*Grand Asian Journal of Biological and Pharmaceutical Sciences*

# Update on management and targeted therapies for small cell lung carcinoma

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**Abstract**

Small-cell lung cancer (SCLC) is an exceptionally lethal subtype of lung cancer mainly coupled with smoking trends and is becoming the most common cause of cancer related deaths in the world. Patients with limited stage SCLC (LS-SCLC) are advised to carry out Prophylactic Cranial Irradiation (PCI) along with Combination therapy comprised of initial dose of thoracic radiation therapy maintained by a cycle of chemotherapy. Chemo-radiation technique is considered as standard for the patients of LS-SCLC. In clinical outcomes of small cell lung cancer immunotherapy has made progress and has led to significant improvement in the treatment of SCLC.The First line standard treatment for extensive stage-SCLC (ES-SCLC) comprises of chemotherapy with etoposide and platinum compounds like cisplatin, carboplatin etc. FDA has recently approved the combination of Carboplatin and Etoposide with Atezolizumab for the patients of ES-SCLC. Some molecule-targeted therapies are used alone or in combination with chemotherapy like Anti-Angiogenesis Drugs, Histone Deacetylase Inhibitors, Apoptosis Targeting Agents and Cell signaling targeting agents. DNA repair proteins like MGMT, PARP1, CHK1 & BRCA1, 2. PARP1 are the important treatment targets in SCLC. Several anti-PD-1 and anti-PD-L1 monoclonal antibodies are under current investigations and have been tested in both front-line setting and as maintenance therapy in pretreated patients with SCLC. Rovalpituzumab-tesirine (Rova-T) is used as Cytotoxic Antibody–Drug Conjugate for SCLC. Keeping in view the current research literature, innovative clinical trial projects are needed to competently discover the increasing number of choices with new drugs and new combinations. This review looks at the diverse options of treatment that have been used over the last few years and tries to highlight the best available.

**Keywords:** LS-SCLC, ES-SCLC, Chemotherapy, monoclonal antibodies, Cytotoxic Antibody–Drug Conjugate

Received: date 13 July 2025
Revised: date 6 August, 2025
Accepted: date 10 August 2025
Published: date 14 August



**ISSN:** 0000-000

## 1. Introduction

Lung cancer has been the most common cancer world wild both in terms of incidence and mortality. Lung cancer is the major cause of death in both males and females in US and around the world. It is most frequently diagnosed cancer (11.6%), followed by female breast (11.6%) and colorectal cancer (10.2%). Incidence rates are on track to increase by 38% to 2.89 million by 2030 world wild which will be dangerous. Mortality rate is

projected to reach 2.45 million by 2030 world wild which is 39% increase since 2018. Extensive prospective epidemiologic data clearly found that cigarette smoking is the major cause of lung cancer. Lung cancer rates and trends vary substantially by sex, age, race/ethnicity, socioeconomic status, and geography because of differences in historical smoking patterns. Lung cancer is of two types first small cell lung cancer (SCLC), the less common type that occurs in 15% cases, second non-small cell lung cancer (NSCLC), the more common type that accounts for 85% cases. NSCLC is further divided into three types: Squamous cell carcinoma, Adenocarcinoma, Large cell carcinoma. The repeated biopsy studies have shown that adenocarcinoma can convert to SCLC histologically because both of these arise from same cell type (Oser et al., 2-15). SCLC has its unique features that were recognized by Barnard in 1926. The clinical features of SCLC were discussed later by Watson and Berg which include central location on chest radiography, high initial response rate to chemotherapy, ability to spread fast at initial stages and particularly high rate of metastases at autopsy. SCLC is the most lethal type of the lung cancers, large number of SCLC patients show response to chemotherapy but most of them (about 95%) die sooner or later. SCLC is most commonly caused by tobacco smoking (Jackman & Johnson 2005). More than 60 mutagens are present in tobacco smoke that binds with DNA and cause mutations in it, for example substitutions in TP53 and KRAS etc. (Pleasance et al., 2010). Tobacco smoking is known to cause the development of SCLC in more than 95% patients. The risk of developing SCLC depends on both how many cigarettes are smoked in a day and the time duration spent on smoking. The risk decreases upon smoking cessation compared to the individuals who continue smoking (Jackman & Johnson 2005). Recently the number of SCLC patients has decreased significantly which can be due to lesser number of cigarette smokers in the recent years or change in the composition of cigarettes i.e., decrease in tar and nicotine (Govindan et al., 2006). SCLC can be diagnosed by its unique characteristics, it is a malignant tumour of epithelial cells consisting of small cells with decreased amount of cytoplasm, the borders of cells are not well-defined, the chromatin material is granular and with the absence of nucleoli (D'Angelo & Pietanza 2010).

**Pathophysiology**

More than 60 mutagens are present in tobacco smoke, which has ability to chemically alter the DNA. They bind with DNA and form large adducts at purine bases (Adenosine and Guanine) as the carcinogens in tobacco smoke target these. This causes distortion of DNA helix resulting in non-Watson-Crick pairing while the copying of DNA if repair mechanism is not activated. The formation of adduct, the type of repair mechanism and the kind of mispairing during replication is determined by the physicochemical properties of the mutagen. One of the repair mechanisms is that when bulky adducts are formed the impede RNA polymerase; RNA polymerase correctly identifies the alterations in DNA and call upon nucleotide excision repair machinery which removes the altered nucleotides preventing mutations. This repair mechanism is responsible for preventing mutations in transcribed strand. Another repair mechanism is responsible for preventing changes on both transcribed and non-transcribed strand i.e., novel expression linked repair pathway (Pleasance et al., 2010).

SCLC shows specific molecular changes as well as cellular changes. The major changes include chromosomal changes, impairment of anti-oncogenes and cell signal pathways, increasing the response of RTKs, factors responsible for growth and cell surface markers (Kadara et al., 2016). Till now no paraneoplastic lesion of SCLC is identified. There is a significantly high incidence of epithelial alterations nearby SCLC than in NSCLC. It leads to widespread and extensive molecular damage in normal tissues surrounding SCLC. So, it may be concluded that SCLC may develop from normal epithelium or epithelium with slight abnormalities (Park et al., 2011). The important genetic and molecular changes include: autocrine growth loops, proto-oncogenes activation and loss or inactivation of tumor suppressor genes. SCLC cell lines produce the peptides i.e., the gastrin-releasing peptide and neuromedin B as well as they express receptors for these peptides. Upto 85% of SCLC cell lines have one of these receptors. The SCLC cell lines secrete these peptides which bind to the receptor resulting in its activation and creating an autocrine growth loop in the tumor cells.

The MYC (CMYC, NMYC and LMYC) is a proto-oncogene that is responsible for encoding of transcription factors and nuclear phosphoproteins which results in regulation of gene transcription, increasing the cell

growth and continuation of cell cycle. In 16-32% SCLC, gene amplification causes the overexpression of MYC gene which results in uncontrolled proliferation with no differentiation. The growth rate was shown to be decreased along with down-regulation of CMYC when SCLC cell lines were treated with MYC antisense DNA and tretinoin (Jackman & Johnson 2005). Human SCLC also showed FGFR1 oncogene amplification7. Like 90% of the tumors, deletion of alleleomorphs from short arm of chromosome 3 also occurs in tumor DNA of SCLC. It is stated that 3p arm carries most of the anti-oncogenes (Jackman & Johnson 2005). Some major tumor suppressor genes that are inactivated or deleted are: FHIT (Fragile histidine triad) gene in which deletion of 3p (14-23) occurs (D'Angelo & Pietanza 2010). FHIT is responsible for producing the enzyme diadenosine triphosphate hydrolase, hence controlling the cell cycle. RASSF1 (RAS effector homologue) is responsible for producing microtubule-binding protein which causes the stability and arrest of cell cycle. Another, retinoic acid receptor β, through which retinoid induce apoptosis and exert activity against activator protein (Oser et al., 2015). FUS1 is responsible for protein myristoylation which is important for tumor suppression. In small-cell-lung-cancer cell lines all of these four genes are mostly deleted or inactivated.

TP53 gene encodes for TF that is responsible for the control of continuation of cell cycle. Mutations of TP53 gene occurs in 75% of SCLC cell lines. RB1 (retinoblastoma) gene encodes for nuclear phosphoprotein that is responsible for the control of continuation of cell cycle. Mutations that lead to inactivation of RB1 are present in 90% of tumors. PTEN gene regulates tyrosine phosphatase activity on phosphatidylinositol triphosphate responsible for inhibition of phosphatidylinositol-3kinase/Akt pathway (Jackman & Johnson 2005). RB1 inactivation is necessary for the development of SCLC but it alone is not sufficient. Hedgehog pathway (Hh pathway) activations are found in most of small cell lung cancer cell lines and tumors. The pharmacological inhibition of Hh pathway leads to significant suppression of SCLC by increasing apoptosis and decreasing proliferation which shows that Hh pathway has significant role in SCLC maintenance8. SCLC shows high expression of neuroendocrine markers. NOTCH pathway is responsible for tumor suppression and regulation of neuroendocrine markers expressed in SCLC (Katoh & Katoh 2020). In SCLC, inhibition of NOTCH pathway is observed which is driven by somatic mutations (LoF NOTCH1 mutations) in genes that encode for NOTCH signaling components (Alberg et al., 2013). All these mutations lead to decrease in pro-apoptotic activity during tumor generation in SCLC. It encourages the rapid growth and survival of tumor cells (D'Angelo & Pietanza 2010). Non-small cell lung cancer is divided into three types, adenocarcinoma, squamous cell carcinoma and large cell carcinoma. Adenocarcinoma shows EGFR activating mutations and biopsy samples shows its ability to transform to SCLC due to common cell of origin. The cell of origin of SCLC are neuroendocrine cells while for adenocarcinoma its type 2 alveolar cells. If RB1 and TP53 genes are inactivated in type 2 alveolar cells it caused the development of SCLC and the resistance usually develops within 12 months or so. The mechanism of resistance is as follows: •Thr790Met changes in EGFR results in increased binding ability of receptor for ATP. Thus, EGFR signaling continues even in the presence of EGFR inhibitors. •MET and HER2 amplification can also result in the resistance to EGFR inhibitors as they bypass requirement for EGFR signaling. •Resistance from EGFR inhibitors can also be due to transformation of adenocarcinoma with EGFR mutations to SCLC. The transformed SCLC tumor maintained its original EGFR activating mechanism. Furthermore, this transformation is not solely because of resistance mechanism as the transformation can occur even if the EGFR inhibitors are not given i.e., independent of EGFR mutational status. While transforming, EGFR expression protein is lost and there are lower levels of EGFR amplification (Oser et al., 2015).

**Risk factors and Environmental exposure**

Smoking is a reputable cause of lung cancer and the risk of lung cancer related with cigarette smoking is high, but less than the perceived risk of cigarette smoking due to improvements in smoking rate and deep breathing. Cigarette tar refers to the residual shortening of cigarette smoke, that is, all the cigarette smoke particles accumulated on a machine's sensor, minus moisture and nicotine. The tar is a varied blend containing a variety of carcinogens (Members, 2018). A dose-response association exists between smoking tobacco and the danger of developing lung cancer (Moir et al., 2008). Tobacco smoke consists of more than 4,000 chemicals known, of which more than 50 are classified as carcinogenic. Most chemicals are created by the burning of tobacco,

including benzene, carbon monoxide, and formaldehyde (Malhotra et al., 2016). Americans have excessively great proportions of lung cancer and menthol cigarettes could be concomitant with lung cancer risk much more severely than non-menthol cigarettes (Moir et al., 2008). In the production of lung malignancy, radon was implicated. From the word-related introduction among uranium miners, the risk of lung malignant growth is resolved. The danger associated with private radon is unknown. Among those exposed to radon, smokers have a greater risk for lung cancer than nonsmokers (Moir et al., 2008). With extended introduction of asbestos, the danger of lung malignant growth has been noted to increase and to be correlated with the main occupational types of asbestos. Asbestos and cigarette smoking are both autonomous roots of lung disease, but they function synergistically in association to produce a particular risk of lung malignancy (Moir et al., 2008).

Studies suggest association between diesel exhaust exposure and lung cancer cause consistent increased risk, i.e hazardous (Travis et al., 2015). The risk of lung malignant growth may be raised by high meat consumption, particularly cooked or very much done red meat, and this may be identified with the formation of nitrosamines during cooking. There is evidence from retrospective examinations that low levels of vitamin D are correlated with the risk of lung malignant development (Moir et al., 2008). Air pollution may derive from approaching outdoor air or, for example, from smoking tobacco, gases, and from heating and cooking indoors. In developed nations, two indoor contaminations that most distinctively increase the risk of lung malignancies in non-smokers are smoking and radon. Indoor air impurity is of significant concern in developing nations because of the use of natural strong fills, remarkably delicate energizes of coal and biomass, for cooking and space warming (NLCS Members, 2018). Epidemiological examinations revealed the relationship between past implementation of air pollution and lung malignancy have been largely restricted by the use of intermediate indicators; for example, the number of inhabitants in the housing and housing network is almost a significant source of contamination. In either case, this information is contradictory and largely represents current levels or levels in the past (Travis et al., 2015).

**Diagnosis**

Histologically SCLC is defined as malignant epithelial tumor containing small cells with ill-defined borders, scant cytoplasm, absent or discreet nucleoli and finely granular nuclear chromatin. SCLC typically involves only small cells and it accounts for roughly 90% cases. Residual cases are categorized as mutualdisease that contains large cell components in tumor(Wang et al., 2019). According to World Health Organization (WHO) classification pathological diagnosis should be made using morphological characteristics. Immunohistochemistry are commonly helpful to confirm diagnosis to recognize markers such asCD56, synaptophysin, MIB-1chromogranin and thyroid transcription factor (Oser et al., 2015). From the chest on the area of tumor, biopsies may be obtained by transthoracic needle aspiration, bronchoscopy, mediastinoscopy, endobronchial ultrasound, or thoracoscopy, if required. Biopsy from a metastatic lesion is the ideal approach, and in ES-SCLC this will stage patient pathologically (Blandin Knight et al., 2017). Auto-fluorescence bronchoscopy (AFB) focuses on the finding that when dysplastic or carcinomatous lesions are produced, the emission array of bronchial mucosa under blue light changes. In one study of lung squamous cell carcinoma, a section of three miRNAs (mir-708, mir-210 and mir-205) had a diagnosis specificity of 72 per cent and a precision of 95 per cent (Halvorsen et al., 2016). MicroRNAs (miRNAs) are important quality expression controllers working via translational inhibition or deterioration of delivery individual RNA (mRNA) objectives. Amendment within miRNA countenance has been linked with the pathogenicity of most carcinomas (Goldstraw et al., 2016). Upregulation of miRNA-21 has been shown in both lung malignancies. MiRNA circulating is present in the bloodstream from both solid controls and patients with pulmonary virulent development. They tend to make up a majority of the RNA segment in the bloodstream and are amazingly immune to RNAse deterioration. This reliability ensures that miRNA can be used as a prognostic indicator (Halvorsen et al., 2016).

An initial computed tomography (CT) scan of the chest and abdomen is recommended. Magnetic resonance imaging scan is favored over contrast-enhanced CT scan. Bone marrow biopsy performed in case of bone marrow invasion and abnormal blood count. Preferred imaging processof choice is 2-fluor-2-deoxy-D-glucose

positron emission tomography (FDG-PET) CT scan, as it can assess the bones, as well (Blandin Knight et al.,) (Komaki, 2003) (Halvorsen et al., 2016)). Normally in the clinic Veterans' Administration classification of lung group is used to stage SCLC. Limited-stage small-cell lung cancer is well-defined as cancerwith or without involvement of regional lymph-node confined to 1 hemithorax, which can be securely incorporated in anacceptable radiation field. Extensive-stage small-cell lung cancer (ES-SCLC) is well-defined as tumor that cannot be carefully incorporated in anacceptable radiation field. At initial diagnosis, extensive stage disease develop in two third of patients (Eze et al., 2018).

**Treatment/Management**

SCLC management is complex by frequent considerable comorbidities due to smoking, by aggressiveness and reduced performance status, which make it difficult to assign patients with SCLC to suitable clinical trials. On staging basis treatment is highly dependent; patients with LS SCLC are dependent on chemotherapy and curative-intent radiation therapy. Patients with ES-SCLC disease are potential candidate for chemotherapy with radiation (RT) reserved for selected candidates and palliation (Komaki, 2003).

**Limited stage small cell lung cancer**

Approximately 1/3rd of patients with SCLC have LS disease. Combined radiation therapy and chemotherapy typically used to treat LS-SCLC. Limited stage is about continuous exposure of radiations to mediastinum and thoracic region. If it was effective, then patient advised to carry out Prophylactic Cranial Irradiation (PCI) in order to secure them from further spreading of tumor to brain (Furuta et al., 2019). LS-SCLC includes; Combination Therapy, Surgical Resection and Chemo radiation therapy.

In past ten years, the treatment of limited stage small lung cancer has been developed vastly. Experiments have shown that the combination therapy in SCLC have higher rates of survivability than treatment with chemotherapy and thoracic radiation therapy. It is also proved by experiments that treatment with combination therapy (Thoracic Radiation Therapy & Chemotherapy) is supercilious than individual and local regional therapy. The procedure of combination therapy consists on initial dose of thoracic radiation therapy and then maintained by a cycle of chemotherapy. The combination therapy for patients showing great response to it and supportive care (GC-Stimulating Factor, antibiotics and erythropoietin) are considered as standard treatment for limited stage-SCLC. The combination therapy proved to be efficacious than individual treatment with TRT and chemotherapy. The survivability rate with the patients treating with combination therapy is 4% and it constitutes a remarkable revamp in the two years survivability rate revealed in 1980s. In combination therapy administered etoposide and cisplatin concurrently with thoracic radiation therapy (Waqar & Morgensztern, 2017).

Recent studies have shown that surgical resection may take part in the systematic eclecticism of early Limited-Stage SCLC. Studies show 68% survivability rate when 82 patients recovered by surgical resection followed by concomitant platinum chemotherapy. Retroactive studies also manifest revamp survivability in local plus regional disorder when treatment is followed by surgical resection. One other retroactive study comprises of 227 patients showed that surgical resection has ameliorate survivability rate when compared with other non-surgical methods. The role of surgery in the treatment of LS-SCLC can be accessed by trials. Some scanning before surgery is recommended which includes CT/PET-CT Scan, Magnetic Resonance Imaging and the evaluation of lymph nodes (Waqar & Morgensztern, 2017). According to National Comprehensive Cancer Network (NCCN)and the American College of Chest Physicians (ACCP) current guidelines patients with stage 1 clinical disease considered for surgery only, and in patients who undergo surgery adjuvant chemotherapy followed by PCI is recommended (Blandin Knight et al.,).

It is the combination of Chemotherapy based on Cisplatin and Radiotherapy. Chemo radiation technique is considered as standard for the patients of LS-SCLC. In a narrative review of 2140 patients by a scientist Pigon

et al, this technique was related to refine survivability vs. chemotherapy alone. The treatment should be started immediately or with a month of chemotherapy. The duration of radiotherapy have a lot of significance if the time period of therapy is less than 30 days. The frequency and dosage of radiation is critically kept under consideration. The dose of Gy is 24-45 while radiation is administered in 1.5Gy twice a day for 3 weeks or 1.8 Gy once a day for 5 weeks. The 1.5 Gy dose of radiation for twice a day is preferred over large dose due to patient's compliance, soearly administration of 45 Gy with parallel 4 to 6 cycles of etoposide and cisplatin recommended(Blandin Knight et al., 2017)

**Extensive Stage Small Lung Cancer**

At the time of diagnosis, patients with SCLC, 60 to 70% patients have extensive-stage disease. Extensive Stage Small Lung Cancer can be describe as spreading of cancer to the other body organs. ES Small Cell Lung Cancer includes Chemotherapy that include 1st Line Standard Chemotherapy, 2nd Line Standard Chemotherapy, Combined Chemotherapy and Immunotherapy, Targeted Therapy (Sunitinib, Alisertib and Antibody-Drug Conjugates) and Radiotherapy (Prophylactic Cranial Irradiation). Standard care for ES-SCLC included combination chemotherapy containing etoposide and platinum agent.

The First line standard treatment for extensive stage-SCLC comprises of chemotherapy with etoposide and platinum compounds like cisplatin, carboplatin etc. and the survival rate from these treatment remains 70% and the patients reoccur disease in the duration of about half a year. In Japan, the combination of Platinum with Irinotecan was use and it was successful at that time. After further experiments in North America, the benefits of combination of Platinum based compounds with etoposide and Irinotecan remained controversial and due to rapid recurrent of disease a new compound known as Topotecan got approval from FDA and it is the only available systemic treatment for fighting against relapse of disease at that time. Survival rate from chemotherapy is around 10 months. Sensitivity of Small cell lung cancer towards preliminary treatment is high but most patients have relapsed the disease after the preliminary therapy (Blandin Knight et al., 2017). Other techniques like Prophylactic Cranial Irradiation (PCI) and Thoracic region radiation also done but not recommended because it is not a standard treatment for all patients (Armstrong & Liu, 2020). Combination chemotherapy proved to be more effective even in older patients and in patients with immunocompromised health status. In the middle 1980's, the combination of Etoposide and Cisplatin had used after getting approval from FDA. When this combination compared to other one that are using previously, no remarkable difference found in the result. Etoposide and Cisplatin combination have 61% reaction rate, 10% full reaction rate and average survival rate of 8.6 months whereas the survival rate of previous one's was 8.3 months. Studies found that this combination has no noteworthy difference as compare to previous one. It was the first combination that was well tolerated against SCLC than others due to its good efficacy and easy administration. The next combination that replaces the Cisplatin was Carboplatin, it got no fame due to its toxicity profile, and no improvement had seen while using this combination and it causes higher rates of myelosuppression in the patients. Next major advancement in the first line standard treatment was the combination of Platinum with Etoposide or Irinotecan with Platinum. The combination of Irinotecan and Platinum has significant value over etoposide due to its high potential of killing cancerous cells. It improved the survival rate up to 12.8 months. Later, the combination of Etoposide with Carboplatin discovered to be more attractive but the world gave no importance due to lack of research (Armstrong & Liu, 2020).

The second top choice in case of SCLC is Topotecan but its efficacy is low as compared to other drugs, which are used in first-line therapy. Hematological toxicity has also reported with this drug in some patients. For relapsed or refractory SCLC, most widely used chemotherapy regimen is Topotecan. Survival rate from second line chemotherapy is only 26 weeks. If patients are getting supportive care then the survival rate reduced to 14 weeks. Only in Japan, approved newer anthracycline agent for second line therapy is Amrubicinis (Yang et al., 2019).

Recently a combination of chemotherapy and immunotherapy appraised to be beneficial for the patients suffering from ES-SCLC. 4 cycles of carboplatin and etoposide run with the drug atezolizumab/placebo, accompanied by the same. The experiment revealed that atezolizumab is the beneficial drug as it showed average accompanied survival rate of 22.9 months and enhance the overall survival rate at 18 months by 13% in atezolizumab. The toxicity remained same by both groups. The change in hematological factors and PDL1 did not prove to be the signs of betterment. By considering all these factors, the combination of Carboplatin and Etoposide with Atezolizumab got approval from FDA in March 2019. Moreover, it proved to be the top choice therapy against Extensive Stage-Small Cell Lung Cancer in adults. In September 2019, a new drug (Durvalumab) added instead of Atezolizumab, with Carboplatin and Etoposide and it increase the survival rate. It established itself as a new first-line treatment against Extensive-Stage SCLC. Despite it, a cytotoxic drug ipilimumab when comes in combination with chemotherapeutic agents, not improve the survival rate of ES-SCLC but it increases the patient survival without worsening the disease. Generally, healthcare professionals advise four to six cycles of chemotherapy. The exact duration of treatment is unknown(Armstrong & Liu, 2020).

**Targeted therapies**

Some molecule-targeted therapies are used alone or in combination with chemotherapy again small cell lung cancer. Amidst of these were;

1) Anti-Angiogenesis Drugs

2) Histone Deacetylase Inhibitors

3) Apoptosis Targeting Agents

4) Cell signaling targeting agents

Sunitinib is the first drug that shows its action only in its target site. It improves the quality of life by ameliorating progression free survival. Due to angiogenesis, small cell lung cancer outspread vastly and damages other organs. VEGF Protein is a stimulus to human SCLC as it shows increase in cellular response when tested in mice and enhances the vessel thickening of tumorous parts. In past researches, the VEGF protein worsens the survival rate when it interacts with cells after chemotherapy. Sunitinib is an oral tumor angiogenesis inhibitor that targets the VEGF proteins and improves the progression free survival.

Patients suffering from SCLC cause intensification in their genome especially in the genes of MYC family. The upregulation of MYC gene occurs in the subject model and leads to formation of the tumor inside lung rapidly with widespread of cancerous cells. Alisertib administered orally and inhibits the Aurora Kinase-A, which mediates the tumor distantly. The side effects that are associated with Alisertib are thrombocytopenia, neutropenia, leukopenia and anemia.

A recombinant monoclonal antibody combines with chemicals that have toxic effect on cells via strong forces and form Antibody-Drug Conjugates (ADC). Two Antibody-Drug Conjugates are Lovortuzumabmertansine and Rovalpituzumabtesirine. Lovortuzumabmertansine comprises of anti CD95 antibody that strongly bonded to tubulin binding maytansinoid DM1 via disulfide bridges. CD95 is a glycoprotein that is present in Natural killer T-cells, neuroendocrine cells and in some of T-lymphocytes. We can see a wide number of CD95 antibodies in cancerous cells. Lovortuzumabmertansine used in combination with chemotherapeutic agents such as etoposide, carboplatin and a median survival rate achieved with it. The healthcare providers should minimize the dose of Lovortuzumabmertansine because at higher doses it will cause peripheral neuropathy. Rovalpituzumabtesirine comprises of a monoclonal antibody IgG1, a dimer pyrrolobenzodiazepine (PBD) and a

linker that helps it in binding. Pyrrolobenzodiazepine bind to DNA to form PBD-DNA complex which apprehend tumor at G2-M following apoptosis. It is a third choice in the treatment of SCLC(Armstrong & Liu, 2020).

**Radiotherapy**

The patient suffering from lung cancer might have greater chances to develop brain metastases. In ES-SCLC, those patients who receive chemotherapeutic agents systemically might have chances to develop tumor inside the brain. As chemotherapeutic agents did not cross the blood brain barrier, increase the risk of getting brain metastases or relapse of the disease. Prophylactic cranial irradiation therapy when used after the chemotherapy, enhance the overall survival rate of the patient. Researches had shown after PCI, reduction in the occurrence of brain metastases, PCI boosts up the survival rate in the patients after chemotherapy. Patients with ES-SCLC accomplishing full or limited feedback after getting preliminary treatment must be subjected to PCI because it appreciably boost up the survival rate. The dose of 25 Gy/10 considered standard for PCI therapy but the overall duration for the PCI treatment is unknown until now. Patient having brain metastases, treated by whole brain radiation therapy (WBRT) at dose of 30 Gy/10 /day mostly. In addition, MRI and CT monitor systemic therapy adopted in patients having brain metastases without any symptoms. Radiosurgery recommended in patients in which tumor progression continued even after getting PCI (Dómine et al., 2020).

**Current therapeutic targets of interest**

Many trials are testing for the development of new medicines for SCLC in the systemic therapy. The main focus of the therapy is the genome of the small cell lung cancer in which the main target is the promoters of SCLC. Current therapeutic targets, drugs and prognostic biomarkers summarized in table 1.

**Table 1: Novel treatment targets, drugs and biomarkers in SCLC**

| Targets | Drugs | Biomarkers |
|---|---|---|
| PARP | Talazoparib<br>Veliparib<br>Olaparib<br>Niraparib<br>Rucaparib | SLFN11 |
| ATM/ATR | VX-803<br>VX-970<br>AZD6738 | NA |
| WEE1 | AZD(Halvorsen et al., 2016)75 | NA |
| CHK1 | Prexasertib | MYC |

| | | |
|---|---|---|
| | SRA 737 | |
| | MK-8776 | |
| | GDC-0575 | |
| | PF-477736 | |
| AURKA/B | Alisertib | MYC |
| | Barasertib | |
| | AMG 119 | |
| DLL3 | AMG 757 | DLL3 |
| | Rova-T | |
| | Pembrolizumab | |
| PD-1 | | Tumor mutation burden |
| | Nivolumab | |
| | Durvalumab | |
| PD-L1 | | NA |
| | Atezolizumab | |
| CTLA-4 | Ipilimumab | Tumor mutation burden |
| | Ponatinib | |
| FGFR | | NA |
| | Lucitanib | |
| LSD 1 | T-3775440 | NA |
| | Tazemetostat | |
| EZH2 | | NA |
| | DS-3201b | |
| CDK7 | YKL 5-124 | NA |
| RNA polymerase II | Lurbinectedin | NA |

**Targeting Genome Modifications**

Genomic background of SCLC is not described by a set of commonly special targetable driver oncogenes in contrast to lung adenocarcinoma. The main role in the targeting genome alterations is of transcription. Some recent pathways of signaling affected in SCLC are cell cycle regulation, receptor tyrosine kinase/PI3K signaling, and Notch signaling. Aberrantly expressed number of genes concerned in DNA damage repair on a proteomic level.

## DNA Damage Repair Pathway and Hindering Cell-Cycle Progression

There are some DNA repair proteins which are the important treatment targets in SCLC. These targets repair proteins are named as MGMT, PARP1, CHK1 & BRCA1 (Jackman & Johnson, 2005). PARP1 is useful in for the restoring of single-stranded DNA (SSDNA). Several PARP inhibitors are Cisplatin, Etoposide, Veliparib and Temozolomide. CHK1 is meant for the repair of double-stranded DNA (DSDNA) and agent associated with this repair mechanism is Prexasertib (Burgess et al., 2020). The spontaneous mutation incidence of SCLC is probably due to the heavy correlation of this disease with significant exposure to tobacco, with just 2% of reported cases in non-smokers. Due to down regulation of RB1 and TP3 there is loss of function of cell cycle checkpoints that increase SCLC's susceptibility to oxidative damage. Certainly several studies have credibly stated to DNA damage response pathways as malicious activities in SCLC in the past couple of years. In SCLCC, the targeting of central DDR moderators such as poly ADP-ribose polymerase (PARP), control point kinase 1 (CHK1), ataxia telangiectasia, ataxia telangiectasia mutated (ATM), RAD3-related protein (ATR), and WEE1 have already shown efficient treatment options.

Multiple mechanisms involved in the anti-tumor behaviors of PARP inhibitors comprising: (1) Restricting the enzyme to single-strand DNA breaks (SSBs) by avoiding the use of nicotinamide adenine dinucleotide (NAD), (2) Hindering poly ADP ribosylation and DNA adhesion of PARP. The PARP antagonist AZD2281 was found to be better than NSCLCs against SCLC cell types. SCLC cell lines sensitized by PARP inhibitors and patient-derived xenografts to ionising radiation with its trapping activity. The initial positive action of the PARP trapping drug talazoparib was reported in a phase 1 trial, with in individuals with SCLC. Efficiency of addressing the CHK1/ATR axis in SCLC was revising, both in vitro and in vivo activity against SCLC, with ATR antagonist in an independent preclinical study. ATR modulation via DNA damage triggers multiple gene expression, including CHK1, which stops the cell cycle progression at the G2-M level. In SCLC cell lines, the G2/M backdoor controller WEE1 is also significantly increased relative to normal lung tissue, but in several SCLC cell lines, the WEE1 inhibitor AZD1775 showed development. Aurora kinase A or B inhibition hinders in vitro and in vivo propagation and SCLC formation. A recently published clinical trial found that in patients with cMYC positive SCLC, the auroral kinase A blocker alisertib plus paclitaxel upgraded dramatically PFS vs. paclitaxel alone. Eventually, several clinical and preclinical trials have said that a viable approach could be to incorporate DDR antagonists with chemotherapeutics or other targeted agents (Taniguchi et al., 2020).

The technique anticipates curative chances by inhibiting the promoters of the cell-cycle. The promoters of cell cycle are PARP and Aurora Kinase A&B. The drug on which the phase-I trials established is Olaparib and for Phase-II trials the drugs are Carboplatin with Durvalumab + Tremelimumab. These multiple-targeted drugs have great effectiveness in treating SCLC than single target drugs. Another advantage for using these multiple target drugs is that they reduce systemic toxicity. Doses of single target drugs (HDAC/PI3K blockers) can be calibrated, but these have chances to cause severe adverse effects that may cause resistance. But by combining these two inhibitors, a synergistic effect produces which block the development of tumor. These two pathways (HDAC/PI3K) are blocked by CUDC907 concomitantly. And this concomitant blockage have greater efficacy than blocking these two alone. CUDC907 shows its action by apoptosis and arresting cell cycle. Moreover, CUDC907 also showed raised effectiveness of PARP inhibitor (Olaparib) in SCLC. When Olaparib and CUDC907 used in combination it acts synergistically as compare to using it alone (Ma et al., 2020).

## Targeting Epigenetic Modifiers

In epigenetic process the disruption of methylation and acetylation of the gene-promoter region and histone occurs that leads to mutations in chromatin material and all secondary factors. The enzymes required for the process are acetyltransferases and deacetlyases which are important for regulation of histone and enhanced the reachability of promoter’s region. Chromatin modifications due to changes in the genes have been observed in SCLC in the recent studies using next generation sequencing. Histone deacetylase inhibitors have shown some activity against SCLC. Romidepsin showed response by decreasing telomerase activity. Other drugs such as valproate, trichostatin A and panobinstat were shown to inhibit the cell growth in SCLC and to increase the effectiveness of chemotherapeutic drugs (Arcaro, 2015).

Decitabine (5-AZA-dC) is a unique rehabilitation blocker. DNA methyltransferase (DNMT1), which leads to reduced methylation of DNA activation of the transcriptionally silenced gene expression. This in turn can progress to the initiation of proliferation of cancerous cells, cell cycle, and assault, injury to your DNA and cell death. Histone acetylation regulates gene transcription by modifying the structure of chromosomes and is

dependent on the contrary action of histone acetyltransferase and HDAC. HDAC inhibitors, like DNMT inhibitors, reveal their antitumor properties by increasing differentiation, cell cycle arrest, apoptosis, growth inhibition and necrosis by transcriptional modulation of anti - apoptotic and proapoptotic genetics through DNA damage. From silenced tumor suppressor genes, mRNA expression was symbiotically recovered by coupling 5-AZA-dC with the HDAC inhibitor trichostatin A or phenylbutyrate. Sequential therapy of 5-AZA-dC tumor cells and HDAC depsipeptide or trichostatinA blockers significantly improved HDAC-induced autophagy via inhibitors. 5-AZA-dC can also trigger cytotoxicity by introducing it into the DNA with DNA damage initiation. When integrated into the DNA, 5-AZA-dC, covalent bonds connected to DNMT, causing DNA damages either structural variability at its site of convergence or by blocking synthesis of DNA. Mechanism of DNA damage occurs through differences in the shape of chromosomes and is correlated with the histone protein acetylation. In addition, HDAC inhibitors can disrupt the withdrawal of the 5-incorporated DNA AZA-dC and dramatically raise DNA damage inflicted by 5- AZA-C. We therefore examined whether the blocker of methylation was in combined effect with HDAC inhibitors may have potentiating effects on the cell death of human small cell lung cancer cells. We've found the synergistic effect of 5-AZA-dC and HDAC inhibitors, with one isoform specific for HDAC class and one pin inhibitor to reduce the vulnerability of SCLC cells. This was mainly due to damage of DNA rather than cell death. There was a connection between resistance to synergism combination and basal induction form of the IFN-stimulated gene (ISG) (Luszczek et al., 2010). Studies showed that some drugs can decrease the levels of bcl-2 proteins that are anti-apoptotic in nature thus inducing apoptosis in SCLC. When HDAC and DNMT inhibitors were given in combination, caspase-8 expression and trial sensitivity was observed that showed activity in pre-clinical SCLC models. Panobinostat was discontinued in phase 2 trial despite of its safe profile due to no response (Arcaro, 2015).

**Other Emerging Targets in SCLC**

Notch signaling pathway is essential in development regulation and homeostasis. The notch pathway is important in inhibition of tumor in different tissues constituting neuroendocrine tumors. This pathway is also applicable in re-establishment of stem cells of cancer and on their spreading resulting in the monoclonal antibody development and to target its receptor. Tarextumab is a monoclonal antibody that targets the receptor of notch signaling pathway; it shows its action by binding of Notch Ligand to Notch Extra Cellular Domain at the receptor site and results into the liberation of Notch Intracellular Domain. The receptor cleaved by the enzyme Gamma-Secretase which results into the transfer of nucleus of Notch Intracellular domain (NICD) and interacts with a factor called Recombining Binding Protein for Immunoglobulin kappa G region (RBPJ). RBPJ triggers the action of HES-1 (target gene), high expression of the HES-1 in Non-Neuroendocrine Cells suppresses the action the neuroendocrine gene while high expression of HES-1gene in Neuroendocrine cells results in lower expression neuroendocrine gene. Many biological processes occur by the activation of Notch Signaling Pathway and triggers tumor-genesis, chemoresistance and poor prognosis. The higher the level of Notch ligand in neuroendocrine cells leads to higher expression of Notch receptors in non-neuroendocrine cells. Higher expressions of HES-1 lead to worse prognosis, and this activation of Notch pathway triggers the response of Small Cell Lung Cancer. This action can be inhibited by Gamma-Secretase blockers and by the antibodies which target the Notch pathway. Tarextumab a Gamma-Secretase Inhibitor is using to target the Notch receptors which block the activity of Notch signaling pathway, hence not supporting the spread of SCLC. With Tarextumab a delay occur in growth of Chemo-resistance, so a combination of Tarextumab (Notch2/3 Antagonist) with Cisplatin results in greater efficacy rather than administering Tarextumab alone (Burgess et al., 2020).In exome sequencing analysis of SCLC most recent target is RPTOR independent companion of MTOR, complex 2 (RICTOR) which is the utmost procurable gene mutation. It is subunit of MTOR blocker in cell signaling. A MTOR blocker Vistusertib is explored in the patients in which SCLC recurring has seen (Jiang & Ji, 2019).

Recent studies in the treatment of SCLC involve imatinib, c-KIT inhibitor, PDGFR and bcrabl TK. The IHC of SCLC cell lines show 2/3 expressed c-KIT. Targeting c-KIT can show effectiveness against SCLC. A study was conducted in which SCLC patients were treated with 600mg imatinib. Only 21% of these patients had KIT receptor (CD117). This study failed to show any anti-tumor activity. Another study was performed using higher dose of imatinib i.e., 400mg bid. Upon immunohistochemistry, 78% of the tumor samples expressed c-KIT. But it also failed to show any effectiveness against SCLC, confirming the previous study. Another multicenter study was conducted to check the effectiveness imatinib in untreated extensive disease small cell lung cancer. Imatinib in dose of 600mg/day was used in combination with irinotecan and carboplatin. Upon im-

munohistochemistry, most of the tumor samples were positive for c-KIT and the response rate was 66%. Hematologic and non-hematologic toxicity was observed but overall this therapy was well tolerated. The study concluded that the results observed were not very different from the result expected from chemotherapy alone. The possibility of this failure is either that c-KIT pathway is not so important in survival of SCLC or imatinib cannot effectively inhibit the KIT kinase (Joshi et al., 2012).

**Biomarkers development**

**Biomarkers of immunotherapy**

SCLC is characterized bylow prevalence of PD-L1 expression, low numbers of tumor-infiltrating lymphocyteswhich remains of unknown prognostic value. Several commercially available anti-PD-1 and anti-PD-L1 monoclonal antibodies are under current investigations and have been tested in both front-line setting and as maintenance therapyin pretreated patients with SCLC35. In phase 1b trial Pembrolizumab was investigated in patients with pretreated relapsed/refractory PD-L1-expressing in patients (Kim et al., 2018). In phase 1-2 Nivoluma has been investigated in patients with pretreated SCLC, initial findings showed long-lasting responses and hopeful survival.FDA has also approved nivolumabin metastatic SCLC for third-line treatment (Cho et al., 2018). Patients enrolled in the CheckMate 032 trial, detailed retrospective biomarker investigation suggested that there was improved OS, ORR and PFS of nivolumab monotherapy or nivolumab plus ipilimumab combination therapy with higher tumor mutation burden in patients relative to the patents with low TMB28.Recent Studies on immunotherapy shown in table 2.

**Table 2: Studies of immunotherapy in ES-SCLC**

| Phase | Study | Treatment arms | Clinical Trials. gov identifier | Completion date |
|---|---|---|---|---|
| 1st line | | | | |
| II | Reaction | Carboplatin/cisplatin+pembrolizumab+etoposide vs. carboplatin/cisplatin +etoposide | NCT02580994 | August 2020 |
| III | Caspian | Tremelimumab+Durvalumab +cisplatin/carboplatin + etoposide vs. durvalumab +cisplatin/ carboplatin + etopside vs. etopside+ cisplatin/carboplatin | NCT03043872 | September 2019 |
| Maintenance | | | | |
| III | CheckMate- 451 | Nivolumab vs. nivolumab +ipilimumab vs. placebo | NCT02538666 | October 2918 |
| Relapsed | | | | |
| I/II | CheckMate-331 | Amrubicin vs. Nivolumab vs. topotecan | NCT0248(Goldstraw et al., 2016)30 | August 2018 |
| I/II | MEDIOLA | Olaparib + durvalumab vs. durvalumab +olaparib + bevacizumab | NCT02734004 | March 2023 |
| I/II | CA 001-030 | BMS-986012vs. BMS-986012+ nivolumab | NCT02247349 | October 2019 |
| II | Winship 3112-15 | Durvalumab + tremelimumab vs. tremelimumab + durvalumab + radiation | NCT02701400 | January 2020 |
| II | AFT-17 | Pembrolizumab vs. topotecan | NCT02963090 | May 2019 |

**Biomarkers of Targeted therapy**

Approximately 20% of SCLC cases, genetic alteration of MYC, mostly gene amplification, were observed in patients, and it is most common genetic abnormalities after TP53 and RB1. In SCLC high expression level of MYC suggested sensitivity to Aurora kinase and CHK1 inhibition. Multiple studies suggested that schlafen11 expression is potential biomarkers of sensitivity of both DNA damaging chemotherapy and PARP inhibition. Currently in clinical development in tumor tissues, many novel cytotoxic agents engineered through linkage

a monoclonal antibody or by pegylation. Long-acting topoisomerase-I inhibitor called Etirinotecanpegol is under development. In a phase 2-3 study antiglycolipiddisialoganglioside antibody Dinutuximab, that makes tumor lysis via cell mediated, antibody-dependent, and complement-dependent cytotoxicity, is being studied in a combination with irinotecan vs irinotecan alone (Kim et al., 2018). Transcription inhibitor including Lurbinectedin binds DNA minor groove and cause RNA polymerase II inhibition, showed mPFS of 4.2 months and in platinum refractory SCLC results showed acceptable tolerability (Calvo et al., 2017). Rovalpituzumab-tesirine (Rova-T), a DLL3-targeted antibody–drug conjugate, consisting of a humanized DLL3-specific IgG1 monoclonal antibody, DLL3 is a member of the Notch receptor family that inhibits Notch activation and is expressed in most SCLC and large-cell neuroendocrine tumors. ORR of (Halvorsen et al., 2016)% in patients with SCLC, response rates of 35% in DLL3-high tumors and 0% in DLL3-low tumors in a phase 1 trial produced by Rova-T in relapsed or refractory disease (Rudin et al., 2017).

### Conclusion and Recommendations

Small cell lung cancer is a deadly neuroendocrine tumor with no single effective targeted therapy. Even though the recent advancement occurs in the identification of novel therapeutic targets, ongoing research carried out but there is limitation in single-target drugs.So, there is need of multiple-target drugs that increases treatment effectiveness and also decreases systemic toxicity. To enhance physician recruitment and retention in rural Pakistan, policymakers should implement comprehensive reforms, including competitive financial packages that directly address income disparities (reflecting findings where 50.8% of doctors earn ≤100,000 PKR/month). Mandatory rotations for postgraduate trainees in rural facilities would build early-career exposure while expanding clinical capacity. Recognizing rural service through privileged experience certificates—valuable for future career advancement—would incentivize participation, alongside guaranteed provision of basic living necessities (secure housing, utilities, transport) to mitigate infrastructure gaps. Additionally, allocating special quotas for candidates from rural backgrounds would leverage community ties and prior adaptation to local challenges, creating a sustainable pipeline of committed healthcare workers.

**Supplementary Materials:** Not Applicable**.**

**Author Contributions:** Both authors equally contribute.

**Funding:** Not Applicable.

**Institutional Review Board Statement:** Not Applicable.

**Informed Consent Statement:** Not Applicable.
**Data Availability Statement:** Not Applicable.

**Acknowledgments:** Acknowledged parent institutes

**Conflicts of Interest:** The authors declare no conflicts of interest.

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