

Small cell lung cancer: an overview of the targets

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Lung cancer is the leading cause of cancer deaths worldwide. Small cell lung cancer (SCLC) accounts for approximately 15% of all lung cancer cases. Despite a frequently good response to first-line treatment with chemotherapy and/or radiotherapy, early relapse occurs in the majority of patients and 5-year survival is only about 5%. This histological subtype of lung cancer is strongly associated with tobacco smoking. The behavior of SCLC is unique within solid tumors. Initially, it positively responds to chemotherapy or radiotherapy. However, at relapse, which occurs early in the majority of cases, the tumor is resistant to available therapy and eventually will cause the death of the patient. These results in an overall 5-year survival of approximately 5% for the entire population of patients diagnosed with SCLC. This dismal prognosis has not significantly changed in past years. There is an urgent need for discovery targets to select patients more prone to having a proper response to the treatment, avoiding to reduce their resistance and resulting the increase of overall and progression-free survivals.

Keywords: Small cell lung cancer. Targeted therapies. Immunotherapy. Apoptosis. DLL-3. Receptor tyrosine kinase inhibitors.

INTRODUCTION

Small cell lung cancer (SCLC) is extremely aggressive, undifferentiated neoplasia that originated from the precursors of neuroendocrine cells, that has an early metastasis spread and high proliferation rate (Pesch, *et al.*, 2012). SCLC covers around 15% of all diagnosed lung cancer cases, it is typically correlated with cigarette smoking and it is a very aggressive form of lung cancer associated with a poor prognosis (van Meerbeek, Fennell, De Ruysscher, 2011).

Due to the implementation of strategies for smoking cessation, the incidence of SCLC has declined in the past decade, besides to the recognition of large cell neuroendocrine carcinoma, which before 1990 was considered to be SCLC (Parsons, *et al.*, 2010). There is also a correlation between the increase of SCLC and

the exposure of chloromethyl ether as occupational carcinogens, as well as with the high radon levels for uranium miners. The others 85% of lung cancers are non-small cell lung cancer (NSCLC). SCLC is morphologically and histologically distinct from NSCLC. The worldwide estimate of SCLC for 2015 is 260,000 new cases, with over 11,000 in Europe. The mortality in SCLC is expected to be about 90% in 5 years (Churg, 1994).

Patients with SCLC are divided into two groups or stages: the limited and extensive diseases. Limited disease (LD) is defined as tumor confined to one hemitorax with or without loco-regional adenopathies that could be included in a single radiation field. In addition, it could be treated with combination chemotherapy and radiation therapy, with median survival lower than 24 months. Patients with very limited disease may benefit from surgical treatment. Extensive disease (ED) spreads beyond the ipsilateral lung and regional lymph nodes and cannot be included in a single radiation field and includes the presence of hematogenous metastasis and malignant pleural effusion (Kalemkerian *et al.*, 2013).

Patients with ED-SCLC are treated with chemotherapy alone and their median survival rate is 7

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to 12 months. At initial diagnosis, only 30% of SCLC patients present LD, and the remaining present metastatic disease (van Meerbeeck, Fennell, De Ruyscher, 2011).

SCLC is a chemo refractory disease if progression occurs during first-line therapy or with 90 days of its completion (Carter *et al.*, 2017). Chemotherapy is based on cisplatin, even as NSCLC. Patients receiving platinum-based treatment may be empirically divided into refractory, resistant and sensitive to platinum based on their response to first-line chemotherapy as well as their progression free interval (PFI). Refractory patients are

those with progressive disease during first line treatment. Those showing an initial response but progressing within the first 3 months after treatment completion is defined as resistant. Finally, patients with a PFI longer than 3 months after the end of the first line treatment are classified as sensitive. When this last group of patients relapses, it is globally accepted to receive the same chemotherapy as for first-line treatment. For the former two groups, presenting worse prognosis, treatment with anthracyclines or topotecan is recommended (Califano *et al.*, 2012), as shown in Figure 1.

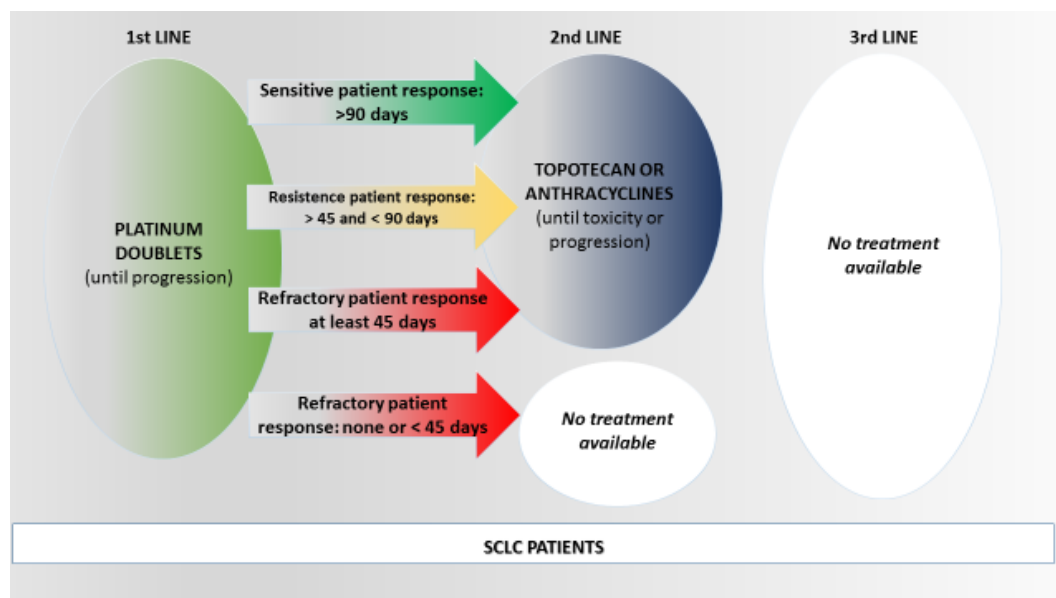


FIGURE 1 - standard treatment for ED-SCLC.

GENETIC ALTERATIONS IN SCLC

The evaluation of whole - exome sequencing of surgically resected samples has showed a considerable prevalence of inactivating mutations in tumor suppressor genes TP53 and RB1, amplifications of MYC family members and mutations of histone modifiers (Peifer *et al.*, 2012; Rudin *et al.*, 2012a; Umemura *et al.*, 2014; Arriola *et al.*, 2008). Ross *et al.* (2014), could also observed a high prevalence of several candidate driver genes (TP53, RB1, CREBBP and EP300) performing target sequence in protein coding exons for >200 genes using specimens of advanced SCLC.

Rudin *et al.* (2012a) reported the presence of PTEN mutations in several cases; additionally, they noted SOX2 amplification and the presence of a recurrent RLF-MYCL1 fusion in SCLC specimens, suggesting that transcriptional deregulation may play a central role in the biology of SCLC (Pietanza, Ladanyi, 2012).

Umemura *et al.* (2014) reported that a comprehensive genomic analysis performed in an Asian cohort revealed a high prevalence of genetic alterations in the PI3K/AKT/mTOR pathway, and they showed that the PI3K/AKT/mTOR pathway is distinguishable in SCLC genomic alterations. Wakuda *et al.* (2014) have performed molecular profiling in a Japanese SCLC cohort and

reported that driver mutations were found in 16% of SCLC patients and *PIK3CA* amplification seemed to be relatively frequent in SCLC.

George *et al.* (2015) sequenced the genomes of 110 SCLC and they presented excellent findings, such as the incidence of bi-allelic inactivation of TP53 and RB1, sometimes by complex genomic rearrangements; somatic genomic rearrangements of TP73; SCLC tumors exhibited kinase gene mutations in rare cases; and they have observed inactivating mutations in NOTCH family genes in a quarter of human SCLC. All these findings suggest that complex genomic rearrangements might further contribute to the pathogenesis of SCLC.

MAIN TARGETS FOR SMALL CELL LUNG CANCER

Receptor tyrosine kinases inhibitors

Driver receptor tyrosine kinase (RTK) inhibitor compounds targeting specific RTKs have been developed and tested in clinical trials in SCLC (Krystal *et al.*, 2000). Various RTKs have been studied in SCLC, including epidermal growth factor receptor (EGFR), fibroblast growth factor receptors (FGFRs), v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (c-Kit), tyrosine-protein kinase receptor Met (c-Met) and insulin-like growth factor-1 receptor (IGF-1R). It is remarkable that multiple receptor tyrosine kinases may have redundant functions in SCLC, needing to co-target multiple receptors to achieve effectiveness (Warshamana-Greene *et al.*, 2004).

SCLC expresses c-Met, the receptor for hepatocyte growth factor (HGF), but an autocrine loop is only rarely present (Maulik *et al.*, 2002) and phosphorylation of c-Met was correlated with poor survival in SCLC patients (Arriola *et al.*, 2011). *MET* is also mutated in a fraction of SCLC (Voortman *et al.*, 2013). A small molecule inhibitor of c-Met also inhibited proliferation and invasion in SCLC cell lines with mutant *MET* (Arriola *et al.*, 2011). The c-Met inhibitor SU11274 was reported to enhance the efficacy of SN-38, an irinotecan derivative, in SCLC cell lines (Rolle *et al.*, 2014).

Unlike what usually occurs in patients with non-small cell lung cancer (NSCLC), *EGFR* mutations are

very rare in SCLC tumor and it is reported around 4% (Tatematsu *et al.*, 2008) and TKIs such as gefitinib, erlotinib and afatinib have failed to show significant clinical benefit for treatment of unselected patients with relapsed SCLC (Moore *et al.*, 2006).

The FGFR family of receptors are fascinating targets for the development of targeted therapies in SCLC. The *FGFR1* gene was reported to be amplified in 5–6% of SCLCs and it may represent a very promising therapeutic approach (Peifer *et al.*, 2012). FGF-2 stimulates the proliferation and chemo resistance of SCLC cells, through ribosomal protein S6 kinases (S6K) and extracellular signal-regulated kinase (Erk) (Pardo *et al.*, 2001 and 2002). PD173074, a small molecule inhibitor of FGFR that is an ATP-competitive inhibitor, may reduce proliferation and induce apoptosis in cancer cells and it has blocked SCLC growth in vitro and in vivo (Pardo *et al.*, 2009).

The IGF-1R is another promising target RTK which is being evaluated in clinical trials in SCLC and it has been reported to be over-expressed in SCLC (Badzio *et al.*, 2010). The IGF-1 can function as an autocrine growth factor in SCLC (Macaulay *et al.*, 1990).

In cell lines depending on IGF-1 signaling, inhibition of the IGF-1R tyrosine kinase activity by NVP-ADW742 was shown to inhibit signaling by the receptor and SCLC growth (Warshamana-Greene *et al.*, 2004). When SCLC cell lines co-expressing SCF/c-Kit and the IGF-1R, it is required both RTKs to inhibit SCLC cell growth (Camirand, Pollak, 2004). Agents targeting the IGF-1R are able to sensitize SCLC to the cytotoxic effects of chemotherapy and radiotherapy (Ferte *et al.*, 2013).

The pre-treatment levels of phosphorylated extracellular signal regulated-kinase (Erk) were recently shown to predict sensitivity to the IGF-1R tyrosine kinase inhibitor OSI-906 in SCLC cell lines (Zinn *et al.*, 2013). Both small molecule inhibitors of the IGF-1R tyrosine kinase activity (OSI-906) and humanized neutralizing antibodies (figitumumab, cixutumumab, MK-0646) are being studied. Single agent trials and combinations with standard chemotherapy have been initiated in SCLC patients. A figitumumab trial was terminated because of the halting of the figitumumab development program (Di Maio, Scagliotti, 2015).

High levels of expression of c-KIT protein, which is a member of the type III RTK family, and high levels of its ligand, the stem cell factor (SCF) have been widely found in SCLC tumors. Anomalous expression of c-KIT may be involved by autocrine and paracrine stimulations of the SCF/c-KIT signaling pathway in pathogenesis of SCLC (Rygaard, Nakamura, Spang-Thomsen, 1993).

The PI3K/Akt/mTOR pathway

The *PI3K/Akt/mTOR* (PAM) pathway is one of the intracellular signaling pathways most frequently deregulated in cancer (Wong, Engelman, Cantley, 2010). Various inhibitors of single key components of the PAM pathway, including PI3K, AKT and mTOR, have been developed due to the key role of PI3K/AKT/mTOR pathway activation in mediating aberrant cell proliferation, survival and resistance to chemotherapy and radiotherapy in SCLC (Krystal, Sulanke, Litz, 2002; Wojtalla *et al.*, 2013; Marinov *et al.*, 2009; Walls *et al.*, 2014).

The PAM pathway has been found to be activated in SCLC (Kraus *et al.*, 2002). Various components of the PAM pathway, including *PTEN* and *PIK3CA* are targeted by genetic alterations in SCLC (Rudin *et al.*, 2012a; Peifer *et al.*, 2012). The PAM/PTEN pathway was reported to mediate SCLC cell growth, survival and resistance to chemo- and radiotherapy (Cui *et al.*, 2014).

Everolimus, an mTOR inhibitor, was active in a subset of SCLC cell lines characterized by an activation of the PAM pathway and low expression of anti-apoptotic Bcl-2 family proteins. The combination of everolimus with drugs targeting Bcl-2 displayed enhanced effects in SCLC (Marinov *et al.*, 2009).

PI3K isoforms can be used as target therapies for SCLC and may represent another promising method for developing new drugs for this disease. Targeting the PI3K isoform p110 induced apoptosis and autophagy in SCLC cell lines by down-regulating selected anti-apoptotic Bcl-2 family proteins, showing that PI3K inhibitors may be more potent than rapamycin analogs (rapalogs) in SCLC (Wojtalla *et al.*, 2013; Arcaro, 2013). The PI3K inhibitor PF-4989216 was shown to impair cell growth *in vitro* and *in vivo* in SCLC cell lines with *PIK3CA* mutations.

In untreated extensive-stage SCLC, everolimus could be safely combined with etoposide and cisplatin, only when prophylactic granulocyte colony-stimulating factor (G-CSF) was included in the treatment protocol (Walls *et al.*, 2014).

The identification of biomarkers which can predict sensitivity or resistance to everolimus and other mTOR inhibitors could be helpful to select patients for treatment and could also suggest novel potential drug combinations to improve their efficacy in the clinical setting (Marinov *et al.*, 2009).

Hedgehog pathway

Hedgehog (Hh) signaling was another pathway under investigation to develop targeted therapies for SCLC (Neal, Sequist, 2010). SCLC is known to have primitive neuroendocrine features. These tumors maintain their malignant phenotype *in vitro* and *in vivo* through ligand-dependent Hh pathway activation (Watkins *et al.*, 2003). The pharmacological inhibition of signaling inhibited the growth SCLC in human and mouse SCLC models (Park *et al.*, 2011). The Hh pathway was also reported by Castellone *et al.*, (2015), to cross-talk with the bombesin neuropeptide receptor pathway in SCLC.

Anti-angiogenesis

Vascular endothelial growth factor (VEGF) is a potent angiogenic factor and was found to correlate with poor survival in SCLC patients (Zhan *et al.*, 2009). SCLC expresses the receptors VEGFR-2 and VEGFR-3 and co-targeting of VEGFR and c-Kit using SU5416 impaired SCLC growth. VEGF levels were also shown to be controlled by c-Kit in SCLC (Litz *et al.*, 2004).

Bevacizumab, a monoclonal anti-body neutralizing VEGF-A was evaluated in clinical trials in SCLC and was shown to be active. Comparing the overall survival (OS) and progression-free survival (PFS), OS and PFS were higher when bevacizumab was added to cisplatin and irinotecan in patients with extensive stage SCLC, although the primary endpoint of the phase 2 trial was not met (Ready *et al.*, 2011). The addition of bevacizumab to cisplatin or carboplatin plus chemotherapy treatment in previously untreated extensive SCLC were evaluated in a phase II-III study. The results have shown that

bevacizumab after induction chemotherapy is not an option in extensive disease SCLC (Pujol *et al.*, 2015).

Tiseo *et al.* (2017) performed a randomized phase III trial to assess the efficacy of adding bevacizumab to first-line cisplatin and etoposide for treatment of extensive-disease SCLC, where the primary end point was overall survival (OS). ED-SCLC patients were randomized in two arms, one receiving only cisplatin plus etoposide and the other receiving the same regimen plus bevacizumab. The addition of bevacizumab to the regimen had an acceptable toxicity profile and led to a statistically significant improvement in progression-free survival, which, however, did not translate into a statistically significant increase in OS.

The addition of aflibercept, a ligand trap which binds VEGF, to weekly topotecan as treatment of patients with progressive SCLC was tested in a randomized phase II trial. The 3-month PFS significantly improved with the addition of aflibercept in the group of patients who had platinum refractory disease (27% vs. 10%; $P=0.02$) but not in the group of patients with platinum-sensitive disease (24% vs. 15%; $P=0.22$). Aflibercept shown higher disease control rate in both groups of patients and no differences in OS were observed, although the addition of aflibercept increased toxicity (Allen *et al.*, 2014).

Other anti-angiogenic therapy that has been tested is the NGR-hTNF, a recombinant protein generated by the fusion of the CNGRCG peptide interacting with CD13 on blood vessels to the N-terminal domain of murine (m) or human (h)TNF. NGR-hTNF is specifically designed to act on tumor blood vessels. This drug can improve the intratumoral doxorubicin penetration by normalizing tumor vasculature and decreasing tumor interstitial fluid pressure. It was demonstrated that combining NGR-hTNF and doxorubicin was safe in relapsed SCLC patients and showed evidence of antitumor activity and promising PFS which appeared to be weakly correlated with platinum sensitivity in the subset analyses (Viganò *et al.*, 2011).

Other agents targeting VEGF/VEGRs have been evaluated in SCLC, such as vandetanib (Yoh *et al.*, 2017), a multi-kinase inhibitor, and sunitinib, a tyrosine kinase inhibitor with broad specificity (Han *et al.*, 2013). Sunitinib may delay progression in sequence with chemotherapy. A Phase II study of maintenance sunitinib

following irinotecan and carboplatin for patients with ED SCLC was performed and this trial provides a 1-year OS of 54% of patients, giving support for further study of sunitinib maintenance therapy following platinum-doublet chemotherapy in patients with ES-SCLC (Spigel *et al.*, 2012).

Recently, pazopanib, a potent, small molecule competitive inhibitor of the tyrosine kinase activity of (VEGFR 1), VEGFR 2, VEGFR 3, platelet derived growth factor (PDGF), and c kit, was evaluated in a Phase II study in the maintenance after first-line etoposide and platinum chemotherapy in patients with extensive disease SCLC and pazopanib maintenance significantly prolonged PFS in patients with ED-SCLC. Given the toxicity profiles, however, relevant biomarkers to select patients for benefit from pazopanib should be further investigated (Sun *et al.*, 2018).

Agents targeting apoptosis

As it occurs in several types of cancer, the apoptotic machinery is one of the most explored targets in SCLC, and is characterized by overexpression of anti-apoptotic B-cell lymphoma 2 (Bcl-2) family proteins. The combination of Inhibition of Bcl-2 and cisplatin and etoposide in human SCLC lines in tissue culture and in murine xenografts increased the efficacy of cisplatin and etoposide, suggesting this combination may significantly increase the antitumor efficacy of cytotoxic chemotherapy alone (Zangemeister-Wittke *et al.*, 1998).

Bcl-2 family inhibitors, including the Bcl-2 antisense complementary to the first six codons of the Bcl-2 mRNA oligonucleotide oblimersen (G3139), ABT-737, S44563 (Loriot *et al.*, 2014), navitoclax (ABT-263) and obatoclax (CX15-070), have been tested in clinical trials in SCLC. Exploratory analyses suggested some potential predictive biomarkers, such as neuron-specific enolase, circulating tumor cell (CTC) number, plasma baseline levels of cytokeratin 19 fragment antigen 21-1, which was correlated with tumor Bcl-2 copy number, and progastrin-releasing peptide (pro-GRP) (Rudin *et al.*, 2012b).

The combination of navitoclax and the mTOR inhibitor ZD8055 induced marked apoptosis in cell

lines and significant tumor regressions in multiple SCLC xenograft models. It is attributed probably because mTORC1/2 inhibition is able to reduce the expression of MCL-1. This study suggests a synergistic combination of BCL-2 and mTOR inhibitors for therapy of SCLC patients (Faber *et al.*, 2015).

Histone deacetylase inhibitors

Histone deacetylase (HDAC) are enzymes involved in the remodeling of chromatin which result from modifying the structure of nucleosomes comprised by a histone octamer around where DNA is wrapped. The opposing activities of histone acetyltransferases (HAT) and HDACs tightly regulate expression of a large number of genes involved in the control of cell cycle and proliferation and many other cellular processes through chromatin modification (Bolden, Peart, Johnstone, 2006). HATs transfer acetyl groups to amino-terminal lysine residues in histones, resulting in local expansion of chromatin and increased accessibility of regulatory proteins to DNA, whereas HDACs catalyze the removal of acetyl groups, leading to chromatin condensation and transcriptional repression. The capacity of HDAC inhibitors to selectively induce apoptosis in tumor cells is their therapeutic potential (Tsurutani *et al.*, 2003; Hubaux *et al.*, 2010).

Some HDAC inhibitors were tested, including Romidepsin (FR901228) shown to inhibit the growth of SCLC cell lines, which was associated with decreased telomerase activity (Tsurutani *et al.*, 2003). Valproate, Trichostatin A and panobinostat were shown to inhibit SCLC cell growth *in vitro* and *in vivo*, and to augment the efficacy of chemotherapeutic drugs (Platta *et al.*, 2007; Crisanti *et al.*, 2009; Hubaux *et al.*, 2010).

Valproate and Panobinostat also induced apoptosis in SCLC, which was associated with decreased levels of anti-apoptotic Bcl-2 family proteins. HDAC and DNA methyltransferases (DNMT) inhibitors combined were shown to be active in pre-clinical SCLC models (Luszczek *et al.*, 2010), which was associated with a restoration of caspase-8 expression and sensitivity to Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) (Kaminsky *et al.*, 2011).

Heat Shock Protein

Heat Shock Protein 90 (Hsp90) is a chaperone protein that regulates the folding, stabilization and function of a great number of proteins including the products of activated oncogenes. Cancer cells have a higher need of chaperones than normal cells to prevent the toxic effects of intracellular protein misfolding and aggregation. Heat shock proteins (HSPs) belong to these chaperones; they are classified into families according to molecular size. HSPs are upregulated in many cancers and inhibition can inhibit tumor growth by destabilizing proteins necessary for tumor survival (Hendriks, Dingemans, 2017).

Many types of cancer have increased expression of Hsp90, suggesting Hsp90 inhibition as a promising therapeutic target (Trepel *et al.*, 2010). An inhibitor of Hsp90, STA-9090, which is thought to be involved in regulating apoptosis or cell death in small cell lung cancer, is in a phase II study in patients with relapsed or refractory SCLC (NCT01173523) (Hendriks, Dingemans, 2017).

Immunotherapy

Lung cancers show one of the highest mutation frequencies of all tumor types, probably related to exposure to well known carcinogens from tobacco smoke (Luszczek *et al.*, 2010). Several immunotherapies have been developed showing promising results with immune checkpoint inhibitors in lung cancer. SCLC is characterized by high expression of PD-L1 and high mutational burden, suggesting that activation of the PD-1/PD-L1 is a major mechanism through which tumor cells escape immune surveillance and that these cells can be particularly sensitive to the PD-1/PD-L1 pathway blockade. High PD-L1 expression has been also correlated with survival. Ipilimumab is a fully humanized IgG1 anti-CTLA-4 monoclonal antibody that blocks binding of CTLA-4 to its ligand increasing antitumor immune responses (Ishii *et al.*, 2015).

Pembrolizumab, a humanized antibody used in cancer immunotherapy is in an ongoing phase II study testing pembrolizumab in extensive stage SCLC patients as maintenance treatment following combination therapy (NCT02359019). Pembrolizumab is also in a phase I

study testing pembrolizumab plus radiation therapy and combination chemotherapy (NCT02402920). Therapeutic vaccine pathways aimed to elicit antigen-specific immune responses seem limited in patients with SCLC. The p53 protein is altered in >90% of patients with SCLC, mostly as a result of point mutations or abnormalities in degradation of wild-type p53. This leads to accumulation of mutant or wt-p53 protein and expression of p53-derived epitopes on tumor cell surfaces in the context of the MHC class I. Therefore, p53 has been suggested as a potential antigenic target to use with immunotherapeutic strategies (Freeman-Keller, Goldman, Gray, 2015). There are also reports on immunotherapeutic approaches for SCLC using vaccines for specific antigens, such as gangliosides (Pietanza, Rudin, 2012; Hall, Gray, Chiappori, 2013).

Ras

Ras family proteins, such as tipifarnib, mediate RTK signals to their downstream signaling cascades; thus, inhibiting their function in SCLC cells may have cytostatic and cytotoxic effects. Farnesyl transferase inhibitors (FTIs) inhibit Ras protein function by impairing their attachment to the membrane. Epidemiological studies have documented a reduction in the incidence of lung cancer in patients treated with statins to reduce the risk of cardiovascular disease (Nielsen, Nordestgaard, Bojesen, 2012). In SCLC, simvastatin was active in cell lines in vitro and in vivo, which was associated with reduced activation of the downstream signaling pathways activated by Ras (Khanzada *et al.*, 2006).

DLL3-targeted

Increased expression of delta-like protein 3 (DLL3) was discovered in SCLC and confirmed in primary SCLC. DLL3 protein is expressed on the surface of tumor cells but not in normal adult tissues. A DLL3-targeted antibody-drug conjugate (ADC),

rovalpituzumab tesirine (SC16LD6.5), comprised of a humanized anti-DLL3 monoclonal antibody conjugated to a DNA-damaging pyrrolbenzodiazepine (PBD) dimer toxin, induced durable tumor regression in vivo across multiple Patient-derived xenograft (PDX) models (Figure 2). Serial transplantation experiments executed with limiting dilutions of cells provided functional evidence confirming that the lack of tumor recurrence after rovalpituzumab tesirine exposure resulted from effective targeting of DLL3-expressing tumor-initiating cells (TIC). In vivo efficacy correlated with DLL3 expression and responses were observed in PDX models initiated from patients with both limited and extensive-stage disease and were independent of their sensitivity to standard-of-care chemotherapy regimens. Rovalpituzumab tesirine has effectively targeted and eradicates DLL3-expressing TICs in SCLC and LCNEC PDX tumors and is a promising first-in-class ADC for the treatment of high-grade pulmonary neuroendocrine tumors. Several studies with rovalpituzumab tesirine are in progress or have been concluded, including a phase III study of rovalpituzumab tesirine maintenance therapy following first-line platinum-based chemotherapy in patients with extensive disease small cell lung cancer (Komarnitsky *et al.*, 2017).

DNA repair

Targeting the enzyme Poly-(ADP-ribose) polymerase (PARP1), a DNA repair protein was showed to be efficacious in pre-clinical models of SCLC (Byers *et al.*, 2012). The expression levels of DNA repair proteins and the activation status of the PAM pathway were reported to predict SCLC response to the PARP inhibitor BMN673 (Cardnell *et al.*, 2013).

Several clinical trials with veliparib (ABT-888) have been initiated in SCLC, including a phase 1 evaluating veliparib in combination with carboplatin and etoposide in extensive stage SCLC (Ramalingam *et al.*, 2014).

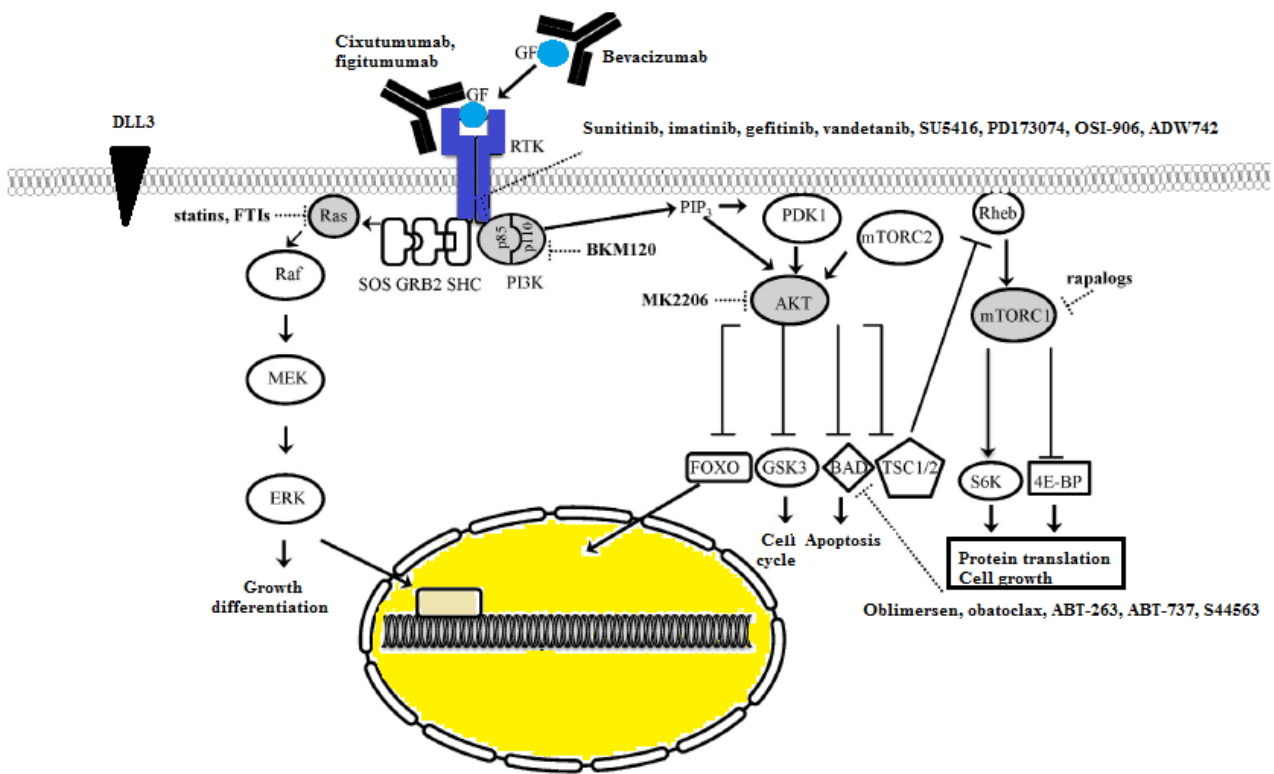


FIGURE 2 - Schematic representation of some classes of targeted drugs that have been evaluated in SCLC, including DLL3. The RTK/Ras/PAM pathway, its regulation by growth factor (GF) binding to receptor tyrosine kinases (RTKs) and the main downstream mediators activated are represented.

CONCLUSION

Small cell lung cancers are responsible for approximately 15% of all lung cancer cases and it is the most aggressive form of neuroendocrine tumor of the lung. Although treatments have not changed significantly, the past decades have shown better improvements in terms of the understanding of the disease, including molecular basis and several targets to develop new therapies. Therefore, IGF-1R inhibitors may be effective therapies for a SCLC subset with low pretreatment phospho-ERK levels (Zinn *et al.*, 2013).

The role of therapeutic vaccines aimed to elicit antigen-specific immune responses seems limited in patients with SCLC. The p53 protein is altered in >90% of patients with SCLC, mostly as a result of point mutations or abnormalities in degradation of wild-type p53. Therefore, p53 has been suggested as a potential antigenic target to exploit with immunotherapeutic

strategies (Hall, Gray, Chiappori, 2013). In addition, the PAM pathway remains one of the most promising targets for SCLC therapies (Markham, 2014).

The DLL3-targeted antibody-drug conjugate, Rovalpituzumab tesirine effectively has shown eradication DLL3-expressing tumor-initiating cells in SCLC and is a promising first-in-class ADC for the treatment of high-grade pulmonary neuroendocrine tumors (Rudin *et al.*, 2017).

SCLC disease is a genetic heterogeneity profile and extremely aggressive nature, thus there is an urgent need for predictive biomarkers to select patients more prone to have proper response to the treatment, avoiding to reduce their resistance and resulting the increase of the overall and progression-free survivals (Sos *et al.*, 2012). Such alterations with immediate therapeutic consequences are rare but present in SCLC, suggesting that individual patients may benefit from genotyping and subsequent targeted kinase inhibitor therapy (George *et al.*, 2015).

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