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Austrian Institute for
Health Technology Assessment
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# Lurbinectedin (ZEPZELCA®) in combination with atezolizumab for extensive-stage small cell lung cancer

Health Technology Assessment

Final Report

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## List of abbreviations

AE(s) .....Adverse event(s)
AIC .....Akaike Information Criterion
AIHTA .....Austrian Institute for Health Technology Assessment
AT.....Atezolizumab
AWMF .....Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
BIA .....Budget impact analysis
BSA.....Body surface area
BSC .....Best supportive care
CHEC.....Checklist for Health Economic Evaluations
CHEERS.....Consolidated Health Economic Evaluation Reporting Standards
CHMP.....Committee for Medicinal Products for Human Use
CI.....Confidence interval
CNS.....Central nervous system
CRR.....Complete response rate
CUP.....Compassionate use programme
CTCAE .....Common Terminology Criteria for Adverse Events
DNA.....Deoxyribonucleic Acid
DoR.....Duration of response
EC.....European Commission
ECOG PS .....Eastern Cooperative Oncology Group Performance Status
EMA.....European Medicines Agency
EORTC QLQ-C30 European Organisation for the Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30
EORTC QLQ-LC13 European Organisation for the Research and Treatment of Cancer Quality-of-Life Questionnaire Lung Cancer Module 13
EQ-5D-5L .....European Quality of Life 5 Dimensions-5 Level
ESMO.....European Society for Medical Oncology
ESMO-MCBS .....European Society for Medical Oncology-Magnitude of Clinical Benefit Scale
ES-SCLC .....Extensive-stage small cell lung cancer
EUnetHTA .....European Network for Health Technology Assessment
FDA .....Food and Drug Administration
G-CSF .....Granulocyte Colony-Stimulating Factor
HR.....Hazard Ratio
HRQoL .....Health-related quality of life
HTA .....Health Technology Assessment
ICD .....International Statistical Classification of Diseases and Related Health Problems
ICER .....Incremental cost-effectiveness ratio
IRF .....Independent Review Facility
IV.....Intravenous
JCA.....Joint Clinical Assessment
LALUCA .....Longitudinal Analysis of Lung Cancer Data
LC .....Lung cancer
LDH.....Lactate dehydrogenase
LKF.....Austrian hospital reimbursement catalogue — Leistungsorientierte Krankenanstaltenfinanzierung
LS-SCLC .....Limited-stage small cell lung cancer
MAH .....Marketing Authorisation Holder
MMRM .....Mixed model for repeated measures
n.a.....Not applicable
NCCN .....National Comprehensive Cancer Network
NSCLC .....Non-Small Cell Lung Cancer
OR .....Odds ratio
ORR .....Objective response rate
OS.....Overall survival
PCI .....Prophylactic cranial irradiation
PD .....Progressive disease
PD-L1 .....Programmed death-ligand 1

PRO.....Patient-reported outcome
PRO-CTCAE.....Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PF.....Progression-free
PFS.....Progression-free survival
PPRI.....Pharmaceutical Pricing and Reimbursement Information
PSA.....Probabilistic sensitivity analysis
QALY.....Quality-adjusted life year
QoL.....Quality of life
RCT.....Randomised controlled trial
RECIST 1.1.....Response Evaluation Criteria in Solid Tumours version 1.1
RoB.....Risk of Bias
R&D.....Research & Development
SCLC.....Small cell lung cancer
SF-36.....Short Form 36 Health Survey
SmPC.....Summary of Product Characteristics
SoC.....Standard of Care
TNM.....Tumour-node-metastasis
TRT.....Tumorregister Tirol
TSH.....Thyroid-stimulating hormone
US.....United States
WHOQOL-100...World Health Organization Quality of Life-100
WTP.....Willingness to pay

# Ergebnisse auf einen Blick

**Kleinzelliges Lungenkarzinom im extensiven Stadium**

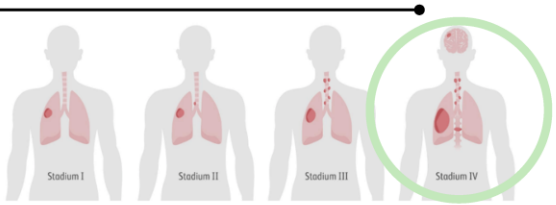
Bösartige Erkrankung der Lunge

15%

SCLC: 15% aller Lungenkrebserkrankungen, davon 60-70% zum Diagnosezeitpunkt bereits im extensiven Stadium

Tritt vor allem bei Raucher:innen auf

Wächst schnell & bildet rasch Metastasen




**Indikation von Lurbinectedin:** In Kombination mit Atezolizumab zur Erhaltungstherapie bei erwachsenen Patient:innen mit kleinzelligem Lungenkarzinom im extensiven Stadium, deren Erkrankung nach einer Erstlinien-Induktionstherapie mit Atezolizumab, Carboplatin und Etoposid keine Krankheitsprogression aufweist.

| Standardversorgung | Lurbinectedin (ZEPZELCA®) NEW |
|---|---|

**Versorgung:**
- Entsprechend der Leitlinien von Onkopedia (2025) und ESMO (2021)
- Weitere aktuelle Leitlinien: AWMF S3 (2026), NCCN (2026), konsistent mit Standard in Ö

**Erstlinie:**
- Platinbasierte Chemotherapie + Etoposid + Checkpoint-Inhibitor (bevorzugt Atezolizumab)

**Bei Therapieansprechen:**
- Erhaltungstherapie mit Checkpoint-Inhibitor (wie in der Erstlinie) bis zu Krankheitsprogression oder inakzeptabler Toxizität

**Typ des Arzneimittels:** Synthetisches Zytostatikum

**Positionierung in der Standardversorgung:** Erhaltungstherapie

**Zulassung durch die EC:** Mai 2026

**Verabreichung:**
- Intravenöse Infusion (Dauer 60 Minuten)
- 3,2 mg/m² alle 21 Tage + Atezolizumab bis zu Progression oder inakzeptabler Toxizität

**Monitoring:**
Einleitung und Überwachung der Therapie durch medizinisches Fachpersonal mit Erfahrung in der Anwendung von Krebsmedikamenten

**Wirksamkeits- & Sicherheitsanalyse**
basierend auf JCA zu Lurbinectedin

- 1 RCT (IMforte, 2025), 2 Phasen: Induktionsphase & Erhaltungsphase
  → 653 Pat. erhielten Induktionstherapie mit Carboplatin/Etoposide und Atezolizumab
  → 483 Pat. randomisiert → Lurbinectedin + Atezolizumab (n=242) vs. Atezolizumab-Monotherapie (n=241)

Ergebnisse der Erhaltungsphase für Analyse herangezogen (basierend auf zweitem Datenschnitt, 12. Februar 2025)

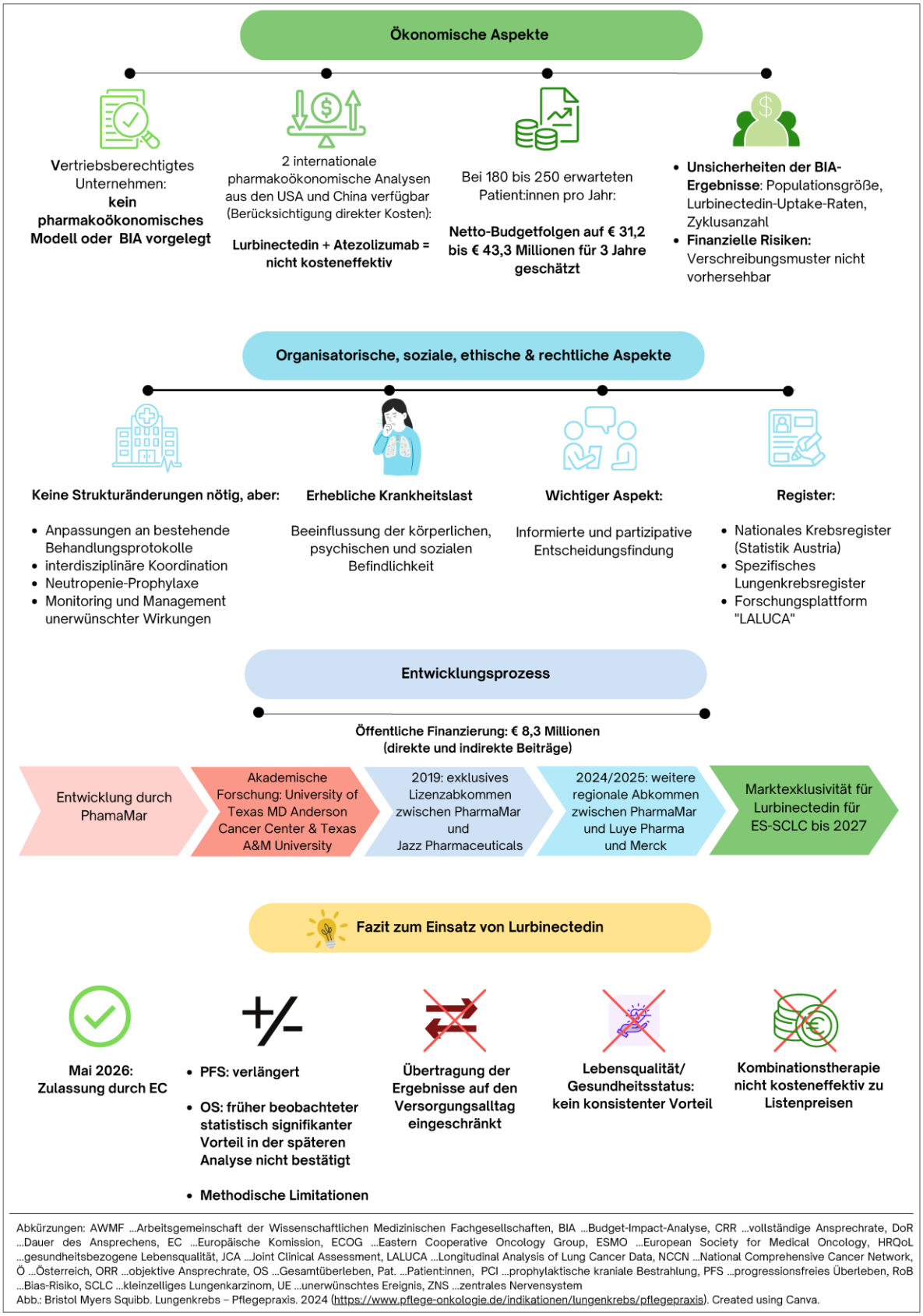
**Wirksamkeit**
- **OS:** kein statistisch gesicherter Vorteil
- **PFS**: verlängert mit Lurbinectedin + Atezolizumab
- **Ansprechrate und -dauer & Symptome:** kein gesicherter Unterschied
- **HRQoL:** kein konsistenter Vorteil der Lebensqualität für Lurbinectedin + Atezolizumab
- **Subgruppe ohne PCI und mit Lebermetastasen:** zeigt höhere Ansprechraten

**Sicherheit**

**Lurbinectedin + Atezolizumab:**
- häufiger **UEs aller Schweregrade** und Therapieabbrüche
- **häufiger UEs ⩾ Grad 3**
- **fatale UEs** numerisch häufiger, ohne statistisch gesicherten Unterschied

**Studienqualität & Limitationen**

- **RoB** insgesamt niedrig, jedoch hoch für PROs, ORR, CRR und DoR
- Änderung des statistischen Analyseplans: Möglichkeit einer früher festgestellten statistischen Signifikanz in der Interimsanalyse
- Unsicherheiten bei der Interpretation von ORR, CRR und DoR
- Daten zu HRQoL, Gesundheitsstatus und Sicherheit: Interpretation durch unterschiedliche Behandlungs- bzw. Beobachtungsdauer eingeschränkt
- Ausschluss von Patient:innen mit ECOG-PS ⩾2 und ZNS-Metastasen
- Reifere Analysen: p-Werte nominal, keine formale statistische Testung bzw. Bestätigung der Signifikanz




Abkürzungen: AWMF ...Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, BIA ...Budget-Impact-Analyse, CRR ...vollständige Ansprechrate, DoR ...Dauer des Ansprechens, EC ...Europäische Komission, ECOG ...Eastern Cooperative Oncology Group, ESMO ...European Society for Medical Oncology, HRQoL ...gesundheitsbezogene Lebensqualität, JCA ...Joint Clinical Assessment, LALUCA ...Longitudinal Analysis of Lung Cancer Data, NCCN ...National Comprehensive Cancer Network, Ö ...Österreich, ORR ...objektive Ansprechrate, OS ...Gesamtüberleben, Pat. ...Patient:innen, PCI ...prophylaktische kraniale Bestrahlung, PFS ...progressionsfreies Überleben, RoB ...Bias-Risiko, SCLC ...kleinzelliges Lungenkarzinom, UE ...unerwünschtes Ereignis, ZNS ...zentrales Nervensystem

Abb.: Bristol Myers Squibb. Lungenkrebs – Pflegepraxis. 2024 (https://www.pflege-onkologie.de/indikationen/lungenkrebs/pflegepraxis). Created using Canva.

# Zusammenfassung

Der vorliegende Health Technology Assessment (HTA)-Bericht evaluiert Lurbinectedin (ZEPZELCA®) in Kombination mit Atezolizumab zur Erhaltungstherapie bei erwachsenen Patient:innen mit kleinzelligem Lungenkarzinom im extensiven Stadium, deren Erkrankung nach einer Erstlinien-Induktionstherapie mit Atezolizumab, Carboplatin und Etoposid keine Krankheitsprogression aufweist. Lurbinectedin war Gegenstand einer gemeinsamen klinischen Bewertung (Joint Clinical Assessment, JCA), die gemäß der Verordnung über die Bewertung von Gesundheitstechnologien (Verordnung [EU] 2021/2282) durchgeführt wurde. Die Darstellung der klinischen Evidenz in diesem Bericht basiert daher auf dem JCA.

## Beschreibung der Erkrankung und Behandlungsoptionen

Das kleinzellige Lungenkarzinom (small cell lung cancer, SCLC) ist ein besonders aggressiver histologischer Subtyp des Lungenkarzinoms, der durch rasches Tumorwachstum und eine frühe Metastasierung gekennzeichnet ist. In der klinischen Praxis hat sich anstelle der üblichen Tumor-Node-Metastasis-Klassifikation (TNM-Klassifikation) ein vereinfachtes zweistufiges System etabliert: das auf einen Hemithorax begrenzte kleinzellige Lungenkarzinom (limited-stage small cell lung cancer, LS-SCLC), das mit kurativer Zielsetzung behandelt wird, und das fortgeschrittene kleinzellige Lungenkarzinom (extensive-stage small cell lung cancer, ES-SCLC), das durch eine Ausbreitung über einen Hemithorax hinaus, einschließlich Fernmetastasen, gekennzeichnet ist und mit nicht kurativer (palliativer) Zielsetzung behandelt wird. Zentrale Therapieziele beim ES-SCLC sind die Verlängerung des Gesamtüberlebens, die Krankheitskontrolle und der Erhalt der Lebensqualität. Der vorliegende Bericht konzentriert sich auf ES-SCLC. Der vorliegende Bericht konzentriert sich auf die Indikation ES-SCLC.

Die Mehrheit der Patient:innen mit SCLC (60-70 %) befindet sich bereits zum Zeitpunkt der Diagnose im fortgeschrittenen Stadium. Tabakrauchen gilt als wichtigster Risikofaktor und liegt bei nahezu allen Betroffenen vor (etwa 98 %). Die Gesamtprognose ist ungünstig; die 5-Jahres-Überlebensrate liegt unter 10 %. In Österreich wird die Prävalenz des SCLC auf etwa 2.600 Personen geschätzt. Jährlich treten rund 617 Neuerkrankungen auf, von denen 581 dem fortgeschrittenen Stadium zuzuordnen sind. SCLC-spezifische Mortalitätsdaten sind auf nationaler Ebene nicht verfügbar.

Die österreichische klinische Praxis beim ES-SCLC orientiert sich in erster Linie an den Leitlinien der European Society for Medical Oncology (ESMO) (2021) und von Onkopedia (2025), die weitgehend mit der aktuelleren Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)-S3-Leitlinie (Version 5.01, 2026) und der National Comprehensive Cancer Network (NCCN)-Leitlinie (Version 2.2026) übereinstimmen. Für Patient:innen mit einem Eastern Cooperative Oncology Group Performance Status (ECOG PS) von 0-1 und ohne Kontraindikation gegen eine Immuntherapie besteht die derzeitige Standardtherapie in der Erstlinie aus einer Induktionstherapie über vier Zyklen mit einem Platinderivat (Carboplatin oder Cisplatin), Etoposid und einem Checkpoint-Inhibitor, gefolgt von einer Erhaltungstherapie mit dem jeweiligen Checkpoint-Inhibitor bis zum Fortschreiten der Erkrankung oder bis zum Auftreten einer nicht akzeptablen Toxizität. Bei Patient:innen, die Atezolizumab als Induktionstherapie erhalten, kann Lurbinectedin im Rahmen der Erhaltungstherapie entsprechend der zugelassenen Indikation in Kombination verabreicht werden.

## Überblick über das neue Arzneimittel

Lurbinectedin ist ein neuartiges alkylierendes Zytostatikum, das als selektiver Inhibitor der onkogenen Transkription wirkt und zur Apoptose von Tumorzellen führt. Die empfohlene Dosierung beträgt 3,2 mg/m$^2$ Körperoberfläche, verabreicht als intravenöse Infusion über 60 Minuten alle 21 Tage in Kombination mit Atezolizumab, bis zum Auftreten einer Krankheitsprogression oder inakzeptabler Toxizität. Bei Abbruch von Atezolizumab aufgrund eines immunvermittelten schweren unerwünschten Ereignisses kann die Behandlung mit Lurbinectedin als Monotherapie fortgesetzt werden.

Lurbinectedin ist in Kombination mit Atezolizumab zur Erhaltungstherapie bei erwachsenen Patient:innen mit ES-SCLC indiziert, deren Erkrankung nach einer Erstlinien-Induktionstherapie mit Atezolizumab, Carboplatin und Etoposid nicht fortgeschritten ist. Am 26. März 2026 erhielt das Arzneimittel eine positive Empfehlung des Committee for Medicinal Products for Human Use (CHMP) der European Medicines Agency (EMA) und wurde am 29. Mai 2026 von der Europäischen Kommission zugelassen. Es wurde als Orphan-Arzneimittel ausgewiesen und unterliegt einer zusätzlichen Überwachung. In den USA erteilte die Food and Drug Administration (FDA) bereits am 2. Oktober 2025 eine Zulassung für dieselbe Indikation.

## Wirksamkeit und Sicherheit

Die Darstellung der klinischen Wirksamkeit und Sicherheit basiert auf dem JCA zu Lurbinectedin. Als Evidenzgrundlage wurde eine einzige klinische Studie identifiziert. IMforte ist eine globale, offene, Phase-3-randomisierte kontrollierte Studie (randomised controlled trial, RCT), in der Lurbinectedin in Kombination mit Atezolizumab versus Atezolizumab-Monotherapie als Erhaltungstherapie bei ES-SCLC untersucht wurde. Von den 660 in die Induktionsphase eingeschlossenen Patient:innen wurden 483, die nach vier Zyklen ansprachen oder eine stabile Erkrankung zeigten, randomisiert (242 vs. 241). Es liegen zwei Datenschnitte vor: der 29. Juli 2024 und der 12. Februar 2025. Aufgrund der längeren Nachbeobachtungszeit dient Letzterer als Hauptdatenquelle für das JCA. Die Baseline-Charakteristika waren weitgehend ausgeglichen, wobei die Interventionsgruppe unter anderem mehr Patient:innen < 65 Jahre umfasste.

Für den letzten präspezifizierten Datenschnitt zeigte sich unter Lurbinectedin plus Atezolizumab ein längeres, durch Prüfärzt:innen beurteiltes progressionsfreies Überleben als unter Atezolizumab allein (HR 0,56; 95%-KI: [0,46; 0,69]; p < 0,0001). Beim vorab geplanten Interimsdatenschnitt (29. Juli 2024) wurde die für das Gesamtüberleben (OS) definierte statistische Signifikanzgrenze erreicht (HR 0,73; 95%-KI 0,57-0,95; p=0,017). Im letzten vorab festgelegten Datenschnitt (12. Februar 2025) betrug der Hazard Ratio für das OS 0,81 (95%-KI 0,65-1,01), bei einem medianen OS von 13,9 gegenüber 11,1 Monaten. Auch bei der objektiven Ansprechrate zeigte sich kein statistisch gesicherter Unterschied zwischen den Behandlungsgruppen. Bei der krankheitsspezifischen Lebensqualität wurde die Zeit bis zu einer klinisch relevanten Verschlechterung (Time to Deterioration, TTD) analysiert. Eine Verschlechterung war dabei als eine Veränderung des EORTC-QLQ-C30-Scores um mindestens 10 Punkte gegenüber dem Ausgangswert definiert. Unter Lurbinectedin plus Atezolizumab war die Zeit bis zur Verschlechterung der körperlichen Funktionsfähigkeit, der Rollenfunktion sowie der Übelkeit/des Erbrechens signifikant kürzer als unter Atezolizumab allein. Für die übrigen Domänen sowie den mit dem EQ-5D-5L erfassten Gesundheitszustand ergaben sich keine signifikanten Unterschiede. In einer weiteren Analyse, in der die Entwicklung der Lebensqualität über die ersten sechs Behandlungszyklen hinweg betrachtet wurde, zeigten sich hingegen keine statistisch signifikanten Unterschiede zwischen den beiden Behandlungsgruppen.

Bei der Sicherheit zeigten sich unter Atezolizumab-Monotherapie insgesamt günstigere Ergebnisse: Unter Lurbinectedin plus Atezolizumab traten unerwünschte Ereignisse insgesamt häufiger auf, ebenso Ereignisse ab Grad 3 (vor allem hämatologische Toxizitäten), schwerwiegende unerwünschte Ereignisse sowie Therapieabbrüche und -unterbrechungen aufgrund unerwünschter Ereignisse. Auch Todesfälle im Zusammenhang mit unerwünschten Ereignissen (Common Terminology Criteria for Adverse Events, CTCAE Grad 5) waren unter Lurbinectedin plus Atezolizumab häufiger als unter Atezolizumab-Monotherapie (5,0 % vs. 2,5 %). Da sich die Behandlungs- und Beobachtungsdauer zwischen den Studienarmen unterschied, ist die Aussagekraft der einfachen Häufigkeitsvergleiche jedoch eingeschränkt.

## Ökonomische Aspekte

Das vertriebsberechtigte Unternehmen legte für Österreich kein pharmakoökonomisches Modell vor. Zwei identifizierte publizierte Kosten-Nutzwert-Analysen (Huang et al. [2025]; Zhu et al. [2026]), die beide auf der IMforte-Studie basierten, kamen unter den jeweiligen länderspezifischen Annahmen und Zahlungsbereitschaftsschwellen zu dem Ergebnis, dass Lurbinectedin plus Atezolizumab nicht kosteneffektiv ist. Die berichteten inkrementellen Kosten-Nutzwert-Verhältnisse (incremental cost-effectiveness ratios, ICERs) der Basisfallanalysen lagen in China bei etwa € 340.000 pro qualitätsadjustiertem Lebensjahr (quality-

adjusted life year, QALY) und in den Vereinigten Staaten bei etwa € 703.000-975.000 pro QALY. Damit überschritten sie die jeweiligen länderspezifischen Zahlungsbereitschaftsschwellen (willingness-to-pay thresholds, WTP-Schwellenwerte) deutlich. Zu den gemeinsamen Limitationen zählen die alleinige Stützung auf eine einzelne randomisierte kontrollierte Studie (IMforte), die Extrapolation der Überlebensdaten über den Studiennachbeobachtungszeitraum hinaus, die daraus resultierende potenzielle Verzerrung sowie die Nichtberücksichtigung gesellschaftlicher Kosten. Die Übertragbarkeit dieser Ergebnisse auf Österreich ist zudem eingeschränkt.

Darüber hinaus wurde keine Budget-Impact-Analyse (BIA) vorgelegt. Das vertriebsberechtigte Unternehmen gibt im eingereichten Dossier jedoch an, dass Lurbinectedin (ZEPZELCA®) in Österreich zu öffentlichen Listenpreisen von € 5.625 pro 4-mg-Durchstechflasche und € 3.234,38 pro 2-mg-Durchstechflasche verfügbar ist, woraus sich bei einem Median von 7 Behandlungszyklen geschätzte direkte medizinische Gesamtkosten der Kombinationstherapie von € 106.778 pro Patient:in ergeben. Davon entfallen 89 % auf die Arzneimittelbeschaffung und 11 % auf die Verabreichung. Im Vergleich dazu betragen die durchschnittlichen Kosten des derzeitigen Behandlungsstandards (Atezolizumab-Monotherapie über einen Median von 4 Zyklen) € 22.196 pro Patient:in. Bei jährlich 180-250 für Lurbinectedin infrage kommenden Patient:innen beläuft sich die Netto-Budgetauswirkung im ersten Jahr auf € 9,1-12,7 Mio. und steigt im dritten Jahr auf € 11,4-15,9 Mio., was einer kumulativen Netto-Budgetauswirkung von € 31,2-43,3 Mio. über drei Jahre entspricht. Ein Szenario, in dem die Behandlungsdauer in beiden Armen gleich lang ist (4 Zyklen, was von klinischen Expert:innen als realistischer eingeschätzt wurde), würde die Netto-Budgetauswirkung über drei Jahre auf € 14,3-19,9 Mio. reduzieren, was den ausschließlich auf Lurbinectedin als Add-on zum Behandlungsstandard entfallenden Zusatzkosten entspricht. Diese Schätzungen unterliegen einer erheblichen Unsicherheit hinsichtlich der Anzahl infrage kommender Patient:innen, der tatsächlichen Versorgungspraxis und der verfügbaren Kostendaten.

## Soziale, organisatorische, ethische und rechtliche Aspekte

Nach Einschätzung österreichischer klinischer Expert:innen kann Lurbinectedin ohne wesentliche strukturelle Änderungen in die bestehende klinische Praxis integriert werden. Organisatorische Anpassungen an bestehende Behandlungsprotokolle, interdisziplinäre Koordination, Neutropenie-Prophylaxe sowie ein umfassendes Monitoring und Management unerwünschter Wirkungen sind dennoch erforderlich. Österreichische klinische Expert:innen betonen insbesondere die Bedeutung der Schulung des Personals im Umgang mit neuen Therapien.

SCLC führt bei den betroffenen Patient:innen zu einer erheblichen Krankheitslast und beeinflusst deren körperliche, psychische und soziale Befindlichkeit. Die Perspektive von Patient:innen ist in diesem Bericht ausschließlich auf Grundlage der verfügbaren Literatur dargestellt, da es trotz intensiver Bemühungen nicht möglich war, Patient:innen für die Befragung im Rahmen des HTAs zu gewinnen. Auch im JCA zu Lurbinectedin wurden keine Patient:innen einbezogen. Die Darstellung der (kollektiven) Perspektive von Betreuenden wird durch die Beteiligung eines Mitglieds einer österreichischen Selbsthilfegruppe ermöglicht. Auf europäischer Ebene konnte im Rahmen des JCA zu Lurbinectedin ebenfalls eine betreuende Person eingeschlossen werden.

Ein wesentlicher Aspekt, der im Rahmen der Berichterstellung identifiziert werden konnte, betrifft den Entscheidungsfindungsprozess in der Therapie. Nach Einschätzung österreichischer klinischer Expert:innen ist eine offene Kommunikation über verfügbare Therapieoptionen und deren potenzielle Auswirkungen wesentlich, um Patient:innen eine informierte Entscheidungsfindung zu ermöglichen.

In Österreich werden epidemiologische Daten zu Krebserkrankungen im Nationalen Krebsregister (Statistik Austria) erfasst. Zusätzlich steht ein spezifisches Lungenkrebsregister zur Verfügung. „LALUCA“ (Longitudinal Analysis of Lung Cancer Data), eine österreichische Forschungsplattform, dokumentiert zusätzlich repräsentative Daten zu molekularen Untersuchungen, zum Ablauf der systemischen Therapie und anderer Behandlungsformen sowie zum Krankheitsverlauf bei Patient:innen mit Lungenkrebs.

## Öffentliche Investition

Lurbinectedin wurde von PharmaMar, einem spanischen pharmazeutischen Unternehmen, entwickelt. Die Entwicklung war überwiegend industriegetrieben. Die gesamten Entwicklungskosten wurden nicht öffentlich bekannt gegeben. Die identifizierbaren direkten und indirekten öffentlichen Beiträge belaufen sich auf etwa € 8,3 Mio. Diese Beiträge stammten hauptsächlich von spanischen nationalen Institutionen, darunter die Agencia Estatal de Investigación und das Centro para el Desarrollo Tecnológico Industrial, sowie indirekt von US-amerikanischen Bundesbehörden und Behörden des Bundesstaates Texas, die damit zusammenhängende Grundlagenforschung zu marinen Wirkstoffen und entsprechende klinische Studien unterstützten. Der Marktschutz umfasst ein US-Patent, dessen Ablauf für 2029 erwartet wird, sowie einen Orphan-Drug-Marktschutz bis 2027. Für eine zusätzliche Indikation könnte ein erweiterter Patentschutz bis 2032 bestehen.

## Weitere Entwicklungen (Landscape Overview)

Es wurden zehn laufende klinische Studien zu Lurbinectedin gefunden: neun zum SCLC und eine zum Blasenkrebs. Der Wirkstoff wird überwiegend in Kombination und nicht als Monotherapie untersucht, gemeinsam mit Zellgiften (Irinotecan, Topotecan), dem ATR-Hemmer Berzosertib, Strahlentherapie und mehreren Checkpoint-Inhibitoren (Atezolizumab, Durvalumab, Avelumab, Serplulimab). Damit kommt er sowohl als Erhaltungstherapie nach einer einleitenden Chemo-Immuntherapie als auch als Option bei Rückfällen über mehrere Behandlungslinien hinweg in Betracht. Getrennt davon wurden sechs Kombinationstherapien gefunden, meist monoklonale Antikörper sowie ein Antikörper-Wirkstoff-Konjugat, die für SCLC entwickelt werden, überwiegend für die Erstbehandlung, mit erwarteten Entscheidungen der Europäischen Kommission zwischen August 2028 und September 2030.

## Schlussfolgerung

Insgesamt führt Lurbinectedin plus Atezolizumab gegenüber einer Atezolizumab-Monotherapie als Erhaltungstherapie beim ES-SCLC zu einer statistisch signifikanten Verbesserung des progressionsfreien Überlebens. Der beim Interimsdatenschnitt beobachtete statistisch signifikante Vorteil im Gesamtüberleben blieb beim jüngsten Datenschnitt numerisch bestehen, fiel jedoch geringer aus und war mit größerer statistischer Unsicherheit verbunden. Eine Verbesserung der gesundheitsbezogenen Lebensqualität konnte nicht konsistent nachgewiesen werden, während unter Lurbinectedin plus Atezolizumab häufiger unerwünschte Ereignisse auftraten. Die Interpretation der klinischen Ergebnisse wird darüber hinaus durch das offene Studiendesign, Unterschiede in der Behandlungsexposition sowie die eingeschränkte Übertragbarkeit der Studienpopulation auf die klinische Routinepraxis begrenzt.

Für Österreich wurden weder ein pharmakoökonomisches Modell noch eine BIA eingereicht. Die verfügbaren internationalen gesundheitsökonomischen Bewertungen deuten darauf hin, dass Lurbinectedin plus Atezolizumab zu den derzeitigen Preisen und unter den untersuchten Annahmen wahrscheinlich nicht kosteneffektiv ist. Gleichzeitig ist die geschätzte Budgetauswirkung für Österreich erheblich und mit beträchtlicher Unsicherheit verbunden. Der Gesamtwert der Therapie wird daher davon abhängen, ob eine längere Nachbeobachtung einen Vorteil im Gesamtüberleben bestätigt, wie die Preisverhandlungen ausfallen und wie Lurbinectedin künftig in einer sich weiterentwickelnden Therapielandschaft positioniert wird.

# Summary

This health technology assessment (HTA) report evaluates lurbinectedin (ZEPZELCA®) in combination with atezolizumab for the maintenance treatment of adult patients with extensive-stage small cell lung cancer whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin and etoposide. Lurbinectedin was the subject of a Joint Clinical Assessment (JCA), conducted in accordance with the Regulation on Health Technology Assessment (Regulation (EU) 2021/2282). The presentation of the clinical evidence in this report is therefore based on the JCA.

## Disease background

Small cell lung cancer (SCLC) is a particularly aggressive histological subtype of lung cancer, characterised by rapid tumour growth and early metastatic spread. Clinically, instead of the standard tumour-node-metastasis (TNM) classification, a simplified two-stage system has become established: limited-stage SCLC (LS-SCLC), confined to one hemithorax and treated with curative intent, and extensive-stage SCLC (ES-SCLC), with spread beyond one hemithorax including distant metastases and treated with non-curative (palliative) intent. Key treatment goals in ES-SCLC are the prolongation of overall survival, disease control, and the preservation of quality of life. The present report focuses on ES-SCLC.

The majority of patients (60-70%) are already diagnosed at the ES stage. Tobacco smoking is considered the main risk factor, present in nearly all affected individuals (around 98%). The overall prognosis is poor, with a 5-year survival rate below 10%. In Austria, the prevalence of SCLC is estimated at approximately 2,600 individuals; around 617 new cases occur annually, of which 581 are attributable to the ES stage. SCLC-specific mortality data are not available at the national level.

Austrian clinical practice for ES-SCLC is guided primarily by the European Society for Medical Oncology (ESMO) (2021) and Onkopedia (2025) guidelines, which are largely consistent with the more recent Association of the Scientific Medical Societies in Germany (AWMF) S3 guideline (Version 5.01, 2026) and National Comprehensive Cancer Network (NCCN) guideline (Version 2.2026). For patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-1 and no contraindication to immunotherapy, the current standard first-line treatment is induction therapy (4 cycles) with a platinum agent (carboplatin or cisplatin), etoposide, and a checkpoint inhibitor, followed by maintenance treatment with the respective checkpoint inhibitor until disease progression or unacceptable toxicity. For patients receiving atezolizumab, lurbinectedin may be added during maintenance treatment in accordance with its approved indication.

## Overview of the new medicinal product

Lurbinectedin is a novel alkylating antineoplastic agent that acts as a selective inhibitor of oncogenic transcription, leading to apoptosis of tumour cells. The recommended dose is 3.2 mg/m$^2$ of body surface area, administered as an intravenous infusion over 60 minutes every 21 days in combination with atezolizumab, until disease progression or unacceptable toxicity occurs. If atezolizumab is discontinued due to an immune-related severe adverse event, treatment with lurbinectedin may be continued as monotherapy.

Lurbinectedin, in combination with atezolizumab, is indicated for the maintenance treatment of adult patients with ES-SCLC whose disease has not progressed following first-line induction therapy with atezolizumab, carboplatin, and etoposide. On 26 March 2026, the medicinal product received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) and was authorised by the European Commission on 29 May 2026. It has been designated an orphan medicinal product and is subject to additional monitoring. In the United States, the Food and Drug Administration (FDA) had already granted approval for the same indication on 2 October 2025.

## Clinical effectiveness and safety

The clinical evidence is based on the JCA of lurbinectedin, which included data from a single phase 3, global, open-label randomised controlled trial (RCT), IMforte. The trial evaluated lurbinectedin plus atezolizumab versus atezolizumab monotherapy as maintenance treatment for ES-SCLC. Of the 660 patients enrolled in the induction phase, 483 patients who achieved a response or had stable disease after four cycles were randomised to lurbinectedin plus atezolizumab or atezolizumab monotherapy (242 vs 241 patients). Two data cut-offs were available: 29 July 2024 and 12 February 2025. The latter, which provided longer follow-up, constituted the main data source for the JCA. Baseline characteristics were largely balanced between the treatment groups, although the intervention group included a higher proportion of patients aged under 65 years.

At the latest prespecified data cut-off, investigator-assessed progression-free survival (PFS) was statistically significantly improved with lurbinectedin plus atezolizumab compared with atezolizumab monotherapy (hazard ratio (HR) 0.56 [95% CI 0.46; 0.69]; $p<0.0001$). At the prespecified interim data cut-off (29 July 2024), the prespecified statistical significance boundary for overall survival (OS) was crossed (HR 0.73; 95% CI 0.57-0.95; $p=0.017$). At the latest prespecified data cut-off (12 February 2025), the hazard ratio for OS was 0.81 (95% CI 0.65-1.01), with a median OS of 13.9 months versus 11.1 months. No statistically significant differences were observed in objective response rate (ORR), complete response rate (CRR) or duration of response (DoR). For disease-specific health-related quality of life (HRQoL), time to deterioration (TTD) was analysed. Deterioration was defined as a change of at least 10 points in the EORTC QLQ-C30 score. The time to deterioration in physical functioning, role functioning and nausea/vomiting was statistically significantly shorter with lurbinectedin plus atezolizumab than with atezolizumab monotherapy. No statistically significant differences were observed for the remaining domains or for health status measured with the EQ-5D-5L. In a further analysis of changes in health-related quality of life over the first six treatment cycles, no statistically significant differences were observed between the two treatment groups.

Safety results favoured the atezolizumab monotherapy arm: more adverse events (AEs), grade ≥3 events (notably haematologic toxicities), serious AEs, and treatment discontinuations/interruptions occurred with lurbinectedin plus atezolizumab. Deaths due to adverse events (Common Terminology Criteria for Adverse Events [CTCAE] grade 5) were also more frequent in patients receiving lurbinectedin plus atezolizumab than in patients in the atezolizumab monotherapy group (5.0% vs 2.5%). Overall, differing treatment and observation durations between arms limit interpretability of these results.

## Economic aspects

The health technology developer (HTD) did not submit a pharmacoeconomic model for Austria. Two identified published cost-utility analyses (Huang et al. 2025; Zhu et al. 2026), both based on the IMforte trial, concluded that lurbinectedin plus atezolizumab was not cost-effective under the respective country-specific assumptions and willingness-to-pay thresholds. The reported base-case incremental cost-effectiveness ratios (ICERs) were approximately €340,000 per quality-adjusted life-year (QALY) in China and approximately €703,000-€975,000 per QALY in the United States, substantially exceeding the respective national willingness-to-pay (WTP) thresholds. Shared limitations include reliance on a single RCT (IMforte) without broader comparative evidence, extrapolation of survival beyond trial follow-up, potential bias introduced, and the exclusion of societal costs. The transferability of these findings to Austria is limited.

No budget impact analysis (BIA) was submitted by the HTD. However, the HTD stated in its dossier that lurbinectedin (ZEPZELCA®) is available in Austria at public list prices of €5,625 per 4-mg vial and €3,234.38 per 2-mg vial. This results in estimated total direct medical costs for the combination therapy of €106,778 per patient for a median of seven treatment cycles, of which approximately 89% is attributable to drug acquisition and 11% to administration. By comparison, the estimated average cost of the current standard of care, atezolizumab monotherapy for a median of four cycles, is €22,196 per patient. Assuming 180-250 eligible patients per year, the estimated net budget impact ranges from €9.1 million to €12.7 million in year 1 and from €11.4 million to €15.9 million in year 3, resulting in a cumulative three-year net budget impact of €31.2 million to €43.3 million. In a scenario assuming an equivalent treatment duration of four

cycles in both treatment groups, which clinical experts considered more realistic, the estimated three-year net budget impact decreases to €14.3 million to €19.9 million. This scenario primarily reflects the incremental cost attributable to adding lurbinectedin to the existing standard of care. These estimates are subject to considerable uncertainty regarding the number of eligible patients, treatment duration, uptake, current treatment practice and available cost data.

## Social, organisational, ethical and legal aspects

For the integration of lurbinectedin into Austrian clinical practice, no substantial structural changes are anticipated. However, organisational adjustments in line with specific treatment protocols, interdisciplinary coordination, neutropenia prophylaxis, and careful monitoring and management of AEs are essential. Austrian clinical experts highlighted in particular the importance of training personnel in the use of new therapies.

SCLC imposes a substantial burden on patients, impacting patients' physical, psychological and social well-being. For this report, information on patients' perspectives could be obtained solely from the literature. Despite intensive efforts, no eligible patients could be recruited to answer the questionnaire provided by the AIHTA. No patients were involved in the respective JCA either. The carer perspective could be captured through the involvement of one member of an Austrian support group, who provided a collective perspective on patients with lung cancer. At the European level, one carer was successfully involved.

A relevant aspect identified during the preparation of this assessment concerns the process of treatment decision-making. Austrian clinical experts emphasised the importance of openly discussing treatment options and their associated effects to enable patients to make informed decisions.

To document lung cancer cases, the Austrian National Cancer Registry collects epidemiological data. A specific lung cancer registry aims to improve treatment quality through detailed data analysis and collaboration among hospitals. In addition, the Austrian research platform "LALUCA" (Longitudinal Analysis of Lung Cancer Data) documents representative data on molecular testing, sequence of systemic treatment and other treatment modalities, and the course of disease in patients with lung cancer.

## Public investment aspect

Lurbinectedin was developed by PharmaMar, a Spanish pharmaceutical company, and its development was primarily industry-driven. Total development costs have not been publicly disclosed. Identifiable direct and indirect public contributions amount to approximately €8.3 million. These contributions originated mainly from Spanish national bodies, including the Agencia Estatal de Investigación and the Centro para el Desarrollo Tecnológico Industrial, and more indirectly from US federal and Texas state agencies that supported related basic research on marine-derived compounds and associated clinical studies. Market protection includes a US patent expected to expire in 2029 and orphan drug exclusivity until 2027, with potential additional protection for a further indication until 2032.

## Landscape overview

Ten ongoing clinical trials of lurbinectedin were identified, nine in SCLC and one in bladder cancer. Lurbinectedin is primarily being investigated in combination regimens rather than as monotherapy, including combinations with cytotoxic agents such as irinotecan and topotecan, the ATR inhibitor berzosertib, radiotherapy and several immune checkpoint inhibitors, including atezolizumab, durvalumab, avelumab and serplulimab. These trials investigate lurbinectedin both as maintenance treatment following initial chemoimmunotherapy and as a treatment option after relapse across several lines of therapy. In addition, six competing combination therapies, predominantly monoclonal antibodies and one antibody-drug conjugate, were identified in development for SCLC, mainly in the first-line setting. European Commission decisions are expected between August 2028 and September 2030.

## Conclusion

Overall, lurbinectedin plus atezolizumab provides a statistically significant improvement in PFS compared with atezolizumab monotherapy as maintenance treatment for ES-SCLC. At the latest data cut-off, the OS benefit remained numerical, but the difference was not statistically secured. The study did not demonstrate a consistent improvement in HRQoL, and treatment was associated with more frequent adverse events. Interpretation of the clinical findings is further limited by the open-label design, differences in treatment exposure and the restricted generalisability of the trial population to routine clinical practice.

No Austrian pharmacoeconomic model or BIA was submitted. Available international economic evaluations indicate that lurbinectedin plus atezolizumab is unlikely to be cost-effective at current prices under the assumptions assessed, while the estimated budget impact for Austria is substantial and subject to considerable uncertainty. Its overall value will therefore depend on the maturity of the survival data, the outcome of price negotiations and its future positioning within an evolving treatment landscape.

# 1 Introduction

The objective of this report is to evaluate the clinical effectiveness and safety, as well as the economic and organisational aspects of lurbinectedin (ZEPZELCA®) in combination with atezolizumab for the maintenance treatment of adult patients with extensive-stage small cell lung cancer whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin and etoposide for the Austrian healthcare context. Lurbinectedin was subject to a Joint Clinical Assessment (JCA) conducted under the Regulation on Health Technology Assessment (Regulation (EU) 2021/2282). Therefore, the presentation of the clinical evidence in this report is based on the JCA [1].

HTA zu Lurbinectedin für erwachsene Pat. mit ES-SCLC basierend auf JCA

## 1.1 Disease background

### Overview

Lung cancer (LC) is a primary malignant neoplasm originating in the lungs or bronchi and represents the second most common cancer diagnosis in Austria [2]. It is one of the leading causes of cancer-related death, characterised by a particularly poor prognosis and a high mortality-to-incidence ratio [3]. Histologically, approximately 78% of LC are classified as non-small cell lung cancer (NSCLC) and approximately 15% as small cell lung cancer (SCLC) [4].

LC: zweithäufigste Krebsdiagnose; 2 Hauptsubtypen: NSCLC und SCLC

SCLC is the most aggressive histological subtype, characterised by rapid tumour growth and early metastatic spread [1]. It accounts for a substantial proportion of LC-related mortality due to its highly aggressive clinical behaviour and limited curative treatment options [1].

SCLC: aggressivster Subtyp, hohe Mortalität, kaum kurative Optionen

### Classification and stages

According to the International Statistical Classification of Diseases and Related Health Problems (ICD), SCLC is coded as 2C25.1 in ICD-11 [5]. The classification of SCLC follows the tumour-node-metastasis (TNM) staging system, as applied to other solid tumours [4].

SCLC: ICD-11 2C25.1, Stadieneinteilung nach TNM-System

In clinical practice, a simplified two-stage system remains widely used due to its practical relevance for treatment decision-making. This system distinguishes between limited-stage SCLC (LS-SCLC) and extensive-stage SCLC (ES-SCLC). In general, LS-SCLC refers to disease confined to one hemithorax and encompassable within a single radiation field, whereas ES-SCLC is characterised by spread beyond one hemithorax, including distant metastases. Within the LS-SCLC, TNM stages I and II are referred to as 'Very Limited Disease', while stage III corresponds to 'Limited Disease'; the ES-SCLC designation is applied from stage IV onwards. The key clinical distinction lies in the therapeutic intent: LS-SCLC is approached with curative, whereas ES-SCLC due to its advanced stage is managed with non-curative (palliative) intent [4]. Key treatment goals in ES-SCLC are the prolongation of overall survival, disease control, and the preservation of quality of life. The latter is the focus of the present report.

zwei-Stadien-System häufig verwendet: LS-SCLC (kurativ) vs. ES-SCLC (palliativ) → Fokus des Berichts

## Clinical manifestations

ES-SCLC: respiratorische, systemische, neurologische und paraneoplastische Symptome

Patients with ES-SCLC commonly present symptoms related to either the primary thoracic tumour or metastatic disease. Frequent respiratory manifestations include a persistent cough, dyspnoea, wheezing and haemoptysis. Tumour involvement of central airways and mediastinal structures may lead to complications such as superior vena cava syndrome, dysphagia, or vocal cord paralysis due to nerve compression. Systemic manifestations such as fatigue, anorexia, and weight loss are also common, reflecting the frequently metastatic course of the disease. Neurological and paraneoplastic syndromes may also occur, arising from ectopic hormone production or immune-mediated mechanisms [1].

## Diagnosis and risk factors

60-70% der SCLC-Diagnosen im ES; Erkrankungsalter meist 60-70 Jahre

SCLC is frequently diagnosed at an advanced stage, with 60-70% of patients presenting with ES-SCLC at diagnosis, reflecting the tumour's rapid proliferation and early dissemination to distant organs [1]. The median age at diagnosis typically ranges from the mid-60s to the early 70s, with 44% of patients older than 70 years [1].

Diagnostik: Bildgebung, Histologie/Zytologie, Metastasenabklärung

The diagnostic work-up in suspected LC-cases follows sequential steps, as illustrated in Figure 1-1: imaging confirmation of a thoracic mass, complemented by laboratory investigations; histological or cytological verification of the diagnosis; and assessment of organ metastasis [4].

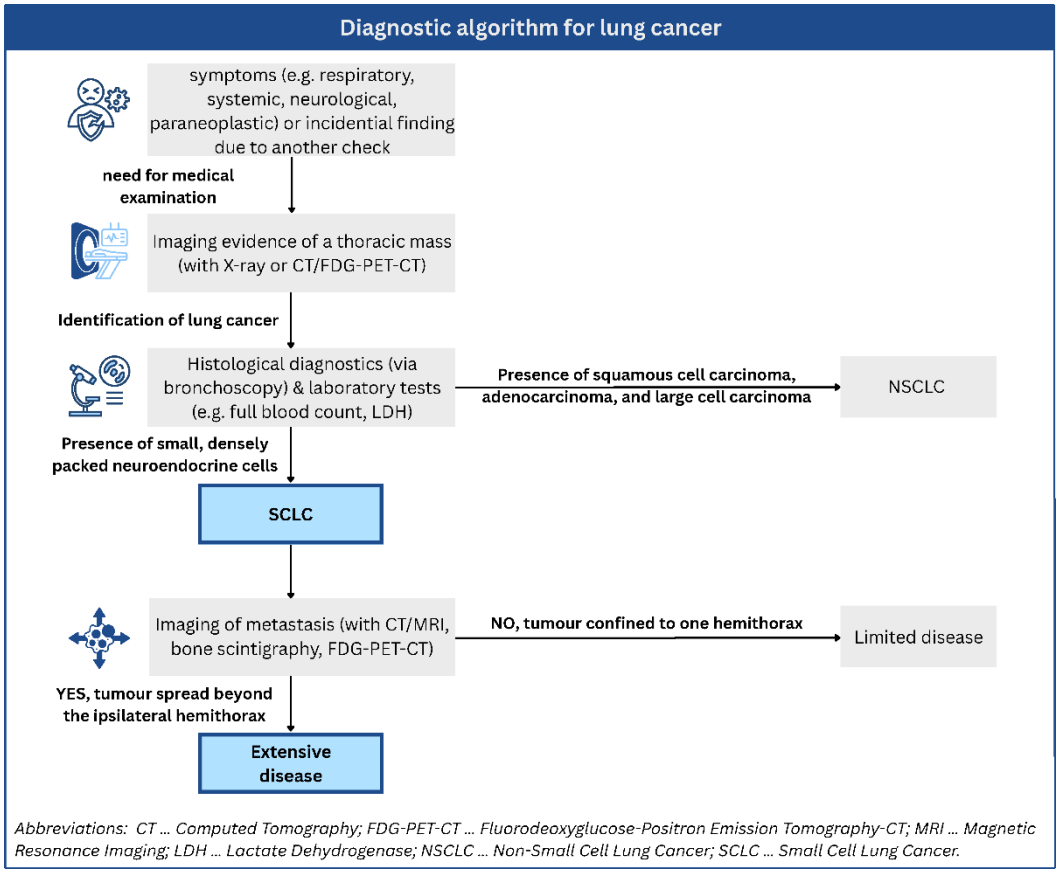



*Figure 1-1: Diagnostic algorithm for LC (own illustration based on [4]).*

### Risk factors

Hauptrisikofaktor: Tabakrauch (98 %)

Tobacco exposure represents the principal risk factor, with approximately 98% of patients having a history of tobacco smoking. Additional environmental and occupational risk factors include exposure to radon gas, ionising radiation, and air pollution [1].

### Prognosis

schlechte Prognose bei: hohem ECOG PS, hohem LDH, Metastasen (Leber, Hirn)

The prognosis of SCLC is influenced by several clinical factors. High Eastern Cooperative Oncology Group Performance Status (ECOG PS), older age, elevated lactate dehydrogenase (LDH) level, weight loss, and metastatic disease, particularly involving the liver and brain, are associated with poorer outcomes [1].

SCLC: 5-Jahres-Überlebensrate <10 %; im ES: medianes Überleben ~12 Monate mit 1L Chemoimmuntherapie

The overall prognosis remains poor, with a 5-year survival rate of less than 10% after diagnosis. In the ES, the prognosis with chemoimmunotherapy (first-line therapy) is a median survival of 12 months (1-year survival rate: 50%), a 2-year survival rate of 20-25%, and a 3-year survival rate of 15-20% [4].

### Epidemiology

Prävalenz SCLC in AT (2024): 2.600 Personen; Inzidenz in AT: ca. 617 Neuerkrankungen/ Jahr, davon 581 ES-SCLC

In Austria, the prevalence of SCLC is estimated at approximately 2,600 individuals, based on data from Statistik Austria (2024) [2] and the assumption that SCLC accounts for 15% of all LC diagnoses [4]. Prevalence is estimated to be similar among men and women. Annually, the total number of patients with SCLC in Austria is estimated at 617 cases, of whom 581 present with ES-SCLC [6].

SCLC als aggressive Lungenkrebsform mit hohem Anteil an der Lungenkrebsmortalität

Regarding mortality, LC caused an average of approximately 4,161 deaths per year in Austria between 2022 and 2024 (age-standardised rate: 43.7 per 100,000 persons) [2]. No Austria-specific epidemiological data are available to quantify the proportion of LC deaths attributable to SCLC. As mentioned above, given that SCLC represents the more aggressive form of LC [1], its proportional contribution to LC mortality is expected to be high.

## 1.2 Standard of care in Austria

Referenzleitlinie in AT: ESMO 2021 und Onkopedia 2025

According to Austrian clinical experts [7], the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for Small-Cell Lung Cancer (2021) [8] and the Onkopedia guideline (2025) [4] are used in clinical practice to manage ES-SCLC in Austria. The Onkopedia guideline, jointly authored by German and Austrian oncology societies, adapts recommendations to the Central European context and explicitly addresses the use of lurbinectedin [4]. The referred ESMO guideline is old and has not since been updated [8], which was also discussed with the clinical experts [7].

weitere aktuelle Leitlinien: AWMF S3 2026, NCCN 2026 – konsistent mit AT-Standard

The most recent international guidelines identified are: the S3 Guideline on Prevention, Diagnosis, Treatment and Follow-up of Lung Cancer (Version 5.01, April 2026[1]) from the Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) [9]; and the Clinical Practice Guidelines in Oncology: Small Cell Lung Cancer (Version 2.2026, September 2025) from the National Comprehensive Cancer Network (NCCN) [10]. Overall, the therapeutic recommendations in these international guidelines are consistent with the Austrian standard of care described by Austrian clinical experts [7].

SoC 1L ES-SCLC (ECOG 0-1): Platin/Etoposid + Checkpoint-Inhibitor

falls Atezolizumab → Erhaltungstherapie: Atezolizumab + Lurbinectedin

As illustrated in the treatment algorithm in Figure 1-2 patients with ES-SCLC typically receive systemic therapy. For patients with an ECOG PS 0-1 and no contraindication to immunotherapy, the current standard recommendation is first-line induction treatment (4 cycles) with platinum (carboplatin or cisplatin) combined with etoposide and a checkpoint inhibitor (atezolizumab, durvalumab, serplulimab or tislelizumab) followed by maintenance treatment with the respective immune checkpoint inhibitor until disease progression or unacceptable toxicity. In the case of atezolizumab, it is recommended that maintenance therapy be continued in combination with lurbinectedin, the new medicinal product under evaluation in this report. In the absence of head-to-head comparative trials, the efficacy of the available immune checkpoint inhibitors is considered to be comparable, and treatment selection is based on the treating physician's clinical judgment [7].

If immunotherapy is not recommended, contraindicated or not available, platinum-based chemotherapy remains the preferred treatment option [7].

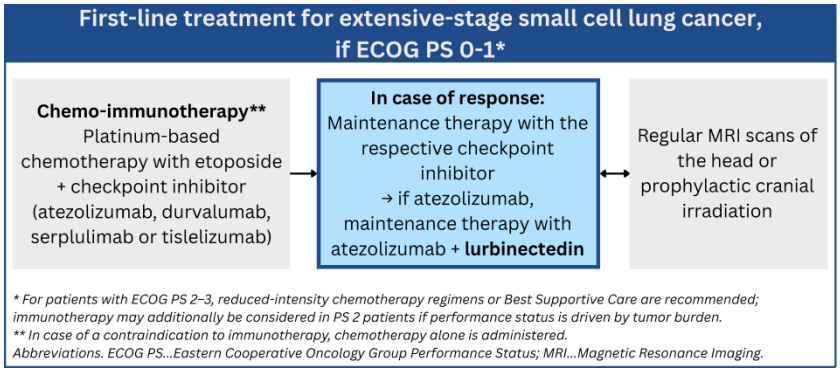



*Figure 1-2: First-line treatment for ES-SCLC (own illustration based on [4]).*

[1] At the time of the data cut-off, Version 5.01 (April 2026) was a consultation/draft. The final version, valid from 1 July 2026 onwards, is now available via: https://www.leitlinienprogramm-onkologie.de/leitlinien/lungenkarzinom/

### Follow-up care

Follow-up in ES-SCLC is comprehensive, encompassing structured and frequent follow-up visits alongside supportive measures such as smoking cessation support. The key recommendations from the AWMF guideline in this regard are summarised in Figure 1-3. These recommendations apply generally to patients with ES-SCLC receiving systemic therapy[2] [9].

umfassendes, strukturiertes Follow-up beim ES-SCLC




*Figure 1-3: AWMF guideline recommendations on structured follow-up, smoking cessation support, and response evaluation for patients with ES-SCLC receiving systemic therapy (own illustration based on [9]).*

## 1.3 Medicinal product under evaluation

The medicinal product under evaluation is lurbinectedin (ZEPZELCA®), classified as a novel alkylating antineoplastic compound [11].

Lurbinectedin: alkylierendes Zytostatikum

Lurbinectedin is a selective inhibitor of the oncogenic transcription process through:

- binding to CG-rich sequences of DNA, located within promoters of protein-coding genes;
- the eviction of oncogenic transcription factors from their binding sites and
- he stalling of elongating RNA polymerase II and its specific degradation by the ubiquitin/proteasome machinery with all these processes leading to subsequent cell cycle arrest and tumour cell apoptosis.

Wirkweise: s elektiver Inhibitor onkogener Transkription

tzusätzlich: TAM-Suppression

Lurbinectedin has a direct effect on the tumour microenvironment by modifying the immunoregulatory properties of tumour associated macrophages, significantly inhibiting the transcription of CCL2, CXCL8 and VEGF, and reducing their infiltration in human tumours implanted in mice, resulting in significant antitumour activity [1].

[2] Systemic therapy refers to treatment administered via the bloodstream to act throughout the body, as opposed to local treatment approaches such as surgery or radiotherapy.

Table 1-1 summarises the most important characteristics about this product.

*Table 1-1: Characteristics of lurbinectedin (ZEPZELCA®) [11]*

| INN | |
|---|---|
| Product name | ZEPZELCA® |
| Active substance(s) | Lurbinectedin |
| Anatomical Therapeutic Chemical (ATC Code) | L01XX69 |
| Pharmacologic class | Antineoplastic agent |
| Manufacturer/HTD | PharmaMar S.A. |

*Abbreviations: HTD … health technology developer, INN … international non-proprietary name*

## Regulatory status

EMA-CHMP: positive Opinion im März 2026

On 26 March 2026, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for lurbinectedin (ZEPZELCA®), in combination with atezolizumab, intended for the maintenance treatment of adult patients with ES-SCLC whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin and etoposide [11].

EC-Zulassung im Mai 2026

The European Commission (EC) granted marketing authorisation on 29 May 2026 [11]. Lurbinectedin (ZEPZELCA®) has been designated an orphan medicine by the EMA, as it was developed for a rare, life-threatening condition unlikely to have been developed without incentives. It is furthermore subject to additional monitoring[3], meaning that it is monitored more intensively than other medicines [11].

FDA-Zulassung im Oktober 2025

On 2 October 2025, the United States (US) Food and Drug Administration (FDA) approved lurbinectedin (Zepzelca, Jazz Pharmaceuticals, Inc.) in combination with atezolizumab (Tecentriq, Genentech Inc.) or atezolizumab and hyaluronidase-tqjs (Tecentriq Hybreza, Genentech Inc.) for the maintenance treatment of adult patients with ES-SCLC whose disease has not progressed after first-line induction therapy with atezolizumab or atezolizumab and hyaluronidase-tqjs, carboplatin, and etoposide [12].

Table 1-2 summarises the most important regulatory information about this product.

Lurbinectedin im Rahmen eines JCA bewertet, veröffentlicht am 08.07.2026

Lurbinectedin was subject to a Joint Clinical Assessment (JCA) conducted under the Regulation on Health Technology Assessment (Regulation (EU) 2021/2282). Date of endorsement by the Member State Coordination Group on HTA was 22 June 2026, and the date of conclusion of the procedural review by the European Commission was 1 July 2026. The JCA report was finally published on 8 July 2026. For an overview of the procedural steps and their dates, see JCA report [1].

[3] Additional monitoring is a regulatory pharmacovigilance measure routinely applied to new active substances and newly authorised biologics.

*Table 1-2: EMA regulatory information on lurbinectedin (ZEPZELCA®) [11]*

| Category | Status |
|---|---|
| Orphan medicinal product | Yes (EU/3/19/2143) |
| Conditional marketing authorisation | No |
| Specific obligations of the conditional marketing authorisation | No |
| Additional monitoring | Yes |
| Accelerated approval | No |
| Exceptional circumstances | No |
| ATMP | No |
| PRIME | No |
| First approved indication | Yes |
| Details of ongoing early access programs in Austria (as provided by the MAH) | Compassionate Use Program |

*Note. The compassionate use program was closed as Zepzelca® (lurbinectedin) became commercially available. At the time the report was prepared, the study was still ongoing.*

*Abbreviations: ATMP … Advanced Therapy Medicinal Products, EMA … European Medicines Agency, MAH … Marketing Authorisation Holder, PRIME … Priority Medicines by EMA*

*Note: For further details on ongoing early access programs, please refer to the submission dossier.*

## Posology and method of administration

Lurbinectedin must be reconstituted and further diluted prior to administration. The recommended dose of lurbinectedin is 3.2 mg/m$^2$ of body surface area, administered as an intravenous infusion (IV) over 60 minutes repeated every 21 days in combination with atezolizumab, until disease progression or unacceptable toxicity [13].

Dosierung: 3,2 mg/m² i. v. über 60 Min., alle 21 Tage + Atezolizumab bis Progression oder inakzeptabler Toxizität

In case atezolizumab is discontinued due to an immune-related severe adverse event, treatment with lurbinectedin may continue at its current dose as a single agent. If immune toxicity re-occurs despite discontinuation of atezolizumab, the patient will also discontinue lurbinectedin [13].

bei Abbruch Atezolizumab: Lurbinectedin-Monotherapie möglich

## Requirements for pre- and post-medication and monitoring

Prior to administration of lurbinectedin, the following medications must be infused for antiemetic prophylaxis: corticosteroids (dexamethasone 8 mg IV or equivalent) and serotonin antagonists (ondansetron 8 mg IV or equivalent) [13].

Prämedikation IV: Kortison + Antiemetikum

Following administration of lurbinectedin, primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is recommended to reduce the risk of severe neutropenia/febrile neutropenia. In addition, post-medication may include extended antiemetic therapy for up to two days: corticosteroids (oral dexamethasone 4 mg or equivalent), or serotonin antagonists (oral ondansetron 8 mg or equivalent) or metoclopramide (IV or oral 10 mg or equivalent every 8 hours) [13].

Postmedikation (bei G-CSF-Indikation): Dexamethason p. o., Ondansetron p. o. oder Metoclopramid i. v./p. o.

Special warnings and precautions for use, including monitoring, dose adjustments, and prophylactic measures, may be required in patients with conditions such as bone marrow suppression, neutropenia, hepatotoxicity, extravasation resulting in tissue necrosis, and rhabdomyolysis. For detailed information, please refer to the EMA Summary of Product Characteristics (SmPC) [13].

Warnhinweise: Knochenmarksuppression, Neutropenie, Hepatotoxizität, Extravasation, Rhabdomyolyse

## Use in specific populations

Information on the use of lurbinectedin in specific populations, derived from the EMA SmPC [13], is summarised in Table 1-3.

spezielle Populationen: Angaben laut EPAR-Fachinformation

*Table 1-3: Use of lurbinectedin (ZEPZELCA®) in specific populations [13]*

| | |
|---|---|
|  | Lurbinectedin is not recommended during pregnancy and in women of childbearing potential not using highly effective contraception.<br>Lurbinectedin is contraindicated during breastfeeding. |
|  | No dose adjustment is needed in patients aged ≥65 years. |
|  | Lurbinectedin should not be administered in patients with severe renal impairment (CrCL < 30 mL/min) or end-stage renal disease. |
|  | Lurbinectedin should not be administered in patients with elevated AST or ALT (AST or ALT > 3 × ULN). |

*Abbreviations: ALT … alanine aminotransferase, AST … aspartate aminotransferase, CrCL … creatinine clearance, ULN … upper limit of normal.*

# 2 Scope of assessment

The objective of this report is to evaluate the clinical effectiveness, safety, as well as the economic and organisational aspects of lurbinectedin (ZEPZELCA®) in combination with atezolizumab for the maintenance treatment of adult patients with extensive-stage small cell lung cancer whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin and etoposide for the Austrian healthcare context. Lurbinectedin was subject to a Joint Clinical Assessment (JCA) conducted under the Regulation on Health Technology Assessment (Regulation (EU) 2021/2282). Therefore, the clinical evidence presented in this report is based on the JCA [1].

## 2.1 Research questions

The following research questions will be answered in the present report:

- **Clinical domain:**

  In patients with ES-SCLC, is lurbinectedin in combination with atezolizumab more effective and safer compared to the current standard treatment in Austria regarding patient-relevant outcomes?

  klinische Domäne: Wirksamkeit und Sicherheit

- **Non-clinical domains:**

  What are the economic, ethical, organisational and social consequences of implementing lurbinectedin into the Austrian healthcare system?

  What were the key contributions of publicly funded research institutions and private companies in discovering and developing lurbinectedin as a therapy for extensive-stage small cell lung cancer, and how did the transfer of intellectual property rights impact the therapy's advancement through clinical trials to market authorisation?

  nicht-klin. Domänen: ökonomisch, ethisch, organisatorisch, sozial Konsequenzen, sowie öffentliche Beiträge zu Entwicklungskosten

## 2.2 PICO

The presentation of the clinical evidence in this report is based on the JCA [1], specifically on the PICO relevant to the Austrian healthcare context included in the JCA (see Table 2-1).

Einschlusskriterien für relevante klinische Studien

Regarding the non-clinical domains, relevant economic literature was included with information about lurbinectedin prices, other direct medical costs and health economic evaluations. In addition, relevant literature for the organisational, ethical and social domain as well as literature on public investment, such as information on public grants, funding and contributions, was considered.

zusätzliche Literatur für nicht klin. Bereiche berücksichtigt

*Table 2-1: Assessment scope, including the patient, intervention, comparison and outcome (PICO) question for the clinical domain*

| | |
|---|---|
| P | Adult patients with extensive-stage small cell lung cancer whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin and etoposide. |
| I | Lurbinectedin in combination with atezolizumab |
| C | Atezolizumab monotherapy |
| O | Efficacy<br>■ Overall survival<br>■ Symptoms of the disease<br>■ Progression-free survival<br>■ Objective response rate<br>■ Complete response rate<br>■ Duration of response<br>■ Patient-reported outcomes<br>■ Health-related quality of life (e.g. SF-36)<br>■ Health-related quality of life, disease specific (e.g. EORTC QLQ-C30 and EORTC QLQ-LC13)<br>■ Health status (as EQ-5D)<br>Safety<br>■ Safety outcomes according to the guidance on outcomes for JCA<br>■ Immune-related adverse events |
| Studies | - |
| Languages | - |

*Abbreviations: EORTC QLQ-C30 … European Organisation for the Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30, EORTC QLQ-LC13 … European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Lung Cancer Module 13, EQ-5D … European Quality of Life 5 Dimensions, JCA … Joint clinical assessment, SF-36 … Short Form 36 Health Survey*

*Notes: Outcomes are based on the PICO-Survey conducted in the course of the JCA [1].*

# 3 Methods

Multi-Methoden-Ansatz: EUnetHTA-Leitfragen

Daten-Cut-off: 8. Mai 2026

This health technology assessment (HTA) employed a multi-domain assessment approach, following the European Network for Health Technology Assessment (EUnetHTA) methodology (the guiding questions are provided in Chapter 3 of the Appendix) [14]. Methods for the economic, organisational and ethical aspects were tailored to address the three research questions defined in Chapter 2. For these research questions, the data cut-off was 29 May 2026. The clinical chapter and the respective methodology are based on a JCA published on 8 July 2026.

## Systematic literature search and study selection

systematische Suche durch Hersteller & Suche nach laufenden Studien durch JCA Autor:innen

The scope and the clinical chapter of this assessment are based on a JCA [1]. During the JCA, the assessor and co-assessor reviewed the appropriateness of the sources and search strategies submitted by the health technology developer (HTD). The completeness of the information retrieval results included in the HTD submission dossier was checked against searches of clinical trial registries. No additional studies were identified by the JCA assessors. Searches were conducted in three registries (ClinicalTrials.gov, EU Clinical Trials Register, and Clinical Trials Information System) on 26 November 2025. Details are provided in Appendix B of the JCA report [1].

Quellen aus dem Dossier des Herstellers

Sources provided by the HTD in the dossier:

- List of HTD-sponsored studies in the therapeutic indication for which the dossier was prepared (no status date reported by the HTD)
- Bibliographic search for lurbinectedin + atezolizumab (last search on 8 October 2025).
- Search in study registries/study results databases for ‘lurbinectedin + atezolizumab (last search on 8 October 2025)
- Search for HTA reports on lurbinectedin (last search on 8 October 2025)
- Submission files provided to the European Medicines Agency (EMA) for lurbinectedin (no date reported by the HTD).
- Search in patient registries (last search on 8 October 2025).

zusätzliche Suche nach laufenden Studien

For the preparation of this report, the information retrieval was supplemented at the national level by additional searches in three clinical trial registries (ClinicalTrials.gov, WHO-ICTRP, EU Clinical Trials) on 4 May 2026, which yielded 43 potentially relevant hits. In addition, the HTD submitted a national dossier on 8 May 2026, containing supplementary information to support the assessment of lurbinectedin in the Austrian context.

## Clinical effectiveness and safety assessment

The presentation of the clinical effectiveness and safety is based on the publicly available JCA [1].

Datenextraktion im 4-Augenprinzip

Data extraction from the JCA for this assessment was systematically performed by one reviewer (MR) and cross-checked by a second reviewer (EM).

The risk of bias (RoB) of the included clinical evidence was assessed at outcome level using the Cochrane Risk of Bias 1.0 tool [15] by the assessor and co-assessor of the JCA.

RoB 1.0-Tool in JCA angewendet

The evidence synthesis followed a narrative approach according to the JCA. Therefore, the strength of evidence was not assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [16].

keine GRADE-Bewertung

## Economic evaluation methods

To collect price information on lurbinectedin, the Austrian National Public Health Institute (Gesundheit Österreich GmbH, GÖG) was contacted. In addition, the Pharmaceutical Pricing and Reimbursement Information (PPRI) network conducted a confidential survey to gather data on the economic aspects of lurbinectedin, including pricing and managed entry agreements, across multiple European Union member states.

Preis-Infos von GÖG

Umfrage im PPRI-Netzwerk (vertraulich)

For health economic evaluations of lurbinectedin in combination with atezolizumab compared to atezolizumab monotherapy, both submissions by the HTD and published analyses would have been considered. For the latter, we screened the literature identified through manual searches via PubMed and Google Scholar.

Handsuche nach ökonomischen Analysen zu Lurbinectedin plus Atezolizumab

Besides, in accordance with the implementing regulation §4(2) of the Austrian Appraisal Board, a three-year budget impact analysis (BIA) was conducted, including the gross drug budget impact and additional administration-related costs. The following assumptions were applied:

Budgetfolgenanalyse: Abschätzung der direkten medizinischen Kosten & getroffene Annahmen:

- Patient population estimates and expected market shares were derived from published epidemiological data, the HTD dossier, and clinical expert estimates, and presented as ranges to account for the uncertainty.
  ... Ranges der epidemiologischen Daten berücksichtigt
- A payer perspective from the healthcare system was adopted for the BIA, focusing solely on direct medical costs.
  ... Gesundheitssystem-perspektive
- The available Austrian list prices for lurbinectedin were considered from the HTD dossier, and for atezolizumab from the Warenverzeichnis Apothekenverlag.
  ... verfügbare Listenpreise herangezogen
- For the cost calculations, inpatient treatment cost data from the Austrian procedure- and diagnosis-related groups (Leistungsorientierte Krankenanstaltenfinanzierung, LKF) catalogue were taken.
  ... Krankenhaus-kostendaten: LKF-Katalog
- Minor cost categories, such as pre-treatment and follow-up costs, were excluded from the analysis because the clinical experts considered them negligible relative to drug acquisition and administration costs.
  ... Kosten für Vor- & Nachbehandlungen nicht berücksichtigt
- In the base-case scenario, we considered the median number of treatment cycles reported in the clinical studies. Based on clinical expert opinion, this number was deemed too high for the intervention group. Thus, we accounted for the clinical expert estimate of treatment cycles in a scenario analysis.
  Base-Case: mediane Therapiezyklenanzahl von klinischen Studien

## Organisational, ethical and social assessment

4 Quellen: Expert:innen-Konsultationen, Informationen aus JCAs & Literaturquellen

For the organisational, ethical and social aspects assessment, data was gathered from four sources:

- Expert consultations with six leading clinicians (see Chapter 6.1 in the Appendix for details).
- Inclusion of relevant information from the JCA.
- Manual literature search.
- In addition, a search for eligible patients, carers, and/or members of patient organisations in Austria was conducted, to include their perspectives via structured patient questionnaires (see Chapter 6.2 in the Appendix for details). One member of a support group could be identified and offered a collective perspective.

kollektive Perspektive eines Mitglieds einer Selbsthilfegruppe

## Development costs and public contributions

Entwicklungskosten und öffentliche Beiträge erhoben

The methodology for assessing development costs and public contributions involved several steps:

- Identifying product origins through searches for generic/non-proprietary names and trade names.
- Searching for the earliest references to identify basic research and de-velopment support and research grants.
- Exploring databases on clinical trials and research funding.
- Examining company websites for information on funding rounds, sponsors, mergers, and acquisitions.
- Searching US Securities and Exchange Commission (SEC) reports for information on acquisitions, patents and shareholders.
- Reviewing business news sources for additional information.

Identifizierung von: generischen oder (nicht) geschützten Bezeichnungen; Produktherkunft & Grundlagenforschung; Finanzierungsrunden, Fusionen & Übernahmen

All funding amounts that were identified were converted to € using the conversion rates as of 26 May 2026 from the Austrian National Bank [17]. Any relevant information found that was not in English or German was translated using DeepL [18].

öffentliche Beiträge in € umgerechnet und Übersetzungen mittels DeepL

## Landscape overview

Überblick zu SCLC-Therapien in Entwicklung

Ongoing studies, except phase 1 studies, both active and recruiting evaluating lurbinectedin independent of origin found in ClinicalTrials.gov were shortly summarised and reported. Additionally, a landscape overview of other therapies, which are in the development for ES-SCLC was compiled using the International Horizon Scanning Initiative (IHSI) database [19].

# 4 Clinical effectiveness and safety

This chapter evaluates the clinical effectiveness and safety of lurbinectedin in combination with atezolizumab compared to atezolizumab alone for the maintenance treatment of ES-SCLC. This chapter is based on the JCA on lurbinectedin and provides an overview of the main findings. Further details are provided in the relevant sections and tables of the main JCA report [1] and the summary report [20].

## 4.1 Outcomes

Relevant outcomes for the assessment scope of the JCA were defined using the Guidance on outcomes [21] provided by the HTA Coordination Group and are presented in Table 4-1 (based on Tables 11 and 26 in the JCA).

definierte Endpunkte

*Table 4-1: Overview of outcomes requested in the assessment scope*

| Outcome | Notes | Outcome reported in the included study | Results included in the JCA report |
|---|---|---|---|
| Overall survival | According to Guidance on outcomes for JCA [21]. | yes | yes |
| Symptoms of the disease | Measured preferably by a validated instrument [1]. | yes[a] | yes[a] |
| HRQoL, generic | Measured by a validated generic questionnaire, preferably as SF-36 [1]. | no[b] | no[b] |
| HRQoL, disease-specific | Measured by validated disease-specific questionnaires, preferably as EORTC QLQ-C30 and EORTC QLQ-LC13 (details provided in the JCA Appendix C [1]). | yes | yes |
| Health status | Measured preferably as EQ-5D (details provided in the JCA Appendix C [1]). | yes | yes |
| Progression-free survival | See [21]. | yes | yes |
| Progression-free survival 2 | Defined as the time from randomisation to second objective disease progression, or death from any cause, whichever occurred first [1]. | no[b] | no[b] |
| Objective response rate | See [21]. | yes | yes |
| Complete response rate | See [21]. | yes | yes |
| Duration of response | See [21]. | yes | yes |
| Safety outcomes | According to Guidance on outcomes for JCA [21]. | | |
| Any AE | - | yes | yes |
| Serious AE | - | yes | yes |
| Severe AE (CTCAE grade ≥ 3) | - | yes | yes |
| Death related to AE (CTCAE grade 5) | - | yes | yes |
| Treatment discontinuation due to AE | - | yes | yes |
| Treatment interruption due to AE | - | yes | yes |
| Immune-related AE | - | yes | no[c] |
| PRO-CTCAE | - | yes | no[c] |

*Abbreviations: AE … adverse event, CTCAE … Common Terminology Criteria for Adverse Events, EORTC QLQ-C30 … European Organisation for the Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30, EORTC QLQ-LC13 … European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Lung Cancer Module 13, EQ-5D … European Quality of Life 5 Dimensions, HRQoL … health-related quality of life, JCA … joint clinical assessment, PRO-CTCAE … Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events, SF-36 … Short Form 36 Health Survey*

*Notes:*

[a] *a specific symptom scale was not used in the study. However, information on a number of symptoms of the disease can be derived from the specific scales of the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires used to assess disease-specific health-related quality of life.*

[b] *outcome not recorded in the study IMforte.*

[c] *Results not included in the JCA report due to methodological flaws and inappropriate analysis methods (see main JCA report).*

## 4.2 Characteristics of the included studies

1 klinische Studie

One clinical study evaluating the clinical effectiveness and safety of lurbinectedin in adults with ES-SCLC was identified. IMforte, published by Paz-Ares et al (2025), was a global, multicentre, open-label, phase 3 randomised controlled trial [22]. The results of this study are summarised and analysed in the JCA [1].

Induktionstherapie

During the enrolment phase (induction treatment, 4 cycles), patients received:

- Atezolizumab by IV infusion at a fixed dose of 1,200 mg on day 1 of each 21-day cycle;
- Carboplatin AUC 5 mg/mL/min over 30-60 minutes administered by IV infusion on day 1 every three weeks;
- Etoposide 100 mg/m$^2$ IV over 60 minutes on day 1 (following carboplatin administration), day 2 and day 3 every three weeks (details are provided in Table 15 in the JCA report).

Randomisierung zu Lurbinectedin + Atezolizumab oder Atezolizumab-Monotherapie

Patients were then randomised into one of the following treatment arms:

- Lurbinectedin 3.2 mg/m$^2$ IV with atezolizumab 1,200 mg IV once every three weeks until disease progression or unacceptable toxicity, or
- Atezolizumab 1,200 mg IV once every three weeks until disease progression or unacceptable toxicity.

2. Daten-Cut-Off als primäre Quelle für JCA

For the relevant population, two data cut-offs are available for the study IMforte (Table 4-2). The second data cut-off, being the last prespecified, is considered the main data source for the JCA report. For the first data cut-off, results for the outcomes overall survival and progression-free survival (PFS), which were controlled for multiplicity by study design, are available in the main JCA report. Independent-review facility (IRF) assessment of tumour-related outcomes was stopped after the first data cut-off, therefore only investigator-assessed PFS, objective response rate (ORR), complete response rate (CRR) and duration of response (DoR) are available for the second one (JCA Summary Report [20]).

Detailed characteristics are provided in Table 4-2 and in the main JCA report in Table 15.

*Table 4-2: Characteristics of included studies*

| Reference/ID | IMforte [22] in [1] | | |
|---|---|---|---|
| Study type and design | Phase III, global, multicentre, open-label, parallel group, superiority randomised controlled trial | | |
| Study population | Randomised phase: Adult patients with ECOG PS 0-1 and an ongoing response or stable disease per RECIST 1.1 after completion of 4 cycles of induction treatment with carboplatin, etoposide, and atezolizumab qualified for screening for the randomised phase. | | |
| Study arms and sample size | Enrolment phase (induction treatment): n=660<br>Randomised phase (maintenance treatment):<br>■ Lurbinectedin + atezolizumab: n=242<br>■ Atezolizumab: n=241 | | |
| Study duration, data cut-off(s) and locations | Enrolment: 17/11/2021 – 11/01/2024<br>Randomisation: 24/05/2022 – 30/04/2024<br>Data cut-off: 29/07/2024 (planned final analysis for IRF-based PFS and interim analysis for OS)<br>Data cut-off: 12/02/2025 (planned final analysis for OS)<br>Study completion (estimated): 13/08/2026<br>Location: 96 centres across 13 countries (Belgium, Germany, Greece, Hungary, Italy, Mexico, Poland, Republic of Korea, Spain, Taiwan, Turkey, United Kingdom, United States) | | |
| Study endpoints | Primary endpoint:<br>■ IRF-assessed PFS<br>■ OS | Key secondary outcomes:<br>■ Investigator-assessed PFS<br>■ IRF-assessed confirmed ORR<br>■ Investigator-assessed confirmed ORR<br>■ IRF-assessed DoR<br>■ Investigator-assessed DoR<br>■ PFS rates at 6 and 12 months (investigator- and IRF-assessed)<br>■ OS rates at 12 and 24 months<br>■ Time to confirmed deterioration in physical functioning (EORTC QLQ-C30)<br>■ Time to confirmed deterioration in global health status/quality of life (EORTC QLQ-C30)<br>■ Safety | Exploratory endpoints:<br>■ HRQoL (change from baseline in physical functioning and global health status as assessed by EORTC QLQ-C30)<br>■ HRQoL (change from baseline as assessed by EORTC QLQ-LC13)<br>■ Health status (change at specified timepoints in EQ-5D-5L scores)<br>■ Safety |

*Abbreviations: DoR … duration of response, ECOG PS … Eastern Cooperative Oncology Group Performance Status, EORTC QLQ-C30 … European Organisation for the Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30, EORTC QLQ-LC13 … European Organisation for the Research and Treatment of Cancer Quality-of-Life Questionnaire Lung Cancer Module 13, EQ-5D-5L … European Quality of Life 5 Dimensions-5 level, HRQoL … health-related quality of life, IRF … Independent review facility, n … number, ORR … objective response rate, OS … overall survival, PFS … progression-free survival, RCT … randomised controlled trial, RECIST 1.1 … Response Evaluation Criteria in Solid Tumours version 1.1*

## 4.3 Study population

483/660 Pat. randomisiert

Of the 660 patients enrolled in the induction treatment phase, 653 received induction treatment with atezolizumab, carboplatin and etoposide. Overall, 571 patients completed four cycles of this treatment, and 483 of these patients with an ongoing response to the induction treatment or stable disease were subsequently randomised to one of the two maintenance treatments.

### Patient baseline characteristics

größtenteils ausgeglichene Pat.- und Krankheitsmerkmale

mehr Pat. < 65 Jahre in Interventionsgruppe

Demographic and disease characteristics at baseline were largely balanced between the treatment groups (see Table 4-3). There were some imbalances regarding the distribution of patients aged <65 years and ≥65 years at randomisation, as well as for primary tumour stage and the occurrence of distant metastases at enrolment. More patients <65 years of age were randomised to the intervention group than to the comparator group (48.8% vs 37.3%), and fewer patients in the intervention group had a stage T4 primary tumour (50.8%) vs 58.8%) or distant metastases of stage M1C (47.5% vs 58.9%). The majority of patients had a partial response to induction treatment (85.0% vs 88.7%) [1].

Beobachtungszeit variierte zwischen den Behandlungsarmen

Treatment duration was short compared to the total observation period of the study: The mean duration for the treatment with lurbinectedin was 6.2 months (±5.7), the intervention group received atezolizumab for 6.3 months (mean, SD ±5.7), while the control group received it for 4.4 months (mean, SD ±5.7). The main reason for treatment discontinuation in both treatment groups was disease progression (approx. 80% in the intervention group vs 89% in the comparator group (JCA, Table 24). As the median time to progression differs considerably between the treatment groups (5.55 months vs 2.73 months for investigator-assessed PFS; JCA, Table 27), the differences in treatment duration mainly reflect these differences in time to progression.

Since data collection for PROs and safety outcomes was tied to the study treatment, the duration of observation for these outcomes also differed between treatment groups, with longer observation in the intervention group (further details in the main JCA report, Tables 16 & 17) [1].

Induktions- und Erhaltungsphase

The IMforte trial used a two-phase design with different eligibility criteria at each stage: All patients enrolled entered the induction phase. Only patients who completed all four induction cycles (carboplatin, etoposide, and atezolizumab) without disease progression were eligible to proceed to the randomised maintenance phase, where lurbinectedin plus atezolizumab was compared against atezolizumab alone. Inclusion and exclusion criteria for the maintenance phase are provided in Table 4-4, for details and inclusion criteria for the induction phase see [22].

*Table 4-3: Baseline demographics of participants in the IMforte study*

| Characteristic | IMforte [22] in [1] | |
|---|---|---|
| Parameter | Lurbinectedin + atezolizumab (n=242) | Atezolizumab (n=241) |
| Age [years], mean (SD) | 65.1 (7.6) | 66.0 (8.0) |
| Female, n (%) | 91 (37.6) | 90 (37.3) |
| Male, n (%) | 151 (62.4) | 151 (62.7) |
| Asia-Pacific, n (%) | 30 (12.4) | 31 (12.9) |
| Europe and Middle East, n (%) | 194 (80.2) | 190 (78.8) |

| Characteristic | IMforte [22] in [1] | |
|---|---|---|
| Parameter | Lurbinectedin + atezolizumab (n=242) | Atezolizumab (n=241) |
| North America, n (%) | 14 (5.8) | 17 (7.1) |
| Central and South America, n (%) | 4 (1.7) | 3 (1.2) |
| Tobacco use history, n (%) | | |
| Never | 7 (2.9) | 5 (2.1) |
| Current | 88 (36.4) | 73 (30.3) |
| Previous | 147 (60.7) | 163 (67.6) |
| ECOG PS, n (%) | | |
| 0 | 101 (41.7) | 93 (38.6) |
| 1 | 141 (58.3) | 148 (61.4) |
| Primary tumour stage, n (%) | | |
| T3 | 58 (24.0) | 32 (13.4)* |
| T4 | 123 (50.8) | 140 (58.8)* |
| Prior receipt of PCI, n (%) | | |
| Yes | 34 (14.0) | 37 (15.4) |
| No | 208 (86.0) | 204 (84.6) |
| LDH (eCRF), n (%) | | |
| ≤ULN | 176 (72.7) | 179 (74.3) |
| >ULN | 66 (27.3) | 62 (25.7) |

*Abbreviations: ECOG PS … Eastern Cooperative Oncology Group Performance Status, eCRF … electronic case report form, LDH … lactate dehydrogenase, n … number, PCI … prophylactic cranial irradiation, SD … standard deviation, ULN … upper limit of normal*

*Note: * Percentages for primary tumour stage are based on patients with available data (n=238 in the atezolizumab arm).*

*Table 4-4: Inclusion and exclusion criteria for maintenance phase*

| Eligibility criteria | IMforte [22] |
|---|---|
| Inclusion criteria | ■ Patients with ongoing complete/partial response or stable disease after completion of four cycles of induction treatment.<br>■ Adult patients with an ECOG PS of 0 or 1.<br>■ Randomised within five weeks (35 days), from the day of the administration of the last dose of atezolizumab, carboplatin or etoposide. Participants receiving PCI must be randomised within nine weeks (63 days) from the last dose of induction treatment.<br>■ Toxicities attributed to prior induction anti-cancer therapy or PCI must have resolved to Grade 1 or better.<br>■ Adequate haematologic and end-organ function obtained within seven days prior to randomisation into the maintenance phase. |
| Exclusion criteria | ■ Patients with a presence or a history of CNS metastases.<br>■ Consolidative chest radiation.<br>■ Uncontrolled tumour-related pain.<br>■ Lesions (e.g., bone metastases) requiring palliative radiotherapy.<br>■ Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures.<br>■ Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, and inherited liver disease, or current alcohol abuse. |

*Abbreviations: CNS … central nervous system, ECOG PS … Eastern Cooperative Oncology Group Performance Status, PCI … prophylactic cranial irradiation*

# 4.4 Results on relative effectiveness and safety

## 4.4.1 Clinical effectiveness outcomes

Wirksamkeitsergebnisse

A concise overview of effectiveness results is provided in Table 4-5 below. Unless otherwise stated, results refer to the last prespecified data cut-off of 12 February 2025. P-values for this data cut-off were nominal and should therefore be interpreted descriptively (for details see Tables 27-29 in the main JCA report [1]).

### Overall survival

kein stat. gesicherter Vorteil im Gesamtüberleben beim späteren Datenschnitt

Overall Survival (OS) did not differ statistically significantly between the lurbinectedin plus atezolizumab and atezolizumab monotherapy groups (HR 0.81 [95% CI 0.65; 1.01], nominal p=0.0605). Further details are provided in Table 27 of the main JCA report [1].

### Progression-free survival

stat. sign. längeres PFS in der Interventionsgruppe

Investigator-assessed PFS results show a statistically significant increase in PFS in favour of lurbinectedin plus atezolizumab over atezolizumab (HR 0.56 [95% CI 0.46; 0.69], p < 0.0001, second data cut-off, 12 February 2025). IRF-assessed PFS was only observed until the first data cut-off (29 July 2024) and also favoured lurbinectedin plus atezolizumab (see Table 32 in the main JCA report). Detailed relative efficacy results from the IMforte trial for the PFS outcome are presented in Tables 27 and 32 of the main JCA report [1].

### Overall response rate, complete response rate and duration of response

kein stat. sign. Unterschied in der Ansprechrate und -dauer

Investigator-assessed overall response rate (ORR), complete response rate (CRR) and duration of response (DoR) did not differ statistically significantly between treatment groups (ORR: RR 1.42 [0.91; 2.20], p=0.1197; CRR: RR 1.03 [0.15; 7.01], p=0.9764; DoR: HR 1.34 [95% CI 0.67; 2.69], p=0.4135). Relative efficacy results for the outcome ORR and CRR are presented in Table 28, and results for DoR are presented in Table 27 of the main JCA report [1].

### Symptoms of the disease

kein stat. sign. Unterschied bezgl. Symptome

The results of the symptoms were included in the EORTC QLQ-C30 and -LC13 questionnaires, showing no statistically significant differences between study groups (see Table 4-5) [1].

### Health-related quality of life

#### Generic

generische Ergebnisse nicht verfügbar

Relative effectiveness results were not available for generic health-related quality of life.

### Disease-specific

HRQoL: stat. sign. höhere Verschlechterungsrate in der Interventionsgruppe bei 3 Subskalen

Relative efficacy results for health-related quality of life (HRQoL, including symptoms of the disease) assessed via the questionnaires EORTC QLQ-C30 and EORTC QLQ-LC13 are presented in Table 27 (time-to-event analysis) and Table 29 (change from baseline) of the main JCA report. Time-to-confirmed deterioration analyses[4] showed a statistically significantly higher rate of deterioration with lurbinectedin plus atezolizumab than with atezolizumab monotherapy for the scales of physical functioning, role functioning, and nausea and vomiting. The results of the mixed-model for repeated measures (MMRM) analyses, including data up to Cycle 6, do not show statistically significant differences between the intervention and control groups on any scale (Table 4-5) [1].

### Health status (EQ-5D-5L)

kein. stat. sign. Unterschied bezgl. Gesundheitsstatus

Relative effectiveness results for health status assessed via EQ-5D-5L are presented in Table 27 of the main JCA report (time-to-event outcome) and Table 29 (continuous outcome). Neither the responder analyses on the time to first deterioration nor the MMRM analyses (including data up to Cycle 6) show any statistically significant differences between the intervention and the control group for any of the scales [1].

*Table 4-5: Selected clinical effectiveness results of the IMforte trial*

| Study reference/ID | IMforte trial [22] in [1] | | | |
|---|---|---|---|---|
| Outcome measure (data cut-off: 12 February 2025) | Lurbinectedin + Atezolizumab<br>Median time to event in months [95% CI]<br>Patients with event n (%) | Atezolizumab<br>Median time to event in months [95% CI]<br>Patients with event n (%) | HR [95% CI] | p-value |
| Overall survival | 13.90 [12.26; 16.13]<br>159 (65.7) | 11.14 [10.12; 13.01]<br>169 (70.1) | 0.81 [0.65; 1.01] | 0.0605 |
| Investigator-assessed PFS | 5.55 [4.50; 6.77]<br>204 (84.3) | 2.73 [2.53; 2.83]<br>217 (90.0) | 0.56 [0.46; 0.69] | <.0001 |
| Investigator-assessed DoR | 6.41 [4.37; 13.18]<br>27 (65.9) | 11.93 [8.38; NE]<br>15 (53.6) | 1.34 [0.67; 2.69] | 0.4135 |
| Investigator-assessed ORR | NA<br>41 (20.0) | NA<br>28 (13.7) | RR 1.42 [0.91; 2.20] | 0.1197 |
| Investigator-assessed CRR | NA<br>2 (1.0) | NA<br>2 (1.0) | RR 1.03 [0.15; 7.01] | 0.9764 |
| Global health status/QoLa | 9.101 [6.965; NE][b]<br>99 (40.9) | 17.413 [11.565; NE]<br>74 (30.7) | 1.263 [0.922; 1.731] | 0.1455 |
| Physical functioninga | 15.934 [9.101; NE][b]<br>82 (33.9) | NE [NE; NE]<br>51 (21.2) | 1.583 [1.106; 2.264] | 0.0113 |
| Role functioninga | 8.575 [5.684; 13.010][b]<br>103 (42.6) | NE [9.002; NE]<br>71 (29.5) | 1.406 [1.032; 1.915] | 0.0300 |
| Nausea and vomitinga | NE [17.084; NE][b]<br>68 (28.1) | NE [NE; NE]<br>42 (17.4) | 1.641 [1.109; 2.427] | 0.0124 |

[4] Confirmed clinically meaningful deterioration is defined as a decrease of ≥10 points from baseline in a given EORTC scale, sustained at two consecutive assessment, or an initial decrease of this magnitude followed by cancer-related death within six weeks of the last recorded PRO assessment (JCA Table 25 [1])

*Abbreviations: CI … confidence interval, CRR … complete response rate, DoR … duration of response, HR … hazard ratio, n … number, NA … not applicable, NE … not estimable, ORR … objective response rate, PFS … progression-free survival, QoL … quality of life, RR … risk ratio*

*Notes:*

*Table shows OS/PFS/ORR/DoR/Global health status plus the only 3 of 30 QoL/symptom scales reaching nominal p<0.05 for time-to-deterioration; MMRM change-from-baseline analyses showed no statistically significant difference for any QoL scale, and these p-values are not multiplicity-adjusted; relative effectiveness results for PFS2 and generic HRQoL not available; Symptoms of the disease are included in the EORTC QLQ-C30 and -LC13 questionnaires; further details provided in the JCA summary report Table 7*

[a] *EORTC QLQ-C30*

[b] *time-to-confirmed deterioration*

### Subgroup analyses

Subgruppenanalysen

The assessment scope (Table 12, JCA) requested subgroup analyses for three characteristics: prior receipt of PCI, presence of brain metastases, and presence versus absence of measurable disease at baseline (complete response vs partial response/stable disease after induction). A subgroup analysis for brain metastases could not be performed, as patients with current or prior CNS metastases were excluded from the trial. To address the two remaining requested subgroups for the prespecified data cut-off (12 February 2025), the HTD provided analyses on patients with prior receipt of PCI at enrolment and on patients with a complete response vs partial response or stable disease after induction treatment [1].

To address the requested subgroups for the prespecified data cut-off (12 February 2025), the HTD provides analyses on patients with prior receipt of prophylactic cranial irradiation (PCI) at enrolment and on patients with a complete response vs partial response or stable disease after induction treatment.

stat. sign. höhere Ansprechrate bei Pat. ohne PCI und bei Lebermetastasen

For investigator-assessed ORR, subgroup analyses showed significant interactions between treatment and prior PCI receipt, ethnicity, and liver metastases. In the main analysis, the results for this outcome do not show statistically significant interactions between the intervention and the control group (see Table 28 in the JCA). This is also the case for patients of either ethnicity, despite a significant interaction for this characteristic. In contrast, statistically significantly higher response rates were observed with lurbinectedin plus atezolizumab than with atezolizumab monotherapy, both in patients not receiving PCI and in those with liver metastases (see JCA, section 4.3.1.3.2.2) [1].

## 4.4.2 Safety outcomes

unterschiedlich. Dauer der Beobachtungszeit

According to the JCA, relevant differences in the duration of observation between the treatment groups were observed for safety outcomes in IMforte (see section 4.2.1.4 in the JCA). In the dossier, the HTD provided time-to-event analyses for almost all safety outcomes, accounting for these differences (except Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events, PRO-CTCAE) [1].

Werte des 2. Daten-Cut-Offs wurden als relevant gewertet

In addition, for the first data cut-off, the HTD also provides risk ratio (RR), risk difference (RD) and odds ratio (OR) as effect estimates for these outcomes. These data are not used in the JCA because the second rather than the first data cut-off was considered relevant for the assessment, and because the RR, RD and RO were considered potentially less valid due to the differences in the duration of observation for AEs [1].

According to the JCA, immune-related AE and PRO-CTCAE were not considered comprehensive enough.

## Adverse events and serious adverse events

### AEs of all grades – general overview

mehr unerwünschte Ereignisse und Therapieabbrüche in der Interventionsgruppe

Overall, more AEs in general, severe and serious AEs occurred in the intervention group compared to the control group. Furthermore, treatment was discontinued or interrupted more often in the intervention group compared to the control group (Table 4-6). However, the duration of observation differed between the treatment groups for safety outcomes in the IMforte study, which limits the interpretability of the results. Descriptive safety outcomes are presented in detail in Table 30 of the JCA. Time-to-event analyses for safety outcomes accounting for these differences are shown in the main JCA report (Appendix C.3.1) [1].

*Table 4-6: Descriptive safety outcomes of the IMforte trial [22] in [1]*

| Study reference/ID | IMforte trial, n (%) | |
|---|---|---|
| Adverse event | Lurbinectedin + atezolizumab (n=242)a | Atezolizumab (n=240)a |
| Any AE | 235 (97.1) | 196 (81.7) |
| Severe AE (CTCAE grade ≥3) | 112 (46.3) | 65 (27.1) |
| Grade 3 | 103 (42.6)[b] | 51 (21.3)[b] |
| Grade 4 | 29 (12.0)[b] | 12 (5.0)[b] |
| Death related to AE (CTCAE grade 5) | 12 (5.0) | 6 (2.5) |
| Serious AE | 83 (34.3) | 43 (17.9) |
| Treatment discontinuation due to AE | 17 (7.0) | 10 (4.2) |
| Treatment interruption due to AE | 100 (41.3) | 38 (15.8) |

*Abbreviations: AE … adverse event, CTCAE … Common Terminology Criteria for Adverse Events, n … number*

*Notes:*

[a] *safety analysis set*

[b] *The values reported in the dossier do not align with those reported in the safety update document, which lists grade 3 AE as 76 (31.4) vs 48 (20) and grade 4 AE as 24 (9.9) vs 11 (4.6). According to the individual patient data the HTD provided for the study IMforte, both numbers are correct. In the safety update only the AE of the highest CTCAE grade per patient is counted. In the dossier, the HTD presents all patients with AEs of the respective CTCAE grade regardless of events of a higher grade occurring in the same patients.*

### Grade ≥3 adverse events

stat. sign. mehr Grad 3 unerwünschte Ereignisse in der Interventionsgruppe

AEs of grade 3 or higher occurred in statistically significantly more patients who received the combination of lurbinectedin and atezolizumab, notably diseases of blood and lymphatic system, including anaemia, neutropenia and thrombocytopenia (Table 4-7; JCA, Table 39 [1]).

*Table 4-7: Grade ≥3 adverse events occurring in at least 5% of patients in either group or yielding statistical significance between groups [22] in [1]*

| Study reference/ID | IMforte trial, n (%) | | | |
|---|---|---|---|---|
| Adverse event | Lurbinectedin + atezolizumab (n=242) | Atezolizumab (n=240) | HR [95% CI] | p-value |
| Blood and lymphatic system disorders | 43 (17.8) | 4 (1.7) | 10.345 [3.707; 28.864] | <.0001 |
| Anaemia | 23 (9.5) | 2 (0.8) | 10.512 [2.474; 44.669] | <.0001 |
| Neutropenia | 12 (5.0) | 1 (0.4) | 11.006 [1.428; 84.838] | 0.0039 |
| Thrombocytopenia | 11 (4.5) | 1 (0.4) | 10.049 [1.294; 78.020] | 0.0065 |
| General disorders and administration site conditions | 16 (6.6) | 9 (3.8) | 1.481 [0.651; 3.374] | 0.3463 |
| Infections and infestations | 23 (9.5) | 16 (6.7) | 1.240 [0.652; 2.357] | 0.5109 |
| Metabolism and nutrition disorders | 19 (7.9) | 12 (5.0) | 1.346 [0.650; 2.789] | 0.4220 |
| Respiratory, thoracic and mediastinal disorders | 15 (6.2) | 6 (2.5) | 2.112 [0.815; 5.475] | 0.1158 |

*Abbreviations: HR … hazard ratio, n … number*

*Note: Only adverse events occurring in ≥5% of participants in at least one study arm, or with a statistically significant between-group difference, are reported. For a complete listing of adverse events, refer to Appendix C of the JCA report [1].*

### Deaths (AEs of Grade 5) and treatment discontinuation

mehr Todesfälle in der Interventionsgruppe

At the time of the second data cut-off 215 (88.8%) patients in the intervention group and 219 patients (91.3%) in the control group discontinued from treatment, mainly due to progressive disease (79.5% vs 88.6%). Treatment discontinuation due to death affected 16 (7.4%) patients in the intervention group and 6 (2.7%) in the control group (details are provided in Table 24 in the main JCA report). Twelve (5%) deaths in the IG and six (2.5%) in the CG were related to AEs (Table 4-6) [1].

## 4.4.3 ESMO-MCBS scorecard for lurbinectedin

ESMO-MCBS Score 3

According to the European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS), lurbinectedin was rated with a score 3, indicating that it has a clinical benefit with a statistically significantly higher OS, however QoL data is pending, and there is an increased toxicity as well as mortality. The results of the ESMO-MCBS are based on the first data cut-off (29 July 2024), which is why the outcomes may differ from the ones presented previously. A short summary can be found in Table 4-8 [23].

*Table 4-8: ESMO-MCBS of lurbinectedin [23]*

| Scale | Int. | Form | MG ST | MG | HR (95% CI) | Score calculation | PM | Toxicity | QoL | AJ | FM |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Original | Non-curative | 2a | OS: 10.6 months | OS: +2.6 months | 0.73 (0.57-0.95) p=0.017 | HR ≤0.65 AND gain ≥2-3 months | 3 | Increased toxicity. Mortality 5% (3% more than control) | Pending data | Pending data | 3 |

*Abbreviations: AJ … adjustment, CI … confidence interval, ESMO-MCBS … European Society for Medical Oncology-Magnitude of Clinical Benefit Scale, FM … final magnitude of clinical benefit grade, HR … hazard ratio, Int … intention, MG … median gain, OS … overall survival, PM … preliminary grade, PR … partial response, QoL … quality of life, ST … standard treatment*

## 4.5 Certainty of the evidence

### 4.5.1 Risk of bias

Gesamt-RoB: niedrig

RoB für PROs, ORR, CRR; DoR hoch

The overall RoB for the study results of IMforte caused by aspects affecting the effect estimates of all outcomes is considered low. On the level of the results for individual outcomes, RoB is considered low for overall survival and PFS. For the PROs, investigator-assessed ORR, CRR, DoR and all safety outcomes the RoB is considered high (see JCA Table 19) [1]. The main reasons included the open-label design, outcome-specific measurement limitations, post-randomisation selection for DoR, missing or informatively censored PRO data, and differences in observation periods for safety outcomes [1].

The RoB was also assessed for results on multiplicity-controlled outcomes at the first data cut-off (29 July 2024) resulting in unclear (OS) and low (IRF assessed PFS and investigator-assessed PFS) overall RoB. Details are provided in Table 20 of the main JCA report.

Further limitations are provided on pages 80, 81 and 82 in the main JCA report, mainly focusing on the definitions and analyses for ORR, CRR and DoR [1].

### 4.5.2 Statistical analysis and inconsistencies

Änderung der stat. Analyse – frühere stat. Signifikanz dadurch möglich

For the interim analysis of overall survival in the IMforte trial, an O'Brien-Fleming boundary was pre-specified but at a later stage replaced with a Hwang-Shih-DeCani α-spending function with $\gamma$=-1.5. This amendment shifts α to earlier time points, meaning earlier analyses carry more liberal significance thresholds. According to the study protocol, the amendment was justified by the need to mitigate the impact of non-protocol anticancer treatments after discontinuation of study treatment on overall survival. The stated justification is methodologically invalid, as α-spending functions are instruments for controlling the type 1 error rate across multiple analyses, not for controlling post-randomisation bias. The actual effect of the amendment is that statistical significance could be declared earlier on the basis of comparatively limited event data, and the late timing of the amendment does not exclude that emerging trial information influenced this decision [1].

Details on the statistical methods of the IMforte trial are provided in section 4.3.1.2.3 in the JCA. These include the methodology for time-to-event analyses and continuous analyses of PROs, handling of missing data as well as outcome-specific aspects and the subgroup analysis [1].

### 4.5.3 Uncertainties and limitations according to the JCA

Unsicherheiten in der Studie:

Analyse von ORR & CRR

The following uncertainties applied to specific outcomes assessed in the study IMforte [1]:

- The analyses for ORR and complete response rate are based exclusively on patients with measurable disease at randomisation. As absence of measurable disease and complete response are not synonymous under RECIST 1.1, patients without measurable disease at baseline could potentially still achieve a complete response during maintenance treat-

ment. The results may therefore not be meaningful for patients without measurable disease at baseline.

- The analysis of the outcome DoR is not randomised, as it is based on patients with a response during the course of the randomised study phase. The results are therefore potentially biased. — Analyse DoR
- For the outcomes disease-specific HRQoL and health status, data collection was tied to the end of the treatment period. As treatment duration was notably longer in the intervention group than in the comparator group, the observation period for these outcomes differed substantially between groups. Conclusions on the comparison between groups are therefore limited to the respective, differing observation periods and should be interpreted with caution. — Daten für HRQoL, Gesundheitsstatus und Sicherheit: unterschiedl. Behandlungsende in den Gruppen
- For safety outcomes, data collection was also tied to the end of the treatment period. Conclusions on the comparison between the intervention and control groups can only be drawn for this shortened observation period.
- The study population of IMforte does not cover the entire population of the full claimed indication. Patients with an ECOG PS of 2 or higher were excluded from the study, as were patients with CNS metastases at baseline or a history of CNS metastases. — Exklusion von Pat. mit ECOG ≥ 2 und ZNS-Metastasen
- Following the sequential test strategy prespecified for the study IMforte, formal hypothesis testing was not performed for any of the outcomes at the last prespecified data cut-off. Therefore, all reported p-values are nominal, do not represent the result of prespecified hypothesis testing and are not controlled for multiplicity, which limits their interpretability. However, the statistical significance of the results for the last prespecified data cut-off based on a nominal 5% alpha level is reported in the JCA. — nominale p-Werte

Limitations of the definition for ORR, complete response rate and DoR as well as limitations of the analyses for disease-specific HRQoL and health status are provided in sections 4.3.1.2.1.2 and 4.3.1.2.1.3 in the main JCA report [1].

## 4.6 Interpretation of findings

The IMforte trial, a phase 3 RCT, showed a statistically significant improvement in PFS with lurbinectedin plus atezolizumab compared to atezolizumab monotherapy. OS was statistically significantly improved at the prespecified interim analysis. At the later data cut-off, the OS benefit remained numerical but was less pronounced, and the 95% CI included 1 [22]. The direction of the treatment effect was consistent across both data cut-offs, though. This may be partly explained by the tendency of interim analyses to overestimate treatment effects, as well as by the more frequent use of subsequent anticancer therapies in the control group, which may have reduced between-group differences over longer follow-up. The difference in median OS was approximately 2.8 months, the clinical relevance of this difference needs to be considered in the context of the uncertainty surrounding the OS estimate.

sign. Verlängerung des PFS

OS: kein gesicherter Vorteil

HRQoL results were inconsistent. Time-to-deterioration analyses showed earlier deterioration in physical functioning, role functioning, and nausea/vomiting with lurbinectedin plus atezolizumab, whereas a further analysis over the first six treatment cycles showed no statistically significant differences between groups. The inconsistency of the HRQoL results may partly be explained by the study design: because patient-reported outcome collection was tied to treatment duration, the longer observation in the intervention group may have biased the time-to-deterioration analyses against the combination. Additional time-to-deterioration sensitivity analyses and a post hoc Q-TWiST analysis, submitted at a later stage and not assessed in the JCA, showed no statistically significant differences and suggests a gain in quality-adjusted survival, respectively.

Lebensqualität: inkonsistente Ergebnisse

zusätzliche Analysen durchgeführt

The open-label study design is a potential source of bias, particularly for outcomes that depend on investigator assessment or patient-reported outcomes. IRF-assessed PFS was a co-primary endpoint and was formally analysed at the first data cut-off. At subsequent data cut-offs, only investigators assessed PF. Reliance on investigator-assessed PFS at subsequent data cut-offs may introduce assessment bias and warrants caution when interpreting later PFS results, though IRF-assessed and investigator-assessed PFS were consistent. This limitation is particularly relevant for outcomes such as ORR, DoR and PROs, which are more susceptible to assessment or reporting bias than objective outcomes such as OS.

offenes Studiendesign erhöht Bias-Risiko

PFS: Bewertung durch IRF nur für ersten Daten-Cut-Off geplant

The safety profile was characterised by a higher incidence of adverse events in the intervention group, including haematological toxicities. This might not be unexpected, given the addition of a cytotoxic agent to immunotherapy and the longer treatment exposure in the intervention group. However, time-to-event analyses accounting for the differing observation periods confirmed a higher risk of severe haematological AEs. Fatal AEs were numerically more frequent with the combination, but the small number of events does not allow firm conclusions. These safety findings need to be considered alongside the observed PFS benefit, the uncertain magnitude of the OS benefit, and the inconsistent HRQoL results.

unerwünschte Wirkungen: überwiegend hämatologisch,

An additional methodological consideration is the starting point of the survival analyses. In IMforte, OS and PFS were measured from randomisation into the maintenance phase, about 3.2 months after starting induction chemotherapy. Consequently, the reported survival estimates do not reflect survival from the start of first-line treatment, which limits direct cross-trial comparability with studies in which survival is measured from the initiation of first-line treatment. Thus, the reported OS and PFS estimates relate specifically to the period following randomisation into maintenance treatment.

Startzeitpunkt der OS-Analyse schränkt Vergleichbarkeit ein

Exploratory subgroup analyses suggested potential differences in treatment effects according to the presence of liver metastases and prior PCI. However, these findings should be interpreted with caution and do not provide a sufficiently robust basis for treatment selection.

2 Subgruppen weisen bessere Ergebnisse auf: Lebermetastasen, keine vorangegangene PCI

Finally, the generalisability of the findings is also limited by the selected study population. Eligibility criteria restricted inclusion to patients with an ECOG performance status of 0-1 and excluded patients with central nervous system metastases. This restriction largely reflects the maintenance setting, in which patients are selected by response to and tolerance of induction therapy. Nevertheless, the evidence is less directly applicable to patients with poorer performance status or CNS metastases encountered in routine clinical practice,

Zahl der geeigneten Patient:innen könnte gering sein

and according to clinical expert feedback, the number of patients eligible for this treatment in routine practice is expected to be limited [7].

# 5 Economic evaluation and budget impact analysis

This part includes confidential information!

The GÖG found no additional price information for lurbinectedin during their research.

GÖG: keine zusätzlichen Preise identifiziert

The HTD states in the submitted dossier that Austria is the first European country to have a public list price. The list prices for the 4-mg and 2-mg vials of ZEPZELCA (lurbinectedin) are €5,625 and €3,234.38, respectively. The price of the 4-mg vial is the same as that applied in the CUP, currently ongoing in Austria.

Angaben des Unternehmens: publizierter Listenpreis in Ö für 4 mg: € 5.625

## 5.1 Pharmacoeconomic model(s)

### 5.1.1 Submitted pharmacoeconomic model

The HTD did not submit a pharmacoeconomic model to demonstrate the cost-effectiveness of lurbinectedin in Austria.

kein Modell übermittelt

### 5.1.2 Economic evaluation based on pharmaco-economic models

#### Characteristics of the economic evaluations and applied models

##### Country and perspective

Two cost-utility analyses were identified: Huang et al. (2025) [24] assessed the cost-effectiveness of lurbinectedin (3.2 mg/m$^2$) plus atezolizumab (1,200 mg) administered IV every three weeks compared to atezolizumab monotherapy (1,200 mg) as a first-line maintenance treatment for ES-SCLC from both the Chinese and US healthcare system perspectives. In addition, Zhu et al. (2026) [25] evaluated the same comparison exclusively from the US healthcare system perspective. A societal perspective was not considered, subsequently, no indirect costs were included in either analysis.

2 Kosteneffektivitäts-analysen

Anm.: Zahlerperspektive, daher keine indirekten Kosten (Produktivität, Pflege) berücksichtigt

##### Intervention, comparator, and target population

Efficacy data for both arms were sourced from the Phase 3 IMforte RCT. Huang et al. (2025) [24] defined the target population as adults aged 18 years or above with initially treatment-naive ES-SCLC who had completed four cycles of induction therapy with atezolizumab, carboplatin, and etoposide before entering the maintenance phase. In contrast, Zhu et al. (2026) [25] simulated a hypo-

Wirksamkeitsdaten aus IMforte (Phase III RCT)

Zhu et al. (2026) zu Pat.-Kohorte ab 65 Jahre

thetical cohort of 65-year-old patients with ES-SCLC, confirmed by histology or cytology, who had similarly completed four cycles of induction therapy with atezolizumab plus etoposide and platinum without disease progression before entering the maintenance phase.

In accordance with NCCN and CSCO guidelines, topotecan-based chemotherapy was assumed as the standard second-line treatment for both arms following disease progression in the Huang et al. (2025) analysis, with the remaining patients receiving BSC (best supportive care) [24]. In the Zhu et al. (2026) model, subsequent antitumour therapy following progression included agents such as carboplatin and etoposide, and patients who did not receive further active treatment were considered to have received BSC [25].

Zweitlinien-Standardtherapie:
Topotecan (NCCN/CSCO) bei Huang et al. (2025);
Carboplatin + Etoposid bei Zhu et al. (2026);
Rest jeweils BSC

### Model structure and time horizon

Both studies employed a partitioned survival analysis model with three mutually exclusive health states: PFS, progressive disease (PD) and death. All patients entered the model in the PFS state, with death as the absorbing state. In Huang et al. (2025), the log-logistic distribution was selected for both PFS and OS curves in both treatment arms. The model used a cycle length of 21 days over 102 cycles, corresponding to a time horizon of 8.5 years, within which 99% of patients were projected to have died [24]. Zhu et al. (2026) selected a restricted cubic spline model for OS for the lurbinectedin arm and a log-logistic model for the atezolizumab arm. For PFS, a Royston-Parmar hazard spline model was applied to the lurbinectedin arm and a Royston-Parmar normal spline model to the atezolizumab arm. The base-case time horizon was set at 10 years with a cycle length of 21 days, justified by the reported 10-year ES-SCLC survival rate of 1.2%. Scenario analyses were conducted at 5, 15, and 20 years [25].

Partitioned-Survival-Modell:
3 Zustände (PFS/PD/Tod);

Zykluslänge 21 Tage über 8,5-10 J. Horizont

### Cost categories and utility values

Both analyses focused exclusively on direct medical costs, including drug acquisition costs, routine follow-up, diagnostic tests, BSC, management of grade ≥3 AEs (Huang et al. (2025) [24]: with an incidence exceeding 5% and hospice care; Zhu et al. (2026) [25]: grade 3-4 AEs regardless of incidence threshold and end-of-life care). In Huang et al. (2025), drug costs for the Chinese analysis were sourced from national tender prices, while US drug costs were derived from Drugs.com. In Zhu et al. (2026), drug costs were based on wholesale acquisition costs from the RED BOOK, with healthcare service costs sourced from 2024 CMS rates. All costs were expressed in 2024 US dollars, with currency conversion at 1 USD = 7.12 CNY.

direkte med. Kosten (Medikamente, Follow-up, Diagnostik, BSC, AEs Grad ≥ 3 mit Inzidenz > 5 %, Hospiz/AEs Grad 3-4)

In addition, Zhu et al. (2026) modelled the drug wastage as a cost component in the base case. As lurbinectedin is supplied in single-dose vials with unused portions to be discarded, individual doses were calculated based on the BSA and rounded up to the nearest available vial size. Drug wastage was estimated at 2.18 mg per patient-cycle, corresponding to approximately $4,496 per patient-cycle and a wastage rate of approximately 27%, increasing total costs in the lurbinectedin group by approximately 13%. No vial sharing or cross-patient pooling was assumed in the base case [25].

Zhu et al.: Arzneimittelverschwendung explizit modelliert;
~27 % Verschwendungsrate;
~ $ 4.496/Pat.-Zyklus;
+13 % Gesamtkosten

Utility values were not collected within the IMforte trial and were therefore obtained from published literature. Huang et al. (2025) [24] specified values of 0.673 for the PFS state and 0.473 for the PD state sourced from You et al. (2024). To account for treatment-specific toxicity differences between arms, disutility decrements for grade ≥3 AEs with an incidence exceeding 5% [24]/ grade 3-4 AEs [25] were incorporated, including values for anaemia (–0.073

Nutzwerte aus Literatur;
Disutilities für AEs für Anämie, Neutrophile, Thrombozyten, Neutropenie, Thrombozytopenie

[24]/–0.07 [25] ), decreased neutrophil count (–0.200 [24]), decreased platelet count (–0.050 [24]), neutropenia (–0.090 [24]), and thrombocytopenia (–0.190 [24], –0.25 [25]). In Zhu et al. (2026), AE disutilities were applied as one-time decrements in the first treatment cycle only [25]. Neither study applied a severity modifier.

### Uncertainty testing and discount rates

Huang et al. (2025) applied an annual discount rate of 5% to both costs and health outcomes in the base case, with a range of 0-8% explored in sensitivity analyses [24]. Zhu et al. (2026) applied a lower annual discount rate of 3% to both costs and QALYs, with values ranging from 0% to 8% in sensitivity analyses [25]. In addition, one-way, probabilistic sensitivity analysis (PSA) and scenario analyses were presented in both studies.

Diskontierung 3-5 % p. a. (Kosten & Outcomes); verschiedene Sensitivitätsanalysen in beiden Studien durchgeführt

### Model assumptions and limitations

Both studies assumed BSC for patients who did not receive subsequent active treatment after progression. Key differences related to second-line treatment assumptions were: Huang et al. (2025) [24] specified topotecan-based chemotherapy as standard second-line therapy (37% in the lurbinectedin plus atezolizumab vs 49% in the atezolizumab arm; duration 1.73 months), while Zhu et al. (2026) [25] assumed carboplatin and etoposide; and to utility inputs, where Zhu et al. (2026) applied NSCLC proxy values in the absence of ES-SCLC-specific data.

beide Studien: BSC nach Progression. Unterschiede: Zweitlinientherapie; NSCLC-Nutzwerte als Proxy

Detailed characteristics of the pharmacoeconomic evaluations are presented in Chapter 5 in the Appendix (Table 5-1).

## Results of the pharmacoeconomic evaluations

An overview of the cost-effectiveness results is presented in Table 5-1 below. Additionally, detailed results of the pharmacoeconomic evaluations are presented in Chapter 5 in the Appendix (Table 5-2).

The analysis by Huang et al. (2025) [24] reported incremental costs of $78,958 in the Chinese setting and $226,057 in the US setting. The incremental effect was identical across both country analyses at 0.21 QALYs, as the same clinical efficacy data from the IMforte trial and the same utility values were applied in both models. Consequently, the base-case ICER was $374,167 per QALY (∼ €340,000) in China and $1,071,238 per QALY (∼ €975,000) in the US. Both ICERs substantially exceed their respective willingness-to-pay (WTP) thresholds of $40,365 per QALY in China[5] and $150,000 per QALY in the US, rendering lurbinectedin plus atezolizumab not cost-effective in either setting.

Huang et al. (2025) ICER CN: ~ € 340.000/QALY, ICER US ~ € 975.000/QALY

basierend auf nationalen Schwellenwerten → Lurbinectedin plus Atezolizumab nicht kosteneffektiv

The US-only analysis by Zhu et al. (2026) [25] reported incremental costs of $229,342 (total costs: $382,776 for lurbinectedin plus atezolizumab vs $153,434 for atezolizumab alone) and incremental QALYs of 0.30 (1.26 vs 0.96), yielding a base-case ICER of $773,428 per QALY (∼ €703,000), which similarly substantially exceeds the applied WTP threshold of $100,000 to $150,000 per QALY. Notably, 88% of total costs in the lurbinectedin plus atezolizumab group were incurred during the PFS state, while only 35% of QALYs were accumulated in that state, indicating a relatively low conversion of expendi-

Zhu et al. (2026) ICER US ~ € 703,000/QALY → ebenso nicht kosteneffektiv

[5] Equivalent to three times the 2024 per capita GDP per Chinese pharmacoeconomic evaluation guidelines.

ture into survival benefit during the PFS state. The majority of QALYs were accumulated in the PD state across both treatment groups.

einflussreichster Parameter auf ICER in Huang et al. (2025): Nutzwert PFS, danach Lurbinectedin Preis

95 % CI ICER CN: ~ € 246.000-445.000/QALY
95% CI ICER US: ~ € 716.000-1.317.000/QALY

Regarding uncertainty analyses, the deterministic one-way sensitivity analysis identified the utility of PFS as the single most influential parameter in both country models, Huang et al. (2025) [24], followed by the cost of lurbinectedin, BSA, and the cost of atezolizumab. Notably, even when the price of lurbinectedin was reduced to zero, lurbinectedin plus atezolizumab remained non-cost-effective in both settings, an effect attributed to the prolonged duration of atezolizumab administration in the lurbinectedin plus atezolizumab arm, which substantially increases total treatment costs without delivering proportional clinical benefit. The ICER consistently exceeded the WTP threshold across all parameter variations in the one-way sensitivity analysis. The PSA yielded 95% CIs of $270,324 to $488,936 per QALY (~ €246,000-€445,000) in China and $786,394 to $1,446,804 per QALY (~ €716,000-€1,317,000) in the US, with a probability of lurbinectedin plus atezolizumab being cost-effective of 0% at both WTP thresholds.

einflussreichster Parameter auf ICER in Zhu et al. (2026): PD Nutzwert-Status, danach Lurbinectedin Preis

0 % Wahrscheinlichkeit der Kosteneffektivität von Lurbinectedin zu aktuellen Listenpreisen

In Zhu et al. (2026) [25], the one-way sensitivity analysis identified the utility value in the PD state as the most influential parameter, followed by the prices of lurbinectedin and atezolizumab, the utility value in the PFS state, and post-progression treatment costs in the lurbinectedin plus atezolizumab group. A 30% reduction in the price of lurbinectedin reduced the ICER by 24% but was insufficient to alter the overall conclusion of non-cost-effectiveness. The PSA confirmed 0% probability of cost-effectiveness at the $150,000/QALY threshold at current drug prices. When prices were reduced to 20% of their original level, lurbinectedin plus atezolizumab remained non-cost-effective. Only at 10% of the original price did the probability of cost-effectiveness reach 97.3% at the $150,000/QALY threshold (12.8% at $100,000/QALY), and at 5% of the original price, cost-effectiveness was achieved at the $100,000/QALY threshold.

Szenarien: längere Laufzeit → günstiger, aber nie unter Kosteneffektivitäts-schwellenwert

Verschwendungs-minderung reduziert ICER, ändert Schlussfolgerung jedoch nicht

Scenario analyses in Huang et al. (2025) [24] showed that while longer treatment durations improved cost-effectiveness, none of the scenarios resulted in lurbinectedin plus atezolizumab meeting either country's WTP threshold. A further sensitivity analysis adjusting survival curve parameters to account for potential ethnic differences in the trial population did not alter the conclusion of non-cost-effectiveness. Zhu et al. (2026) [25] conducted an extensive series of scenario analyses examining both time-horizon variation and drug-wastage mitigation strategies. Across alternative time horizons, shorter horizons yielded markedly higher ICERs, while longer horizons produced progressively more favourable results, reflecting the tail effect of the combination therapy, allowing continued QALY accumulation as monotherapy patients transitioned to the death state. However, no time horizon scenario resulted in lurbinectedin plus atezolizumab meeting the WTP threshold at current prices. Regarding drug wastage mitigation, eliminating wastage entirely (zero-waste scenario) reduced the ICER and lowered incremental costs, but still required an 81% joint price reduction to achieve cost-effectiveness [25]. In the most optimistic scenario (20-year horizon, no drug wastage), the ICER fell to $350,361/QALY (~ €319,000/QALY), requiring a 65% price reduction to achieve cost-effectiveness at $150,000/QALY. Across all scenarios, conclusions were consistent: lurbinectedin plus atezolizumab is not cost-effective at current prices [25].

Both studies consistently identified high drug acquisition costs relative to modest incremental QALY gains as the primary driver of unfavourable cost-effectiveness. Shared limitations include reliance on a single RCT (IMforte) without broader comparative evidence, survival extrapolation beyond trial follow-up introducing potential bias, and the exclusion of societal costs. Study-specific limitations include Huang et al. (2025)'s restricted generalisability to Chinese populations given limited Asian representation in the IMforte trial, and uncertain real-world applicability of second-line treatment assumptions [24]. Zhu et al. (2026) additionally acknowledged the unvalidated use of NSCLC utility proxies, theoretical rather than empirically validated drug wastage estimates, the inapplicability of vial sharing in certain healthcare systems, unconfirmed tolerability of dose rounding for lurbinectedin, and the practical implausibility of the 65-85% price reductions required to achieve cost-effectiveness through existing negotiation mechanisms [25]. Overall, the transferability of the study results to the Austrian context is limited, as both studies rely on Chinese and US cost data, evidence from the single IMforte RCT with limited European representation, and utility and survival estimates not validated against European data.

Limitationen beider Studien: 1 RCT, Survivalextrapolation, keine Gesellschafts-perspektiven

Übertragbarkeit der Ergebnisse auf Ö limitiert

*Table 5-1: Main results of the included pharmacoeconomic evaluation of lurbinectedin plus atezolizumab in adults with extensive-stage small cell lung cancer after first-line induction therapy without progression*

| Author, year | Country | Analysis | Incremental costs | Incremental QALYs | Base-case ICER | PSA results (95% CI) | Key assumptions | Limited transferability to the Austrian context |
|---|---|---|---|---|---|---|---|---|
| Huang et al., 2025 [24] | China | Base case | $78,958 | 0.21 | $374,167/ QALY (~ €340,000) | $270,324-$488,936/QALY (~ €246,000-€445,000) | Log-logistic PFS & OS; topotecan-based 2nd-line (37% LU-AT vs 49% AT); 5% discount rate; drug costs from national tender prices | Drug acquisition from Chinese national tender prices and US Drugs.com/US RED BOOK/CMS sources<br>Service and administration costs are based Chinese tender data or 2024 CMS tariffs<br>Reliance on the single IMforte RCT with limited European representation raises<br>Utility values and survival extrapolations are not validated against Austrian or broader European data or preference weights |
| | US | Base case | $226,057 | 0.21 | $1,071,238/ QALY (~ €975,000) | $786,394-$1,446,804/QALY (~ €716,000-€1,317,000) | Same clinical data & utilities as China analysis; drug costs from Drugs.com; 5% discount rate | |
| Zhu et al., 2026 [25] | US | Base case | $229,342 | 0.30 | $773,428/ QALY (~€703,000) | 0% probability of cost-effectiveness at $150,000/QALY at current prices | Independent parametric survival models per arm; drug wastage explicitly modelled (~27% wastage rate); RED BOOK drug costs; 2024 CMS service costs; 3% discount rate; NSCLC utility proxy values | |

*Abbreviations: AT … atezolizumab, CI … confidence interval, ICER … incremental cost-effectiveness ratio, LU-AT … lurbinectedin plus atezolizumab, OS … overall survival, PFS … progression-free survival, PSA … probabilistic sensitivity analysis, QALY … quality-adjusted life year*

*Notes: EUR equivalents based on approximate European Central Bank reference rates, August 2025: 1 USD ≈ 0.91 EUR.*

## Quality assessment

The quality assessment of the included economic evaluations using the CHEERS checklist [26] and the CHEC quality list [27] indicates that both studies are of moderate to good quality overall (Tables 5-3 and 5-4 in the Appendix).

beide Analysen mit moderater bis guter Qualität

Both studies achieved comparable reporting quality (Huang et al (2025): 20/28 CHEERS, 15/19 CHEC; Zhu et al. (2026): 21/28 CHEERS, 15/19 CHEC), with core methodological elements transparently documented and well justified in both cases. Huang et al. (2025)'s key strength lies in its dual-country perspective and comprehensive sensitivity and scenario analyses [24]. Zhu et al. (2026) is distinguished by its survival modelling approach, with independent parametric models fitted per arm; its novel explicit modelling of drug wastage as a base-case cost component, with accompanying mitigation scenario analyses; and its thorough characterisation of uncertainty through PSA based on 10,000 Monte Carlo simulations [25].

Stärken Huang et al. (2025): 2-Länder-Perspektive, umfangreiche Sensitivitätsanalysen; Zhu et al. (2026): Survivalmodelling, Arzneimittelverschwendung modelliert, PSA mit 10.000 Simulationen

However, both studies share several common limitations: Although the IMforte trial collected both EORTC QLQ-C30 and EQ-5D-5L data, neither analysis derived utility values from the trial. Instead, both borrowed them external sources of uncertain comparability (You et al., 2024 in Huang et al. (2025) [24]; NSCLC proxy values in Zhu et al. (2026)). Furthermore, no prespecified health economic analysis plan was reported; no formal subgroup analyses were conducted; no patient or stakeholder engagement was undertaken, survival analyses and outcome extrapolations were not informed by individual patient data, and effectiveness data were derived solely from a single RCT without supporting systematic review or network meta-analysis. Study-specific limitations include Huang et al. (2025)'s exclusion of indirect costs without explicit justification [24], and Zhu et al. (2026)'s reliance on theoretical rather than empirically validated drug wastage estimates, non-incorporation of toxicity-related dose reductions, limited generalisability of vial sharing findings across healthcare systems, and the practical implausibility of the 65-85% price reductions required for cost-effectiveness in near-term reimbursement contexts [25]. The generalizability to the Austrian setting is further limited by the differing assumptions: neither analysis accounted for the 2 mg vial presentation of lurbinectedin, which could reduce drug wastage, nor did either incorporate subsequent therapies and treatment durations reflective of Austrian clinical practice.

Limitationen: externe Nutzwerte, keine Analysepläne, keine Subgruppenanalysen, einzelnes RCT

zusätzlich Huang et al. (2025): indirekte Kosten ausgeschlossen; Zhu et al. (2026): theoretische Verschwendungsschätzungen, Preisreduktionen von 65-85 % unrealistisch

## 5.2 Budget impact analysis

### 5.2.1 Budget impact analysis submitted by the manufacturer

The HTD states in the dossier that, due to tight submission timelines, no BIA could be submitted. Nevertheless, the HTD presents estimates of the eligible population in Austria, market shares for the first three years, and drug acquisition costs based on the lurbinectedin public list price. We incorporated the HTD's estimates into the BIA we conducted.

kein BIA vom HTD; aber Pat.-Schätzungen, Marktanteile & Listenpreise übernommen für eigene BIA

## 5.2.2 Austrian budget impact analysis

### Eligible population and market share in years 1-3

Lurbinectedin, in combination with atezolizumab, is indicated for the maintenance treatment of adult patients with ES-SCLC whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin and etoposide. The HTD derived the eligible population for Austria as follows [6]: The total number of patients with SCLC in Austria is estimated at 617 cases [28]. Of these, 70.8% (n=437) present with ES-SCLC, while 29.2% (n=180) present with LS-SCLC [29]. Approximately 80% of patients with LS-SCLC (n=144) are expected to progress to ES-SCLC, reflecting the highly aggressive nature of the disease [30]. Considering both *de novo* ES-SCLC cases and those progressing from LS-SCLC, the total ES-SCLC population in Austria is estimated at 581 patients [6].

SCLC in Österreich: 617 Fälle gesamt; 70,8 % ES-SCLC (n=437); 80 % LS-SCLC-Progression zu ES-SCLC (n=144); Gesamt ES-SCLC: ~581 Pat.

It is further estimated that 85% of ES-SCLC patients (n=494) receive first-line induction therapy in routine clinical practice ([31]; PharmaMar Internal Market research). Among treated patients, approximately 80% (n=395) receive a combination of immunotherapy plus chemotherapy as first-line treatment, reflecting current real-world treatment patterns [32]. It is assumed that 75% of patients receiving first-line chemoimmunotherapy are treated with atezolizumab in combination with chemotherapy (n=296) [6]. The HTD further assumes, based on data from the IMforte trial, that around 74% (219 patients) do not experience disease progression following induction and are therefore eligible for maintenance therapy [22]. As a result, the HTD estimates that approximately 219 patients in Austria would be candidates for maintenance therapy following first-line induction with atezolizumab plus chemotherapy.

85 % ES-SCLC erhalten 1L-Induktion (n=494); davon 80 % Chemo-Immuntherapie (n=395); 75 % Atezolizumab-basiert (n=296); ~74 % ohne Progression nach Induktion (IMforte) → ~219 Pat. für Erhaltungstherapie in Österreich

According to the HTD's projections, the market share of lurbinectedin plus atezolizumab combination will be 60% (n= 132) in year 1 following the introduction of lurbinectedin. The uptake is assumed to increase over time, reaching 70% (n=153) and 75% (n=164) in years 2 and 3, respectively. As a result, HTD assumes that, overall, 449 patients will be treated with the combination of lurbinectedin and atezolizumab in the first three years [6].

Marktanteil: Jahr 1: 60 % (n=132), Jahr 2: 70 % (n=153), Jahr 3: 75 % (n=164); gesamt 3 Jahre: 449 Pat.

By contrast, the consulted clinical experts estimated the eligible population in Austria at approximately 180 to 250 patients per year. Applying the HTD's market share projections to this figure yields 108 to 150 patients treated with lurbinectedin plus atezolizumab in year 1, 126 to 175 in year 2 and 135 to 188 patients in year 3, respectively. These numbers represent the upper and lower bounds of the treated patient population in the current BIA. In total, we estimated that 369 patients would be treated with lurbinectedin plus atezolizumab in the lower-bound case and 513 in the upper-bound case over the first three years.

Klinische Expert.: 180-250 erwartete Pat./Jahr; Jahr 1: 108-150, Jahr 2: 126-175, Jahr 3: 135-188

### Direct medical costs of lurbinectedin plus atezolizumab treatment

The direct medical costs of lurbinectedin plus atezolizumab treatment include drug acquisition and administration costs.

### Acquisition costs

Lurbinectedin: € 8.859/Zyklus → 7 Zyklen (IMforte-Median): € 62.016/Pat.

Lurbinectedin is available in 4-mg and 2-mg vials, priced at €5,625 and €3,234.38, respectively (list prices submitted by the HTD). The recommended dose of lurbinectedin is 3.2 mg/m$^2$ every 21 days. Based on the mean BSA observed in the IMforte trial (1.84 m$^2$), one 4-mg and one 2-mg vial of lurbinectedin are administered per treatment cycle, totaling €8,859 per patient per cycle. Assuming patients receive a median of seven treatment cycles in the IMforte trial, the acquisition cost of lurbinectedin is €62,016 per treated patient.

Atezolizumab: € 32.923/Pat.

Gesamt: € 94.938/Pat.

Lurbinectedin is used in combination with atezolizumab, which is administered as a fixed dose of 1,200 mg every 21 days. Seven 1,200-mg vials of atezolizumab, costing €32,923 in total, are required to treat one patient for the median number of treatment cycles from the IMforte trial ( [22] Appendix p. 20). The overall acquisition cost of lurbinectedin plus atezolizumab combination therapy per patient is €94,938.

Gesamtkosten: Jahr 1: € 10-14 Mio.; Jahr 3: € 13-18 Mio.

These costs are shown in Table 5-2. In this table, total costs per item by year are computed using both the lower and upper bounds of the patient population assumed to be treated in each year. Total costs for drug acquisitions in year 1 are between €10 and €14 million, rising with market share to around €13 to €18 million in year 3.

### Administration costs

Administrationskosten (nicht stationär): gesamt € 11.840/Pat.

The recommended dose of lurbinectedin is administered IV over 60 minutes in a hospital outpatient clinic setting. We accounted for the administration costs using a per-diem hospital outpatient clinic tariff of €845.71. Given the median of seven treatment cycles, the administration costs of lurbinectedin in Austria amount to €5,920. Atezolizumab is also administered IV over 60 minutes in a hospital outpatient clinic setting, in a separate infusion. If the first infusion is well tolerated, all subsequent infusions may be administered over 30 minutes; however, the same tariff is assumed to apply irrespective of the infusion duration. Consequently, the overall administration cost of the combination therapy is estimated at €11,840.

Prämedikation in Tagessatz enthalten; G-CSF-Prophylaxe: nicht kostenrelevant

According to the SmPC of ZEPZELCA, all patients should be pre-treated with IV dexamethasone 8 mg and IV ondansetron 8 mg to prevent nausea [13]. We assumed that these routinely applied items are covered by the tariff applied for IV administration at an oncology outpatient clinic. In addition, it is recommended to administer post-infusion granulocyte colony-stimulating factor (G-CSF) for primary prophylaxis of neutropenia. However, the clinical experts deemed the cost of this item negligible compared to the acquisition and administration costs, therefore, we excluded it from our BIA calculation.

These costs are also shown in Table 5-2. Total costs for drug administration in year 1 are between €1.3 and €1.8 million, rising with market share to around €1.6 to €2.2 million in year 3.

### Additional treatment costs

Schilddrüsenfunktionstests (TSH): nicht kostenrelevant für BIA

Thyroid function tests are recommended to be performed periodically on patients treated with atezolizumab [33]. As the thyroid function is primarily assessed via a blood test measuring thyroid-stimulating hormone (TSH) values, the cost of this item was deemed negligible for the BIA calculation.

*Table 5-2: Per-patient and per-treated-population costs of lurbinectedin plus atezolizumab treatment (for the median of seven treatment cycles from the IMforte trial)*

| Cost categories | Cost per patient | Year 1 (108-150 treated pts) | Year 2 (126-175 treated pts) | Year 3 (135-188 treated pts) | Total (range) | Share of total costs (%) |
|---|---|---|---|---|---|---|
| Drug acquisition | €94,938 | €10,253,326-€14,240,730 | €11,962,213-€16,614,185 | €12,816,657-€17,800,913 | €35,032,196 - €48,655,828 | 88.9% |
| Drug administration | €11,840 | €1,278,714-€1,775,991 | €1,491,832-€2,071,990 | €1,598,392-€2,219,989 | €4,368,938-€6,067,969 | 11.1% |
| Total direct medical costs of lurbinectedin with atezolizumab treatment | €106,778 | €11,532,039-€16,016,721 | €13,454,046-€18,686,175 | €14,415,049-€20,020,901 | €39,401,134-€54,723,797 | 100.0% |

*Abbreviations: pts … patients*

## Standard of care costs

The standard of care (SoC) is represented by atezolizumab monotherapy. In the IMforte trial, the median duration of treatment with atezolizumab was 4.2 months (range, 2.0-7.6) in the lurbinectedin plus atezolizumab arm and 2.1 months (range, 0.8-4.2) in the comparator atezolizumab arm. A median of 7 (range, 3-11) atezolizumab doses were received in the lurbinectedin plus atezolizumab arm, while a median of 4 (range, 2-7) doses were received in the atezolizumab monotherapy arm [22]. Consequently, we assume that atezolizumab monotherapy is associated with an average per-patient cost of €22,196: €18,813 for acquisition costs and €3,383 for administration costs.

SoC = Atezolizumab-Monotherapie

IMforte: median 4 Dosen; € 18.813 Erwerb + € 3.383 Administration = € 22.196/Pat.

These costs are presented in Table 5-3. In this table, the total annual costs are calculated assuming the intervention is not introduced and that all patients continue with the SoC. The cost range reflects uncertainty concerning the size of the eligible population, estimated to range from 180 to 250 patients. As a result, the total SoC costs range from €4 to €5.5 million per year and from €12 to €16.6 million over three years.

SoC-Gesamtkosten: € 4-5,5 Mio./Jahr; € 12-16,6 Mio. über 3 Jahre (180-250 Pat./Jahr)

*Table 5-3: Cost of the SoC scenario without lurbinectedin (for the median of four treatment cycles from the IMforte trial)*

| Cost categories | Cost per patient | Year 1 (180-250 treated pts) | Year 2 (180-250 treated pts) | Year 3 (180-250 treated pts) | Total | Share of total costs (%) |
|---|---|---|---|---|---|---|
| Drug acquisition | €18,813 | €3,386,318-€4,703,220 | €3,386,318-€4,703,220 | €3,386,318-€4,703,220 | €10,158,955-€14,109,660 | 84.8% |
| Drug administration | €3,383 | €608,911-€845,710 | €608,911-€845,710 | €608,911-€845,710 | €1,826,734-€2,537,130 | 15.2% |
| Total direct medical costs of SoC | €22,196 | €3,995,230-€5,548,930 | €3,995,230-€5,548,930 | €3,995,230-€5,548,930 | €11,985,689-€16,646,790 | 100.0% |

*Abbreviations: SoC … standard of care, pts … patients*

## Net drug-budget impact in years 1-3

Table 5-4 presents the overall projected costs of treating the population eligible for lurbinectedin maintenance treatment (i.e., adult patients with ES-SCLC whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin and etoposide), encompassing both lurbinectedin-treated patients and those remaining on SoC, over the next three years. Combined direct medical costs of the lurbinectedin scenario, including the costs for the patients remaining on the SoC, range from around €13.1 to €18.2 million in the first year and from around €15.4 to €21.4 million in the third year, reflecting the increasing market share of lurbinectedin.

Gesamtkosten Intervention (inkl. SoC-Pat.):
Jahr 1: € 13,1-18,2 Mio.;
Jahr 3: € 15,4-21,4 Mio.
(steigend mit Marktanteil)

*Table 5-4: Cost of the intervention scenario, including remaining SoC costs*

| Cost categories | Year 1 | Year 2 | Year 3 | Total |
|---|---|---|---|---|
| Eligible population (pts.) | 180-250 | 180-250 | 180-250 | 540-750 |
| Lurbinectedin plus atezolizumab market share | 60% | 70% | 75% | - |
| Lurbinectedin plus atezolizumab costs | €11,532,039-€16,016,721 | €13,454,046-€18,686,175 | €14,415,049-€20,020,901 | €39,401,134-€54,723,797 |
| Residual SoC costs | €1,598,092-€2,219,572 | €1,198,569-€1,664,679 | €998,807-€1,387,233 | €3,795,468-€5,271,484 |
| Total direct medical costs of the lurbinectedin scenario, including the remaining SoC costs | € 13,130,131-€ 18,236,293 | € 14,652,615-€ 20,350,854 | € 15,413,856-€ 21,408,134 | € 43,196,602-€ 59,995,280 |

*Abbreviations: pts…patients, SoC … standard of care*

Depending on the eligible population and the uptake of lurbinectedin, the net budget impact of reimbursing lurbinectedin in Austria is projected to range from around € 31.2 to €43.3 million over the three-year horizon. In the first year following the introduction, with a projected 60% market share, the additional costs compared to the current SoC range from €9.1 million (assuming 180 eligible patients) to €12.7 million (assuming 250 eligible patients). By year 3, as the market share of lurbinectedin is expected to increase to 75%, the additional costs would rise to €11.4 to €15.9 million. The detailed breakdown of the net budget impact is presented in Table 5-5 below.

Netto-Budgetauswirkung Lurbinectedin-Einführung:
Jahr 1 (60 % Marktanteil):
€ 9,1-12,7 Mio.
Jahr 3 (75% Marktanteil):
€ 11,4-15,9 Mio.
Gesamt 3 Jahre:
€ 31,2-43,3 Mio.

*Table 5-5: Net budget impact of lurbinectedin plus atezolizumab vs atezolizumab monotherapy over three years (base case)*

| Cost categories | Year 1 | Year 2 | Year 3 | Total |
|---|---|---|---|---|
| Total direct medical costs of the SoC-only scenario | € 3,995,230-€ 5,548,930 | € 3,995,230-€ 5,548,930 | € 3,995,230-€ 5,548,930 | € 11,985,689-€ 16,646,790 |
| Total direct medical costs of the lurbinectedin scenario | € 13,130,131-€ 18,236,293 | € 14,652,615-€ 20,350,854 | € 15,413,856-€ 21,408,134 | € 43,196,602-€ 59,995,80 |
| NET BUDGET IMPACT | € 9,134,901-€ 12,687,363 | € 10,657,385-€ 14,801,924 | € 11,418,627-€ 15,859,204 | € 31,210,913-€ 43,348,490 |

*Abbreviations: SoC … standard of care*

## Scenario analysis

The base-case BIA assumes that the treatment duration in Austrian clinical practice corresponds to the median number of cycles observed in the pivotal IMforte trial, both in the intervention and the control arm. However, clinical experts consulted during the analysis hypothesised that the real-world treatment duration with the lurbinectedin-atezolizumab combination regimen is unlikely to deviate from that observed with atezolizumab monotherapy. Accordingly, the scenario analysis assumes an equivalent treatment duration of four cycles across both arms, such that the resulting net budget impact effectively represents the incremental cost attributable solely to lurbinectedin as an add-on to the SoC (Table 5-6).

Behandlungsdauer-Annahmen Szenarioanalyse: 4 Zyklen beide Arme

Lurbinectedin-Effekt: reine Add-on-Kosten

*Table 5-6: Net budget impact of lurbinectedin plus atezolizumab vs atezolizumab monotherapy over three years (scenario analysis)*

| Cost categories | Year 1 | Year 2 | Year 3 | Total |
|---|---|---|---|---|
| Total direct medical costs of the SoC-only scenario | € 3,995,230-<br>€ 5,548,930 | € 3,995,230-<br>€ 5,548,930 | € 3,995,230-<br>€ 5,548,930 | € 11,985,689-<br>€ 16,646,790 |
| Total direct medical costs of the lurbinectedin scenario | € 8,187,131-<br>€ 11,371,984 | € 8,886,595-<br>€ 12,342,493 | € 9,235,978-<br>€ 12,827,748 | € 26,310,402-<br>€ 36,542,225 |
| NET BUDGET IMPACT | € 4,192,599-<br>€ 5,823,054 | € 4,891,365-<br>€ 6,793,563 | € 5,240,749-<br>€ 7,278,818 | € 14,324,713-<br>€ 19,895,435 |

*Abbreviations: SoC … standard of care*

## Limitations

The findings of this BIA demonstrate that the introduction of lurbinectedin in combination with atezolizumab as first-line maintenance therapy for ES-SCLC in Austria would result in a substantial increase in healthcare expenditure compared with atezolizumab monotherapy alone. The cumulative net budget impact is estimated at €31.2 million to €43.3 million over three years, depending on the assumed eligible patient population.

Einführung von Lurbinectedin – Mehraufwand: kumulativer Netto-Budgetimpact: € 31,2-43,3 Mio. über 3 Jahre

The presented BIA is subject to several limitations, primarily attributable to uncertainties in the Austrian eligible population, treatment patterns, and cost data:

Limitationen:

First, the eligible patient population in Austria is associated with considerable uncertainty due to the lack of Austrian epidemiological data to underpin the assumptions. The sequential application of multiple proportional assumptions by the HTD, including ES-SCLC incidence, first-line induction treatment, concomitant immunotherapy use, atezolizumab-based induction, and eligibility for maintenance following response or stable disease, yielded a theoretically derived population of 219 patients per year meeting the indication. Clinical experts, on the other hand, considered a range of 180-250 patients per year to be more appropriate than a single point estimate of 219 patients, better reflecting the uncertainty surrounding the true size of the eligible population in Austria. Furthermore, the market share trajectory, rising from 60% in year 1 to 75% from year 3 onwards, is based on company estimates rather than empirical Austrian prescribing data, and any deviation in real-world adoption would materially alter the projected budget impact.

fehlende österreichische Epidemiologiedaten;

HTD-Populationsschätzung theoretisch hergeleitet;

Marktanteilsannahmen (60-75%) unternehmensbasiert

Second, actual treatment costs may differ from projected costs due to variations in clinical treatment patterns. In some centres in Austria, the subcutaneous formulation of atezolizumab , with a slightly lower acquisition cost is preferred over the intravenous formulation however, the proportion of patients expected to receive subcutaneous atezolizumab was not considered in the analysis. We also opted for a range of conservative assumptions that could overestimate the budget impact of lurbinectedin in relation to the actual clinical practice, such as not accounting for possible vial sharing or relative dose intensity. In addition, lurbinectedin could be used off-label in clinical practice in combination with a different PD-L1-binding antibody than atezolizumab.

Behandlungsdauer basiert auf der medianen Zyklenanzahl von IMforte → Abweichungen in der Praxis?

Further uncertainties arise regarding the cost data used. The chosen costing approach relied on list price of lurbinectedin (Zepzelca) from the company dossier, ex-factory drug prices from the Austrian Warenverzeichnis Apothekerverlag, and an estimate of drug administration costs based on LKF catalogue reimbursement codes. The administration costs associated with the combination therapy were accounted for by applying the same outpatient clinical tariff separately to each agent, potentially duplicating the actual administration costs when both agents are given on the same day. By contrast, several clinically relevant cost items were classified as cost-irrelevant based on expert opinion, including G-CSF primary prophylaxis with filgrastim, dexamethasone and ondansetron pre-medication, thyroid function monitoring, and full blood count follow-up, all of which could cumulatively represent measurable costs in routine Austrian clinical practice.

unsichere Kostendaten: HTD-Dossier, österreichisches Warenverzeichnis, LKF-Katalog

Finally, standardised and widely accepted data on indirect healthcare costs are unavailable in Austria. Therefore, we followed the healthcare perspective for the analysis and did not consider indirect costs.

keine indirekten Kosten berücksichtigt

## 5.3 Interpretation of findings

The economic evidence assembled in this chapter raises substantial concerns about the value for money of lurbinectedin plus atezolizumab at current list prices. Both identified cost-utility analyses, despite differing in geographic perspective and modelling assumptions, converge on the same conclusion: adding lurbinectedin to atezolizumab maintenance therapy for ES-SCLC is not cost-effective at any evaluated WTP threshold. The incremental QALY gains of 0.21 (Huang et al.) to 0.30 (Zhu et al. [25]) are modest and insufficient to offset the substantial additional treatment costs, yielding base-case ICERs of $773,428 and $1,071,238 per QALY gained from the US perspective and $374,167 per QALY gained from the Chinese perspective. While neither study adopted an Austrian perspective, the magnitude of this cost-effectiveness gap leaves little reason to expect a qualitatively different conclusion for Austria.

Kosteneffektivität Lurbinectedin plus Atezolizumab: aktuelle Listenpreise (USA und China) nicht kosteneffektiv

für Österreich ähnliches Ergebnis zu erwarten

Unterschiede in den präsentierten internationalen ICER aufgrund verschiedener Methoden

The divergence in ICERs between the two studies reflects meaningful differences in modelling choices rather than contradictory clinical evidence. Zhu et al. employed a 10-year horizon, flexible survival models, and explicitly incorporated drug wastage, whereas Huang et al. adopted a shorter 8.5-year horizon, uniform log-logistic distributions, and did not model wastage. Crucially, both studies relied on survival extrapolation well beyond the observed IMforte trial follow-up, meaning that a substantial share of the incremental QALY benefit is derived from projected rather than observed data. Zhu et al. demonstrated this sensitivity explicitly: the ICER rose to $1,336,736 per QALY gained at a 5-year horizon but fell to $444,522 per QALY gained at 20 years, underscoring the dependence of the economic case on long-term survival projections that are inherently uncertain in a disease with a 5-year survival rate below 10%.

Kosteneffektivität: Überlebens-Projektion-abhängig: limitierte Aussagekraft

strukturelles Kosteneffektivitäts-Hindernis: Zwei-Agenten-Erhaltungsregimen: gleichzeitige Langzeit-Administration: dominante Kostenkomponente

Both studies agree that lurbinectedin-based combination therapy is not cost-effective, even under optimistic assumptions. Huang et al. found that reducing the price of lurbinectedin to zero would still not achieve cost-effectiveness due to the additional costs of prolonged atezolizumab administration. Similarly, Zhu et al. estimated that an 85% joint price reduction for both lurbinectedin and atezolizumab would be needed to reach even a 50% probability of cost-effectiveness at a $150,000 per QALY threshold. This finding shows that the cost-effectiveness barrier is structurally embedded in a maintenance regimen that requires concurrent administration of two high-cost agents over an extended period, not solely in the price of the new agent.

Unsicherheitsquellen Budget-Impact: Populationsgröße, Uptake-Raten, Zykluszahl

The Austrian budget impact analysis adds a critical population-level dimension. With 180 to 250 expected eligible patients per year and a projected lurbinectedin market share rising from 60% to 75% over three years, the cumulative net budget impact is projected at approximately €31.2 million to €43.3 million in the base-case scenario[6], representing a roughly three- to fourfold increase over current SoC expenditure of €4.0 million to €5.5 million annually. In contrast, a scenario analysis assuming similar treatment cycles in both arms, as per the clinical experts, resulted in reduced net budget impacts, reflecting the incremental cost attributable solely to lurbinectedin as an add-on to the SoC. The substantial spread between scenario bounds, driven primarily by uncertainty in eligible population size, uptake rates and number of treatment cycles, indicates that the true budget impact depends on treatment patterns that cannot currently be predicted with confidence, introducing further financial risk for the Austrian healthcare system.

Wirtschaftlichkeit bei aktuellen Listenpreisen fraglich; substanzielle Preisreduktion bzw. Managed-Entry-Arrangement erforderlich

Taken together, the international cost-effectiveness evidence and the Austrian budget projections present a consistent picture: at current list prices, lurbinectedin plus atezolizumab maintenance treatment raises concerns whether it represents reasonable value for money. The clinical benefit observed in the IMforte trial translates into only modest incremental QALY gains heavily dependent on survival extrapolation, while the high acquisition costs of both agents, compounded by drug wastage, produce ICERs several multiples above commonly applied international willingness-to-pay thresholds even under favourable assumptions. A substantial confidential price reduction or managed entry arrangement appears necessary for improving the economic profile of lurbinectedin adoption in the Austrian setting, and any such arrangement would need to address not only the price of lurbinectedin itself but also the cumulative cost implications of prolonged combination therapy.

[6] Lurbinectedin plus atezolizumab vs atezolizumab monotherapy median number of treatment cycles: 7 vs 4.

# 6 Extended perspectives

Perspektiven von Gesundheitsdienstleistern, Betroffenen und weitere relevante Aspekte

This chapter summarises the perspectives of healthcare providers, patients and carers, along with other relevant considerations. This combined approach provides a more multidimensional view of patient experiences, expectations, and concerns relevant to the HTA report. It outlines existing registries and describes frameworks for documenting the use of lurbinectedin in Austria.

## 6.1 Healthcare provider perspective

Lurbinectedin als mögliche Behandlungsoption

In Austria, lurbinectedin may be considered as a subsequent treatment option during routine clinical cancer management, based on treatment response and disease progression.

### Implementation considerations within the Austrian clinical practice context

Einschätzung österr. klin. Experten

keine wesentlichen strukturellen Änderungen erforderlich

Austrian clinical experts were consulted to provide specific guidance for the clinical practice context as part of the assessment. As with every new product, integrating lurbinectedin into clinical practice requires careful consideration of healthcare infrastructure, training needs of all parties involved, and patient support needs. Although substantial structural changes are not anticipated, organisational adjustments may be required to accommodate treatment protocols specific to lurbinectedin [7].

Neutropenie-Prophylaxe und umfassendes Monitoring notwendig

interdisziplinäre Zusammenarbeit essenziell für erfolgreiche Therapie

For organisational efficiency, lurbinectedin and atezolizumab are both administered on the same day [7]. To achieve effective treatment, Austrian clinical experts emphasise the importance of careful management of AEs. Hence, prior to the administration of lurbinectedin and atezolizumab, primary prophylaxis with a colony-stimulating factor (e.g., pegfilgrastim) is usually applied [7] to reduce the duration of neutropenia and the incidence of febrile neutropenia [34]. For the early detection and treatment of immune-mediated AEs, several parameters are monitored, including blood count, liver and renal function tests, and endocrinological and respiratory assessment if required. In addition, interdisciplinary coordination is considered essential to ensure successful treatment [7].

erste positive Erfahrungen mit Lurbinectedin in Österreich

Initial, single clinical experiences with lurbinectedin were described as positive, with AEs considered manageable. However, compared with subcutaneous atezolizumab monotherapy, the administration of lurbinectedin requires more resources, due to its intravenous use. Overall, clinical experts emphasised the need for training, particularly in departments without prior experience [7].

## 6.2 Patient and carer perspective

### 6.2.1 Patient perspective

#### Findings from the literature

wenig Evidenz über Krankheitslast und Bedürfnisse von Patient:innen mit SCLC vorhanden

The paucity of published qualitative research on the unique needs of patients with SCLC and their caregivers limits the current understanding of perceived symptom burden and leaves a gap in the knowledge needed to carry out patient-centred drug development in SCLC. Insights into the lives of affected patients are provided by a mixed-methods study conducted by Bebb and colleagues (2023), two qualitative interview studies by Altmann et al. (2023) and Brown et al. (2015), and a quantitative study by Santos (2025) [35-40]. To synthesise the findings, outcomes were structured using the domains of the World Health Organization Quality of Life-100 (WHOQOL-100) framework (Figure 6-1) [41].

Krankheit betrifft alle Domänen der Lebensqualität

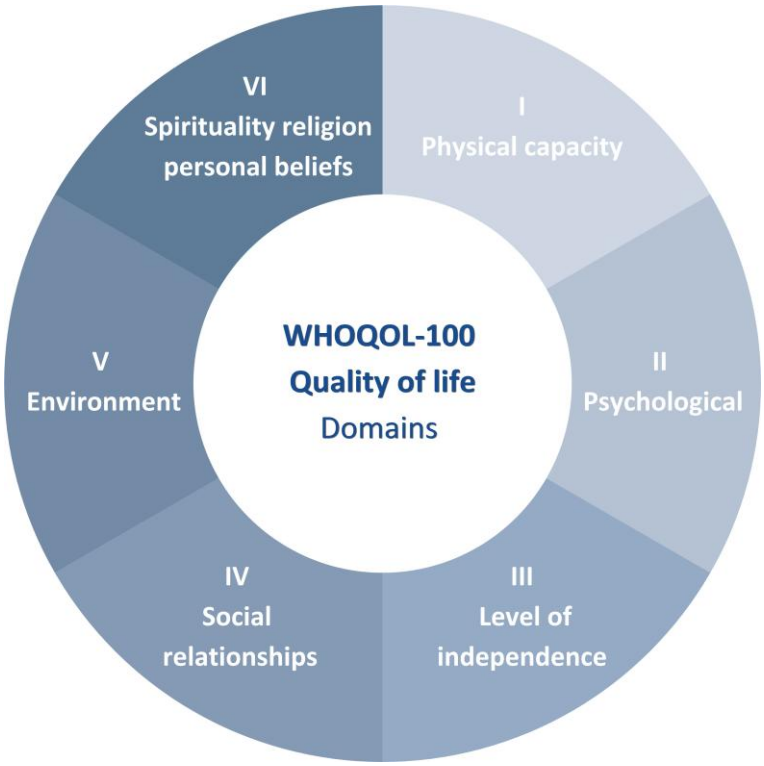



*Figure 6-1: World Health Organization Quality of Life-100; schematic representation of the domains [41]*

#### Physical capacity

Atemnot als anhaltendes Symptom, in schweren Fällen Gabe von Sauerstoff notwendig

The most common impactful symptoms in patients with SCLC were shortness of breath, coughing, hoarseness, chest pain, fatigue and nausea or vomiting. Shortness of breath was a constant symptom, worsening with exertion and sometimes arising spontaneously at rest. Patients differentiated between dry coughs and those producing blood or phlegm, and some reported difficulty taking deep breaths, requiring the use of oxygen tanks.

Overall, a wide range of symptoms was reported, attributed to either the disease or treatment, including hot flashes, arm/shoulder/back pain, cold extremities, hair loss, port area pain and discomfort, change in taste, dizziness, hazy or drugged feeling, difficulty or pain swallowing, voice loss/change, neuropathy pain in bones, jerking and cramping of muscles, or lack/loss of appetite. Participants also reported difficulty sleeping and stated that SCLC symptoms, particularly coughing and pain, interfered with their sleep [35, 36, 38].

breites Spektrum an Symptomen, verursacht durch die Erkrankung selbst oder als unerwünschte Wirkung einer Therapie

### Psychological

Patients with SCLC experienced emotional effects, particularly those who had not achieved success with treatment. Mental health was impacted substantially among patients with advanced disease. The patients were afraid of dying and reported difficulties coming to terms with this. They understood that treatments were not curative, and most just hoped to go into remission as a means of gaining more time. They also expressed sadness regarding their QoL, though treatment burden was considered worthwhile if it extended survival [36, 38].

erhebliche Auswirkungen auf die mentale Gesundheit durch die unheilbare Erkrankung

Hoffnung auf Lebensverlängerung

Patients differed in how they coped with symptoms and side effects. Most were determined to continue with life as usual despite physical challenges, finding it helpful to maintain perspective, a sense of humour, and to rationalise their difficulties [36, 38].

Einstellung spielt wichtige Rolle: unterschiedliche Herangehensweisen einzelner Patient:innen

### Level of independence

Patients with SCLC reported impacts on leisure and hobbies, work, household chores, and daily errands outside their homes. Symptoms limited their daily activities, including cooking, cleaning, driving, taking care of personal hygiene, travelling long distances, and doing physical activity, whereas the reported strength of impact varied from "minor" (e.g., reducing vigorous exercise) to "very severe" (e.g., too tired to get out of bed) [35, 36, 38].

Symptome schränken alle Bereiche des täglichen Lebens ein

Patients reported reduced endurance, strength, and balance as underlying factors that limit physical functioning, including the ability to bend, squat, and walk. These limitations on work or hobbies are negatively affecting their QoL. However, maintaining independence in daily life was a high priority: patients tended to seek assistance only after exhausting their own efforts employing strategies such as rationing their energy, taking rest breaks or completing tasks more slowly. Once help was required, there was a hierarchy of preferences for support, with most preferring help from family, particularly spouses and children, over the broader social network or external agencies. [35, 36, 38].

Ausdauer, Kraft und Gleichgewicht reduziert

Aufrechterhaltung der Unabhängigkeit hat hohe Priorität

meist direkte Angehörige für Hilfe im Alltag verantwortlich

### Social relationships

Family dynamics were substantially affected among patients with SCLC, as the condition made them feel unable to participate in family activities or to be a good parent/grandparent/partner. They also felt they sometimes had to pretend to their families that they were fine. Extrafamilial social interactions were substantially affected, as patients tended to retreat socially due to lack of energy and willpower or embarrassment at appearing in their current state (e.g., someone who coughs all the time) [36, 38].

Familiendynamik und außerfamiliäre soziale Kontakte durch Krankheit stark beeinträchtigt; Betroffene ziehen sich oftmals zurück

In this regard, participants identified unique benefits of talking to other cancer patients rather than doctors, family, friends, or counsellors. Across their cancer journey, patients experienced a wide range of emotions, including shock, sadness, frustration, fear, hope, luckiness, uncertainty and isolation, and found that peer connection provided a sense of having a "fellow traveller" [36, 38].

Austausch mit anderen Betroffenen wird als hilfreich empfunden

### Environment

Patients relied almost exclusively on verbal information from their doctors about diagnosis and prognosis, valuing honesty and open discussion. Many participants preferred to ask more questions or seek a second opinion from another doctor rather than turn to the internet or other sources for help [38].

offener, ehrlicher Dialog mit behandelnden Ärzten wird besonders geschätzt

Although the interviewed participants were aware of available emotional support services, they expressed little interest in them, preferring to manage their emotions alone or with close family. Barriers to accessing support groups or helplines included stigma sensitivity, reluctance to open up to strangers, a wish to avoid topics such as cancer and death, fatigue, and lack of time [38].

kaum Nutzung von Selbsthilfegruppen etc.: Stigma, Dialog mit Unbekannten, Vermeidung belastender Themen

### Spirituality/Religion/Personal beliefs

Santos et al. (2025), assessed the correlation of spirituality with the HRQoL in patients with lung cancer. They identified that the facets of spirituality, including connection to a spiritual being or force, meaning in life, admiration, wholeness and integration, spiritual strength, inner peace, hope, optimism, and faith, positively contribute to the health-related QoL of LC patients, encouraging reflection on the subject through a spiritual context. This approach promotes positive coping, resilience and the development of individualised care plans for patients and their families [40].

Aspekte der Spiritualität können Lebensqualität Betroffener positiv beeinflussen

Förderung von Coping und Resilienz

### Patient involvement by the Austrian Institute of Health Technology Assessment (AIHTA)

As part of this HTA, the aim is generally to obtain additional patients' perspectives through a questionnaire, as described in the methods section (Chapter 3). Unfortunately, despite intensive efforts, no patients could be identified.

keine Patient:innen für Befragung identifizierbar

### Results from the JCA

Patients are involved in the joint HTA work as individual experts contributing to JCAs. They are selected and involved in the JCA after the European Commission has assessed their declarations of interest, to ensure they participate in an independent and transparent manner, free from conflict of interest [42]. An involvement is possible during the preparation of the assessment scope and in commenting on the report. However, in the JCA for lurbinectedin, no patients were included.

JCA: Beteiligung von Patient:innen grundsätzlich vorgesehen

Lurbinectedin: keine Beteiligung

## 6.2.2 Carer perspective

### Findings from the literature

In their mixed-methods study, Bebb et al. (2023) also included unpaid caregivers of patients with SCLC, demonstrating that the disease imposes a high personal and psychological burden on them. Caregivers of patients with ES-SCLC observed similar symptoms and impacts of the disease on the patients as those reported by the patients themselves, including shortness of breath, fatigue, and weakness. They considered fatigue one of the disease's most significant impacts. Furthermore, they reported that shortness of breath affected the patient's ability to perform simple activities such as climbing stairs, doing chores, and showering.

Betreuende: starke persönliche und psychische Belastung

Pflegeaufgaben manchmal überwältigend

Leben von betreuenden Personen eingeschränkt

Particularly for patients with ES-SCLC, caregiving duties were sometimes considered overwhelming. Although none of the interviewed caregivers left employment specifically to care for their patient, they wished they had more time for their careers, families, and hobbies. The caregivers further reported a reduced ability to participate in their own social lives. They also commented on their emotional impact, including anger, frustration, and the inability to do what they wanted or needed to do. This triggered feelings of hidden resentment and associated guilt [36]. Caregivers may face many of the same challenges with work, finance, self-esteem, isolation, and negative emotions as patients [43].

### Involvement by the AIHTA

kollektive Perspektive von Mitglied einer Selbsthilfegruppe für Atemwegserkrankungen

Einblick in Herausforderungen

Lurbinectedin nicht bekannt

generell hohe Erwartungen an neue Therapien

As described in the methods section (Chapter 3), this HTA aims to obtain additional carers' perspectives through a questionnaire, for which a member of an Austrian LC support group agreed to provide a collective response.

The interviewed member described that affected patients suffer from shortness of breath, they can't manage their daily life, and their social lives are restricted. Shedding light on the situation of relatives, the person stated that, fearing for the patients' lives, feeling sorry for them, and even worrying about whether they would be affected are essential concerns. The current healthcare situation for LC treatment in Austria was rated as "good". In general, expectations for new treatment options for LC are that surgeries will become redundant. The interviewed member does not know lurbinectedin yet; however, they described their feelings regarding the new product as "that it is, or becomes, a miracle drug" [44].

### Results from the JCA

JCA: eine betreuende Person inkludiert

In the JCA process, carer involvement is intended [42]. With lurbinectedin, one carer was included, providing comments on the JCA report and summary report [1].

Zweifel an Übertragbarkeit der Daten

In the comments, the carer noted that the study's inclusion criteria did not align with the clinical factors influencing SCLC prognosis and thus do not resemble real-world settings. Based on these concerns, the carer questioned whether access to the product could differ across countries [1].

Besorgnis hinsichtlich Langzeitwirkung und Einfluss auf Lebensqualität

Hinweis auf wichtige Unterscheidung der Symptomursache

Further concerns included reduced confidence in understanding the real long-term impact of treatment on symptoms, daily functioning, and QoL due to the described study limitations, a lack of a full understanding of the benefits of long-term treatment, and a lack of stratification of outcomes by patient characteristics. The carer also highlighted the importance of distinguishing between the symptoms of the illness and side effects. According to the carer's opinion, patient participation in the study design stage would make the outcome "less disappointing for patients" [1].

## 6.3 Further considerations

österr. klin. Experten betonen Wichtigkeit des offenen Gesprächs um den Patient:innen eine freie Entscheidungsfindung zu ermöglichen

Just as patients prefer an open approach to their illness [38], Austrian clinical experts also emphasise the importance of openly discussing prognosis, treatment options and their associated effects. After receiving primary chemotherapy, patients with ES-SCLC often experience a so-called "honeymoon phase", referring to a time when the patients feel better before deteriorating again and further therapy is required. The subsequent treatment line (e.g. lurbinectedin) aims to prolong OS, although the expected benefit may be limited and treatment may again affect QoL. Therefore, Austrian clinical experts considered it ethically important that patients are supported in making an informed and autonomous decision about whether to receive further treatment [7].

## 6.4 Austrian registries and documentation of lurbinectedin use

nationales Krebsregister von Statistik Austria, nur epidemiologische Daten

In Austria, all cancer cases are recorded in the Austrian National Cancer Registry, maintained by Statistics Austria. It includes cancer cases diagnosed or treated in hospitals [2]. Of note, it is an epidemiological registry that collects incidence and mortality data, but not information on diagnoses, disease stages, or treatment.

Lungenkrebsregister von Wiener Gesundheitsverbund und Karl Landsteiner Institut

In 2020, a specific lung cancer registry was established by the Vienna Health Network in collaboration with the Karl Landsteiner Institute for Lung Research and Pneumological Oncology. The aim of this registry is to improve treatment quality through detailed data analysis and collaboration among hospitals [45, 46].

LALUCA: Forschungsplattform mit Fokus auf diagnostische Prozesse, therapeutische Entscheidungen, und Prognose im klinischen Alltag

In addition, the Karl Landsteiner Institute for Lung Research and Pneumological Oncology established the Austrian research platform "LALUCA" (Longitudinal Analysis of Lung Cancer Data). The purpose of this project is to document representative data on molecular testing, sequence of systemic treatment and other treatment modalities, and the course of disease in patients with LC. It particularly focuses on molecular biomarker testing and next generation sequencing of patients before the start of first-line treatment. The data are intended to assess the current state of care and develop recommendations for areas that can be improved [47].

## 6.5 Interpretation of findings

Anpassung von Behandlungsprotokollen, aber keine tiefgreifenden Strukturänderungen nötig

From an organisational perspective, the consulted clinical experts do not expect substantial structural changes with the implementation of lurbinectedin in Austria. However, for successful treatment, organisational adjustments in line with specific treatment protocols, interdisciplinary coordination, neutropenia prophylaxis, and careful monitoring and management of AEs were considered essential. The clinical experts further highlighted the importance of training less experienced personnel [7].

Patient:innenperspektive ausschließlich aus Literaturquellen

For this report, information on patients' perspectives could be obtained solely from the literature. Despite intensive efforts, no eligible patients could be recruited to answer the questionnaire provided by the AIHTA. There might be two limiting factors why those affected are so difficult to identify: on the one hand, patients are at a very serious stage of their disease and have limited capacities. On the other hand, the timeframe for patient involvement is limited, making the timely identification of eligible patients difficult.

Patient:innen sind schwer krank

hohe Erwartungen an neues Produkt

A member of an Austrian support group kindly agreed to provide a collective perspective on patients with lung cancer [44]. In describing the situation of affected patients, the statements of the person interviewed by the AIHTA align with the literature. Although the person had not yet been informed about lurbinectedin specifically, high expectations regarding the new treatment option were expressed.

Beteiligung Betroffener gesetzlich vorgeschrieben und moralisch wünschenswert

The involvement of affected persons within the Austrian appraisal board process is not only a legal requirement [48] but may also be important from an ethical and patient-centred perspective, offering the opportunity for patients, carers and members of patient organisations to participate. Although potential input from a single person is neither generalisable nor representative, valuable aspects (particularly regarding the Austrian context) can still be identified.

JCA: eine betreuende Person einbezogen, äußert Bedenken hinsichtlich der Übertragbarkeit der Daten

At a European level, it is generally intended to involve patients and carers in the JCAs [42]. In the case of lurbinectedin, however, no patient was successfully involved, but one carer was. When commenting on the report, the person noted concerns about the data's applicability to real-world settings and reduced confidence in understanding the long-term impact of treatment on symptoms, daily functioning, and QoL [1].

wesentlicher Aspekt: Möglichkeit der informierten Entscheidung

One relevant aspect identified during the preparation of this HTA concerns the process of treatment decision-making. Patients value when their doctors discuss their condition and prognosis openly [38]. This is consistent with the approach of Austrian clinical experts, who emphasise the importance of openly discussing treatment options and their associated effects to enable patients to make informed decisions [7].

# 7 Development costs and public contributions

## 7.1 Own development costs, acquisitions and licences

Übersicht zu Entwicklungskosten

Neither PharmaMar nor Jazz Pharmaceuticals has published the total amount of research and development (R&D) expenses attributed to ZEPZELCA®. As this chapter is based solely on publicly accessible information, any funding amounts related to the development of lurbinectedin may be incomplete. Table 7-1 provides a brief summary of the key development points of lurbinectedin.

*Table 7-1: ZEPZELCA® development history and public contribution overview*

| Originator | Developer | Information on acquisitions | Public contribution | Type of public funding |
|---|---|---|---|---|
| PharmaMar | PharmaMar<br>Jazz Pharmaceuticals<br>Roche | 2019: Exclusive licensing agreement between PharmaMar and Jazz Pharmaceuticals | Roughly €8.3 million in identified direct and indirect public funding | Basic research funding |

### Basic research and clinical development

Entwicklungsgeschichte von Lurbinectedin

The development of lurbinectedin for the treatment of ES-SCLC originated with PharmaMar, which retained the originator rights to the compound. The funding records describe lurbinectedin as a "marine-origin antitumour compound." As described in Chapter 7 in the Appendix, beyond PharmaMar's in-house program, research relevant to lurbinectedin has been carried out at academic institutions including the University of Texas MD Anderson Cancer Center, which conducted a phase 2 basket trial of lurbinectedin in patients with pretreated germline breast cancer gene 1/2 metastatic breast cancer, and Texas A&M University, which conducted long-running structural and synthetic studies of bioactive marine agents [49].

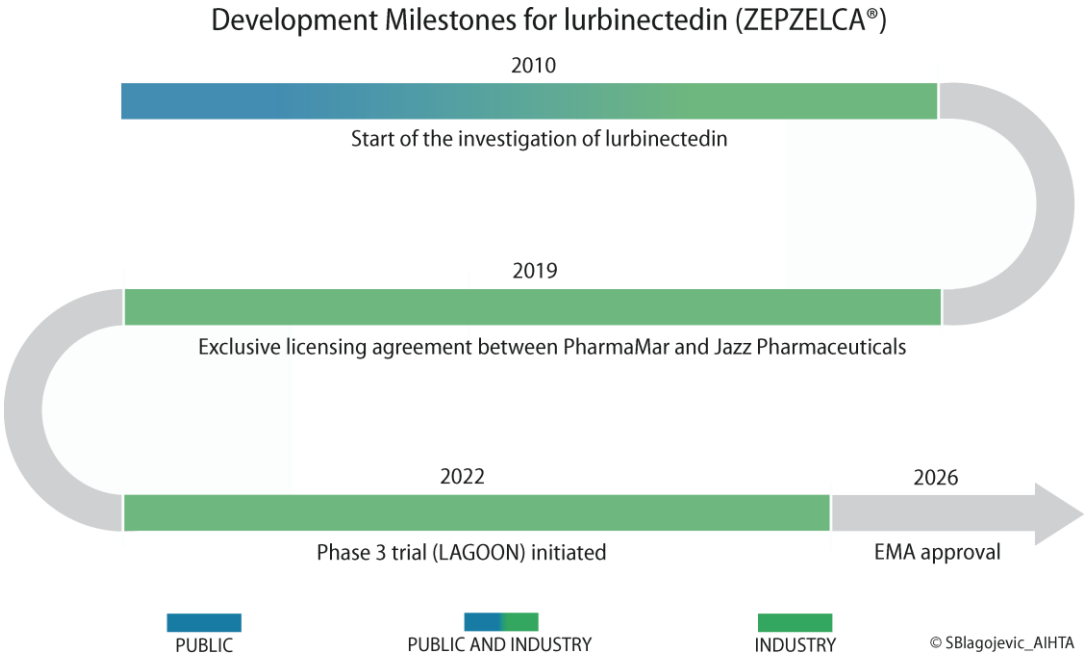



*Figure 7-1: Development milestones for lurbinectedin*

## 7.2 Public contributions to drug development

### Research funding and collaborations

This part includes confidential information!

spanische öffentliche Beiträge für die Entwicklung von Lurbinectedin

As documented in Chapter 7 in the Appendix, Spanish national funding bodies provided several relevant grants. The Agencia Estatal de Investigación awarded €74,045 in 2010 for research on the physicochemical stability in plasma and aqueous vehicles of four antitumour molecules under preclinical evaluation, and €2,290,860 in 2010 for the POLYSFERA project on polymeric nano capsules for controlled delivery of antitumour drugs, the primary target of which was docetaxel, with stated implications for lurbinectedin. The Centro para el Desarrollo Tecnológico Industrial funded efficacy studies of lurbinectedin in selected advanced solid tumours (Grant ID: IDI-20150006); the specific amount was not publicly disclosed [50].

US-amerikanisch finanzierte Grundlagenforschung, die nur indirekt zur Entwicklung Lurbinectedins beigetragen hat

In the US, Texas A&M University received $6,540,193 between 1995 and 2019 from the National Institute of General Medical Sciences for the project "Structural/Synthetic Studies of Bioactive Marine Agents", research broadly relevant to marine-derived compounds. The University of Texas Health Science Center at Houston received $335,040 from the National Cancer Institute in 2013 for research on informatics to enable routine personalised cancer therapy. The University of Texas MD Anderson Cancer Center's Phase 2 basket trial referenced above was funded by the Cancer Prevention & Research Institute of Texas, a Texas state-funded entity; the specific amount was not disclosed [49].

### Company structure and financials

exklusives Lizenzabkommen zwischen PharmaMar und Jazz Pharmaceuticals

In December 2019, PharmaMar entered into an exclusive licence agreement with Jazz Pharmaceuticals granting Jazz exclusive US development and commercialisation rights to ZEPZELCA®. The agreement became effective in January 2020, with Jazz making an upfront payment of $200 million. Under the agreement, PharmaMar is eligible to receive up to $800 million in additional regulatory and commercial milestone payments, plus tiered royalties on future net sales ranging from the high teens up to 30%. In June 2020, PharmaMar received a further non-refundable payment of $100 million (€88.5 million). The licence agreement was subsequently amended in 2020 to expand Jazz's commercialisation rights to Canada. In October 2025, PharmaMar received a $50 million milestone payment (€42.586 million) following FDA full approval of ZEPZELCA® in combination with atezolizumab as first-line maintenance treatment for adults with metastatic SCLC [51, 52].

weitere regionale Abkommen zwischen PharmaMar und Luye Pharma und Merck

PharmaMar has established additional regional partnerships. In December 2024, Luye Pharma Group received conditional marketing approval for ZEPZELCA® from China's National Medical Products Administration for adult patients with metastatic SCLC, and PharmaMar received a $5 million (€4.409 million) payment in connection with this approval. In April 2025, PharmaMar entered into an exclusive licence agreement with Merck Healthcare KGaA for the development and commercialisation of ZEPZELCA® in Japan, receiving an upfront payment of €22 million, with additional regulatory and commercial milestones and royalties on sales contemplated under the agreement [51].

### Patents and market exclusivity

keine Generika vor Juni 2036; Patentschutz möglicherweise bis 2042

Regulatory data protection in the EU rules out generic entry until 1 June 2036, with a possible extension to 1 June 2037, so no generic price comparators are expected within this period. European patent application EP4430075A1, which covers the authorized dosing regimen of lurbinectedin with atezolizumab as first-line maintenance treatment of ES-SCLC, is still pending. If granted, it could extend protection for this indication until November 2042 [53].

Marktexklusivität für Lurbinectedin für ES-SCLC in den USA bis 2027

According to Jazz Pharmaceuticals' 2025 10-K filing, one Orange Book-listed US patent (expiring in 2029, with granted patent term extension) covers a genus of compounds including lurbinectedin and their use in treating various cancers. A request for a Certificate of Supplementary Protection has also been filed in Canada. ZEPZELCA® has been granted orphan drug exclusivity in the US for the treatment of adults with metastatic SCLC who have progressed on or after platinum-based chemotherapy until 2027. The exclusivity for the new chemical entity expired in 2025. Orphan drug exclusivity for the second indication is anticipated and, if granted, would expire in October 2032 [51].

## 7.3 Interpretation of findings

€ 8,3 Millionenöffentliche, direkte und indirekte Beiträge identifiziert

The identifiable public research funding linked to lurbinectedin and to related basic research is comparatively limited. The development history of ZEPZELCA® reflects a primarily industry-led trajectory originating from PharmaMar, supplemented by some public research funding, mainly from Spanish national sources and more indirect public funding from US federal and Texas state agencies supporting related work on marine-derived compounds and clinical studies of lurbinectedin. The identifiable public contributions linked to lurbinectedin are roughly €8.3 million – most of it for indirect contributions in the US.

# 8 Landscape overview

## 8.1 Ongoing studies on lurbinectedin

11 laufende klinische Studien identifiziert, die Lurbinectedin untersuchen

Ten ongoing clinical studies evaluating lurbinectedin were identified via ClinicalTrials.gov (Table 8-1). Nine are for SCLC, one for bladder cancer and one for metastatic leiomyosarcoma. These include two studies currently recruiting (NCT06496048, NCT06228066), five active, but not recruiting (NCT05091567, NCT05153239, NCT04802174, NCT04607954, NCT06088290), three not yet recruiting (NCT06497530, NCT07459634, NCT06501976), and one clinical trial with an unknown status (NCT04253145).

Lurbinectedin in Kombination mit anderen Wirkstoffen wird in klinischen Studien untersucht

Of the studies for SCLC, lurbinectedin is being investigated with other combinations: irinotecan (NCT06496048, NCT05153239), topotecan (NCT06496048), atezolizumab (NCT05091567, NCT04253145), berzosertib (NCT04802174), durvalumab (NCT04607954, NCT07459634), serplulimab (NCT06497530), and radiotherapy (NCT06501976). One study not for SCLC (NCT06228066) is investigating lurbinectedin in combination with avelumab and the other study (NCT06088290) is investigating lurbinectedin in combination with doxorubicin

5 klinische Studien untersuchen Lurbinectedin als Erstlinientherapie

In the first-line/maintenance setting for ES-SCLC, five trials pair lurbinectedin with immunotherapy as maintenance after induction chemoimmunotherapy. IMforte (NCT05091567, Phase 3) and the 2SMALL study (NCT04253145, Phase 1/2) combine it with atezolizumab; CROC-24-02 (NCT06497530, Phase 2) uses serplulimab; and NCT07459634 (Phase 2) in combination with durvalumab. NCT06501976 (Phase 2) tests lurbinectedin with radiotherapy as consolidation in locally-advanced (limited-stage) SCLC after first-line therapy.

3 klinische Studien untersuchen Lurbinectedin als Zweitlinientherapie

In the second-line/relapsed setting are three trials: LAGOON (NCT05153239) and NCT06496048, both testing lurbinectedin alone or with irinotecan versus topotecan/irinotecan in relapsed SCLC. NCT04607954 (MC1923, Phase 2) adds durvalumab to the treatment of relapsed/refractory disease.

2 klinischen Studien untersuchen Lurbinectedin nicht nach Therapielinie

The remaining two trials are not strictly line-defined: the berzosertib (ATR inhibitor) combination (NCT04802174) in SCLC and high-grade neuroendocrine cancers, and LASER (NCT06228066), which is in small cell carcinoma of the bladder rather than lung.

## 8.2 Treatments in development

6 Therapien in der IHSI-Datenbank identifiziert für SCLC

Using the IHSI database [54], a total of six combination therapies were identified as under development for SCLC with atezolizumab, carboplatin or etoposide (see Table 8-3): Atigotatug/nivolumab, durvalumab, pembrolizumab, pumitamig, tarlatamab, turmetabart adizutecan, and 225ac-abd147. All but one (225ac-abd147) of the identified therapies are indicated as first-line treatment. 225ac-abd147 is for the second line. All but one (turmetabart adizutecan) are various types of monoclonal antibodies. Turmetabart adizutecan is an antibody-drug conjugate.

voraussichtliches Datum für EC-Entscheidungen

For SCLC with atezolizumab, carboplatin or etoposide, the expected EC decision times are as follows: pembrolizumab (Aug 2028), atigotatug/nivolumab (August 2029), pumitamig (August 2029), tarlatamab (April 2030), 225ac-abd147 (July 2030), and turmetabart adizutecan (September 2030).

## 8.3 Interpretation of findings

Lurbinectedin wird meist in Kombination untersucht, v. a. mit Immun-Checkpoint-Inhibitoren

The clinical development of lurbinectedin, mainly in combination therapy, is heavily weighted toward SCLC, with nine of ten ongoing trials in this indication and one in bladder cancer. Lurbinectedin is rarely tested as monotherapy but instead paired with cytotoxic agents such as irinotecan and topotecan, the ATR inhibitor berzosertib, radiotherapy, and – reflecting the field's growing emphasis on chemoimmunotherapy – a range of immune checkpoint inhibitors including atezolizumab, durvalumab, avelumab, and serplulimab. This position of lurbinectedin is both as a maintenance after induction chemoimmunotherapy in the first-line setting and as a relapse-directed option, underscoring its potential role across multiple lines of ES-SCLC treatment.

6 weitere Therapien in Entwicklung, die zum Teil eine Alternative für Lurbinectedin sein könnten

The emerging SCLC treatment landscape demonstrates a robust pipeline of combination therapies predominantly incorporating monoclonal antibodies alongside standard chemotherapy, with regulatory approval anticipated over the next two to four years. While most candidates target first-line treatment settings, reflecting efforts to improve initial therapeutic outcomes, the inclusion of one second-line option (225ac-abd147) suggests attempts to address treatment-resistant disease. The EC decision timeline, spanning from August 2028 to September 2030, indicates gradual market entry of these therapies, potentially offering clinicians multiple sequential or alternative combination strategies for SCLC management in the near term.

*Table 8-1: List of ongoing studies with lurbinectedin for SCLC*

| Title | Trial ID | Other IDs | Phase | Status | Estimated study completion date | Additional information |
|---|---|---|---|---|---|---|
| Study to Assess Safety, Tolerability, Efficacy of PM01183 and Atezolizumab in Patients w/Advanced SCLC[7] | NCT04253145 | 2SMALL | 1/2 | Unknown status | 05.2025 | Interventional |
| Clinical Trial of Lurbinectedin as Single-agent or in Combination With Irinotecan Versus Topotecan or Irinotecan in Patients With Relapsed SCLC (LAGOON)[8] | NCT05153239 | PM1183-C-008-21 | 3 | Completed | 04.2026 | Interventional |
| Maintenance Lurbinectedin in Combination With Serplulimab for Patients With ES-SCLC | NCT06497530 | CROC-24-02 | 2 | Not yet recruiting | 12.2026 | Interventional |
| An Exploratory Study of Lurbinectedin With Radiotherapy in Locally-advanced SCLC After First-line Therapy | NCT06501976 | NCC4493 | 2 | Not yet recruiting | 06.2027 | Interventional |
| Lurbinectedin With Berzosertib, an ATR Kinase Inhibitor in Small Cell Cancers and High-Grade Neuroendocrine Cancers | NCT04802174 | 10000176<br>000176-C | 1/2 | Active, not recruiting | 01.12.2027 | Interventional |
| A Phase III, Open-Label Study of Maintenance Lurbinectedin in Combination With Atezolizumab Compared With Atezolizumab in Participants With ES-SCLC (IMforte) | NCT05091567 | GO43104<br>2023-503868-16-00 | 3 | Active, not recruiting | 28.02.2028 | Interventional |
| A Study of Lurbinectedin in Combination With Durvalumab for the Treatment of Participants With ES-SCLC | NCT07459634 | 2025-524566-13-00 | 2 | Not yet recruiting | 30.04.2028 | Interventional |
| Lurbinectedin or in Combination with Irinotecan Versus Topotecan in Patients with Relapsed SCLC | NCT06496048 | LY01017/CT-CHN-302 | 3 | Recruiting | 30.06.2028 | Interventional |
| Durvalumab and Lurbinectedin for the Treatment of Relapsed or Refractory SCLC | NCT04607954 | MC1923<br>20-001531 | 2 | Active, not recruiting | 01.05.2031 | Interventional |

*Abbreviations: ES-SCLC … extensive-stage small cell lung cancer, SCLC … small cell lung cancer*

*Table 8-2: List of ongoing studies with lurbinectedin for other indications*

| Title | Trial ID | Other IDs | Phase | Status | Estimated study completion date | Additional information |
|---|---|---|---|---|---|---|
| Lurbinectedin With or Without Avelumab in Small Cell Carcinoma of the Bladder (LASER) | NCT06228066 | 10001523<br>001523-C | 2 | Recruiting | 01.09.2028 | Interventional |

[7] Unknown status

[8] Study completed but results have not been published

| Title | Trial ID | Other IDs | Phase | Status | Estimated study completion date | Additional information |
|---|---|---|---|---|---|---|
| Study of Lurbinectedin in Combination With Doxorubicin Versus Doxorubicin Alone as First-line Treatment in Participants With Metastatic Leiomyosarcoma (SaLuDo) (SaLuDo) | NCT06088290 | PM1183-C-010-22<br>2022-502975-45 | 3 | Active, not recruiting | 30.08.2029 | Interventional |

*Table 8-3: Landscape overview for combination therapies in development for small cell lung cancer*

| Intervention and indication | Active ingredient | NCT Number | Phase | Treatment line | Developer | Drug class | Estimated EC decision |
|---|---|---|---|---|---|---|---|
| Pembrolizumab | | | | | | | |
| Pembrolizumab in combination with concurrent chemoradiation therapy followed by pembrolizumab and olaparib for first-line treatment of newly diagnosed limited-stage SCLC in adults and elderly | Pembrolizumab | NCT04624204 | 3 | first line | MSD | Monoclonal antibody | Aug 2028 |
| Atigotatug/nivolumab | | | | | | | |
| Atigotatug/nivolumab in combination with carboplatin plus etoposide for first-line treatment of ES-SCLC in adults and elderly | Atigotatug/nivolumab | NCT06646276 | 3 | first line | Bristol Myers Squibb | Fixed-dose combination of two monoclonal antibodies | Aug 2029 |
| Pumitamig | | | | | | | |
| Pumitamig in combination with chemotherapy for first-line treatment of ES-SCLC in adults and elderly | Pumitamig | NCT06712355 | 3 | first line | BioNTech | Bispecific immunoglobulin (monoclonal antibody) | Aug 2029 |
| Tarlatamab | | | | | | | |
| Tarlatamab in combination with durvalumab, carboplatin and etoposide for first-line treatment of extensive stage, stage IV SCLC in adults and elderly | Tarlatamab | NCT07005128 | 3 | first line | Amgen | Bispecific T-cell engager (BiTE) antibody construct | Apr 2030 |
| Study Comparing Tarlatamab and Durvalumab Versus Durvalumab Alone in First-Line Extensive-Stage Small-Cell Lung Cancer (ES-SCLC) Following Platinum, Etoposide and Durvalumab (DeLLphi-305) | | NCT06211036 | 3 | first line | Amgen | | Sep 2029 |
| 225ac-abd147 | | | | | | | |
| 225ac-abd147 monotherapy for second-line treatment of locally advanced or metastatic SCLC in adults and elderly | n.a. | NCT06736418 | 1 | second line | Abdera Therapeutics | Actinium-225 radiolabeled monoclonal antibody (radiopharmaceuticals) | Jul 2030 |
| Turmetabart Adizutecan | | | | | | | |
| Turmetabart adizutecan in combination with atezolizumab for first-line treatment of ES-SCLC in adults and elderly | Turmetabart adizutecan | NCT07155174 | 2 | first line | AbbVie | Antibody-drug conjugate | Sep 2030 |

*Abbreviations: EC … European Commission, ES-SCLC … extensive-stage small cell lung cancer, SCLC … small cell lung cancer, n.a. …not applicable*

# 9 Conclusion

This report assessed lurbinectedin (ZEPZELCA®) in combination with atezolizumab for the maintenance treatment of adult patients with ES-SCLC whose disease has not progressed after first-line induction therapy with atezolizumab. Lurbinectedin was subject to a JCA, conducted in accordance with the Regulation on Health Technology Assessment (Regulation (EU) 2021/2282).

Klinik:
sign. PFS-Verbesserung,
OS nicht signifikant,
methodische Limitationen,
eingeschränkte
Generalisierbarkeit

In the phase 3 IMforte trial, lurbinectedin plus atezolizumab achieved a statistically significant improvement in median PFS compared with atezolizumab monotherapy, while the evidence for an OS benefit was less consistent across data cut-offs. In selected quality-of-life domains, time to deterioration was shorter with lurbinectedin plus atezolizumab, favouring atezolizumab monotherapy. The interpretation of these results is shaped by the open-label design, the fact that independent radiological review of PFS was performed only at the first data cut-off, with subsequent PFS analyses based on investigator assessment, and the measurement of survival from randomisation into the maintenance phase. AEs were more frequent with lurbinectedin plus atezolizumab and were predominantly haematological among severe adverse events. Exploratory subgroup analyses suggested potential differences in treatment effects according to the presence of liver metastases and prior PCI, but these findings should be interpreted with caution and do not provide a robust basis for treatment selection. Eligibility was restricted to a relatively fit patient population (ECOG performance status 0-1, without CNS metastases), which may limit the generalisability of the findings to routine clinical practice. The combination lurbinectedin plus atezolizumab has been included in several international clinical practice guidelines [4, 9, 10, 55]. These recommendations are based on the same pivotal trial (IMforte trial). No evidence from completed randomised controlled trials is currently available for lurbinectedin in combination with immune checkpoint inhibitors other than atezolizumab.

Kombinationstherapie
nicht kosteneffektiv
zu Listenpreisen,
Budget-Impact abhängig
von Pat.-Anzahl,
Uptake & Zyklenanzahl

The economic evidence from two published cost-utility analyses indicates that the combination is not cost-effective at current list prices across the evaluated WTP thresholds, with incremental QALY gains largely dependent on survival extrapolation and ICERs sensitive to the modelling horizon and drug wastage. For Austria, the estimated treatment cost is €106,778 per patient. The analyses point to costs arising from the concurrent administration of two agents rather than from lurbinectedin alone. Depending on the eligible population and the uptake of lurbinectedin, the net budget impact of reimbursing lurbinectedin in Austria is projected to range from around €31.2 to €43.3 million over the three-year horizon. These estimates are subject to substantial uncertainty regarding the eligible population size (range: 180-250 patients), uptake rates (60%-75%), and the number of treatment cycles.

Organisation:
keine
Strukturänderungen, aber
Protokollanpassungen
nötig

From an organisational perspective, no major structural changes are anticipated. However, treatment-protocol adjustments, interdisciplinary coordination, neutropenia prophylaxis, monitoring of AEs, staff training, and documentation in appropriate registries were identified as relevant for implementation. Evidence on the patient and carer perspective was available only from the literature and a single collective statement, highlighting the serious disease burden, high expectations toward new treatments, and the importance of informed treatment decisions.

ZEPZELCA® (lurbinectedin) was developed primarily through an industry-led effort originating with PharmaMar. Total R&D expenditure has not been publicly disclosed. Identifiable public funding is comparatively limited, amounting to roughly €8.3 million in direct and indirect contributions. The broader treatment landscape includes several additional combination therapies in development, with anticipated market entry over the next two to four years.

überwiegend industriegetriebene Entwicklung, rund € 8,3 Mio. öffentliche Förderung identifiziert

Across all domains, several important uncertainties remain, including the maturity and robustness of the survival data, the outcome of price negotiations, and the future positioning of lurbinectedin within an evolving treatment landscape. It remains to be determined how these open questions will be addressed and what implications they may have for the assessment and potential use of lurbinectedin in ES-SCLC in the future.

offene Fragen zu Überlebensdaten, Preisverhandlungen, neue Positionierungen von Lurbinectedin

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