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# Administration of ZEPZELCA™ (Irbinitectin)

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ICD-10 Coordination & Maintenance Committee Meeting  
March 9, 2021





# Topics

- ZEPZELCA (lurbinectedin) Indication and Regulatory Approval
- Metastatic Small Cell Lung Cancer (SCLC) / Unmet Treatment Need
- Dosing and Administration; Need for ICD-10-PCS Procedure Code
- ZEPZELCA Clinical Evidence

# ZEPZELCA (lurbinectedin), a Transcription Inhibitor

- **FDA approval and indication:** ZEPZELCA was approved June 15, 2020, under the U.S. Food & Drug Administration's (FDA) Accelerated Approval Program, in advance of the previously announced Prescription Drug User Fee Act (PDUFA) target action date of August 16, 2020
  - ZEPZELCA 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).
- **Consensus Guidelines:** Immediately following FDA approval, ZEPZELCA was listed as a preferred regimen by the NCCN Clinical Practice Guidelines for the second-line treatment of patients with chemotherapy free interval (CTFI)  $\leq$  6 months and a recommended regimen for patients with a CTFI  $>$  6 months<sup>1</sup>
- **Peer-reviewed Publications:** Results from Study B-005, the single arm study of lurbinectedin in previously treated SCLC patients were published in *Lancet Oncology* in March 2020<sup>2</sup> and have been presented at multiple scientific conferences<sup>3-7</sup>

## High Unmet Clinical Need In SCLC; No Approved Treatments for Second-line Treatment of SCLC since 1998

- Most cases of SCLC occur in individuals 60 to 80 years of age<sup>8</sup>
- Approximately 60-70% of patients with SCLC have clinically disseminated or extensive disease at diagnosis;<sup>9</sup> many have substantial comorbidities<sup>10</sup>
- Approximately 80% of limited-disease SCLC patients and almost all patients with extensive-stage (ES) SCLC relapse or progress after first-line treatment<sup>11</sup>
- Without second-line chemotherapy, the median survival time is 2 to 4 months<sup>11,12</sup>

- Hycamtin (topotecan) was approved in 1998 for the treatment of SCLC sensitive disease after failure of first-line therapy.<sup>13</sup>
  - Efficacy ranges reported in the literature:<sup>14-17</sup>
    - Objective Response Rate (ORR) 16.9% to 25.0%
    - Progression-free Survival (PFS) 2.7 to 4.1 months
    - Median survival 6.8 to 7.8 months
  - Efficacy results are achieved with a high rate of Grade 3/4 hematologic treatment-emergent adverse events (TEAEs), namely neutropenia, leukopenia, thrombocytopenia and anemia<sup>13</sup>

**The challenging risk-benefit profile of topotecan warrants additional second-line treatment options for metastatic SCLC with disease progression on or after platinum-based chemotherapy**

## There Is No ICD-10-PCS Procedure Code to Identify Administration of ZEPZELCA in the Inpatient Setting

- ZEPZELCA is indicated for the treatment of adult patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy.
  - ZEPZELCA is administered intravenously as a 3.2 mg/m<sup>2</sup> dose over the course of one hour, repeated every 21 days until disease progression or unacceptable toxicity.
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- ZEPZELCA is expected to be primarily administered in the outpatient setting.
  - There is no diagnosis code specific to SCLC. Inpatient cases where ZEPZELCA is administered will be identified by ICD-10-CM category C34 as the primary or a secondary diagnosis, along with the ZEPZELCA-specific ICD-10-PCS code, if approved.
    - Many patients with SCLC have substantial comorbidities<sup>19</sup> which may necessitate hospitalization
    - A patient receiving ZEPZELCA in the outpatient setting may also require occasional short hospitalizations given age and comorbid conditions, e.g., cardiovascular and orthopedic issues.
  - Its every 21-day dosing schedule may result in less therapy in the clinic or hospital for SCLC patients treated with ZEPZELCA as compared to other treatment options.

# BASKET Trial: Phase 2 Study (B-005) of Lurbinectedin as a Single Agent in Second-line SCLC

**Study design:** Phase 2 multicenter study of single-agent lurbinectedin in patients with 9 different tumor types, including second-line SCLC (NCT02454972)

## SCLC Specific Inclusion Criteria

Pathologically confirmed diagnosis of SCLC

ECOG PS 0-2

One prior chemotherapy line

Adequate major organ function

Minimum interval between any previous treatment and study commencement had to be: 3 weeks for chemotherapy, 4 weeks for IO or RT, and 2 weeks for any investigational therapy

No restriction on LDH

Known CNS involvement was excluded

Lurbinectedin 3.2 mg/m<sup>2</sup>, 1 hour IV, q21 days (one cycle)

≥2 responses in first 25 patients

Enroll up to 100 patients

Prophylactic use of G-CSF was not permitted

## Primary Endpoint

ORR by RECIST v.1.1 (confirmed responses by investigator assessment)

## Secondary Endpoints

ORR by IRC

Duration of Response (DOR) by IA/IRC,

Disease Control Rate (DCR)

Progression-free Survival (PFS)

Overall Survival (OS)

Safety

PK

ECOG PS, Eastern Cooperative Oncology Group performance status; CNS, central nervous system; RECIST, Response Evaluation Criteria In Solid Tumors.

## Study B-005 SCLC Demographics and Baseline Characteristics

- At cutoff (January 15, 2019), 105 patients had been treated with ZEPZELCA, with a median age of 60 years (range, 40-83 years; 35% were  $\geq$  65 years old)
  - Most patients (92%) had a history of smoking
  - Most (70%) had extensive disease at diagnosis, with 75% having a median number of tumor sites  $\geq$  3
- Patients had received a median of one prior line of chemotherapy for advanced disease (range, 1-2 lines)
  - All (100%) had been treated with platinum-based chemotherapy
- With respect to CTFI
  - 43% of treated patients had platinum-resistant SCLC, CTFI < 90 days (20% with CTFI < 30 days)
  - 57% had platinum-sensitive SCLC (CTFI  $\geq$  90 days) (20% with CTFI > 180 days)

# ZEPZELCA Provides a Substantial Safety Improvement Over Safety Results Previously Reported in the Literature for a Comparable Patient Population

- ZEPZELCA safety data was reported by Trigo et al, 2020<sup>2</sup> as acceptable and manageable, where treatment-related SAEs occurred in 10.5% of patients; neutropenia and febrile neutropenia were most common (5% each).
  - Dose administration was delayed in 23 (22%) patients and reduced in 28 (26%) because of treatment-related AEs; a low discontinuation rate of 2%.

## Study B-005: Hematological Abnormalities During Treatment - Worst Grade per Patient; All Ages (N=105); (Data on file, Jazz)

Parameter	Gr 1-2	Gr 3	Gr 4
Anemia	91 (86.7%)	9 (8.6%)	0
Leukopenia	53 (50.5%)	20 (19.0%)	10 (9.5%)
Lymphopenia	45 (42.9%)	39 (37.1%)	6 (5.7%)
Neutropenia	27 (25.7%)	22 (21.0%)	26 (24.8%)
Thrombocytopenia	39 (37.1%)	3 (2.9%)	4 (3.8%)

## Hematologic Adverse Reactions Experienced in ≥5% of Patients with SCLC: Study 090, HYCAMTIN (topotecan)<sup>13</sup>

Hematologic Adverse Reaction	Topotecan Arm (N=107) Grade 3/4 (%)
Grade 4 neutropenia (<500/mm <sup>3</sup> )	70
Grade 3 or 4 anemia (Hgb <8 g/dL)	42
Grade 4 thrombocytopenia (<25,000/mm <sup>3</sup> )	29
Febrile neutropenia	28

- TEAEs for ZEPZELCA in Study B-005 are lower than the associated hematological toxicities reported in the Hycamtin (topotecan) prescribing information;<sup>13</sup> no treatment-related deaths in Study B-005 vs 7.9-11.2% in topotecan studies<sup>14-16</sup>
- The ZEPZELCA safety profile was consistent across age groups (≥ 65 and < 65 years of age)

# Pooled Safety Analysis and CORAIL Safety Analysis Provide Further Evidence of the Substantially Improved Safety Profile of ZEPZELCA

**CORAIL Safety Profile (lurbinectedin vs topotecan): Grade 3/4 Adverse Events (related or unknown) and Laboratory Abnormalities (regardless of relationship)**

	Lurbinectedin 3.2 mg/m <sup>2</sup> 1-h iv q3wk		Topotecan 1.5 mg/m <sup>2</sup> D1-D5 iv q3wk	P-value CORAIL (L vs. T)
	L Pool (n=554)	L CORAIL (n=219)	T CORAIL (n=87)	
<b>Neutropenia</b>	40.6	<b>32.0</b>	78.2 <sup>a</sup>	<.0001
<b>Leukopenia</b>	29.6	<b>23.7</b>	57.5 <sup>a</sup>	<.0001
<b>Anemia</b>	17.1	<b>17.8</b>	56.3	<.0001
<b>Thrombocytopenia</b>	9.9	<b>9.1</b>	33.3	<.0001
<b>ALT increase</b>	6.9	<b>6.8</b>	3.6	0.42
<b>Fatigue</b>	6.7	<b>7.3</b>	13.8	0.08
<b>FN</b>	6.3	<b>5.5</b>	11.5 <sup>a</sup>	0.08
<b>Nausea</b>	3.2	<b>5.9</b>	4.6	0.79
<b>Vomiting</b>	2.9	<b>5.5</b>	3.4	0.57
<b>Diarrhea</b>	0.9	<b>0.9</b>	4.6	0.06

<sup>a</sup>Primary G-CSF prophylaxis allowed. Lurbinectedin, USAN of ZEPZELCA

CORAIL is a controlled, randomized Phase 3 trial (n=420) where lurbinectedin was compared to pegylated liposomal doxorubicin or topotecan in platinum-resistant ovarian cancer patients.

Pooled analysis: 335 patients in Phase 2 Basket Study with selected solid tumors (9 indications including 105 patients with SCLC) and 219 with platinum-resistant ovarian cancer in the Phase 3 CORAIL study.

Leary A, et al, ASCO2020<sup>7</sup>

# Higher ORRs Achieved Following Treatment With ZEPZELCA Than ORR Previously Reported in the Literature for a Comparable Patient Population

- Study B-005 Primary Endpoint: ORR 35.2% (95% CI: 26.2%-45.2%)<sup>2</sup>
  - 65% of patients had reduction in target lesions including 18% with CTFI < 90 days
  - ORR 45% (32.1%-58.4%) and 22% (11.2%-37.1%) in preplanned analysis by CTFI (≥ 90 days vs < 90 days or longer, respectively)
- Responses were consistent regardless of baseline characteristics, including age
  - ≥ 65 years: ORR 32.4% (18.0%-49.8%)
  - < 65 years: ORR 36.8% (25.4%-49.3%)
- After median follow-up of 17.1 months, median DOR was 5.3 months (4.1-6.4)<sup>2</sup>
  - DOR of 6.2 (3.5-7.3) months with CTFI ≥ 90 days (sensitive disease)
  - DOR of 4.7 months (2.6-5.6) with CTFI < 90 days (resistant disease)

- ORR of 35.2% is higher than reported for topotecan in three Phase 3 and one Phase 2 studies: range 16.9% to 25.0% in similar patient population<sup>14-17</sup>
- Median DOR for topotecan was reported by von Pawel et al at 4.2 months in a trial of amrubicin vs topotecan (Intent-to-treat population including subjects who were sensitive and refractory for first-line treatment)<sup>17</sup>

# Clinically Meaningful OS Rates Were Achieved With ZEPZELCA

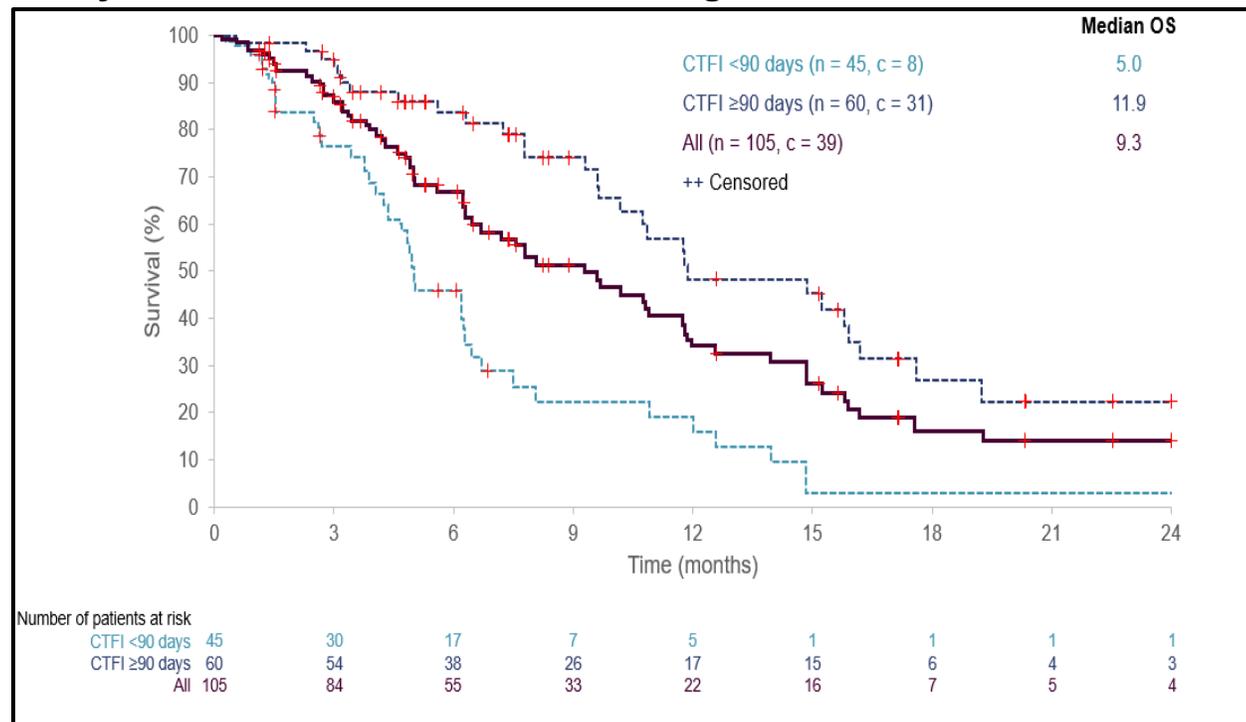
Highest OS rates reported in more than two decades for patients with metastatic SCLC whose disease progresses on or after platinum-based chemotherapy

## Study B-005: PFS and OS in Patients with SCLC

	Overall Population (n=105)	CTFI ≥ 90 (n=60)	CTFI < 90 (n=45)
Median PFS	3.5 months (2.6-4.3)	4.6 months (2.8-6.5)	2.6 months (1.3-3.9)
Median OS	9.3 months (6.3-11.8)	11.9 months (9.7-16.2)	5.0 months (4.1-6.3)
Patients alive at study end	36 (34%)	29 (46%)	7 (16%)

- Median OS among ZEPZELCA responders (37) was 12.6 months (10.8-15.8) in the overall population
  - In patients with sensitive disease: 15.8 months (10.2-not reached)
  - In patients with resistant disease: 10.9 months (6.3-14.0)
- Results for median PFS for topotecan was reported at 2.7 to 3.5 months; median OS was reported at 6.8 to 7.8 months<sup>14-17</sup>

## Study B-005: Overall Survival According to CTFI in Patients with SCLC



Trigo et al, *Lancet Oncol* 2020<sup>2</sup>

# ZEPZELCA May Represent a Valuable Alternative to Platinum Rechallenge in the Platinum-sensitive relapsed SCLC Population<sup>4,6</sup>

## Study B-005: Activity of ZEPZELCA in Second-line SCLC Patient Candidates for Platinum Rechallenge (Investigator Assessment)

	CTFI >90 days (n=60)	CTFI >180 days (n=20)
ORR (95% CI), % Confirmed Responses	45.0 (32.1-58.4)	60.0 (36.1-86.9)
DCR at 8 weeks, %	81.7 (69.6-90.5)	95.0 (75.1-99.9)
Median DOR (95% CI), months	6.2 (3.5-7.3)	5.5 (2.9-11.2)
Median OS (95% CI), months	11.9 (9.7-16.2)	16.2 (9.6-NR)
OS at 12 months (95% CI), %	48.3 (32.5-64.1)	60.9 (35.7-86.2)

CI, confidence interval; DCR, disease control rate; DOR, duration of response; ORR, objective response rate; OS, overall survival  
Subbiah V, et al, ESMO 2020; Subbiah V, et al, IASLC 2020<sup>4,6</sup>

- 60 patients with CTFI >90 days (20 patients with CTFI >180 days) pretreated with one prior platinum-based line
- Median age was 59 (range, 44-78)
- Main AEs were hematological
  - Grade 3/4 Neutropenia: 25%
  - Febrile neutropenia: 1.7%
  - Grade 3/4 anemia: 10%
  - Grade 3 fatigue: 10%

- NCCN guidelines recommend platinum rechallenge if CTFI > 180 days based on small clinical trials mostly conducted in the 1980s<sup>1</sup>
- Recent data on rechallenge with CTFI > 90 days showed ORR of 45-49% and median OS of 7.5-7.9 months<sup>16,18</sup>

## In Summary, ZEPZELCA Meets the High Unmet Need in SCLC

- ZEPZELCA is the first drug approved since 1998 as a second-line treatment option for metastatic SCLC in patients whose disease progresses while on or after platinum-based chemotherapy
- Median ORR and median OS provide clinically meaningful improvements over current therapy
- Importantly, ZEPZELCA provides substantial safety improvement over that reported for currently available therapy
- ZEPZELCA was recognized in the NCCN guidelines immediately upon FDA approval, further highlighting the significant unmet need in this patient population
- The benefit-risk profile of ZEPZELCA represents an important advancement for the treatment of metastatic SCLC for Medicare patients whose disease has progressed on or after platinum-based chemotherapy
- Additionally, ZEPZELCA has demonstrated safety and effectiveness as an alternative to platinum rechallenge

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