

LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

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Looking Ahead to New Therapies in Small Cell Lung Cancer



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H&O How common is small cell lung cancer (SCLC)?

CR Approximately 25,000 to 30,000 cases of SCLC occur each year in the United States, a number that has been decreasing somewhat in recent years. SCLC is associated more than any other cancer with exposure to tobacco carcinogens—almost all the patients are or were heavy smokers. As smoking rates have declined in the United States, we have seen a corresponding subsequent decrease in the rate of SCLC diagnoses. Smoking rates have increased in other parts of the world, however, so SCLC remains a prevalent disease worldwide.

H&O What is the current prognosis for patients with SCLC?

CR The prognosis for a patient with SCLC depends on the stage. For making treatment decisions, we generally place patients into either of 2 functional stage groups—those with extensive-stage disease, which is defined as disease that has spread beyond a single radiation port, and those with limited-stage disease, which is confined to one side of the chest and can be safely encompassed within a single radiation port. Most patients—approximately 65% to 70%—have extensive-stage disease at the time of diagnosis. The prognosis for patients with extensive-stage disease is quite poor, with a median survival of 9 or 10 months from the time of diagnosis. The prognosis is somewhat better for those with limited-stage disease, but median survival is still less than 2 years.

H&O What are the characteristics of SCLC that cause the prognosis to be worse than that of non-small cell lung cancer (NSCLC)?

CR The biology of SCLC is a quite different from that of NSCLC. It tends to be a very aggressive tumor that grows rapidly and spreads early, such that in most cases it is metastatic at the time of diagnosis. For this reason, SCLC is much less likely to be amenable to surgical resection and cure.

We also have been hindered in our efforts to develop treatments for SCLC because of the difficulty in defining substrates for targeted therapies. Two of the main drivers of SCLC are loss-of-function mutations in 2 key tumor suppressor genes: *TP53* and *RBI*. We have made tremendous progress in lung adenocarcinomas because we have been able to define mutations in driver oncogenes and develop therapies that specifically target them. SCLC is difficult to treat in part because you can't target an absent protein the way you can target a mutant protein—there's nothing against which a drug can be directed.

H&O What is the current first-line treatment for SCLC?

CR First-line chemotherapy in the United States is the combination of a platinum drug—either cisplatin or carboplatin—and etoposide. This has been our standard of care since about 1980. In Japan, a large phase 3 trial by Noda and colleagues found that combining a platinum agent with irinotecan was superior to combining a platinum agent with etoposide. Subsequent trials here in the United States have not confirmed this finding, however, so our standard of care remains platinum/etoposide.

In addition to chemotherapy, patients with limited-stage disease receive concomitant chest radiation. Patients with limited-stage disease who have a good response to therapy also are generally offered prophylactic cranial irradiation after completion of their chemoradiotherapy.

Recent studies, including one by Slotman and colleagues, have suggested that selected patients with extensive-stage disease may benefit from consolidative chest radiation, but this remains investigational. Prophylactic cranial irradiation also used to be offered to patients with extensive-stage disease and an excellent response to chemotherapy. Recent data from Takahashi and colleagues, however, suggest that if these patients are assessed radiologically and have no evidence of central nervous system disease after chemotherapy, they may not benefit from this prophylactic approach.

H&O What is the second-line therapy for SCLC?

CR The only therapy approved by the US Food and Drug Administration (FDA) as second-line therapy in SCLC is topotecan. Other agents, however, are commonly used off label in place of or after topotecan, including irinotecan, paclitaxel, docetaxel, temozolomide, nivolumab (Opdivo, Bristol-Myers Squibb), ipilimumab (Yervoy, Bristol-Myers Squibb)/nivolumab, vinorelbine, etoposide, gemcitabine, and cyclophosphamide/doxorubicin/vincristine (CAV). Amrubicin is approved for second-line use in Japan, but subsequent trials here in the United States have not shown it to be more effective than topotecan, and it is not available in this country.

H&O What are the limitations of the current standard treatments?

CR Chemotherapy is remarkably effective at inducing responses in SCLC; most patients have at least some response, and some have a dramatic response. The problem is that the responses are generally not durable; the disease recurs quickly, and often in a chemotherapy-resistant form. Also, topotecan is associated with substantial toxicities, so many oncologists prefer to move on to other agents or to investigational approaches in clinical trials.

When patients need second-line or later treatment, I tend to recommend clinical trials or—in the absence of an appropriate trial—consider immunotherapy or irinotecan. The National Comprehensive Cancer Network (NCCN) recently gave a 2A recommendation to nivolumab alone and to nivolumab plus ipilimumab as options for subsequent therapy in patients who have a relapse within 6 months after primary therapy. Although these therapies are not FDA-approved for use in SCLC, they appear promising—with clear responses, and in some cases durable responses. Most of the practitioners contributing to the NCCN panel felt that it is reasonable to offer those therapies to patients at this time. To some extent, I think that their opinion reflects dissatisfaction with the toxicity-to-benefit ratio of topotecan.

H&O What other treatment approaches are being studied?

CR Several large first-line phase 3 trials are looking at immunotherapy combined with chemotherapy in SCLC. KEYNOTE-604 (A Study of Pembrolizumab in Combination With Etoposide/Platinum for Participants With Extensive Stage Small Cell Lung Cancer; NCT03066778) is looking at the first-line treatment of SCLC with platinum/etoposide with or without pembrolizumab (Keytruda, Merck). IMpower 133 (A Study of Carboplatin Plus Etoposide With or Without Atezolizumab in Participants With Untreated Extensive-Stage Small Cell Lung Cancer; NCT02763579) will be looking at first-line treatment with platinum/etoposide with or without the programmed death ligand 1 (PD-L1) inhibitor atezolizumab (Tecentriq, Genentech). Caspian (Durvalumab +/- Tremelimumab in Combination With Platinum Based Chemotherapy in Untreated Extensive-Stage Small Cell Lung Cancer; NCT03043872) is looking at first-line therapy with 1 of 3 regimens: platinum/etoposide, platinum/etoposide plus the programmed death 1 (PD-1) inhibitor durvalumab (Imfinzi, Astra-Zeneca), and platinum/etoposide plus durvalumab and the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitor tremelimumab. Going beyond first-line treatment, CheckMate 451 (An Investigational Immuno-therapy Study of Nivolumab, or Nivolumab in Combination With Ipilimumab, or Placebo in Patients With Extensive-Stage Disease Small Cell Lung Cancer After Completion of Platinum-based Chemotherapy; NCT02538666) is looking at maintenance treatment with nivolumab vs ipilimumab/nivolumab vs placebo, and CheckMate 331 (Effectiveness Study of Nivolumab Compared to Chemotherapy in Patients With Relapsed Small-cell Lung Cancer; NCT02481830) is looking at the second-line treatment of SCLC with nivolumab vs topotecan or amrubicin. The initial data on immunotherapy are exciting, and I'm looking forward to seeing more data from these larger trials so we can learn how durable the responses are and how these agents stack up against our current standards of care.

We have seen encouraging initial data with an antibody-drug conjugate called rovalpituzumab tesirine, also known as Rova-T. This agent is directed against a target called delta-like protein 3 (DLL3), which is a Notch ligand that is markedly upregulated and overexpressed in SCLC. Rovalpituzumab tesirine showed initial activity in a phase 1 study of SCLC that our group published in *Lancet Oncology*, specifically in those patients whose tumors had a high level of expression of DLL3. If these results hold up, this agent may be the first biomarker-directed therapy for SCLC. We still need to see confirmation of

Table. Ongoing Studies of Checkpoint Blockade in Small Cell Lung Cancer

Immunotherapy	Study Name	Study Phase	ClinicalTrials.gov Identifier	Estimated Primary Completion Date
LS-SCLC				
Nivolumab + ipilimumab	STIMULI	2	NCT02046733	October 2019
Pembrolizumab and concurrent radiotherapy ± chemotherapy (cisplatin/carboplatin and etoposide)	NA	1	NCT02402920	July 2023
ES-SCLC: first-line therapy				
Pembrolizumab with cisplatin/carboplatin and etoposide	KEYNOTE-011	1	NCT01840579	June 2019
Cisplatin/carboplatin and etoposide ± pembrolizumab	REACTION	2	NCT02580994	June 2020
ES-SCLC: maintenance therapy				
Nivolumab ± ipilimumab vs placebo	CheckMate 451	3	NCT02538666	September 2018
ES-SCLC: second-line therapy and beyond				
Nivolumab vs topotecan or amrubicin	CheckMate 331	3	NCT02481830	March 2018
Carboplatin and etoposide + atezolizumab or placebo	IMpower 133	1/3	NCT02763579	June 2019
Tremelimumab and durvalumab ± radiation	NCI-2016-00026/ Winship3112-15/ ESR-14-10531	2	NCT02701400	April 2019
Pembrolizumab vs topotecan	AFT-17	2	NCT02963090	May 2019
BMS-986012 ± nivolumab	CA001-030	1/2	NCT02247349	October 2018
Durvalumab + olaparib	MEDIOLA	1/2	NCT02734004	October 2018

ES-SCLC, extensive-stage SCLC; LS-SCLC, limited-stage SCLC; NA, not applicable; SCLC, small cell lung cancer.

Source: Sabari JK et al. *Nat Rev Clin Oncol.* 2017;14(9):549-561. Adapted with permission.

the early data: a larger phase 2 trial of rovalpituzumab tesirine called TRINITY (Study of Rovalpituzumab Tesirine for Third-line and Later Treatment of Subjects With Relapsed or Refractory Delta-Like Protein 3-Expressing Small Cell Lung Cancer; NCT02674568) has completed accrual, and multiple ongoing studies will further evaluate the activity of this agent in recurrent SCLC. We are eagerly awaiting the results of these trials.

In addition, poly(ADP-ribose) polymerase (PARP) inhibitors have shown initial activity in SCLC. We and others in the field, on the basis of a protein called Schlafen Family Member 11 (SLFN11), have defined some biomarkers that may enrich for a population particularly sensitive to PARP inhibitors in SCLC. A high level of SLFN11 appears to correlate with sensitivity to PARP inhibitors in preclinical models and cell lines. Several clinical trials involving PARP inhibitors in SCLC are ongoing or recently completed. As one recent example, at the 2017 meeting of the American Society of Clinical Oncology,

Dr Taofeek Owonikoko and colleagues presented the results of a study in which the addition of veliparib to doublet chemotherapy improved progression-free survival in patients with extensive-stage SCLC.

BCL2 is also being considered as a potential target in SCLC, which is an especially interesting approach because synergy appears to exist between inhibition of BCL2 and inhibition of mammalian target of rapamycin (mTOR). A trial is now being launched to look at a combination of drugs targeting those 2 pathways (NCT03366103). Other trials are looking at epigenetic dysregulation and modification of proteins such as enhancer of zeste homolog 2 (EZH2) and lysine specific demethylase 1 (LSD1), which are altered in SCLC. Finally, alterations in *TP53* and *RB1* may make SCLC especially sensitive to the G2 checkpoint kinase WEE1.

H&O What is it about SCLC that makes it respond to immunotherapy?

CR It is important to realize at the outset that most patients with SCLC unfortunately do not have immunoresponsive disease—only about 20% of patients demonstrate a response to the combination of ipilimumab and nivolumab. However, we do know of some factors that may make this disease a good target for the immune system. SCLC has a very large mutation burden, probably because of its close association with heavy tobacco exposure. In addition, defects in *TP53* and *RBI* inherently promote genomic instability and may increase the number of genomic alterations in the tumor. This should in theory present the immune system with a lot of potential targets. We are now seeing across disease types that the larger the mutation burden of a tumor, the more likely it is that the immune system can recognize that tumor as foreign. Some data presented in 2017 at the International Association for the Study of Lung Cancer (IASLC) 18th World Conference on Lung Cancer by Dr Scott Antonia and colleagues suggested that the tumor mutation burden in patients who have SCLC treated with immunotherapy could substantially enrich for the likelihood of a response and survival.

H&O Where do you think the treatment of SCLC will be in 10 years?

CR Despite the history of clinical research in this disease, I am very optimistic about the likelihood of substantial change in the next decade. I expect that in the next 10 years, we will have multiple new effective drugs in SCLC. Some of these will be targeted therapies for biomarker-defined subsets of SCLC. Some of them will include immunotherapy. I would expect to see immunotherapy targets in SCLC extend beyond the PD-1 and CTLA-4 targets that are currently in favor to include targets such as activators of natural killer cells and tumor-associated macrophages.

This is a disease with a terrible prognosis and in tremendous need of clinical progress, but there is real hope that meaningful change will be accomplished with emerging targets and therapies.

Disclosure

Dr Rudin has been a paid consultant regarding oncology drug development for AbbVie, Araxes Pharma, AstraZeneca, Bristol-Myers Squibb, Celgene, G1 Therapeutics, Harpoon Therapeutics, and Seattle Genetics.

Suggested Readings

Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol*. 2016;17(7):883-895.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Small Cell Lung Cancer. Version 2.2018. https://www.nccn.org/professionals/physician_gls. Updated January 17, 2018. Accessed September 26, 2017.

Noda K, Nishiwaki Y, Kawahara M, et al; Japan Clinical Oncology Group. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med*. 2002;346(2):85-91.

Owonikoko TK, Dahlberg SE, Sica G, et al. Randomized trial of cisplatin and etoposide in combination with veliparib or placebo for extensive stage small cell lung cancer: ECOG-ACRIN 2511 study [ASCO abstract 8505]. *J Clin Oncol*. 2017;35(15)(suppl).

Rudin CM, Pietanza MC, Bauer TM, et al; SCRX16-001 investigators. Rovalpituzumab tesirine, a DLL3-targeted antibody-drug conjugate, in recurrent small-cell lung cancer: a first-in-human, first-in-class, open-label, phase 1 study. *Lancet Oncol*. 2017;18(1):42-51.

Sabari JK, Lok BH, Laird JH, Poirier JT, Rudin CM. Unravelling the biology of SCLC: implications for therapy. *Nat Rev Clin Oncol*. 2017;14(9):549-561.

Slotman BJ, van Tinteren H, Praag JO, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. *Lancet*. 2015;385(9962):36-42.

Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(5):663-671.

Weiss GJ, Waypa J, Blaydorn L, et al. A phase Ib study of pembrolizumab plus chemotherapy in patients with advanced cancer (PembroPlus). *Br J Cancer*. 2017;117(1):33-40.