



Treatment approach for large-cell neuroendocrine carcinoma of the lung using next-generation sequencing

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We thank J. N. McCutcheon, X. Zhao, and G. Giaccone for their insightful commentary on our article regarding genomic studies for large-cell neuroendocrine carcinoma (LCNEC) of the lung (1). We would like to take this opportunity to comment on some of the points that they raised and to discuss our data reported in the original manuscript further (2).

Although LCNEC is distinguished from small cell lung carcinoma (SCLC) based on histological criteria such as a larger cell size and abundant cytoplasm, LCNEC shares many similarities with SCLC in terms of immunohistochemical (IHC) staining results and molecular biology (3,4). However, a multi-center prospective phase II study examining combination chemotherapy with irinotecan and cisplatin resulted in a somewhat poorer outcome among LCNEC patients than among those with SCLC (5), suggesting a possibility of biological distinction between LCNEC and SCLC. Due to its rarity, information about biologically relevant genetic alteration in LCNEC is insufficient. Thus, we examined LCNECs for biologically relevant genomic alterations using next-generation sequencing (NGS) and compared the genomic profiles of LCNECs with those of SCLCs.

McCutcheon *et al.* pointed out that we have proposed the ongoing movement in genomics to deliver “personalized” treatment approaches to patients with LCNEC (1). We reported that a group of LCNEC patients harbored targetable activating alterations in receptor tyrosine kinase signaling pathways, such as the PI3K/AKT/mTOR pathway and *EGFR*, *ERBB2* and *FGFR1* (2). Our results showed that sequencing-based molecular profiling is warranted, since it was capable of identifying a population of LCNEC patients

who were likely to benefit from novel targeted therapies even if it was a small population.

Our results showed that LCNEC and SCLC had similar genomic profiles (2). LCNEC is a rare disease, so NGS-based analyses might be helpful for developing novel targeted therapies along with other types of lung cancer, such as SCLC. Rekhtman *et al.* also reported that the *TP53* and *RB1* genes were the most commonly mutated genes in LCNEC, in agreement with our data; however, they showed that LCNEC represented a biologically heterogeneous group of tumors with distinct subsets exhibiting the genomic signatures of SCLC, NSCLC, and, in rare cases, highly proliferative carcinoids (6). Although the more than 200 genes that are included in the target-sequencing panel encompass most known, functionally important cancer-related genes, studies utilizing whole-genome/exome sequencing technologies will be desirable to obtain a detailed understanding of the similarities between LCNEC and SCLC. In addition, analysis of a larger cohort of cases will be needed to capture a full spectrum of genomic profiles in LCNEC.

As McCutcheon *et al.* pointed out, the genomic analysis of combined LCNEC is challenging (1). We found that 5 of the 10 cases of LCNECs combined with NSCLCs harbored candidate driver gene alterations that have been previously reported for NSCLC. We diagnosed combined LCNEC as follows: LCNEC with an additional component of some other NSCLC histology that was clearly separated from the LCNEC component. In most cases, the size of the NSCLC component in the combined LCNEC was relatively small. Therefore, we used the core of the specimen for DNA extraction to obtain as much DNA sample as possible. In

this study, the median and mean read coverages for all the LCNEC samples (including the NSCLC components) were 360 and 359, respectively. To avoid contamination, pathologists reviewed all the tumor samples before and after tissue punching and evaluated the tumor cell contents of the punched-out sites: a minimum of 50% tumor cells were included in all the samples, and no additional micro-dissection was needed. The variant frequency of the mutations in the NSCLC component tended to be lower than that shared with the LCNEC component. We suppose that the tumor contents in the NSCLC component were generally less than those in LCNEC component. The relatively high concordance rate might be due to the common origin of different components and not due to contamination of the samples during the DNA extraction (2).

LCNEC is a rare and lethal disease with no approved disease-specific targeted therapies (7). Ongoing efforts to collect and analyze samples using more advanced research tools are likely to enable the development of effective and novel targeted therapies. Integrated omics analyses, including RNA sequencing and metabolomics as well as whole exome or whole genome analyses, might provide a stronger interpretation of the LCNEC biology. In addition, co-clinical studies using patient tumor-derived and/or circulating-tumor cell derived xenografts could be used to guide therapeutic strategies for individual patients in the same way as those for SCLC (8,9).

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