MEET THE EXPERTS

ISSUE 8

SMALL CELL LUNG CANCER

FEATURED EXPERTS

Frank Weinberg, MD, PhD
UI Health
Chicago, IL

Firas Badin, MD, MBA-HSM
Baptist Health
Lexington, KY

INSIDE THIS ISSUE:

- Patient considerations: how support systems and resources impact treatment selection
- Importance of diversity and equity in clinical data
- Considering administration logistics and infrastructure requirements for treatment options
- Exploring efficacy, tolerability, and safety data for an alkylating agent

> ***"Every patient is unique; we look at their performance status, treatment-free interval, support, and the patient's preferences. We discuss every regimen's potential and safety. Then, the patient and I decide together what might be the best option for them."***
>
> — Firas Badin, MD

CONSIDER THE WHOLE PATIENT

WHEN SELECTING SECOND-LINE TREATMENT OPTIONS IN SMALL CELL LUNG CANCER

*Dr Badin and Dr Weinberg are paid consultants 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 authors and Jazz Pharmaceuticals and do not necessarily reflect the opinions of Baptist Health or UI Health.

A LOOK AT **PATIENT CONSIDERATIONS** AND **CHALLENGES ACCESSING TREATMENT** AFTER RELAPSE

Q. Can you describe the average patient with SCLC you see in your practice?

FB. I practice in Kentucky, where the rate of smokers is still very high. About 20% of our lung cancer cases are SCLC compared with the national average of 15% or so.[1] I see anywhere from 1-3 cases a week. Unfortunately, most of those—maybe 2/3 of patients—are extensive stage. Patients with SCLC almost always have a history of tobacco use, and many of them continue to smoke. They tend to be sicker, symptomatic, and have other comorbidities; almost all of them have COPD, and many of them have coronary-artery disease.[2]

Many of the patients who I see with SCLC might have limited access to healthcare. We have satellite clinics, and we serve patients in rural areas—often underserved areas. They may not have access to specialty services without having to travel for a distance.

FW. At the University of Illinois, UI Health sees about 25 or 30 patients with SCLC each year. My patients are primarily from the west and south sides of Chicago, so 70% of my patients are African American, and 15% are Hispanic—we are the academic setting for the underrepresented folks in the Chicago region. I see patients through consults in the hospital, through referrals, or we also have over 2,500 patients enrolled in a lung cancer screening program; we've picked up several early-stage, T1, or T2 small cell lung cancers that way, which is pretty unique.

Q. How do you discuss relapse and subsequent therapy with your patients?

FB. At least initially, I highlight the big picture and set the expectation that we're trying to slow down this disease and help patients to live longer and to try to minimize their symptoms. That's the first thing that I need to make sure the patient understands. Then, with follow-up appointments, I explain more and more to the patient. It may take more than 1 appointment to make sure that the message has been delivered appropriately to the patients.

We have to make sure that we explain things simply and repetitively and share updates when needed. Patients are grasping for hope. So, I touch base on the "today" approach, and then what their treatment might look like in the near future as well. I tend to talk about future research with patients and to tell them, "Hey, the landscape for this disease has been changing: there are new options for patients these last few years."[3,4]

FW. There's an educational aspect to it. The first time I ever see a patient, I'm going very systematically through diagnosis, what the cancer is, where the cancer is, and what the treatment is. Because in general, our patients come in with lower health literacy. And it's not just the first time—it's every single time; it's continual education. We provide handouts, we provide patient-centered materials, and we make sure that we use patient-centered language.

Q. How do you involve your multidisciplinary team in overcoming patient's challenges when accessing treatment?

FW. Many of our patients struggle; they're potentially taking care of multiple family members; they might be single parents; they might have to work 2 or 3 jobs; their transportation may not be reliable; they might be unhoused or have housing insecurity; they might have food insecurity. We always have to think about these things. Working within a multidisciplinary team is so important; it lets us optimize patients carefully. We have cardiothoracic surgeons, radiation oncologists, nurse navigators, dietary support, and palliative care. So I tell my patients, "We're a team. We're going to work together, and we're going to come up with the best treatment plan for you."

FB. Patients are not only worried about a copayment or their cost, they're also worried about their pain and access to pain medicine; they're worried about their family risk of cancer; they're worried about their diet and what to eat and what not to eat. We have access to a financial advisor, a social worker,

"It's on me and my team to figure out how to make treatment work for the patient. It's a lot of work, but so much of our patients' care relies on advocacy. We work together to get patients the support that they need so that they can actually go on and benefit from treatment."

— Frank Weinberg, MD, PhD

genetic counselors, a cardiac clinic, and a dietitian. Anything we can do to relieve the extra burdens on my patients, my team tries to do it.

Q. How is your clinic working to overcome a lack of diversity in clinical trials?

FW. Traditionally, academic centers have not had diverse population groups represented in clinical trials.[5] All patients deserve access to standard-of-care treatments, clinical trials, and the best treatment that we have available. So, I talk to every patient about clinical trials. I put in the time to sit and talk to them about what a clinical trial is, discuss their concerns, and answer their questions. Trust in the physician is really the #1 thing that stands out for patients when considering enrollment in a clinical trial. And that's led to about a 33% clinical trial enrollment rate at our clinic, and about 60% of our enrollment are underrepresented patients.

Now, obviously, if a patient comes in with comorbidities or a performance status that makes them ineligible for a clinical trial, then I will tailor my treatments. The patient still needs to be able to benefit from the best care that they can receive.

FB. Research has been a challenge for SCLC. But I can speak from my own experience: it's much easier to enroll a patient in a real-world evidence (RWE) study or phase 4 study than to put them on a phase 2 or phase 3 clinical trial.[5] The travel requirements are much easier—there's usually no travel, really—with RWE. And that's without even talking about health criteria or therapeutic and support needs that may be excluded. RWE is not replacing phase 3, randomized, controlled trials (RCTs). Those are the gold standard, really, for any oncologist. But with RWE, I think you definitely include more diverse, more underserved, patients than phase 3 studies,[5] and it can give us a better representation about what happens for patients similar to those who I see in the clinic every day.

COPD=chronic obstructive pulmonary disease; SCLC=small cell lung cancer.

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

> *"For me, the data just prove the point—ZEPZELCA can be a viable option for patients with relapsed SCLC. My patients are able to stay on ZEPZELCA for a good amount of time."*
>
> — Frank Weinberg, MD, PhD

Q. What has been your experience when treating patients with a second-line treatment like ZEPZELCA?

FB. The clinical trial results have matched what we've seen in my practice. In the phase 2 study in adult patients with metastatic SCLC who progressed on or after platinum-based chemotherapy, patients had an overall response rate (ORR) of 35% and a median duration of response (DoR) of 5.3 months based on investigator assessment (IA).[6] The ORR from the independent review committee (IRC) was 30%, with a median DoR of 5.1 months.

The study included both platinum-sensitive and platinum-resistant populations.[7] In the platinum-resistant group, the IA ORR 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: ORRs 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. This exploratory subgroup analysis was not powered to determine statistical significance. Results are descriptive only. The study also included a small cohort of 20 patients who progressed beyond 6 months. I highlight this cohort because I use ZEPZELCA in patients who progressed beyond 6 months.

FW. ZEPZELCA is one of my go-to second-line options. When determining how to sequence the medications available to us, we have to weigh different aspects, but I always think about DoR when I'm considering medications in the second-line setting for SCLC—DoR and ORR are meaningful in the SCLC setting.[6,7] These patients don't live long, so DoR can be very meaningful; if you're responding to therapy for a median of over 5 months, that's very significant for a patient.

> *"Based on the efficacy data from the phase 2 study and given its manageable safety profile, I think ZEPZELCA is a win-win situation for appropriate patients and the treating oncologist."*
>
> — Firas Badin, MD

Study Design[6]
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.

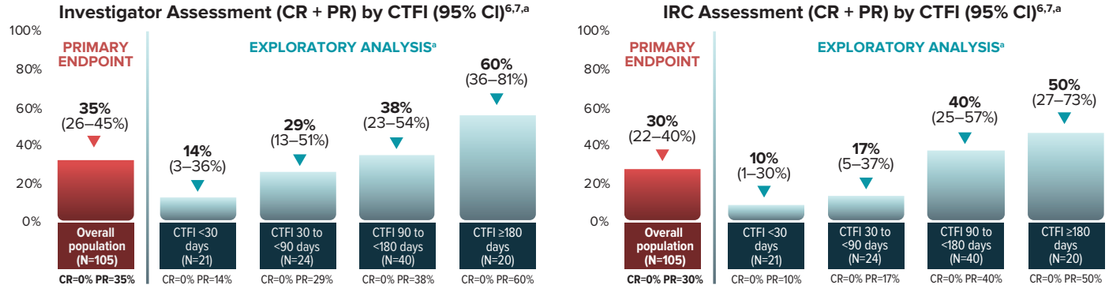
ECOG PS=Eastern Cooperative Oncology Group Performance Status; RECIST=Response Evaluation Criteria in Solid Tumors.

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.

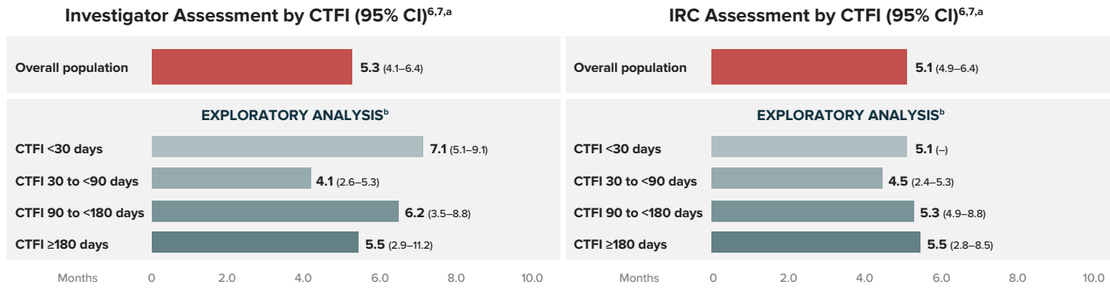
This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

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.

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



[a]Duration of response analysis is based on patients who responded to treatment.[6]
Of 8 patients who had received prior immunotherapy as first- or second-line treatment[8,b]:
• Duration of response was consistent with the overall population at a median of 5.3 months (range: 2.8–6.4 months)[6,9,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

Myelosuppression
ZEPZELCA can cause severe and fatal myelosuppression including febrile neutropenia and sepsis, thrombocytopenia and anemia.

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 neutrophils, red blood cells and platelets prior to each ZEPZELCA administration. For neutrophil count less than 500 cells/mm^3 or any value less than lower limit of normal, administer G-CSF. Withhold, reduce the dose, or permanently discontinue ZEPZELCA based on severity.

In clinical studies of 554 patients with advanced solid tumors receiving ZEPZELCA as a single agent, 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.

ZEPZELCA® (lurbinectedin) for injection 4 mg

Please see pages 10-11 for Important Safety Information and CLICK HERE for full Prescribing Information.

CLINICAL EXPERIENCE: DOSING AND ADMINISTRATION OF ZEPZELCA® (LURBINECTEDIN)

> ***ZEPZELCA is convenient for my patients—it's a single agent, not a combination of drugs; it's 1 day, not a series of days in a cycle; and it's every 21 days, not every 2 weeks or more often.***
>
> — Firas Badin, MD

Q. How does ease of administration and timing impact how you and your patients consider treatment?

FB. The administration schedule is very important. It's infrequent—every 21 days.[6] In my experience, it's usually almost always outpatient; there's no mandatory observation period after the infusion. It's a 1-hour infusion, and then patients can go home. From a patient perspective, I think it's fairly convenient, and the schedule is well tolerated by patients. From a practice perspective, you don't have to occupy that infusion chair for a very long period of observation time, or you don't have to admit the patient to the hospital. ZEPZELCA is really convenient.

FW. Logistically, it's a very convenient option. Once every 21 days, or every 3 weeks, is something very manageable for most patients, as opposed to coming every single day for an infusion for 5 days in a row.[6] Those sorts of things are important to patients.

Q. What practices do you use in your clinic to monitor patients treated with ZEPZELCA?

FB. With ZEPZELCA, we really just have to monitor scans, symptoms, and simple labs, such as blood counts, liver enzymes, and CPK. It's a very simple lab profile that you have to check every now and then. So, the monitoring is fairly easy in my experience.

FW. We monitor our patients treated with ZEPZELCA like we do other chemotherapies: every 3 weeks they get labs, and obviously, in the meantime, if they develop fever or report anything significant, then we're following up with them. In terms of monitoring requirements, it's not a monitoring-heavy treatment.

RECOMMENDED DOSAGE OF ZEPZELCA® (lurbinectedin)[6]

ZEPZELCA for injection	60-minute IV infusion	Administered every 3 weeks
3.2 mg/m²	**60 minutes**	**21 days** Until disease progression or unacceptable toxicity

Initiate treatment with ZEPZELCA only if absolute neutrophil count is ≥1,500 cells/mm³ and platelet count is ≥100,000/mm³.[6]

Premedication

Consider administering the following pre-infusion medications for antiemetic prophylaxis[6]:

- Corticosteroids (intravenous dexamethasone 8 mg or equivalent)
- Serotonin antagonists (intravenous ondansetron 8 mg or equivalent)

CPK=creatine phosphokinase; IV=intravenous.

IMPORTANT SAFETY INFORMATION (continued)

Hepatotoxicity
ZEPZELCA can cause hepatotoxicity which may be severe.

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

In clinical studies of 554 patients with advanced solid tumors receiving ZEPZELCA as a single agent, 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.

IMPORTANT SAFETY INFORMATION (continued)

Extravasation Resulting in Tissue Necrosis
Extravasation of ZEPZELCA can cause skin and soft tissue injury, including necrosis requiring debridement. 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® (lurbinectedin) for injection 4 mg

Please see pages 10–11 for Important Safety Information and CLICK HERE for full Prescribing Information.

CLINICAL EXPERIENCE: TOLERABILITY OF ZEPZELCA® (LURBINECTEDIN)

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

FB. ZEPZELCA is very well tolerated. If you look at the discontinuation rate due to adverse events, it was 1.9%.[6] In my experience, this is a very low discontinuation rate due to adverse events in the second-line setting. Patients are able to stay on the drug; the vast majority of the patients were able to stay on treatment. I think that speaks highly about the tolerability of ZEPZELCA.

In my clinic, I very rarely find my patients requiring a dose reduction, but it's very effective when utilized. I've found that when I use a dose modification because of a toxicity, it's fairly effective in eliminating that toxicity—whether it's neutropenia, thrombocytopenia, or elevated liver enzymes. And dose modifications are relatively straightforward to do. You have 2 step-down doses that you can use for patients.[6]

FW. One of the big things I hear from my patients is, "What are the side effects?" We spend a lot of time going over those side effects with patients because my patients tend to be really concerned about side effects from chemotherapy. I make sure to explain that not all chemotherapies have similar adverse events and that ZEPZELCA was well tolerated.[6] With ZEPZELCA, the most common issue that I have seen is myelosuppression.[a] Oftentimes, I don't even have to use growth factor support—I've been very successful managing it with a dose reduction.

Anecdotally, I don't find that dose reductions have made any difference in terms of efficacy or outcomes for my patients. I've had good outcomes with patients being able to stay on ZEPZELCA for a good amount of time and tolerating the medication well. Overall, the reason why ZEPZELCA has been one of my go-to treatments is because my patients tolerate it.

[a]Please see pages 10-11 for Important Safety Information.

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

FB. ZEPZELCA has had accelerated approval for several years now, so we have durability of the data.[6] We've been giving it for a long time, and it's a very predictable drug. We know what to expect. I think having an established safety profile, easy administration—1 drug every 21 days—all of that stands out to me about ZEPZELCA.

FW. I agree. We have to balance the side effects and the benefits of treatment with tolerability for the patient. It's the art. You adjust the dosing; you adjust the schedule to make treatment work. And certainly, ZEPZELCA has been around for a while, and because of its mechanism of action, a lot of us are comfortable practicing that art with ZEPZELCA.

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.

"If you look at the whole picture—the ease of use, durability data, and long-term safety data—ZEPZELCA is my preferred option for patients with relapsed SCLC."

— Firas Badin, MD

Permanent discontinuation due to an adverse reaction occurred in 1.9% of patients with SCLC (2 of 105).[6]
- Adverse reactions resulting in permanent discontinuation in ≥1% of patients included peripheral neuropathy and myelosuppression

Dosage reductions due to an adverse reaction occurred in 25% of patients.[6]
- Adverse reactions requiring dosage reductions in ≥3% of patients included neutropenia, febrile neutropenia, and fatigue

Dosage interruptions due to an adverse reaction occurred in 30.5% of patients.[6]
- Adverse reactions requiring dosage interruption in ≥3% of patients included neutropenia and hypoalbuminemia

A STRAIGHTFORWARD DOSE-REDUCTION SCHEDULE TO HELP MANAGE ADVERSE REACTIONS[6]

Recommended starting dose	First dose reduction	Second dose reduction
3.2 mg/m^2 every 21 days or until disease progression or unacceptable toxicity	2.6 mg/m^2 every 21 days[b]	2 mg/m^2 every 21 days[b]

[b]Please refer to the full Prescribing Information for specific adverse event-related dose modifications.

Initiate treatment with ZEPZELCA only if absolute neutrophil count (ANC) is at least 1,500 cells/mm^3 and platelet count is at least 100,000/mm^3.[6]

Permanently discontinue ZEPZELCA in patients who are unable to tolerate 2 mg/m^2 or require a dose delay greater than 2 weeks.[6]

IMPORTANT SAFETY INFORMATION (continued)

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.

ZEPZELCA® (lurbinectedin) for injection 4 mg

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Hepatotoxicity

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Extravasation Resulting in Tissue Necrosis

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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.

ADVERSE REACTIONS

Serious adverse reactions occurred in 34% of patients who received ZEPZELCA. Serious adverse reactions in ≥3% of patients included pneumonia, febrile neutropenia, neutropenia, respiratory tract infection, anemia, dyspnea, and thrombocytopenia.

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 and older than in patients <65 years of age (49% vs. 26%, respectively). The serious adverse reactions most frequently reported in patients 65 and older were related to myelosuppression and consisted of febrile neutropenia (11%), neutropenia (11%), thrombocytopenia (8%), and anemia (8%). There was a higher incidence of Grade 3 or 4 adverse reactions in patients 65 and older compared to younger patients (76% vs. 50%, respectively).

HEPATIC IMPAIRMENT

Avoid administration of ZEPZELCA in patients with severe hepatic impairment. If administration cannot be avoided, reduce the dose. Monitor for increased adverse reactions in patients with severe hepatic impairment.

Reduce the dose of ZEPZELCA in patients with moderate hepatic impairment. Monitor for increased adverse reactions in patients with moderate hepatic impairment.

No dose adjustment of ZEPZELCA is recommended for patients with mild hepatic impairment.

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Please CLICK HERE for full Prescribing Information.

> *I have a lot of experience with ZEPZELCA. The efficacy is there; the tolerability is there. To see a medication that has good efficacy and an established safety profile—that's a no-brainer to me.*
>
> — Frank Weinberg, MD, PhD

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

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Firas Badin, MD, MBA-HSM, is Medical Director of Oncology Research at Baptist Health Lexington in Kentucky. Dr Badin earned his medical degree from the University of Damascus Medical School in Syria. In addition, he received a master's degree in business administration and health systems management from Morehead State University in Morehead, Kentucky. Dr Badin completed his residency at Beth Israel Medical Center in Newark, New Jersey, and a fellowship in hematology/oncology at the University of Kentucky in Lexington. His clinical and research interests include the treatment of several malignancies, including lung cancer. Dr Badin is a member of the American Society of Clinical Oncology and American Society of Hematology.

Frank Weinberg, MD, PhD, is a medical oncologist at UI Health in Chicago, Illinois, and Assistant Professor of Medicine in the Division of Hematology and Oncology at the University of Illinois College of Medicine in Chicago. Dr Weinberg earned his medical degree at the University of Illinois College of Medicine and his doctorate at Northwestern University in Chicago. He fulfilled his internal medicine residency and a hematology/oncology fellowship at the University of Michigan in Ann Arbor. Dr Weinberg specializes in the clinical research and treatment of lung cancer using immunotherapy and the lung microbiome. He holds professional memberships with the American Society of Clinical Oncology, American Association for Cancer Research, and International Association for the Study of Lung Cancer.

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