MEET THE EXPERT

ISSUE 9

SMALL CELL LUNG CANCER

FEATURING

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> *"This momentum is tremendous for patients, patients' families, and certainly all the care teams."*
>
> —Wade Iams, MD, MSCI

INSIDE THIS ISSUE:

- Clinical progress in first-line SCLC: induction and maintenance strategies
- Evaluating a chemo-immunotherapy maintenance approach: efficacy, tolerability, and safety insights
- Maximizing survival potential: the case for early use of active therapies

MAINTAIN MOMENTUM

ADVANCES IN MAINTENANCE TREATMENT IN SMALL CELL LUNG CANCER (SCLC)

*Dr Iams 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 Tennessee Oncology.

USING MAINTENANCE TREATMENT TO IMPROVE OUTCOMES FOR PATIENTS WITH SCLC

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

A. On average, I see about 30 patients with SCLC per year. The majority have ES-SCLC, and I'll probably meet 25% of them when they're in the hospital at the time of initial diagnosis with ES-SCLC. I also do see a fraction—probably 30% or so—to evaluate for clinical trials or a second opinion from within our group or referrals within the region.

At diagnosis, the patients usually have a large lung mass that's caused symptoms, either significant hypoxia, significant dyspnea, or significant pain, and that caused them to present to a local emergency room. Many times, they're then sent to my hospital, St. Thomas West, here in Nashville, for the biopsy and additional evaluation with Oncology. And so, that's typically how the new-diagnosis patients arrive—there's some symptom from their cancer.

> *"My goal is to make sure my patients have the information they need for planning but also have hope or what they're striving for—what we're all striving for—with the treatment."*
>
> —Wade Iams, MD, MSCI

Q. How do you discuss diagnosis, expectations, and therapy with your patients?

A. That first conversation is usually the patient processing the initial diagnosis, treatment, and prognosis. For the hospitalized new-diagnosis patients, I am typically the first to go through any of that information. When first hit with the news "You have cancer," most people wonder, "Can I be cured?" and that's where it depends on the stage of SCLC. For patients with limited-stage disease, there is a potential for cure.[1] In patients with extensive-stage disease—which, unfortunately, most patients are at the time of diagnosis[2]—I tend to be direct about the incurable nature; the goal is to control the cancer for as long as possible with as good a quality of life as possible.[3] The goal is to shrink this cancer quickly, which we achieve in most patients. I tell them, "We think we can improve your symptoms."

Over subsequent conversations, we discuss the innovations in the treatment of SCLC, the new regimens, planning for relapse, and what we should be looking at as our next steps. Treatments are always evolving; average survival is ever-increasing.[4]

Q. How has the increased number of treatment options impacted how you think about improving outcomes for your patients?

A. There's a significant drop-off with every line of therapy in SCLC.[5,6] We see PFS results translate into OS results because so many patients with SCLC just don't proceed to the next lines of therapy. So we want to give our best drugs first because the clinical decline that we see with SCLC progression can be so dramatic.

A component of improving outcomes is intervening early—in the maintenance phase.[7] In my practice, 90% of my patients are eligible for and move on to maintenance. I don't approach it, really, as a debate in my practice. If the symptoms and scans are not clearly worsening, then I move right on to maintenance therapy. I think that's absolutely buying time for disease control and, ultimately, for patient survival.

There is a small subset of patients—~10%—who have really benefited long term from the addition of immunotherapy to the maintenance setting, and it has been a real miracle for these patients.[8] But most patients have residual disease; we know that from ctDNA studies of induction in ES-SCLC.[9] So, I think improving outcomes involves additional chemotherapy in the maintenance phase that can help suppress that residual disease.

ctDNA=circulating tumor DNA; DNA=deoxyribonucleic acid; ES-SCLC=extensive-stage small cell lung cancer; OS=overall survival; PFS=progression-free survival.

CLINICAL EXPERIENCE: MAINTENANCE TREATMENT FOR SCLC WITH ZEPZELCA® (lurbinectedin) + atezolizumab

Q. What is your impression of the data behind maintenance treatment with ZEPZELCA + atezolizumab?

A. IMforte was a very direct assessment of introducing ZEPZELCA to atezolizumab maintenance for patients with ES-SCLC vs continuing atezolizumab maintenance alone.[10] It asked an important question, "If we add ZEPZELCA after the completion of 4 cycles of platinum doublet induction + atezolizumab, does that result in improved progression-free, and ultimately overall, survival?"

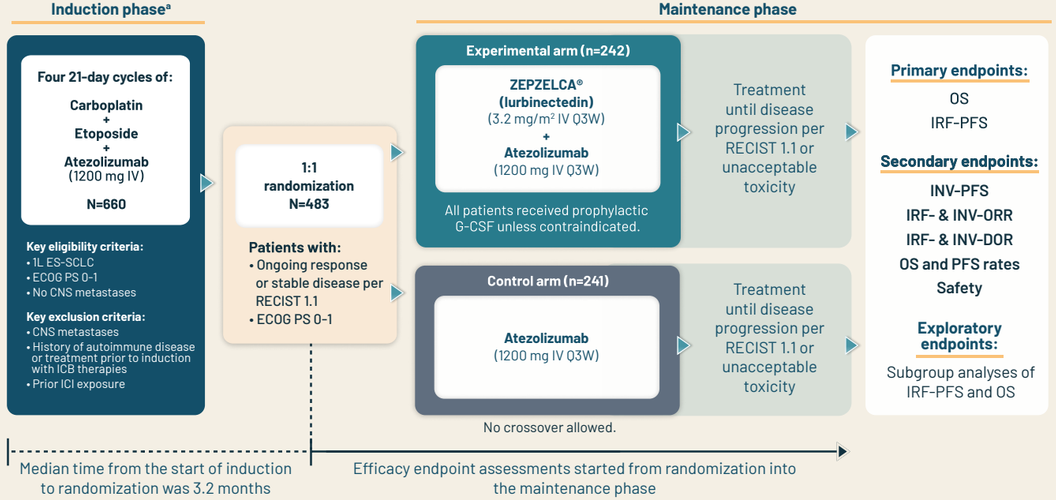
It was a phase 3, randomized, multicenter, open-label study in 483 adult patients with first-line ES-SCLC whose disease had not progressed after the completion of 4 cycles of atezolizumab, carboplatin, and etoposide induction treatment and who had an ECOG PS of 0 or 1.[10]

Patients were randomized 1:1 to either ZEPZELCA 3.2 mg/m^2 IV with atezolizumab 1200 mg IV once every 3 weeks or to atezolizumab 1200 mg IV once every 3 weeks until disease progression or unacceptable toxicity. Primary endpoints were OS and IRF-assessed PFS per RECIST v1.1 in patients randomized into the maintenance phase. Additional efficacy outcomes included IRF-assessed PFS rates at 6 months and 12 months and OS rates at 12 months.[10]

Efficacy endpoint assessments started from randomization into the maintenance phase; the median time from the start of induction to the time of randomization was 3.2 months.[11]

CNS=central nervous system; DOR=duration of response; ECOG PS=Eastern Cooperative Oncology Group Performance Status; G-CSF=granulocyte colony-stimulating factor; ICB=immune checkpoint blockade; ICI=immune checkpoint inhibitor; INV=investigator-assessed; IRF=independent review facility; IV=intravenous; ORR=objective response rate; PD-1=programmed cell death protein-1; Q3W=every 3 weeks; RECIST=Response Evaluation Criteria in Solid Tumors.

IMforte: A large phase 3 trial with >450 adult patients with ES-SCLC in the maintenance phase[10,11]



ZEPZELCA was studied only with intravenous atezolizumab. For information on the use of atezolizumab administered subcutaneously, see the atezolizumab and hyaluronidase-tqjs prescribing information.

[a]Following induction therapy but before randomization, participants may receive prophylactic cranial irradiation at the investigator's discretion per local standard.

INDICATION

ZEPZELCA® (lurbinectedin) for injection 4 mg, in combination with atezolizumab or atezolizumab and hyaluronidase-tqjs, is indicated for the maintenance treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) whose disease has not progressed after first-line induction therapy with atezolizumab or atezolizumab and hyaluronidase-tqjs, carboplatin and etoposide.

Q. Do the demographics and baseline characteristics of patients in the IMforte trial align with those of patients in your practice?

A. It's a representative group for my practice: the vast majority of patients were current or previous smokers, and no major concerns about the background characteristics being unrepresentative.[11] But I'm always looking forward to real-world studies that will give us more information about the patients we see every day. I'll still treat patients who have brain metastases with ZEPZELCA + atezolizumab. Significant underlying cardiovascular disease wouldn't prohibit me from using ZEPZELCA + atezolizumab either—it certainly hasn't prevented me from doing that in the past—patients with cardiovascular disease are very common with SCLC.[12]

Baseline characteristics were well balanced between arms in the randomized population[10,11,a]

	ZEPZELCA® (lurbinectedin) + Atezolizumab (n=242)	Atezolizumab (n=241)
Median age, years (range)	65 (60-71)	67 (61-72)
≥65 years, n (%)[a]	124 (51)	150 (63)
Male, n (%)	151 (62)	151 (63)
Race, n (%)[b]		
White	195 (81)	199 (83)
Asian	31 (13)	31 (13)
Black or African American	3 (1)	1 (<1)
Not reported	12 (5)	10 (4)
Response to induction treatment, n (%)[c]		
CR/PR	206/236 (87)	213/240 (89)
SD	28/236 (12)	25/240 (10)
PD	2/236 (1)	2/240 (1)
ECOG PS 0 at randomization baseline, n (%)[d]	105 (43)	102 (42)
ECOG PS 1 at randomization baseline, n (%)[d]	137 (57)	139 (58)
LDH > ULN at randomization baseline, n (%)[d]	66 (27)	62 (26)
Liver metastases at enrollment baseline, n (%)[d]	100 (41)	94 (39)
Prior PCI, n (%)[d]	34 (14)	37 (15)

CR=complete response; LDH=lactate dehydrogenase; PCI=prophylactic cranial irradiation; PD=progressive disease; SD=stable disease; ULN=upper limit of normal.

[a]There was a higher proportion of younger patients (age <65 years) in the ZEPZELCA + atezolizumab group.[11] [b]American Indian or Alaska Native: 0 in atezolizumab arm; 1 (<1%) in ZEPZELCA + atezolizumab arm.[11] [c]Seven randomly assigned patients did not have a maintenance screening tumor assessment.[11] [d]Data were obtained from electronic case-report forms.[11]

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. To reduce the risk of febrile neutropenia during treatment with ZEPZELCA in combination with atezolizumab or atezolizumab and hyaluronidase-tqjs, administer granulocyte colony-stimulating factor (G-CSF). 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 the IMforte study, primary prophylaxis of G-CSF was administered to 84% of patients. Based on laboratory values, decreased neutrophils occurred in 36%, including 18% Grade 3 or Grade 4 in patients who received ZEPZELCA in combination with atezolizumab. The median time to onset of Grade 3 and 4 decreased neutrophil cells was 31 days and

ZEPZELCA® (lurbinectedin) for injection 4 mg

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

CLINICAL EXPERIENCE: SURVIVAL DATA WITH ZEPZELCA® (lurbinectedin) + atezolizumab

Q. Why do you consider recommending ZEPZELCA + atezolizumab to your maintenance patients?

A. In the IMforte clinical trial, patients treated with maintenance ZEPZELCA + atezolizumab had 13.2 months median OS vs 10.6 months median OS for patients treated with atezolizumab monotherapy maintenance. Patients had 5.4 months median PFS vs 2.1 months median PFS, respectively.[10]

The OS benefit stands out the most to me. Clearly, there's a cohort of patients whose disease is controlled for longer, which results in an OS benefit. The IMforte data are immediately practice-changing for me because of the incremental survival benefit.[10] If I had a patient moving into the maintenance phase tomorrow, my goal would be to add ZEPZELCA to their atezolizumab maintenance.

PFS is also good to see. A lot of lung cancer patients don't receive more than 1 line of therapy.[5] I think that's especially true in SCLC. To me, it's a very different mentality when you think about something like PFS, which was also extended in the IMforte study from the time of maintenance by introducing ZEPZELCA + atezolizumab.[10] These improvements in PFS translate to OS benefits. In my experience, if you can improve the PFS by 3 months, you're going to have an improvement in OS because the proportion of patients who drop off is so high in this disease.

The shape of the PFS curve represents the patient trajectories that we're likely going to see. I think what that displays is that we'll see a large cohort of patients whose disease is controlled for longer,[10] which is always the goal.

Q. How do you explain your recommendation for first-line maintenance ZEPZELCA + atezolizumab to a patient?

A. The usual time for induction is a little over 3 months.[11] So, a lot of us think in terms of the previous ES-SCLC chemo-only regimens that resulted in a median overall survival of around 10 months; that improved to 12-13 months with the addition of immune checkpoint inhibitors.[7] When you add a little over 3 months for induction to the 13.2 months reported here,[10] that's a 16- to 17-month median OS. So now, instead of quoting patients an average of a year survival with treatment, the reality is that it's an average of almost a year and a half survival. I think that has a different meaning to all patients. I do sometimes talk in terms of major life events that patients are trying to make, whether it's a grandchild's birthday, a graduation, or a wedding—those types of events are obviously very important to all of us, and many patients are striving to be able to witness those major life events for their families. So, having an additional window for potential life events is extremely important when talking to them about their treatment options.

When I describe the maintenance regimen to my patients, I explain that, without additional treatment, most patients will relapse quickly.[7] I describe the regimen as, "Initially, we treat with a combination of strong chemotherapy + immunotherapy, as induction to debulk your disease, and then we go to a lighter chemotherapy + immunotherapy to maintain the benefit."

IMPORTANT SAFETY INFORMATION (continued)

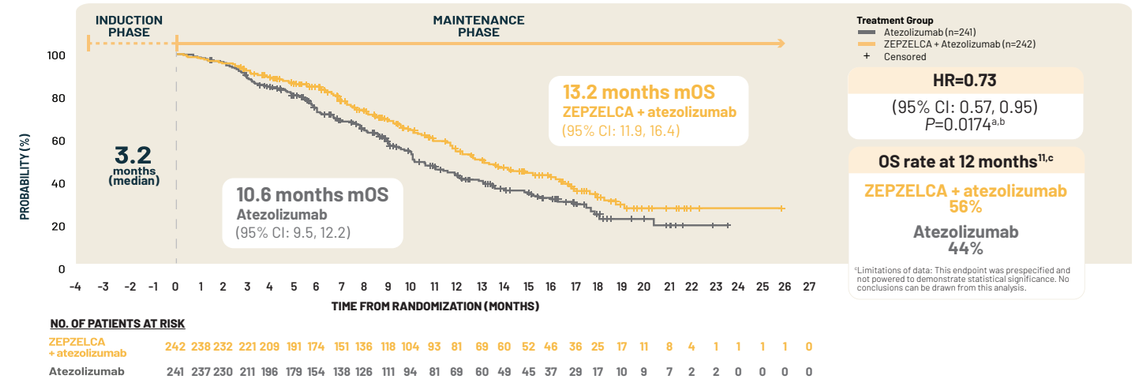
Myelosuppression (continued)
a median duration of 10 days. Febrile neutropenia occurred in 1.7%. Sepsis occurred in 1%. There were 7 fatal infections: pneumonia (n=3), sepsis (n=3), and febrile neutropenia (n=1).

Based on laboratory values, decreased platelets occurred in 54%, including 15% Grade 3 or Grade 4 in patients who received ZEPZELCA in combination with atezolizumab. The median time to onset of Grade 3 and 4 decreased platelet cells was 31 days and a median duration of 12 days.

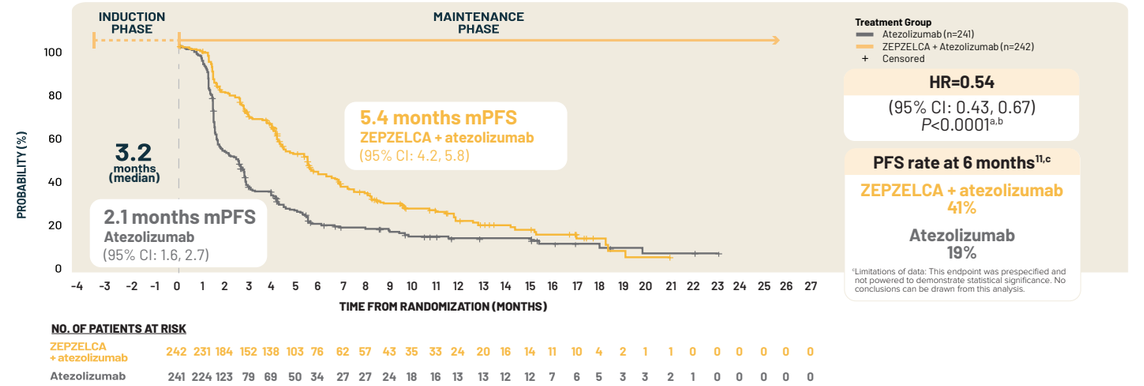
Based on laboratory values, decreased hemoglobin occurred in 51%, including 13% Grade 3 or Grade 4 in patients who received ZEPZELCA in combination with atezolizumab. The median time to onset of Grade 3 and 4 decreased hemoglobin was 64 days and a median duration of 8 days.

"To me, the headline takeaway from IMforte is an improvement in OS for patients who received ZEPZELCA + atezolizumab vs patients who received atezolizumab maintenance alone."

— Wade Iams, MD, MSCI



CI=confidence interval.
[a]Based on the 2-sided stratified log-rank test.
[b]Compared to the allocated alpha of 0.0313 (2-sided) for this interim OS analysis.



[a]Based on the 2-sided stratified log-rank test.
[b]Compared to the allocated alpha of 0.001 (2-sided) for this final PFS analysis.

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 the IMforte study, based on laboratory values, increased alanine aminotransferase (ALT) occurred in 25%, including 3% Grade 3 or Grade 4 in patients who received ZEPZELCA in combination with atezolizumab.

ZEPZELCA® (lurbinectedin) for injection 4 mg

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CLINICAL EXPERIENCE: TOLERABILITY OF ZEPZELCA + atezolizumab, SAFETY PROFILE, AND FLEXIBLE DOSING

Q. What do the safety results and adverse events from IMforte tell you about ZEPZELCA + atezolizumab?

A. I think ZEPZELCA + atezolizumab has been well received, but with any new combination regimen, it's always a trade-off of additional toxicity with any additional therapy, and what are you gaining in terms of OS. We all have experience of when patients get to a point where they can't tolerate any more therapy… So, if the question is, "Is this going to be generally well tolerated by our patients?" then, to me, I'm thinking about what proportion of patients discontinue due to drug toxicity. Around 5% of patients in the ZEPZELCA + atezolizumab arm of IMforte discontinued due to drug toxicity.[10] I think that's a low rate of discontinuation. So, we didn't see a major uptick in cessation of maintenance therapy due to drug toxicity, which I think is reassuring. And ultimately, I think the overall survival benefit is worth the slight uptick in toxicity that was observed in the study.

Q. How do you manage toxicities when treating patients with ZEPZELCA + atezolizumab?

A. In IMforte, there was an increase in adverse events in general in the patients who received ZEPZELCA + atezolizumab, but cytopenias are the driver of the high rates of toxicity in treatment-related adverse events when you look at the numbers.[10] In my experience, cytopenias are asymptomatic, besides some degree of fatigue, or febrile neutropenia—those are what's most clinically meaningful to patients. When you drill down to key adverse events of interest like we talked about—neutropenic fever with G-CSF support—that was 2% of patients who received ZEPZELCA + atezolizumab.[10] That speaks to exactly the reason to do G-CSF prophylaxis. We can get the rate near 0 for neutropenic fever by using G-CSF support, so I think that should be the standard approach. I think the broader prophylaxis approach with ZEPZELCA + atezolizumab maintenance allows the maximum number of patients to receive the treatment for a longer duration, with fewer complications.

No new or unexpected safety signals were observed beyond the established safety profiles of ZEPZELCA and atezolizumab[10,11,13]

Adverse reactions (≥10% of patients receiving ZEPZELCA® (lurbinectedin) + atezolizumab)[10]

	ZEPZELCA + Atezolizumab (n=242)		Atezolizumab (n=240)	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Gastrointestinal disorders				
Nausea	36	3	4	1
Diarrhea[a]	15	0	8	0
Vomiting	14	1	3	0
Constipation	12	0	6	1
General disorders and administration site conditions				
Fatigue[b]	32	5	13	2
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[c]	19	2	16	1
Metabolism and nutrition disorders				
Decreased appetite	17	0	7	0
Respiratory, thoracic, and mediastinal disorders				
Cough[d]	12	0	8	0
Dyspnea[e]	11	2	10	2

Select lab abnormalities (≥20% of patients receiving ZEPZELCA® (lurbinectedin) + atezolizumab) worsening from baseline[10]

	ZEPZELCA + Atezolizumab (n=242)		Atezolizumab (n=240)	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Hematology				
Decreased lymphocytes	55	17	31	11
Decreased platelets	54	15	15	3
Decreased hemoglobin	51	13	12	3
Decreased neutrophils	36	18	7	4
Chemistry				
Increased alkaline phosphatase	29	1	14	0
Decreased sodium	27	4	30	5
Increased ALT	25	3	18	2
Increased AST	24	3	22	1
Decreased calcium	24	3	8	1
Increased creatinine	21	3	14	0

Graded per NCI CTCAE v5.0.
ALT=alanine transaminase; AST=aspartate transferase; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

[a]Includes diarrhea and colitis. [b]Includes fatigue and asthenia. [c]Includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, and pain in extremity. [d]Includes cough, productive cough, and upper-airway cough syndrome. [e]Includes dyspnea and dyspnea exertional.

IMPORTANT SAFETY INFORMATION (continued)

Hepatotoxicity (continued)
Increased aspartate aminotransferase (AST) occurred in 24% including 3% Grade 3 or Grade 4. The median time to onset of Grade ≥3 elevation in transaminases was 52 days (range: 6 to 337).

> *"In my experience, ZEPZELCA + atezolizumab once every 3 weeks has been well received; toxicity is low, generally."*
> —Wade Iams, MD, MSCI

Q. How does the dosing structure of ZEPZELCA + atezolizumab impact your patients?

A. I think the important thing to contextualize about a once-every-3-weeks maintenance is these are patients coming off of 3 days in a row of chemo for the platinum/etoposide.[10,14] This is one-third of what patients and families have just been experiencing.

The dosing is also good for keeping patients on treatment longer. If we're able to continue the full dose with G-CSF support or trilaciclib support, I think that's the best strategy. But everybody should know that dose reduction is an option.[10] This treatment isn't written in stone once you start; there's flexibility to adjust for any side effects, and then we take it month by month with how they're doing with treatment thereafter.

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

A. In my practice, the standard of care for first-line maintenance is now ZEPZELCA + atezolizumab.

Most adverse reactions were Grade 1 or 2[10,a]

Discontinuation
Low discontinuation rate of ZEPZELCA (5%) due to adverse reactions in patients receiving ZEPZELCA + atezolizumab[10]
The adverse reaction resulting in permanent discontinuation in ≥1% of patients who received ZEPZELCA was decreased neutrophil count

Dose reduction
15% of patients receiving ZEPZELCA + atezolizumab had dose reductions of ZEPZELCA due to an adverse reaction[10]
Adverse reactions which required dosage reduction in ≥2% of patients included decreased platelet count, fatigue, nausea, and vomiting

Interruption
25% of patients receiving ZEPZELCA + atezolizumab had an adverse reaction leading to interruption of ZEPZELCA[10]
Adverse reactions which required dosage interruption in ≥2% of patients included anemia, fatigue, decreased neutrophil count, and decreased platelet count

Adverse reactions
Fatal adverse reactions occurred in 5% of patients receiving ZEPZELCA + atezolizumab[10]
These included pneumonia (3 patients), sepsis (3 patients), cardio-respiratory arrest (2 patients), myocardial infarction (2 patients), and febrile neutropenia (1 patient)

[a]242 patients in the ZEPZELCA + atezolizumab group and 240 patients in the atezolizumab group were included in the safety analysis set.

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. 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.

ZEPZELCA® (lurbinectedin) for injection 4 mg

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INDICATION

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IMPORTANT SAFETY INFORMATION

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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. To reduce the risk of febrile neutropenia during treatment with ZEPZELCA in combination with atezolizumab or atezolizumab and hyaluronidase-tqjs, administer granulocyte colony-stimulating factor (G-CSF). 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 the IMforte study, primary prophylaxis of G-CSF was administered to 84% of patients. Based on laboratory values, decreased neutrophils occurred in 36%, including 18% Grade 3 or Grade 4 in patients who received ZEPZELCA in combination with atezolizumab. The median time to onset of Grade 3 and 4 decreased neutrophil cells was 31 days and a median duration of 10 days. Febrile neutropenia occurred in 1.7%. Sepsis occurred in 1%. There were 7 fatal infections: pneumonia (n=3), sepsis (n=3), and febrile neutropenia (n=1).

Based on laboratory values, decreased platelets occurred in 54%, including 15% Grade 3 or Grade 4 in patients who received ZEPZELCA in combination with atezolizumab. The median time to onset of Grade 3 and 4 decreased platelet cells was 31 days and a median duration of 12 days.

Based on laboratory values, decreased hemoglobin occurred in 51%, including 13% Grade 3 or Grade 4 in patients who received ZEPZELCA in combination with atezolizumab. The median time to onset of Grade 3 and 4 decreased hemoglobin was 64 days and a median duration of 8 days.

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 the IMforte study, based on laboratory values, increased alanine aminotransferase (ALT) occurred in 25%, including 3% Grade 3 or Grade 4 in patients who received ZEPZELCA in combination with atezolizumab. Increased aspartate aminotransferase (AST) occurred in 24% including 3% Grade 3 or Grade 4. The median time to onset of Grade ≥3 elevation in transaminases was 52 days (range: 6 to 337).

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. 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.

In the IMforte study, extravasation resulting in skin necrosis occurred in one patient who received ZEPZELCA in combination with atezolizumab.

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.

In the IMforte study, among 235 patients who had a creatine phosphokinase laboratory evaluation, increased creatine phosphokinase occurred in 9% who received ZEPZELCA in combination with atezolizumab.

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 31% of patients receiving ZEPZELCA in combination with atezolizumab. Serious adverse reactions occurring in >2% were pneumonia (2.5%), respiratory tract infections (2.1%), dyspnea (2.1%), and decreased platelet count (2.1%). Fatal adverse reactions occurred in 5% of patients receiving ZEPZELCA with atezolizumab including pneumonia (3 patients), sepsis (3 patients), cardio-respiratory arrest (2 patients), myocardial infarction (2 patients), and febrile neutropenia (1 patient).

The most common adverse reactions (≥30%), including laboratory abnormalities, in patients who received ZEPZELCA with atezolizumab were decreased lymphocytes (55%), decreased platelets (54%), decreased hemoglobin (51%), decreased neutrophils (36%), nausea (36%), and fatigue/asthenia (32%).

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 242 patients with ES-SCLC treated with ZEPZELCA and atezolizumab in IMforte, 124 (51%) patients were 65 years of age and older, while 29 (12%) patients were 75 years of age and older. No overall differences in effectiveness were observed between older and younger patients. There was no overall difference in the incidence of serious adverse reactions in patients ≥65 years of age and patients <65 years of age (33% vs. 29%, respectively). There was a higher incidence of Grade 3 or 4 adverse reactions in patients ≥65 years of age compared to younger patients (45% vs. 31%, 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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