# MEET THE EXPERT

ISSUE 6 SMALL CELL LUNG CANCER

**INSIDE THIS ISSUE:**

- Considering patient characteristics and goals in small cell lung cancer (SCLC)
- Efficacy, tolerability, and safety considerations in treatment selection
- Exploring data for an alkylating agent

**FEATURING**
**Nagla Karim, MD, PhD***
Fairfax, VA

> ***In my clinical practice, it's so important to initiate a second-line treatment as soon as we detect systemic progression, so we are able to help patients feel better before they have symptoms from disease progression.***
>
> —Nagla Karim, MD, PhD

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

*Dr Karim 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.

# A LOOK AT SECOND-LINE SCLC
# PATIENT CONSIDERATIONS AND TREATMENT STRATEGIES

with Dr Nagla Karim

**Q. How does the biology of small cell lung cancer (SCLC) make it challenging to treat?**

**A.** Small cell lung cancer biology is very unique—it is aggressive and spreads fast.[1] In thoracic neuroendocrine tumors, there are 4 categories: typical carcinoid, atypical carcinoid, large cell neuroendocrine tumors, and SCLC. SCLC is among the most aggressive thoracic neuroendocrine tumors and is the most aggressive of all lung cancers.[2,3] Because of this, many SCLC patients are diagnosed at a later stage—as extensive-stage SCLC.[4] Patients with SCLC have had poor survival up to this point due to difficult disease biology and a lack of effective treatment options.[5]

**Q. What are the biggest challenges when it comes to SCLC?**

**A.** Patients with SCLC are all different: we have to be careful if we're treating an elderly patient, if we're treating a patient with multiple comorbidities, or if we're treating a patient who is a heavy smoker and dealing with chronic obstructive pulmonary disease or recurrent pneumonias or infections.[4,6-8] Is this a limited-stage patient or an extensive-stage patient? Does the patient have a painful bone metastasis? If so, we need radiation. We must constantly evaluate patients' needs and status to achieve a better quality of life. We use a multidisciplinary approach that includes chemoradiation, palliative care, and pharmacy support—they are all critical to ensure the patient gets the best care. We take it a step at a time; we hold the patient's hand as a team and go through the journey together.[9]

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

**A.** A lot; approximately 80% of my patients. Even though most respond to first line and feel better for a while, nearly all of them will relapse.[7,10] Some patients don't respond to first-line treatment—that's why we need to keep a close eye on our patients and follow them thoroughly.[10,11] It's so important to initiate a second-line treatment as soon as we detect progression so we can help patients feel better before they have symptoms from disease progression.[5]

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

**A.** Every patient is different. Some patients will need tailored approaches with doses, patients may have different sites of metastasis that need radiation, they may have bulky disease, and so on.[5] It's always about how the patient presents after relapse and how they responded to their previous treatment. If someone relapsed less than 6 months after previous treatment, they have a difficult disease. I wouldn't rechallenge if it's 3 months, 4 months, etc. In my experience, my patients have often done better with another, different type of treatment. If there is a chance to take another approach, in my experience, it's better to take the different approach.[10,12]

**Q. How do you explain to your patients the importance of continuing therapy after relapse?**

**A.** I reinforce that we need to get another treatment as soon as possible to ensure that we get the disease under control. I start by telling the patients we have options: there are approved second-line treatments, and there may be clinical studies that could be an option.[12] We talk about benefits and about outcomes. We ask them, "How much do you want to know?". Some patients want to go into the details of survival: months and timelines, but others tell us, "I don't want to hear about timelines. I really want to take it one day at a time." Either way, we want to be transparent about the expected outcomes as much as possible.



*"SCLC is challenging. It's important that we take it one step at a time and get patients started on second-line therapy as soon as the disease progresses."*

— Nagla Karim, MD, PhD

**Q. What is your #1 piece of advice to other practitioners working with patients with SCLC?**

**A.** Talk with your patients; hear from them; be a good listener. A lot of times, there are aspects they want to ensure are addressed during our visits. Sometimes, even though it might be a minor complaint, it could be major to the patient, interfering with their daily activities. Sometimes there are specific symptoms that we can control well—something that we can take care of with supportive measures or radiation if they need adjunctive treatment[5,10]—and that can allow us to take more control of the disease and continue therapy.

# **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 second-line treatment?**

**A.** In my experience, patients with progressive disease (other than the controlled oligometastatic disease), will have an option with subsequent systemic therapy. When deciding on what to do, I return to patient characteristics: what stage is the disease? What was the patient's duration of response to their previous treatment? And then, on top of that, what was their previous experience—was it a tolerable treatment for that patient? These can impact the decision to change the mechanism of action, especially in the second-line setting where the patient's disease is resistant or refractory to platinum.[1,10]

ZEPZELCA, a marine-derived transcription inhibitor, is an alkylating agent that covalently binds to DNA, generating double-strand breaks and disrupting DNA–protein interactions in RNA transcription.[13-15] It also may modulate the tumor microenvironment in different ways by affecting tumor-associated macrophages and reducing inflammatory chemokines and vascular endothelial growth factor.[15,16]

**DID YOU KNOW?**

There have been over 40 failed phase 3 clinical trials for second-line treatments in SCLC since the 1970s.[1] Scientists explored the ocean and were inspired by *Ecteinascidia turbinata* to develop ZEPZELCA.[17] ZEPZELCA was granted accelerated approval in 2020 and is the first FDA-approved treatment for adults in over 20 years for relapsed SCLC.[18]

(Please see full indication below)

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

**A.** I see ZEPZELCA as my preferred second-line option for a few different reasons. ZEPZELCA has a notable overall response rate, and it has an even higher response rate in patients with platinum-sensitive disease. ZEPZELCA's duration of response rates are also important to consider because we want to keep our patients' disease controlled for longer.[15]

In the phase 2 trial in adults with metastatic SCLC with disease progression on or after platinum-based chemotherapy, patients had 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.[15]

In the platinum-resistant group, the IA response rate was 14% in patients with a chemotherapy-free interval (CTFI) of <30 days and 29% in patients with a CTFI of 30 to <90 days. The IRC responses were 10% and 17%, respectively. Data for platinum-sensitive patients (those with a CTFI of ≥90 days) were particularly interesting: response rates were 38% by IA and 40% by IRC in patients with a CTFI of ≥90 to <180 days and 60% by IA and 50% by IRC in the CTFI ≥180 days group.[19] This exploratory subgroup analysis was not powered to determine statistical significance. Results are descriptive only.

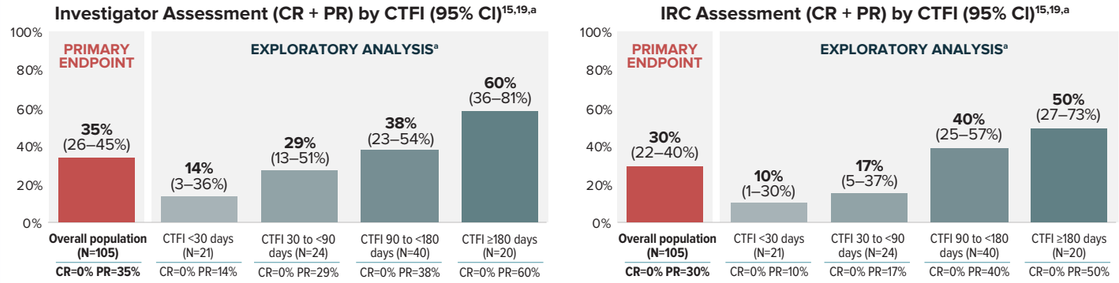
## INDICATION

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.

**Study Design**

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 ranked efficacy outcome measures included DoR and an IRC-assessed ORR using RECIST version 1.1.[15]

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

## 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.

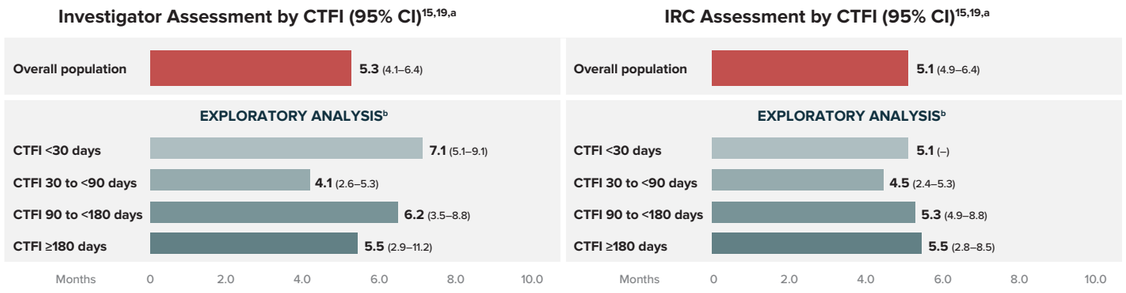
ZEPZELCA® (lurbinectedin) for injection 4 mg

**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)

> *"We are trying hard to ensure that we offer a second-line therapy to our patients... An option like ZEPZELCA, with its safety and tolerability profile, can be important to help maintain patients on treatment for as long as possible."*
>
> — Nagla Karim, MD, PhD

## 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[20,b]:**

- Duration of response was consistent with the overall population at a median of 5.3 months (range: 2.8–6.4 months)[15,20,b]

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

## 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.

**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.



> *"ZEPZELCA's dosing and administration schedule is nice in terms of both the time it takes to administer and the minimal infusion visits. ZEPZELCA helps us be flexible and tailor our treatment options to the patient."*
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**Q. What do the safety results and adverse events from the clinical trial tell you about ZEPZELCA?**

**A.** ZEPZELCA is my preferred second-line treatment option. If I give a therapy with a tolerable safety profile, patients will receive more treatment. But we must talk with the patients about side effects* that can occur so that they can seek medical advice at the right time, and we don't just talk about efficacy.

***Please see pages 8-9 for Important Safety Information.**

ZEPZELCA has been tolerable for most of my patients. We want them to stay on treatment longer and benefit from it, so at times I've discussed dose holds or dose reductions. We know our patients, and it's been patient-by-patient. But if I have to do a dose reduction, it's okay because that will make the patient stay on treatment longer than discontinuing treatment.[15]

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

**A.** We have a few options for second-line treatment: I also consider clinical trials if they are available, and there's rechallenge. Not all patients are candidates to be rechallenged, and many patients have had toxicities with platinum and don't want to be rechallenged. I'd rather give a second-line treatment like ZEPZELCA, which could be different.[10,12]

The phase 2 clinical trial data showed that ZEPZELCA provided efficacy in both platinum-resistant and platinum-sensitive patients.[15] And as I mentioned before, ZEPZELCA's duration of response is important to keep in mind because we want to control patients' disease for as long as possible. This goes hand-in-hand with close monitoring and supportive care to ensure the best treatment duration and tolerability for patients.

ZEPZELCA's dosing and administration schedule is nice in terms of both the time it takes to administer and the minimal infusion visits of every 21 days.[15] We want to help give patients flexibility. So while we need to treat and monitor patients' wellness, clinical status, and disease status, ZEPZELCA also helps us be flexible and tailor our treatment options to the patient.

## IMPORTANT SAFETY INFORMATION (continued)

**Extravasation Resulting in Tissue Necrosis (continued)**

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.

ZEPZELCA® (lurbinectedin) for injection 4 mg

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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

*"For our patients with SCLC, we have the option to jump in with a second-line therapy that could have a favorable outcome for this difficult disease."*

— Nagla Karim, MD, PhD

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

**ZEPZELCAPRO.COM**

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

Nagla Karim, MD, PhD, is Associate Director of Experimental Therapeutics in the Division of Hematology and Oncology at the University of Cincinnati in Ohio and Professor of Medicine at the University of Virginia in Charlottesville. She earned her medical degree at the University of Cairo in Egypt and fulfilled her residency in internal medicine at Cleveland Clinic's Fairview Hospital in Ohio.

Dr Karim completed a fellowship in hematology and oncology at the University of Cincinnati and medical oncology at the University of Cairo's National Cancer Institute. She earned her doctorate at the University of Cairo Faculty of Medicine and the University of Washington in Seattle. Dr Karim specializes in the clinical research and treatment of a broad range of solid malignancies, including lung cancer and melanoma. She has authored more than 100 journal articles, abstracts, and book chapters and has given numerous lectures and presentations worldwide.

Dr Karim has been a principal investigator on several clinical trials and is a member of the Frontiers in Oncology, BMC Pulmonary Medicine, Annals of Internal Medicine, and PLoS One editorial boards. She holds professional memberships with the American Society of Clinical Oncology, Southwest Oncology Group, and International Association for the Study of Lung Cancer.

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