Editorial

Recalcitrant small cell lung cancer: the argument for optimism

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The US passed the Recalcitrant Cancer Research Act of 2012 to target malignancies with 5-year survival rate less than 50%, to include lung malignancies, with the goal to reduce mortality by fifty percent (1). Small cell lung cancer (SCLC) is the third most common histology of lung cancer accounting for approximately 15% of lung cancer worldwide. While the treatment of non-small cell lung cancer (NSCLC) has made many new advances in the last decade to include immunotherapy, identification of driver mutations and tyrosine kinase inhibitors in patients with EGFR and ALK mutations (2-4), treatment for SCLC has seen little advances since platinum based double agent chemotherapy became the standard of care. SCLC is initially highly responsive to chemotherapy with significant tumor burden reduction after treatment, however the initial success is often followed by relapse and development of chemotherapy resistance. To date the only second line agent approved for SCLC is topotecan and no treatments are approved as third line therapy. New modalities and targets are needed to improve survival and quality of life to our patients.

SCLC has complex genetics and heterogeneity that contributes to the malignancy's resistance to traditional chemotherapy in the second line setting (5,6). This complex genetic environment can be utilized by discovering driver mutations that can direct future targeted therapies. Also, a complex genetic environment with a known high mutational load suggests the formation of neo-antigens that can also lend itself to immunotherapy treatment options. To date clinical trials investigating EGFR, BCR-ABL TKI, mTOR inhibitors, and VEGF inhibitors have not yet been successful in finding survival advantages in these novel therapeutic options. However, significant progress has have been made to better understand the genomic landscape of SCLC. Two publications have confirmed the biallelic loss of TP53 and RB1 and consequent inactivation of both tumor suppressor genes are found in nearly all SCLC (7-9). Currently investigated potential therapeutic targets include EZH2, PARP, cyclin-dependent kinase 1 (CDK1), MCL1, Bcl-2, BIM, Sonic Hh, WNT, NOTCH1, Aurora kinase, FGFR, PIK3CA, RET, THZ1, JAK-STAT, FAK, CXCR4, PDL1, Fuc-GM1, CD56, and CD47 (10).

Limitations to ongoing research include the paucity of SCLC tumor tissue available, as the disease is rarely treated surgically. Additionally, patients are rarely biopsied after their initial diagnosis leaving only pretreatment biopsies for review. Clinical responses are often short lived and patients progress within months of initial response to platinum based chemotherapy. This swift progression places research on a compressed timetable to test new agents with a small window to observe treatment efficacy. A recently published article in *Lancet Oncology* demonstrated promising data with treatment of recurrent SCLC with rovalpituzumab, a DLL3 targeted antibody drug conjugate and member of the Notch-1 signaling pathway (11). Further research is needed to both understand the driver of small cell disease and from there develop therapeutic options.

Semenova *et al.*'s work identifying the transcription factor NFIB as a driver of progression helps to better understand the mechanism of tumor progression and acquired resistance to chemotherapy (12). By using an inactivation of TP53 and Rb1 for a mouse model of SCLC,

they overcame the first struggle with SCLC: paucity of tissue samples available for investigation. Additionally, through *in vivo* experiments Semenova's team identified that NFIB expression is associated with decreased tumor latency and accelerated tumor initiation and progression in the lung. Chromosomal instability on chromosome 4 was identified and hypothesized to reflect clonal evolution resulting in heterogeneity believed to contribute to chemotherapy resistant disease. NFIB overexpression was also associated with increased metastatic disease and increased volume of metastatic disease. Mouse NFIB overexpression resulted in upregulation in genes for cellular growth/proliferation, with cellular movement and cell death being upregulated to an even higher level. The authors then went further and obtained 48 pNET human tumor samples and evaluated their NFIB expression. They found a high expression in SCLC and large cell neuroendocrine tumors, with an expected low expression in typical carcinoid and intermediate grade atypical carcinoid. This paralleled the mouse study data suggesting the findings could be generalizable to human SCLC.

How can we use this information clinically? Two clinical hallmarks of SCLC that makes it such a recalcitrant disease are its disseminated stage at presentation and initial response to treatment that is typically followed within months by chemotherapy resistance. The results of this study help us further understand how SCLC disseminates and develops heterogeneity through chromosomal instability. As the authors state NFIB is a transcription factor with a high amount of potential targets, however determining which targets are therapeutically relevant is required to translate these finding into an effective treatment. We must also continue to search for options for earlier disease detection, as NFIB suppression may help in advanced SCLC progression, or may have no clinical effect at all.

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Footnote

Conflict of Interest: The authors have no conflicts of interest to declare.

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