

Small cell transformation of non-small cell lung cancer on immune checkpoint inhibitors: uncommon or under-recognized?

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ABSTRACT

Background Histological transformation of oncogene-driven lung adenocarcinoma to small cell lung cancer (SCLC) following treatment with tyrosine kinase inhibitors (TKIs) is a well-described phenomenon. Whether a similar transformation may drive acquired resistance to immune checkpoint inhibitors (ICPIs) in non-SCLC (NSCLC) is uncertain. Hence, tissue biopsies are not universally recommended at progression of NSCLC on ICPIs, unlike TKIs.

Case presentation We report a case of a woman in her mid-60s with a 35 pack-years tobacco history and stage IV squamous cell lung carcinoma with no targetable genomic alterations, whose disease progressed within 4 months of first line carboplatin/gemcitabine therapy. Her treatment was switched to second line nivolumab monotherapy which resulted in sustained partial response lasting 21 months. She subsequently developed rapid, bulky progression of mediastinal disease. Biopsy showed transformation to SCLC. Comparison of genomic profiling results from the initial NSCLC diagnosis and SCLC transformation revealed near-identical tumor profiles. Her disease responded to next line carboplatin/etoposide, though lasting for only 10 months. She died 14 months after detection of neuroendocrine transformation of her NSCLC.

Systematic review We performed a systematic review of the literature to identify similar cases of NSCLC-to-small cell transformation on ICPIs. Nine patients, including our index case, were identified, with seven (77.8%) on nivolumab and two (22.2%) on pembrolizumab monotherapy. Median survival time since small cell transformation was 13.0 months (95% CI 2.0 to 16.0). Using our patient case as a framework, we further discuss the lack of consensus criteria to distinguish small cell transformation from *de novo* metachronous SCLC.

Conclusions Histological transformation to SCLC is a potential mechanism of acquired resistance to ICPIs in NSCLC. Repeat tissue biopsies should be considered at the time of progression, similar to oncogene-directed therapies. Prospective larger studies are warranted to further characterize NSCLC-to-small cell transformation on ICPIs using molecular fingerprinting with paired tumor genomic profiles, evaluation of neuroendocrine features at baseline and consideration of initial response.

BACKGROUND

Resistance to tyrosine kinase inhibitors (TKIs) in epidermal growth factor receptor (*EGFR*) mutated non-small cell lung cancer (NSCLC) is well established to be mediated by histological transformation to SCLC in 3%–14% of cases.^{1–3} Similarly, transformation of prostate adenocarcinoma to small cell carcinoma on androgen-deprivation therapy is reported to occur at an incidence of 17% and is associated with poor survival outcomes.^{4,5} More recently, reports have emerged regarding SCLC transformation of NSCLC as a resistance mechanism to immune checkpoint inhibitors (ICPIs). However, unlike disease progression on TKIs, repeat tissue biopsies are not universally recommended at the time of NSCLC progression on ICPIs.

CASE PRESENTATION

In our practice, we cared for a patient who had small cell transformation of stage IV poorly differentiated squamous cell carcinoma of the lung after prolonged nivolumab monotherapy (*figure 1*). She was in her mid-60s with a history of 35 pack-years of smoking at the time of diagnosis of her lung cancer (metastatic to lungs, mediastinal lymph nodes and L1 vertebral body) with no targetable genomic alterations. After a short-lived response to first-line platinum-gemcitabine chemotherapy lasting less than 4 months, she had progression of her disease. She was then switched to nivolumab monotherapy, with sustained partial response for 21 months. On follow-up imaging, she was noted to have bulky mediastinal and right hilar lymphadenopathy; biopsy showed SCLC. Review of the biopsy at initial NSCLC diagnosis did not show any small cell component. Tumor genomic profiling performed at initial

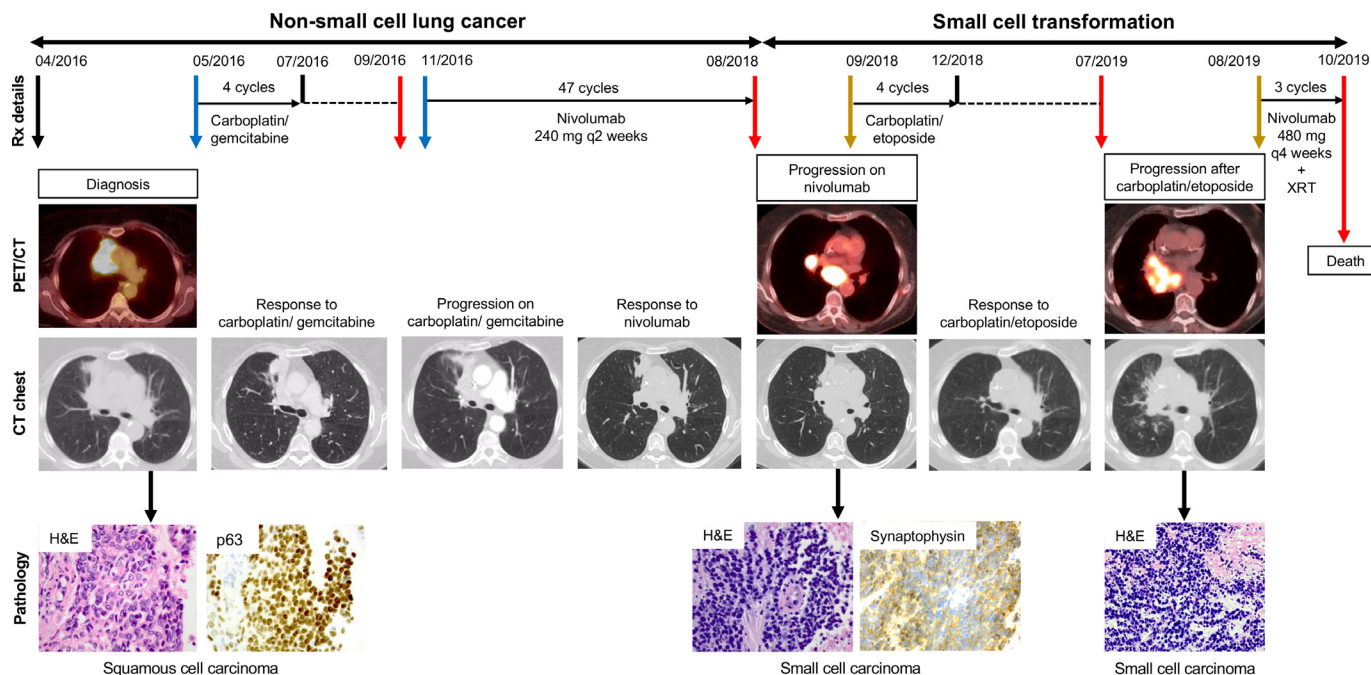


Figure 1 Case presentation of small cell transformation of non-small cell lung cancer on nivolumab monotherapy, including treatment details, and radiographic and pathological findings. Time on therapy is not drawn to scale. CT, computed tomography; H&E, hematoxylin and eosin; PET, positron emission tomography; Rx, treatment; XRT, radiotherapy.

diagnosis and following disease progression on nivolumab showed nearly identical results (table 1). Treatment with carboplatin/etoposide led to near-complete response, however, lasting for only 10 months. Biopsy of the tumor again confirmed small cell histology. She was treated with concurrent nivolumab and radiotherapy to the chest, though ultimately elected to pursue comfort focused care and died 14 months after the detection of neuroendocrine transformation.

SYSTEMATIC REVIEW

We performed a systematic review of the literature, in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines, to identify similar published reports of NSCLC-to-small cell transformation on ICPIs (figure 2). We searched PubMed, Embase and the American Society of Clinical Oncology/International Association for the Study of Lung Cancer virtual meeting library databases on 7 December 2019, using the keywords small cell transformation/neuroendocrine transformation with or without ICPIs/anti-PD-1/pembrolizumab/nivolumab/atezolizumab/durvalumab. Two investigators (KS and AV) independently reviewed abstracts and full-text articles. Patients with advanced NSCLC who had received molecularly targeted therapies prior to small cell transformation or non-lung primary cancers were excluded. Nine patients were identified from five articles (three case series^{6–8} and two case reports^{9,10}) and one meeting abstract (index case).

All patients were on treatment with ICPIs at the time of detection of SCLC, with seven (77.8%) on nivolumab and two (22.22%) on pembrolizumab monotherapy.

Five (55.6%) were male; median age was 68 years (range 65–75 years). All eight (100%) patients for whom smoking history was described had history of tobacco exposure. The median number of treatments received before ICPI was 1 (range 0–3). All (100%) patients had received chemotherapy before switch to either second line or maintenance ICPI. After detection of small cell transformation, seven (77.8%) patients received carboplatin/etoposide as the next immediate line of therapy. Among eight patients for whom survival data was available, median survival since detection of small cell transformation was 13.0 months (95% CI 2.0 to 16.0 months; Stata/IC V.15.1), which was comparable to 10.9 months (95% CI 8.0 to 13.7 months) previously reported with transformed *EGFR*-mutant lung adenocarcinoma on TKIs.¹¹ The full clinicopathological and tumor genomic details of these cases are summarized in table 1.

DISCUSSION AND CONCLUSIONS

No consensus guidelines exist on how to define NSCLC-to-small cell transformation and distinguish it from new primary SCLC. Absence of neuroendocrine features on initial biopsy, protracted response to nivolumab monotherapy and the near-identical genomic profile of the two tumors favored the diagnosis of histological transformation in our patient. Proof of transformation with molecular fingerprinting was described in only two of the other eight patients (table 1). The genomic profiles of ‘transformed small cell tumors’ in three patients were completely different from the ‘original’ NSCLC tumors, which raises the question of true treatment-induced transformation versus metachronous primary

Table 1 Summary of clinical and tumor genomic characteristics of patients included in the review

Source	Age/sex at NSCLC dx	Smoking status at NSCLC dx	Histology/ neuroendocrine features on initial bx	Genomic profile of original NSCLC	Treatment of NSCLC prior to ICPI	ICPI details	Initial best response to ICPI	Site of repeat biopsy showing SCLC	Genomic profile of SCLC	Treatment for SCLC	Site of PD of SCLC	Patient outcome post-SCLC dx
Index case	Mid-60s F	Smoker (35 pack-years)	Poorly diff squamous/ no	TP53 mut (R283fs*62 and G325), CDKN2A R58 mut, SOX2 amp, PIK3CA amp, ERBB4 amp, REL amp, KRAS amp, ZNF703 amp, FGFR1 amp (Foundation Medicine)	CBDCA/GEM (4 cycles)	Nivo q2wk (second line, 47 cycles)	PR	Lung and level 7 and 4R mediastinal lymph nodes	TP53 R283fs*62 mut, CDKN2A R58 mut, SOX2 amp, PIK3CA amp, PIK3CA E545K, CCND2 amp, CCND3 amp, MYCL1 amp, CSF3R amp, FGF23 amp, FGF6 amp, C17orf39 amp, KDM5A amp, PRKCI amp, TERC amp, VEGF amp (FoundationOne CDx)	CBDCAVP16 (1st line, 4 cycles) -> 8 month no therapy holiday Nivo q4wk (3 cycles) + XRT to chest (2nd line)	Systemic	Died 14 mo post SCLC dx
Iams et al ⁶	75 F	Smoker (30 pack-years)	Adeno/ not specified	KRAS G12C mut	CBDCA/PEM/BEV (6 cycles) -> maint. PEM/BEV > 16mo therapy holiday	Nivo q2wk (2nd line, 33 cycles) -> 11 mo therapy holiday	SD	Station 7 mediastinal lymph node	KRAS G12C mut, TP53 R273C mut	CBDCAVP16 (1st line, 4 cycles) -> 4 mo therapy holiday Nivo/Ipi (2nd line, 3 cycles) Irinotecan (3rd line, 10 cycles)	Not specified	Died 16 mo post SCLC dx
Iams et al ⁶	67 F	Smoker (50 pack-years)	Adeno/ not specified	KRAS G12C mut	CBDCA/PTX (4 cycles) -> 17 mo therapy holiday	Nivo q2wk (2nd line, 36 cycles)	Response	Pericardial and pleural effusion	TP53 S315S frameshift mut, RB1 splice site mut	CBDCAVP16 (1st line, 6 cycles) -> 2 mo therapy holiday PTX (2nd line, 8 cycles)	Not specified CNS	Died 11 mo post SCLC dx
Bar et al ⁷	70 F	Active Smoker	Squamous/ yes	TP53 mut (Arg249Ser and Arg196Ter)	Palliative XRT to D5 vertebral lesion -> CBDCA/GEM (1st line, 5 cycles) Single dose XRT to left lung hilum (3rd line) Trial NCT02052492* (4th line, 3-4 mo)	Nivo q2wk (2nd line, 3 cycles); (5th line, 10 mo)	PseudoPD	Adrenal gland	TP53 mut (Arg249Ser and Arg196Ter)	Continued nivo for 2 mo - stopped 2/2 pneumonitis -> 5 mo systemic therapy holiday Left adrenalectomy Re-started nivo	NA NA	Alive 9 mo post SCLC dx; then lost to follow-up
Bar et al ⁷	75 M	Past Smoker (>10 pack-years)	Squamous/ yes	TP53 mut (Asn131fs and Pro177Ser), FBXW7 Arg441Phe mut	Palliative XRT to mediastinal lesion -> CBDCA/GEM (5 mo) -> 3 mo therapy holiday	Nivo (2nd line, 6 mo); stopped 2/2 pneumonitis -> 2 mo therapy holiday	PR	Lung	TP53 Cys238Phe mut	CBDCAVP16 -> XRT to chest (1st line, 3-4 mo) -> 2 mo therapy holiday Nivo (2nd line, 2 mo) DTX (3rd line, 1 mo), stopped 2/2 toxicity Gefitinib (4th line, 1 mo)	Systemic Systemic NA Not specified	Died 13 mo post SCLC dx
Abdallah et al ⁸	65 M	Smoker (35 pack-years)	Adeno/ limited specimen	Negative for EGFR/ALK alterations	CBDCA/PEM (6 cycles) -> maint. PEM (9 cycles)	Nivo (2nd line, 5 cycles)	PD	Lung	Not described	CBDCAVP16 (2 cycles at the time of report)	NA	Response to chemotherapy
Abdallah et al ⁸	68 M	Not described	Two primaries (Squamous and poorly diff)/ limited specimen	Not described	Pembro/CBDCA/PTX (4 cycles) -> maint. Pembro (26 cycles)	Pembro/CBDCA/PTX (4 cycles) -> maint. Pembro (26 cycles)	PR	Right hilar lymph node	Not described	CBDCAVP16 (4 cycles) -> definitive XRT to chest	NA	Alive with no evidence of disease 18 mo post SCLC dx

Continued

Table 1 Continued

Source	Age/sex at NSCLC dx	Smoking status at NSCLC dx	Histology/ neuroendocrine features on initial bx	Genomic profile of original NSCLC	Treatment of NSCLC prior to ICPI	ICPI details	Initial best response to ICPI	Site of repeat biopsy showing SCLC	Genomic profile of SCLC	Treatment for SCLC	Site of PD of SCLC	Patient outcome post-SCLC dx
Imakita <i>et al</i> ³	75 M	Smoker (50 pack-years)	Poorly diff/ no	Negative for EGFR/Alk alterations	DTX/BEV (2-3 cycles) -> 2-3 mo therapy holiday 2/2 toxicity	Nivo (2nd line, 3 cycles)	PD	Pleural fluid and subcutaneous tumor of chest	Not described	Amrubicin	Systemic	Died 2 mo post-SCLC dx
Okeya <i>et al</i> ¹⁰	66 M	Smoker (45 pack-years)	Adeno/ limited specimen	Indeterminate for EGFR mut, Negative for Alk alterations	CBDCA/PEM/BEV (4 cycles) -> maint, PEM/BEV (2 cycles)	Pembro (2nd line, 2 cycles, 5 weeks)	HyperPD	Pleural fluid	Not described	CBDCA/VP16 (1st line, 3 cycles) Amrubicin (2 nd line, 3 cycles)	Not specified	Died 5 mo post-SCLC dx

Bold red font represents shared genomic alterations in initial NSCLC and transformed SCLC.

³NCI T02052492 = single arm phase I clinical trial of vitamin D binding protein macrophage activator as immunotherapy.

-> followed by; 2/2, secondary to; adeno, adenocarcinoma; amp, amplification; BEV, bevacizumab; bx, biopsy; CBDCA, Carboplatin; CNS, central nervous system; diff, differentiated; DTX, Docetaxel; dx, diagnosis; EGFR, epidermal growth factor receptor; F, female; GEM, gemtactabine; ICPI, immune checkpoint inhibitor; ipi, ipilimumab; M, Male; maint, maintenance; mo, months; mut, mutation; NA, not applicable; Nivo, nivolumab; NSCLC, non-small cell lung cancer; PD, progressive disease; PEM, pemetrexed; Pembro, pembrolizumab; PR, partial response; PTX, paclitaxel; SCLC, small cell lung cancer; SD, stable disease; VP16, Etoposide; XRT, Radiotherapy.

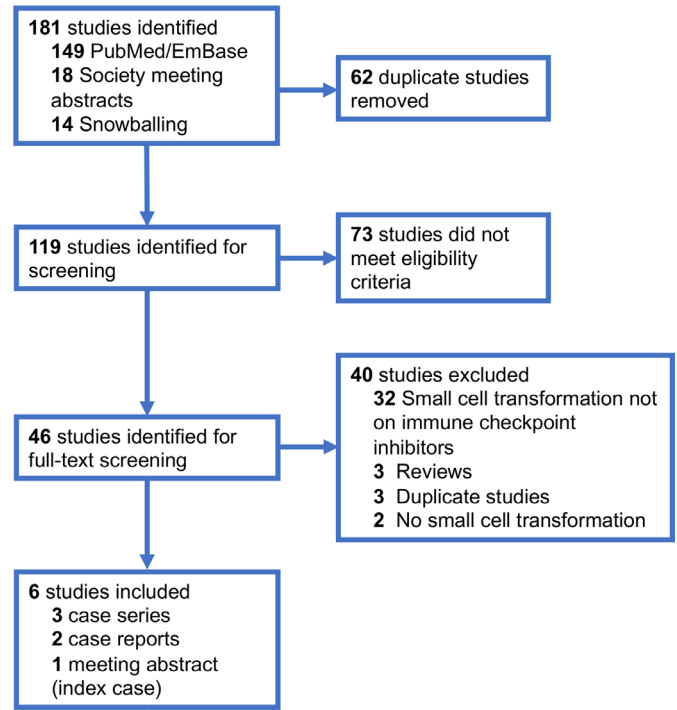


Figure 2 PRISMA diagram detailing selection of published reports of small cell transformation of non-small cell lung cancer with immune checkpoint inhibitors. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

SCLC. Genomic profiling was not described in the remaining four cases. Presence of mixed small cell and non-small cell histology at diagnosis, minimum duration of therapy and attainment of initial response with ICPIs are other criteria which merit further investigation. Of note, two patients in [table 1](#) had received less than four cycles of ICPIs, while three patients did not have any on-treatment response.

The real-world frequency of histological transformation with ICPIs remains uncertain—and is likely under-recognized and under-reported due to the infrequency of tumor rebiopsy in advanced NSCLC being treated with sequential chemotherapies and/or ICPIs. Bar *et al* studied biopsies at the time of NSCLC progression on ICPIs at a single institution and reported a small cell transformation rate of 25% in 8 patients with NSCLC with available with preprogression and postprogression tissue biopsies (with two postprogression biopsies not showing any tumor cells).⁷ However, Gettinger *et al* did not find any clear changes in lung cancer histology (0%) on evaluation of 23 NSCLC cases (all with tumor cells) from a single institution with acquired resistance to anti-PD-1 drugs.¹² Both studies are hampered by small sample sizes, which makes it prudent to study this putative phenomenon prospectively.

The underlying evolutionary genomic/epigenetic alterations responsible for this mechanism of therapeutic resistance warrant more detailed exploration. Insights from small cell transformation in *EGFR*-mutated

lung adenocarcinoma and prostate adenocarcinoma may help direct further mechanistic investigations towards study of common cell-of-origin, drug-tolerant persist state and stromal interactions.^{2 3 13–15} In the meanwhile, we recommend that tissue biopsies should be considered at the time of NSCLC progression on ICPIs similar to TKIs, if safe and feasible from the patient perspective.

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Contributors KS and DBC conceptualized and designed the study. KS and AV independently screened all the studies. All authors participated in the acquisition, analysis or interpretation of data, and in the drafting, critical revision, and approval of final version of the manuscript.

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