MEET THE EXPERT

ISSUE 2

SMALL CELL LUNG CANCER

INSIDE THIS ISSUE:

- How to handle the aggressive nature of small cell lung cancer
- Efficacy, tolerability, and safety considerations in treatment selection
- Exploring the mechanism of action and clinical data for an alkylating agent

FEATURING

David Berz, MD, PhD, MPH*

Valkyrie Global

Los Angeles, CA

"Small cell lung cancer is one of the most aggressive solid tumor malignancies in terms of local regional growth and metastatic dissemination."

— David Berz, MD, PhD, MPH

THE IMPORTANCE OF SECOND-LINE TREATMENT OPTIONS IN SMALL CELL LUNG CANCER

*Dr Berz 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 Valkyrie Global.

A LOOK INTO SCLC
TREATMENT CHALLENGES
AND MANAGEMENT STRATEGIES

with **Dr David Berz**

"The right thing to do is prepare the patient up front by explaining that relapse may happen. Then you pursue aggressive disease surveillance during treatment and monitoring of treatment efficacy."

— David Berz, MD, PhD, MPH

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

A. One of the biggest challenges from diagnosis is the aggressive nature of the disease. SCLC is one of the most aggressive solid tumors; characterized by a rapid doubling time, high growth fraction, and early development of widespread metastases.[1-3] At diagnosis, approximately 70% of patients with SCLC have extensive-stage disease.[3] Even if an initial response is established, the majority of patients will relapse. In fact, nearly all patients will relapse within 12 months of initial treatment.[4]

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

A. Because of the high relapse rate, one of the most important things you can do is to prepare the patient up front by explaining that relapse is likely to occur.[4] Having this discussion with the patient helps them manage their expectations and helps you to create a relapse treatment plan. I aim to catch relapse as early as possible by using aggressive and relatively active disease surveillance during treatment, along with monitoring treatment efficacy during maintenance therapy. I typically do surveillance scans every 2 months, along with circulating cell free tumor DNA assays to assess for progression. My imaging surveillance strategy includes either a CT of the chest, abdomen, and pelvis, or a whole body PET scan, along with a brain MRI on a regular basis.

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

A. Almost all patients with SCLC will require second-line therapy eventually.[4] Despite performance status often declining, I tend to treat, unless there is a very good reason not to. I find it important to continue treatment because not only is the symptom burden likely improved, but there may also be a beneficial impact on longevity. Timely intervention at the first sign of relapse may help to improve outcomes,[5-7] and without disease treatment, patients will continue to actively progress and eventually die from their disease. Five-year survival is historically a mere 7% for patients with SCLC, which clearly calls for aggressive attempts to improve our patients' options.[5]

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

A. The first thing I do is outline the expected toxicities for each therapy option. It is like weighing options on a scale—I try to balance the symptom improvement from the disease versus the side effects from the treatment.

CT=computed tomography; MRI=magnetic resonance imaging; PET=positron emission tomography.

"I find it beneficial to keep the patient on treatment because longevity can be improved and disease symptoms become more manageable."

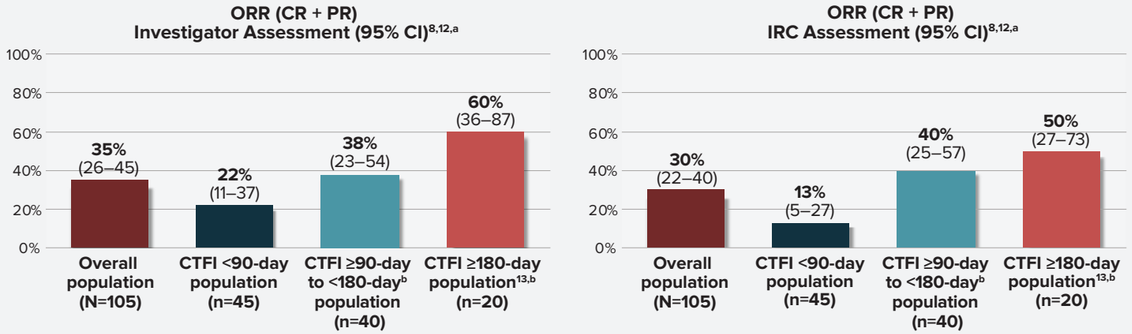
— David Berz, MD, PhD, MPH

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

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

A. Increasingly, I've used ZEPZELCA for my patients who relapse, regardless of platinum sensitivity. There are 3 main reasons for this. First, ZEPZELCA has a different MOA than platinum compounds and topoisomerase inhibitors.[8-10] It is an alkylating drug that binds guanine residues in the minor groove of DNA, resulting in events that could affect subsequent activity of transcription factors and DNA repair pathways, leading to cell death.[8] Second, I have found the tolerability profile of ZEPZELCA to be favorable. Lastly, the efficacy and safety data from the ZEPZELCA pivotal phase 2 trial align closely with the experiences I have had with my patients. In the phase 2 trial in adults with metastatic SCLC with disease progression on or after platinum-based chemotherapy, ZEPZELCA provided an ORR of 35% by IA and 30% by IRC. The median DoR was 5.3 months by IA and 5.1 months by IRC.[8,11]

For adults with metastatic SCLC with disease progression on or after platinum-based chemotherapy, **ZEPZELCA PROVIDED SUBSTANTIAL EFFICACY IN BOTH PLATINUM-RESISTANT AND PLATINUM-SENSITIVE PATIENTS[8]**



[a]According to RECIST v1.1. CR: Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm. PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.[14]

[b]These subgroup exploratory analyses were not powered to determine statistical significance. Results are descriptive only.[13]

CI=confidence interval; CR=complete response; CTFI=chemotherapy-free interval; DoR=duration of response; IA=investigator assessment; IRC=independent review committee; MOA=mechanism of action; ORR=overall response rate; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors.

INDICATION

ZEPZELCA® (lurbinectedin) 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).

Q. Can you explain further about ORR and why it matters to you and your patients?

A. ORR is the summation of 2 values, complete response and partial response.[14] In an aggressive disease like small cell lung cancer, having my patients' disease respond to treatment is very important. When I can tell my patients "your cancer has not grown," they are relieved. They understand how fast this cancer proliferates and knowing this allows them a window of relief. In my practice, response to treatment is often associated with improved quality of life and longevity, although this has not been formally studied.

> ***"I've used ZEPZELCA for my patients who relapse for 3 main reasons: it has a different MOA than platinum, the tolerability profile is favorable, and the efficacy and safety data."***
>
> — David Berz, MD, PhD, MPH

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 (one 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 0–1 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.[8,11]

ECOG PS=Eastern Cooperative Oncology Group Performance Status.

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 page 7 for Important Safety Information and CLICK HERE for full Prescribing Information.

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

"After first-line failure, my treated patients go on ZEPZELCA because of its favorable side-effect profile, distinct MOA, and attractive dosing schedule."

— David Berz, MD, PhD, MPH

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

A. In my experience, ZEPZELCA has a predominantly favorable tolerability profile and has matched what was seen in the pivotal trial. The permanent discontinuation rate in the trial due to an adverse reaction was 1.9%; 29% of patients were on ZEPZELCA for ≥6 months and 6% were on it for >1 year. There were 11 patients (10.5%) who had an SAE, and in 9 of these cases it was related to hematological events; all SAEs resolved.[8,12] This is similar to what I have seen in my practice.

SAE=serious adverse reaction.

Please see Important Safety Information below and on the opposite page.

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

A. Looking at the clinical trial data, ZEPZELCA provided efficacy in both platinum-resistant and platinum-sensitive patients. After the introduction of ZEPZELCA to market, there are only 2 options I use for my patients after first-line failure: they are either given ZEPZELCA or they go on a clinical trial. I've used ZEPZELCA successfully in both platinum-resistant and platinum-sensitive patients and can recommend an interesting retrospective analysis (Subbiah et al. 2020) that examines efficacy and safety outcomes amongst ZEPZELCA and platinum rechallenge.[13]

I've used ZEPZELCA successfully in a wide range of patients with varying platinum sensitivity. The introduction of ZEPZELCA monotherapy into the treatment paradigm is an attractive option due to its balanced efficacy, safety profile, and dosing schedule.[8,10-12] Additionally, the dosing schedule of a 1-hour infusion every 3 weeks can be attractive for patients.[8]

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.

INDICATION

ZEPZELCA® (lurbinectedin) 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).

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.

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.

Please CLICK HERE for full Prescribing Information.

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%)

ZEPZELCA® (lurbinectedin) for injection 4 mg

“There are a few things that caught my attention with ZEPZELCA—it’s effective, with an attractive dosing schedule, and it has a favorable tolerability profile.”

— David Berz, MD, PhD, MPH

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

ZEPZELCAPRO.COM

Dr Berz has more than 15 years of experience treating patients with SCLC as a physician and researcher.

David Berz, MD, PhD, MPH, is the Chief Medical Officer/Principal Investigator of Valkyrie Clinical Trials in Los Angeles, California. He also serves as a hematologist/oncologist at both Valkyrie Global in Los Angeles and Bakersfield Hematology Oncology Group in Bakersfield, California. Dr Berz earned his medical degree and doctorate from Humboldt University in Berlin, Germany, as well as a master’s degree in public health from Brown University in Providence, Rhode Island. He completed his residency in internal medicine at Yale University/Norwalk Hospital in Norwalk, Connecticut, and his fellowship in hematology/oncology at Brown University. Dr Berz is a member of the American Society of Clinical Oncology, the American Society of Hematology, and the Society for Melanoma Research.

REFERENCES: 1. Cordony-Servat J, Verlicchi A, Rosell R. Cancer stem cells in small cell lung cancer. *Transl Lung Cancer Res*. 2016;5(1):16-25. **2.** Elias AD. Small cell lung cancer: state-of-the-art therapy in 1996. *Chest*. 1997;112(4 suppl):251S-258S. **3.** Huber RM, Tufman A. Update on small cell lung cancer management. *Breathe*. 2012;8(4):315-330. **4.** Hurwitz JL, McCoy F, Scullin P, Fennell DA. New advances in the second-line treatment of small cell lung cancer. *Oncologist*. 2009;14(10):986-994. **5.** Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2017. National Cancer Institute. https://seer.cancer.gov/csr/1975_2017/. Accessed March 10, 2022. **6.** Rudin CM, Brambilla E, Faivre-Finn C, et al. Small-cell lung cancer. *Nat Rev Dis Primers*. 2021;7(1):3. doi:10.1038/s41572-020-00235-0. **7.** Glatzer M, Rittmeyer A, Müller J, Sage J. Treatment of limited disease small cell lung cancer: the multidisciplinary team. *Eur Respir J*. 2017;50(2):1700422. doi:10.1183/13993003.00422-2017. **8.** ZEPZELCA (lurbinectedin). Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **9.** Carboplatin [package insert]. Princeton, NJ: Bristol-Myers Squibb Company: 2010. **10.** Topotecan [package insert]. Research Triangle Park, NC: GlaxoSmithKline: 2007. **11.** Trigo J, Subbiah V, Besse B, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. *Lancet Oncol*. 2020;21(5):645-654. **12.** Data on file. LUR-2020-003. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **13.** Subbiah V, Paz-Ares L, Besse B, et al. Antitumor activity of lurbinectedin in second-line small cell lung cancer patients who are candidates for re-challenge with the first-line treatment. *Lung Cancer*. 2020;150:90-96. **14.** Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247. **15.** Trigo J, Subbiah V, Besse B, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial [supplementary appendix]. *Lancet Oncol*. Published online March 27, 2020. http://dx.doi.org/10.1016/S1470-2045(20)30068-1. Accessed March 12, 2021.

Please see page 7 for Important Safety Information and CLICK HERE for full Prescribing Information.

Jazz Pharmaceuticals

PharmaMar

ZEPZELCA® (lurbinectedin)