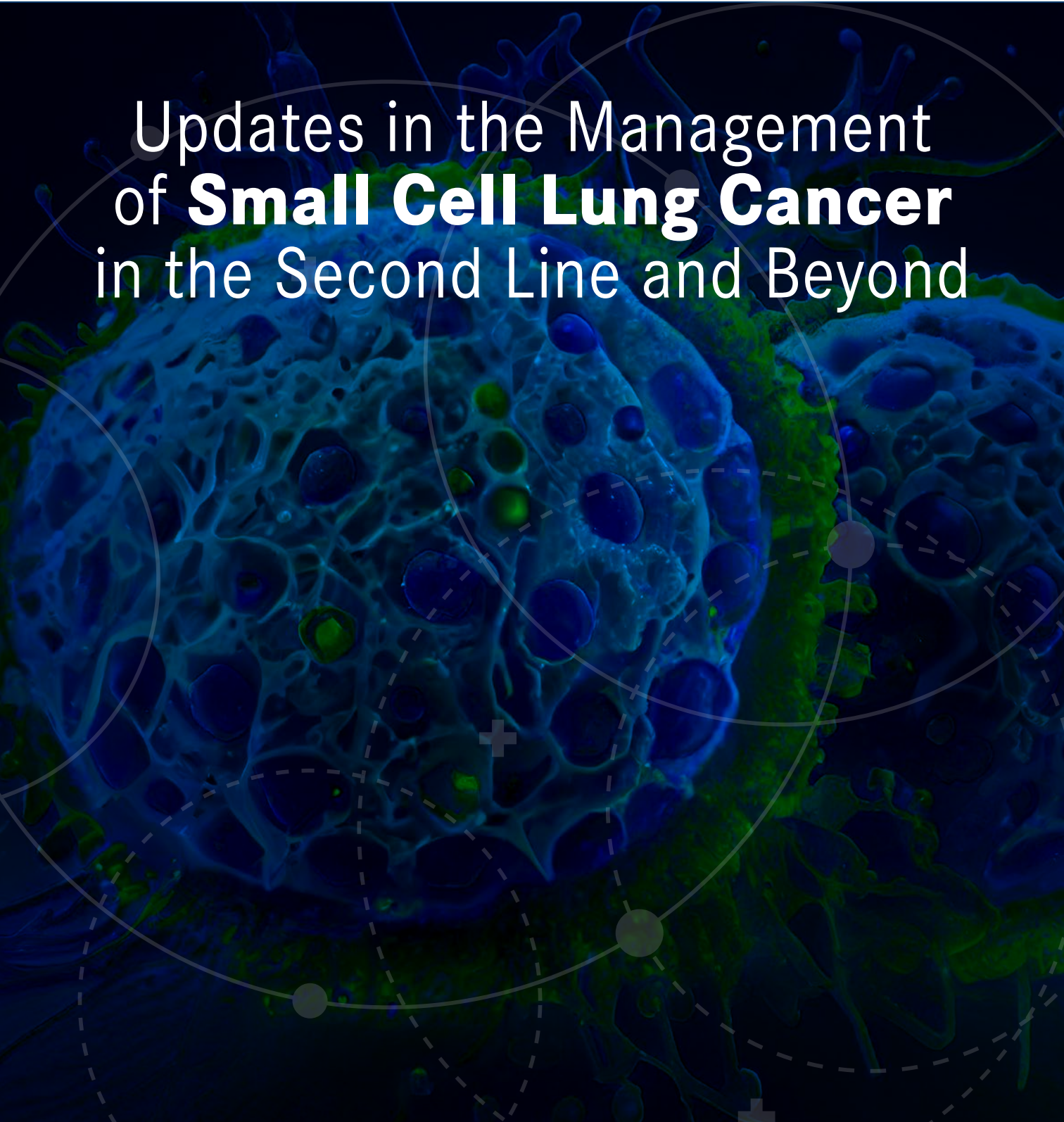


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SMALL CELL LUNG CANCER
NOVEMBER 12, 2022
VIRTUAL WORKSHOP

SCIENTIFIC INTERCHANGE & WORKSHOP

Updates in the Management
of **Small Cell Lung Cancer**
in the Second Line and Beyond



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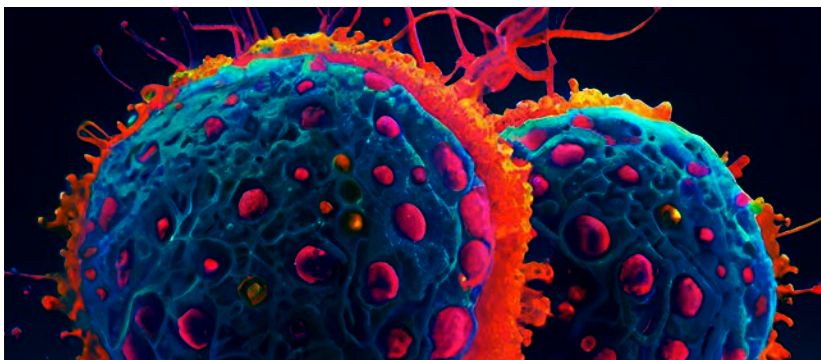
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SCLC



KEY TAKEAWAYS

- ▶ Decreasing incidence of small cell lung cancer (SCLC) has led to a continued decline in correlating mortality rates; however, compared with non-small cell lung cancer (NSCLC), low survival rates persist for SCLC. There remains a lack of treatment options, particularly in the second-line treatment setting.
- ▶ The lack of biomarkers for SCLC remains a major barrier to early diagnosis and treatment. Future research is needed to gain a greater understanding of the unique biology of extensive-stage SCLC (ES-SCLC) and to identify biomarkers to help enhance early disease detection, guide treatment decision-making, and drive the development of improved therapies.
- ▶ Following FDA approval for use in metastatic SCLC, lurbinectedin has become a preferred treatment option in the second-line setting for SCLC; it offers a more convenient dosing schedule than does irinotecan.^{1,2}
- ▶ Antibody-drug conjugates (ADCs) are anticipated to impact the future treatment landscape for SCLC. This drug class offers improved delivery of cytotoxic agents with reduced toxicity and expanded options for second-line combination treatment approaches with immunotherapy.
- ▶ Participation of elderly and frail patients with SCLC in clinical trials remains low; improved study designs are needed to allow greater participation and insight into optimal second-line treatment approaches for these patient populations.

Updates in the Management of Small Cell Lung Cancer in the Second Line and Beyond

INTRODUCTION

On November 12, 2022, a select group of oncologists participated in a virtual workshop to discuss the management of small cell lung cancer (SCLC) in the second-line setting and beyond. **Balazs Halmos, MD**, professor of medicine and associate director of clinical science at the Montefiore Einstein Cancer Center in Bronx, New York, was the moderator. Goals of the workshop were to analyze the unmet needs and factors influencing patient trajectory along the

disease continuum, assess current and emerging approaches for the management of relapsed/refractory (R/R) SCLC, examine recent updates to treatment guidelines, and discuss strategies to incorporate these findings into daily practice. This article provides a summary of key discussion points and stakeholder insights.

UNMET NEEDS IN SECOND-LINE MANAGEMENT OF SCLC

SCLC accounts for 10% to 15% of all lung cancers in the United States; approximately 24,000 to 35,000 new cases were diagnosed in 2022.^{3,4} From 2011-2017, the 5-year survival rate for SCLC was only 7%, which is less than one-third of the 5-year survival rate for all lung cancers (22.9%).^{3,5} Mortality rates have decreased not from treatment advances, but from reduced incidence.⁶ Extensive-stage SCLC (ES-SCLC) accounts for approximately 60% to 65% of all SCLC cases; although response rates to first-line treatment remain high (67% to 80%), nearly all patients experience disease recurrence.^{7,8} The most common genetic alterations in SCLC are *TP53* and *RB1* inactivation, a hallmark feature of the disease.⁹

STAKEHOLDER INSIGHTS

Faculty acknowledged that numerous unmet needs in second-line management of SCLC have slowed progress and kept survival rates much lower than those seen with NSCLC.⁵ A lack of biomarkers in SCLC, partially related to a limited availability of tumor tissue, is a major contributing factor to this observed difference. An improved biomarker profile would aid earlier detection, improve selection of treatment regimens, and drive newer and improved therapies.

A minimal number of elderly and frail patients take part in

clinical trials due to numerous factors including the negative impact of induction therapy on patient performance status, adverse events (AEs) from toxic chemotherapies that impart minimal benefit. Clinical trials need participants to drive progress. Underserved populations have higher rates of SCLC due to a higher incidence of smoking and socioeconomic factors. Some research has occurred in SCLC disease subtypes; however, clinicians do not use subtyping in clinical practice. Subtyping could aid SCLC treatment strategies. There is limited understanding of the biology of SCLC—a short duration of response (DOR) to first-line treatment is common, and disease change after relapse results in chemoresistant tumor cells.

A lack of biomarkers and the rapid development of the disease are major barriers to earlier diagnosis. Participants expressed that socioeconomic factors also prevent earlier diagnosis, since underserved populations have minimal access to screening and higher rates of disease. Research is required to improve the biomarker landscape in SCLC, which would lead to the development of targeted therapies, more screening tools, and, ultimately, earlier diagnosis. Also, clinicians could be more aggressive with biopsy techniques to increase availability of tumor tissue.

One of the greatest challenges in treating metastatic SCLC is a limited understanding of the biology of SCLC. This has resulted in poor treatment options, which is another challenge in treating metastatic disease. The change in disease after relapse and the resulting chemoresistance of tumor cells have left us with

limited treatment options and bleak outcomes. Following first-line chemotherapy, the faculty noted, SCLC characteristics can change significantly and essentially present as an altogether different disease, which highlights the need for clinical studies focused on second-line treatment approaches.

MANAGEMENT OF EXTENSIVE-STAGE SCLC

Systemic therapy in SCLC has evolved through various chemotherapies to checkpoint inhibitors. Immunotherapies to manage ES-SCLC in the first-line setting have been evaluated in several trials, including the IMPower133 (NCT02763579), CASPIAN (NCT03043872), ATLANTIS (NCT02566993), and RESILIENT (NCT03088813) studies.

IMPower133 Trial

The international, double-blind, randomized, placebo-controlled IMpower133 study compared the efficacy and safety of the PD-L1 inhibitor atezolizumab plus chemotherapy (carboplatin and etoposide) with chemotherapy alone in patients (N = 403) with untreated ES-SCLC.¹⁰ Overall survival (OS) was significantly longer in patients given atezolizumab plus chemotherapy compared with those receiving chemotherapy alone (median, 12.3 vs 10.3 months, respectively; HR 0.70; *P* = .007).¹⁰ Median progression-free survival (PFS) was longer in patients receiving atezolizumab plus chemotherapy compared with those receiving chemotherapy alone (5.2 vs 4.3 months).¹⁰ Any-grade AEs were reported in 94.9% of patients in the atezolizumab group compared with 92.3% in the chemotherapy alone group. Neutropenia, anemia, and decreased neutrophil count were the most common grade 3 or 4 AEs.¹⁰

CASPIAN Trial

The open-label, phase 3 CASPIAN

study investigated the safety and efficacy of the PD-L1 inhibitor durvalumab plus tremelimumab, an anti-CTLA4 monoclonal antibody (mAb), in combination with EP (etoposide plus cisplatin/carboplatin), durvalumab plus EP, or EP alone in patients (N = 805) with untreated ES-SCLC. Data showed sustained OS improvement with durvalumab plus EP compared with EP alone (HR, 0.71; $P = .0003$); the median OS was 12.9 to 10.5 months, respectively, and the 36-month OS was 17.6% to 5.8%. Durvalumab plus tremelimumab and EP resulted in a median OS of 10.4 months and a 36-month OS of 15.3%.¹¹ Serious AEs were observed in 47%, 32%, and 36% of patients receiving durvalumab plus tremelimumab and EP, durvalumab plus EP, and EP alone, respectively.¹¹

ATLANTIS Trial

In the randomized, open-label, phase 3 ATLANTIS trial, lurbinectedin plus doxorubicin was evaluated as a second-line therapy among patients (N = 613) with relapsed ES-SCLC.¹² OS in the intention-to-treat population was the primary end point.¹² In the lurbinectedin plus doxorubicin group, the median OS was 8.6 months compared with 7.6 months in the control group (given investigator's choice of CAV [cyclophosphamide, doxorubicin, and vincristine] or topotecan).¹² Twelve patients died because of treatment-related AEs (TRAEs), including 2 of 303 patients (< 1%) in the lurbinectedin plus doxorubicin group and 10 of 289 patients (3%) in the control group.¹² Compared to the control group, fewer patients in the lurbinectedin plus doxorubicin group experienced grade 3 or greater hematologic AEs (anemia, 38% vs 19%, respectively; neutropenia, 69% vs 37%; and thrombocytopenia, 31% vs 14%).¹² Investigators concluded that lurbinectedin plus doxorubicin did not increase OS compared with CAV or topotecan in patients with relapsed ES-SCLC. However, when compared with CAV or topotecan, therapy

with lurbinectedin plus doxorubicin demonstrated a favorable hematologic safety profile.¹²

RESILIENT Trial

The ongoing, 2-part, phase 2/3 RESILIENT trial is evaluating the efficacy, safety, and tolerability of intravenous (IV) liposomal monotherapy in patients with SCLC who experienced disease progression following first-line treatment with platinum-based chemotherapy.¹³ Part 2 of the trial, a phase 3, open-label study design, will include an estimated 450 patients randomly assigned (1:1) to receive IV liposomal irinotecan or IV topotecan.¹³ OS will be the primary end point, and PFS, objective response rate (ORR), and the percentage of patients reporting symptom improvement will be secondary end points. Patients will continue study-related therapy until disease progression, intolerable AEs, or study withdrawal occurs, at which point they will be monitored for survival until study conclusion or death.¹³

NOVEL THERAPEUTIC APPROACHES

Second-line therapeutic strategies for ES-SCLC is an active area of research; novel treatment approaches currently under investigation include bispecific T-cell engagers (BiTEs), antibody-drug conjugates (ADCs), and bispecific antibodies.

Tarlatamab

Tarlatamab is a half-life extended BiTE that targets DLL3, thereby activating endogenous T cells to attack and kill DLL3-expressing tumor cells.¹⁴ An open-label, multicenter, dose-escalation study (NCT03319940) assessed tarlatamab in patients with SCLC with disease progression after at least 1 platinum-based chemotherapy.¹⁴ At the data cutoff on March 22, 2021, with a median follow-up of 11.2 months, the demonstrated median DOR and median time to response (TTR) in patients

with confirmed partial response (PR) (n = 13) were 18.7 months and 8.0 months, respectively. Ten of 66 patients (≈ 15%) completed more than 6 months of treatment.¹⁴ Three patients (5%) discontinued therapy due to TRAEs, including dose-limiting toxicities of grade 5 pneumonitis (2%) and grade 3 encephalopathy (2%). Symptoms of cytokine release syndrome (CRS) included fever, tachycardia, nausea, fatigue, and hypotension; they typically occurred in the first cycle of treatment and were mostly transitory and treatable with supportive care, corticosteroids, and anti-IL-6R agents.¹⁴ Investigators concluded that these findings supported the use of tarlatamab as the first immunoncology treatment for SCLC, since it has an acceptable safety profile and durable response profile.¹⁴

Antibody-Drug Conjugates in SCLC

ADCs are a novel class of sophisticated biopharmaceutical molecules that are comprised of mAbs joined to cytotoxic agents via a linker and are among the fastest growing therapeutic classes in oncology.¹⁵ The mechanism of action of ADCs is initiated upon mAb binding to the target antigen, followed by internalization, linker breakdown, and release of the cytotoxic payload.¹⁵ The majority of circulating ADC molecules exist in a stable form, but plasma can also contain naked antibodies and free payloads. Depending on the associated ADC design, some payloads may be delivered to the tumor microenvironment without requiring internalization. Payload-associated hydrophobic properties control the bystander effect (ie, a phenomenon involving the diffusion of drug payload from targeted cells to neighboring cells), thereby leading to induced cytotoxic effects in antigen-negative tumor cells.¹⁵ ADCs being studied in SCLC include rovalpituzumab tesirine (Rova-T), lorvotuzumab mertansine (LM), and sacituzumab govitecan (SG).¹⁵

Rova-T, the first-in-class ADC, consists of a DLL3-targeting mAb linked to a pyrrolobenzodiazepine cytotoxic payload via a protease-cleavable linker. Rova-T has been the subject of numerous phase 2 and 3 trials as a result of the optimistic results reported from a phase 1 study (NCT01901653), which showed an ORR of 18% in 60 assessable patients, including 10 (38%) of 26 patients with DLL3-high expression (in $\geq 50\%$ of tumor cells).¹⁶ Rova-T and topotecan were compared as second-line treatments for DLL3-high ES-SCLC in the phase 3, randomized TAHOE trial (NCT03061812).¹⁷ In the Rova-T and topotecan arms, the median OS was 6.3 and 8.6 months, respectively. Due to the shorter OS (as well as greater rates of serosal effusions, photosensitivity responses, and peripheral edema) noted with Rova-T compared with topotecan, the independent data monitoring committee recommended that study enrollment be discontinued.¹⁵ Similarly, the phase 3 MERU study (NCT03033511), which assessed Rova-T in the maintenance setting following first-line chemotherapy, was discontinued due to a lack of survival benefit in the ROVA-T arm.¹⁸

LM is an ADC composed of an anti-CD56 mAb coupled to the cytotoxic maytansinoid payload DM1 compound via a cleavable disulfide linker.¹⁹ A phase 1/2 study (NCT01237678) compared the safety and efficacy of LM plus first-line chemotherapy (carboplatin plus etoposide) with chemotherapy alone in patients with ES-SCLC. LM plus chemotherapy did not perform any better than chemotherapy alone (median PFS, 6.2 vs 6.7 months, respectively).¹⁹ Peripheral neuropathy was the most frequently reported treatment-emergent AE (TEAE) resulting in treatment discontinuation (29%), and 18 of 94 patients who received LM plus chemotherapy died due to a grade 5 TRAE.¹⁹ Although CD56 represents an intriguing target in SCLC, therapeutic

optimization is required to lessen AEs and increase efficacy.¹⁵

SG is an ADC consisting of a TROP2-directed mAb coupled to SN-38, an anti-topoisomerase I payload via the hydrolysable CL2A linker.²⁰ The phase 1/2 IMMU-132-01 basket trial (NCT01631552) evaluated the safety and efficacy of SG in 62 patients with refractory SCLC.^{15,20} The reported ORR was 17.7%; median DOR and OS were 5.7 months and 7.1 months, respectively. Although the results were promising in this area of unmet clinical need, large prospective trials are still needed to establish efficacy of SG in this patient population. Ongoing studies are being conducted to compare SG with PARP inhibitors in SCLC. To assess its position in the current SCLC treatment landscape, a prospective, randomized study comparing its efficacy to second-line conventional regimens involving topotecan, CAV, or lurbinectedin may be necessary.¹⁵

DS-7300

DS-7300 is a novel, B7-H3 (CD276)-directed ADC composed of 3 components: a humanized B7-H3-targeting mAb conjugated to the anti-topoisomerase I payload deruxtecan (DXd) via a cleavable tetrapeptide linker.²¹ A phase 1/2, dose-finding study (NCT04145622) assessed the safety and efficacy of DS-7300 in patients with advanced solid tumors, including SCLC.²² Reported findings demonstrated DS-7300 to be generally well-tolerated and to exhibit early signs of anticancer efficacy.

Extended follow-up data from 91 evaluable patients reported observed responses in 30 patients (33%); among these were 7 of 9 patients with SCLC, 2 of 5 patients with squamous NSCLC, and 16 of 42 patients with metastatic, castrate-resistant prostate cancer. The median DOR was 4.4 months (95% CI, 2.8 months to not attained) among 6 patients with SCLC with a confirmed PR. The general safety was comparable with those of earlier results. TEAEs

were observed in 124 patients (98%); the most frequently reported (> 30%) were nausea (61%), infusion-related reactions (35%), and vomiting (31%).²² Investigators concluded that these findings showed evidence of durable anticancer efficacy of DS-7300 in heavily pretreated patients with SCLC and supported further investigation with a phase 2, dose-optimization study using starting doses of 8 mg/kg and 12 mg/kg.

Bispecific Antibodies: Talazoparib and Temozolomide

Talazoparib is a poly (ADP-ribose) polymerase inhibitor that elicits cytotoxic effects by inhibiting PARP1 and PARP2 proteins.²³ When coupled with talazoparib in SCLC models, the alkylating agent temozolomide has enhanced antitumor response.^{23,24} The phase 2, open-label UCLA/TRIO-US L-07 trial (NCT03672773) evaluated the safety and efficacy of talazoparib in combination with temozolomide as a second-line therapy approach in R/R ES-SCLC.²³ The primary end point was ORR in comparison with second-line topotecan, the historical control (ORR, 15%); secondary end points were PFS, OS, DOR, and TTR.²³ The reported ORR was comparable among those who were platinum-refractory (3 of 6 patients), platinum-resistant (4 of 9 patients), and platinum-sensitive (4 of 13 patients). However, time of observed progression varied between subgroups, with patients who were platinum-refractory progressing during treatment or within 28 days of final platinum-based therapy (FPBT), patients who were platinum-resistant within 28 to 90 days of FPBT, and patients who were platinum-sensitive more than 90 days after FPBT. As for reported results for secondary end points, median TTR was 1.8 months, DOR was 5.8 months, PFS was 4.5 months, and OS was 11.9 months.²³ The most commonly observed TRAEs of grade 3 or greater were thrombocytopenia (61.3%), anemia (54.8%), neutropenia

(41.9%), and atypical pneumonia (3.2%), which were manageable with dose holds, dose reductions, transfusion, or administration of growth factors.²³

The reported response rate for the study was higher than expected. This was the second trial to show beneficial outcomes in patients with SCLC using a combination approach with PARP inhibition and low-dose temozolomide, but a phase 3 study is needed to further verify the effectiveness of this treatment strategy relative to currently approved second-line therapies.²³

STAKEHOLDER INSIGHTS

Although the IMpower133 study results are among the most favorable reported within the last decade for SCLC, faculty acknowledged that when compared with the placebo arm, observed differences in response remain small. Considering a relatively early drop off in treatment response reported in the IMpower133 and CASPIAN trials, participants expressed that earlier intervention before disease progression occurs, such as during the maintenance treatment phase, may be helpful to improve or prolong treatment response. Because patients with SCLC tend to have shorter OS, panel experts expressed a general preference for continuation of immunotherapy in the majority of patients in the second-line setting.

Lurbinectedin is approved by the FDA in the second-line treatment of patients with metastatic SCLC. The experts generally prefer irinotecan and lurbinectedin to topotecan in patients who progress, so lurbinectedin and irinotecan are quite often the second-line therapies of choice. Some clinicians use irinotecan before lurbinectedin, while others use lurbinectedin as second-line therapy and irinotecan as third-line treatment, although lurbinectedin

has a more convenient dosing schedule. Lurbinectedin is not used as second-line therapy in patients with brain metastases, as it does not work within the central nervous system. Lurbinectedin is tolerated well by healthy patients, so most experts do not routinely use growth factor support with the drug.

Faculty discussed several ongoing trials evaluating combination treatment strategies with lurbinectedin, including LUPER (NCT04358237,) a phase 1/2 study of lurbinectedin plus pembrolizumab; IMforte (NCT05091567), a phase 3 study of lurbinectedin plus atezolizumab; and MC1923 (NCT04607954), a phase 2 study of durvalumab plus topotecan or lurbinectedin. Among the combination trials, experts expressed the most anticipation for results from the phase 3 IMforte study of lurbinectedin plus atezolizumab in ES-SCLC, which will provide insight into the potential role of the lurbinectedin plus atezolizumab combination in SCLC.

Panel experts expressed disappointment in the results reported from the phase 3 RESILIENT trial for liposomal irinotecan monotherapy compared with standard of care. However, participants noted that liposomal irinotecan has shown potential in targeting DLL3, so there is certainly potential in SCLC for DLL3 as a target for treatment and as a possible biomarker, but more research is required.

UPDATED SCLC GUIDELINES

Halmos presented slides concerning the updated National Comprehensive Cancer Network guidelines for the treatment of ES-SCLC. In general, faculty found the updates somewhat confusing, and they questioned the rationale for the order of therapies listed as “other recommended

regimens.” Overall, the experts believed that the updated guidelines would not influence treatment decisions in the clinical setting for second-line SCLC. In terms of treatment rechallenge with the original first-line regimen or a similar platinum-based regimen, some clinicians expressed a preference to rechallenge after 3 months in combination with immunotherapy.

LOOKING AHEAD

As the interchange concluded, faculty were asked to comment on key takeaways from the discussion. The experts briefly discussed the main unmet needs and their expectations for the SCLC landscape in 5 to 10 years. Participants noted the lack of biomarkers, limited treatment options, differing biology in SCLC versus ES-SCLC, minimal participation of elderly or frail patients in clinical trials, and continued poor outcomes in underserved populations as current areas of unmet need for SCLC. Future research and investment are needed to gain greater understanding of the unique biology of ES-SCLC and to identify improved biomarkers to help guide treatment decision-making. Clinical trials are needed in ES-SCLC to improve knowledge of the value of novel therapies like ADCs and fuel the development of new and improved therapies. Improved study designs are also needed that would allow increased participation of elderly or frail patients in clinical trials.

The faculty anticipate the incidence of SCLC to further decline over the next decade as smoking rates continue to decrease. They believe that ADCs that are already being tested in early trials for SCLC will significantly change the treatment landscape of ES-SCLC by offering improved delivery of cytotoxic agents with reduced toxicity and better partnering agents for combination treatment approaches with immunotherapy. Due to the relative efficacy of frontline therapy for SCLC,

faculty expressed that they do not anticipate significant changes in this treatment setting. ■

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Expert Perspectives: Management of Small Cell Lung Cancer in the Second-line Setting



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INTRODUCTION

There are very few treatment options for patients with small cell lung cancer (SCLC) in the second-line setting, and advances in the treatment of SCLC occur slowly. In video interviews with *OncLive*[®], Balazs Halmos, MD; Fred R. Hirsch, MD, PhD; and Nagashree Seetharamu, MD, MBBS; shared insights into evidence-based approaches to the management of SCLC, and discussed how recent outcomes of clinical trials involving investigational agents may fit into the treatment paradigm in the future. Ahead are highlights from their interviews.

**Interview transcripts are edited for readability.*

➤ TO WATCH THE VIDEO INTERVIEWS, VISIT [ONCLIVE.COM](https://www.onclive.com)

***OncLive*[®]: How do you approach patient care and disease management of SCLC in the second-line setting?**

NAGASHREE SEETHARAMU, MD, MBBS: [My approach] depends on a lot of things. It depends on [what the] patient performance status [is], what [treatment] they received in the first-line [setting], when they received it, if they were on active treatment at the time of progression, how they tolerated the first-line treatment, and what [kind of] progression [there] is. Is it oligoprogression or CNS (central nervous system)–only progression? It kind of depends on several factors.

FRED R. HIRSCH, MD, PhD: There are a couple of options for second-line therapy of extensive small cell lung cancer. Standard of care is either topotecan or lurbinectedin. However, there is an option [that depends on whether the patient] progressed immediately on first-line

treatment [or] if the [patient was] sensitive to etoposide immunotherapy and [progressed after having] stopped therapy. [In the latter case], you could retreat the patient with [the drug used in the] first-line setting.

BALAZS HALMOS, MD: Small cell lung cancer remains a very serious disease, especially when it presents at the extensive stage. [At] that stage, we have seen slight improvements in terms of management with the introduction of immunotherapy into the first-line setting. IMpower133 and CASPIAN are the key clinical trials we reference in terms of patient management, and this treatment approach certainly leads to a high chance of early response. With the introduction of immunotherapy, we have patients who can stay [on treatment] long term, but 80% to 90% of patients with extensive-stage small cell lung cancer will ultimately progress.

After progression on frontline chemotherapy and immunotherapy, our [current] treatment approaches are not so successful. It remains a great unmet need to identify better approaches and potential biomarkers that can [help determine] treatments that might be more successful. A lot of ongoing research is necessary. Some might say the number 1 highlight is that [we are] considering clinical studies in the context of second-line treatment for extensive small cell lung cancer. But, of course, we do have some conventional approaches to consider, [including] old-fashioned approaches with second-line chemotherapy such as topotecan, which has been approved for 20-plus years. It has limited efficacy, is difficult to administer, and has a lot of toxicities, so it is not a favorite [option] for patients or providers. We have seen shifts lately with the introduction of lurbinectedin, which has shown activity in the second-line setting through initial studies. It is a little bit easier to both give and tolerate. [It has] an easier toxicity profile, which mainly includes hematological and GI (gastrointestinal) toxicities and some phlebitis, but [lurbinectedin is] generally well-tolerated. We are looking forward to, maybe, better combinations and other approaches to improve the current landscape.

Lately, we have also seen a kind of renaissance for the rechallenge approach, in which we [retreat with] the original treatment regimen. That has been used, traditionally, for patients [in whom] the disease has progressed after a long interval—generally 6 months as a kind of conventional approach. Through the [open-label, randomised, phase 3 trial done in France], we have seen that rechallenging with the original regimen could [be] more effective than [using] second-line chemotherapy such as topotecan. [These results] have led to significant changes in terms of practice. Rechallenge is now used more frequently, and the NCCN (National Comprehensive Cancer Network) guidelines now list rechallenge as a primary approach alongside clinical trial participation. If you look at [the results of the] study, the real benefit of rechallenge [was] better for patients whose progression occurred at a significant time after completion of primary therapy. [For] platinum-sensitive patients [who progress] after 6 months, [rechallenge] is definitely the right approach. [If] progression occurs in less than 3 months, it is unlikely that rechallenge will be a realistic approach, and, admittedly, [it] can be quite toxic and challenging given the treatment schedule for etoposide. That is where we are currently, and, of course, a lot of research should go on in terms of improving on the current standard of care.

Onclive®: What are some of the factors that may influence the decision to continue treating a patient or potentially recommending hospice care?

SEETHARAMU: Performance status is perhaps the number 1 factor. If a patient has declined significantly, and continuing treatment is not in their best interest, that would

be [when] we would advocate for [hospice care]. Patient preference is an extremely important thing, as well. There are patients who, after knowing the pros and cons of continuing versus discontinuing [treatment], decide to discontinue. That has to be honored. That takes precedence over any available treatments. Lastly, I would say [that] availability of a suitable treatment [is a factor]. It is possible that as we move to subsequent lines [of therapy], organ function [and] comorbidities [factor into] what patients are actually able to receive in a meaningful fashion.

HIRSCH: Hospice care is certainly the last stage. First of all, you have exhausted the recommended therapeutic options, and patients are in poor performance status. There are clinical trials going on in small cell lung cancer [for which] we are very thankful, because this is a field that needs new therapeutic options and approaches. But for the patient to qualify for a clinical trial, there are certain requirements around performance status. If [a] patient has a good performance status, and you have exhausted the standard of care [treatment] options in the first- and second-line [settings], then a clinical trial would certainly be an option. [However], if the patient [has a] poor performance status, and [available] therapeutic options have been exhausted, then, of course, you need to communicate with the patient and the family [about the option for hospice care].

HALMOS: The question of hospice care is definitely prudent, especially thinking about second-line small cell lung cancer [management] and recognizing [that] treatments are truly marginally effective. [This has] to be balanced against the potential toxicity of the agents [that] we plan to use and the particular patient in front of us and their comorbidities, performance status, and disease sites of involvement. Is [the disease] mostly in the CNS, or is it mostly systemic disease? And, of course, patient [preference should be considered]. The patient should be in the driver's seat, guiding the clinician as to [a] reasonable [treatment] option, which should include palliative care for some patients. We always want to [assure the] patient that if they do opt for a palliative care approach, we will provide excellent attention to make sure that supported palliative care and pain management are provided in a very compassionate, proactive fashion.

Onclive®: Could you briefly summarize some of the recent changes to the NCCN guidelines for small cell lung cancer? How have these changes affected your treatment decisions?

SEETHARAMU: NCCN guidelines are helpful, but they are really [just] guidelines. We follow them, but we also look at personal experience, institutional pathways, and what makes logical sense. The guidelines may not apply to every patient. What is new is the addition of lurbinectedin in the second-line [setting]. It is definitely something that has been added [to the guidelines, but] the strength [of the] recommendation

is not high. With regards to what is actually recommended, whether retreating a particular patient with platinum doublet chemotherapy or treating with lurbinectedin, it is more [based on] personal experience. I know there are a lot [of] physicians who probably retreat patients before they go on to [treatment with] lurbinectedin. I have learned to do it the other way around and use lurbinectedin first and then use platinum-doublet chemotherapy in later settings. This is because a change in treatment strategy is probably helpful, but, again, it depends on when the patient progressed. The guidelines have been all over the place for retreatment [relative to] when progression occurs—3 months versus 6 months. If recurrence [occurs] within 6 months of initial treatment, I tend to move on to another line of treatment [with] a different mechanism of action. For patients who still have good performance status, I may go back to the original platinum doublet combination at a later time.

OncLive®: The phase 3 RESILIENT trial recently reported negative results for intravenous (IV) liposomal irinotecan monotherapy versus standard of care. Is there still the potential for IV liposomal irinotecan to fit into the treatment paradigm or benefit a subgroup of patients in small cell lung cancer?

HALMOS: Unfortunately, [the RESILIENT trial] was a negative study. As much as we have seen activity in preliminary studies and in some other cancer types, we did not see a significant benefit in this study. It failed in reaching its primary end point [versus] the comparative standard of care. Liposomal irinotecan monotherapy is not [a therapy that] I would begin with. It is a companion drug [with which] we are very familiar. We need to look elsewhere if we want to make some real impact in the management of patients with extensive small cell lung cancer.

The current focus is on novel drugs, such as antibody-drug conjugates (ADCs) and BiTE (bispecific T-cell engager) molecules. I hope that excitement will transform into some real practice-changing studies. But these agents are in very early trials. The DLL3-targeting BiTE molecule and the anti-B7-H3 ADC have shown notable activity in early studies, but [we still need] confirmatory studies [to determine where they will fit] into the current [treatment] landscape. And lastly, of course, biomarkers remain a great interest. We have seen a lot of excellent science emerging to molecularly subdivide small cell lung cancers that [may] actually make an impact in terms of being able to better select patients for certain treatment approaches. We will have to see how these biomarkers ultimately play out in helping the clinician [decide whether a] particular patient subset could benefit from treatment approach A versus B.

SEETHARAMU: Irinotecan has been in our tool kit for a very long time. I do think that it has several advantages over

topotecan, particularly from a myelotoxicity standpoint. [Small cell lung cancer] is a tough disease to prove [treatment] benefit. A lot of agents have shown benefit in earlier phase studies, but, when you move on to phase 3, they do not [show a benefit]. I wonder if the needle has to be moved a little bit for a disease like small cell [lung cancer] to be less stringent on what the process should be, because it is such a difficult [disease]. Any additional treatment is really adding new agents into the potential treatment armamentarium that we have. I do think there is a benefit [to irinotecan treatment], and I hope that it will be proven either in real-world data or [in results from] other large phase studies. I do think that agents such as irinotecan are very [beneficial], particularly in patients who have CNS disease. I hope that it will have an approval at some point, and I do [think] agents like this will have a role as more and more patients are able to tolerate more than 2 lines of treatment.

OncLive®: Based on the post-hoc analysis of the ATLANTIS trial, what are your thoughts on the safety and efficacy of the lurbinectedin monotherapy after lurbinectedin plus doxorubicin in relapsed SCLC?

HALMOS: We are all excited about having a new molecule for the management of our patients with small cell lung cancer in the second-line setting. It definitely has some noted activity, and it is reasonably well-tolerated in the context of alternate approaches. Of course, it has toxicities—mainly hematological [and] GI [effects] and phlebitis—which are significant issues for clinicians to remember. But with all that stated, it is a reasonable treatment for patients. However, a little bit of disappointment came from the [results of the] ATLANTIS trial. There was an unusual study design, in that lurbinectedin [was given] at lower dose than the currently approved dose in the United States. It was combined with doxorubicin, and the combination was compared to standard of care treatment. [Although] the study did not reach its primary end points, it showed fairly equivalent overall survival and a slight trend towards benefit in terms of progression-free survival as compared to the conventional standard of care. There is no question that this is a somewhat disappointing result. Is the outcome [due to the] unusual study design? [It is] hard to tell. There are a number of other studies emerging, which we will need to watch out for, [including lurbinectedin] in the maintenance setting as well as in combination with other [agents] (for example, with immunotherapies). We are looking forward to seeing [the results of] those [studies]. Post-hoc analysis of the ATLANTIS study looked at the benefit and toxicity of lurbinectedin monotherapy after completing a certain dose of doxorubicin. I have not found those post-hoc analyses all that helpful. The analysis used milestones that are very hard to figure out. What is the right comparator to use? I do view the study as, overall, somewhat disappointing, but it

does not take away from our eagerness to use lurbinectedin based on the phase 2 study approved dosage. But it definitely puts it into some balance. That is where the rechallenge with the original regimen, based on the French study, has become a reasonable approach to consider within the landscape.

OncoLive®: How early in the course of SCLC disease do you think patients should be diagnosed? How can early diagnosis be improved?

HIRSCH: In rare cases, [small cell lung cancer] can be diagnosed in the very early stage, meaning very localized stage. Of course, surgery has evolved with good potential outcome. But [it] is, unfortunately, very rare [that the disease is diagnosed early]. We do not know what screening means for small cell lung cancer. There is a whole open space there. Hopefully, over the next few years, we will get more data on lung cancer screening in relation to small cell lung cancer. But, in rare cases, it can be diagnosed in a very early stage—T1-2N0M0—and then lobectomy surgery can be relevant with potentially good outcomes. But this is, unfortunately, too rare a situation. In most situations, the patients have either local/regional disease or extensive disease.

HALMOS: You're asking a very challenging question. Of course, the whole field is very much looking forward to expanding lung cancer screening for patients based on excellent results from the NLST (National Lung Screening Trial) studies. I work at an institution where we have an excellent lung cancer screening program, and we do our absolute best to expand that to the right patient population. One issue that has come up with the screening studies for small cell lung cancer is that screening does not make much of an impact. The problem is that SCLC emerges fast, and annual CT scan screening timelines are just not the right match for it. Many times, we will see it emerging in between scans as a symptomatic disease. So screening does not make a real impact in terms of early diagnosis. The biggest impact will come from continued investment in smoking cessation. That is the bottom line, and, generally speaking, we have seen a lot of improvement in that. For example, in the United States, currently, the number of smokers is down to 12% from a historical high of 40% to 50%, if I remember correctly. Although those are all tremendous [changes], we need to continue to focus on certain vulnerable patient populations, [such as] teenagers, for example, who get hooked on smoking in different ways. So continued investment into good public health campaigns for smoking cessation and prevention is the most critical aspect [of preventing small

cell lung cancer]. There will be [ongoing] investment in better screening strategies, such as using circulating tumor DNA analysis. We have seen some papers [that are] looking at artificial intelligence incorporated into CT scan screenings. So, potentially, there will be some other ways to enhance our ability to detect these cancers. But, in reality, the best cure is prevention.

SEETHARAMU: Theoretically, I think that's what we hope for—that we diagnose it really, really early, like stage I. We do not use the AJCC (American Joint Committee on Cancer) stages; we only use [the terms] limited and extensive [stages] for practical purposes. There is more and more reason to use the AJCC [stages], especially with stage I disease [for which] surgery can be introduced. We do know that when surgery is able to be performed, patients tend to do better. That is really the gist of what screening programs can perhaps bring to light. [With] more rigorous screening programs and more deference to the screening programs, I think we could detect more small cell lung cancers at an earlier stage. That, coupled with some of the biomarker tests that seem to be promising, [may allow us to] recognize small cell [lung cancer] even before [it metastasizes to the] lymph nodes.

OncoLive®: What message would you share with your colleagues regarding these evolving approaches in this population?

HALMOS: We view these [evolving] approaches with great excitement. But we need to keep our foot on the gas pedal in terms of pushing on with experimental therapeutics, because improvements that [have been made] are really marginal compared with some of the dramatic advances seen in the management of non-small cell lung cancer in terms of both molecular and targeted approaches as well as biomarker-based immunotherapies. [For] small cell lung cancer, the advances that have been made are really just tiny. We need to continue to invest in the emerging approaches, molecular selection, and very specific targeting with novel ADCs. Hopefully, [by] working together as an international global community, [we can] make larger impacts on this otherwise devastating disease.

SEETHARAMU: I know there are several other agents [under investigation] that are promising. However, they are all in the very early stages [of testing], and, as we know from the history of small cell [lung cancer research], [new agents] that seem to be promising in the early stages [do not always] prove to be beneficial. Only time will tell. We will continue to see it move slowly, but surely, in the right direction. ■

