation at exon 22
		TP53 LOH + out-of-frame fusion between *TP53* exon 1 and *ITNL2* exon 8
17	SCLC	*EGFR* Ser768Ile
		ABCB11 Ala762Ser
		DOCK8 Ala325Thr
		NOTCH3 Pro48Leu
		RAD51D Ser46Cys
18	Adenocarcinoma	*EGFR* exon 19 del
		TP53 Ile332Asn
19	Adenocarcinoma	*EGFR* exon 19 del
		RB1 Glu352Ter
		ATRX Ser519Tyr
		TP53 Gln104Ter
		TSC2 Ser526Cys
		PIK3CA Glu453Lys
		PTEN loss
20	Adenocarcinoma	Not genotyped
21	Adenocarcinoma	*EGFR* Leu858Arg
		CIC Ser1058Ter
		BRCA1 Ile1568Met
		MSH6 His588Tyr
22	Mixed NSCLC and SCLC	*EGFR* Leu858Arg
		TP53 splice acceptor variant
		ALK Pro40Leu
		BRCA1 Ser1294Gly
		RB1 loss
		PTEN loss
		MDM2 gain
23	Mixed NSCLC and SCLC	*EGFR* Leu858Arg
24	Adenocarcinoma	*EGFR* exon 19 del
25	Adenocarcinoma	Not genotyped
26	SCLC	*EGFR* Gly719Cys
		EGFR Ser768Ile
		TP53 Cys135Trp
		SOX17 (8q11.23) del
		LYN (8q12.1) del
		PREX2 (8q13.2) del
		PRDM14 (8q13.3) del

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TABLE A3. Genetic Findings of All SCLC Cases (continued)

Patient No.	Histology at Diagnosis	Mutation Reported
		NOTCH4 Arg1914His
		RB1 exon1 splicing variant p.X46_splice
		TET1 exon12 Ala1868Val
27	Adenocarcinoma	*EGFR* exon19 del
		EGFR Thr790Met
		PIK3CA Glu545Lys
		TP53 Arg342Pro
		SRC (20q11.23) del
		TOP1 (20q12) del
		PTPRT (20q13.11) del
		IKZF1 Arg511Gln
		RB1 exon 12 splicing variant
28	Adenocarcinoma	*EGFR* Leu858Arg
		TP53 Pro152RArgfs*18
		RAD21 (8q24.11) amp
		MYC (8q24.21) amp
		PMAIP1 (18q21.32) amp
		ELF3 (1q32.1) amp
		PTPRT (20q13.11) amp
		TGFBR2 (3p24.1) del
		ABL1 Trp423*
		CTNNB1 Ser37Phe
		CYLD Glu694Leu
		HIST1H3H Gln20Profs*54
		MYC Gly295Val
		NOTCH2 Glu1025Lys
		PIK3C2G Glu1160Asp
		RB1 exon 17 splicing variant X500_splice
		SMYD3 His206Asp
29	Adenocarcinoma	*EGFR* exon 19 del
30	Adenocarcinoma	*EGFR* exon 19 del
		EGFR Thr790Met
31	Mixed NSCLC and SCLC	*EGFR* exon 19 del
		PIK3CA Glu545Lys
32	Adenocarcinoma	*EGFR* Leu747_Pro753delinsSer
		EGFR Gly719Cys
		PIK3CA Glu 542 Lys
		TP53 Val173Leu
33	Adenocarcinoma	*EGFR* exon 19 del
34	Adenocarcinoma	*EGFR* exon 19 del
35	Adenocarcinoma	*EGFR* Gly719X
		EGFR Glu709Ala
		TP53 Val157Gly

(continued on following page)

TABLE A3. Genetic Findings of All SCLC Cases (continued)

Patient No.	Histology at Diagnosis	Mutation Reported
36	Adenocarcinoma	*EGFR* exon 19 del
		TP53 Val274Phe
37	Adenocarcinoma	Not genotyped
38	SCLC†	*EGFR* Ala767Val
		EGFR Leu858Arg
39	Adenocarcinoma	*EGFR* exon 19 del
		TP53 Arg282Gly
40	Adenocarcinoma	Not genotyped
41	Adenocarcinoma	*EGFR* exon 19 del
		TP53 c.554_559delinsT
42	Adenocarcinoma	*EGFR* exon 19 del
		TP53 Pro278Ser
43	Adenocarcinoma	*EGFR* Leu62Arg
		EGFR Leu858Arg
		MET amp
		MAP2K1 amp - equivocal
		MYC amp
		BCL2L2 amp
		CCNE1 amp
		FOXP1 Asn505fs*9
		NFKBIA amp
		NKX2-1 amp
		TP53 Phe134Leu
		APC Ala2778Ser
		ATM Ser310Gly
		BRCA2 Val1186Ile
		CARD11 Ala534Asn + amp
		CHD2 Arg1245Pro
		DOT1L Leu800Met
		PMS2 amp
		RAC1 amp
		SMAD3 amp
		Microsatellite stable
44	Adenocarcinoma	*EGFR* exon 19 del
		KMT2C Leu732Phe
		RB1 loss exons 1-23
		TP53 Arg65*
		ARID1B Met960Thr
		ESR1 Gly145Ser
		GATA6 Met546Ile
		GPR124 Cys1196Tyr
45	Adenocarcinoma	Not genotyped

(continued on following page)

TABLE A3. Genetic Findings of All SCLC Cases (continued)

Patient No.	Histology at Diagnosis	Mutation Reported
46	Adenocarcinoma	*EGFR* exon 19 del
		TP53 His179Tyr
		BRCA2 Thr3033fs*11
		RB1 Glu587*
		BCL2L2 amp
		NFKBIA amp
		NKX2-1 amp
		ARFRP1 amp
		MYC amp
47	Adenocarcinoma	*EGFR* exon 19 del
		TP53 Leu194His
48	Adenocarcinoma	Not genotyped
49	Adenocarcinoma	*EGFR* exon 19 del
50	Adenocarcinoma	Genotyped, but mutations unavailable
51	Adenocarcinoma	Genotyped, but mutations unavailable
52	Adenocarcinoma	Genotyped, but mutations unavailable
53	Adenocarcinoma	(Mutations identified on cfDNA assay)
		EGFR exon 19 del
		EGFR Glu205Glu
		EGFR amp
		TP53 Arg175His
		PIK3CA Glu545Lys + amp
		CCNE1 amp
		HER2 amp
		RB1 Leu550fs
		PIK3CA Val344Gly
		APC Ser1345Leu
54	Adenocarcinoma	*EGFR* Leu858Arg
55	NSCLC NOS	*EGFR* exon 19 del
56	Adenocarcinoma	*EGFR* exon 19 del
		EGFR Thr790Met
57	Adenocarcinoma	Genotyped, but mutations unavailable
58	Adenocarcinoma	Genotyped, but mutations unavailable
59	Adenocarcinoma	*EGFR* exon 19 del
		PIK3CA Glu545Lys
60	Adenocarcinoma	*EGFR* exon 19 del
		EGFR amp
		TP53 Arg248Gln
		PIK3CA Glu545Lys
61	Adenocarcinoma	*EGFR* exon 19 del
		PTEN loss exons 2-6
		RICTOR amp
		FGF10 amp

(continued on following page)

TABLE A3. Genetic Findings of All SCLC Cases (continued)

Patient No.	Histology at Diagnosis	Mutation Reported
		RB1 splice site 2663 + 1G>A
		TP53 Arg248Gln
62	Adenocarcinoma	*EGFR* Leu861Gln
		EGFR amp
		TP53 Arg283Pro
		PIK3CA Cys420Arg
63	Mixed NSCLC and SCLC	*EGFR* exon 19 del
		KRAS Gly12Arg
64	Adenocarcinoma	Not genotyped
65	SCLC	*EGFR* Leu858Arg
		TP53 Gly245Val
		MYC amp
66	Adenocarcinoma	*EGFR* Leu858Arg
		EGFR Thr790Met
		EGFR amp
		TP53 Val274Leu
		RB1 Ser567*
67	Adenocarcinoma	*EGFR* Leu858Arg
		TP53 Ile195Thr
		MET Thr1010Ile

NOTE. Genotyping assay used varies across patients. Similarly, definitions of gene amplification can vary across assays and should be interpreted with caution. Mutations are listed at the protein level unless otherwise indicated.

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non–small-cell lung cancer; SCLC, small-cell lung cancer.

†Genotyped after first-line therapy.