Editorial Commentary

New potential targeted strategies in small cell lung cancer

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Small cell lung cancer (SCLC) represents 15% of all global lung cancer diagnoses. It is one of the most aggressive forms of lung cancer, characterized by a rapid growing time and a fast develop of metastases. The initial response rate to treatment is up to 80%. However, most of the patients will soon relapse and present fatal disease-related complications including the appearance of central nervous system metastases or even the death due to progressive disease, with a 5-year overall survival of <10% (1,2).

Although lung cancer patients' survival has increased during the last decades (3), this malignancies continue being the principal cause of cancer-related deaths around the world. Most of the survival improvement is reduced to non-small cell lung cancer (NSCLC), due to the incorporation of immunotherapy to the standard of care (SOC) and, most importantly, the discovery of multiple driver mutations which can be targeted by different and effective drugs. However, treatment of SCLC has barely changed during the last three decades, consisting in chemotherapy schemes based on platine-combination doublets. Recently, the addition of atezolizumab or durvalumab to standard chemotherapy treatment of advanced SCLC has shown to increase overall survival, so immunotherapy has finally been incorporated to the first line of metastasic SCLC. Nevertheless, the benefit is modest and median overall survival of SCLC patients is still poor, with an overall survival of 12.3 months with the combination of chemotherapy with atezolizumab (4) or 13.0 months, in case of durvalumab combination (5), with statistical significance compared with the SOC therapy.

To find new therapies, translational research in SCLC is currently focused on increasing the molecular knowledge in this cancer. Mutations in TP53 and RB1 have been identified as mandatory in the pathogenesis of this tumour, as they are found in most of the molecular reports. Other frequent mutations identified are those affecting NOTCH family genes, described in around 25% human SCLC. These molecular alterations have been tested as an effective driver alteration in pre-clinical models. Also, SCLC has been shown to be the malignancy with the highest tumour mutational burden, despite not getting a great benefit from monotherapy treatment with immunotherapy (6,7). Recently, four molecular subtypes of SCLC have been identified based on the expression of different transcription factors: ASCL1 (SCLC-A), NEUROD1 (SCLC-N), POU2F3 (SCLC-P) and YAP-1 (SCLC-Y). Further investigation is need to know if therapeutic or prognostic differences can be observed based on these subtypes (8).

Based on the molecular findings, many studies investigate the potential of new therapies for SCLC. Due to the high mutation rate and the finding of an increased expression of PARP1/checkpoint kinase 1 (CHK1), PARP inhibitors (PARPi) have been widely studied for this purpose. They have shown significant growth inhibition of SCLC *in vitro* and *in vivo* studies (9). Also, clinical trials showed a modest benefit when treating with PARPi, as monotherapy or

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combined with chemotherapy. In an early phase clinical trial, talazoparib showed an objective response rate (ORR) of 8.7% (9). No benefit was observed for maintenance treatment with olaparib after first-line chemotherapy with a platine-combination doublet (10) or for the addition of veliparib to first-line chemotherapy, with no significant differences in terms of progression-free survival (PFS) or overall survival (OS) (9).

Regarding combinations of chemotherapy and PARPi in successive treatment lines, discordant results have been reported (9). Temozolomide plus veliparib showed no benefit in terms of survival (9). However, the combination of temozolomide plus olaparib have shown activity, with a response rate of 41.7% a PFS and OS of 4.2 and 8.5 months, respectively (9). No benefits have been reported in PARPi combinations with different anti-PD-1/PD-L1 immunotherapies (9).

Other different targeted therapies are being investigated. Some studies have tried to target TP53 unsuccessfully (11) while tumour regression has been observed when acting on p73 and p63 in preclinical models when p53 is affected (12). Other studies focus on the apoptosis pathways, as the treatment against BCL-2, frequently overexpressed in SCLC (13). NOTCH protein family, which plays an important role in the neuroendocrine differentiation of SCLC, is also being studied as a potential therapeutic target, mainly Delta-like ligand 3 protein (DLL3) (14,15). BET inhibitors were found to regulate the expression of many different genes critical in the ethiopathogenesis of SCLC, as NEUROD-1 or MYC (16), so different studies are being carried out to determine their potential therapeutic effect. Also, PI3K/AKT pathway seems to be implied in the development of resistance to chemotherapy in SCLC, raising the hypothesis that chemotherapy-resistant cell lines could be sensitive to PI3K inhibitors (17).

Related to kinasa genes, the number of mutations observed in SCLC is much modest than in NSCLC. PIK3CA and FGFR mutations can be found in SCLC and clinical trials targeting them are ongoing. However, RAF-MEK-ERK are extremely rare and KRAS is virtually never found (18).

Beyond all that has been previously described, today we will focus on the ubiquitin proteasome system (UPS) (19). UPS is fundamental for the correct functioning of eukaryote cells. Ubiquitin proteins work binding other proteins and targeting them to be degraded by the proteasome. This protein degradation is involved in numerous physiological processes such as cell-cycle progression, apoptosis, and DNA damage repair. Oncogenic mutations in the ubiquitination process are associated to alterations in the control of cell growth and death. Thus, UPS alterations are involved in the pathogenesis of many cancers, including SCLC (20).

After the clinical success of some proteasome inhibitors as bortezomib and ixazomib in multiple myeloma treatment (21), the interest in targeting UPS components in SCLC has arisen. First studies focused on the main enzymes of UPS, UBA1 and UBA6. TAK-243 is the first molecular inhibitor proved to be effective in targeting UBA1 in preclinical models. It irreversibly inhibits this enzyme by forming a TAK-243-ubiquitin adduct, blocking protein ubiquitination and resulting in impaired cell cycle progression, defective DNA repair and, finally, cell death. TAK-243 caused death of different cancer cell lines and also demonstrated antitumor activity in cell-line derived xenografts (22).

In the present manuscript commented, Majeed *et al.* investigate the role of UPS in the pathogenesis of SCLC and the possible therapeutic applications (19). First, they analysed the expression of UBA1 in 20 different disease sites and observed a high mean expression in SCLC compared to other cancers as NSCLC, what suggests an upregulation of this protein in SCLC. Based on these results, they investigated the effect of the previous mentioned drug, TAK-243, in SCLC cell lines. Different responses were observed, identifying NCI-H1184 as the most sensitive line and NCI-H196 as most resistant to TAK-243. Therefore, they tried to identify genes that could increase sensitivity or resistance to TAK-243. Eight different sets of potential biomarkers were found, also associated with the different SCLC molecular subtypes previously mentioned. Sensitizer genes were related to processes involving the cell cycle, DNA and chromatin organization, and DNA damage repair while resistor genes were associated with cellular respiration. To confirm these results, gene sets were applied into two different patient-derived xenografts (PDX) models. *In vitro* results were confirmed as SCRX-Lu149 PDX model was shown to be sensitive to TAK-243 while JHU-LX33 CN PDX was found to be resistant.

They also studied the synergy of TAK-243 with chemotherapy (carboplatin plus etoposide) and PARPi. This *in vitro* experiment confirmed synergy of both combinations in all but one cell line of SCLC (NCI-H146). Sinergy was independent on whether cell lines were sensitive or resistant to TAK-243 monotherapy. Afterwards, they also studied the combination of TAK-243 and olaparib in PDX models. The combination reported only modest benefit in sensitive PDX (SCRX-Lu149) while significant synergy was observed in

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PDX resistant to TAK-243 monotherapy (JHU-LX33 CN). Finally, they also observed a great inhibition of tumour growth when combining TAK-243 with radiotherapy in the sensitive PDX model. This last finding could lead to the application of TAK-243 also in non-advanced SCLC.

To sum up, this study shows *in vitro* and *in vivo* efficacy of TAK-243 on SCLC. It identifies different gene profiles associated with sensitivity and resistance to this drug, which could act as future biomarkers. Sinergy when combining TAK-243 with chemotherapy or PARPi is observed in resistant cell lines and PDX.

Taken together with all the investigations previously mentioned, Majeed *et al.* contribute importantly to the finding of new therapies for SCLC and, consequently, to improve the prognostic of these patients. However, these promising results must be confirmed in clinical trials so further investigation is required before being able to use all these drugs in the daily practice of medical oncology.

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