MEET THE EXPERT

ISSUE 5

SMALL CELL LUNG CANCER

INSIDE THIS ISSUE:

- Treatment strategies and expectations in small cell lung cancer (SCLC)
- Patient characteristics, efficacy, and tolerability considerations in SCLC treatment selection
- Considering patient goals when choosing a treatment

FEATURING

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Atlanta, GA

> ***Managing small cell lung cancer continues to be a significant clinical challenge for both clinicians and patients who are undergoing and navigating a new diagnosis of SCLC.[1,2]***
>
> —Ticiana Leal, MD

ADDRESSING UNMET NEEDS IN SECOND-LINE TREATMENT OPTIONS IN SMALL CELL LUNG CANCER

*Dr Leal is a paid consultant of Jazz Pharmaceuticals. This content is intended for informational purposes only and is not a substitute for your clinical knowledge or professional judgment. The views and opinions expressed in this article are those of the author and Jazz Pharmaceuticals and do not necessarily reflect the opinions of Emory University School of Medicine.

A LOOK INTO SCLC **TREATMENT CHALLENGES** AND TREATMENT STRATEGIES

with Dr Ticiana Leal

> *"I reach for platinum rechallenge less and less because I realized a lot of my patients had difficulty with their first platinum course in SCLC, and their bone marrow is now more vulnerable or susceptible to myelosuppression.[3,4]"*
>
> — Ticiana Leal, MD

Q. What are the biggest challenges when it comes to treating small cell lung cancer (SCLC)?

A. The biology of small cell lung cancer isn't completely understood and it's also a very heterogeneous disease.[5] SCLC is an aggressive disease marked by rapid cell division, high levels of replication stress, and the ability of SCLC tumor cells to cope with metabolic stresses and evade apoptosis.[2,6,7,8] It is a challenge that we don't have predictive biomarkers to understand who will benefit from different treatment strategies.[5,9] SCLC has a propensity for early metastasis, which reflects why the majority of our patients have a high burden of disease with extensive-stage SCLC at initial diagnosis.[2] About 10% to 20% of initial diagnoses require inpatient admission, where patients may have significant electrolyte abnormalities, organ dysfunction, and a high symptom burden.[8] A major challenge is stabilizing the patient clinically, including addressing medical comorbidities that may also impact the patient's ability to receive initial first-line therapy.[10] Taken together, these factors contribute to the overall poor prognosis of SCLC.

Q. What are some of the important points practitioners should keep in mind regarding relapse after first-line therapy in SCLC?

A. In the setting of an advanced and incurable malignancy like extensive-stage SCLC, achieving a response (overall response rate, ORR) and duration of response (DoR) are important endpoints that are quite meaningful to me.

SCLC responds rapidly to first-line therapy, but there is a high rate of relapse.[5] In the first line, the expectation we have is a response rate of 60% to 70%, with low rates of a complete response, but even with chemotherapy in combination with immunotherapy, the median progression-free survival is an average of 5 to 6 months; and we have to monitor the patient for immune-mediated adverse events.[2,5,11,12,13]

It is important to maintain active follow-up for patients receiving maintenance therapy and perform routine clinical follow-ups and imaging to capture clinical or radiographic progression before rapid onset of decline.[2,5] Complications may occur that limit the ability of the patient to receive second-line therapy.[14]

In patients who relapse where we're considering rechallenge, the outcome from rechallenge is less than what they experienced with initial platinum treatment.[2,15] That is something that I clearly outline to patients. Where I favor rechallenge has been in platinum-sensitive patients who have not received prior immunotherapy early on in the course of their disease with extensive-stage SCLC.[5]

Q. How many of your patients with SCLC require a second-line treatment option?

A. The vast majority of patients develop progression of their disease and relapse, which requires second-line treatment.[2] There are still about 10% to 15% of people in my practice who do not receive second-line therapy, either because they choose not to, they had complications of therapy in the first line, their performance status has declined too rapidly, or other medical comorbidities may make hospice or palliative care a better option.[14]

Q. What patient characteristics or medical criteria do you keep in mind when you're considering a second-line option?

A. Several clinical factors may help us and the patient decide on the optimal second-line treatment strategy. Important factors include performance status, the patient's functional status at the time of progression, their symptoms and disease burden, the presence of organ dysfunction, and their response to prior therapy.[5,14] Tolerability to their prior therapy is also very important when thinking about the possibility of platinum rechallenge, or other options, depending on platinum-sensitive or platinum-refractory disease.[2,16]

Personally, I reach for platinum rechallenge less and less because I realized a lot of my patients had difficulty with their first-line platinum course in SCLC; I would avoid platinum-rechallenge after first-line complications such as myelosuppression.[2-4]

Other important factors to consider include patient preference, social support, their emotional/psychological state, and barriers they may face that we need to help them with such as transportation.[14]

Q. How would you explain the importance of continuing therapy after relapse to either a colleague or a patient?

A. In speaking to clinicians, the discussion is about getting the best therapies to patients so they may derive benefits and improve their quality of life.[14] There is still a lot of skepticism in treating patients with SCLC given the overall historic poor prognosis, so continuing to educate other clinicians about the data, the outcomes, and the advances that we have is important.[17]

From a patient perspective, it is shared decision-making. This is a key component of the care that we deliver—discussing these decisions, the test results, the treatment options, and the care plans, all based on our best available evidence. We need to balance risks and benefits and have conversations about expected outcomes that align with the patient's preferences and values.[14]

Because the majority of the patients require second-line treatment, we talk about it while we're in maintenance each time we do a computed tomography (CT) scan.[14] It's an opportunity to open that discussion up to patients so they have the opportunity to ask questions about what happens next. It helps to get patients on board with second line so they may derive benefits from second-line strategies. Maximizing quality of life during therapy is also a key goal, and we frequently work with palliative care to improve symptom control and address the emotional and psychological aspects of dealing with such a challenging disease.[5,14]

CLINICAL EXPERIENCE: SECOND-LINE TREATMENT FOR SCLC WITH ZEPZELCA® (lurbinectedin)

Q. How important is it to take the approach of changing the mechanism of action in the second line by using ZEPZELCA?

A. In the second-line setting, we've had many studies, of multiple agents, dating back more than 20 years. The median progression-free survival (PFS) in these studies–ranging from 1 to 4 months–aligns with expectations that the disease has become more resistant after relapse.[16,18,19]

There is value in changing the mechanism of action when you're reaching for an option for patients in the second-line setting.[2,5]

ZEPZELCA is a marine-derived transcription inhibitor.[20] It's an alkylating agent that covalently binds to DNA, generating double-strand breaks, and disrupting DNA–protein interactions in RNA transcription.[21,22] Based on preclinical studies, ZEPZELCA may modulate the tumor microenvironment in different ways by affecting the tumor-associated macrophages and reducing inflammatory chemokines and VEGF.[22,23]

DID YOU **KNOW?**

Over 40 failed clinical trials for second-line treatments in SCLC since the 1970s.[9] Driven by the lack of therapeutic advancement, scientists explored the depths of the ocean, which led to the discovery and accelerated approval of ZEPZELCA, the first FDA-approved treatment in over 20 years for relapsed SCLC.[20,22,24]

(Please see full indication below)

Q. Why do you consider prescribing ZEPZELCA for your patients with SCLC who have relapsed?

A. ZEPZELCA is my preferred treatment option for my adult patients with relapsed SCLC, as supported by the phase 2 basket trial data, which included 105 patients with small cell lung cancer who had disease progression on prior platinum-based chemotherapy.[22]

The infusion schedule is something that patients are familiar with from first-line platinum therapy.[22,25] It suggests minimal infusion visits, which supports the use of ZEPZELCA in clinical practice.

Regarding outcomes, the approval was based on the overall response rate and duration of response in the phase 2 trial in adults with metastatic SCLC with disease progression on or after platinum-based chemotherapy, with an overall response rate of 35% and a median response duration of 5.3 months based on investigator assessment (IA). The overall response rate from the independent review committee (IRC) was 30%, with a median duration of response of 5.1 months.[22]

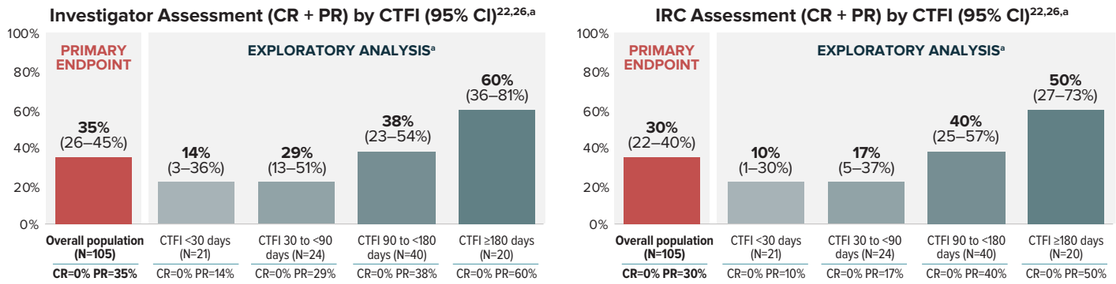
In the platinum-resistant group, the IA and IRC response rates were 14% and 10%, respectively, in patients with a chemotherapy-free interval (CTFI) of <30 days, and 29% and 17%, respectively, in patients with a CTFI 30 to <90 days. The response rates by IA and IRC were 38% and 40%, respectively, in patients with a CTFI ≥90 to <180 days and 60% and 50%, respectively, in the CTFI ≥180 days group.[26] This exploratory subgroup analysis was not powered to determine statistical significance. Results are descriptive only.

INDICATION

ZEPZELCA® (lurbinectedin) for injection 4 mg, is indicated for the treatment of adult patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

OVERALL RESPONSE RATE WAS EVALUATED IN BOTH PLATINUM-RESISTANT AND PLATINUM-SENSITIVE SUBGROUPS



[a]**Limitations of Data:** This exploratory subgroup analysis was not powered to determine statistical significance. Results are descriptive only.

CI=confidence interval; CR=complete response; PR=partial response.

> ***In my opinion, the data we have support the use of ZEPZELCA in both platinum-sensitive and platinum refractory populations.***
>
> — Ticiana Leal, MD

IMPORTANT SAFETY INFORMATION

Myelosuppression

ZEPZELCA can cause myelosuppression. In clinical studies of 554 patients with advanced solid tumors receiving ZEPZELCA, Grade 3 or 4 neutropenia occurred in 41% of patients, with a median time to onset of 15 days and a median duration of 7 days. Febrile neutropenia occurred in 7% of patients.

Sepsis occurred in 2% of patients and was fatal in 1% (all cases occurred in patients with solid tumors other than SCLC). Grade 3 or 4 thrombocytopenia occurred in 10%, with a median time to onset of 10 days and a median duration of 7 days. Grade 3 or 4 anemia occurred in 17% of patients.

Administer ZEPZELCA only to patients with baseline neutrophil count of at least 1,500 cells/mm^3 and platelet count of at least 100,000/mm^3.

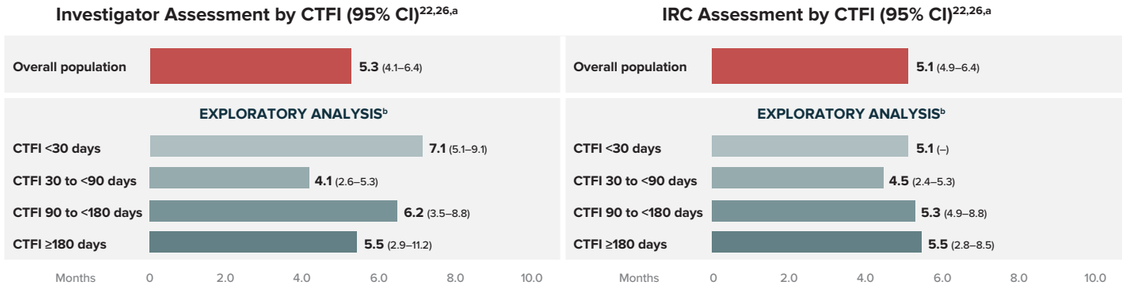
Monitor blood counts including neutrophil count and platelet count prior to each administration. For neutrophil count less than 500 cells/mm^3 or any value less than lower limit of normal, the use of G-CSF is recommended. Withhold, reduce the dose, or permanently discontinue ZEPZELCA based on severity.

ZEPZELCA® (lurbinectedin) for injection 4 mg

Please see pages 8-9 for Important Safety Information and CLICK HERE for full Prescribing Information.

CLINICAL EXPERIENCE: SECOND-LINE TREATMENT FOR SCLC WITH ZEPZELCA® (lurbinectedin)

ZEPZELCA DEMONSTRATED CLINICALLY MEANINGFUL DURATION OF RESPONSE (MEDIAN, IN MONTHS)



[a]Duration of response analysis is based on patients who responded to treatment.

Of 8 patients who had received prior immunotherapy as first- or second-line treatment[27,b]:

- Duration of response was consistent with the overall population at a median of 5.3 months (range: 2.8–6.4 months)[b]

[b]**Limitations of Data:** This exploratory subgroup analysis was post hoc and not powered to determine statistical significance. Results are descriptive only.

Study Design[22,27]

The phase 2 trial was a multicenter, open-label, multi-cohort trial evaluating ZEPZELCA as a single agent in 105 adult patients with advanced or metastatic SCLC with disease progression on or after platinum-based chemotherapy. Patients received ZEPZELCA 3.2 mg/m^2 by intravenous infusion every 21 days (1 cycle) for a median of 4 cycles (range: 1 to 24 cycles). The median age was 60 years (range: 40 to 83 years). Baseline ECOG PS was 0 or 1 in 92% of patients. The primary efficacy outcome was confirmed ORR by IA. Additional efficacy outcome measures included DoR and an IRC-assessed ORR using RECIST version 1.1.

ECOG PS=Eastern Cooperative Oncology Group Performance Status; RECIST=Response Evaluation Criteria in Solid Tumors.

IMPORTANT SAFETY INFORMATION (continued)

Hepatotoxicity

ZEPZELCA can cause hepatotoxicity. In clinical studies of 554 patients with advanced solid tumors receiving ZEPZELCA, Grade 3 elevations of ALT and AST were observed in 6% and 3% of patients, respectively, and Grade 4 elevations of ALT and AST were observed in 0.4% and 0.5% of patients, respectively. The median time to onset of Grade ≥3 elevation in transaminases was 8 days (range: 3 to 49), with a median duration of 7 days.

Monitor liver function tests prior to initiating ZEPZELCA, periodically during treatment, and as clinically indicated. Withhold, reduce the dose, or permanently discontinue ZEPZELCA based on severity.

"The clinical responses I've seen with ZEPZELCA mirror what we saw in the study, and I have patients on prolonged therapy with good tolerability."

— Ticiana Leal, MD

Q. What do the safety results and adverse events from the clinical trial tell you about ZEPZELCA?

A. Within managing symptoms and comorbidities that come along with having a diagnosis of SCLC, the tolerability of the regimen is an important factor.[28] We balance all of these together to have a discussion with the patient about their goals and quality of life. Patient-reported outcomes are increasingly important as we think about the development of new treatments for patients.[29,30]

Most of the patients start on a full dose of ZEPZELCA, and I've been able to keep patients on schedule for the vast majority of the patients I've treated.[22]

When thinking about cytotoxic chemotherapies in general, myelosuppression is a major concerning side effect that we've seen across the board. With that comes the risk of neutropenic fever, but the rates of febrile neutropenia are manageable with ZEPZELCA.[3,4,22]

If needed, there are certainly situations I've required discussions about dose hold or dose reduction. In my practice, dose reductions have been few, and most of the times, if there are side effects, we can dose delay and then stay on the same dose.

A major consideration we deal with is fatigue, which is sometimes very hard to tease out. Is it from therapy, the active cancer that the patient is managing, or other medical comorbidities?[22]

Q. How do you feel ZEPZELCA fits into the treatment landscape?

A. I consider it a viable option for most of my patients with SCLC who have relapsed.[3,22,24] It has been shown to lead to favorable responses and duration of response in second line for relapsed SCLC.[22]

My overall experience using ZEPZELCA in clinical practice is quite favorable.[22] The treatment strategy of getting patients into the clinic every 3 weeks is something that we and the patients are used to doing. The clinical responses I've seen mirror what we saw in the study, and I have patients on prolonged therapy with good tolerability.

In my opinion, the data we have support the use of ZEPZELCA in both platinum-sensitive and platinum-refractory populations.[22]

Thinking about patients eligible for second-line treatment, I definitely frequently think about ZEPZELCA as an important treatment strategy and commonly use ZEPZELCA in the second line for my adult patients.

IMPORTANT SAFETY INFORMATION (continued)

Extravasation Resulting in Tissue Necrosis

Extravasation of ZEPZELCA resulting in skin and soft tissue injury, including necrosis requiring debridement, can occur. Consider use of a central venous catheter to reduce the risk of extravasation, particularly in patients with limited venous access. Monitor patients for signs and symptoms of extravasation during the ZEPZELCA infusion.

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Monitor blood counts including neutrophil count and platelet count prior to each administration. For neutrophil count less than 500 cells/mm^3 or any value less than lower limit of normal, the use of G-CSF is recommended. Withhold, reduce the dose, or permanently discontinue ZEPZELCA based on severity.

Hepatotoxicity
ZEPZELCA can cause hepatotoxicity. In clinical studies of 554 patients with advanced solid tumors receiving ZEPZELCA, Grade 3 elevations of ALT and AST were observed in 6% and 3% of patients, respectively, and Grade 4 elevations of ALT and AST were observed in 0.4% and 0.5% of patients, respectively. The median time to onset of Grade ≥3 elevation in transaminases was 8 days (range: 3 to 49), with a median duration of 7 days.

Monitor liver function tests prior to initiating ZEPZELCA, periodically during treatment, and as clinically indicated. Withhold, reduce the dose, or permanently discontinue ZEPZELCA based on severity.

Extravasation Resulting in Tissue Necrosis
Extravasation of ZEPZELCA resulting in skin and soft tissue injury, including necrosis requiring debridement, can occur. Consider use of a central venous catheter to reduce the risk of extravasation, particularly in patients with limited venous access. Monitor patients for signs and symptoms of extravasation during the ZEPZELCA infusion.

If extravasation occurs, immediately discontinue the infusion, remove the infusion catheter, and monitor for signs and symptoms of tissue necrosis. The time to onset of necrosis after extravasation may vary.

Administer supportive care and consult with an appropriate medical specialist as needed for signs and symptoms of extravasation. Administer subsequent infusions at a site that was not affected by extravasation.

Rhabdomyolysis
Rhabdomyolysis has been reported in patients treated with ZEPZELCA.

Monitor creatine phosphokinase (CPK) prior to initiating ZEPZELCA and periodically during treatment as clinically indicated. Withhold or reduce the dose based on severity.

Embryo-Fetal Toxicity
ZEPZELCA can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise female patients of reproductive potential to use effective contraception during treatment with ZEPZELCA and for 6 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZEPZELCA and for 4 months after the last dose.

Lactation
There are no data on the presence of ZEPZELCA in human milk, however, because of the potential for serious adverse reactions from ZEPZELCA in breastfed children, advise women not to breastfeed during treatment with ZEPZELCA and for 2 weeks after the last dose.

MOST COMMON ADVERSE REACTIONS

The most common adverse reactions, including laboratory abnormalities, (≥20%) are leukopenia (79%), lymphopenia (79%), fatigue (77%), anemia (74%), neutropenia (71%), increased creatinine (69%), increased alanine aminotransferase (66%), increased glucose (52%), thrombocytopenia (37%), nausea (37%), decreased appetite (33%), musculoskeletal pain (33%), decreased albumin (32%), constipation (31%), dyspnea (31%), decreased sodium (31%), increased aspartate aminotransferase (26%), vomiting (22%), decreased magnesium (22%), cough (20%), and diarrhea (20%).

DRUG INTERACTIONS

Effect of CYP3A Inhibitors and Inducers
Avoid coadministration with a strong or a moderate CYP3A inhibitor (including grapefruit and Seville oranges) as this increases lurbinectedin systemic exposure which may increase the incidence and severity of adverse reactions to ZEPZELCA. If coadministration cannot be avoided, reduce the ZEPZELCA dose as appropriate.

Avoid coadministration with a strong CYP3A inducer as it may decrease systemic exposure to lurbinectedin, which may decrease the efficacy of ZEPZELCA.

GERIATRIC USE

Of the 105 patients with SCLC administered ZEPZELCA in clinical studies, 37 (35%) patients were 65 years of age and older, while 9 (9%) patients were 75 years of age and older. No overall difference in effectiveness was observed between patients aged 65 and older and younger patients.

There was a higher incidence of serious adverse reactions in patients ≥ 65 years of age than in patients < 65 years of age (49% vs. 26%, respectively). The serious adverse reactions most frequently reported in patients ≥ 65 years of age were related to myelosuppression and consisted of febrile neutropenia (11%), neutropenia (11%), thrombocytopenia (8%), and anemia (8%)

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ZEPZELCA® (lurbinectedin) for injection 4 mg

"It is very gratifying to have ZEPZELCA to reach for as a treatment option for my adult patients with SCLC."

— Ticiana Leal, MD

LEARN MORE ABOUT A SECOND-LINE OPTION FOR YOUR PATIENTS WITH RELAPSED SCLC AT

ZEPZELCAPRO.COM

Dr Leal is a leading expert in treating patients with SCLC, both as a physician and researcher.

Ticiana Leal, MD, is Associate Professor of Medicine and serves as Director of the Thoracic Medical Oncology Program in the Department of Hematology and Medical Oncology at the Winship Cancer Institute of Emory University School of Medicine. She serves as a member of the Board of Directors of the GASCO (Georgia Society of Clinical Oncology). Board certified in medical oncology and palliative care, Dr Leal specializes in caring for patients with lung cancer, mesothelioma, and thymic malignancies. Dr Leal's clinical research focuses on clinical trials of chemotherapy and/or immunotherapy agents to treat cancers of the lung. She is the NCI LUNG-MAP Chair, ECOG-ACRIN representative and NCI LUNG-MAP, Chair of the Scientific and Sub-Study Leadership Committee.

Dr Leal has authored or coauthored numerous peer-reviewed original research articles, book chapters, and posters. She served as Associate Editor and as a member of the Executive Editorial Board of *The Journal of the National Comprehensive Cancer Network*. She also serves as Lung Cancer Section Editor of *Current Treatment Options in Oncology* and on the editorial advisory boards of *Cancer*.

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