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# Immunotherapy and small cell lung cancer (SCLC)

**Timothy Allen[1]*, Nepton Sheikh-Khoni[1] and Naveed Basha Court[2]**

[1]Global Allied Pharmaceuticals, Center for Excellence in Research and Development, 160 Vista Oak Dr. Longwood, FL 32779, USA

[2]Hyderabad, India

## Abstract

Lung cancer is the leading cause of cancer death worldwide. Lung cancers are mainly of two types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Small cell lung cancer accounts for about 15% of all the types of lung cancers. The SCLC is also known as small cell undifferentiated carcinoma, oat cell carcinoma and oat cell cancer. Neuroendocrine tumors are another group of tumors that are found in lungs and show a spectrum of tumors, ranging from slow growing non metastatic carcinoid tumors to highly malignant small cell resembling cancers. SCLC has a unique biology with specific molecular and cellular changes. Chromosomal alterations, tumor suppressor genes, oncogenes, aberrant signaling pathways, receptor tyrosine kinases and growth factors are known to occur in SCLC. Immunotherapy might be beneficial for small cell lung cancer (SCLC). There is no immunotherapeutic, which is approved by FDA approved for SCLC, However, a wide variety of immumotherapeuticsare under clinical trials for the treatment of SCLC.

## Abbreviations

CPI: Check point inhibitors; CGH: Comparative genomic hybridization analyses; CIK: Cytokine-induced killer; HPV: Human papilloma virus; HCV: Hepatitis C virus; LAK: Lymphokine-activated killer; MHC: Major histocompatibility complex; mTOR: Mammalian target of rapamycin; MRD: Minimal residual disease; MAB: Monoclonal Antibody Drugs; NSCLC: Non-small cell lung cancer; RTK: Receptor tyrosine kinases; SCLC: Small Cell lung cancer; TSG: Tumor Suppressor Genes; 4EBP1: 4E-binding protein 1; S6K1: Ribosomal protein S6 kinase 1

## Introduction/Epidemiology

Lung cancer is the leading cause of cancer death worldwide. Lung cancers are mainly of two types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). In 2014, American Cancer Society estimated that there were 224,210 (116,000 in men and 108,210 in women) new cases and in the same year, 159,260 (86,930 in men and 72,330 among women) cases of death wereestimated in the United States for both (NSCLC) and (SCLC) [1]. SCLC accounts for 10-15% of all the lung cancers.

The SCLC is also known as small cell undifferentiated carcinoma, oat cell carcinoma and oat cell cancer [2].

## Etiology/Predisposing factors

Small cell lung cancer accounts for about 15% of all the types of lung cancers. Neuroendocrine tumors are another group of tumors that are found in lungs and show a spectrum of tumors, ranging from slow growing non metastatic carcinoid tumors to highly malignant small cell resembling cancers. The various common signs and symptoms of SCLC are voice change, recurrent bronchitis or pneumonia, chest pain, hemoptysis, and persistent cough. The most common risk factors of SCLC are smoking cigarettes, cigars, or pipes, radiation therapy to the chest or breast, air pollution, family history of lung cancer, exposure to chromium, asbestos, arsenic, radon, and nickel in the workplace, and HIV [3]. About 87% cases of lung cancer occur due to smoking in the United States [4].

## Pathophysiology/Molecular basis

SCLC has a unique biology with specific molecular and cellular changes. Chromosomal alterations, tumor suppressor genes, oncogenes, aberrant signaling pathways, receptor tyrosine kinases and growth factors are known to occur in SCLC.

## Chromosomal alterations

The majority of SCLCs have deletions, affecting multiple chromosomal sites, with recurrent losses at 3p, 5q, 13q and 17p, which are the loci for tumor suppressor genes, including p53. Comparative genomic hybridization analyses (CGH) have revealed that a large number of SCLCs harbor gains of 1p, 2p, 3q, 5p, 8q and 19p. These regions encode well-known oncogenes, such as MYC and KRAS. SCLC cell lines are found to have amplifications of 1p, 2p and 3q, with the deletions of 18q, displaying a more aggressive phenotype of the disease [5]. Allelic loss on chromosome 3p occurs with a frequency greater than 90% in SCLC, and is believed to be an early event in lung cancer [6]. Distinct areas of loss that have been identified, include 3p21.3, 3p12, 3p14.2 and 3p24 [7].

Several genes on these regions have tumor suppressor activity and often lose their expression by epigenetic mechanisms. The 3p21 tumor

***Correspondence to:*** Timothy Allen, Global Allied Pharmaceuticals, Center for Excellence in Research and Development, 160 Vista Oak Dr. Longwood, FL 32779, USA, Tel: 13219454283; E-mail: timothy.allen@gapsos.com

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suppressor genes include RASSF1A, FUS1, SEMA3B and SEMA3F. RASSF1A gene is inactivated by tumor acquired promoter hyper-methylation. It encodes a protein similar to RAS effectors proteins and is inactivated in greater than 90% of SCLC [8]. The 3p24 region contains the RARβ gene, which is methylated in 72% of SCLC, leading to the loss of its expression. RARβ plays an important role in the growth regulation of epithelial cells and suppression of tumorigenesis [9].

### Tumor suppressor genes (TSGs)

The tumor suppressor gene p53, located on chromosome 17p13, is the gatekeeper of the cell and protects the cell against genetic instability by regulating cell survival and damage response pathways. It acts as a negative regulator of cellular proliferation by targeting downstream genes, involved in cell cycle arrest (G1 andG2) [p21], DNA repair (GADD45) and apoptosis (BAX) [10]. Inactivating mutations of p53 are seen in approximately 90% of SCLC, of which most of the mutations are missed mutations in the DNA binding domain, while some of them being, homozygous deletions [6].

## Non-receptor oncogenes

### Bcl-2 genes

Theup regulation of Bcl-2 is present in 75–95% of SCLC [11]. Inhibition of bcl-2 shows antitumor activity in SCLC cell lines and in xenograft models [12-14].

### MYC-genes

Amplification of the chromosomal bands, 1p32, 2p23 and 8q24.1 regions, encoding for C-MYC, N-MYC and L-MYC, respectively, has been detected through CGH. The use of genespecific probes has confirmed that C-MYC, N-MYC and L-MYC genes are amplified in small cell lung cancer. The MYC gene encodes for a transcription factor, which aids cell proliferation. This proliferation is induced by the activation of growth-promoting genes and occasionally by repression of growth suppressing sequences [15]. MYC activation has been reported in 18–31% of SCLC and correlates with decreased survival [7].

### Phosphoinositide 3-kinase (PI3K)/AKT/mTOR signaling pathway

The mTOR is a major downstream mediator of PI3K/AKT that targets eukaryotic translation establishment factor 4E-binding protein 1 (4EBP1) and ribosomal protein S6 kinase 1 (S6K1) [16], which controls the protein synthesis [17,18]. The PI3K/AKT/mTOR signaling pathway is an imperfect pathway in small cell lung cancer (SCLC). The SCLC cells keeps an essentially active PI3K [19] and port PTEN and PI3K mutations [20]. The phosphorylated AKT exists in 70% of the tumors in SCLC patients [21]. The protein expression of 4EBP1, S6K1 and mTOR are raised in the SCLC cells as compared to the type-2 epithelial cells [22].

### Receptor tyrosine kinases and growth factors

There are various tyrosine kinase receptors, which are overexpressed in the SCLC. They are alsoassociated with the activation of downstream signaltransduction molecules, migration and survival, cell proliferation, and modification of reactive oxygen group. The numerous defective tyrosine kinase receptors and their particular growth factors comprise FGFR/FGF, c-Kit/SCF, IGF-1R/IGF, c-MET/HGF, and VEGFR/VEGF in SCLC. Throughout the activation of several pathways, as well as the activation of the PI3K/AKT/mTOR,these signaling pathwaysare recognized to be dys-regulated in SCLC. These are also concerned in the translation, apoptosis, survival, and cell cycle regulation [7]. The inhibitors of tyrosine kinase receptors have developed into probable anti-tumor agents in the SCLC.

## Immunotherapy

Current immunotherapy option for SCLC are discussed in following categories: kinase inhibitors, monoclonal antibodies, mTOR inhibitors, Preteosome inhibitors and vaccine therapy.

### Kinase inhibitors

Non-FDA approved Kinase Inhibitors: (Table 1)

### Mammalian target of rapamycin (mTOR) Immunotherapy

Non-FDA approved Mtor Inhibitors: (Table 2)

### Monoclonal antibody drugs (MABs) and check point inhibitors (CPIs)

Non-FDA Approved drugs: (Table 3)

### Proteasome inhibitors

Non-FDA Approved proteasome inhibitors: (Table 4)

### Vaccines

Non-FDA Aapproved vaccines: (Table 5)

### Miscellaneous

**Cytokine-induced killer (CIK) cells:** A preparation of autologous lymphocytes with potential immunopotentiating and antineoplastic activities. Cytokine-induced killer (CIK) cells are CD3-and CD56-positive, non-major histocompatibility complex (MHC) -restricted, natural killer (NK) -like T lymphocytes, generated ex-vivo by

**Table 1.** Non-FDA approved tyrosine kinase drugs [23-28].

| Drug | Clinical trial identifier number | Phase | Study design | Target |
|---|---|---|---|---|
| Sunitinib malate | NCT00453154 | Phase 2 | Randomized, Double blind, Safety/Efficacy Study | VEGF |
| Sorafenib | NCT00182689 | Phase 2 | Open label, Efficacy Study | RAF/VEGF |
| Trametinib | NCT02079740 | Phase 2 | Open label, Safety/Efficacy Study | MEK 1 and 2 |
| BIBF 1120 | NCT01441297 | Phase 2 | Open label, Efficacy Study | VEGFR, PDGFR, FGFR |
| Pazopanib | NCT01713296 | Phase 2 | Open label, Efficacy Study | VEGFR, PD-GFR |
| Ponatinib | NCT01935336 | Phase 2 | Open Label, Efficacy Study | Bcr-Abl |

**Table 2.** Non-FDA approvedmTOR drugs [29,30].

| Drug | Clinical trial identifier number | Phase | Study design | Target |
|---|---|---|---|---|
| Everolimus | NCT00374140 | Phase 2 | Open label, Treatment | mTOR |
| ME-344 | NCT02100007 | Phase 1, 2 | Open Label, Safety Study | mTOR |

**Table 3.** Non-FDA approved MAB drugs [31-40].

| MABs | Clinical trial identifier number | Phase | Study design | Target |
|---|---|---|---|---|
| Ipilimumab | NCT01450761 | Phase 3 | Efficacy Study, Double blind | CTLA4 |
| Bevacizumab | NCT00118235 | Phase 2 | Open label, Efficacy Study | VEGF |
| Dalotuzumab | NCT00869752 | Phase 1, 2 | Non-Randomized, Open label, Safety/Efficacy Study | IGF1R |
| BIW-8962 | NCT01898156 | Phase 1, 2 | Open label, Safety/Efficacy Study | GM2-expressing tumor cells |
| Nivolumab | NCT01928394 | Phase 1, 2 | Open label, Efficacy Study | PD-L1 |
| Pembrolizumab | NCT02331251 | Phase 1, 2 | No-Randomized, Open label, Safety/Efficacy Study | PD-1 |
| Mogamulizumab | NCT01929486 | Phase 1 | No-Randomized, Open label, Safety/Efficacy Study | CCR4 |
| Tremelimumab | NCT02261220 | Phase 1 | Non-Randomized, Open Label | B7-1 and B7-2 |
| Monoclonal antibody Hu3S193 | NCT00084799 | Phase 1 | Treatment | Lewis Y antigen |
| SC16LD6.5 | NCT01901653 | Phase 1, 2 | Open Label, Safety/Efficacy Study | Fyn3 |

**Table 4.** Non-FDA approved proteasome inhibitor drugs [41,42].

| Proteasomeinhibitors | Clinical trial identifier number | Phase | Study design | Target |
|---|---|---|---|---|
| Carfilzomib | NCT01941316 | Phase 1 | Open label, Safety/Efficacy Study | 20S proteasome |
| Bortezomib | NCT00720785 | Phase 1 | Non-Randomized, Open label, Safety/Efficacy Study | (NF)-kappaB |

**Table 5.** Non-FDA approved vaccines [43,44].

| Cancer vaccine | Clinical trial identifier number | Phase | Study design | Target |
|---|---|---|---|---|
| HLA-A*2402-restricted CDCA1 and KIF20A peptides | NCT01069653 | Phase 1 | Non-Randomized, Open label, Safety/Efficacy Study | 20S proteasome |
| NY-ESO-1 | NCT01584115 | Phase 1, 2 | Open label, Safety/Efficacy Study | Cancer cells |

**Table 6.** Miscellaneous drugs [45-48].

| Treatment | Clinical trial identifier number | Phase | Study design | Target |
|---|---|---|---|---|
| CIK cells | NCT01498055 | Phase 2, 3 | Randomized, Safety/Efficacy Study | Cancer cells |
| Ganetespib | NCT02261805 | Phase 1, 2 | Open Label, Safety/Efficacy Study | Hsp90 |
| MGN1703 | NCT02200081 | Phase 2 | Randomized,Open Label, Safety/Efficacy Study | T-helper 1 cell |
| Iscomatrix | NCT01258868 | Phase 2 | Open Label, Safety Study | Cancer cells |

incubation of peripheral blood lymphocytes (PBLs) with anti-CD3 monoclonal antibody, interleukin (IL) -2, IL-1, and interferon gamma (IFN-gamma) and then expanded. When reintroduced back to patients after autologous stem cell transplantation, CIK cells may recognize and kill tumor cells associated with minimal residual disease (MRD). CIK cells may have enhanced cytotoxic activity compared to lymphokine-activated killer (LAK) cells.

**Ganetespib:** A synthetic small-molecule inhibitor of heat shock protein 90 (Hsp90) with potential antineoplastic activity. Ganetespib binds to and inhibits Hsp90, resulting in the proteasomal degradation of oncogenic client proteins, the inhibition of cell proliferation and the elevation of heat shock protein 72 (Hsp72); it may inhibit the activity of multiple kinases, such as c-Kit, EGFR, and Bcr-Abl, which as client proteins depend on functional HsP90 for maintenance. Hsp90, a 90 kDa molecular chaperone upregulated in a variety of tumor cells, plays a key role in the conformational maturation, stability and function of "client" proteins within the cell, many of which are involved in signal transduction, cell cycle regulation and apoptosis, including kinases, transcription factors and hormone receptors. Hsp72 exhibits anti-apoptotic functions; its up-regulation may be used as a surrogate marker for Hsp90 inhibition.

**MGN1703:** A synthetic oligonucleotide based on a proprietary double stem-loop immunomodulator design with potential immuno-stimulating activity. TLR9 agonist MGN1703 binds to and activates intracellular Toll-like receptor 9 (TLR9) in monocytes/macrophages, plasmacytoidal and myeloid dendritic cells (DCs), and natural killer (NK) cells, initiating immune signaling pathways and inducing T-helper 1 cell (Th1) production, leading to the production of memory T-cells and a Th1-mediated immune response. By activating the immune system, MGN1703 may attack tumor associated antigens (TAAs). TLR9 is a member of the TLR family, which plays a fundamental role in pathogen recognition and activation of innate immunity.

**Iscomatrix:** An adjuvant comprised of saponin, derived from the bark of Quillaiasaponaria Molina, cholesterol and phospholipid with antigen-delivery and immunostimulatory activities. This saponin-based adjuvant in combination with various antigens, including those for human papilloma virus (HPV), hepatitis C virus (HCV), and the human cancer antigen NY-ESO-1, may result in potent antibody, CD4+ T-helper-cell, and CD8+ cytotoxic T-cell responses against the targeted antigen. In addition, this agent may reduce the amount of antigen necessary to induce an efficient immune response in the host (Table 6).

## Conclusion

Immunotherapy might be beneficial for small cell lung cancer (SCLC). There is no immunotherapeutic, which is approved by FDA approved for SCLC, However, a wide variety of immumotherapeuticsare under clinical trials for the treatment of SCLC. The recent activities have increased our understanding of the tumor microenvironment, various immunotherapeutic modalities or combination therapy (like chemotherapy with immunotherapy). Proper preclinical and clinical designs are the important pillars in understanding the future of immunotherapy in treating patients, suffering from lung cancer.

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