Small Cell Lung Cancer: Therapies and Targets

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Abstract

Small cell lung cancer (SCLC) remains a very fatal disease due to limited therapeutic options. Systemic chemotherapy is the bedrock of treatment for both the limited and extensive stages of the disease. However, the established management paradigm of platinum-based chemotherapy has reached an efficacy plateau. A modest survival improvement, approximately 5%, was witnessed with the addition of cranial or thoracic radiation to systemic chemotherapy. Other strategies to improve outcome of platinum-based chemotherapy in the last 2 decades have met with minimal success. The substitution of irinotecan for etoposide in the frontline treatment of SCLC achieved significant efficacy benefit in Japanese patients but similar benefit could not be reproduced in other patient populations. Salvage treatment for recurrent or progressive SCLC is particularly challenging where topotecan remains the only agent with regulatory approval to date. Ongoing evaluation of biologic agents targeting angiogenesis, sonic hedgehog pathway, DNA repair pathway and immune checkpoint modulators hold some promise for improved outcome in this fatal disease. It is hoped that the coming decade will witness the application of new molecular biology and genomic research techniques to improve our understanding of SCLC biology and identification of molecular subsets that can be targeted appropriately using established and emerging biological agents similar to the accomplishments of the last decade with non small cell lung cancer.

Introduction

Lung cancer remains the most common cause of cancer related mortality in the United States, with over 159,000 deaths projected in 2013.¹ Small cell lung cancer (SCLC) constitutes approximately 13% of all cases.² ³ SCLC is a unique disease that is distinct from
non-small cell lung cancer (NSCLC) in its propensity for early metastases, and exquisite sensitivity to initial systemic cytotoxic chemotherapy. Despite the high initial response to therapy most patients eventually succumb to recurrence of the disease. Current management approaches have reached a plateau of therapeutic efficacy. The advances in molecular profiling and development of targeted therapies witnessed with NSCLC in the last decade remain to be successfully replicated in SCLC. This review summarizes the current management approaches in SCLC as well as emerging approaches to personalize SCLC treatment.

Staging

The widely employed SCLC staging system for SCLC includes the limited stage (LS-SCLC) and extensive stage (ES-SCLC) disease categories and was developed in the 1950s by the Veterans’ Administration Lung Study Group (VALSG). An updated staging system by the International Association for the Study of Lung Cancer (IASLC) refined the limited disease group to include contralateral mediastinal and supraclavicular lymph nodes as well as ipsilateral pleural effusion. More recently an updated IASLC/AJCC staging for SCLC using the TNM staging methodology was released based on survival outcome from 8,000 cases of SCLC treated between 1990 and 2000 around the world. TNM staging of SCLC provides additional prognostic information including correlation of T stage with 5-year survival and greater survival difference between N1 and N2 status. Additionally, effusion in the setting of limited stage disease portends worse survival 12 vs. 18 months in comparison to median survival of 7 months, p=0.0001 for extensive stage disease.

Management of newly diagnosed SCLC

Platinum-based therapy: Chemotherapy is the mainstay of therapy for both LS and ES-SCLC. McIlmurray and colleagues first reported increased response rate and improved survival in SCLC patients treated with multi-agent chemotherapy. The study randomized 103 patients to single agent etoposide versus cyclophosphamide, doxorubicin, and vincristine (CAV) regimen. The overall complete response rate was 23% and more patients in the CAV group achieved CR compared to the etoposide group (23% vs. 7%, p<0.05). There was no overall survival (OS) difference due to allowance for crossover between arms.

The introduction of platinum-based chemotherapy into lung cancer management led to randomized comparison of cisplatin/etoposide (EP) combination to the CAV regimen. In a Japanese study, 300 patients were randomized to CAV, EP or alternating CAV with EP. Non-responding patients in the CAV or EP arms were allowed to cross over to a different regimen. Patients with limited stage disease received thoracic but no cranial radiation after 4 cycles of chemotherapy. The platinum-containing arms achieved a higher response rate than the CAV only arm (78% EP, 76% CAV/PE and 55% CAV, p<0.005). Patients treated with the alternating regimen achieved a significantly longer survival but only in the LS-SCLC subset (median OS: 16.8 vs. 11.7 months, p=0.014). Similarly, Roth et al compared the CAV regimen to EP within ES-SCLC and observed no significant difference in response rate or median OS. Sundstrom and colleagues directly compared EP to CEV without alternating the regimens and showed that EP was superior to CEV in LS-SCLC (OS: 14.5
vs. 9.7 months; p=0.0001) but comparable to CEV in patients with ES-SCLC (8.4 vs. 6.5 months, p=0.21). This study confirmed EP to be a superior regimen to CEV in LS-SCLC and a preferred regimen over CEV in ES-SCLC.

Baka and colleagues also compared EP to the European Organization for Research and Treatment of Cancer (EORTC), reference regimen, ACE, consisting of doxorubicin 50 mg/m², cyclophosphamide 1000 mg/m², and etoposide 120 mg/m² IV on day 1 followed by etoposide 240 mg/m2 orally on days 2 and 3, given on 21 day cycles. Patients with LS-SCLC who achieved at least a PR received consolidation thoracic radiation therapy to the chest. The response rate, and 1-year survival rates were comparable across the two arms (72% vs. 77% and 34% vs. 38%, for ACE and EP respectively, p=0.497). The significantly higher rate of grade 3 or 4 neutropenia and infections with the ACE regimen (90%/73%, vs. 57%/29%, p<0.005 supported the preference for EP.

Carboplatin or Cisplatin: The toxicity profile of cisplatin promoted the use of carboplatin as a substitute for cisplatin in regular clinical management of SCLC. However, since most of the studies that established platinum-based chemotherapy as the preferred regimen in SCLC employed cisplatin, establishing the equivalence of carboplatin and cisplatin with respect to efficacy became important. A prospective randomized study compared cisplatin with carboplatin each administered along with etoposide in 147 untreated SCLC patients. Patients with LS-SCLC also received thoracic and cranial irradiation. The dose intensity (74% vs. 80%), response rate (57% vs. 58%) and median survival (12.5 vs. 11.8 months) were comparable between the cisplatin and carboplatin groups. Toxicity (leukopenia with or without infections, nausea, vomiting and neurotoxicity) was worse in the cisplatin group.

Many other prospective studies have been conducted to establish the equivalence of carboplatin and cisplatin-based regimens in SCLC with varying results. An individual patient data meta-analysis of 4 randomized studies was recently published. There was no difference between carboplatin and cisplatin in terms of response rate (67% vs. 66%; HR: 0.98, 95% CI 0.84–1.16, p=0.83), median PFS (5.5 vs. 5.3 months, HR: 1.10, 0.94–1.29, p=0.25) or median OS (9.4 vs. 9.6 months; HR: 1.08, 95% CI 0.92–1.27, p=0.37). Hematologic toxicity was higher with carboplatin while non-hematologic toxicities of nausea/vomiting, neurotoxicity, and nephrotoxicity were more common with cisplatin. This metaanalysis shows the equivalence of cisplatin and carboplatin in the treatment of SCLC and supported the choice of either agent as appropriate for the patient’s comorbidities and tolerance of potential toxicities.

A therapeutic ceiling encountered with platinum-based doublet chemotherapy led to various strategies to improve efficacy including substitution for etoposide as partner chemotherapy, dose intensification and maintenance therapy post frontline therapy.

**Substitution of partner chemotherapy in the frontline**

Irinotecan in SCLC: The efficacy of irinotecan in the relapsed setting supported the evaluation of this agent as partner chemotherapy in the frontline along with cisplatin instead of etoposide. The Japanese Cooperative Oncology Group conducted a randomized phase III study of irinotecan (60 mg/m² on days 1, 8, and 15 every 28 weeks along with cisplatin (60 mg/m² on day 1) (IP) in comparison to standard EP regimen in the frontline therapy of ES-SCLC.
SCLC. Improved efficacy of IP over EP was demonstrated at a preplanned interim analysis after enrolling 154 of the planned 230 patients. The median OS with IP was 12.8 months compared to only 9.4 months in EP arm (p=0.002). The 2-year survival rate (19.5% and 5.2%, respectively) and median PFS (6.9 vs. 4.8 months, p=0.003) were also in favor of the IP regimen. The toxicity profile was however different with IP regimen inducing a higher incidence of grade 3 or 4 diarrhea (16% vs. 0%, p<0.001) while myelosuppression was more common with the EP regimen, with grade 3 or 4 neutropenia/thrombocytopenia seen in 92.2% vs. 65.3%, p<0.001 and 18.2% vs. 5.3%, p=0.02 respectively. While the result of this study led to the adoption of IP as preferred regimen for treatment naïve SCLC patients in Japan, two randomized studies conducted in the US failed to establish the superiority of IP over EP in non Japanese SCLC patient population.

Similarly, a third study conducted in Europe enrolled 404 patients to compare frontline IP against EP in patients with extensive stage SCLC. This study also failed to establish the superiority of IP over EP (OS of 10.2 months vs. 9.7 months; HR 0.81, 95% CI 0.65–1.01, p=0.06). Potential pharmacogenomics differences between the Japanese and North American population, such as with genetic polymorphism in UDP-glucuronosyltransferase (UGT1A1) enzyme that metabolizes irinotecan may in part explain the differences in the efficacy and toxicity profiles of irinotecan between Japanese and Western patient population. EP remains the preferred frontline regimen for SCLC treatment in the West while IP is a preferred regimen in Japanese patients.

The substitution of etoposide with amrubicin or topotecan remains under active clinical investigation with no established superiority demonstrated over standard EP regimen in the frontline setting. Two phase III randomized comparative trial of topotecan/cisplatin against EP showed that topotecan/cisplatin is non inferior to EP but has increased toxicity over EP.

Amrubicin combined with cisplatin (AP) was also compared to EP in a phase III study that enrolled 299 treatment naïve patients from China. The ORR PFS (7.13 months vs. 6.37 months), and median OS (11.79 months vs. 10.28 months) all favored the AP regimen. There was however, a higher rate of grade 3 or 4 neutropenia (54.4% vs. 44%) and leukopenia (34.9% vs. 19.3%) despite the lower dose of cisplatin (60mg/m² vs. 80mg/m²) in the AP regimen.

**Dose intensification**

Triplet chemotherapy that included an additional cytotoxic agent along with the backbone of platinum plus etoposide has been evaluated as a potential strategy to improve on the efficacy plateau of EP regimen. Triplet regimens that include ifosfamide, topotecan or paclitaxel have been studied in the frontline setting. The paclitaxel, etoposide and carboplatin regimen was compared to carboplatin, etoposide, and vincristine in a phase III clinical trial. The study enrolled a total of 608 evaluable patients and demonstrated reduced risk of death with the addition of paclitaxel (HR 1.22, 95%CI: 1.03–1.45; P =0.024). Across a large number of randomized trials, the improved efficacy with dose intensification was attained at the cost of increased toxicity and mortality. This factor has weighed heavily against widespread adoption of this strategy in the management of SCLC.
**Maintenance therapy**

Both the continuation and switch maintenance strategies have been evaluated in non-progressing SCLC patients following completion of frontline induction chemotherapy. Schiller et al treated 402 eligible patients and subsequently randomized 223 non-progressing patients to observation or topotecan maintenance. Expectedly, PFS was significantly better with topotecan (3.6 vs. 2.3 months; \(P <0.001\)) but OS was not improved (8.9 vs. 9.3 months; \(P=0.43\)). Similar evaluation of temsirolimus as maintenance therapy in a phase II study failed to improve on the historical experience in terms of PFS (2.2 months, 95% CI: 1.8–2.9) or OS (8 months, 95% CI: 6.5–9.5). Finally, continuation maintenance with irinotecan following induction IP did not result in improved PFS or OS in comparison to observation alone. A metaanalysis of 21 randomized studies encompassing 3,688 SCLC patients showed no benefit in OS (HR 0.93, 95% CI 0.87–1.00; \(p=0.05\)) or PFS (HR 0.98, 95% CI 0.91–1.06; \(p=0.63\)) with maintenance therapy. Overall, maintenance therapy in unselected, non-progressing SCLC patients is not an effective strategy and is not recommended outside of a defined clinical trial setting.

**Management of relapsed SCLC**

**Retreatment with frontline regimen**

The high initial response seen with SCLC patients is not durable and most patients succumb to disease recurrence and progression within the first year post-frontline therapy. In general, patients who progress through frontline platinum-based therapy are deemed platinum-refractory. Initial disease control followed by early progression within 90 days of platinum-based therapy indicates platinum resistance while lack of progression within 90 days indicates platinum sensitive disease. Durable response lasting 6 months or longer is an indication for retreatment at the time of progression with the same platinum-based frontline regimen. This is an established practice that is associated with meaningful clinical benefit.

**Non cross-reacting second line regimen**

The quality and duration of response to frontline therapy is a strong predictor of response to an alternative second line regimen based on retrospective analyses as well as prospective studies and metaanalyses of second line trials. Owonikoko and colleagues in a review of 21 studies of patients who received second-line chemotherapy for relapsed disease showed that patients with sensitive relapse had better ORR (27.7% vs. 14.8%, \(p=0.0001\)) and longer median OS (7.7 months vs. 5.4 months, \(p=0.0035\)).

Topotecan: this is the only agent with regulatory approval for the treatment of relapsed SCLC. In a phase III study of 211 patients with relapsed SCLC randomized to topotecan IV (1.5 mg/m\(^2\) on days 1–5) or CAV (cyclophosphamide 1000 mg/m\(^2\) IV, doxorubicin 45 mg/m\(^2\) IV, and vincristine 2 mg IV on day 1) topotecan and CAV showed comparable efficacy (RR: 24.3% vs. 18.3%, \(p=0.285\)), median OS (25 weeks vs. 24.7 weeks, \(p=0.795\)) but improved symptom control in patients on topotecan (\(p<0.043\)).

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Another study of oral topotecan versus best supportive care (BSC) in 141 patients with relapsed SCLC also showed the benefit of topotecan on survival (13.9 weeks to 25.9 weeks, p=0.0104) and improved quality of life and symptom control. Amrubicin: This is an anthracycline, and DNA topoisomerase II inhibitor, with intriguing activity in SCLC. Initial comparison to topotecan was conducted in Japanese patients with relapsed SCLC and showed superiority over topotecan (RR: 38% vs. 13%) irrespective of platinum sensitivity in the frontline setting. Amrubicin did result in more non-hematologic (fatigue, anorexia, and nausea) and hematologic toxicities (grade 4 neutropenia and febrile neutropenia, 79% and 14% with amrubicin vs. 43% and 3% with topotecan, respectively). Further development of amrubicin for relapsed SCLC is currently on hold following a negative phase III study where amrubicin and topotecan achieved nearly identical median OS of 7.5 vs. 7.8 months respectively.

Although the clinical development of therapeutic agents for SCLC progressing following frontline therapy has witnessed tremendous failure across various classes of anticancer agents, a number of promising agents such as picoplatin, belotecan and bendamustine remain under active clinical evaluation.

Radiation
Thoracic Radiation

Systemic chemotherapy remains the bedrock of treatment for all stages of SCLC. The addition of radiation therapy however, improves outcomes in limited stage disease. In a meta-analysis of 2,103 patients in 13 trials, Pignon and colleagues showed a 5.4% absolute survival benefit at 3 years and a relative risk of death of 0.86 (95% CI 0.78–0.94, p=0.001) with the addition of radiation to chemotherapy in patients with limited stage disease. This benefit was especially pronounced in younger patients, (RR: 0.72; 95% CI 0.56–0.93) less than 55 years. In a separate meta-analysis, Warde et al. showed a 5.4% absolute survival benefit at 2 years with the addition of thoracic radiation compared to chemotherapy alone (p<0.05). These two studies established the benefit of thoracic radiation in LS-SCLC.

The optimal timing of radiation when administered along with systemic chemotherapy was the focus of several studies. A Japanese study randomized 231 patients with LS-SCLC to concurrent hyperfractionated radiation (45 Gy) starting day 2 of the first cycle of chemotherapy or sequential radiation starting after the completion of four cycles of chemotherapy. While there was no difference in response and local failure rates between the two treatment arms, the median survival time was 19.7 months in the sequential arm compared to 27.2 months in the concurrent arm (p=0.097).

The survival benefit of early administration of radiation in LS-SCLC was also demonstrated in a meta-analysis of 1524 patients enrolled in 7 randomized controlled trials. Early initiation of radiation was associated with better survival at 2 years (OS relative risk 1.17, 95% CI 1.02–1.35, p=0.03). This benefit was limited to patients treated with hyperfractionated radiation (17% at 2 years (p<0.001) and with platinum based chemotherapy (10% at 2 years, p=0.001).
A pooled analysis of data from 4 phase III trials utilizing platinum and etoposide with two different radiation schedules examined the effect of the timing of radiation by using the endpoint of start of any treatment to end of radiation (SER).\textsuperscript{60} The shorter the SER the better the survival at 5 years (relative risk: 0.62, 95% CI 0.49–0.80, p=0.0003). Furthermore, the earlier the initiation of thoracic radiation after the start of chemotherapy, the better the survival outcomes (RR 0.63, 95% CI 0.45–0.88, p=0.007).

In a prospective randomized study Turrisi et al demonstrated that hyperfractionated thoracic radiation improved survival compared to a standard fractionation schedule.\textsuperscript{61} Patients were randomized to 45 Gy administered as daily fractions over 5 weeks or twice daily fractions over 3 weeks along with standard EP chemotherapy for both arms. A higher median OS (23 vs. 19 months) and 2 and 5-year survival rates of 47% and 26% were observed in the hyperfractionation arm compared to 41% and 16%, respectively in the standard fractionation arm. The rates of local failure and combined local and distant failure were lower in the hyperfractionated arm but resulted in higher rates of grade 3 esophagitis (p<0.001). Whether the improved outcome of hyperfractionation will be maintained in comparison to biologically equivalent dose of 60Gy is the objective of an ongoing randomized phase III RTOG0538 study (NCT00632853).

**Prophylactic Cranial Irradiation (PCI)**

The brain is a common site of distant failure for patients with both limited and extensive stage SCLC following the completion of induction therapy. In 1999, Auperin and colleagues performed a metaanalysis of 7 trials that randomized 987 patients to PCI or control after achieving CR with induction chemotherapy.\textsuperscript{62} The RR death in the treatment group compared to control was 0.84 (0.73–0.97, p=0.01), with a 5.4% absolute increase in 3-year survival from 15.3% to 20.7% with PCI. The cumulative incidence of brain metastases decreased over 25% at 3 years (RR 0.46, 95% CI 0.38–0.57, p<0.001). A separate analysis of PCI use in 670 patients with LS-SCLC using the Surveillance, Epidemiology, and End Results (SEER) database, found that patients treated with PCI had almost double the survival rates of those not treated with PCI 42%, 19%, 9% at 2, 5, and 10 years compared to 23%, 11%, and 6% (p<0.001).\textsuperscript{63} The benefit of PCI in patients with ES-SCLC was also established in a European study of 246 patients randomized to PCI, or observation after completing frontline chemotherapy.\textsuperscript{64} PCI was associated with reduced risk of symptomatic brain metastases (HR 0.27, 95% CI 0.16–0.44, p<0.001) and increased survival (HR 0.68, 95% CI 0.52–0.88).

**Targets and novel biologic therapies**

Critical understanding of the biological drivers of SCLC has lagged significantly behind NSCLC. Consequently, efficacy of targeted biological therapy remains to be established in SCLC. Promising results from interrogation of SCLC cell lines and archival tissue samples using NextGen sequencing and other genomic analysis platforms are beginning to provide encouraging insights into the biology of this disease.\textsuperscript{65–67} The following represent a summary of competed or ongoing studies of targeted agents in SCLC.
C-kit

The high level expression of c-kit and its ligand, stem cell factor, in SCLC and the growth inhibition observed when SCLC cell lines were exposed to a c-kit inhibitor, imatinib, in preclinical studies suggested this target to be biologically relevant and a potential therapeutic target in SCLC. Three prospective studies of imatinib were conducted in relapsed SCLC. In the first of these studies, 9 patients with untreated ES-SCLC and 10 with sensitive relapse were treated. There were no objective responses but only 21% of the patient samples showed c-kit receptor expression by immunohistochemistry (IHC). Two other studies of imatinib in relapsed SCLC patients also failed to show any responses despite demonstrable c-kit expression in approximately 70% of the patients. The disappointing and unexpected result may be ascribed to the absence of activating C-KIT mutations in SCLC.

Angiogenesis in SCLC

Angiogenesis is critical for development and progression of cancer. Efficacy of targeted therapy against mediators of angiogenesis such as vascular endothelial growth factor (VEGF) is well-established in NSCLC. Studies of bevacizumab in SCLC have however produced mixed results. The addition of bevacizumab (15 mg/kg) to standard EP frontline chemotherapy followed by maintenance bevacizumab was evaluated in a 65-patient single arm phase II study, ECOG 3501. A tepid efficacy outcome was observed with ORR of 63.5%, 6 month PFS rate of 30.2%, median PFS 4.7 months and median OS of 10.9 months. A more promising outcome was reported from another single arm phase II study combining bevacizumab with IP regimen with ORR of 84% and median OS of 12.1 months. However, in a randomized comparison, bevacizumab in combination with EP failed to show superior efficacy over EP. Despite increased response rate (58% vs. 48%) and PFS (5.5 vs. 4.4 months; HR: 0.53; 95% CI, 0.32–0.86), the median OS was not improved (9.4 vs. 10.9 months, HR: 1.16; 95% CI, 0.66 to 2.04). This result along with the experience with other agents targeting angiogenesis such as thalidomide and cediranib has dampened enthusiasm for anti-angiogenesis strategy in SCLC.

Bcl-2 Antagonists

Overexpression of native and phosphorylated forms of Bcl-2 family of anti-apoptosis protein in small cell lung cancer supported the clinical evaluation of agents targeting this pathway. An antisense Bcl-2 oligonucleotide, oblimersen, combined with EP in the first-line setting resulted in worse OS (HR 2.13, p=0.02). Similarly, evaluation of small molecule Bcl-2 inhibitors in the relapsed setting has met with disappointing results. For instance, gossypol, an oral inhibitor of anti-apoptotic bcl-2 proteins (Bcl-2, Bcl-xL, Bcl-W, and Mcl-1) and inducer of the pro-apoptotic PUMA and noxa, showed no activity in patients with sensitive relapsed SCLC. The combination of obatoclax with topotecan in relapsed disease also failed to meet the expected efficacy threshold for further development. More recently, navitoclax, a more selective Bcl2 family inhibitor targeting Bcl-2 and Bcl-xL, was shown have limited activity in recurrent SCLC (ORR 2.6%; stable disease 23%). Plasma pro-gastrin-releasing peptide level was identified as a predictive marker of navitoclax efficacy presumably due to its association with Bcl-2 amplification (R = 0.93). Perhaps,
the use of this marker for patient selection may guide the successful integration of Bcl2 antagonists into the management strategy for SCLC in the future.

**Sonic hedgehog pathway**

Signaling through the sonic hedgehog pathway is critical in embryogenesis and airway epithelial progenitor stem cell maintenance. This pathway is implicated in SCLC tumorigenesis. Vismodegib, erismodegib and saridegib are all inhibitors of the hedgehog pathway currently under clinical evaluation as potential therapy for SCLC. Vismodegib was studied in combination with EP in treatment naïve ES-SCLC patients. The addition of vismodegib to EP as frontline therapy was no better than EP alone. The outcome of other studies of hedgehog pathway inhibitors in ES-SCLC (NCT01579929, NCT00927875, NCT01722292) is still awaited in order to validate or repudiate the strategy of hedgehog pathway inhibition in SCLC management.

**DNA Damage repair pathways**

The underlying mechanism for the commonly employed therapeutic agents in SCLC involves induction of DNA damage to trigger cell death. Also, preclinical studies showed that inhibitors of the DNA damage repair pathway potentiate the activity of cytotoxic agents in SCLC and may also overcome resistance to cisplatin. Amuvatinib, a multikinase inhibitor and inhibitor of RAD51 was studied in combination with platinum etoposide in 23 patients with relapsed platinum insensitive SCLC. Two patients achieved partial response while 3 patients had durable disease control. E2511, a randomized phase II study and several other clinical studies evaluating PARP enzyme inhibitors in SCLC are currently ongoing (NCT01642251; NCT01638546; NCT01286987).

**Immunotherapy in Small Cell Lung Cancer**

The role of immune modulating agents in SCLC is an active area of investigation. The result of a phase II study of a replication-competent picornavirus, the Seneca Valley virus (NTX-010), with specific tropism for neuroendocrine markers on SCLC cells was recently reported. Patients with ES-SCLC who did not progress following 4 cycles of induction platinum therapy were randomized to NTX-010 or placebo. The median PFS was identical in both arms at 1.7 months. Due to this disappointing activity further development of NTX-010 in SCLC has been halted.

More interesting is the use of agents that can overcome the natural inhibitory checkpoints that modulate T-cell activation including Programmed Death-1 (PD-1) and Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4). In a phase II study of 130 treatment naïve ES-SCLC patients, ipilimumab, a CTLA-4 antagonist, combined with carboplatin and paclitaxel had improved immune related PFS (irPFS) (HR 0.64, p=0.03), and improved median OS (12.9 vs. 9.9 months) compared to control. This has formed the basis for an ongoing phase III study of ipilimumab combined with EP in the frontline therapy of patients with ES-SCLC. Other studies examining the combination of CTLA-4 and PD-1 blockade with ipilimumab and nivolumab in patients with relapsed SCLC are also ongoing (NCT01450761, NCT01331525, Clinicaltrials.gov).
Conclusions and future directions

The management of SCLC remains very challenging while disease outcome has remains stubbornly poor due mainly to limited options for effective treatment. This efficacy plateau can still be breached with improved understanding of SCLC biology leading to the development of therapeutic agents for carefully validated pathways. The astounding success recorded with targeted therapy approach in the NSCLC field indicates that similar success is also possible with SCLC if improved biological understanding of SCLC resulted in effective targeted agents for defined subsets of the disease.

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