

Small Cell Lung Cancer: Current and Future Strategies

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Abstract

Small cell lung cancer (SCLC) represents approximately 15% of all lung cancer diagnoses and over the last 20 years, in the Western world, the proportion of patients with SCLC has decreased to 13% due to world campaign for smoking cessation. Due to high growth fraction of the disease, to early dissemination with widespread metastases and also to early development of drug resistance, the treatment of SCLC remains discouraging. The median survival time without treatment is 2-4 months and with treatment the 5-year survival rate remains low at <7% overall and the most of the patients relapse within one year after first-line treatment. Chemotherapy with a platinum regimen and etoposide is the gold of standard of treatment for limited (LD) and extensive disease (ED), by adding radical thoracic radiotherapy for patients with good performance status, with LD. The new TNM classification should be used also for SCLC. For the patients who have any response is indicated the prophylactic cranial irradiation (PCI) due to high risk of brain metastases. The benefit from second-line therapy is limited and maintenance therapy did not appear to improve overall survival (OS) or progression free survival (PFS) for patients with SCLC. Many targeted agents have been investigated in LD and ED, almost all of them in unselected populations, but also with pessimistic results. Due to unchanged therapeutic options for almost four decades, is required desperately to understand better the molecular basis of SCLC and to proceed in to clinical trials for new drugs and targeted agents.

Key words: Small cell lung cancer, strategies

Introduction

Small cell lung cancer (SCLC) is a neuroendocrine tumor that accounts for approximately 15% of all cases of lung cancer. The new cases that are estimated in the United States in 2015 were 221,200 and the deaths from lung cancer

were 158,040. [1] Lung cancer may be diagnosed with symptoms or it can be found casually on chest imaging. From patients with SCLC, about 30% of them, they will have limited-stage disease (LD). [2] This means that the tumors of these patients are

restricted to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes. When the tumors are spread beyond the supraclavicular areas, then these patients have extensive-stage disease (ED). Patients with distant metastases are also considered to have ED. [3,4]

The American Joint Committee on Cancer (AJCC) Tumor, Node, and Metastasis (TNM) defines LD as any T, except for T3-4, any N, and M0 (due to LD the disease must fit in a tolerable radiation field). [5] This corresponds to TNM stages I to IIIB. Extensive disease is TNM stage IV with distant metastases (M1) and includes the malignant pleural effusions. [3,4] The limited stage of disease is a favourable prognostic factor. Good prognostic factors also are the good performance status, the female sex and the age < 50 years old. [2] Also the smoking cessation improves survival and the smoking prevention will undoubtedly remain the primary and most important intervention to further decrease mortality. [5] The median survival time for patients with SCLC without treatment is between 2 and 4 months. For the patients with limited disease and who submitted in treatment the median survival is 15-20 months and for those with extensive disease the survival reduced in 7-11 months. [6] Not very often, patients with SCLC may develop paraneoplastic syndromes like Cushing syndrome from secretion of adrenocorticotrophic hormone, inappropriate antidiuretic hormone secretion, Lambert-Eaton myasthenic syndrome or paraneoplastic cerebellar degeneration. [7] Also due to physical examination may noticed supraclavicular lymphadenopathy, and some of these patients could present signs of chronic obstructive pulmonary disease or pneumonia. The pathologic classification of SCLC includes the Small Cell Lung Carcinoma and the combined small cell carcinoma. [8] SCLC arising from neuroendocrine cells and the neuroendocrine tumors include the typical carcinoid, low grade, the atypical carcinoid, intermediate grade and the neuroendocrine tumors, high grade. The SCLC comprised to the high grade, neuroendocrine tumors. SCLC is a carcinoma that is composed of small round, oval or spindle shaped cells with scanty cytoplasm. These carcinomas are discrete by their finely granular nuclei salt and pepper chromatin and by nuclear molding with small inconspicuous nucleoli. [9] In small biopsies there are fragmentation and crush artifact. Immuno-histochemistry is positive for neuroendocrine markers as neuron specific enolase, neyral cell adhesion molecule (NCAM) (DD56), Leu-7 (CD57) and synaptophysin. The expression of dopa decarboxylase, insulin-like growth factor 1, calcitonin, neuron-specific enolase, CD56, chromogranin A and

gastrin-releasing peptide are noticed in neuroendocrine and neural differentiation. To the 75% of cases with SCLC could be observed one or more markers of neuroendocrine differentiation. [10] Concerning preinvasive or in situ malignant changes are very infrequent in tumors with SCLC. [11]

Treatment Option for SCLC

Standard treatment options are described in Table 1.

Table 1. Standard treatment options for patients with SCLC.

Stage	Standard Treatment Options
Limited-stage disease	Chemotherapy and radiation therapy
	Combination chemotherapy alone
	Surgery followed by chemotherapy or chemoradiation therapy
	Prophylactic cranial irradiation
Extensive-stage disease	Combination chemotherapy
	Radiation therapy
	Prophylactic cranial irradiation
Recurrent disease	Chemotherapy
	Palliative therapy

Standard Treatment Options for Patients with Limited-Stage SCLC

Surgery

A very small percentage of people who have limited-stage small cell lung cancer and no lymph node tumors may benefit from surgery, after which adjuvant chemotherapy is given. [12-16] The stage of disease of these patients is T1, 2 N0, 1 M0, they have a more favorable outcome and 5-year survival rates of 50% have been reported with surgery. In patients who receive chemoradiotherapy, with the addition of surgery, there is no evidence of improvement in survival. [16] In patients with clinical T1-2 N0-1, who are candidates for surgery, meticulous mediastinal node exploration should be performed. Surgery may be indicated in patients with absence of mediastinal involvement and resection should be followed by adjuvant chemotherapy. Postoperative radiotherapy must be considered for pathologic N1 and unforeseen N2 disease. (Table 2)

Table 2. Tumor stages.

SCLC						
Limited Disease				Advanced Disease		
N0	N0	N1	N1	N2	N3	Any
IA	IB	IIA	IIB	IIIA	IIIB	IV
Surgery				No surgery		

Chemotherapy and radiation therapy

Chemotherapy and radiation therapy have demonstrated that they improve survival for patients with SCLC. Chemotherapy may improve the survival of patients with LD or ED, but the cure achieved only in a small number of cases. [17,18] Surgical resection of tumor or radiation therapy very rare lead to long term survival due to the fact that patients with SCLC are inclined to present distant metastases. [14] Combined-modality treatment with concurrent chemotherapy with etoposide and cisplatin with thoracic radiation therapy (TRT) is the treatment of choice for patients with LD SCLC, meaning patients with T1-4, N0-3 M0 tumours who are in a good performance. There were also prospective randomized trials, whose results showed that the combined-modality therapy offers a better survival (5% at 3 years), compared with chemotherapy alone.[2,19,20] There are also clinical trials that they showed median survivals of 18 to 24 months and 40% to 50% 2-year survival rates with less than a 3% treatment-related mortality.[2,21-24] There are studies that they didn't show benefit from increased dose intensity, from the administration of an additional drug to etoposide and to the platinum-based agent or from maintenance chemotherapy. [24-32] In patients with good performance status, the thoracic radiotherapy should be initiated with the first or second cycle, of chemotherapy. [33-36] There is an analysis which includes four trials, in which the therapy completed in less than 30 days and this fact was associated with an improved 5-year survival rate. [25] Concerning the chest radiation have been used 2 schedules in one randomized study. The schedule to one of them was with once daily chest radiation and the other one was with twice daily chest radiation. This study showed a survival advantage for the group of twice-daily radiation therapy given for 3 weeks compared with once-daily radiation therapy to 45 Gy given for 5 weeks ($p=0.04$) [30,37] But due to increased toxic effects from the twice-daily radiotherapy, like increased esophagitis, this type of radiation has not been widely used. The usually used radiotherapy schedule is the once-daily fractions to higher doses of greater than 60 Gy. [38-42]

Combination chemotherapy alone

For the patients who there is a contraindication to radiation therapy they will submit only in chemotherapy. For the patients who present superior vena cava syndrome they submitted immediately in chemotherapy, in radiotherapy or in both depends on the clinical situation of patient

Patients with a contraindication to radiation

therapy, such as acute infection, failure, severe pulmonary insufficiency of compensatory lung cancer, peripheral blood leukocytes less than $4 \times 10^6/l$ or platelets less than $80 \times 10^6/l$, could be treated with chemotherapy alone. The recommended treatment of patients with superior vena cava syndrome at presentation is chemotherapy, radiation therapy, or both, in a combination, depending on the severity of symptoms of the syndrome, in order to reduce the tumour that is causing the obstruction. [43,44]

PCI

The prophylactic cranial irradiation (PCI) is performed after the delivery of chemotherapy in order to minimize the risks of neurotoxicity. It is associated with alopecia and a short-term decrease in quality of life. The risk to present patients with SCLC, central nervous system (CNS) metastases could be reduced by more than 50% by the administration of PCI. [45] All patients with T1-4, N0-3 M0 disease without disease progression after treatment and who have a good PS should be considered for administration of PCI. Patients with SCLC have a 60% risk of developing CNS metastases to the next 2 - 3 years after starting treatment. [16,46] Most of the patients with SCLC they develop only brain metastasis and they die due to this metastasis.

Neurologic affect

It is noticeable that there are some retrospective studies that have been showed that the patients who leave more than 2 years, regardless if they submit in PCI [46], they present a high of developing neurocognitive side effects, especially patients >65 years old and/or with important vascular disease. [16,46]

Extensive-Stage SCLC Treatment

The standard of care for patients with ED SCLC is the combination of platinum based drug and etoposide, as in LD SCLC. Because cisplatin is associated with increased toxic effects requires a big amount of fluid hydration and this may be a major problem for cardiovascular patients, so it is preferably used carboplatin, which is also active in SCLC, and the dosage adapted to the renal function of the patient and has fewer toxic effects. Most of the patients, when they diagnosed with ED of SCLC, have reduced performance status. To this group of patients favored to be administered single agents and low dose regimens. Nevertheless, the prognosis is poor. What applies for the performance status did not for the age of patients? The data shows that there is no difference in RR or in PFS or in OS of older patients compared

with those that are younger. The standard chemotherapy combinations become tolerate and to the older patients. The performance status most of the patients ED SCLC is significant low and the prognosis of these patients is poor. Due to the fact that the chemotherapy meliorates the survival, the question is the kind of chemotherapy schema. The recommended chemotherapy is single agent chemotherapy, either intravenous or oral, and semimonthly regimens in low dose. [4,7] Patients in elderly at the time of diagnosis presented medical characteristics making difficult the selection of treatment. The available data show that when the geriatric patients, who are in good clinical condition, with good performance status (0-1), normal liver and renal function and they are not under polypharmacy, receive the recommended chemotherapy schema, as the general population, they have the same DFS and OS as the general population. [40] There are also and other regimens that are less common in use, as cisplatin and irinotecan, ifosfamide, cisplatin and etoposide, cyclophosphamide, doxorubicin and etoposide, cyclophosphamide, doxorubicin, etoposide and vincristine, cyclophosphamide, etoposide and vincristine, ad also cyclophosphamide, doxorubicin and vincristine. (Table 3)

Table 3. Combination Chemotherapy for Extensive-Stage SCLC.

Standard treatment	Etoposide + carboplatin
	Etoposide + cisplatin
Other regimens	Cisplatin + irinotecan
	Ifosfamide + cisplatin + etoposide
	Cyclophosphamide + doxorubicin + etoposide
	Cyclophosphamide + doxorubicin + etoposide + vincristine
	Cyclophosphamide + etoposide + vincristine
	Cyclophosphamide + doxorubicin + vincristine

The patients with ED SCLC showed overall response rate of 50% to 80% and complete response rates of 0% to 30%. [47,48] There are 2 meta-analyses that they estimate the platinum based combinations versus the non-platinum. The one of them, a meta-analysis of 19 clinical trials, showed a benefit in survival for the patients who received a platinum based therapy. [48] The other one, a Cochrane analysis, did not show any survival difference. [49] Another trial was this from the Hellenic Oncology Group, a phase III trial, in which the patients randomized to receive cisplatin and etoposide or carboplatin plus etoposide. [50] In the cisplatin arm the median survival was 11.8 months and in the

carboplatin 12.5 months.

Combination chemotherapy regimens

The results from 5 trials and two meta-analyses have been assessed, in which compared the combination of etoposide and cisplatin versus irinotecan and cisplatin. No one trial show superiority of some combination except from one that conducted in Japanese people, and it showed superiority the combination with irinotecan and cisplatin. [50] From all the trials the conclusion was the clinical benefit was equivalent. The difference that noticed was due to the toxicity profiles. [51,52] No inferiority for survival also showed and a randomized trial, in which the patients randomized to receive oral topotecan and cisplatin or etoposide and cisplatin. [53] Also not reported improvement to OS when added and a third regimen, as paclitaxel to etoposide and cisplatin, ifosfamide to cisplatin and etoposide, thalidomide to carboplatin and etoposide, bevacisumab to carboplatin or to cisplatin. [54-58]

Duration of chemotherapy

The results from several trials demonstrates that more than 5 to 6 chemotherapy cycles do not increase the survival. [29,59]

Maintenance for SCLC

The results from 11 randomized trials considered marginally effective the maintenance therapy (HR=0.89, p=0.02). [60] Also, from 14 randomized trials, was reported increase of OS of 9% in 1-year and 4% in 2-year OS. [61] A noticeable trial is this one with sunitinib. A phase II trial in which patients randomized to receive sunitinib or placebo after 4-6 cycles of chemotherapy with cisplatin or carbo and etoposide. The PFS on maintenance arm was 2.3 versus 3.8 months for those who receive sunitinib (HR=1.53; 90% CL: 0.97-1.78; p=0.27). [62]

Dose intensity chemotherapy

There have been studies that did not report consistently improvement in OS and the data showed that the high doses associated with significant toxicity. [63-66] However; there are studies that they report improvement in OS with a modest increase in dose intensity of 25%-34%. [63,67-69] Therefore the role of dose intensification in patients who receive chemotherapy for SCLC remains ambiguous.

Radiation therapy

The treatment of choice is the radiation therapy for the patients with extensive disease, for the metastatic sites and especially for the bones, the epidural, and the brain, which in this case the patients

are treated with whole-brain radiation therapy. [70] The group of patients, with extensive disease, who submitted in chemotherapy and they revealed any response, they should be undergo assessment for thoracic radiation therapy. There is a big randomized trial, in which almost 500 patients after completing the chemotherapy schema, they randomized to receive radiation therapy or observation. For the patients who submitted in radiotherapy, the 2-year OS was 13% (95% CI, 9-19) and for those who not only 3% group (95% CI, 2-8; $p = 0.004$) and the PFS was 24% (95% CI, 19-30) versus 7% (95% CI, 4-11; $p=0.001$), respectively. [71] Patients with good performance status, without progression, they should be offered PCI, in 10 fractions with TD 25 Gy. In a randomized trial of 286 patients, after they completed the chemotherapy (4 or 6 cycles), they randomized to be submitted in PCI or observation only. Into the first year the risk of brain metastasis for those who received PCI was 14.6% (95% CI, 8.3-20.9) and for those who not the risk elevated to the 40.4% (95% CI, 32.1- 48.6). [72] Although PCI increases long term survival the patients >65 years old and/or with important vascular disease they have elevated risk of developing neurocognitive side effects. [73]

Recurrent SCLC Treatment

Chemotherapy

SCLC recurs in the most of the patients, even though most of them respond to first-line therapy. The majority of the patients relapse after 1-2 years after 1st line chemotherapy. The median survival after 2nd line therapy is less than 6 months. The selection of patients with treatment with 2nd line therapy is based on treatment-free survival, on extent of response to 1st line therapy, on residual toxicity from 1st line therapy and as in every treatment on performance status. The patients who receive 2nd line treatment have better outcomes than those on best supportive care. But only 32% of patients with relapsed disease may receive 2nd line chemotherapy. [74] The patients divided in 2 categories, sensitive and resistant. Patients with sensitive disease have an interval from 1st line response more than 3 months and there is evidence of survival benefits and improvement of symptoms for this group of patients. [75] It has been shown that the sensitive patients respond to the initial regimen combination in almost 50%. [76] Resistant are patients whom PFS is less than 3 months. And there are and the refractory patients which they are not responding or progressing during chemotherapy. For these patients the outcome is very poor and the clinical benefit of further systemic therapy is limited. The

standard of chemotherapy for recurrent disease is the topotecan, a topo 1 inhibitor. A randomized, phase III trial, showed that in the 2nd line, in chemosensitive disease, the oral and the I.V. topotecan have the same efficacy, but they have different toxicity profile. The median survival for the patients who received oral topotecan was 33 weeks, and for those who receive it intravenously 35 weeks. For oral topotecan the 1st year survival was 32.6% and the 2nd 12.4%, and respectively for i.v. topotecan was 29.2% and 7.1%. [77] A phase III trial comparing oral topotecan with best supportive care (BSC) showed that the patients of the arm with oral topotecan had better OS, 25.9 weeks versus 13.9 weeks (HR 0.64, $p=0.01$) and also better symptom control. [75] Another phase III randomized trial, for the second line therapy, compared topotecan with cyclophosphamide, doxorubicine and vincristine. The efficacy was equal with similar RRs, TTP and OS. [78] Several clinical trials of cytotoxic chemotherapies and molecular targeted agents investigated in the treatment of relapsed SCLC but no one showed significant clinical activity to exceed topotecan as 2nd line chemotherapy.

Amrubicin

Amrubicin is a third-generation anthracycline and potent topoisomerase II inhibitor that showed superiority to topotecan in a Japanese population but not in western patients. [79,80] But it is noticeable, that to the trial that participate western population, there was an improvement in OS, to the refractory patients, that were treated with amrubicin. [79,80] In another trial compared amrubicin with irinotecan and cisplatin, in the first line, did not demonstrate superiority for amrubicin. [81] And also when compared with etoposide and cisplatin did not show clinical benefit. [82]

Targeted Therapies

Due to discovery of many targeted and immunotherapy drugs in non-small cell lung cancer (NSCLC), the investigators tried to develop similar drugs and to SCLC but the results were disappointing. A variety of targeted therapies such as anti-GD3 immunization, metalloproteinase inhibitors, angiogenesis inhibitors (e.g. bevasizumab), GFR inhibitors, apoptosis promoters and p53 cancer vaccine have been previously examined as 1st line treatment, but most of the trials failed to show improved PFS or OS. [82-87] There are current studies that are focusing on the Hedgehog pathway, epigenetic regulatory pathways, and DNA damage repair mediated by PARP1. [88,89] Although preclinical studies showed very hopeful potency of

vismodegib, which is a Hedgehog inhibitor. When this drug combined with cisplatin and etoposide, did not show any superiority to OS or to PFS. [90] Another old drug this time, tested through a phase II, clinical trial, in which temozolomide administered in patients with relapsed sensitive or refractory small cell lung cancer, with assessment of methylguanine-DNA methyltransferase, and temozolomide showed activity in relapsed SCLC, especially in those patients with brain metastasis. [91] In other trial temozolomide administered for 5 days temozolomide in patients with relapsed small cell lung cancers with assessment of methylguanine-DNA methyltransferase and this trial showed that this dosage is tolerable and the drug is active in patients with relapsed SCLCs. [92] mTOR inhibitors act on intracellular serine/threonine protein kinases that

regulate cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription. [93,94] Temsirolimus and everolimus are the mTOR inhibitors that have been evaluated in SCLC, through clinical trials, either as maintenance therapy, or as a monotherapy in treatment of relapsed SCLC. [95,96] The results of all the trials did not show improvement in OS or in PFS. Targeted therapies that are at this time under investigation are PARP inhibitors as the olaparib, the velaparib, the niraparib and the BMN673-PARP trap and the aurora kinases as the A MLN8237 and the B AZD1152-alisertib. [97,98] Also was not observed improvement in OS and when a target agent added to chemotherapy, as when added bevasizumab to paltinum etoposide combination for extensive-disease of SCLC. [58]

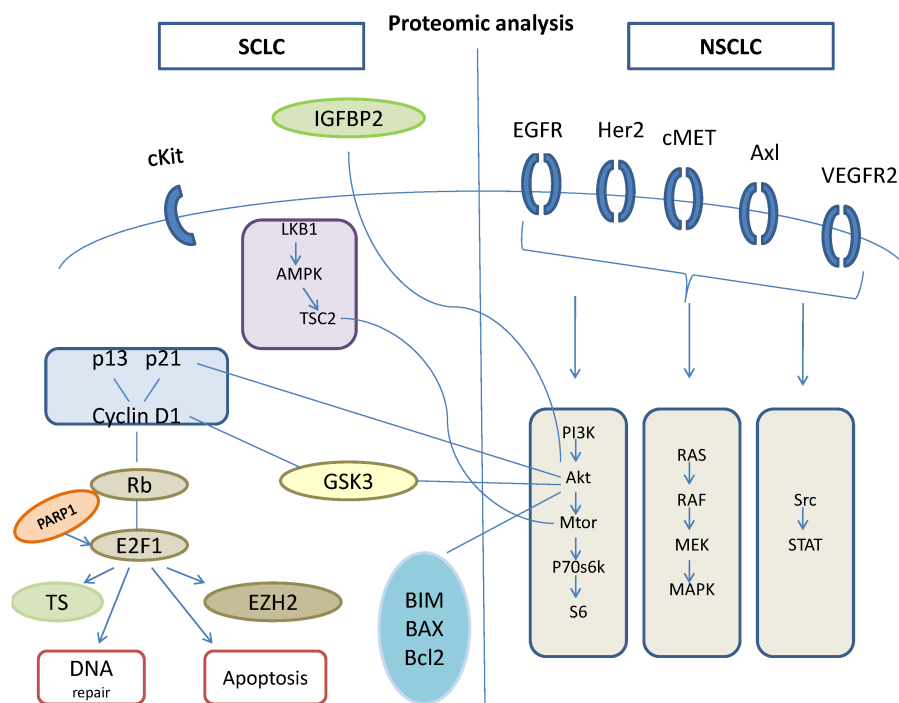


Figure 1. Proteomic analysis.

Immunotherapy

The tumor immunotherapy has the potential to settle and precipitate the immune system to recognize and extinguish the tumor cells. When ipilimumab administered in combination with paclitaxel and carboplatin in extensive-disease of SCLC, in the first-line therapy, the results were promising-improved irPFS versus control. [99] [108]

Ongoing trials

The clinical trials that are on-going are [100]:

- Cisplatin and Etoposide with or without Veliparib in Treating Patients with Extensive Stage Small Cell Lung Cancer or Metastatic Large Cell Neuroendocrine Non-small Cell Lung Cancer.
- This is a phase I, dose-escalation study of veliparib followed by a phase II study.
- Temozolomide with or without Veliparib in Treating Patients with Relapsed or Refractory Small Cell Lung Cancer.
- This randomized phase II trial studies how well

temozolomide with or without veliparib works in treating patients with small cell lung cancer that has returned or does not respond to treatment.

- Topotecan Hydrochloride or Cyclodextrin-Based Polymer-Camptothecin CRLX101 in Treating Patients with Recurrent Small Cell Lung Cancer.
- This randomized phase II trial studies how well giving topotecan hydrochloride or cyclodextrin-based polymer-camptothecin CRLX101 works in treating patients with recurrent small cell lung cancer.
- Pegylated Irinotecan NKTR 102 in Treating Patients with Relapsed Small Cell Lung Cancer.
- This phase II trial studies how well pegylated irinotecan NKTR 102 works in treating patients with small cell lung cancer that has returned after a period of improvement.
- Pembrolizumab in Treating Patients with Extensive Stage Small Cell Lung Cancer After Completion of Combination Chemotherapy.
- This phase II trial studies how well pembrolizumab works in treating patients with extensive stage small cell lung cancer after completion of combination chemotherapy.
- Topotecan Hydrochloride and Doxorubicin Hydrochloride in Treating Patients with Small Cell Lung Cancer That Has Relapsed or Not Responded to Treatment.
- This phase I trial is studying the side effects and best dose of topotecan hydrochloride when given together with doxorubicin hydrochloride in treating patients with small cell lung cancer (SCLC) that has returned or not responded to treatment.
- Chloroquine as an Anti-Autophagy Drug in Stage IV Small Cell Lung Cancer (SCLC) Patients.
- Chloroquine might very well be able to increase overall survival in small cell lung cancer by sensitizing cells resistant to chemotherapy and radiotherapy.

Conclusions

The treatment of SCLC remains an important challenge for the investigators. In spite of the at least 40 clinical trials since the 1970s, the options for the combination of the chemotherapeutic agents remains the same, as for the past decades. All the trials did not demonstrate any significant change to the OS for the patients with SCLC, who submitted in therapy. Despite the fact that SCLC is heterogeneous, there have been reported tumor suppressors and oncogenes

that target somatic mutations. These attempts are needed to be emphasized for the development of validated biomarkers in order to achieve a better impact on patient survival.

Conflict of Interest

None to declare.

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