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# Clinical correlation of extensive-stage small-cell lung cancer genomics

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**Background:** Genomic studies in small-cell lung cancer (SCLC) lag far behind those carried out in nonsmall-cell lung cancer (NSCLC). To date, most SCLC studies have evaluated patients with surgically resectable disease. Here we sought to evaluate the genomic mutation spectrum of 'every-day' SCLC patient tumors with extensive stage disease (ES-SCLC) and to correlate mutations with the main clinical outcomes of response to chemotherapy, progression-free (PFS) and overall (OS) survival.

**Patients and methods:** A total of 50 SCLC patient tumors were examined in this study; targeted exome sequencing was obtained on 42 patients and whole-exome sequencing on 8 patients. Mutated genes were correlated with clinical outcomes using Kaplan–Meier methods (PFS, OS) and logistic regression (chemo-response). RB1 protein expression was detected by either western blotting of cultured cell lysates or immunohistochemistry of tumor specimens.

**Results:** In all, 39 patients had ES-SCLC; 15 patients had either primary refractory/resistant disease and 21 patients had sensitive disease. The two most frequently mutated genes were *TP53* (86%) and *RB1* (58%); other frequently mutated genes (>10% patients) were involved in epigenetic regulation as well as the mTOR pathway. We identified a number of low-frequency, targetable mutations, including *RICTOR*, *FGFR1*, *KIT*, *PTCH1* and *RET*. Using multivariate analysis, *RB1* was the only significant factor ($P = 0.038$) in predicting response to first-line chemotherapy, with an odds ratio of 5.58 comparing mutant *RB1* with wild-type. Patients with mutant *RB1* had both better OS (11.7 versus 9.1 months $P = 0.04$) and PFS (11.2 versus 8.6 months, $P = 0.06$) compared with patients with wild-type *RB1*. Interestingly, ~25% of SCLC cell lines and tumor specimens expressed RB1 protein, possibly representing the subgroup with wild-type *RB1*.

**Conclusions:** We found that SCLC tumors harboring no mutation in *RB1* had a poor response to chemotherapy.

**Key words:** small-cell lung cancer, gene mutations, genomic analysis, survival, *TP53*, *RB1*

## introduction

Small-cell lung cancer (SCLC) accounts for ~13% of all lung cancers [1]. It is a highly aggressive malignancy frequently presenting with metastases at time of diagnosis. Traditionally, SCLC has been divided into limited-stage disease (LS-SCLC, disease that can fit into one radiation portal, corresponding to stages I, II and III) and extensive stage disease (ES-SCLC, corresponding generally to stage IV disease). The majority of patients have ES-SCLC at diagnosis. The standard treatment for LS-SCLC is combination chemotherapy and radiation whereas patients with ES-SCLC are treated mainly with chemotherapy alone [2]. Although response rates to chemotherapy are high, 90% for LS-SCLC and 70% for ES-SCLC, the survival outcome is poor, with 5-year survival rates of <2% for ES-SCLC and 20%–25% for LS-SCLC [3]. Furthermore, there has been only minimal therapeutic advance in the systemic therapy of SCLC over the past 30 years [4], although some hope has been shown for immunotherapy using anti-PD-1 monoclonal antibodies [5].

One potential reason for this lack of progress in SCLC therapeutics is the paucity of in-depth genomic evaluation of human SCLC tumors. These studies lag far behind those carried out in nonsmall-cell lung cancer (NSCLC). Although three seminal genomic studies in SCLC have recently been conducted [6–8], these studies for the most part evaluated patients with surgically resectable tumors, a rare entity (<1% of patients) termed peripheral SCLC.

Unlike NSCLC, no data exist for ES-SCLC on the association of tumor gene mutations with clinical behavior. To pursue this goal, we have established a prospective, clinical–pathologic database of SCLC patients treated at our medical center that now totals over 600 patients. Patient features (e.g. age, sex, race,

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