MEET THE EXPERT

ISSUE 4

SMALL CELL LUNG CANCER

INSIDE THIS ISSUE:

- Patient characteristics and treatment strategies from an academic viewpoint
- Efficacy, tolerability, and safety considerations in second-line treatment selection
- Exploring treatment response and what that means for patients

FEATURING

Neal Ready, MD, PhD*

Duke Cancer Institute

Durham, NC

> *"Previously treated SCLC has been a major area of unmet clinical need.*[1,2]*"*
>
> — Neal Ready, MD, PhD

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

*Dr Ready 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 Duke Cancer Institute.

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

with Dr Neal Ready

"I typically look toward balancing the clinical benefit of the agent with its tolerability profile, looking at whether the patient will see an improvement in symptoms versus the side effects from the treatment."

— Neal Ready, MD, PhD

"SCLC is a cancer with a high total mutational burden—a factor you think would lead to an immunologically hot tumor, but it's just not the case.[3,4]"

— Neal Ready, MD, PhD

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

A. As a thoracic medical oncologist at a large medical center, one of my foci in clinical research has been small cell lung cancer since I view this as an area with many unmet needs. SCLC tends to be resistant to chemotherapy after relapse and very challenging to treat.[5] In my experience, this has remained the largest hurdle to overcome for decades. Initially, SCLC tends to be sensitive to first-line chemotherapy, but the vast majority relapse within 2 years.[6] This remains true even though there have been clinical trials focused on new cytotoxics, new antibody drug conjugates, new immune therapy combinations, and other approaches to try to improve outcomes for patients.[6]

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

A. At diagnosis, there is no way to test a patient's likelihood of relapsing, so we must assume the unfortunate reality that they will. As practitioners, we must ensure that our patients have appropriate expectations about their disease; therefore, communication about relapse is essential.[7] A patient's response to initial treatment can potentially dictate treatment options when relapse occurs, and the time frame in which a patient's cancer progresses is a key determinant of what second-line therapies may have clinical benefit.[2] Even though it may be difficult, you must be honest with them, and within my practice, close monitoring is the best way to personalize treatment for each patient.

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

A. The vast majority will relapse within 2 years of the initiation of front-line therapy.[6] Once relapse occurs, most of my patients with SCLC will be offered second-line therapy.[2] Patients who relapse soon after the completion of platinum-based chemotherapy are deemed platinum-resistant, and these patients tend to do worse with whatever second-line treatment you give them.[8] Patients who have a longer duration of response to front-line therapy are more likely to benefit from second-line therapy and will have more treatment options available.[2,8] This doesn't mean that those who relapse early can't benefit from another option; it just means that they are a little less likely to.

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

A. As I mentioned earlier, if a patient progresses early on platinum-based therapy, the likelihood that they will benefit from additional chemotherapy is low.[2] Depending on the patient's age, performance status, and comorbid medical problems, that patient may be a prime candidate for a clinical trial or even hospice.[8] For those who relapse early, but are in good shape, I would evaluate them for a different type of cytotoxic agent. I typically look toward balancing the clinical benefit of the agent with its tolerability profile, looking at whether the patient will see an improvement in symptoms versus the side effects from the treatment.

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. I use ZEPZELCA since it's produced clinically significant responses in both platinum-resistant and platinum-sensitive patients.[9] ZEPZELCA is a cytotoxic with a different mechanism of action (MOA) from first-line therapies, interfering with transcription and then leading to cell death.[9-11] By focusing on transcription, it allows us to go after some of the vulnerability in rapidly dividing cells. In SCLC, we have cancer cells that are rapidly dividing, meaning they need to replicate their DNA rapidly and efficiently; anything that interferes with that puts them at a vulnerability relative to normal cells in the body. So, ZEPZELCA interfering in a general way with transcription of the genome makes sense based on the basic biology of small cell lung cancer as a particularly rapidly growing malignancy.[2,9]

The data from the pivotal phase 2 trial align closely with the experiences I have had in my clinical practice. In the phase 2 trial in adults with metastatic SCLC with disease progression on or after platinum-based chemotherapy, ZEPZELCA provided an overall response rate (ORR) of 35% by IA and 30% by independent review committee (IRC). The median duration of response (DoR) was 5.3 months by IA and 5.1 months by IRC.[9,12]

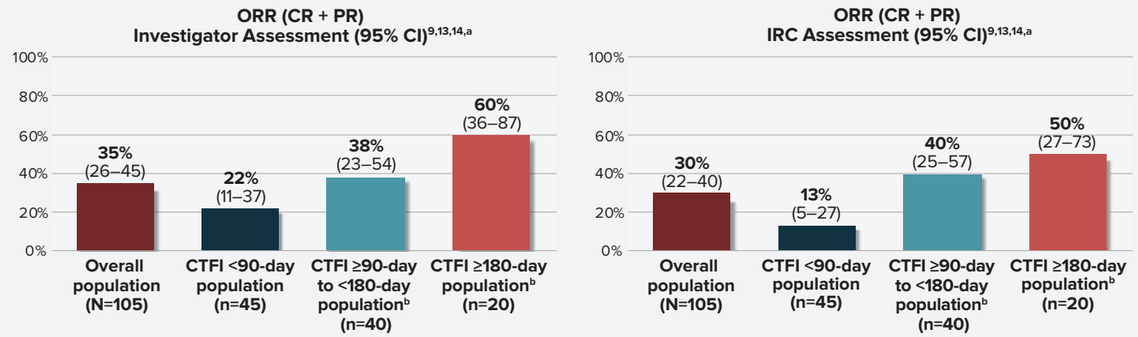
"ZEPZELCA provides substantial efficacy in both platinum-resistant and platinum-sensitive patients. Responses have also been demonstrated in patients regardless of age or prior lines of therapy."

— Neal Ready, MD, PhD

"The therapeutic index or clinical benefit to side-effect ratio with ZEPZELCA is a step forward."

— Neal Ready, MD, PhD

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[9]**



[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.[15]

[b]**Limitations of subgroup analyses: These subgroup exploratory analyses were not powered to determine statistical significance. Results are descriptive only.[14]**

CI=confidence interval; CR=complete response; CTFI=chemotherapy-free interval; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors.

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 efficacy outcome measures included DoR and an IRC-assessed ORR using RECIST version 1.1.[9,12]

ECOG PS=Eastern Cooperative Oncology Group Performance Status; IA=investigator assessment.

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.

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)

"With second-line options like ZEPZELCA, if we are able to hit pause and keep the disease stable, or even shrink the tumor, it's considered meaningful."[9,13]

— Neal Ready, MD, PhD

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

A. When treating patients, I want to see that the clinical outcome is proportional to the toxicity of the treatment. If we can gain a little bit of survival, but that survival is at the cost of ruining the quality of life, then that is not a good trade-off. As a practicing medical oncologist, when I give someone a treatment and talk to them about what the expected side effects are, I want to be confident that, for the vast majority of the time, the patient will experience tolerability that is within the bounds of what I told them. My experience with ZEPZELCA is that it has a generally tolerable safety profile that is aligned with what was seen in the pivotal trial. Most adverse reactions were Grade 1 or 2.[9] The permanent discontinuation rate in the trial due to an adverse reaction was 1.9%; ARs include peripheral neuropathy and myelosuppression.[9] Twenty-nine percent of patients were on ZEPZELCA for ≥6 months, and 6% were on it for >1 year.[9] Eleven patients (10.5%) had an SAE, and 9 of these cases were related to hematological events; all SAEs were resolved.[13]

AR=adverse reaction; SAE=serious adverse event.

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

A. ZEPZELCA provides substantial efficacy in both platinum-resistant and platinum-sensitive patients.[9] Responses have also been demonstrated in patients regardless of age or prior lines of therapy.[16] As such, ZEPZELCA is an option for most patients with SCLC who have relapsed.[9]

ZEPZELCA also has a known tolerability profile[9]; the vast majority of the time the patient is going to experience toxicity that is within the bounds of what was told to them. The introduction of ZEPZELCA monotherapy into the treatment paradigm is a step forward due to its balanced efficacy and safety profile, along with the dosing schedule of a 1-hour infusion every 3 weeks.[9]

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

IMPORTANT SAFETY INFORMATION (continued)

Myelosuppression (continued)

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.

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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.

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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 is a second-line option that has clinically significant responses, with both a reasonable and known tolerability profile, in both platinum-resistant and platinum-sensitive patients.[9]"

— Neal Ready, MD, PhD

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

ZEPZELCAPRO.COM

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

Neal Ready, MD, PhD, is a medical oncologist specializing in the treatment of patients with lung cancer and head and neck cancer at Duke Cancer Institute. He also serves as Professor of Medicine in the Division of Medical Oncology at the Duke University School of Medicine. Dr Ready earned his medical degree at Vanderbilt University School of Medicine and received a doctorate from the University of California, Irvine. He completed his residency in internal medicine at Rhode Island Hospital, followed by fellowships in hematology and medical oncology at Rhode Island Hospital and New England Medical Center, respectively. Dr Ready has published research on advanced non-small cell lung cancer (NSCLC) and SCLC therapeutics in multiple peer-reviewed medical journals.

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