

Genomic alterations in small cell lung cancer and their clinical relevance

Gary Wildey, Afshin Dowlati

Department of Hematology & Oncology, University Hospitals Case Medical Center, Case Western Reserve University, Cleveland, Ohio, USA

Correspondence to: Afshin Dowlati, MD. Department of Hematology & Oncology, University Hospitals Case Medical Center, 11100 Euclid Avenue, Cleveland, Ohio 44016, USA. Email: axd44@case.edu.

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We thank Karachaliou *et al.* for their insightful editorial (1) regarding genomic studies on small cell lung cancer (SCLC), which included analysis of our own recent study (2). They raise several interesting points, such as the potential use of *ARID1A* mutations and alterations in the PIK3-AKT-mTOR pathway as biomarkers for response to PARP inhibition, that support the idea that real therapeutic progress against this cancer can be gained from genomic studies. The authors specifically pointed out two of our results, however, which they found inconsistent with previous genomic studies of SCLC. The first was our finding that only 58% of our patient cohort carried exome mutations in *RB1*. Our *RB1* results are within the range, however, of several earlier exome studies, which ranged from 39–74% (3–7). This wide range of results is likely caused by the small cohort sizes studied, as well as the divergent demographic populations of the cohorts. The most recent analysis of our cohort (N=67) yielded a 76% mutation rate in *RB1*. As Karachaliou *et al.* correctly point out, a recent whole genome study of SCLC (8) indicates that the *RB1* gene may be altered in >90% of all SCLC tumors, approaching the mutation rate of *TP53* in this cancer. Whatever the true frequency is, we still believe that a small subset of SCLC tumors express RB1 protein, as evidenced by our results in Figure 3, and that this may affect clinical outcome. Even if ≤10% of all SCLC tumors harbored wild type *RB1*, this would still represent a significant population in SCLC because the vast majority of genes mutated in SCLC occur at a similar low frequency. We are currently investigating the question of whether or not the RB1 pathway is functional when RB1 protein is expressed in SCLC. Thus, we remain open to the idea that other

genes, besides *RB1*, can participate with *TP53* loss in a ‘two-hit’ paradigm for SCLC. While it is true that mouse models of SCLC can be produced by double knockout of *TP53/RB1*, we do not feel this eliminates other possible gene combinations. Interestingly, there is a long latency in tumor formation in this mouse model of SCLC (6–9 mo) (9,10), suggesting that additional oncogenic events may take place during tumorigenesis. Concerning *MYC* amplifications, our low rate of detection may simply imply that *MYC* amplification is more commonly seen in relapsed SCLC, after failure of platinum based therapy. Our patient population was mainly comprised of chemo-naïve patients. The challenge before us is to acquire much larger cohorts of SCLC patients for genomic studies so that we can improve our understanding of the clinical significance of gene mutations in this cancer.

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Footnote

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