Amsterdam, 26 March 2026
EMA/87579/2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zepzelca

International non-proprietary name: Lurbinectedin

Procedure No. EMEA/H/C/006673/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

%Diff	Percentage Difference
µg	microgram
µM	micromolar (micromole per litre)
1L	First-line
2L	second line
AAG	alpha-1-acid glycoprotein
ABC	adenosine triphosphate-binding cassette
ADA	anti-drug antibody
ADME	absorption, distribution, metabolism, and elimination
AE	adverse event
AEG35	adverse events of grade 3 to 5
AESI	adverse events of special interest
AI	Acceptable intake
Al	Aluminium
ALB	albumin
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
AP	alkaline phosphatase
API	Active pharmaceutical ingredient
AR	Assessment report
ASMF	Active substance master file
AST	aspartate aminotransferase
AUC	area under the curve
AUC0-21d	area under the concentration-time curve during dosing interval at cycle 1
AUC0-∞	area under the plasma concentration-time curve from time zero to infinity
AUC0-last	area under the plasma concentration-time curve from time zero to the time of the last measurable concentration
AUC0-t	area under the plasma concentration-time curve from time zero to time t
AUCss	area under the concentration-time curve during dosing interval at steady state
AUCtot	total area under the plasma concentration-time curve
AUCu	area under the unbound concentration vs time curve
BANC	absolute neutrophil count at baseline
BCS	Biopharmaceutical classification system
BET	Bacterial endotoxins
BID	twice daily
BLQ	below the limit of quantification
BRCA	Breast Cancer Gene
BSA	Body Surface Area
CAT	Committee for Advanced Therapies
CCOD	Clinical Cutoff Date
CE	Carboplatin and Etoposide
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
Cmax	maximum plasma concentration
Cmin	minimum plasma concentration
CNS	Central Nervous System
CoA	Certificate of Analysis
CPCA	Carcinogenic potency categorization approach
CPK	Creatine Phosphokinase
CPP	Critical process parameters
CR	Complete Response
CrCL	creatinine clearance
CRP	c-reactive protein
CSP	Clinical Study Protocol
CSR	Clinical Study Report

CT	Computed Tomography
CTCAE	common terminology criteria for adverse events
CTFI	Chemotherapy-free Interval
CTLA-4	Cytotoxic T-lymphocyte Antigen 4
CUI	clinical utility index
CV%	percent coefficient of variation
CWRES	conditional weighted residuals
CYP	cytochrome p450
DDI	drug-drug interaction
DFS	disease-free survival
DLT	dose limiting toxicity
DMSO	Dimethylsulfoxide
DNA	deoxyribonucleic acid
DOR	Duration of Response
DP	Drug product
DS	Design space
DSC	Differential Scanning Calorimetry
DTA	Differential thermal analysis
DTC	differentiated thyroid cancer
EBE	empirical bayes estimates
EC50	half maximal effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDTA	ethylenediaminetetraacetic acid
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
Emax	maximum effect
EMD	enhanced model document
EOI	end of infusion
EORTC	European Organisation for Research and Treatment of Cancer
E-R	exposure-response
ESMO	European Society of Medical Oncology
ES-SCLC	Extensive-stage Small Cell Lung Cancer
FAS	Full Analysis Set
Fc	fragment crystallizable
FD	Flat Dose
FDA	Food and Drug Administration
FDM	Freeze-drying microscopy
FiH	First-in-Human Study
FU	Follow-up
G≥3	grade ≥3
G3-5	grade 3 to 5
G4	grade 4
GC	Gas chromatography
GCSF	granulocyte colony-stimulating factor
G-CSF	Granulocyte colony-stimulating factor
GEM	gem = gemcitabine
GHS	Global Health Status
GLP	Good Laboratory Practice
GM	geometric mean
GMP	Good manufacturing practice
HB	haemoglobin
HCC	hepatocellular carcinoma
hERG	human ether-à-go-go related gene
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
HR	Hazard Ratio

HRQoL	Health-related Quality of Life
i.v.	Intravenous
IC50	maximum inhibitory concentration
IERAES	integrated exposure response analysis of efficacy and safety
IgG1	immunoglobulin g1
IIV	inter-individual variability
IL	interleukin
IL46	Item List 46 (EORTC)
INR	international normalised ratio
IPC	In-process control
IR	Infrared
IRC	Independent Review Committee
IRF	Independent Review Facility
ISR	Incurred sample reanalysis
ISS	Integrated Summary of Safety
IV	intravenous
IWRES	individual weighted residuals
IxRS	Interactive Voice or Web-Based Response System
K3EDTA	Tripotassiom ethylenediaminetetraacetic acid
Kd	dissociation constant
KDIGO	Kidney Disease: Improving Global Outcomes
KF	Karl Fisher
Km	substrate concentration at half maximal velocity
LC	Liquid Chromatography
LC-MS/MS	Liquid Chromatography Tandem Mass Spectrometry
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of Quantification
LOA	Letter of access
LOD	Loss on drying
LOD	Limit of detection
LOQ	Limit of quantification
LRT	likelihood ratio test
LSC	Liquid Scintillation Counting
LTS	Long-term Stability
Lurbi Mono	Lurbinectedin Monotherapy
LVEF	left ventricular ejection fraction
m2	square meter
mAb	monoclonal antibody
MAH	Marketing authorisation holder
MDD	Maximal daily dose
MDR1	multidrug resistance protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MeOH	Methanol
Min	Minimum
MPE	mean prediction error
MPR	parent ratio
MRI	Magnetic Resonance Imaging
MRM	Multiple Reaction Monitoring
MS	Mass Spectrometry
MS	Mass spectrometry
MTD	Maximum Tolerated Dose
MTT	mean transit time
mUC	metastatic urothelial carcinoma
MUGA	Multiple-gated Acquisition Scan
NADPH	nicotinamide adenine dinucleotide phosphate
NCA	noncompartmental analysis
NCCN	National Comprehensive Cancer Network (US)
NCI	national cancer institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

NCI-ODWG	national cancer institute organ dysfunction working group
ND	Not detected
NDPE	normalized prediction distribution errors
NE	Not Estimable / Not Evaluable
NHP	non-human primate
NMR	Nuclear magnetic resonance
NMT	Not more than
NONMEM	nonlinear mixed effects modelling
NPT	Non-protocol Anticancer Therapy
NSCLC	non-small cell lung cancer
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
ºC	Degrees Celsius
OD	Optical Density
ORR	Objective Response Rate
OS	Overall Survival
PA	Polyamide
PACMP	Post approval change management protocol
PAR	Proven acceptable range
PARPi	Poly (ADP-ribose) Polymerase Inhibitors
PBPK	physiologically-based pharmacokinetics
PBS	Phosphate Buffered Saline
PCI	Prophylactic Cranial Irradiation
PCR	Polymerase Chain Reaction
pcVPC	prediction-corrected visual predictive check
PD	Progressive Disease
PD-1	programmed cell death protein 1
PDE	Permitted daily exposure
PD-L1	Programmed Death-ligand-1
PFS	Progression-free Survival
P-gp	p-glycoprotein
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PK/PD	Pharmacokinetic/Pharmacodynamic
PL	Patient leaflet
PLD	Pegylated Liposomal Doxorubicin
PLT	platelets
PLTB	platelets at baseline
PO	per oral
PopPK	Population Pharmacokinetic
PR	Partial Response
PRAC	Pharmacovigilance risk assessment committee
PRO	Patient-reported Outcome
PRO-CTCAE	Patient-reported Outcome Common Terminology Criteria for Adverse Events
PS	Performance Status
PT	Preferred Term
PVC	Polyvinyl chloride
Q2	intercompartmental clearance from the central compartment to the first peripheral compartment
Q2W	every 2 weeks
Q3	intercompartmental clearance from the central compartment to the second peripheral compartment
Q3W	every 3 weeks
Q4W	every 4 weeks
QD	every day
QLQ-C13	Quality of Life Questionnaire Lung Cancer Module
QLQ-C30	Quality of Life Questionnaire Core 30
QoL	Quality of Life
QOS	Quality overall summary

QP	Qualified person
QTc	corrected qt interval
QTcF	Fridericia's corrected qt
RBC	Red Blood Cells
RD	Recommended Dose
RECIST	Response Evaluation Criteria in Solid Tumours
RED	Rapid Equilibrium Dialysis
RH	Relative humidity
RMP	Risk management plan
RMSE	root mean squared prediction error
RRT	Relative retention time
RV	Residual Variabilities
SAE	Serious Adverse Event
SAS	Safety Analysis Set
SB	Summary of Biopharmaceutic Studies and Associated Analytical Methods
SCLC	Small Cell Lung Cancer
SCM	stepwise covariate model
SCP	summary of clinical pharmacology
SD	Stable Disease
SDev	Standard Deviation
SE	standard error
SLE	Supported liquid extraction
SM	Starting material
SmPC	Summary of Product Characteristics
SOC	System Organ Class
t1/2	terminal half-life
TAM	Tumour associated macrophage
TC	Tumour cell
TEAE	Treatment-emergent Adverse Event
TKI	Tyrosine Kinase Inhibitor
Tlast	time of last measurable concentration
TLC	Thin liquid chromatography
TLS	Tumour lysis syndrome
tmax	time after dosing when c_{max} was observed
TMB	Tetramethylbenzidine
TQD	Triple quadrupole detector
TR	test-reference
TRA	Total Radioactivity
TSH	Thyroid Stimulating Hormone
TTC	Threshold of toxicological concern
TTCD	Time to Confirmed Deterioration
TTE	time-to-event
UB	upper bound
UC	urothelial cancer
ULN	Upper Limit of Normal
UPLC-MS/MS	Ultra performance LC-MS/MS
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
v:v	Volume:volume
V1	volume of distribution for the central compartment
V2	volume of distribution for the (first) peripheral compartment
V3	volume of distribution for the second peripheral compartment
VALG	veterans administration lung study group
Vmax	maximum velocity rate constant
VPC	visual predictive check
Vss	volume of distribution at steady-state
Vz	volume of distribution during the terminal phase
WBC	White Blood Cell
XRD	X-Ray Diffraction

1. Administrative/regulatory information and recommendations on the procedure

1.1. Information on the product

Product data	
Product name	Zepzelca
Active substance	lurbinectedin
INN or common name	lurbinectedin
Applicant	Pharma Mar S.A. Avenida De Los Reyes 1 Poligono Industrial La Mina 28770 Colmenar Viejo SPAIN
EMA product number	EMEA/H/C/006673
ATC code and pharmacotherapeutic group	L01XX69 L Antineoplastic and immunomodulating agents L01: antineoplastic agents, L01X OTHER ANTINEOPLASTIC AGENTS L01XX Other antineoplastic agents
Pharmaceutical form(s) and strength (s)	Powder for concentrate for solution for infusion 2 mg and 4 mg
Packaging	vial (glass)
Package size(s)	1 vial
Route of administration	Intravenous use
Device or diagnostic	Not applicable
Orphan designation	Yes, ODD EU/3/19/2143 for the treatment of small cell lung cancer, granted on 26 Feb 2019
Orphan indication status confirmed	Yes
PRIME scheme	Not applied for
Type of marketing authorisation granted at opinion	Standard
Legal basis	Article 8.3 of Directive 2001/83/EC Mandatory Scope (Article 3(1) of Regulation (EC) No 726/2004)
Final indication	ZEPZELCA, in combination with atezolizumab, is indicated for the maintenance treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin and etoposide.
New active substance status	Granted

1.2. Protocol assistance

Table 1 Scientific advice and protocol assistance

Date	Topic (quality/ non-clinical/ clinical)	Reference number / Coordinator(s)	Brief summary of the advice
22 July 2021	clinical	EMA/SA/0000053581 Paolo Foggi Pierre Demolis	The Scientific Advice pertained to the following clinical aspects: The overall design of proposed randomized, open-label, Phase III Study GO43104 and specifically: target population and stratification factors, active comparator arm, proposed dual primary endpoints, biomarker analysis plan and the planned HRQoL assessments, statistical analysis plan, particularly the type 1 error control and analysis of primary endpoints, dosage and treatment regimen, safety monitoring plan and risk mitigation strategy, and the overall approach to use Study GO43104 to support an extension application in the proposed indication.

EMA/SA/0000053581: Roche Registration GmbH received Scientific Advice on the development of atezolizumab (Tecentriq) in combination with lurbinectedin for the maintenance treatment of extensive-stage small cell lung cancer in adult patients whose disease has not progressed after first-line induction therapy with Tecentriq and platinum-based chemotherapy and etoposide.

1.3. Eligibility to the centralised procedure

The applicant Pharma Mar S.A. submitted on 20 May 2025 an application for marketing authorisation to the European Medicines Agency (EMA) for Zepzelca (lurbinectedin), through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 October 2024.

The applicant applied for the following indication: Zepzelca, in combination with atezolizumab, is indicated for the maintenance treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin and etoposide.

1.4. Legal basis and dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, and non-clinical and clinical data based on applicant's own tests and studies and bibliographic literature substituting/supporting certain test(s) or study(ies).

1.5. Information on paediatrics

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA decision P/0446/2020 on the granting of a product-specific waiver.

1.6. Information on orphan market exclusivity

Zepzelca was designated as an orphan medicinal product EU/3/19/2143 on 26 Feb 2019 in the following condition: Treatment of small cell lung cancer.

1.6.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products from the start of the procedure, Hetronifly (serplulimab).

1.7. Applicant's requests for consideration

1.7.1. Accelerated assessment request

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004. The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest based on the available data at time of assessment of the request. This was based on the fact that at time of the request assessment the improved efficacy in delaying disease progression and death was deemed insufficient in terms of effect size, to fulfil the unmet medical need in patients that receive first-line ES-SCLC to a relevant extend over other available methods of treatment, including the immune checkpoints inhibitors authorised as part of an induction regimen, in combination with chemotherapy and then followed as monotherapy. The safety profile of the combination was also considered more burdensome.

1.7.2. New active substance status

The applicant requested the active substance lurbinectedin contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.7.2.1. CHMP recommendation on new active substance status

Based on the review of available data on the active substance, the CHMP considers that lurbinectedin is to be qualified as a new active substance in itself, as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to the appendix on new active substance status claim assessment report.

1.8. Steps taken for the assessment of the product

The rapporteur and Co-rapporteur appointed by the CHMP were:

Rapporteur:	Selma Arapovic Dzakula
Co-rapporteur:	Elita Poplavska

The application was received by the EMA on	20 May 2025
An application for accelerated assessment was filed by the applicant. Accelerated assessment procedure was not agreed-upon by CHMP on	25 April 2025
The procedure started on	19 June 2025
The CHMP rapporteur's first assessment report was received on	09 September 2025
The CHMP Co-rapporteur's first assessment report was added to the rapporteur's report on	12 September 2025
The PRAC rapporteur's first assessment report was added to the rapporteurs' report and circulated to all PRAC and CHMP members on	19 September 2025
<The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on>	02 October 2025
The Quality working party agreed on the Assessment Overview during their meeting on	08 October 2025
The CHMP agreed on the consolidated list of questions (LoQ) to be sent to the applicant during the meeting on	16 October 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	27 November 2025
The following GCP inspection was requested by the CHMP its their outcome taken into consideration as part of the quality/safety/efficacy assessment of the product: A GCP inspection at 2 investigator and one sponsor sites in Turkey, Poland and Canada between 06 October and 25 November 2025. The outcome of the inspection carried out was issued on.	24 July 2025 16 February 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs joint assessment report on the applicant's responses to the list of questions (LoQ) to all CHMP and PRAC members on	06 January 2026
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	15 January 2026
The CHMP agreed on a list of outstanding issues (LoOI) to be sent to the applicant on	29 January 2026
The applicant submitted the responses to the CHMP list of outstanding issues on	23 February 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs Joint assessment report on the applicant's responses to the list of outstanding issues to all CHMP and PRAC members on	11 March 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Zepzelca on	26 March 2026
The CHMP adopted a report on similarity of Zepzelca with Hetronifly on (see appendix on similarity)	26 March 2026
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see appendix on NAS)	26 March 2026

International collaboration

The European Medicines Agency (EMA) was an observer of the review conducted under the FDA project Orbis for this indication.

1.9. CHMP outcome

1.9.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 2.5 of this report.

The European Medicines Agency has waived the obligation to submit the results of studies with ZEPZELCA in all subsets of the paediatric population in the treatment of SCLC.

1.9.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 1.6. of this report.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Zepzelca as an orphan medicinal product in the approved indication. The positive outcome of the COMP review on maintenance of the orphan designation can be found here: Zepzelca | European Medicines Agency (EMA).

1.9.2.1. Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Zepzelca is not similar to Hetronifly within the meaning of Article 3 of Commission Regulation (EC) No 847/2000. See the appendix on similarity.

1.9.3. Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Zepzelca is favourable in the following indication(s):

Zepzelca, in combination with atezolizumab, is indicated for the maintenance treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin and etoposide.

The CHMP, therefore, recommends the granting of the marketing authorisation subject to the conditions described in the following sections.

1.9.4. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

1.9.5. Other conditions and requirements of the marketing authorisation

1.9.5.1. Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

1.9.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.9.6.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

2. Introduction

2.1. Therapeutic context

Small cell lung cancer (SCLC) accounts for approximately 15% of all lung cancer cases and is distinguished from non-small cell lung cancer (NSCLC) by its rapid growth rate and early development of metastatic disease, resulting in most patients being diagnosed with extensive-stage disease (Govindan et al 2006). The number of new lung cancer cases worldwide every year is estimated to be 2,480,675 (Bray et al 2022) which, assuming a 15% of SCLC cases amongst all lung cases, would result in approximately 370,000 new SCLC cases worldwide.

Nearly all cases of SCLC are attributable to cigarette smoking (Pesch et al, 2012). Poor prognostic factors for survival in patients with SCLC include extensive-stage disease, poor Eastern Cooperative Oncology Group (ECOG) performance status (PS), weight loss, presence of liver metastases, and markers associated with excessive bulk of disease such as elevated lactate dehydrogenase (LDH) (Yip et al 2000, Foster et al 2009, Ma et al 2021). SCLC has a very high rate of attrition with fewer patients eligible for therapy in later lines (Armstrong et al 2019).

The majority (approximately 70%) of patients with SCLC are initially diagnosed with extensive-stage small cell lung cancer (ES-SCLC), which has poor survival prospects: median overall survival (OS) of approximately 10-12 months (Socinski et al 2009, Horn et al 2018).

The current standard first-line treatment for patients with ES-SCLC is atezolizumab plus carboplatin/etoposide (CE), as induction therapy, followed by atezolizumab maintenance therapy, or durvalumab plus platinum (cisplatin or carboplatin) and etoposide as induction therapy, followed by durvalumab maintenance therapy (ESMO 2021, NCCN 2025).

Atezolizumab combined with CE for the first-line treatment of patients with ES-SCLC was approved by the European Medicines Agency (EMA) in 2019 based on the results of the GO30081 (IMpower133) study (EMEA/H/C/004143/II/0018). In the randomised phase 3 study IMpower133, a total of 201 patients were randomly assigned to the atezolizumab plus CE group, and 202 patients to the placebo plus CE group. At a median follow-up of 13.9 months, the hazard ratio (HR) for death was 0.70 (95% CI, 0.54-0.91; p=0.007) with a median OS of 12.3 months in the atezolizumab plus CE group and 10.3 months in the placebo plus CE group. The HR for progression-free survival (PFS) was 0.77 (95% CI, 0.62-0.96; p=0.02) with a median PFS of 5.2 months and 4.3 months, for atezolizumab plus CE and placebo plus CE, respectively. The safety profile of atezolizumab plus CE was consistent with the previously reported safety profile of the individual agents, with no new findings observed (Horn et al 2018).

Durvalumab was approved in 2020 by EMA for the first-line treatment of adults with ES-SCLC in combination with a choice of chemotherapies, etoposide plus either carboplatin or cisplatin, based on the results of the CASPIAN trial (EMEA/H/C/004771/II/0014/G) that met the primary endpoint of OS for durvalumab plus chemotherapy, reducing the risk of death by 27% versus chemotherapy alone (based on a HR of 0.73; 95% CI 0.59-0.91; p=0.0047), with median OS of 13.0 months versus 10.3 months for chemotherapy alone (Paz-Ares et al 2019).

Recently, in February 2025, serplulimab in combination with CE was approved by EMA for the first-line treatment of patients with ES-SCLC based on data from the phase III ASTRUM-005 trial (EMEA/H/C/006170/0000, Cheng et al 2022). In this double-blind phase 3 randomised clinical trial, patients were randomised 2:1 to receive either 4.5 mg/kg of serplulimab (n=389) or placebo (n=196) i.v. every 3 weeks (q3wk). All patients received intravenous carboplatin and etoposide q3wk for up to 12 weeks. At the time of the OS interim analysis (with a median follow-up of 12.3 months), the median OS was 15.4 months (95% CI, 13.3 months-not evaluable) for serplulimab vs. 10.9 months (95% CI, 10.0-14.3 months) for placebo (HR=0.63; 95% CI, 0.49-0.82). The median PFS (assessed by an independent radiology review committee) was 5.7 months (95% CI, 5.5-6.9 months) for serplulimab vs. 4.3 months (95% CI, 4.2-4.5 months) for placebo (HR=0.48; 95% CI, 0.38-0.59).

Finally, in March 2025, tislelizumab in combination with etoposide and platinum chemotherapy was approved by the EMA for the first-line treatment of adult patients with ES-SCLC. The recommendation was supported by data from the phase 3 RATIONALE-312 trial (EMEA/H/C/005919/II/0016), which showed that at a median follow-up of 14.2 months, patients treated with the combination of tislelizumab and chemotherapy (n=227) achieved a median OS of 15.5 months (95% CI, 13.5-17.1) compared with 13.5 months (95% CI, 12.1-14.9) for those given placebo plus chemotherapy (n=230; HR=0.75; 95% CI, 0.61-0.93; p=0.0040). Tislelizumab plus chemotherapy generated a median PFS of 4.7 months (95% CI, 4.3-5.5) compared with 4.3 months (95% CI, 4.2-4.4) for placebo plus chemotherapy (HR=0.64; 95% CI, 0.52-0.78; p<0.0001) (Cheng et al 2024).

2.2. Aspects of development

The evidence in support of the proposed indication (maintenance treatment of ES-SCLC in patients whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin and etoposide) is derived from the efficacy, safety, and clinical pharmacology results from one pivotal phase 3 randomised study (IMForte), see section 5.3.2.1. .

The clinical developmental programme included dedicated clinical pharmacology studies, see section 5.1.2. .

To support the dose and efficacy of lurbinectedin in ES-SCLC, a high-level summary of efficacy results from the following studies is also provided: (i) A-001: this was the first-in-human dose-finding and pharmacokinetic (PK) study of lurbinectedin in patients with advanced solid tumours, in which 31 patients received doses from 0.02 to 5.0 mg/m2 q3wk of lurbinectedin as single agent. (ii) B-005: this was a phase 2 basket clinical trial evaluating the efficacy and safety of lurbinectedin as a single agent administered at 3.2 mg/m2 q3wk. The study was designed to investigate anticancer activity for nine difficult-to-treat tumour types with disease progression after available therapy. The study comprised of 335 treated patients, including a cohort of 105 patients with SCLC.

2.3. Description of the product

The mechanism of action: lurbinectedin inhibits the oncogenic transcription process through (i) its binding to CG-rich sequences of DNA, located within promoters of protein-coding genes; (ii) the eviction of oncogenic transcription factors from their binding sites; and (iii) the 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.

Lurbinectedin suppresses the expression of inflammatory and motility-related genes at non-toxic nanomolar concentrations in vitro, while also inhibiting cell migration and adhesion. At higher concentrations, it induces apoptosis in monocytes and macrophages through caspase-8 activation. *In vivo* (murine models), antitumour dosing (0.18–0.20 mg/kg) restricts tumour growth, reduces specific immune cell populations, and decreases tumour vascularity.

The claimed therapeutic indication is as follows: "Lurbinectedin in combination with atezolizumab is indicated for the maintenance treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin and etoposide."

ZEPZELCA therapy should be initiated and supervised by health professionals experienced in the use of anticancer products.

Posology

The recommended dose of lurbinectedin is 3.2 mg/m^2 every 21 days until disease progression or unacceptable toxicity when it is administered in combination with atezolizumab.

When administering lurbinectedin on the same day, atezolizumab should be administered first.

For the recommended intravenous or subcutaneous dose of atezolizumab, as well as for recommendations regarding dose modification due to toxicity, refer to their prescribing information.

Treatment with ZEPZELCA should be initiated only if absolute neutrophil count (ANC) is at least 1.5 x 10^9/L and platelet count is at least 100 x 10^9/L.

Treatment continuation and treatment delays

Further treatment cycles (i.e., cycle 2 or subsequent) will be administered every 21 days if the patient fulfils all the treatment continuation criteria listed above (see also Table 3 for dose modifications criteria for ZEPZELCA adverse reactions).

If a patient does not meet the requirements for treatment continuation on Day 1 of any cycle after Cycle 1, treatment will be withheld until appropriate recovery, for a maximum of 21 days after the treatment due date. If there is no recovery after a 21-days delay, treatment must be stopped.

In case atezolizumab is discontinued due to an immune-related severe adverse reaction, treatment with lurbinectedin may be continued at its current dose as a single agent. If immune toxicity re-occurs despite discontinuation of atezolizumab, treatment with lurbinectedin should also be discontinued.

Pre-infusion medicinal products

The following pre-infusion medicinal products should be administered for antiemetic prophylaxis:

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

Post-infusion medicinal products

Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is recommended to reduce the risk of severe neutropenia/febrile neutropenia.

If needed, post-medication can include administration of extended antiemetic treatment for 2 days:

- Corticosteroids (oral dexamethasone 4 mg or equivalent), or
- Serotonin antagonists (oral ondansetron 8 mg or equivalent) or
- Metoclopramide (intravenous or oral 10 mg or equivalent every 8 hours)

Dose adjustment for adverse reactions

The recommended dose reductions for adverse reactions are listed in Table 2

Table 2 Dose reduction for ZEPZELCA for adverse reactions

Recommended starting dose	**1st Dose reduction**	**2nd Dose reduction**	**3rd Dose reduction**
3.2 mg/m^2	2.6 mg/m^2	2.0 mg/m^2	Stop
1.6 mg/m^{2*}	1.3 mg/m^2	1.0 mg/m^2	Stop

*Dose reduction schedule applicable to the 50% reduced dose (i.e., 1.6 mg/m2) used in cases of moderated hepatic impairment or co-administration with strong or moderate CYP3A inhibitors.

The recommended dose modifications for adverse reactions are presented in Table 3.

Table 3 Dose modifications criteria for ZEPZELCA for adverse reactions

Adverse reaction	**Severity[a]**	**Dose modification**
Neutropenia[b] *(see section 4.4)*	Grade 4 OR any grade febrile neutropenia OR associated with infection/sepsis at any grade	Withhold ZEPZELCA until Grade ≤ 1 and resolution of any associated fever/infection/sepsis, AND Resume ZEPZELCA at a reduced dose[b]
Thrombocytopenia *(see section 4.4)*	Grade 3 with bleeding OR	Withhold ZEPZELCA until platelet ≥ 100 x 10^9/L, AND

	Grade 4	Resume ZEPZELCA at reduced dose
Hepatotoxicity (see section 4.4) and other adverse reactions	Grade 2	Withhold ZEPZELCA until Grade ≤ 1 (for AST and ALT until ≤ 3 ULN), AND Resume ZEPZELCA at same dose
	Grade ≥ 3	Withhold ZEPZELCA until Grade ≤ 1 (for AST and ALT until ≤ 3 ULN). AND Resume ZEPZELCA at reduced dose
Rhabdomyolysis	Grade 2	Withhold ZEPZELCA until Grade ≤ 1, AND Resume ZEPZELCA at same dose
	Grade ≥ 3	Permanently discontinue ZEPZELCA
Non-haematological toxicity	Grade 2	Withhold ZEPZELCA until Grade ≤ 1, AND Resume ZEPZELCA at same dose
	Grade ≥ 3	Withhold ZEPZELCA until Grade ≤ 1, AND Resume ZEPZELCA at reduced dose
Tumour Lysis Syndrome	Grade 2	Withhold ZEPZELCA until Grade ≤ 1, AND Resume ZEPZELCA at same dose
	Grade ≥ 3	Permanently discontinue ZEPZELCA
Any adverse reaction that requires frequent or prolonged (>2 weeks) dose delays	-	Reduce the dose of ZEPZELCA or discontinue

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.
[b] Patients with isolated Grade 4 neutropenia (neutrophil count less than 500 cells/mm^3) and who had not received G-CSF as primary prophylaxis, may receive G-CSF prophylaxis rather than undergo lurbinectedin dose reduction.

2.4. Inspection issues

2.4.1. Good manufacturing practice (GMP) inspection(s)

No inspection required.

2.4.2. Good laboratory practice (GLP) inspection(s)

No inspection required.

2.4.3. Good clinical practice (GCP) inspection(s)

A request for a routine GCP inspection has been adopted for the following clinical study GO43104. The outcome of this inspection and the satisfactory responses to its findings are an integral part of this procedure (EMA/IN/0000288097, 16 February 2026).

The investigators' inspections identified several major findings affecting eligibility criteria assessment and documentation on investigator sites. However, after a systematic review of the primary objectives

data and some safety and secondary objectives data, the efficacy and safety data were considered reliable. The clinical trial was generally performed in compliance with GCP requirements and the data obtained, documented and reported are reliable. The trial was conducted in accordance with internationally accepted ethical standards. The data quality was assessed as acceptable and the trial data have been considered reliable following GCP and ethical standards; therefore the efficacy and safety data can be used in support of the Marketing Authorisation Application submitted to EMA for lurbinectedin.

3. Quality aspects

3.1. Introduction

The finished product is presented as a powder for concentrate for solution for infusion containing 2 mg or 4 mg of lurbinectedin as active substance. One ml of reconstituted solution contains 0.5 mg of lurbinectedin.

Other ingredients are sucrose, lactic acid, and sodium hydroxide.

The product is available in 20 ml (2 mg) or 30 ml (4 mg), clear type I glass vials with butyl rubber stoppers and white (2 mg) or blue (4 mg) aluminium overseals.

3.2. Active substance

3.2.1. General information

The active substance lurbinectedin is a new chemical entity not included in any pharmacopoeia.

The structure of lurbinectedin is given below in Figure 1. The chemical name of lurbinectedin is (1*R*,6'*R*,6a'*R*,7'*R*,13'*S*,14'*S*,16'*R*)-8',14'-dihydroxy-6,9'-dimethoxy-4',10',23'-trimethyl-19'-oxo-2,3,4,6',7',9,12',13',14',16'-decahydro-6a'*H*-spiro[β-carboline-1,20'-[7,13]epimino[6,16](epithiopropanooxymethano)[1,3]dioxolo[7,8]isoquino[3,2-b][3]benzazocin]-5'-yl acetate corresponding to the molecular formula $C_{41}H_{44}N_4O_{10}S$. It has a relative molecular mass of 784.87.

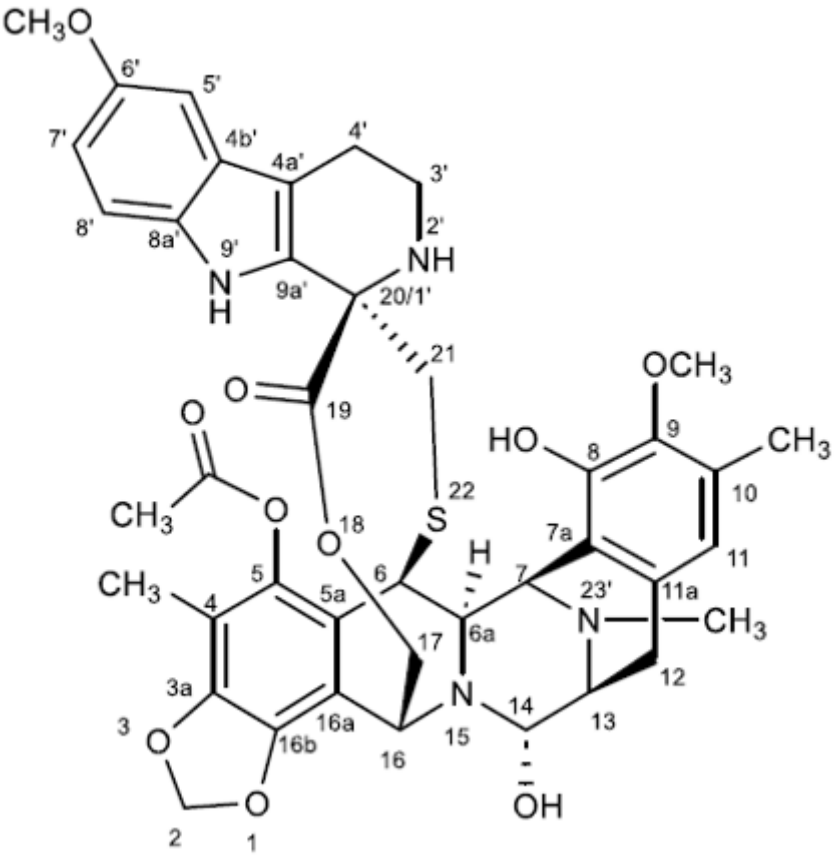


Figure 1: active substance structure

The active substance structure of lurbinectedin was elucidated using elemental analysis, IR spectroscopy, mass spectrometry, ^{1}H and ^{13}C NMR spectroscopy and UV spectroscopy, optical rotation and x-ray crystallography. Physicochemical characterisation was performed by thermal analysis (DSC and TGA), determining dissociation constant (pKa), partition coefficient (Log P) and investigation of hygroscopicity. Lurbinectedin is a white to off-white partially crystalline solid which picks up water at high humidity. It is practically insoluble in water, with slightly increased solubility at acidic pH. Polymorphic form and particle size are not relevant as the first step in finished product manufacture is dissolution of the active substance.

Lurbinectedin contains seven stereocentres and is isolated as a single isomer. Chiral purity is ensured by a test for specific optical rotation.

3.2.2. Manufacture, characterisation, and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF, and it was considered satisfactory. Confirmation of compliance with GMP has been provided in the QP declaration.

The active substance is synthesised in multiple steps using well defined starting materials with acceptable specifications. In the initial submission, the justification and control strategy for one proposed starting material introduced in the penultimate manufacturing step, were not justified resulting in a major objection. In response, the applicant provided a justification in line with ICH Q11 principles, including a description of the synthetic process to the starting material, a detailed overview

of impurity fate and purge, and revised the specification, including tightening of impurity limits, to ensure the quality of the material. The major objection was considered resolved.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on the chemistry of active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised. Since the medicinal product has an advanced cancer indication, ICH M7 does not apply, although potentially mutagenic impurities were evaluated.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified in that they improve the quality of the active substance.

The active substance is packaged in borosilicate glass vials with PTFE-lined silicone septa which comply with Commission Regulation (EU) 10/2011, as amended. Secondary packaging is plastic bottles with screw cap, containing bags of calcium bentonite to avoid any moisture uptake, especially during container opening after frozen storage. The combined containers provide adequate light protection.

3.2.3. Specification

The active substance specification, used by both the API and finished product manufacturers, includes tests for colour and appearance, identification (IR, HPLC-UV), water content (Ph. Eur.), related substances (HPLC-UV), residual solvents (GC-FID), sulphated ash (Ph. Eur.), assay (HPLC-UV), and bacterial endotoxins (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and/or clinical studies and appropriate specifications have been set.

Particle size testing as well polymorphic identification are not included in the specification which is acceptable as the active substance is dissolved during the manufacture of the drug product. The omission of the microbiological quality testing from the active substance specification is adequately justified. A test for specific optical rotation is included in an intermediate in lieu of the active substance.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards has been presented.

Batch analysis data from 13 batches of the active substance used throughout clinical development, including for process qualification and validation are provided including data from 3 commercial scale batches. The results were within the specifications at the time of release and are consistent from batch to batch and demonstrate that the process produces active substance of suitable quality.

3.2.4. Stability

Stability data from 4 representative production scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (-20 ºC ± 5 ºC). One of these batches was also stored at 5 ºC ± 3 ºC for up to 6 months and two were stored at 25 ºC ± 2 ºC / 60% RH ± 5% RH for up to 6 months. Colour, appearance, identification, water content, related substances, and assay were all monitored. The analytical methods

used were the same as for release. No significant changes were observed, all tested parameters remained within the specification limits across long term and accelerated studies.

Lurbinectedin stress testing studies were carried out under thermal, oxidative, acid, and alkaline conditions. Photostability was studied according to ICH Q1B. The active substance was unstable under all tested conditions, especially under alkaline conditions. The studies demonstrate that the HPLC-UV method is stability indicating. The combination of primary and secondary packaging provides sufficient protection from light. The active substance was also shown to be stable to multiple freeze-thaw cycles supporting frozen storage.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months stored at -20 ºC ± 5 ºC in a freezer inside the original package to protect from light and moisture.

3.3. Finished medicinal product

3.3.1. Description of the product and pharmaceutical development

Lurbinectedin 2 mg and 4 mg powder for concentrate for solution for infusion is presented as a sterile, preservative-free, white to off white, lyophilised powder in a 20 ml (2 mg) or 30 ml (4 mg), single-dose, type I clear glass vial. Before use, the powder is reconstituted with 4 ml (2 mg) or 8 ml (4 mg) of water for injections (WFI) to give a solution containing 0.5 mg/ml of lurbinectedin. The reconstituted solution is then further diluted in either 0.9% sodium chloride or 5% glucose solution for infusion.

The quantitative composition and function of each component in the lyophilised finished product and reconstituted finished product was stated.

The aim of the pharmaceutical development was to obtain a formulation which could be administered by intravenous infusion after appropriate dilution with an infusion medium. The finished product is a lyophilised formulation of lurbinectedin for intravenous infusion, prompted by the active substance's poor aqueous solubility which is somewhat higher at acidic pH.

The selection of excipients was justified based on prior knowledge of similar formulations, and experimental studies. The selected excipients are well-established in parenteral formulations. All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. No overage or overfill is applied.

The manufacturing process includes compounding, sterile filtration, aseptic filling, lyophilisation, and sealing. The development history, including formulation changes, facility transfers, and process optimisation have been adequately described and sufficient details and rationale for each change has been provided. A thorough risk assessment supported identification of CPPs and the overall control strategy.

The choice of sterilisation method (sterile filtration) is mandated due to the thermal instability of the active substance. Heat sterilisation and ionising radiation both lead to significant degradation.

Development and optimisation of the freeze-drying cycle for each strength was presented, including determination of key thermal parameters (e.g., collapse temperature) using standard analytical techniques. The main difference between the lyophilisation cycles of the 4 mg and 2 mg strengths is the pressure applied during primary drying.

The primary packaging is clear type I glass vials with butyl rubber stoppers and aluminium overseals. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The risk of extractables and leachables was assessed under worst-case conditions (4 mg vial), and results confirm no safety concern. The extrapolation of data from the 4 mg to the 2 mg presentation is scientifically justified based on identical formulation, process, and packaging materials.

Compatibility and in-use stability testing was performed only on the 4 mg strength, using different aged batches produced at all proposed manufacturers, and the outcome of this is reflected in the product information. The compatibility of diluted lurbinectedin 4 mg solutions (0.9% sodium chloride or 5% glucose solution) with commercially available infusion tubing sets and implantable venous access systems was investigated over a 3-hour infusion period. Significant adsorption of lurbinectedin to nylon membrane filters was observed when the product was diluted in 0.9% sodium chloride. Therefore, infusion sets containing nylon membrane filters should not be used when the reconstituted solution is diluted with 0.9% sodium chloride. The in-use physicochemical and microbiological stability of the reconstituted and diluted drug product solutions was demonstrated for up to 24 hours, including infusion time, at both room temperature (with ambient light exposure) and under refrigerated conditions (5 ºC ± 3 ºC).

3.3.2. Manufacture of the product and process controls

For all sites involved in the manufacture, control and batch release of the finished product sufficient evidence of GMP compliance has been provided.

The manufacturing process is comprised of preparation of the bulk solution, sterile filtration and aseptic filling in depyrogenated vials, followed by half stoppering and lyophilisation, sealing and packing. The manufacturing process is considered non-standard due to the inclusion of lyophilisation and aseptic processing.

Validation of the 4 mg strength was conducted on 3 production scale batches from each manufacturing site. However, in the initial submission, data from only 1 batch of the 2 mg strength was provided. Considering the differences in process parameters, particularly for the lyophilisation step, the CHMP requested validation data as a major objection. In response, the applicant provided data from 3 consecutive production scale batches of the 2 mg strength demonstrating its capability.

The validation studies for both strengths covered all aseptic process steps including sterile filtration and filling, lyophilisation, unloading, and sealing. Holding times have been justified by the provided data, and media fill simulations to support the proposed process have been verified. Satisfactory information has also been provided regarding vial depyrogenation conditions. The major objection was thus considered resolved.

It has been demonstrated that the manufacturing process is capable of producing both strengths of finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process pharmaceutical form. Container closure integrity is assured by validated leak testing (dye ingress tests with qualitative and quantitative UV/Vis detection methods) included as an in-process control.

3.3.3. Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form including appearance, identification (HPLC-UV, UV-Vis), colour and pH of solution (Ph.

Eur.), reconstitution time (visual), visible and sub-visible particles (Ph. Eur.), water content (colorimetric titration), assay (HPLC), impurities and degradation products (HPLC), uniformity of dosage units (Ph. Eur.), sterility (Ph. Eur.), and bacterial endotoxins (Ph. Eur.). All parameters relevant to the parenteral preparations according to ICH Q6A and Ph. Eur. are included. Impurity limits are set according to relevant ICH guidelines.

The potential presence of elemental impurities in the finished product was assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Confirmatory studies on batches of both 4 mg and 2 mg strengths from both manufacturers were provided demonstrating that all relevant elemental impurities were below 30% of the PDE. Based on the risk assessment and batch data presented, no specific elemental impurity controls are necessary.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product was performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards has been presented.

Batch analysis results were provided for 36 batches of the 4 mg strength up to production scale and covering both manufacturers, as well as 3 production scale batches of the 2 mg strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

3.3.4. Stability of the product

Stability data from 9 batches of 4 mg vials up to production scale and covering all manufacturers stored for up to 60 months under long term conditions (5 ºC ± 3 ºC) and for up to 6 months under accelerated conditions (25 ºC / 60% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were stored in both upright and inverted positions with no differences in behaviour observed.

Samples were tested according to the shelf-life specifications. Results for all parameters under long-term conditions for all batches were within the proposed limits, with no trends observed. Under accelerated conditions, a small within-specification increase in impurities was observed.

In the initial dossier, the stability data submitted to support the claimed shelf-life and storage conditions of the 2 mg strength were not considered adequate. Either a different manufacturing process had been used, or insufficient timepoints were available. Furthermore, data from the 4 mg vials was not considered representative considering the different lyophilisation conditions, resulting in a major objection.

In response, the applicant provided further data from representative batches. Data was also provided from 3 batches of 2 mg vials up to production scale from the proposed manufacturer stored for up to 12 months under long term conditions and for up to 6 months under accelerated conditions. Results for all parameters under long-term conditions within the proposed limits, with no trends observed. Under accelerated conditions, a small within-specification increase in impurities was observed. In addition, the proposed shelf-life was tightened from 36 to 18 months and thus, the major objection was considered resolved.

Forced degradation studies were carried out for the HPLC assay and related substances method by which it was demonstrated that the method is stability indicating. An increase in degradation products was observed under acidic, alkaline, oxidative and thermal conditions.

Photostability was adequately tested in line with ICH Q1B demonstrating that the finished product is photostable.

A freeze-thaw was carried out on one 4 mg batch between -20 °C and 25 °C/60 % RH with no changes observed. Short-term freezing and excursions above the prescribed storage temperature have no impact on the product quality.

In-use stability was studied to evaluate physicochemical and microbiological properties of the reconstituted and diluted finished product solutions under conditions of clinical use. Chemical and physical in-use stability has been demonstrated for 24 hours including infusion time at either 2 to 8 °C or 25 °C. From a microbiological point of view, the product should be used immediately.

The proposed post-approval stability protocol and stability commitments are acceptable.

Based on available stability data, the proposed shelf-lives of 60 months for the 4 mg strength and 18 months for the 2 mg strength, both at 2 to 8 °C, as stated in the SmPC (section 6.3) are acceptable.

3.3.5. Post approval change management protocol

The applicant proposed a post approval change management protocol (PACMP) to add an additional active substance manufacturer. The protocol also documents an increase in production scale from to increase security and reinforce the supply chain. The protocol was considered sufficiently detailed and was accepted on the basis of alignment of specification of intermediates from the newly proposed manufacturing site.

3.3.6. Adventitious agents

No excipients derived from animal or human origin have been used.

3.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. A new 2 mg strength was introduced towards the end of development, and it was considered that insufficiently representative process validation and stability data had been submitted, resulting in two major objections. In response, the applicant provided further data, deemed adequate, coupled with a reduction in the initially proposed shelf-life. Following resolution of these major objections, both proposed finished product strengths were considered acceptable.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

3.5. Recommendations for future quality development

Not applicable.

4. Non-clinical aspects

4.1. Introduction

The non-clinical program for lurbinectedin, was conducted in line with ICH S9 guidelines, included pharmacology, pharmacokinetics, and toxicity studies to support its clinical development for the treatment of SCLC patients who progressed after platinum-based therapy. The testing strategy matched the proposed clinical use and dosing regimen (3.2 mg/m², 1-hour IV infusion every 3 weeks). The drug substance and product batches used in key toxicology studies were comparable in content and impurity profile to those used in clinical trials.

Pharmacological activity was investigated in numerous non-GLP studies, most of which have results published in peer-reviewed journals and the manuscripts are publicly available. The objectives of the pharmacology program for lurbinectedin were to understand the mechanism of its activity, to establish the antineoplastic activity *in vitro* and *in vivo*, to study the mechanism for potential tumour resistance, to search for potential effective drug-drug combination regimens, and to establish the pharmacological safety on vital organ systems.

The disposition after bolus i.v. administration of lurbinectedin, including plasma kinetics, tissue distribution, metabolism (*in vitro* and *in vivo*) and excretion was investigated in mice, rats, non-human primates (NHP), dogs, and mini-pigs and compared to data obtained from patients. Lurbinectedin was evaluated in vitro for plasma protein binding properties, whole blood distribution and the ability to interact with hepatic metabolic enzymes and drug-transporter systems.

Toxicology program for lurbinectedin was investigated in rats, dogs and NHPs for up to 24 weeks. Local tolerance was performed in rabbits. Genotoxic and phototoxicity potential was assessed *in vitro*. Pivotal toxicity studies were performed according to GLP.

4.2. Analytical methods

Various analytical methods were developed and validated to quantify lurbinectedin and its metabolites across nonclinical species and human samples. Initially, non-validated LC-MS/MS methods were used in early rat and dog studies, involving liquid-liquid extraction and tandem mass spectrometry. A more robust bioanalytical method (Pernice et al 2016) was later validated (S17-012-PM, S16-266-PM) and applied to pivotal toxicokinetic studies in rats and non-human primates (NHPs), demonstrating selectivity, precision, accuracy, and stability within specified concentration ranges. These methods also supported quantitation of metabolites such as PM030047 and the unstable metabolite 1, which was biosynthesized for quantification due to challenges with chemical synthesis. LC-RAD method (PMAR14-

NC032) was used for the in vitro metabolic profiling following lurbinectedin incubation with liver microsomes from several nonclinical species and human. This method was also used for the quantification of ^{14}C-lurbinectedin and its metabolites in plasma samples that were obtained in the mass balance study conducted in NHP. Radiolabelled ^{14}C-lurbinectedin (labelled at the C4 indole) was used in *in vitro* and *in vivo* absorption, distribution, metabolism and elimination (ADME) studies, with radioactivity measured by liquid scintillation. Formulation analysis used LC-UV and LC-MS/MS methods, initially non-validated and later fully validated, for confirming lurbinectedin concentrations in toxicology and safety studies in animals, including *in vitro* assessments like the hERG assay.

4.3. Pharmacology

4.3.1. Pharmacodynamics

4.3.1.1. Primary pharmacodynamics

The primary pharmacodynamics of lurbinectedin was comprehensively investigated, with results publicly available in peer-reviewed journals.

Mechanism of action

Binding to DNA

The DNA binding characteristics of lurbinectedin were studied by a combination of electrophoretic mobility shift assays, fluorescence-based melting kinetic experiments and computational modelling methods. Electrophoretic mobility shift assays demonstrated that lurbinectedin forms mono **adducts in the minor groove of DNA**. Lurbinectedin reacts with the exocyclic amino group of guanines forming a covalent bond. The pentacyclic skeleton is mostly responsible for DNA minor groove recognition and binding, which is dependent on the presence of the reactive hemiaminal moiety in the drug. Fluorescence-based thermal denaturation experiments showed that the most favourable DNA triplets providing a **central guanine** for covalent adduct formation are AGC, CGG, AGG and TGG. Adducts of the compound do not distribute uniformly through the genome, but they concentrate in **CG rich areas** within the promoters of active protein-coding genes.

Inhibition of transcription

Lurbinectedin shows a precise effect on oncogenic-driven transcription. Treatment of Ewing sarcoma cells with lurbinectedin induced the eviction of the oncogenic EWS/FLI1 transcription factor from its binding sites in chromatin, and its re-localisation within the nucleolus. Similarly, lurbinectedin inhibited the oncogenic transcription factor EWS/WT1 by redistributing the protein within the nucleus to the nucleolus, which was associated with the loss of EWS/WT1 activity and its downstream targets.

In addition to **displacement of transcription factors** from their binding sites, lurbinectedin inhibited active transcription through the specific and rapid degradation of the catalytic subunit of elongating RNA polymerase II (Pol IIo, Rpb1). ChemSeq experiments demonstrated that lurbinectedin specifically binds to the **promoter area of active transcribed genes (CG-rich sequences)**, inhibiting transcription in a seemingly specific way. Both active transcription and proteasome activity are essential for this process since pre-treatment with transcription inhibitors (initiation or elongation) or with proteasome inhibitors (such as MG-132) prevent lurbinectedin-induced degradation of Pol II. Thus, when lurbinectedin is bound to the DNA, the elongating (phosphorylated) Pol II is stalled in front of the lurbinectedin-DNA adduct, and although DNA breaks appear on the genome, it fails to promote the elimination of the lesion. This is followed by the subsequent **degradation of the RNA**

polymerase by the ubiquitin/proteasome-pathway, and the consequent **inhibition of transcription.**

Effects on nucleotide excision repair (NER) and formation of DNA double strand breaks (DSB)

Subsequently to arrest of the elongating RNA Pol II and its degradation by the ubiquitin/proteasome machinery, the recruitment of DNA repair factors, including XPF nuclease, generates an accumulation of double-strand breaks that leads to apoptosis (see below).

In vitro treatment of cancer cells with nM concentrations of lurbinectedin induced the **formation of DSBs**, demonstrated through the appearance of histone γ-H2AX foci. Pre-treatment with kinase inhibitors completely inhibited the formation of DSBs in A549 lung adenocarcinoma cells *in vitro*, showing that the process is transcription-specific and not random. DNA DSBs formation, following a disappearance of Pol II, likely results from failure in the removal of adducts by the transcription coupled repair (TCR) mechanism. In this sense, lurbinectedin is able to **interfere with the nucleotide excision repair (NER) machinery**, thereby attenuating the repair of specific NER substrates. In addition, other DNA repair systems were demonstrated to be involved in the activity of lurbinectedin, such as homologous recombinant repair (HRR), Ataxia-telangiectasia mutated (ATM) and ATM and RAD3-related (ATR) kinases, Fanconi Anaemia complementation complex (FANC), DNA mismatch repair (MMR) and RNase H1.

Effect on cell cycle

An **S-phase cell cycle arrest** has been reported in NSCLC (A549), colorectal (HCT-116 and HT-29), breast (MDA-MB-231) and patient-derived malignant pleural mesothelioma (MPM) cell lines treated with lurbinectedin. Lurbinectedin delayed IGROV ovarian tumour cells entering the S phase as indicated by the increase of cells remaining in G0/G1 phase.

Apoptosis

Visible signs of apoptotic cell death, including **chromatin condensation**, have been observed shortly after lurbinectedin treatment in experimental systems *in vitro* (ovarian, lung, melanoma, malignant pleural mesothelioma cell lines) and *in vivo* (ovarian xenograft model). **PARP1 cleavage**, a typical marker of apoptosis, has been observed in lung cancer cells treated with lurbinectedin as early as 6 h after drug exposure. Dose-dependent induction of apoptosis was observed in cells derived from chronic myelomonocytic leukaemia patients, where the cells were positive for **caspase-8** cleavage after 24 h lurbinectedin treatment, as well as in malignant pleural mesothelioma (MPM) cell lines, as evidenced by the activation of **caspase 3.**

The *in vivo* pro-apoptotic effect of lurbinectedin was confirmed in two engrafted murine orthotopic models of ovarian cancer by immunodetection of **caspase-3**. The presence of cells with **abnormal mitotic figures**, of seriously **defective chromosome** alignment and a failure to progress through mitosis was evident in lurbinectedin-treated cells with respect to controls. *In vivo* induction of **apoptotic bodies** was clearly detectable also in xenografts of SW1990 (pancreas), A2780 (ovarian) and H460 (lung) cells treated with lurbinectedin.

Immunogenic cell death (ICD)

Lurbinectedin has been demonstrated to induce robust ICD *in vitro* in a broad panel of solid tumours, as evidenced by calreticulin (CALR) exposure, ATP release, high-mobility group box 1 (HMGB1) exodus, and type-1 interferon responses. Lurbinectedin induced the production of double-stranded DNA fragments that **activate the cGAS/STING pathway**, thereby triggering ICD, in MPM model. This activation was further supported by MPM-PBMC co-culture experiments, where lurbinectedin treatment led to a significant increase in CD8+ T cells and NK cells within the co-cultures, suggesting an enhanced antitumor immune response.

Effects on tumour microenvironment (TME)

In vitro, lurbinectedin induced **caspase-8-dependent apoptosis** of human purified monocytes, whereas at low doses it significantly inhibited the production of inflammatory/growth factors (CCL2, CXCL8 and VEGF) and impaired monocyte adhesion and migration ability. A global gene expression analysis of human monocytes treated with lurbinectedin revealed an **inhibition of the Rho GTPase pathway**, which impacts on monocyte-macrophage functional activities. The lurbinectedin-mediated effect on the tumour microenvironment was confirmed *in vivo* using a drug-resistant fibrosarcoma cell line (MN/MCA1-RES). Even in conditions where tumour cells were totally unresponsive *in vitro* to lurbinectedin, a significant antitumour activity was observed, along with decreased number of circulating monocytes and the tumour macrophages, as well as reduced tumour angiogenesis (decreased number of vessels in tumour tissue). In mice xenografted with two human pancreatic cancer cell lines (SW-1990 and MIA PaCa-2), lurbinectedin also induced a reduction of TAM (F4/80, a mouse macrophage marker) within the tumour.

In circulating mononuclear cells (leukemic B cells and non-malignant leukocytes) from chronic lymphocytic leukaemia (CLL) patients, it was found that lurbinectedin induces a dose- and time-dependent death in all cell types evaluated, with B cells, monocytes and monocytic myeloid derived suppressor cells (Mo-MDSC) being the most susceptible populations. At sub-apoptotic doses, lurbinectedin decreased the expression of CCR7 in B-CLL cells and impaired their migration towards CCL19 and CCL21.

Mechanism of action and anti-proliferative effects in SCLC

To investigate lurbinectedin's mechanism of action in SCLC models, markers of DNA damage and replication stress were assayed by Western blot following treatment of SCLC cells from all four molecular subtypes (SCLC-A, SCLC-N, SCLC-P, SCLC-I) with lurbinectedin (0.9 nM/L) for 24 and 48 h. In comparison to DMSO control, all cell lines tested showed increases in markers of replication stress, phospho-CHK1 (S345) and phospho-RPA32 (S4/S8), as well as in phospho-γH2AX, indicating DNA DSBs. Lurbinectedin also induced PD-L1 expression via cGAS-STING pathway activation.

Lurbinectedin exhibited a specificity by preferentially targeting the CpG motifs found in 70% of gene promoters. Among the 2,194 downregulated genes that were targeted by lurbinectedin, 1,672 (76%) were bound by ASCL1 and NEUROD1. RNA-seq analysis showed that lurbinectedin suppresses the expression of ASCL1 and NEUROD1, along with their downstream targets, such as BCL2, INSM1, MYC, and AURKA. These genes play pivotal roles in promoting tumorigenic properties such as apoptosis inhibition, enhanced cell survival, and the maintenance of neuroendocrine characteristics in SCLC.

Further, it was demonstrated that RNA Pol II was stalled upstream of lurbinectedin adduct and that it underwent further ubiquitination rapidly followed by degradation after lurbinectedin treatment in SCLC cell lines. Lurbinectedin reduced cell viability in majority of SCLC models (IC_{50} between 1.905 to 30 nM) and has been shown to induce apoptosis, as evidenced by the cleavage of both PARP and caspase-3.

Lurbinectedin showed an antiproliferative effect in SCLC cell lines, with an average IC_{50} of 0.65 nM (Study PMAR19-CB004). No difference in the cytotoxicity of lurbinectedin between the four molecularly-defined subtypes of SCLC was observed in studies performed. However, these *in vitro* results were not replicated *in vivo*, in PDX SCLC models representing the SCLC-A (LX110), SCLC-N (LX33), and SCLC-P (LX1322) subtypes. *In vivo*, in PDX SCLC models representing the SCLC-A (LX110), SCLC-N (LX33), and SCLC-P (LX1322) subtypes, lurbinectedin delayed tumour growth in LX110 model ($P < 0.0001$) and reduced the tumour growth relative to control (84%), however, minimal anti-tumour effects were achieved in LX33 and LX1322.

Anti-proliferative activity in human cell lines/animal models other than SCLC

Lurbinectedin exhibits potent antiproliferative effect *in vitro*, with IC_{50} values in the pM or low nM range, in the majority of tumour cell lines analysed and representatives of both haematological malignancies (lymphomas, leukaemias) and solid tumours (lung, kidney, ovary, prostate). The antiproliferative activity of lurbinectedin was concentration-dependent in all the experimental systems tested. *In vivo*, weekly 0.18 mg/kg (0.54 mg/m^2) i.v. lurbinectedin bolus for 2 to 5 consecutive weeks exhibited antitumor activity (decrease in the tumour volume or an increase in the survival time) against different experimental models of either subcutaneously or orthotopically xenografted human cell-derived (CDX) and patient-derived (PDX) tumours such as lung, breast, prostate, bladder, kidney, ovary, pancreas and sarcoma.

Activity in resistant cells

No evidence of significant cross-resistance has been found when lurbinectedin was tested in cells resistant to common antiproliferative drugs, including cisplatin. However, lurbinectedin was less active in the doxorubicin resistant cells K562-dox, which overexpresses P-glycoprotein (P-gp). The experiments on ovarian cells stably resistant to lurbinectedin reported that the return to sensitivity was associated to a significantly reduced expression of P-gp achieved by co-treatment with the metabolite of irinotecan, SN-38, providing a confirmation for the P-gp involvement in a poor response to lurbinectedin treatment. In addition, high resistance to lurbinectedin (IC_{50} 235 nM) was observed in SCLC SHP-77 cells, known to overexpress the P-gp drug exclusion pump.

4.3.1.2. Secondary pharmacodynamics

The potential off-target effects of lurbinectedin have been explored in a panel of *in vitro* screening assays evaluating the potential interaction of lurbinectedin with receptors (n=58), ion channels (n=14), transporters (n=6) and enzymes (n=31), in which a single concentration of lurbinectedin (200 nM; ~ 160 ng/mL) above the C_{max} in patients (~ 130 ng/mL) was used (Study FR095-0003616). None of the assays evidenced a significant effect (inhibition or stimulation higher than 50% with respect to the untreated controls).

4.3.1.3. Safety pharmacology

Cardiovascular system

Lurbinectedin inhibited hERG tail current recorded from stably transfected HEK293 cells in a concentration-dependent manner when tested at nominal concentrations of 0.3 to 10 µM, with estimated IC_{50} of 8.8 µM (~ 6900 ng/mL), which is far greater than the C_{max}-values achieved in patients (~ 130 ng/mL) treated at the proposed clinical dosing (3.2 mg/m^2, i.v., 1-h infusion).

In conscious, telemetered Beagle dogs, doses of up to 0.01 mg/kg (0.2 mg/m^2) i.v. had no effects on heart, blood pressure, lead II ECG variables (PR, QT, QTcF and QTcV intervals, and QRS duration), ECG gross morphology or rhythm. At the highest dose of 0.023 mg/kg (0.46 mg/m2), dogs experienced a short-lasting tachycardia during the first 30 min post-administration (mean increase of 89% after 1 min), followed by a rapid normalization. Although a lurbinectedin direct pharmacological effect could not be completely ruled out, other contributing factors to an increase in heart rate were considered as more likely cause, such as lurbinectedin-induced vomiting episodes which occurred in 3 out of 4 animals.

In conscious, telemetered NHPs, lurbinectedin administered at 0.142 mg/kg i.v. (=1.7 mg/m^2, slightly higher than the MTD determined in study RTCA2148) induced effects on blood pressure and heart rate associated with changes in autonomic balance, signs of nausea, arrhythmias concomitant to nausea phases mainly during the first 24 hours post-dosing period and impairment of the nychthemeral cycle

of body temperature during the night period for 48 h post-dose. Delayed mild lowering in blood pressure and increase in heart rate were long lasting (around 36-46 hours post-dosing). The analysis of lurbinectedin plasma levels (and its main metabolites) at 2 min and 4 h after the administration of lurbinectedin revealed the highest lurbinectedin plasma concentration (mean 181 ng/mL) at 2 min, which is similar to that found in patients (124 ng/mL). No relevant differences were seen in the concentration of the main lurbinectedin-related metabolites (PM030047 up to 2.13 ng/mL, M1 up to 1.4 ng/mL, PM01158 below Limit of Quantification (LoQ), PM030036 not detectable) when compared to other studies in which similar doses of lurbinectedin were administered to NHPs (studies PMAR17-NC008 or PMAR17-NC018), and the levels were low or below the LoQ. In contrast, placebo did not induce any changes in arterial blood pressure, heart rate, body temperature or cardiac conduction times (i.e., PQ, PR intervals and QRS complex durations), ventricular repolarisation duration (QTc and QTshift), QT interval short term variability or ST segment when compared to the saline dosed group. No change in the sympatho-vagal balance attributed to the placebo was seen. No disturbance in the Lead II electrocardiogram attributed to placebo was noted. The observed lurbinectedin-induced changes to ABP and heart rate associated with changes in autonomic balance, were attributed to the main lurbinectedin-induced clinical signs which were observed during the course of the study, such as nausea and/or vomiting.

Respiratory system

No significant changes either in the respiratory rate (both genders) or in the tidal volume (female) up to 24 h after lurbinectedin administration. In male rats, lurbinectedin dosed at 0.165 mg/kg (0.99 mg/m2) caused a significant decrease in tidal volume compared to the placebo group (mean ± SD: 1.62 ± 0.12 mL vs. 2.18 ± 0.19 mL) at 24 h post-dose.

Central nervous system

In modified Irwin's test, no significant gross behavioural or physiological changes were caused in rats dosed with lurbinectedin up to 0.165 mg/kg (0.99 mg/m2) and 0.081 mg/kg (0.48 mg/m2) in male and female, respectively.

4.3.1.4. Pharmacodynamic drug interactions

Additive and/or synergistic effects were observed in both *in vitro* and *in vivo* studies when lurbinectedin was assayed in combination with a number of chemotherapy agents used in the clinic.

In vitro, the relative cytotoxicity of the compounds, alone or in combination, was determined by the MTT assay in various cell lines following an incubation with the test compounds for 72 h. Synergistic effects were determined by the combination index (CI) method, which is based on the median-effect principle derived by Chou (Chou et al 2006). Depending on the cell line, synergistic effects were observed for combinations of lurbinectedin with topotecan (Study PMAR10-CB004; Galmarini et al 2013), temsirolimus and everolimus (Study PMAR12-CB002), olaparib (Study PMAR10-CB008), irinotecan (Harlow et al 2016), 5-fluorouracile (Avilés et al 2013), cisplatin (Soares et al 2011, Santamaria Nuñez et al 2017) and with dual inhibition of ATM/Chk2 (ataxia-telangiectasia mutated/checkpoint kinase 2) and ATR/Chk1 (ATM and RAD3-related/checkpoint kinase 1) (Lima et al 2016).

In vivo, two-compound combination studies following the i.v. administration of lurbinectedin (at 0.18 mg/kg and sub-multiples) were performed in mice bearing different types of cell-derived xenografts and interactions were evaluated based on the calculated CI. Noteworthy is the synergism obtained in the combinations with dacarbazine (Study PMAR10-NC032), cisplatin (Studies PMAR10-NC029 and PMAR10-NC034, Vidal et al 2012), 5-fluorouracile (Study PMAR10-NC030), gemcitabine (Study

PMAR10-NC028, Cespedes et al 2016), doxorubicin (Studies PMAR10-NC033, PMAR19-003 and PMAR19-004), irinotecan (Study PMAR10-NC011, Harlow et al 2016), paclitaxel (Studies PMAR10-NC001 and PMAR10-NC010), and vinorelbine (Study PMAR10-NC026). Moreover, in immunocompetent mouse models, lurbinectedin induced antitumor responses, with increasing activity when combined with the dual PD-1 and CTLA-4 immune checkpoint blockade (Xie et al 2019) as well as with anti-PD-L1 therapy (Chakraborty et al 2024, Salaroglio et al 2024).

4.3.2. Pharmacokinetics

The pharmacokinetics of lurbinectedin have been evaluated in both non-GLP and GLP single and/or repeated-dose intravenous studies across multiple animal species including mice, rats, dogs, mini-pigs, and NHPs. The studies were performed either as specific PK studies or as toxicokinetic evaluations of GLP toxicology pivotal studies. The studies were conducted using lurbinectedin in the clinical formulation as required. Due to intended clinical route of administration, a systemic exposure was characterized using plasma concentration-time data following i.v. administration.

4.3.2.1. Absorption

Plasma kinetics after single intravenous dose

Non-GLP and GLP pharmacokinetic (PK) studies of lurbinectedin were conducted in mice, rats, dogs, mini-pigs, and non-human primates (NHPs) following single intravenous doses ranging from 0.02 to 0.4 mg/kg. Across all species, lurbinectedin exhibited a multi-compartmental pharmacokinetic profile with an initial rapid distribution phase followed by a slower elimination phase. Clearance (CL) ranged from 1.3 to 4.9 L/h/kg and volume of distribution at steady state (V_{dss}) from 9.4 to 36.1 L/kg. In plasma, the elimination half-life was long but varied across species (9-10 h in rodents, 13 h in NHPs, 14 h in dogs, 22 h in mini-pigs). The main metabolite, PM030047, showed low-to-moderate plasma exposure across species, with AUC metabolite-to-parent ratios from 1.5% (NHP) to over 100% (dogs). GLP studies confirmed linear pharmacokinetics with dose-proportional increases in exposure, and consistent CL and V_{dss} in rats (CL: 2.6–4.9 L/h/kg; V_{dss}: 15.8–30.0 L/kg), dogs (CL: 2.1–3.1 L/h/kg; V_{dss}: 25.5–42.3 L/kg), and NHPs (CL: 1.9 ± 0.3 L/h/kg; V_{dss}: 16.4 ± 4.0 L/kg), with terminal half-lives up to 14.2 h. PM030047 remained a minor metabolite in GLP studies, with <1.4% of parent exposure.

Plasma kinetics after repeated intravenous dose

Lurbinectedin pharmacokinetics were assessed in rats, dogs, and cynomolgus monkeys after 4 or 8 intravenous dosing cycles (one dose every 3 weeks). In rats (4- and 8-cycle studies), lurbinectedin showed linear, dose-independent kinetics, with moderate clearance (3.5–4.4 L/h/kg), high V_{dss} (5.5–55.8 L/kg), and a terminal half-life of 7 h. Exposure increased proportionally with dose, though 2–3-fold higher C_{max} and AUC values were observed on Day 64 compared to Day 1 in the 4-cycle study, suggesting possible liver effects. No time-dependent accumulation was seen in the 8-cycle study. In NHPs (4- and 8-cycle studies), lurbinectedin showed low clearance (1.5–1.8 L/h/kg), high V_{dss} (12–13.3 L/kg), and a long terminal half-life (8–10 h), with linear, dose- and time-independent kinetics. AUC increased proportionally, while C_{max} did not. Exposure of metabolite PM030047 remained below 2.3% of parent drug levels. In dogs, multiple i.v. doses (0.003–0.03 mg/kg) produced consistent plasma profiles across cycles, with moderate CL (3.6±2.5 L/h/kg), large V_{dss} (15.3±9.7 L/kg), and a terminal half-life of 6.9±6.3 h. Pharmacokinetics were linear and similar between sexes, with no evidence of accumulation.

4.3.2.2. Distribution

Lurbinectedin exhibits high plasma protein binding across species: 95% (mouse), 96% (rat), 88% (guinea pig), 93% (rabbit), 96% (dog), and 98% (human) (Study PUSA00643), independent of concentration from 80 to 800 µM. At clinically relevant concentrations (10–500 nM), plasma protein binding remained >97% in rat, NHP, dog, and human plasma, as well as to human serum albumin (HSA) and α-1-acid glycoprotein (AAG) (Study VNG3561-2015). Blood cell partitioning studies (Study VNG3495-2016) using ^{14}C-lurbinectedin at 200–500 nM showed low blood-to-plasma ratios (0.65-0.79) in rat, NHP, dog, and human, with rapid equilibrium reached within 15 minutes.

Study VNG3665/2015 in SD rats (n=3/sex) investigated the tissue distribution of ^{14}C-lurbinectedin after a single i.v. bolus administration of MTDs (0.2 mg/kg and 0.1 mg/kg for male and female rats, respectively). Blood exposure was higher in males, but tissue radioactivity exposure was comparable or greater in females despite lower dosing, indicating higher tissue uptake/retention. The highest tissue radioactivity was observed in spleen, liver, lymph nodes, thyroid, lung, kidney, and small intestine. Significant sex differences appeared in gonads, with ovarian $AUC_{0\text{-}t}$ and C_{max} 13- and 6-fold higher than testes, respectively. Lowest concentrations were found in brain (<5 ng-eq/g males; <2.3 ng-eq/g females) and testes (<12 ng-eq/g).

4.3.2.3. Metabolism

Metabolism of lurbinectedin was investigated *in vitro* in microsomes (mouse, rat, guinea pig, rabbit, dog, NHP and human), liver S9 fractions (rat, dog and human) and plasma (mouse, rat, rabbit, dog, and human). In vivo metabolism was investigated in plasma of rat, NHP and dog.

In vitro metabolism

In Study PMAR14-NC032, ^{14}C-lurbinectedin (400 nM) was incubated with NADPH-activated microsomes from mouse, rat, dog, NHP, mini-pig, and human. After 10 min, lurbinectedin was extensively metabolized in human (17.8% unchanged), NHP (5.9%–12.2%), mouse (5.2%–9.9%), and mini-pig (14.8%), while higher stability was seen in rat (65.1%–76.9%) and dog (31.4%–56.9%). Seven metabolites were detected of which four were major: PM030047 (N-demethylation), PM01158 (O-demethylation), PM030036 (N,O-demethylation), and Metabolite 1 (ring opening), see Figure 6. NHP and human showed the most similar metabolic profiles. PM030047 and Metabolite 1 were the main human metabolites, at 19.1% and 16.3%, respectively.

Phase II metabolism (Study RPT03283) was investigated in rat, dog, and human liver S9 fractions at 200 nM. With full cofactor sets, extensive metabolism occurred in human (4.3% unchanged), moderate in dog (20%), and mild in rat (60%). In absence of NADPH or cofactors, metabolism was minimal, suggesting a negligible Phase II contribution.

Plasma stability (Study PUSA00620) at 1–100 ng/mL showed low degradation in mouse, rat, dog, and human plasma, with half-lives of 1.4, 2.0, 4.6, and 1.9 h, respectively.

In vivo metabolism

Lurbinectedin-related metabolites were determined in plasma samples from rats, NHPs and dogs, as well as from a mass balance clinical trial in patients (Study PM1183-A-015-16). Main metabolites assessed were M1, PM030047, PM01158, and PM030036. In humans, ^{14}C-lurbinectedin-related radioactivity was mainly attributed to the unchanged compound (*circa* (ca.) 70%) and ca. 19% to major circulating metabolites, metabolite 1 (ca. 10% of total radioactivity; 14% of unchanged lurbinectedin) and PM030047 (ca. 7% of total radioactivity; ca. 10% of unchanged compound).

In rats (8-cycle study RTCA2649), PM030047 was detected with notable gender differences (female exposure was 126%, while male exposure was 13% relative to parent compound). M1 appeared only in cycle 8 at near-BLQ levels, while PM01158 and PM030036 were undetected across all samples and cycles.

In NHPs, studies PMAR16-NC020 (single-dose), PMAR16-NC008 (4-cycle), and PMAR16-NC018 (8-cycle) showed that metabolites PM01158 and PM030036 were consistently below LOQ at all timepoints and doses. M1 was quantifiable with increasing AUC0-t percentages with dose, ranging from 1.4% to 6.6%, without sex-related trends. PM030047 exposure was low, generally <2% of parent AUC. In the mass balance study PMAR17-NC024 (VNG5331-2017), plasma radioactivity within 2 hours post-dose was mainly due to parent drug (65–78%), with C_{max} representing 82% of total radioactivity. M1 and PM030047 accounted for <2%, declining rapidly. In faeces, M1 (3%) and its N-desmethylated form (1.3%) were predominant metabolites. PM030047, PM01158, PM030036, and other minor (<0.6%) oxidized derivatives were also found, likely from degradation.

In dogs (study PMAR16-NC033), after a single 0.03 mg/kg i.v. dose, PM030047 exposure exceeded that of the parent (AUC ratios: 107% in males, 112% in females). M1, PM01158, and PM030036 were also detected.

4.3.2.4. Excretion

Excretion of ^{14}C-lurbinectedin was studied in rats (Study VPT2836-2015) and non-human primates (NHPs) (Study VNG5331-2017). In rats dosed with ^{14}C- lurbinectedin, the radioactivity was principally recovered in the faces (cumulative ca. 90% at 168 h post-dose), with excretion via the urine occurring to a much smaller degree (ca. 3%). In bile cannulated animals, a mean biliary excretion of ca. 58% (male) and 42% (female) of the administered dose was found during the 0-72 h period. Similar results were found in male NHP, with the cumulative (up to 168 h post-dose) excreted radioactivity mainly found in faces (ca. 76%); only ca. 4% was found in urine.

4.3.2.5. Pharmacokinetic drug interactions

No animal dedicated drug-drug interaction studies were conducted. Human in vitro and in vivo pharmacokinetic drug-interaction studies are presented in the clinical pharmacology.

4.3.2.6. Other pharmacokinetic studies

No other pharmacokinetic studies were conducted.

4.4. Toxicology

4.4.1. Single-dose toxicity

Six single-dose toxicity studies with lurbinectedin were performed in three different species. All single-dose toxicity studies were performed by applying a single iv bolus. One study was performed in rats according to GLP principles, three studies were performed in dogs (one according to GLP, others non-GLP) and two studies in non-human primates (one GLP, one non-GLP). Doses applied were normalized for body surface, consistently recalculated from mg/kg and presented as mg/m^2 in accordance to conversion factor (k_m) provided in FDA Guidance for Industry: Estimating the Maximum Safe Starting

Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (July 2005). Conversion factors used are 6 for rats, 12 for dogs and 20 for NHPs.

Toxicities noted in single dose toxicity studies were mostly similar between species. Most common effects were toxicities on hematopoietic organs which are not dose related and which were seen as marked reductions in lymphocyte, reticulocyte and sometimes thrombocyte numbers, severe anaemia seen in bone marrow, gross pathology and microscopically changes (organ weight fluctuations and discoloration, demarcation line changes) in thymus and spleen. Other toxicity in all of the performed studies were gastrointestinal and liver effects. Symptoms and findings included emesis, changes in faces, loss of appetite, body weight, discoloured/yellow mucoid in gastro-intestinal (GI) system, epithelial atrophy in small and/or large intestine, changes in gall bladder. Marked dose-independent effects are also seen in liver. Increases in liver enzymes in some studies were found up to 20-fold. Microscopically, liver was found with discoloration, reduction in size and depressed areas. Most of the changes showed reversibility or a trend toward reversibility.

4.4.2. Repeat-dose toxicity

Seven repeat-dose toxicity studies with lurbinectedin were performed in three different species – three in rats, two in dogs and two in NHPs. All repeat-dose toxicity studies were performed using the clinically relevant schedule, one i.v. dose every 3 weeks.

Studies RTCA2080 (8 cycle study in rats) and RTC72720 (4 cycles in dogs) were early terminated and no toxicological information was either generated or reported. In the rat study, which was terminated early, a problem with the formulation was identified and there was a question of animals receiving the adequate dose. However, in the dog study, animals died from lurbinectedin unrelated lung disease and the formulation was declared adequate. The subsequent dog study was performed with a 2-fold lower doses of lurbinectedin.

Toxicities noted in repeat dose toxicity studies were mostly similar between species. Most common toxic effects were bone marrow atrophy which was associated with dose-related leukopenia, as well as thrombocytopenia and anaemia. Liver abnormalities were reported (multiple dark areas or swollen liver, increased liver function markers, bile duct damage with necrosis and/or oedema, and hepatocellular degeneration/apoptosis and periportal hepatocytic hypertrophy). Additional findings were located in the gastro-intestinal tract (mucosal atrophy), kidneys (cortical tubular degeneration and vacuolation), heart (focal, slight to moderate myocardial degeneration and/or necrosis) and injection site (perivascular/vascular inflammatory reactions). seen as leukopenia, thrombocytopenia and anaemia, liver toxicity seen as marked elevations in liver enzymes and microscopically hepatocellular and bile duct damage (necrosis, degeneration, apoptosis) and injection site reactions. Other findings were atrophy of the GI mucosa, some cortical tubular degeneration in kidneys. Full recovery was seen in most of the effects. In some studies, bone marrow atrophy and injection site reactions persisted.

4.4.3. Genotoxicity

Genotoxicity assessment was conducted in two assays, Ames assay and mouse lymphoma L5178Y

The Ames test was negative - lurbinectedin did not induce two-fold increase in the number of revertant colonies at any dose level (≤120 µg/plate), in any tester strain, in the absence or presence of S9, up to cytotoxic concentrations.

Mouse lymphoma test produced positive results in concentrations from 1.5 ng/ml in presence and 0.188 ng/ml (range from 48 to 0.188 ng/mL) in absence of S9 metabolizing system. The proportion of

small versus large colonies shifted toward small colonies at the concentrations producing mutagenic effect.

4.4.4. Carcinogenicity

No dedicated carcinogenicity studies were performed.

4.4.5. Developmental and reproductive toxicity

No dedicated fertility and early embryonic studies were performed.

In the SmPC part 4.6 under "Women of childbearing potential/contraception in males and females", the use of contraception for 7 months after the last dose for female patients, and 4 months after the last dose for male patients is recommended.

The exploratory study of lurbinectedin embryo-foetal toxicity showed that lurbinectedin causes maternal toxicity to pregnant female rats at 0.1 mg/kg (0.6 mg/m^2) and embryo foetal death of 100 % conceptuses.

No dedicated prenatal and postnatal development toxicity study and no dedicated juvenile animal toxicity study were performed.

4.4.6. Toxicokinetics and exposure margins

Toxicokinetics are reported under pharmacokinetics section. Regarding the interspecies comparison of exposures and safety margins, these are determined based on Maximal Tolerated Doses (MTDs) for general toxicity studies instead of the NOAELs since the NOAELs were determined only in some toxicology studies (and companion toxicokinetics). Exposure margins at MTDs are well below 1 in all of the performed studies and all of the species.

4.4.7. Local tolerance

In a local tolerance test in rabbits, both IV and perivenous administration of lurbinectedin caused slight perivascular and/or vascular chronic inflammatory reactions.

Local tolerance study results are mostly in line with findings from the general toxicity studies with addition of tissue necrosis when administered paravenously. Tissue necrosis is also reported in the clinical setting in cases of extravasation.

4.4.8. Other toxicity studies

Immunotoxicity

No dedicated study on immunotoxicity was performed. The applicant provided a general conclusion on immunotoxicity based on haematology parameters noted in general toxicity studies: dose-dependent decreases in lymphocytes and neutrophils following repeated lurbinectedin administration suggest that there may have been a general decrease in immune responsiveness. This effect is an expected pharmacological effect, commonly observed with a number of drugs used for cancer therapy.

Impurities

A mutagenicity assay with Mouse lymphoma L5178Y cell Tk (thymidine kinase) gene mutation assay

was performed for one impurity (Impurity D). It yielded positive results in S9 positive assay in concentration of 2.19 ng/ml and onwards. The S9 negative part did not cause mutations in the tested concentrations.

Phototoxicity

A GLP in vitro cytotoxicity assay with BALC/c 3T3 fibroblast cells was performed to assess the phototoxic potential of lurbinectedin. On the basis of the obtained results (PIF lower than 2 or the MPE lower than 0.1), it was concluded that lurbinectedin is not phototoxic under the reported experimental conditions.

4.4.9. Ecotoxicity/environmental risk assessment

Table 4: Summary of main study results: Phase I

Substance (INN/Invented Name):	lurbinectedin		
CAS-number (if available):	497871-47-3		
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{OW} (ion-corrected log D_{OW})	OECD107	1.37 (pH 5) 3.17 (pH 7) 3.49 (pH 9)	Potential PBT: N
PBT-statement :	The active substance is considered to be not PBT, nor vPvB		

Phase I			
Calculation	Value	Unit	Conclusion
PEC_{sw}, refined	8×10^{-5}	µg/L	≥ 0.01 threshold: N
Other concerns (e.g. chemical class)			N

The applicant presented an ERA according to the Guideline on the environmental risk assessment of medicinal products for human use, EMEA/CHMP/SWP/4447/00 Rev. 1-Corr., September 2024.

Refined PEC_{SW} for lurbinectedin is below the action limit of 0.01 µg/L. Consequently, a Phase II risk assessment is not required.

A bioaccumulation potential is not indicated based on the log K_{OW} < 4.5. A definitive PBT/vPvB assessment is not required.

4.5. Overall discussion and conclusions on non-clinical aspects

4.5.1. Discussion

Pharmacology

The mechanism of action of lurbinectedin was thoroughly investigated in non-GLP studies, which were performed mainly in academic laboratories, and were published in peer-reviewed journals and/or accepted as abstracts at international congresses. Therefore, the absence of specific study reports is justified.

Lurbinectedin is a tetrahydroisoquinoline that reacts through its hemiaminal moiety with the exocyclic

amino group of specific guanines in the minor groove of DNA, forming a covalent bond. Its sequence specificity depends on the establishment of highly specific hydrogen bonds with the nucleotides both sides of the guanine. The primary mechanism of action of lurbinectedin is considered to be inhibition of oncogenic transcription due to the eviction of oncogenic transcription factors from their recognition sequences within gene promoters. Additionally, the transcription is inhibited by the irreversible stalling of elongating RNA polymerase II on the DNA template and its specific degradation by the ubiquitin/proteasome machinery. Moreover, lurbinectedin binding promotes persistent DNA breaks in its vicinity, which might be considered as a third line of its action. These DNA breaks likely result from failures in DNA repair pathways, such as nucleotide excision repair (NER) and homologous recombination repair (HRR), which are solicited to eliminate lurbinectedin bound to DNA. Collectively, the inhibition of transcription and the accumulation of DNA damage delays progression through the S/G2 phase of the cell cycle and, ultimately, triggers caspase-dependent apoptotic death of tumour cells.

Besides its direct cytotoxicity to tumour cells, lurbinectedin showed traits of immunogenic cell death *in vitro*, while the effects on tumour associated macrophages and modulation of tumour microenvironment (TME) were observed in several *in vitro* and *in vivo* studies. These effects represent dose- and exposure-dependent manifestations of lurbinectedin's primary DNA- and transcription-targeting mechanism. This unified mechanism accounts for both: (i) sub-lethal transcriptional reprogramming in myeloid cells (leading to Rho-pathway downregulation, reduced cytokine/VEGF secretion, and impaired motility) and (ii) selective apoptosis and depletion of monocyte/macrophage populations at antitumour exposures. Although clearly demonstrated *in vitro*, distinguishing these dose-dependent effects *in vivo* appears challenging. The reduction in monocyte and macrophage subsets, including tumour-associated macrophages (TAMs), observed in murine fibrosarcoma and pancreatic cancer xenograft models following administration of full antitumour doses of lurbinectedin may predominantly reflect the apoptotic/cytotoxic effect. The contribution of sub-lethal transcriptional mechanisms at antitumour doses *in vivo* remains unclear, as these effects have been demonstrated only *in vitro* at low concentrations (i.e. there is no *in vivo* confirmation of these effects). Therefore, the description of the mechanism of action regarding the lurbinectedin's effect on TME in section 5.1 of the SmPC specifies the dose ranges and corresponding biological effects of lurbinectedin on TME and mentions the origin of findings (i.e. *in vitro* or *in vivo*).

In a panel of *in vitro* screening assays, in which a single concentration of lurbinectedin (200 nM; 160 ng/mL) above the C_{max} in patients (130 ng/mL) was tested, no significant effects with respect to the untreated controls were observed. However, higher concentrations were not assessed in any assay and it is unknown if binding of lurbinectedin at any off-target may occur at higher concentrations. Therefore, based on the submitted data it can only be concluded that off-target effects seem unlikely at clinically relevant lurbinectedin concentrations. The on target/off tissue effects were not addressed from non-clinical perspective by the applicant, but this is not considered necessary based on the available clinical safety data.

The core battery safety pharmacology assessment was conducted in accordance with ICH S7A and ICH S7B. All studies were GLP compliant. *In vitro* hERG assay investigated appropriate concentration range; the 3 µM of lurbinectedin is well in excess of the anticipated plasma levels that may be achieved in humans. Doses for *in vivo* studies in rats, dogs and NHPs were chosen based on the obtained MTDs in previous studies. The route of administration was the intended clinical route (i.v.). Concentration of lurbinectedin and its main metabolites (M1, lurbinectedin, PM030036) were determined in NHP plasma in study 20160140PCCYP, while no assessment of lurbinectedin plasma concentration was made in dog plasma. Lurbinectedin had no effects on the CNS and limited effects (decrease in tidal volume only in male rats) were observed on respiratory systems. In the patients (n=554) included in the Integrated Safety Analysis or in those included in the IMforte trial

(lurbinectedin plus atezolizumab cohort, n=242 patients), no relevant clinical signs related to changes in CNS, general behaviour or the respiratory function were seen (see Clinical aspects). The effects on the cardiovascular system observed in non-clinical species (dog and NHP) were considered to be related to changes in autonomic balance, associated with clinical signs (nausea/vomiting), with no incidence in the patient population treated with lurbinectedin. Moreover, the results from a dedicated QTc study were negative.

The applicant submitted 3 *in vitro* and 14 *in vivo* studies as well as a number of literature references, in which lurbinectedin was tested in combination with other standard of care anticancer agents of different mechanisms of action in different tumour cell lines and xenograft models, to identify possible synergistic activities, potentially worth of further clinical examination. Synergistic effects were observed when lurbinectedin was combined with a number of anticancer agents, including cisplatin, suggesting the potential for combination therapies.

Pharmacokinetics

The pharmacokinetics of lurbinectedin have been extensively evaluated in both non-GLP and GLP single and/or repeated-dose intravenous studies across multiple animal species including mice, rats, dogs, mini-pigs, and NHPs, using the clinical IV formulation.

Bioanalytical methods

In early GLP rat (RTC69230, RTC72730) and dog (RTC64720, RTC73520) studies, lurbinectedin plasma levels were measured using a non-validated LC-MS/MS method, whereas a validated LC-MS/MS method (Pernice et al 2016) was later implemented in pivotal toxicokinetic studies. Method validations (S17-012-PM, S16-266-PM) showed acceptable accuracy, precision, and stability across 0.1–100 ng/mL (NHP) and 0.2–100 ng/mL (rat). An LC-RAD method (PMAR14-NC032) supported in vitro metabolic profiling of ^{14}C-lurbinectedin. Metabolite 1, which could not be chemically synthesised, was biosynthesised in NHP liver microsomes and quantified using a radiolabelled reference (PMAR17-NC001). Lurbinectedin and PM030047 were quantified in rat and NHP plasma using validated LC-MS/MS methods, while Metabolite 1 was quantified in NHP plasma using a non-GLP method, which is acceptable considering ICH S9 indication.

Radiolabelled ^{14}C-lurbinectedin was used in ADME studies, with total radioactivity measured via liquid scintillation counting. Early in vivo studies used a non-validated LC-UV method, later validated (ZNA14886.006) and applied in safety studies. Separate validated methods supported formulation analysis (RTCA2210) and hERG testing (ZNA14886.008/.009).

Absorption

Single-dose PK studies

Lurbinectedin showed multi-compartment plasma pharmacokinetics across species (mouse, rat, dog, mini-pig, NHP) after single IV bolus, with rapid distribution, slower elimination, and generally linear dose-exposure (C_{max}, AUC) relationships. Clearance was low-to-moderate (1.3–4.9 L/h/kg), volume of distribution was high (9–42 L/kg), and half-life varied by species (9–22 h). Female rats showed higher systemic exposure than males, consistent with known sex differences in rat pharmacokinetics. Variability in half-life and exposure also appeared in dogs and NHPs, but the findings were inconsistent, or from non-GLP studies, raising no concerns. In NHPs, higher exposure in some females occurred only at doses above the maximum tolerated dose determined for lurbinectedin in NHP which might have affected pharmacokinetics of the drug. The metabolite PM030047 was generally low but showed unusually high metabolite-to-parent ratios in dogs (>100% for both sexes), likely due to slower metabolite clearance.

Repeated- dose

Lurbinectedin's plasma toxicokinetics were studied in rats, dogs, and NHPs over 4- and 8-cycle IV bolus regimens (one dose every 3 weeks). Across species, it showed linear, time-independent kinetics with moderate clearance (1.5-4.4 L/h/kg), high volume of distribution (5.5-15.3 L/kg), and long half-life (6.9-10.8 h). In humans, clearance was lower (ca. 0.2 L/h/kg), with a similar Vd (ca. 6 L/kg) and longer half-life (ca. 50 h). Systemic exposure in animals was lower than in humans (AUC ratio <0.2), which is commonly seen with other cytotoxic agents (e.g. for structurally similar compound, trabectedin, animal to human exposure ratios did not exceed 0.3 in any study). This is acceptable in view of the indication and the target population.

In rats, both 4- and 8-cycle studies showed dose-proportional PK and no significant sex differences. Some lurbinectedin accumulation cannot be completely ruled out in rats, due to liver toxicity, however it was observed only in the 4-cycle study, where non-validated method was used for lurbinectedin quantification. In NHPs and dogs, lurbinectedin showed consistent, linear PK with no accumulation over multiple cycles. NHPs showed high C_{max} variability (up to 57%), consistent with clinical data. As in single-dose studies, the metabolite PM030047 showed low exposure (<2.3% of parent AUC), rapid clearance, and no accumulation. In rats, evaluation was inconclusive due to poor analytical quality and possibly due to under-dosing.

Distribution

Lurbinectedin showed high plasma protein binding (88–98%) across all tested species (mouse, rat, guinea pig, rabbit, dog, human), regardless of method or concentration. In humans, it was highly bound (>98%) to both serum albumin and α-1-acid glycoprotein, with a ca. 550-fold higher affinity for the latter. Blood-to-plasma partitioning ratios were low (0.65–0.79 across species), indicating preferential distribution in plasma, consistent with in vivo rat and NHP data. Following a single IV dose in rats, lurbinectedin showed rapid and extensive tissue distribution, with highest levels in liver, kidney, lung, spleen, lymph nodes, thyroid, and small intestine, while low exposure in brain and gonads. These distribution patterns align with target organs in repeat-dose toxicity studies and support clinical monitoring of hepatobiliary and haematolymphoid systems, with limited brain penetration suggesting a low risk of CNS-mediated adverse events. A significant difference in the radioactivity distribution was observed in the gonads, where the concentration in the ovary was five to fifteen folds higher than in testes. Nevertheless, testicular toxicity was observed in rat studies at doses below the recommended clinical dose (see toxicology section). The brain showed the lowest levels, likely due to lurbinectedin being a P-gp substrate. Correspondingly, no CNS-related effects were noted in safety pharmacology studies (ZNA14886.003). No dedicated studies of blood–brain barrier, placental or lactational transfer were submitted. However, the observed low brain exposure together with the proposed contraindications regarding breastfeeding and the recommendation for effective contraception mitigate residual concerns in relation to the intended indication.

Metabolism

In vitro studies demonstrated that lurbinectedin undergoes rapid, NADPH-dependent microsomal metabolism almost exclusively via CYP3A4, with negligible contribution from other CYP isoforms, while Phase II pathways were not meaningful contributors. Metabolic profiling showed that non-human primate and human liver microsomes exhibit the most similar qualitative and quantitative patterns, with two principal metabolites identified: PM030047 (N-desmethyl) and Metabolite 1 (1',3'-dihydroxy via aliphatic ring opening), whereas minor species-restricted metabolites (PM030036, PM01158) were observed mainly in NHP and humans at low levels.

Lurbinectedin-related metabolites were determined in plasma samples from rats, NHPs and dogs, as well as from a mass balance clinical trial in patients. In animals, two human major metabolites, M1 (1', 3'-dihydroxy-lurbinectedin) and PM030047 (N-desmethyl-lurbinectedin), were quantifiable by LC-MS/MS, though with species-specific differences. Both metabolites were measured in NHPs, whereas

only PM030047 was quantifiable in rats and dogs, as M1 was near or below the LOQ. Overall, in vivo exposure to these metabolites in animals was lower than in humans, largely reflecting the lower tolerated doses in animals relative to the clinical dose of 3.2 mg/m². As a result, full toxicological coverage of these metabolites was not achieved in nonclinical species. Nevertheless, this is not considered a significant safety concern in the context of the intended patient population (ICH S9, advanced cancer). In humans, two further metabolites (PM030036 and PM01158) were detected at very low levels. In plasma samples of non-clinical species, metabolites PM030036 and PM01158 could not be quantified (values below LOQ), probably due to under-dosing of animals. However, since both metabolites were detected in faecal samples of NHPs, there is no unique human metabolites for lurbinectedin. Interestingly, the AUC ratios of metabolites M1 and PM030047 to parent compound where < 5.3% for NHPs, without accumulation and without sex-related differences. In rats (females) and dogs, exposure to PM030047 was disproportionately high, in some cases comparable to or exceeding parent compound levels, whereas in NHP (the most translationally relevant species) metabolism is comparable to humans, with PM030047 remaining minor. However, no further non-clinical concern is raised due to: (i) absence of a full toxicological coverage of both human major metabolites (see discussion above), and (ii) ICH S9 Q&A, stating that no additional studies are required with disproportional metabolites.

Excretion

Following single IV doses, lurbinectedin was primarily eliminated via faeces in rats, NHPs, and humans (76-91%), with minimal urinary excretion (3-6%), confirming a consistent faecal-dominant, hepatobiliary elimination pathway across species. No studies have been conducted to assess the excretion of lurbinectedin into milk. Due to the PD and genotoxic effect of lurbinectedin, there is an unacceptable risk for the suckling child. Therefore, contraindication for lactation should be considered (see the discussion on toxicology below).

Toxicology

The non-clinical toxicology programme for lurbinectedin is considered adequate and consistent with ICH S9 expectations for anticancer pharmaceuticals. Acute toxicity information was obtained from single-dose toxicity studies in rats, dogs and NHP, although according to ICH M3(R2) and ICH S9 such stand-alone studies are not strictly required when repeat-dose studies at sufficiently high doses are available. The submitted single-dose studies are therefore supplementary and provide additional value by confirming the target organ profile, establishing MTD values across species, and corroborating the results from the repeat-dose studies. Lurbinectedin single dose toxicity studies revealed a high acute toxicity potential of the product in terms of haematology adverse effects, liver toxicity and GI toxicity.

NOAEL could be determined only in some studies, so the MTD dose was used as the marker for toxicity, which is in line with ICH S9 guideline and acceptable. The MTD following a single bolus i.v. injection was 0.2 and 0.1 mg/kg (1.2 and 0.6 mg/m2) in rats (male and female, respectively), 0.03 mg/kg (0.6 mg/m2) in dogs (both genders) and 0.125-0.167 mg/kg (1.5 mg/m2) in NHP (both genders). Relevant gender differences were reported in the rat.

Repeat-dose toxicity studies were performed in rats, dogs and NHP, adequately reflecting the intended clinical schedule of administration (q3w) and covering 4- and 8-cycle regimens of at least three months' duration, in line with ICH S9 recommendations. Across species, the principal toxicities involved the hematopoietic and lymphoid systems, gastrointestinal tract and liver, with injection-site changes consistently observed. Renal changes were occasionally noted, though less consistent. Recovery periods of three weeks were incorporated, and partial recovery of the major toxicities was consistently documented, as required by ICH S9. Minimal to mild myocardial degeneration and/or necrosis were reported in several nonclinical toxicity studies with lurbinectedin. These findings were apparently more frequent following single dose administration in the rat and NHP, although were also

reported in the repeated-dose studies performed in NHP and dogs. The toxicological profile is predictable, clinically manageable, and consistent with the pharmacology of a DNA-binding cytotoxic agent. MTD was used as marker for toxicity. After 4 cycles the MTD was determined to be 0.06 and 0.03 mg/kg (0.36 and 0.18 mg/m2) in rats (male and female, respectively), 0.03 mg/kg (0.6 mg/m2) in dogs (both genders) and 0.125 mg/kg (1.5 mg/m2) in NHP (both genders). After 8 cycles, the MTD was determined to be 0.06 and 0.03 mg/kg (0.36 and 0.18 mg/m2) in rats (male and female, respectively) and 0.125 and 0.104 mg/kg (1.5 and 1.25 mg/m2) in NHP (male and female, respectively). Gender differences in lurbinectedin-related toxicity were clearly noticed in the rat.

On the basis of a positive in vitro assay on mammalian cells, lurbinectedin can be considered genotoxic (clastogenic) and no further in vivo genotoxicity studies are considered needed.

Genotoxicity assessment was conducted in two assays, Ames assay and mouse lymphoma L5178Y which are both standard tests for the genotoxicity endpoints according to the ICH S2 Guideline. The genotoxicity profile is consistent with the pharmacological class: lurbinectedin was negative in the bacterial reverse mutation assay at interpretable concentrations, but positive in the mouse lymphoma assay, indicating mutagenicity in mammalian cells. In vivo testing was not conducted, but this is acceptable under ICH S2 for strongly cytotoxic compounds targeting rapidly dividing cells. The SmPC appropriately reflects this information (in section 5.3). Long-term carcinogenicity studies were not conducted, in line with ICH S1 and S9 guidance, and their absence is acceptable.

No dedicated fertility and early embryonic studies were performed which is acceptable considering the indication. Considering the pharmacology of lurbinectedin and a clear genotoxic effect, it is reasonable to presume a toxic effect on the fertility and early embryonic development. A proposal for genetic counselling and preserving germ cells before the initiation of treatment in cases where patients are planning to conceive a child after treatment and a recommendation on performing a pregnancy test before initiating treatment in women of child-bearing potential were included in section 4.6 of the SmPC. The recommended duration of contraception in line with the principles laid out in the SWP/NcWP recommendations on the duration of contraception following the end of treatment with a genotoxic drug (EMA/CHMP/SWP/74077/2020 rev. 1*).

According to the Guideline on risk assessment of medical products on human reproduction and lactation: from data to labelling (EMEA/CHMP/203927/2005), and considering the severity of the disease (treatment cannot be postponed and there are no alternative safer options), lurbinectedin should not be contraindicated in pregnancy. Nevertheless, as teratogenicity can be expected for genotoxic compounds like lurbinectedin and was observed in nonclinical studies, a strengthened wording was included, stating that lurbinectedin should not be used during pregnancy unless the clinical condition of the woman requires treatment. In addition, a contraindication for breastfeeding was included in section 4.3 of the SmPC. Due to the PD and genotoxic effect of lurbinectedin, there is an unacceptable risk for the suckling child and exposure to lurbinectedin must be avoided.

Decreases in several blood cell lineages were observed not only after repeated dosing of lurbinectedin but also in single-dose toxicity studies. Leukopenia, lymphopenia, neutropenia, thrombocytopenia and anaemia were consistent with bone marrow toxicity and were observed consistently throughout all general toxicity studies. Also, thymus atrophy, spleen changes and bone marrow changes were noted. Haematology parameters usually showed a trend towards recovery. These findings cumulatively point toward a possible lowered immunological response in patients receiving lurbinectedin, regardless of the duration of treatment. Even a one-time application of lurbinectedin bares a significant risk of immunotoxicity. Accordingly, lurbinectedin may reduce immune responsiveness, as shown by decreases in lymphocytes and neutrophils, but this can be considered as an expected pharmacological effect of anticancer therapy.

Other areas of assessment are considered acceptable. A local tolerance study in rabbits confirmed

acceptable safety via the intended i.v. route, with perivenous administration showing expected extravasation injury. No human-specific metabolites were identified; therefore, additional metabolite studies were not warranted.

The proposed limit for the genotoxic impurity D is acceptable considering the genotoxicity of the active substance, proposed indication and acceptable limits suggested in ICH M7 and ICH S9.

Phototoxicity testing in vitro (3T3 NRU assay) did not indicate phototoxic potential, with results well below the thresholds of concern. The lack of phototoxic potential of lurbinectedin is agreed.

The Environmental Risk Assessment (ERA) was performed according to the new EMA guidance. The refined PEC_{SW} was calculated as 8×10^{-5} µg/L, well below the 0.01 µg/L action limit, not triggering the Phase II assessment. Within the scope of the PBT/vPvB hazard screening assessment, the Applicant experimentally determined the partition coefficient across the environmentally relevant pH range (pH 5–9). Since lurbinectedin exhibits three pKa values, ion-corrected log D_{OW} values were calculated using multiprotic approach described by Avdeef (1992), Csizmadia et al. (1997), and ECETOC Technical Report No. 123 (2013). Overall, the resulting ion-corrected log D_{OW} values at pH 5, 7, and 9 were 1.37, 3.17, and 3.49, respectively. As none of these values exceed the screening threshold of 4.5, further assessment for PBT/vPvB properties was not triggered and lurbinectedin is therefore considered to be not PBT nor vPvB. Although the values at pH 7 and 9 exceed the trigger value of 3 for secondary poisoning, no further assessment, including determination of a bioaccumulation factor (BCF), was required as Phase II was not triggered.

4.5.2. Conclusions

The pharmacological premise and rationale, as well as the characterisation of lurbinectedin as a potential drug for the treatment of SCLC are established.

Lurbinectedin shows linear PK, extensive distribution, high protein binding, CYP3A4-dependent metabolism, and faecal/biliary elimination. The PK package is considered adequate, with NHP providing the most relevant species for safety assessment.

The non-clinical toxicology programme for lurbinectedin is adequate and consistent with ICH S9 and M3(R2). The studies identified predictable, class-consistent toxicities with partial reversibility, established MTDs across species, and provided exposure coverage relative to clinical use. Additionally, lurbinectedin is considered to be not PBT nor vPvB, and is not expected to pose a risk to the environment.

5. Clinical aspects

5.1. Introduction

5.1.1. Good Clinical Practice (GCP) aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

A request for a routine GCP inspection has been adopted for the following clinical study GO43104. The outcome of this inspection and the satisfactory responses to its findings are an integral part of this

procedure and were received by Day 181.

Based on the review of clinical data and the above-mentioned reports, CHMP did not identify the need for a further GCP inspection of the clinical trials included in this dossier (see section 2.4.3.).

5.1.2. Tabular overview of clinical trials

Table 5: Tabular overview of main clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test product(s); Dosage Regimen; Route of Administration	Number of Subjects Treated	Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
5.3.3.2 Patient PK and Initial Tolerability Study Reports									
PK/Safety	**PM1183-A-001-08** **CSR synopsis**	**5.3.3.2**	Determine DLTs, MTD, RD, and PK	First-in-human, open-label, dose-finding, uncontrolled	lurbinectedin: 0.02 to 5.0 mg/m^2 D1 q3wk, i.v. RD: 4.0 mg/m^2 (equivalent to 7.0 mg FD) D1 q3wk, i.v.	31	Advanced solid tumours	Until disease progression, unacceptable toxicity, or withdrawal of consent	Complete; **CSR**
PK/ Safety	**PM1183-A-002-10** **CSR synopsis**	**5.3.3.2**	Determine MTD, RD and PK	Open-label, dose-finding, uncontrolled clinical and pharmacokinetic phase I study	lurbinectedin: 3.5 to 7.0 mg FD D1, D8 q3wk, i.v. RD not defined	24	Haematological malignancies (AAL or relapsed/refractory MDS)	Until disease progression, unacceptable toxicity, or withdrawal of consent	Complete; **CSR synopsis**
					lurbinectedin: 1.0 to 3.0 mg FD D1- D3 q3wk, i.v. RD not defined	18			
PK/ Safety	**PM1183-A-003-10** **CSR synopsis**	**5.3.3.2**	Determine MTD, RD, and PK combination with doxorubicin	Open-label, dose-finding, uncontrolled with expansion cohorts at RD to assess preliminary efficacy in SCLC and endometrial cancer	lurbinectedin: 3.0 to 5.0 mg FD D1 q3wk, i.v. + doxorubicin 50 mg/m^2 D1 q3wk, i.v. RD: lurbinectedin 4.0 mg FD D1 q3wk, i.v. + doxorubicin 50 mg/m^2 D1 q3wk, i.v.	73	Advanced solid tumours	Until disease progression, unacceptable toxicity, or withdrawal of consent	Complete; **CSR synopsis**
					lurbinectedin: 2.0 mg/m^2 D1 q3wk, i.v. + doxorubicin 40 mg/m^2 D1 q3wk, i.v.	47	SCLC or endometrial carcinoma		
PK/ Safety	**PM1183-A-004-10** **CSR synopsis**	**5.3.3.2**	Determine MTD, RD and PK combination with gemcitabine	Open-label, dose-finding, uncontrolled	lurbinectedin: 2.5 to 3.5 mg FD D1, D8 q3wk, i.v. + gemcitabine 800 or 1000 mg/m^2 D1, D8 q3wk, i.v. RD: lurbinectedin 3.0 mg FD D1, D8 q3wk, i.v. + gemcitabine 800 mg/m^2	45	Advanced solid tumours	Until disease progression, unacceptable toxicity, or withdrawal of consent	Complete; **CSR synopsis**

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test product(s); Dosage Regimen; Route of Administration	Number of Subjects Treated	Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
					D1, D8 q3wk, i.v.				
PK/Safety	**PM1183-A-005-11** **CSR synopsis**	**5.3.3.2**	Determine RD and PK	Open-label, dose-finding, uncontrolled	lurbinectedin: 3.0 to 5.0 mg FD D1, D8 q3wk, i.v. RD: 5 mg FD D1, D8 q3wk, i.v.	21	Advanced solid tumours other than colorectal cancer	Until disease progression, unacceptable toxicity, or withdrawal of consent	Complete; **CSR synopsis**
PK/ Safety	**PM1183-A-006-12** **CSR synopsis**	**5.3.3.2**	Determine RD and PK combination with capecitabine	Open-label, dose-finding, uncontrolled	lurbinectedin: 2.0 to 3.0 mg FD D1, D8 q3wk, i.v. + capecitabine 1650 mg/m^2/day b.i.d, D1 to D14 q3wk, p.o. RD: lurbinectedin 2.0 mg FD D1, D8 q3wk, i.v. + capecitabine 1650 mg/m^2/day b.i.d, D1 to D14 q3wk, p.o.	15	Advanced solid tumours	Until disease progression, unacceptable toxicity, or withdrawal of consent	Complete; **CSR synopsis**
					lurbinectedin: 3.0 to 5.0 mg FD or 2.2 to 2.8 mg/m^2 D1 q3wk, i.v. + capecitabine 1650 or 2000 mg/m^2/day b.i.d from D1 to D14 q3wk, p.o. RD: lurbinectedin 2.2 mg/m^2 D1 q3wk, i.v. + capecitabine 1650 mg/m^2/day b.i.d, D1 to D14 q3wk, p.o.	66			
Mass Balance	**PM1183-A-015-16** **CSR synopsis**	**5.3.3.2**	Mass balance; time course of excretion; metabolites	Open-label, uncontrolled	lurbinectedin: 5.0 mg FD first cycle, radiolabelled (subsequent cycles 3.2 mg/m^2) D1 q3wk, i.v.	6	Advanced solid tumours	Maximum of eight cycles, or until disease progression, unacceptable toxicity, or withdrawal of consent	Complete; **CSR**
5.3.3.3 Intrinsic Factor PK Study Reports									
PK/ Safety	**PM1183-A-013-15** **CSR synopsis**	**5.3.3.3**	Define RD schedule and PK	Open-label, dose-finding, uncontrolled	lurbinectedin: 1.5 to 3.5 mg/m^2 D1 q3wk, i.v. with/without primary G-CSF prophylaxis	26	Advanced solid tumours (Japanese patients)	Until disease progression, unacceptable toxicity, or withdrawal of	Complete; **CSR synopsis**

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test product(s); Dosage Regimen; Route of Administration	Number of Subjects Treated	Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
					RD: 2.5 mg/m^2 D1 q3wk, i.v. without primary G-CSF prophylaxis RD: 3.2 mg/m2 D1 q3wk i.v. with primary G-CSF prophylaxis			consent	
Special population PK	**PM1183-A-017-20** **CSR synopsis**	**5.3.3.3**	Assess the influence of hepatic impairment on lurbinectedin total plasma exposure	Open-label, parallel, phase Ib study	lurbinectedin 1.6 or 3.2 mg/m^2 D1 q3wk, i.v.	32	Advanced solid tumours	Until disease progression, unacceptable toxicity, or withdrawal of consent A maximum of 2 cycles per patient	Completed **CSR**
5.3.3.4 Extrinsic Factor PK Study Reports									
DDI	**PM1183-A-018-20** **CSR synopsis**	**5.3.3.4**	Assess the effect of itraconazole on lurbinectedin total plasma exposure	Open-label, two-way crossover phase Ib study	lurbinectedin 0.8 mg/m^2 i.v. + itraconazole 200 mg p.o. (Cycle 1), followed by lurbinectedin 3.2 mg/m^2 i.v. (Cycle 2) lurbinectedin 3.2 mg/m^2 i.v. (Cycle 1), followed by lurbinectedin 0.8 mg/m^2 i.v. + itraconazole 200 mg p.o. (Cycle 2) lurbinectedin 3.2 mg/m^2 i.v. (optional Cycle 3) cycles of 3 weeks	14	Advanced solid tumours	Until disease progression, unacceptable toxicity, or withdrawal of consent A maximum of 3 cycles per patient	Complete **CRS**
DDI	**PM1183-A-019-20** **CSR synopsis**	**5.3.3.4**	Assess the effect of bosentan on lurbinectedin total plasma exposure	Open-label, two-way crossover phase Ib study	lurbinectedin 3.2 mg/m^2 i.v. + bosentan 125 mg p.o. (Cycle 1), followed by lurbinectedin 3.2 mg/m^2 i.v. (Cycle 2) lurbinectedin 3.2 mg/m^2 i.v. (Cycle 1), followed by lurbinectedin 3.2 mg/m^2 i.v. + bosentan 125 mg p.o. (Cycle 2) lurbinectedin 3.2 mg/m^2 i.v. (optional Cycle 3) cycles of 3 weeks	11	Advanced solid tumours	Until disease progression, unacceptable toxicity, or withdrawal of consent A maximum of 3 cycles per patient	Complete **CSR**
5.3.4.2 Patient PD and PK/PD Study Reports									
PK/PD	**PM1183-B-005-14-QT** **CSR synopsis**	**5.3.4.2**	QTc interval assessment	QT evaluation by ECG measurements in patients from study PM1183-B-005-14 with normal cardiac conduction and function,	lurbinectedin: 3.2 mg/m^2 D1 q3wk, i.v.	39	Advanced solid tumours	Maximum of two cycles	Complete; **CSR**

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test product(s); Dosage Regimen; Route of Administration	Number of Subjects Treated	Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
				blood pressure, serum electrolyte levels					
5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication									
Efficacy	**GO43104 (IMforte)** **(PIVOTAL)** **CSR synopsis**	**5.3.5.2**	To evaluate the efficacy of lurbinectedin in combination with atezolizumab compared with atezolizumab	Open-label, randomised, parallel group	Arm A: Atezolizumab 1200 mg i.v. + lurbinectedin 3.2 mg/m2 i.v. on Day 1 of each 21-day cycle. Arm B: Atezolizumab 1200 mg i.v. on Day 1 of each 21-day cycle	660	Extensive-Stage Small-Cell Lung Cancer (ES-SCLC) after first-line induction therapy with carboplatin, etoposide, and atezolizumab	Until disease progression, unacceptable toxicity, or withdrawal of consent	Complete; **CSR**
5.3.5.2 Study Reports of Uncontrolled Clinical Studies									
Efficacy	**PM1183-B-005-14** **CSR synopsis (SCLC)SCLC)** **CSR synopsis (Addendum CSR – SCLC – End of study analysis)** **CSR synopsis (Pooled safety analysis)**	**5.3.5.2**	Determine ORR	Open-label, uncontrolled	lurbinectedin: 3.2 mg/m^2 D1 q3wk, i.v.	335 (SCLC 105)	Advanced solid tumours, including SCLC that progressed following one prior chemotherapy-containing regimen	Until disease progression, unacceptable toxicity, or withdrawal of consent	Complete; **CSR – SCLC** **Addendum CSR – SCLC – End of study analysis** **CSR –Pooled safety analysis**

AAL, advanced acute leukaemia; CAV, cyclophosphamide, doxorubicin and vincristine; CrCL, creatinine clearance; CSR, clinical study report; DDI, drug-drug interaction; DLTs, dose-limiting toxicities; ECG, electrocardiogram; FD, flat dose; G-CSF, granulocyte colony-stimulating factor; i.v., intravenous; GCTs, germ cell tumours; MDS, myelodysplastic syndrome; min, Minutes: MTD, maximum tolerated dose; NETs, neuroendocrine tumours; ORR, overall response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; p.o., oral(ly); q3wk, every three weeks; q4wk, every four weeks; QTc, QT interval corrected; RD, recommended dose; SCLC, small cell lung cancer.

5.2. Clinical pharmacology

5.2.1. Methods

Three plasma and two urine bioanalytical methods for lurbinectedin were used in the clinical studies of lurbinectedin.

Table 6 Overview of lurbinectedin bioanalytical studies, by method and lab facility

		CTI Laboratory Service S.L. (Derio, Spain)	Kymos Pharma Services S.L. (Barcelona, Spain)	Anapharm Europe S.L. (Barcelona, Spain)	NKI (Amsterdam, The Netherlands)	Clinical stdudies where used
Method A		**PhM-0001** Validation in plasma & urine (not fully validated)				A-001 (FIH) **PhM-0002**
Method B	**Plasma**	**PhM-0011** Validation in plasma	**S14/412-PM** Partial validation	**14ANE-2412V** Partial validation		IMforte: **JAZ-0003**
		PhM-0047 Extended LTS at -20				B-005: **s16-055-PM** – KPS
		PhM-0064 Extended LTS at -20ºC, -60ºC &-80ºC				C-004: **15ANE-2577 –** AnE
		PhM-0054 Cross-validation (analysis of QCs and selection of a set of clinical samples from PhM-0036)	**S15/073-PM** Cross-validation (analysis of QCs and clinical samples provided by CTI) (failed)	**14ANE-2424V** Cross-validation (analysis of QCs and clinical samples provided by CTI)		A-017, A-018 & A-019: **PhM-0096**
		PhM-0061 Cross-validation (selection of a second set of clinical samples from PhM-0036 to be sent to Kymos)	**S15/444-PM** Cross-validation (analysis of 2nd set of clinical samples sent from CTI)			
		PhM-0055 Cross-validation (comparison of results from QCs and clinical samples, across laboratories).				
		Jazz-0003 Validation to evaluate the selectivity/specificity and matrix effect of atezolizumab on the determination of lurbinectedin				
	Plasma:PBS	**PhM-0091** Validation for unbound plasma concentration				A-017, A-018 & A-019: **PhM-0097**
		PhM-0092 (SN248) Revalidated or Extended LTS at -80 (91 days)?				
	Metabolites	**PhM-0095 (SN248)** Validation metabolites M1 &M4				A-017, A-018 & A-019: **PhM-0098**
		PhM-0101 (SN248) Extended LTS at -80 (M1: 197 and M4: 237 days)				
Method C					**PRO-077** Validation in plasma	A-015 (mass-balance) **PRO-113**
					PRO-078 Validation in urine	
					PRO-079 LTS in plasma & urine	

Study/document codes are in bold. LTS, long-term stability; QCs, quality controls

Lurbinectedin in plasma

A liquid chromatography-tandem mass spectroscopy (UPLC-MS/MS) ("Method A") assay for the measurement of lurbinectedin in human plasma and urine was employed for the first-in-human (FiH) phase I study with lurbinectedin (A-001). Even though Method A performance data met the established criteria, and 28/32 analytical batches were valid, the incurred sample reanalysis did not meet the predefined acceptance criteria, as 60% of the reanalysed samples exhibited deviations exceeding the ±20% allowable range, which was caused by an unexpected interaction between lurbinectedin and the solvent used in working solutions preparation (methanol). Additionally, the long-term stability showed lurbinectedin was stable only for 13 days at -15ºC, and for 16 days at -70ºC for plasma, and for 17 days at -15ºC for urine. Moreover, plasma samples were not stable at room temperature for 24h while urine sample were stable. Other method characteristics, such as extraction recovery and matrix effect, including the impact of haemolytic and lipemic samples, were not evaluated.

Consequently, a new UPLC-MS/MS plasma assay ("Method B") was developed by modifying several procedures, and validated, and implemented in subsequent studies. The stability of the lurbinectedin working solution (5 and 2500 ng/mL) in acetonitrile:water (1:1, v:v) for at least 7 days at -20°C ± 5°C was not demonstrated therefore, they were prepared on the day of use and not stored. Carry-over was found in the first blank following the ULOQ samples; as a result, samples with expected low values that follow high value samples were separated from the high value samples with a blank sample. The method B at CTI Laboratory Services S.L. for lurbinectedin plasma concentration was used in the pivotal IMforte clinical study, in the A-018 and A-019 drug-drug interaction clinical studies, and in the patients with hepatic impairment study. For IMforte, a validation was performed to evaluate the selectivity/specificity and matrix effect of lurbinectedin determination in human plasma in the presence of atezolizumab. No interference was found to be caused by atezolizumab on the selectivity/specificity, and no matrix effect was observed.

Method B was transferred and partially validated at two independent lab facilities: Kymos Pharma Services S.L. (KPS) (Barcelona, Spain) and Anapharm Europe S.L.U. (AnE) (Barcelona, Spain). Then, the methods were evaluated for cross-validation with CTI as reference laboratory and KPS and AnE as Comparator Laboratories. The KPS method was later employed for the pivotal phase II Basket study (B-005), and the AnE method was employed for the phase III CORAIL study (C-004) (supportive at the Application for safety at the proposed dose of 3.2 mg/m^2).

Method B was revalidated in K_3EDTA:PBS matrix for the determination of unbound lurbinectedin plasma concentration by rapid equilibrium dialysis (RED). Selectivity and matrix effect were not re-evaluated in the new matrix since the addition of PBS will dilute any effect. The method for unbound lurbinectedin plasma concentration was used in the A-018 and A-019 drug-drug interaction clinical studies and in the study in patients with hepatic impairment.

An additional LC-MS/MS method ("Method C") was developed and validated for the measurement of lurbinectedin in plasma and urine in the human mass balance study (PM1183-A-015-16). Plasma, urine, and faeces total [^{14}C]-radioactivity was measured by liquid scintillation counting (LSC). Metabolite profiling for plasma, urine, and homogenised faeces was performed on pooled samples.

Lurbinectedin in urine

Methods A and C were also used for determination of lurbinectedin in urine. The described limitations of Method A in plasma also apply to Method A in urine.

Main lurbinectedin metabolites in plasma

UPLC-MS/MS methods for the quantification of metabolites 1',3'-dihydroxy-lurbinectedin (or metabolite 1, M1), and N-desmethyl-lurbinectedin (or metabolite 4, M4) were developed and validated to be used

in the dedicated drug-drug interaction studies with CY3A4 strong inhibitor itraconazole and moderate inducer bosentan (PM1183-A-018-20 and PM1183-A-019-20), and the hepatic impairment study (PM1183-A-017-20).

Method validation reports for the quantification of itraconazole and bosentan in human plasma were used to confirm patient's compliance in dedicated drug-drug interaction studies of lurbinectedin with these compounds and itraconazole concentrations were used to optimise the PBPK model.

Atezolizumab

An Enzyme Linked ImmunoSorbent Assay (ELISA) was developed and validated to quantify atezolizumab (anti-PD-LI) in human serum and an antibody bridging ELISA to detect antibodies to atezolizumab in human serum (atezolizumab anti-drug antibody (ADA) assay).

Details of atezolizumab validated methods can be found in previous atezolizumab submission (EMEA/H/C/004143/0000, EMEA/H/C/004143/II/0007/G, EMEA/H/C/004143/II/0018, EMEA/H/C/004143/II/0019, EMEA/H/C/004143/X/0017, EMEA/H/C/004143/X/0076).

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

Pharmacokinetic studies were conducted to characterise drug disposition, identify subgroups with potentially altered exposure, and evaluate possible drug–drug interactions. The submitted PK documentation is comprehensive and of good quality, with no major deficiencies, although certain other concerns have been identified and are to be addressed by the applicant.

The clinical pharmacology program for lurbinectedin comprised nine clinical studies in patients with advanced solid tumours, including SCLC (Table 7). Additional data were incorporated into integrated pharmacokinetic (PK) and pharmacokinetic/pharmacodynamic (PK/PD) and exposure-response analyses, encompassing five Phase I trials, four Phase II trials, and one Phase III trial. (For further details please refer to the Table 5.

Table 7 Overview of Key Clinical Pharmacology Studies of Lurbinectedin

Study identifier	Study design	Population
PK / Dose Selection		
A-001	Phase I, first-in-human, open-label, dose-finding, uncontrolled	Advanced solid tumours
B-005	Phase II, open-label, uncontrolled	Advanced solid tumours, including SCLC that progressed following one prior chemotherapy-containing regimen
GO43104 (IMforte)	Phase III, randomised, open-label, multicentre	Extensive-Stage Small-Cell Lung Cancer (ES-SCLC) after first-line induction therapy with carboplatin, etoposide, and atezolizumab
ADME		
A-015	Phase I, open-label, mass balance, uncontrolled	Advanced solid tumours
Intrinsic factors		
A-013	Phase I, open-label, dose-finding, uncontrolled	Advanced solid tumours (Japanese patients)

A-017	Phase Ib, open-label, parallel, hepatic impairment	Advanced solid tumours
Extrinsic factors		
A-018	Phase Ib, open-label, two-way crossover, drug-drug interaction (DDI) Strong CYP3A inhibitor	Advanced solid tumours
A-019	Phase Ib, open-label, two-way crossover, DDI: Strong CYP3A inducer	Advanced solid tumours
Secondary PD		
B-005-QTd	Phase II, open-label, uncontrolled QT evaluation	Advanced solid tumours

An *in vitro* package characterising lurbinectedin metabolism, transporter interactions, protein binding, blood-to-plasma partitioning, and its potential to inhibit or induce enzymes or transporters has also been provided. The first-in-human study evaluated the pharmacokinetics (PK) of lurbinectedin across a dose range of 0.02 to 5.0 mg/m². The proposed dose is 3.2 mg/m², administered as a 60-minute intravenous infusion every 21 days until disease progression or unacceptable toxicity, when given in combination with atezolizumab. Dose reduction is recommended in cases of adverse reactions or moderate hepatic impairment.

Lurbinectedin should not be administered in patients with severe hepatic or renal impairment. Dose adjustments are also required when co-administration with strong or moderate CYP3A inhibitors cannot be avoided, while co-administration with strong CYP3A inducers should be avoided.

Lurbinectedin has five identified metabolites (M1–M5), all of which are pharmacologically active, although their overall contribution to drug effect has not been assessed. Two of these metabolites (M1 and M4) are considered major. In an ADME study, approximately 83% of the administered dose was excreted in faeces. However, a high proportion of the recovered radioactivity (78.4%) remained uncharacterized.

The clinical pharmacology evaluations of atezolizumab and lurbinectedin were based on PK and exposure-response, obtained from IMforte where atezolizumab was administered as a single agent or in combination with lurbinectedin in participants with ES-SCLC during maintenance treatment (randomized phase). During the randomised phase, atezolizumab was administered at the approved dose and schedule of 1200 mg every 3 weeks (Q3W) by intravenous (IV) infusion over 30 to 60 minutes as monotherapy or in combination with lurbinectedin 3.2 mg/m2 Q3W.

5.2.2.2. Evaluation and qualification of models

5.2.2.2.1. Population pharmacokinetics

Report number: CLPH-19-005, *Population Pharmacokinetics of Lurbinectedin in Pooled Phase I to III Studies as Single Agent in Patients with Cancer*

The objective of the popPK model was to characterize the lurbinectedin distribution and elimination after intravenous administration in patients with cancer. More specifically the objectives were:

- To obtain estimates of population PK parameters for lurbinectedin in patients with cancer and quantify their between-subject variability.

• To provide a quantitative assessment of the potential effect of the intrinsic and extrinsic factors on lurbinectedin PK to evaluate the potential need for dose adjustments in the target population of patients with Small Cell Lung Cancer (SCLC).

• To provide post hoc predictions from the PK model to be used in the associated integrated exposure response analysis of efficacy and safety.

The PopPK analysis of lurbinectedin was performed based on total plasma concentrations from nine phase 1 to 3 clinical studies. Patients received intravenous (IV) lurbinectedin as single agent at doses ranging from 0.02 to 5.0 mg/m² on Day 1, or from 3.0 to 7.0 mg flat dose (FD) on Days 1 & 8, or from 1.0 to 3.0 mg FD on Days 1-3, or at 7.0 mg FD on Day 1 and at 3.2 mg/m² on Day 1 every 3 weeks (q3wk). The dataset included 7896 plasma concentrations from 755 subjects.

Overall, the dataset for this PopPK analysis was based on three phase 1 trials (PM1183-A-001-08, PM1183-A-002-10 and PM1183-A-005-11), five phase 2 trials (PM1183-B-001-10, PM1183-B-002-11, PM1183-B-003-11, PM1183-B-004-13 and PM1183-B-005-14) and one phase 3 trial (PM1183-C-004-14 CORAIL).

An open, 3-compartment disposition model parameterized in terms of total plasma clearance (CL), apparent volumes of distribution of the central, shallow and deep peripheral compartment (V1, V2 and V3, respectively) and two intercompartmental distribution flows (Q2 and Q3) was used to describe the time course of lurbinectedin total plasma concentrations. An exponential-error model, with between-subject variability, was used to quantify the residual unexplained variability of the lurbinectedin total plasma concentrations.

Table 8 Final model parameters and bootstrap

Model description **Model parameter**	**Final model** **Estimate (RSE%)**	**Non-parametric bootstrap (n=400)** **Median (RSE%)**	**CI95%**
V1 (L)	12.8 (3.80)	12.4 (3.99)	11.3 - 13.4
CL (L/h)	10.6 (2.25)	10.5 (2.21)	9.95 - 10.9
V3 (L)	454 (2.26)	447 (3.16)	424 – 480
Q3 (L/h)	16.0 (2.05)	15.9 (2.36)	15.2 - 16.7
V2 (L)	37.5 (2.50)	37.0 (2.24)	35.5 - 38.7
Q2 (L/h)	31.8 (2.38)	31.7 (3.13)	29.9 - 33.9
RV (CV%)			
RV	31.7 (2.52)	30.9 (2.39)	29.4 - 32.5
IIV (CV%)			
V1	34.6 (13.2)	31.7 (31.2)	21.7 - 41.3
CL	49.9 (3.96)	50.0 (9.42)	45.7 - 54.4
V3	39.1 (5.33)	37.2 (31.2)	31.5 - 45.5
Q3	27.2 (6.54)	27.0 (19.1)	24.2 - 30.1
V2	33.4 (7.78)	30.7 (15.7)	25.6 - 35.0
RV	59.2 (3.42)	59.6 (15.7)	55.0 - 63.6

AAGC004	54.2 (13.6)	47.1 (27.7)	35.7 - 60.3
IIV correlation (%)			
Q3 – V3	77.0 (6.42)	75.7 (13.2)	77.5 - 72.4
Covariate parameters			
CLAAG	-0.627 (8.36)	-0.727 (10.3)	-0.858 - -0.568
CLALB	0.746 (19.6)	0.633 (28.2)	0.261 - 0.979
CLINH1	-0.408 (12.2)	-0.407 (14.6)	-0.517 - -0.275
Q3AAG	-0.578 (8.57)	-0.603 (8.18)	-0.697 - -0.504
Q3BSA	0.990 (14.2)	0.964 (15.3)	0.658 - 1.227
Q3SEXF	-0.195 (14.4)	-0.198 (16.3)	-0.254 - -0.130
V1AAG	-0.992 (9.78)	-1.032 (9.83)	-1.233 - -0.839
V2AAG	-0.653 (10.6)	-0.675 (9.99)	-0.803 - -0.541
V2BSA	0.423 (25.6)	0.390 (28.5)	0.188 - 0.630
V3AAG	-0.517 (11.8)	-0.600 (17.7)	-0.758 - -0.319
V3BSA	1.915 (8.70)	1.802 (10.1)	1.474 - 2.174
V3SEXF	-0.244 (13.1)	-0.245 (15.1)	-0.312 - -0.174
V1BSA	0.748 (21.3)	0.744 (23.1)	0.436 - 1.129
AAGC004	260 (7.53)	230 (9.42)	201 - 280

RSE, relative standard error; RV, residual variability; IIV, inter-individual variability; CI95%, confidence interval 95%; CL, clearance; Q2, intercompartmental clearance for shallow compartment; Q3, intercompartmental clearance for deep compartment; V1, apparent volume of distribution of central compartment; V2, apparent volume of distribution of shallow peripheral compartment; V3, apparent volume of distribution of deep peripheral compartment; AAG, alpha-1-acid glycoprotein; ALB, albumin; INH, CYP3A inhibitor; SEXF, gender; CLAAG, relationship between CL and AAG; CLALB, relationship between CL and albumin; CLINH, relationship between CL and CYP3A inhibitors; Q3AAG, relationship between Q3 and AAG; Q3BSA, relationship between Q3 and BSA; Q3SEXF, relationship between Q3 and gender; V1AAG, relationship between V1 and AAG; V1BSA, relationship between V1 and BSA; V2AAG, relationship between V2 and AAG; V2BSA, relationship between V2 and BSA; V3AAG, relationship between V3 and AAG; V3BSA, relationship between V3 and BSA; V3SEXF, relationship between V3 and gender; AAGC004, AAG in study C-004 CORA

Figure 2 Diagnostic plots of the final model

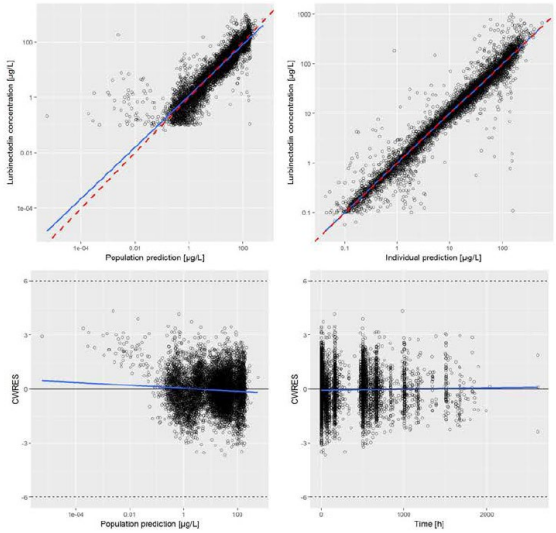
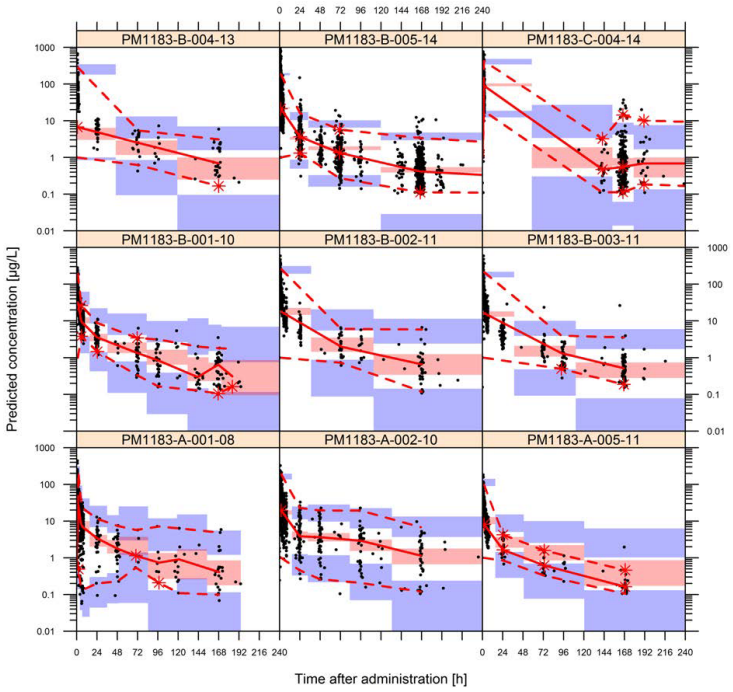


Figure 3 Visual predictive check for the final model



After screening covariates of interest using the stepwise covariate model (scm) approach with forward addition at a significance level of 0.01 and backward elimination at a significance level of 0.001, the covariate effects retained in the final model were Body Surface Area (BSA) on intercompartmental clearance between central and the second peripheral compartment (Q3), volume of distribution of central compartment (V1), volume of distribution for the first peripheral compartment (V2), and volume of distribution for the second peripheral compartment (V3); alpha-1-acid glycoprotein (AAG) on CL, Q3, V1, V2, and V3; Albumin (ALB) on CL; co-medication with a CYP3A inhibitor on CL; and sex on Q3 and V3.

The exploration of covariate effects was performed for PK parameters AUC, AUC_u, CL, CL_u, V1, C_{max} and C_{min} after a single 1h infusion lurbinectedin dose of 3.2 mg/m² or 5.6 mg FD (equivalent to a 3.2 mg/m² for a BSA of 1.75 m²).

A 35.2% decrease in lurbinectedin systemic clearance was associated with a two-fold increase in AAG.

An 87.3% increase in lurbinectedin systemic clearance was associated with a two-fold increase in serum albumin.

A 20% increase in BSA leads to a 39.4% increase in the typical volume of distribution at steady state.

None of the other tested covariates were found clinically significant.

5.2.2.2.2. Physiology based pharmacokinetic model

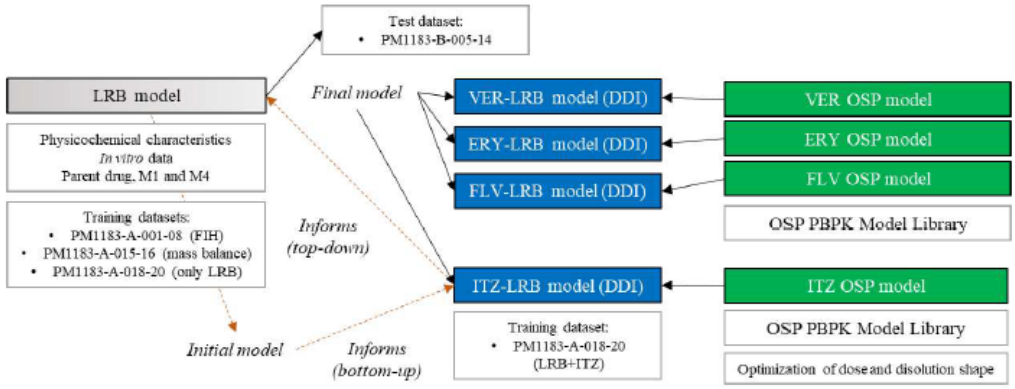
Physiologically-Based Pharmacokinetic Modelling of Lurbinectedin to Simulate the Drug-Drug Interaction with a Moderate CYP3A Inhibitor; Report number: CLPH-23-001

Objectives of the PBPK modelling were to:

- To develop a PBPK model of lurbinectedin using observed drug plasma concentrations from cancer patients.
- To predict the effect of itraconazole on the exposure to lurbinectedin and compare with observed clinical data to validate the PBPK drug-drug interaction (DDI) model.
- To predict the effect of moderate CYP3A4 inhibitors on the exposure to lurbinectedin.

The modelling approach for the lurbinectedin PBPK model development and its applications in DDI predictions is illustrated in Figure 4 below.

Figure 4 Schematic representation of the process for lurbinectedin PBPK model building, verification, and application to DDI evaluation



LRB and PM1183: lurbinectedin; ITZ: itraconazole; VER: verapamil; FLV: fluvoxamine; ERY: erythromycin; OSP: Open Systems Pharmacology; PBPK: physiologically based pharmacokinetic modelling; DDI: drug-drug interaction; FIH: first in humans.

The PK profiles of lurbinectedin following administration of a single IV dose in the FIH dose escalating study (PMl 183-A-001-08) and mass balance study (PMl 183-A-015-16) were used as the dataset for model improvement and refinement. Simulations were performed using the final PBPK model of lurbinectedin to verify the performance of the model by comparing the simulation results to the observed PK profile in SCLC patients from Basket (PMl 183-B-005-14) study and were used as the external data for lurbinectedin PBPK model qualification. In addition, the results of DDI trial with itraconazole (PMl 183-A-018-20) were used to refine the lurbinectedin PBPK model.

The validated model was applied to simulate PK profiles in a virtual population resembling PM1183-A-018-20 patients (n=11) to simulate the DDI with itraconazole; and in an extended population resembling the demographic characteristics of cancer patients (n=200) to explore the DDI of lurbinectedin with all CYP3A4 inhibitors (itraconazole, verapamil, erythromycin, and fluvoxamine).

Lurbinectedin PK profiles were simulated in the oncology population (n=200) after the administration of the RD, 3.2 mg/m² 1h-infusion on the fifth day of perpetrator (verapamil 80 mg q8h PO, erythromycin 500 mg q6h PO or fluvoxamine150 mg q12h PO) administration. Simulations were conducted using the Open Systems Pharmacology Suite (PK-Sim and MoBi) and R software, with all model optimization and performance evaluations carried out through these platforms.

For DDI PBPK models, available models from the Open Systems Pharmacology (OSP) library for itraconazole, verapamil, erythromycin, and fluvoxamine were refined, optimized, and used for the assessment of DDIs.

Results

The lurbinectedin PBPK model showed good performance. In the Phase II study in SCLC (PM1183-B-005-14), the model's predictions matched the observed data well. The model accurately predicted lurbinectedin's time-concentration profiles and its interaction with itraconazole, with most values within a 2-fold limit of observed data, only for study PM1183-A-018-20 when lurbinectedin was given alone, where MRD was 2.25.

Table 9 Lurbinectedin PBPK model performance and validation metrics for training and test datasets

Study	GMFE AUClast	GMFE AUCinf	GMFE CL	GMFE Cmax	GMFE Fe_{urine}	MRD
Training datasets						
PM1183-A-001-08 (FiH study)	1.15	1.00	1.01	0.89	1.07	1.82
PM1183-A-015-16 (Mass Balance)*	1.75	1.74	1.6	1.72	2.19	1.84
PM1183-A-018-20 (LRB alone)	1.91	1.88	1.88	1.55	-	2.25
PM1183-A-018-20 (LRB + ITZ)	1.88	1.73	1.74	1.46	-	1.94
Test Dataset						
PM1183-B-005-14 (Phase 2 in SCLC)#	1.77	1.68	1.7	1.61	-	1.91

FiH: First-in-Human; SCLC: Small Cell Lung Cancer; LRB; lurbinectedin; ITZ: itraconazole; AUClast: area under the concentration-time profile from time of administration to last observed sample; CL: clearance; Cmax: peak or maximum concentration; Feurine: fraction excreted in urine; GMFE: geometric mean fold error; MRD: mean relative deviation. *Reported values excluding one patient (identified as outlier). The corresponding values including the outlier patient are: 2.01, 2.02, 2.03, 1.61, 2.07 and 2.76. !Training datasets for lurbinectedin were used to determine model performance; #Test dataset for lurbinectedin were used for model validation.

The coadministration of lurbinectedin with itraconazole significantly reduced lurbinectedin clearance by 63%; with erythromycin by 53%; with verapamil by 56%, and with fluvoxamine by 25%, with the fold changes in AUC as shown in Table 10 below.

Table 10 Observed or Predicted Increase in Total Lurbinectedin Exposure (AUC) after Coadministration of CYP3A Inhibitors

Type of inhibitor	Co-administered CYP3A Inhibitor	Increase in lurbinectedin AUC
Observed		
Strong CYP3A Inhibitor	Itraconazole (200 mg daily)	2.7-fold
Predicted		
Strong CYP3A Inhibitor	Itraconazole (200 mg daily)	2.7-fold
Moderate CYP3A Inhibitor	Verapamil (80 mg every 8 hours)	2.3-fold
Moderate CYP3A Inhibitor	Erythromycin (500 mg every 6 hours)	2.1-fold
Weak CYP3A Inhibitor	Fluvoxamine (150 mg every 12 hours)	1.3-fold

5.2.2.3. Absorption

Lurbinectedin is administered systemically as an intravenous (IV) infusion.

Study A-001 – Phase I First In Humans Study in Solid Tumours

The doses of lurbinectedin ranged from 0.02 to 5.0 mg/m² (one patient received a 6.9 mg/m² in error in Cycle 1). Plasma samples were taken from 31 patients. A summary of lurbinectedin PK parameters by dose level are given as geometric mean (CV%), in Table 11 below.

Table 11 Summary of geometric mean (CV%) of total plasma pharmacokinetic parameters for lurbinectedin on Day 1 of Cycle 1 (and Cycle 2 at the recommended dose), by dose level (Study A-001).

Dose level mg/m²	Cycle	C_{max} (µg/L)	AUC (h*µg/L)	CL (L/h)	$t_{1/2}$ (h)	V_{ss} (L)	V_z (L)
0.02	1 (n=1)	1.5 (-)	2.7 (-)	15.2 (-)	3.9 (-)	68.9 (-)	86.0 (-)
0.04	1 (n=2)	4.3 (29.3)	7.5 (5.6)	10.6 (9.0)	4.1 (84.3)	46.7 (97.6)	61.9 (90.5)
0.08	1 (n=1)	4.1 (-)	5.6 (-)	26.6 (-)	1.8 (-)	53.8 (-)	69.5 (-)
0.16	1 (n=1)	7.3 (-)	24.5 (-)	11.9 (-)	14.6 (-)	161.9 (-)	250.3 (-)
0.32	1 (n=2)	22.7 (25.1)	113.7 (60.8)	5.7 (78.3)	53.9 (1.2)	292.1 (72.4)	446.4 (77.6)
0.64	1 (n=2)	32.8 (27.1)	117.4 (50.3)	10.7 (57.8)	53.1 (118.9)	527.7 (101.1)	822.1 (93.1)
1.30	1 (n=2)	66.2 (47.7)	285.2 (10.8)	7.9 (1.4)	47.5 (22.7)	356.8 (27.0)	545.0 (24.0)
2.60	1 (n=2)	138.6 (47.1)	448.6 (63.5)	10.8 (65.9)	39.1 (0.0)	314.6 (49.7)	608.2 (65.9)
4.0	1 (n=6)	219.2 (44.3)	698.1 (49.7)	10.9 (47.5)	45.1 (54.0)	377.9 (39.0)	710.2 (33.9)
7.0 mg (FD)	1 (n=9)	139.3 (36.9)	723.1 (99.7)	9.7 (63.7)	56.7 (77.3)	509.3 (39.9)	792.2 (44.2)
	2 (n=6)	144.9 (39.3)	505.9 (36.5)	13.8 (30.7)	50.6 (17.8)	611.5 (30.3)	1011.1 (31.8)
5.6 mg (FD)*	2 (n=1)	103.0 (-)	1057.0 (-)	5.3 (-)	123.4 (-)	799.7 (-)	943.3 (-)
5.0	1 (n=2)	257.2 (51.2)	1021.1 (59.9)	8.6 (52.8)	36.8 (30.8)	312.4 (16.4)	458.2 (24.0)

Dose level mg/m²	Cycle	C_{max} (µg/L)	AUC (h*µg/L)	CL (L/h)	$t_{1/2}$ (h)	V_{ss} (L)	V_z (L)
6.9	1 (n=1)	215.0 (-)	559.7 (-)	19.3 (-)	36.4 (-)	688.5 (-)	1013.0 (-)

*One patient treated at 7.0 mg FD in Cycle 1 who underwent a 20% dose reduction in Cycle 2.

AUC, area under the plasma concentration-time curve from time zero to infinity; CL, total body clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation (%); FD, flat dose; $t_{1/2}$, terminal half-life; V_{ss}, volume of distribution at steady-state; V_z, volume of distribution calculated from terminal phase.

(Geometric means have been recalculated).

Observed Pharmacokinetic Comparison Across Studies

After the first treatment dose of lurbinectedin 3.2 mg/m² IV in combination with 1200 mg IV of atezolizumab on Cycle 1, Day 1, the arithmetic mean (SD) Cmax of lurbinectedin was 115 (109) µg/L (n = 208). The mean (SD) Cmax of lurbinectedin when used as monotherapy on Cycle 1, Day 1 in study PM1183-B-005-14 was 128(100) µg/L (n = 329) across all tumour types and 111 (89.1) µg/L (n = 101) for small cell lung cancer.

Table 12 Summary Statistics (Mean [SD]) of 3.2 mg/m2 Q3W IV Lurbinectedin on Cycle 1 Day 1 (PK Evaluable Lurbinectedin Population

Pharmacokinetic Parameter	3.2 mg/m² Q3W IV in IMforte Arm A	3.2 mg/m² Q3W IV in PM1183-B-005-14
C_{max} (µg/L)	115 (109)	128 (100)
T_{max} (h)	0.95 (0.58 – 1.75)	0.92 (0.8 - 4)

C_{max} = maximum observed concentration; T_{max} = time to maximum observed concentration

IV = intravenous; Q3W = every 3 weeks.

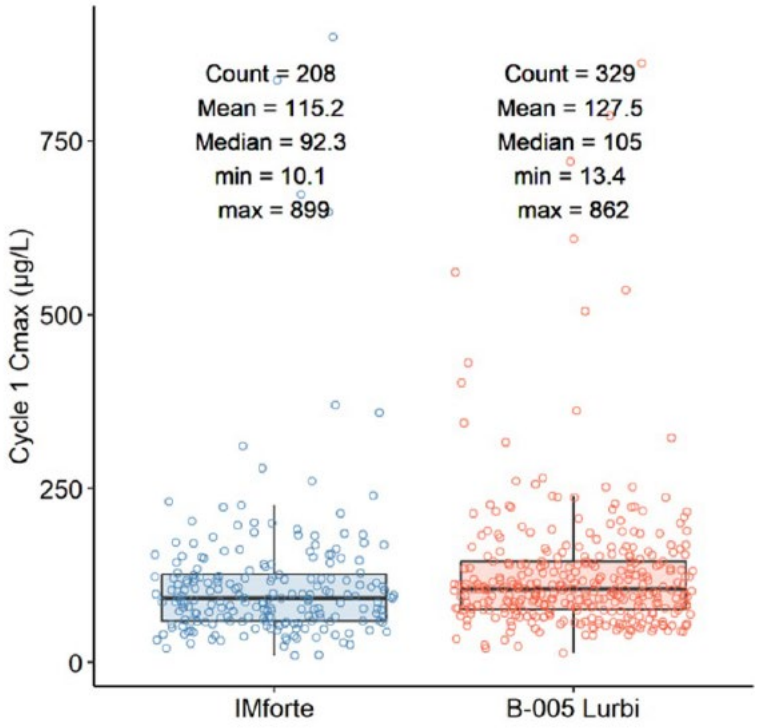
Note: Median (range) is reported for T_{max}.

Table 13 Summary of geometric mean (CV%) of total plasma pharmacokinetic parameters for lurbinectedin on Day 1 of Cycle 1 and Cycle 2 (Study B-005)

Dose level mg/m²	Cycle	C_{max} (µg/L)	AUC (h*µg/L)	CL (L/h)	$t_{1/2}$ (h)	V_{ss} (L)	V_z (L)
3.2	1 (n=329)	106.6 (78.6)	551.4 (94.3)	10.3 (61.3)	36.0 (63.0)	354.7 (75.4)	535.4 (69.3)
	2 (n=270)	100.6 (89.1)	653.6 (101.9)	8.4 (116.6)	17.0 (53.1)	189.7 (57.8)	207.2 (156.3)

AUC, area under the plasma concentration-time curve from time zero to infinity; CL, total body clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation (%); $t_{1/2}$, terminal half-life; V_{ss}, volume of distribution at steady-state; V_z, volume of distribution calculated from terminal phase.

Figure 5 Observed Cycle 1 C_{max} After 3.2 mg/m² Q3W IV Lurbinectedin Administration in the IMforte Study and PM1183-B-005-14 Study



C_{max} = maximum observed concentration; IV = intravenous; Q3W = every 3 weeks

5.2.2.4. Bioequivalence

Lurbinectedin is administered systemically as an IV infusion. The clinical pharmacology program did not include studies for the assessment of bioequivalence or food effect.

5.2.2.5. Distribution

In First In Humans Study in Solid Tumours (A-001) lurbinectedin was found to be widely distributed. The volume of distribution at steady state (Vss) at the maximum tolerated dose (MTD) of 4.0 mg/m2 was 509 L (CV 39.9%).

Population PK analysis estimated a volume of distribution (V1 + V2 + V3) of 504 L (7.2 L/kg for an average body weight of 70 kg) for lurbinectedin. This high volume of distribution is consistent with the lipophilic nature of lurbinectedin and data obtained from nonclinical tissue distribution studies.

The percent of lurbinectedin bound to human plasma proteins is very high (>99%) and independent of drug concentration. Lurbinectedin binds to both human serum albumin and α-1-acid glycoprotein (AAG), with higher affinity to AAG. In vitro binding to AAG is linear and non-saturable at clinically relevant concentrations.

Based on *in vitro* transporter and *in vivo* distribution studies, lurbinectedin is not expected to cross the blood brain barrier and penetrate into the central nervous system in a clinically relevant manner.

The in vitro blood-to-plasma ratios was 0.65 (human), similar to value obtained in the pharmacokinetic and toxicokinetic analysis in nonclinical species (e.g., rat and NHP) and in patients.

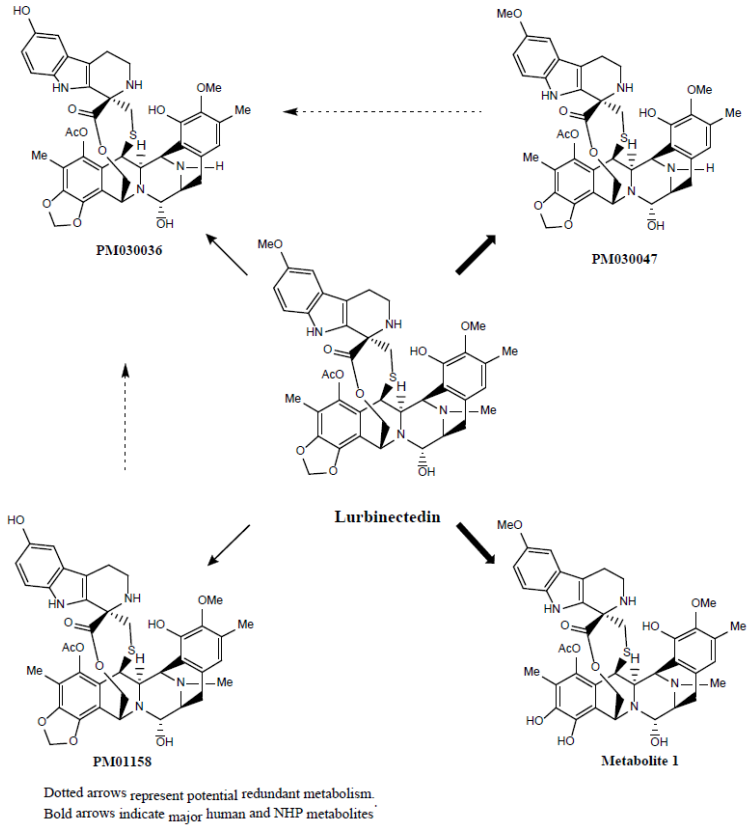
In the mass balance study, the mean blood-to-plasma ratio of parent-related [$^{14}C_1$]-radioactivity was 0.70 and 0.68 for Cmax and AUC0-last, respectively. These values are consistent with those observed in vitro discarding a relevant distribution into red blood cells.

5.2.2.6. Metabolism

- **In vitro** (Studies PMAR14-NC032, Study PMAR18-NC012, PMAR15-NC015 and RPT03283)

Experiments performed with human microsomes (both genders) and selective chemical inhibitors and inhibitory monoclonal antibodies directed against CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 pointed to CYP3A4 as the main CYP isoform involved in the phase I metabolism of lurbinectedin. The involvement of other CYPs in the microsome-mediated metabolism of lurbinectedin was demonstrated to be negligible. The phase II contribution to lurbinectedin metabolism is considered to be negligible.

Figure 6 Proposed metabolite pathway of lurbinectedin following incubation in NADPH-activated HLM



- **In vivo** (Study A-015 - Human Mass Balance)

In plasma, among the five known lurbinectedin metabolites (M1 to M5), which are active, all were detected but only four (M1, M4 [(PM030047], M3 [PM01158], and M2 [PM030036]) were quantified in plasma. The presence in plasma of M5 (PM030779), at low levels, was demonstrated.

Up to 10-hour after the end of infusion, 88.7% of the total [^{14}C]-radioactivity in plasma can be attributed to lurbinectedin (70.2%) plus these four metabolites (18.5%). Based on these results, M1 and M4 (PM030047) were the major metabolites accounting for 10% and 7.3% of circulating radioactivity, respectively, thus representing 14.3% and 10.4% of the parent compound in plasma.

Other minor circulating metabolites were PM030036 and PM01158 (each represents, ca. 0.6% of total radioactivity; 0.8% of unchanged lurbinectedin).

In faeces, metabolic profiling was hampered by a very high inter-patient variability in faecal excretion profile and a very low recovery of radioactivity (ca. 30%). Nevertheless, a higher number of known and newly identified metabolites were detected. M1 was the most abundant metabolite (1.1% of dose) and only trace amounts (<0.2% of dose) of lurbinectedin were detected in faeces. Excretion in urine was the minor route (5.6% of dose), mainly as parent drug (1.1% of dose) and M4 (PM030047) (1.2% of dose).

Metabolic profiling and identification of known and new metabolites suggest that the proposed metabolic pathway for lurbinectedin in humans is mainly through (N and / or O)-demethylation and aliphatic ring-opening, although hydroxylation, carbinolamine oxidation and loss of water are also involved but in lesser extent.

Plasma metabolic profiling demonstrated the major (% compared to unchanged compound) systemic metabolites were N-desmethyl-lurbinectedin (PM030047; up to 10% in patients) and 1',3'-dihydroxy-lurbinectedin (Metabolite 1; up to 14% in patients).

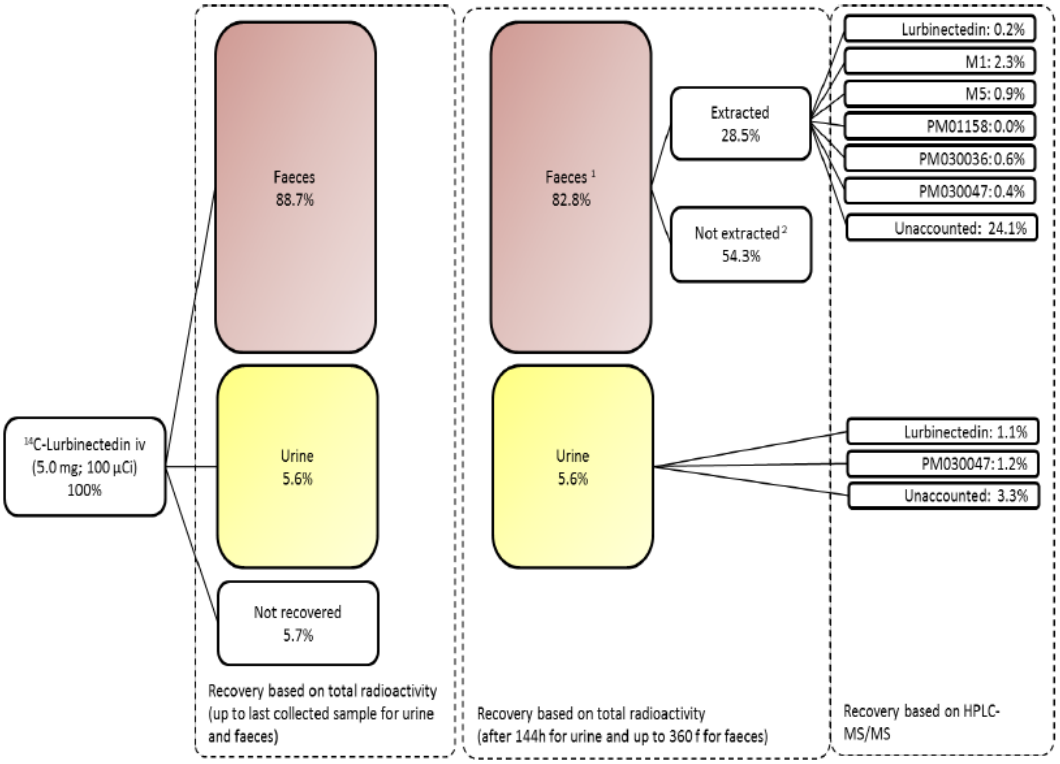
5.2.2.7. Elimination

The excretion of lurbinectedin was investigated in the Human Mass Balance Study (A-015) using urine and faeces collected from patients with advanced solid cancers administered a single-dose of $^{14}C_1$-labelled lurbinectedin as a 1-hour infusion. On average (±SD), 94.3±8.7% of the administered dose was recovered in excreta (88.7±10.1% in faeces and 5.6±2.0% in urine) up to the last collected sample for each matrix (500-hour and 144-hour for faeces and urine, respectively). The excretion of unchanged lurbinectedin in urine was low (1.1% of dose), while only trace amounts (<0.2% of dose) were detected in faeces.

Geometric means of CL and $t_{1/2}$ for lurbinectedin were 10.3 L and 36.0 hours at Cycle 1, respectively, in Study B-005. The Reference popPK estimates for CL (10.6 hours) and t1/2 (51.0 hours) are generally consistent with these NCA results.

As expected from the 21-day interval between cycles and the $t_{1/2}$ of lurbinectedin (42 hours in study B-005), no accumulation in plasma lurbinectedin concentrations was observed after repeated doses.

Figure 7 Average recovery of [^{14}C]-radioactivity in faeces and urine up to the last collected sample for each matrix (Study A-015)



1 The last collected fraction was not added to the pools in order to prevent undesired dilution of the test samples (since activity in these fractions was very low, while volume was high). 2 Not all radioactivity could be extracted from the faeces, despite all efforts made to optimise sample processing. Extraction recovery from faeces was comparable with that at the nonclinical phase.

Urine

The contribution of parent drug to radioactivity in urine was small; based on cumulative excretion up to 144-hour after drug administration, lurbinectedin in urine could only explain 1.1% of the dose. Except for one (M4), no known metabolites were above the limit of quantification. M4 (PM030047) excreted in urine accounted on average for 1.2% of the administered dose.

Faeces

On average, 28.5% of the total dosed radioactivity was extracted from the matrix. In this portion, lurbinectedin, M1, M5 (PM030779), M2 (PM030036) and M4 (PM030047) were (semi-)quantified and accounted for 4.4% of the administered dose, meaning that 24.1% remained unaccounted. The large amount of radioactive fractions in the radiochromatograms implies that an equal large amount of (low abundant) metabolites or degradation products is present in the faeces. Additional experiments suggest the presence of 14 other metabolites.

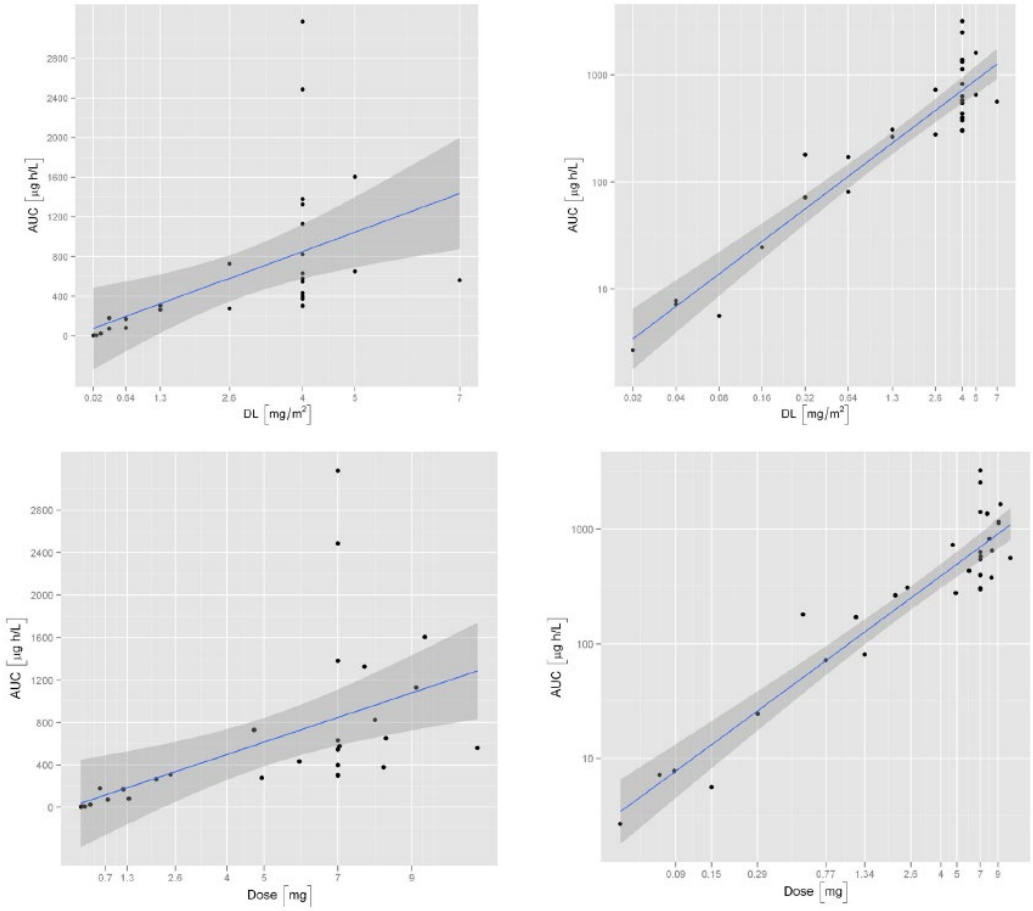
The maximum achievable recovery was ~30%. Initial attempts to (semi)-quantify metabolites in faeces samples using the LC-orbitrap MS/MS with offline LSC method revealed low levels of metabolites.

5.2.2.8. Dose proportionality and time dependency

Dose proportionality for lurbinectedin was evaluated using data from a wide range of doses tested (0.02 to 6.9 mg/m²) at the first-in-man study A-001 in patients with solid tumours (n=31), based on PK parameters derived from NCA; AUC_{inf} (µg·h/L) and C_{max} (µg/L).

A linear regression model was fit to the log-transformed data, with dose (mg/m²) or total dose (mg) as the independent variable.

Figure 8 Correlation between plasma AUC_{0-inf} values and dose level (mg/m²) (upper panels) and total dose (mg) (lower panels), in linear scale (left panels) and logarithmic scale (right panels) (Study A-001)



AUC, area under the concentration-time curve from time zero to infinity; DL, dose level.

Based on the point estimate values and the 95% CI, AUC and C_{max} were deemed dose-proportional.

Results from the Reference popPK analysis that includes nine studies as single agent across a dose range of 0.02 to 6.9 mg/m², supports the dose proportionality.

5.2.2.9. Pharmacokinetics in the target population

Total plasma PK of lurbinectedin was assessed in selected advanced solid tumours, including SCLC.

Study B-005 – Phase II Study in Selected Indications Including SCLC

Three hundred and thirty-one (331) patients were sampled for PK in Cycle 1 and 287 in Cycle 2, among which, 329 (Cycle 1) and 270 (Cycle 2) were suitable for NCA.

Summary PK parameters in Cycle 1 comprised a geometric mean total plasma CL of 10.3 L/h, $t_{1/2}$ of 36.0 h and Vss of 354.7 L, thus being consistent with those obtained in previous studies. Inter-individual variability (CV%) were 61.3% and 75.4%, for CL and V_{ss}, respectively, see Table 13.

SCLC Cohort

Among the 329 patients with NCA results, 101 were patients with SCLC, for which marketing approval is being requested. PK of lurbinectedin in this patient cohort was in line with previous results, thus characterised by a moderate total plasma CL (11.7 L/h), a wide distribution (V_{ss}=390.3 L), and prolonged $t_{1/2}$ (36.3 h). For these parameters, inter-individual variability was moderate to high (CV up to 56.6%).

Table 14 Summary of geometric mean (CV%) of plasma pharmacokinetic parameters for lurbinectedin on Day 1 of Cycle 1 and Cycle 2, in the SCLC cohort (Study B-005).

Dose level mg/m²	Cycle	C_{max} (µg/L)	AUC (h*µg/L)	CL (L/h)	$t_{1/2}$ (h)	V_{ss} (L)	V_z (L)
3.2	1 (n=101)	96.0 (80.0)	488.1 (57.7)	11.7 (50.3)	36.3 (49.0)	390.3 (56.6)	612.9 (67.3)
	2 (n=87)	94.0 (106.0)	674.9 (66.8)	8.2 (125.4)	19.5 (44.0)	213.7 (47.1)	229.6 (44.7)

AUC, area under the plasma concentration-time curve from time zero to infinity; CL, total body clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation (%); $t_{1/2}$, terminal half-life; V_{ss}, volume of distribution at steady-state; V_z, volume of distribution calculated from terminal phase.

Intra- and inter-individual variability

The variability in the PK of lurbinectedin was moderate. The variability for typical CL was 50%, while for all volumes (V1, V2 and V3) was 35%, 33% and 39%, respectively (PopPK model, CLPH-19-005). A moderate to large variability was associated with the NCA-derived CL and Vss of 61.3% and 78.6% (Study B-005)), where variability associated to covariates is not accounted for.
In study B-005, PK of lurbinectedin in Cycle 1 (8 samples) and in Cycle 2 (6 samples) were explored in 333 patients with selected advanced solid tumours, including SCLC, resulting in 210 patients with available PK data in both cycles whose T_{last} values were of at least 24 hours. Intra-patient variability of PK parameters was calculated in patients who had PK assessments in both cycles whose t_{last} values were at least 24 hours (n=210); it was moderate for CL (33%), and large for V_{ss} (59%).

5.2.2.10. Special populations

The applicant conducted two dedicated studies to investigate the influence of intrinsic factors on the PK of lurbinectedin; a clinical study in subjects with hepatic impairment and a study in Japanese patients. The influence of other intrinsic factors, like renal impairment and demographic parameters, has been explored using physiologically based PK models and population PK models.

Impaired renal function

The low mean recovery (6% of administered dose) of total radioactivity in the urine after a single dose of ^{14}C1-labelled lurbinectedin in A-015 study suggests that renal impairment would have little influence on the elimination of lurbinectedin. Thus, a clinical study in patients with cancer to evaluate the effect of renal impairment on lurbinectedin exposure was not conducted. The impact of renal dysfunction on the exposure of lurbinectedin was evaluated in the Reference popPK analysis.

Among the 755 patients, 166 had normal renal function (CrCL >90 mL/min], 165 had mild renal impairment (CrCL 60-89 mL/min), 73 had moderate renal impairment (CrCL of 30-59 mL/min), one (1) had severe renal impairment (CrCL of 26 mL/min) and 350 had a missing value of CrCL.

Mild or moderate renal impairment had no effect on total or unbound CL of lurbinectedin as compared to patients with normal renal function (Table 15).

Table 15 Total and unbound clearance in patients according to renal function (popPK analysis).

Renal function	CrCL (mL/min)	Total plasma CL median [range] (L/h)	Unbound plasma CL median [range] (kL/h)
Normal (n=166)	≥90	9.3 [0.7 - 28.8]	4.7 [0.9 - 12.1]
Mild (n=165)	60 - 90	8.5 [1.0 - 36.3]	4.7 [1.0 - 14.5]
Moderate (n=73)	30 - <60	7.7 [1.0 - 24.6]	4.3 [0.8 - 10.0]
Severe (n=1)	<30	7.9	3.3

CL, clearance; CrCL, creatinine clearance; popPK, population pharmacokinetics.

The PK of lurbinectedin has not been evaluated in a sufficient number of patients with severe renal impairment (CrCL<30 mL/min) (only one patient) and no patient with end stage renal disease or patients on dialysis have been treated with lurbinectedin.

Impaired hepatic function

- In vivo

A-017 – Hepatic Impairment Study

A prospective, open-label, parallel, phase 1b study was conducted in patients with advanced solid tumours who either had hepatic impairment at varying degrees (mild, moderate, or severe) or qualify for the normal hepatic function group according to the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) classification criteria of hepatic impairment: mild (total bilirubin ≤ ULN and AST > ULN, or total bilirubin > 1 to ≤ 1.5 × ULN and AST = any), moderate (total bilirubin > 1.5 to ≤ 3 × ULN and AST = any), or severe (total bilirubin > 3 × ULN).

In total, 33 patients were included. Lurbinectedin was administered as a 1-hour IV q3wk via a central or peripheral vein. Patients with normal hepatic function and those with mild hepatic impairment received lurbinectedin at a dose of 3.2 mg/m², while patients with moderate or severe hepatic impairment were dosed at 1.6 mg/m².

Total plasma CL in patients with normal hepatic function was unexpectedly low compared with historical data; therefore, the mild hepatic impairment cohort was used as reference for statistical comparison with moderate and severe hepatic impairment cohorts, in addition to the normal hepatic function cohort as reference for the statistical comparisons.

Total plasma lurbinectedin exposure

An approximately 16% increase in dose-normalized AUC_{0-t} was observed in patients with severe hepatic impairment compared to those with mild hepatic impairment. When using the normal hepatic function cohort as reference, the increase in systemic exposure in the severe hepatic impairment cohort was lower (10%).

Table 16 Statistical comparison of total plasma lurbinectedin PK parameters between mild hepatic impairment cohort (reference) and moderate and severe hepatic impairment cohorts (evaluable population)

PK Parameter (Units)	Moderate/Mild Ratio; % (90% CI)	Severe/Mild Ratio; % (90% CI)
C_{max}/D (µg/L*mg)	71.08 (46.55 - 108.53)	85.76 (54.18 - 135.73)
AUC_{0-t}/D (µg*h/L/mg)	75.91 (45.71 - 126.04)	115.63 (66.71 - 200.43)
$AUC_{0-\infty}$/D (µg*h/L/mg)	77.31 (46.67 - 128.07)	115.67 (66.91 - 199.97)

AUC_{48}/D (µg*h/L/mg)	75.89 (50.33 - 114.42)	98.78 (61.66 - 158.26)
$t_{1/2}$ (h)	79.79 (48.10 - 132.36)	132.6 (76.58 - 229.59)
Cl (L/h)	129.34 (71.20 - 234.94)	63.32 (33.14 - 120.98)
V_{ss} (L)	121.7 (76.16 - 194.47)	91.8 (55.21 - 152.64)

Ratio = least-squares geometric mean ratio.
Note: ANOVA mixed-effects model included hepatic function cohort (mild vs. moderate or severe) as fixed effect, and patient as a random effect.
The extrapolation in $AUC_{0-\infty}$ for 2 patients (severe hepatic impairment according to the NCI-ODWG criteria) were > 20% extrapolation. AUC_{0-t} instead of AUC0-∞ was used for the analysis.
Abbreviations: ANOVA, analysis of variance; AUC, area under the concentration-time curve; CI, confidence interval; CL, clearance; C_{max}, maximum plasma concentration; PK, pharmacokinetic; $t_{1/2}$, terminal half-life; V_{ss}, volume of distribution at steady state.

Additionally, patients were graded according to the Child-Pugh score classification of hepatic impairment for exploratory purposes. An approximately 18% higher systemic exposure (dose-normalized AUC0-∞) and a 40% lower CL were observed in the Moderate HI Cohort compared to the Mild HI Cohort, and a 4% higher systemic exposure and 22% lower CL in Moderate HI compared to Normal HF Cohort.

Unbound plasma lurbinectedin exposure

Results from statistical analysis show no differences in the PK parameters among cohorts, except for the CL, which was 28% lower in patients with severe hepatic impairment compared to those with mild hepatic impairment (Table 17). This tendency was not observed when using the normal hepatic function cohort as the reference.

Table 17 Statistical comparison of unbound plasma lurbinectedin PK parameters between mild hepatic impairment cohort (reference) and moderate and severe hepatic impairment cohorts (evaluable population)

PK Parameter (Units)	Moderate/Mild Ratio (90% CI)	Severe/Mild Ratio (90% CI)
C_{max}/D (pg/mL*mg)	86.48 (59.73 - 125.23)	73.12 (49.74 - 107.49)
AUC_{0-t}/D (pg*h/mL/mg)	91.5 (53.48 - 156.55)	100.21 (57.3 - 175.26)
$AUC_{0-\infty}$/D (pg*h/mL/mg)	94.63 (55.72 - 160.71)	101.53 (58.5 - 176.2)
$t_{1/2}$ (h)	76.25 (38.93 - 149.32)	113.24 (56.26 - 227.93)
Cl (L/h)	105.67 (53.27 - 209.62)	72.14 (35.36 - 147.17)
V_{ss} (L)	91.11 (51.97 - 159.72)	95.45 (53.22 - 171.22)

Ratio = least-squares geometric mean ratio.
Note: ANOVA mixed-effects model included hepatic function cohort (mild vs. moderate or severe) as fixed effect, and patient as a random effect.
Abbreviations: ANOVA, analysis of variance; AUC, area under the concentration-time curve; CI, confidence interval; CL, clearance; C_{max}, maximum plasma concentration; PK, pharmacokinetic; $t_{1/2}$, terminal half-life; V_{ss}, volume of distribution at steady state.

Total plasma metabolite M1 (1',3'-dihydroxy-lurbinectedin) / parent ratio

Results from the statistical analysis reveal significantly higher dose-normalized C_{max} and AUC metabolic parent ratio (MPR) in patients with moderate and severe hepatic impairment compared to those with mild hepatic impairment. These differences were also observed when using the normal hepatic function cohort as the reference.

Table 18 Statistical comparison of metabolite M1/Parent Ratio in plasma between mild hepatic impairment cohort (reference) and moderate and severe hepatic impairment cohorts (evaluable population)

MPR of PK Parameter (Units)	Moderate/Mild Ratio (90% CI)	Severe/Mild Ratio (90% CI)
C_{max}/D (µg/L/mg)	422.87 (203.99 - 876.62)	273.71 (124.13 - 603.52)
AUC_{0-t} /D (µg·h/L/mg)	865.24 (393.92 - 1900.49)	595.34 (253.57 - 1397.73)

Ratio = least-squares geometric mean ratio.

Note: ANOVA mixed-effects model included hepatic function cohort (mild vs. moderate or severe) as fixed effect, and patient as a random effect.

Abbreviations: ANOVA, analysis of variance; AUC, area under the concentration-time curve; CI, confidence interval, C_{max}, maximum plasma concentration; MPR, parent ratio; PK, pharmacokinetic.

Total plasma metabolite M4 (PM030047, N-desmethyl-lurbinectedin) / parent ratio

Results from statistical analysis indicate a trend in dose-normalized AUC MPR being lower in patients with moderate and severe hepatic impairment compared to those with mild hepatic impairment.

Table 19 Statistical comparison of metabolite M4/Parent Ratio in plasma between mild hepatic impairment cohort (reference) and moderate and severe hepatic impairment cohorts (evaluable population)

MPR of PK Parameter (Units)	Moderate/Mild Ratio (90% CI)	Severe/Mild Ratio (90% CI)
C_{max}/D (µg/L/mg)	99.73 (55.46 - 179.32)	93.51 (47.68 - 183.39)
AUC_{0-t} /D (µg·h/L/mg)	59.16 (21.66 - 161.56)	47.68 (15.05 - 151.07)

Ratio = least-squares geometric mean ratio.

Note: ANOVA mixed-effects model included hepatic function cohort (mild vs. moderate or severe) as fixed effect, and patient as a random effect.

Abbreviations: ANOVA, analysis of variance; AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum plasma concentration; MPR, parent ratio; PK, pharmacokinetic.

Exposure to M1 increased with HI. The dose-normalized C_{max} and AUC ratios of M1 relative to the lurbinectedin parent compound were significantly higher in the Moderate and Severe HI cohorts, compared with the Mild HI Cohort. This finding suggests that CYP3A4 inducibility may compensate for HI status, explaining why parent lurbinectedin metabolism is not affected in a large extent.

In contrast, the dose-normalized AUC ratio of M4 relative to the lurbinectedin parent compound tended to decrease in the Moderate and Severe HI cohorts, compared with the Mild HI Cohort which suggests that it may undergo a less inducible metabolism pathway than CYP3A4, or be directly excreted into bile.

Gender

In the PopPK analysis, gender was not statistically significant.

Ethic factors

A phase I study A-013 was conducted in Japanese patients (n=26) treated with lurbinectedin at doses ranging from 1.5 to 3.5 mg/m². No differences in NCA PK results were observed between Japanese and non-Japanese patients treated in the First-in-Human study A-001 (n=15) and the SCLC cohort of the phase II study B-005 (n=101) (Table below).

Table 20 Summary of lurbinectedin PK in study A-013 in Japanese patients, and studies A-001 and B-005 in non-Japanese patients.

	n	CL_t (L/h)	$t_{1/2}$ (h)	V_{ss} (L)	V_z (L)
A-013 Japanese 3.2 mg/m²	26	12.3 (6.3)	47.4 (19.3)	433.9 (229.4)	788.4 (410.7)
A-001 First in Human (at RD; 4.0 mg/m² or 7.0 mg FD)	15	11.8 (6.5)	61.7 (37.1)	443.1 (185.9)	803.7 (333.6)
B-005 Basket (SCLC cohort) 3.2 mg/m²	101	13.1 (6.6)	41.6 (20.4)	456.5 (258.5)	737.2 (496.0)

(): standard deviation. CL_t: total body clearance; FD: flat dose; n: the number of patients, PK, pharmacokinetics; RD: recommended dose, $t_{1/2}$: terminal half-life, V_{ss}: volume of distribution at steady-state, V_z: volume of distribution based on the terminal phase.

Weight

Body weight as covariate was analysed using popPK model. In the data set, median weight was 70 kg with a range from 39-154 kg. Body weight was not found to be statistically significant.

Another covariate related to body weight, was body surface area (BSA) that was analysed in popPK model. In the data set, median BSA was 1.76 m^2 with a range from 1.29-2.65 m^2. BSA was found to be statistically significant, and was retained in that final model. However, further simulation showed that all volumes of distribution increase with BSA increase but not related to total or unbound clearance. Thus, BSA was not considered clinically relevant.

Elderly

While there was no upper age limit, patients up to the age of 85 years were included in clinical studies. The median (range) age in the popPK data set was 61 (18- 85) years, while there were 37% of patients above 65 years. In the PopPK analyses, age was not a significant predictor of exposure. Overall, no dose adjustment is required based on age.

Paediatric population

There is no data available yet in the paediatric population. A product specific waiver for lurbinectedin (EMEA-002846-PIP01-20) was granted by EMA decision P/0446/2020 of 01 December 2020, in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council, and based on the Paediatric Committee opinion dated 16 October 2020 (ref: EMA/PDCO/417233/2020).

5.2.2.11. Pharmacokinetic interaction studies

PK drug-drug interactions

In vitro

In vitro lurbinectedin was extensively metabolised with in vitro clearance of about 450 µl/min/mg microsomal protein. The main CYP isoform responsible for the metabolism of lurbinectedin was CYP3A4 (>80%). The other CYPs isoforms did not have a clear impact on the metabolism of lurbinectedin or the impact was very low (percentage reduction of intrinsic clearance with and without inhibitor was less than 14% with the selective chemical inhibitors). Altogether, metabolites are suggested to be formed mostly via CYP3A4 (inhibited to nearly 100% via CYP3A4 inhibitor ketoconazole) and highly NADPH dependent.

The lurbinectedin cut-off value calculations are based on the lurbinectedin C_{max} values reported in study CLPH-23-001-R i.e., 135.74 µg/L (172.94 nM) in patients dosed at 3.2mg/m^2, which is deemed

adequate. With the fraction unbound (Fu,p) being 0.01, the 50 × C_{max}(u) is calculated to be 0.09 µM. Since lurbinectedin is administered as a 60 min infusion, as per EMA Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**), the cut-off value for both renal and hepatic uptake and efflux transporters after i.v. administration is also defined as 50 × C_{max}(u).

Lurbinectedin potential for competitive and time-dependent inhibition of CYP enzymes (i.e., CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 enzymes) was examined in study RPT02153. Lurbinectedin was found to be an in vitro inhibitor of CYP2B6 (Ki = 2.36 µM), CYP2C8 (Ki = 4.70 µM), and CYP3A4 (Ki = 2.25 µM (substrate midazolam), Ki = 1.00 µM (substrate testosterone)). Additionally, in study RPT03294 the results indicated that under experimental conditions there was no mechanism-based irreversible CYP3A4 inactivation by lurbinectedin.

In vitro study RPT02094 tested CYP1A2 and CYP3A4 induction potential of lurbinectedin. The results of the study indicate that lurbinectedin does not induce the mentioned enzymes. The study was performed in duplicates using hepatocytes from three donors over a relevant concentration range with an appropriate incubation period.

Interactions of lurbinectedin with the human ABC (efflux) transporters BCRP (ABCG2/MXR), BSEP (ABCB11/sP-gp) and MDR1 (ABCB1/P-gp), and the human SLC (uptake) transporters MATE1, OATP1B1 (OATP2, OATP-C), OATP1B3 (OATP8), OAT1, OAT3, OCT1, and OCT2 were also tested. No relevant fold accumulation of lurbinectedin (fold accumulations were < 2) into the cells was observed at the applied concentrations and time points in the OATP1B1, OATP1B3, OCT1 and MATE1 substrate feasibility experiments. Lurbinectedin has moderate permeability (Papp values in the MDCKII parental cells, in the A-B direction was 2 to 9 x 10^{-6} cm/s) while the recovery values (50-80%) suggest loss of the compound in the assay system.

The time-dependent bidirectional transport of lurbinectedin was measured in the MDCKII-MDR1 and BCRP monolayer efflux assay at three concentrations (0.1, 1 and 10 µM) to evaluate whether lurbinectedin is a substrate of MDR1 or BCRP. Lurbinectedin showed higher permeability in the B-A direction than in the A-B direction, indicating that there was active transport of this compound in the MDCKII-MDR1 cells, but no relevant permeability differences (net ER < 2) were observed between in the B-A direction and in the A-B direction in MDCKII-BCRP assay. In the follow-up monolayer assay, the presence of MDR1-specific inhibitors (10 µM PSC833 and 100 µM verapamil) reduced the ER of lurbinectedin to -0.05 (PSC833) and to -0.09 (verapamil), confirming the contribution of MDR1 to the transport of lurbinectedin across MDCKII-MDR1 monolayers.

Lurbinectedin is an in vitro inhibitor of human MDR1 (P-gp) efflux transporter (as shown in the VT inhibition assay, study PharmaMar-05-20Mar2014), with IC50 value of 3.85 µM (Ki = 1.93 µM) however, no effect on digoxin transport in the monolayer assay up to 10 µM was shown). Additionally, lurbinectedin is likely to be an in vitro inhibitor of human OATP1B1, OATP1B3 and OCT1 uptake transporters.

In silico

Report number 1136392, *Pharmacokinetics of Atezolizumab (PD- L1 inhibitor) single agent or in combination with Lurbinectedin, both following First-Line Induction Therapy With Carboplatin, Etoposide, and Atezolizumab in Patients With Extensive-Stage Small-Cell Lung Cancer (ES-SCLC) – Study IMforte*

Objectives of this analysis were to:

• Assess the PK of atezolizumab in patients with ES-SCLC in the Phase 3 clinical study (IMforte) through external evaluation of the Phase 1 popPK Model

• Derive exposure metrics of atezolizumab in ES-SCLC patients treated with first-line induction therapy in IMforte for a further exposure-response analysis

• Explore the potential impact of lurbinectedin co-administration and other patient factors on atezolizumab PK.

The IMforte population PK dataset included 2247 evaluable atezolizumab serum concentrations from 647 patients with ES-SCLC receiving 1200 mg of atezolizumab q3w by IV infusion, 242 patients in the atezolizumab + lurbinectedin arm (Arm A), 239 patients in the atezolizumab arm (Arm B), and 166 patients who were not randomized.

A population PK model was previously developed for atezolizumab using Phase 1 PK data (subsequently called the "Phase 1 popPK Model") from 2 clinical studies: study PCD4989g and study JO28944. The atezolizumab Phase 1 popPK Model was a two-compartment disposition model with first-order elimination including covariate effects.

Individual CL, V1, and V2 patient-level random effects estimated with the Phase 1 popPK Model and on a subset of data including only Cycle 1 PK data, were used to predict atezolizumab concentration profiles and calculate exposure metrics both at Cycle 1 and Cycle 10 (steady state). Both cycle 1 and steady-state exposure metrics were similar to those estimated in other studies using atezolizumab monotherapy.

Table 21 Summary Statistics (Geometric Mean [Geometric Mean CV%]) of Atezolizumab Exposure Metrics at Cycle 1 and Steady-State in IMforte Predicted Using the Phase 1 PopPK Model in Arm A and Arm B

Exposure metrics	**Arm A**	**Arm B**
	N=242	**N=239**
C_{max},Cycle1 (µg/mL)	373 [15.5]	377 [16.4]
C_{min},Cycle1 (µg/mL)	71.6 [26.6]	72.2 [29.9]
$AUC_{0\text{-}21d}$ (µg*day/mL)	2785 [16.1]	2807 [17.8]
$t_{1/2}$ beta (day)	21.5 [25.2]	21.6 [26.0]
$C_{max,ss}$ (µg/mL)	524 [18.5]	531 [20.0]
$C_{min,ss}$ (µg/mL)	146 [40.4]	148 [44.3]
AUC_{ss} (µg*day/mL)	5059 [26.6]	5127 [29.0]
AUC Accumulation ratio	1.82 [13.9]	1.83 [14.4]

AUC0-21d = area under the concentration-time curve during dosing interval at Cycle 1; AUCss=area under the concentration-time curve during dosing interval at steady state; CI = confidence interval; Cmax = maximum concentration at Cycle 1 or steady state; Cmin = trough concentration at Cycle 1 or steady state; CV = coefficient of variation; N = number of patients; Accumulation ratio is derived as the ratio between AUC and AUCss; at1/2 beta is the terminal half-life based on post-hoc parameter estimates

Report number: CLPH-24-001, *Population Pharmacokinetics Analysis of Lurbinectedin when Administered in Combination with Atezolizumab as First-Line Maintenance to Patients with Extensive-stage Small Cell Lung Cancer in the IMforte Study (Phase III Study GO43104)*

Report date: 27.03.2025.

Objectives of the popPK model were to:

- Assess lurbinectedin PK in ES-SCLC participants receiving intravenous (IV) administration of lurbinectedin in combination with atezolizumab (Arm A) as part of the randomized phase, using external validation of the Reference popPK Model.
- Derive post-hoc lurbinectedin individual exposure metrics from the Reference popPK Model for a subsequent Exposure-Response (E-R) analysis in participants with ES-SCLC in the IMforte study.

An external validation of the reference PopPK model was performed using the lurbinectedin PK data collected in the experimental arm of study IMforte, to evaluate lurbinectedin PK in participants with ES-SCLC treated with this agent as part of their first-line maintenance therapy.

The dataset included 915 plasma concentration records of lurbinectedin from 240 participants out of a total of 242 participants treated in IMforte Arm A. Lurbinectedin PK was evaluated for 233 participants.

The table below provides the summary statistics of the individual exposure metrics at Cycle 1 in IMforte study, compared to PM1183-B-005-14 study (both for all participants and SCLC cohort only). Cycle 1 exposure metrics were similar to those estimated in other studies using lurbinectedin monotherapy, which suggests that lurbinectedin PK is not influenced by the co-administration of atezolizumab in ESSCLC participants (Arm A).

Table 22 Geometric Mean (Geometric CV%) of Lurbinectedin Exposure Parameters Using the Reference PopPK Model and AAG in the IMforte Study and PM1183-B-005-14 Study

Exposure metrics	**IMforte Arm A N=233**	**PM1183-B-005-14 N=331**	**PM1183-B-005-14 (SCLC) N=103**
C_{max} (µg/L)	96.7 (25.4)	109 (34.7)	104 (30.8)
AUC (µgh/L)	472 (49.7)	524 (60.5)	464 (45.5)
AUC_u (ngh/L)	1649 (40.3)	1397 (48.3)	1275 (47.7)
CL (L/h)	12.3 (47.7)	10.9 (60.9)	12.4 (44.8)
V_{ss} (L)	479 (31.8)	435 (48.4)	465 (38.2)
$t_{1/2}$ gamma (h)	45.7 (23.6-100)	44.3 (16.5-157)	45.8 (19.0-109)
AAG (mg/dL)	94.5 (34.3)	126 (40.6)	122 (34.5)

Abbreviations: AAG=alpha-1-acid glycoprotein; AUC=area under the total lurbinectedin plasma concentration-time curve; AUCu=area under the unbound lurbinectedin plasma concentration-time curve; CL=Clearance; Cmax=maximum concentration; N=number; SCLC=small cell lung cancer; =plasma half-life of terminal phase (expressed as median [range]); Vss=volume of distribution at the steady state.

In vivo

Two clinical drug-drug interaction (DDI) studies to evaluate the impact of itraconazole (a strong CYP3A4 inhibitor) and bosentan (a moderate CYP3A4 inducer) on the pharmacokinetics (PK) of lurbinectedin, which was evaluated as the victim drug, were conducted.

In study PM1183-A-018-20, conducted in 8 patients, co-administration of lurbinectedin with multiple oral doses of itraconazole, a strong CYP3A4 inhibitor, increased total plasma lurbinectedin C_{max} by 15% and AUC_{inf} by 2.7-fold compared to lurbinectedin alone administered as one-hour i.v. infusion of 3.2 mg/m^2 dose. The total plasma clearance was also reduced by 63%, when lurbinectedin was given concomitantly with itraconazole (total daily dose of 200 mg during 12 days, 4 days before up to 8 days after the lurbinectedin administration). Additionally, it also increased unbound plasma lurbinectedin

AUC_{inf} by 2.4-fold, almost completely inhibited the conversion of lurbinectedin to its metabolite M1, and reduced by 69% the conversion of lurbinectedin to its metabolite M4, compared to lurbinectedin alone administered as one-hour i.v. infusion of 3.2 mg/m^2 dose.

In study PM1183-A-019-20, conducted in 8 patients, co-administration of lurbinectedin with multiple oral doses of bosentan, a moderate CYP3A4 inducer, decreased total plasma lurbinectedin AUC_{inf} by 20% compared to lurbinectedin alone administered as one-hour i.v. infusion of 3.2 mg/m^2 dose. However, it did not induce any statistically significant modifications in the unbound plasma lurbinectedin PK parameters. Co-administration with bosentan has been shown to increase by 25% the total plasma lurbinectedin clearance mostly by increasing its conversion to metabolite M1; the plasma M1/lurbinectedin exposure ratio was increased by approximately 1.9-fold for C_{max} and by 2.45-fold for AUC_{0-t}, while it did not modify the M4 metabolite/parent ratio for C_{max} nor for AUC_{0-t} compared to lurbinectedin alone administered as one-hour i.v. infusion of 3.2 mg/m^2 dose.

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

Lurbinectedin is an inhibitor of oncogenic transcription that binds guanine residues in the minor groove of DNA, forming adducts, and resulting in a bending of the DNA helix towards the major groove resulting in perturbation of the cell cycle and eventual cell death.

Lurbinectedin, in combination with atezolizumab, is indicated for the maintenance treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin and etoposide.

Tecentriq (atezolizumab) is an Fc-engineered, humanized, monoclonal antibody that binds to programmed death-ligand 1 (PD-L1), a receptor expressed on tumour cells and/or tumour infiltrating immune cells, and blocks its interaction with programmed death-1 (PD-1) and B7.1 receptors found on T cells and antigen presenting cells.

5.2.3.2. Primary and secondary pharmacology

Evidence for the efficacy of the proposed dosing schedule was primarily obtained from a single-arm study B-005 that included 105 patients with SCLC. Overall response rate (ORR) by investigator assessment in all treated patients (primary efficacy analysis) was 36.2% (95% CI, 27.0-46.1%). The study met its primary endpoint.

In early phase prospective clinical studies, lurbinectedin in combination with the anti-PD-L1 inhibitor atezolizumab (2SMALL) or the anti-PD-1 inhibitor pembrolizumab (LUPER) demonstrated promising antitumour activity and a manageable safety profile in relapsed SCLC patients. Of note, 2SMALL (NCT04253145) is an ongoing phase I/II study conducted as an investigator-initiated study assessing the safety, tolerability and efficacy of lurbinectedin in combination with atezolizumab as second line treatment for ES-SCLC. The recommended dose for further studies was lurbinectedin 3.2 mg/m^2 plus atezolizumab 1200 mg on Day 1 q3wk with growth colony stimulating factors (G-CSF). Preliminary data indicate that the novel transcription inhibitor lurbinectedin may synergise with immune checkpoint inhibitors such as atezolizumab by immunogenic cell death or epitope spreading. Considering these observations, the GO43104 study (hereinafter IMforte) was designed to evaluate whether the combination of atezolizumab and lurbinectedin, compared to atezolizumab monotherapy could enhance the antitumour effect during maintenance treatment in patients with non-progressing ES-SCLC after induction therapy with atezolizumab, carboplatin, and etoposide.

Secondary pharmacology

Effect of Lurbinectedin on cardiac repolarization (QTc duration) in patients with selected solid tumours was assessed at lurbinectedin therapeutic dose. A total of 39 evaluable patients were included. In the majority of post-baseline assessments, data from at least 35 patients were available. The Fridericia's formula corrected for the effect of HR on the QT interval reasonably well, with a slight tendency to over-correct resulting QTc values.

The upper bound (UB) of the (two-sided) 90% of LSM ΔQTcF CI at all time points was less than the protocol-specified cut-off of 20 ms at each time point t. Specifically, the maximum LSM ΔQTcF from baseline occurred three hours after the end of Cycle 2 infusion: LSM ΔQTcF=5.4 ms (90% CI, 1.2-9.6 ms).

There was an apparent relationship between lurbinectedin plasma concentrations and ΔQTcF (slope of 2.06 ng/mL). The predicted ΔQTcF and its two-sided 90% CI at the highest clinically relevant lurbinectedin exposure (mean C_{max} of 105 ng/mL) were 2.94 ms (range, 0.79-5.10 ms). The upper bound of the CI (5.10) is below the 10 ms threshold of concern.

A modest increase of mean heart rate (ΔHR of 16.7 ms in Cycle 1, and 17.5 ms in Cycle 2) affecting 44% of patients in Cycle 1 and 49% in Cycle 2, with ΔHR >25%, was typically detected at four hour after the start of the 1-h infusion, thus not related to C_{max}, and usually recovering baseline values in next assessments. Values of PR interval and QRS duration were consistent across all time points.

No new clinically relevant morphological changes were observed, except for a few isolated ST segment, T wave and conduction abnormalities. The pharmacokinetic profile of lurbinectedin was similar to that observed in previous studies. No adverse events were reported suggestive of proarrhythmic potential.

5.2.3.3. Pharmacodynamic interactions with other medicinal products or substances

The potential of lurbinectedin to displace other co-administered compounds from their plasma protein binding was not investigated. Generally, displacement interactions from protein binding are only expected if drug concentration is in the same order of magnitude as the plasma proteins. The comparatively low lurbinectedin concentrations make it unlikely that it displaces other drugs from plasma proteins to a clinically relevant extent.

5.2.3.4. Genetic differences in PD response

No evidence of genetic variability affecting the primary pharmacodynamic interaction (DNA binding) has been reported in the submitted documentation, and none is anticipated.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

Exposure-Response model

To explore the relationship between exposure to lurbinectedin and the efficacy and safety endpoints in SCLS subjects, three exposure response analysis were performed (one when lurbinectedin was administered as single agent and two when lurbinectedin was administered with atezolizumab).

In the first analysis, selected efficacy endpoints were objective response rate (ORR), duration of response (DoR), and overall survival (OS), while the selected safety endpoints were incidence of G4 neutropenia and incidence of grade G≥3 thrombocytopenia.

This analysis was based on available efficacy data from SCLC patients treated with lurbinectedin as single agent from study B-005, and safety data from studies in which patients were treated with lurbinectedin as single agent: PM1183-A-001-08, PM1183-B-001-10, PM1183-B-002-11, PM1183-B-003-11, PM1183-B-004-13, PM1183-B-005-14 (B-005) and PM1183-C-004-14 (C-004 CORAIL) CORAIL.

Results

Exposure Efficacy Analysis

ORR

The prognostic factor for ORR was Chemotherapy Free Interval (CTFI), coded as resistant (1) or sensitive (2). Patients were categorised into 4 groups by quartiles (groups 0, 1, 2 and 3) according to AUC_u and CTFI.

The odds ratios for the three higher quartiles for $cAUC_u$ of (groups 1, 2 and 3) were between 14.6-fold and 35.6-fold higher than the lowest quartile (group 0). CTFI for sensitive patients was 7.8-higher than for resistant patients.

Duration of response (DoR)

Responder patients categorized by CTFI as having resistant (1) or sensitive (2) disease did not show differences in DoR.

Overall survival (OS)

Median OS in patients with sensitive disease (n=59) was 11.9 (95% CI: 9.7 - 16.2) months, and was significantly longer than OS achieved in patients with resistant disease (n=44), 5.0 months (95% CI: 4.1 - 6.5).

Exposure Safety Analysis

G4 Neutropenia

Odds ratios showed that the likelihood of G4 neutropenia for $cAUC_u$ at the highest quartile (group 3) increased 13.0-fold when compared to the lowest quartile (0).

G≥3 thrombocytopenia

Exposure metrics after the first dose AUC_u was categorised according to quartiles into 4 groups $cAUC_u$ and related to G≥3 thrombocytopenia. The quartile with highest exposure (group 3) presented the highest incidence of G≥3 thrombocytopenia, with differences ($p<0.05$) among all groups.

Subsequently, the applicant developed two exposure response analyses for efficacy and safety to determine the effect of lurbinectedin when added to atezolizumab and to explore safety and efficacy of atezolizumab in combination with lurbinectedin.

Exposure-response of lurbinectedin in patients with ES-SCLC (IMforte)

The lurbinectedin exposure-efficacy and exposure-safety analyses were performed on participants (N=233) who received lurbinectedin 3.2 mg/m^2 Q3W IV and atezolizumab (1200 mg), had at least one PK-evaluable sample while on randomisation phase.

PopPK Model-derived exposure metrics based on actual dose schedule information were used to investigate the relationship between lurbinectedin exposure and the selected efficacy and safety endpoints. The selected exposure metric was the unbound lurbinectedin AUC (area under the unbound concentration-time curve (AUC_u)) in Cycle 1 for participants in atezolizumab + lurbinectedin arm of IMforte.

Time-to-event efficacy endpoints (e.g., IRF-assessed PFS and OS) were evaluated using Kaplan-Meier estimates stratified by AUC_u quartiles. Multivariate Cox with a p-value of 0.01 and/or parametric regression analyses on IRF-assessed PFS and OS were conducted to simultaneously incorporate the effects of lurbinectedin exposure and the significant prognostic factors identified.

Descriptive and univariate logistic regression analyses were conducted to evaluate potential associations between AUC_u and the incidence of the selected safety endpoints. A p-value < 0.01 was considered statistically significant.

Results

Exposure-Response Analyses of Efficacy

Overall survival

Lurbinectedin AUC_u did not show a statistically significant association, although the Kaplan-Meyer curves by AUC_u quartiles indicated a trend of prolonged OS in the highest quartile (Q4) of AUC_u.

Progression Free Survival

Kaplan Meier plots showed that participants in the highest quartile (Q4) of AUC_u had the longest IRF-assessed PFS.

Exposure-Response Analyses of Safety

The analysis of the incidence of Grade ≥3 AEs did not show any statistically significant (p>0.01) exposure-response relationship with AUC_u.

The analyses of the incidence of AESI did not show any statistically significant (p>0.01) exposure-response relationship with AUC_u.

The analysis of the incidences of Grade 4 neutropenia and Grade ≥3 thrombocytopenia in the IMforte study shows a statistically significant (p< 0.01) exposure-response relationship with AUC_u.

Exposure-Response of Atezolizumab in Patients with ES-SCLC (IMforte)

Objective was to explore whether there is an exposure-response relationship of atezolizumab with respect to the efficacy and safety in patients with ES-SCLC based on data from IMforte in which atezolizumab is given in combination with lurbinectedin (lurbi) in Arm A, randomization phase of IMforte study.

The following efficacy endpoints were analysed:

- Progression-free survival (PFS) Independent Review Facility (IRF)
- Overall survival (OS)

The frequency of the following adverse events (AE) was analysed:

- Adverse events of Grades 3 to 5 (AEG35)
- Adverse events of special interest (AESI)

Atezolizumab exposure metrics C_{max}, C_{min}, and $AUC_{0\text{-}21d}$ at cycle 1 of the enrolment phase were estimated with the Phase I PopPK Model and IMforte data were used for exposure-response analyses.

For binary endpoints (e.g., incidence or onset of safety events), logistic regression was used with exposure as a continuous variable. Chi-square test p-values were reported for each logistic regression, along with proportions/frequencies and their 95% confidence intervals (CIs) calculated across exposure quartiles.

Time-to-event endpoints (e.g., PFS [IRF] and OS) were initially analysed using Kaplan-Meier estimates stratified by quartiles of exposure metrics, followed by Cox regression with exposure metrics as continuous variables.

Results

Exposure-Efficacy Analysis

The median PFS is 5.36 months 95%CI [4.30-5.78] in Arm A. The KM plots indicate clear overlap in the PFS distributions across exposure quartiles, without any relationship between PFS and exposure.

The Cox proportional hazard models for PFS with exposure metrics showed no statistical significance of any of tested baseline covariates.

The median OS is 13.2 months 95%CI [11.9-16.5] in Arm A. The KM plots show that the OS distribution between exposure quartiles largely overlaps. The KM plot did not allow the distinction of any trend between OS and exposure.

Exposure-Safety Analysis

No significant increase in the incidence of AE Grade 3-5 and AESI with increasing atezolizumab exposure was observed in IMforte Arm A.

Evaluation and Qualification of PK/PD Models

PK/PD model for neutrophil count (ANC)

The primary objectives of the population pharmacokinetic and pharmacodynamic (PopPKPD) analysis of lurbinectedin in cancer subjects were the following:

1) to model time course of absolute neutrophils count (ANC) following the intravenous administration of lurbinectedin as single agent in cancer subjects, and to quantify the between subject variability in the system-related and drug-specific parameters,

2) to evaluate the effects of subjects' demographic characteristics and other covariates on the model obtained from phase I and phase II clinical studies,

3) to explore alternative dose regimens that ameliorates the incidence of severe neutropenia.

The dataset included lurbinectedin plasma concentrations and time course of ANC from two single-agent phase I studies (PM1183-A-001-08 and PM1183-A-005-11) and three single-agent phase II studies (PM1183-B-001-10, PM1183-B-002-11 and PM1183-B-003-11). Overall, the dataset contained 3421 ANC observations from 244 subjects of which 156 were also sampled for lurbinectedin analysis with 2636 samples.

Development of PopPKPD model

The PopPKPD was a multi-compartment transit model, which consisted of eight compartments (see Figure 9):

- one proliferative cells compartment [Prol],
- six transit compartments [Transit1 to Transit6], and
- one compartment for circulating ANC [ANCcirc] which corresponded to the observed ANC.

The maturation chain was managed by a mean transit time (MTT) which represented the time taken for the neutrophil to reach the circulation after leaving the proliferative compartment. Moreover, there were two feedback processes to increase the neutrophil production (FBprol) and to reduce MTT (FBMTT) when [ANCcirc] was lower than the initial ANC baseline (ANC0). The feedback processes were

managed by γ and β, respectively. The neutrophil half-life ($HLANCcirc$) in plasma was fixed to seven hours.

Lurbinectedin plasma concentrations were assumed to reduce the ANC production by using an E_{max} function governed by EC_{50}, E_{max} and lurbinectedin concentrations through an effect compartment (Ce).

Figure 9 Description of the popPKPD model

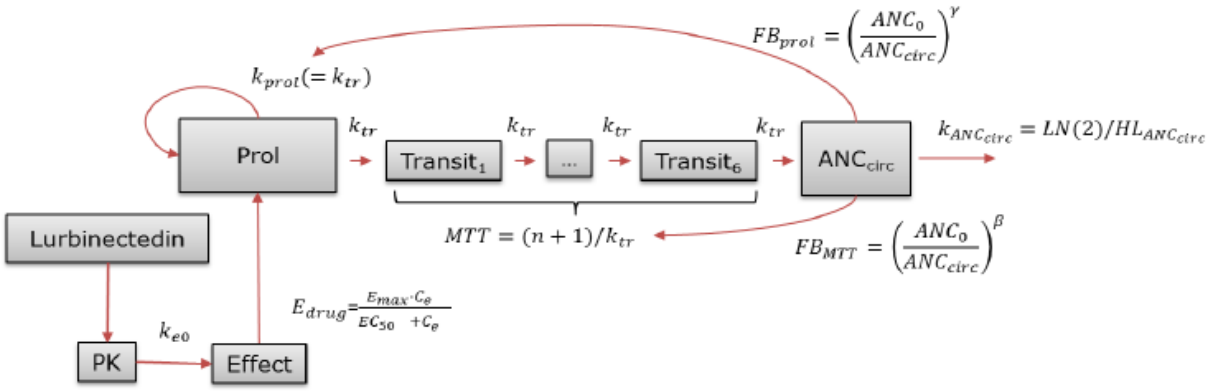


Table 23 Final model parameters

Model parameter	Estimate (RSE%)	ISV, CV% (RSE%)
MTT (h)	140 (1.94)	16.6 (11.0)
E_{max}	1.15 (9.82)	-
EC_{50} (µg/L)	13.5 (15.2)	76.6 (10.1)
β	0.243 (4.97)	-
γ	0.379 (3.68)	-
k_{e0} (x10^{-2} 1/h)	1.99 (7.59)	-
$GCSFEC_{50}$	3.38 (3.72)	-
GCSFMTT	-0.353 (0.695)	-
RV (CV%)	51.8 (4.10)	59.1 (6.18)
Covariate parameters		
EC_{50}AAG (x10^{-3})	7.40 (27.7)	
MTTAAG (x10^{-3})	-1.48 (22.6)	
EC_{50}SENS	-0.377 (21.6)	

MTT, Mean maturation time; Emax, Maximum effect; EC50, concentration at 50% of Emax; β, MTT feedback; γ, proliferative feedback; ke0, compartment effect rate; GCSFEC50, relationship between GCSF and EC50; GCSFMTT, relationship between GCSF and MTT; RV, residual variability; EC50AAG, relationship between EC50 and AAG; MTTAAG, relationship between MTT and AAG; EC50SENS, relationship between sensitive subjects (pancreatic and ovarian cancer subjects) and EC50.

For a typical patient, the drop of neutrophils started about Day 5 after lurbinectedin infusion, with nadir about Day 13, and recover to baseline on Day 21.

The most relevant covariate was ANC at baseline as was a clear predictor of neutropenia grade. Subjects with BANC lower than 3.1 x 109/L had higher risk of neutropenia grade 4.

BSA is related to the distribution volume of lurbinectedin but had a negligible effect on neutropenia. The BSA-dosing of lurbinectedin produced higher neutropenia at higher BSA as higher doses would be used, and therefore the dose should be capped for subjects with BSA larger than 2.0 m².

Sensitive subjects (pancreatic and ovarian cancer subjects) presented lower EC_{50}, and therefore these subjects were more sensitive to develop neutropenia.

The use of CYP3A4 inhibitors produced a 42% (26% vs. 37%) increase of grade 3/4 neutropenia and a 55% (11% vs. 17%) increase of grade 4 neutropenia.

Other covariates explored such as sex and age did not have any effect on neutropenia. Race could not be assessed as most of the subjects were White (96%).

In the stochastic simulations, the dose of 3.2 mg/m² q3wk showed an approximately 21% lower incidence of grade 3/4 (26% vs. 33%) and grade 4 neutropenia (11% vs. 14%) compared to the dose of 7.0 mg FD.

PopPKPD modelling of PLT time course in subjects treated with lurbinectedin

The primary objectives of the population pharmacokinetic and pharmacodynamic (PopPKPD) analysis of lurbinectedin in cancer subjects were the following:

1) to model the time course of platelets (PLT) following intravenous administration of lurbinectedin as single agent in cancer subjects, and to quantify the between subject variability in system-related and drug-specific parameters,

2) to evaluate the effects of subjects' demographic characteristics and other covariates on the model obtained from phase I and phase II clinical studies,

3) to explore alternative dose regimens that ameliorates the incidence of severe thrombocytopenia

The dataset included lurbinectedin plasma concentrations and PLT from two single-agent phase I studies (PM1183-A-001-08 and PM1183-A-005-11) and three single-agent phase II studies (PM1183-B-001-10, PM1183-B-002-11 and PM1183-B-003-11). Overall, the dataset contained 3546 PLT observations from 244 subjects of which 156 were also sampled for lurbinectedin analysis with 2636 samples. Subjects received intravenous (i.v.) lurbinectedin as single agent at doses ranging from 0.02 to 5.9 mg/m2 and given as 1-h infusions on Day 1 or Days 1 and 8 every 3 weeks (q3wk).

The PopPKPD was a multi-compartment transit model, which consisted of eight compartments: one proliferative cells compartment [Prol], six transit compartments [Transit1 to Transit6], and one compartment for circulating PLT [PLTcirc] which corresponded to the observed PLT. The maturation chain was managed by a mean transit time (MTT) which represented the time taken for the PLT to reach the circulation after leaving the proliferative compartment. Moreover, there were two feedback processes to increase the PLT production (FBprol) and to reduce MTT (FBMTT) when [PLTcirc] was lower than the initial PLT baseline (PLT0). The feedback processes were managed by γ and β, respectively. Information related to the administration of pooled.

Lurbinectedin plasma concentrations were assumed to reduce the PLT production by using an E_{max} function governed by EC_{50}, Emax and lurbinectedin concentrations (C).

Figure 10 popPKPD model of PLT time course

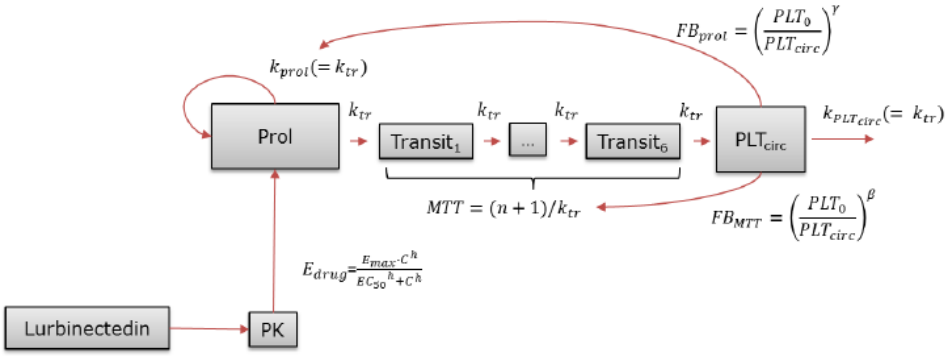


Table 24 Final model parameters

Model parameter	Estimate (RSE%)	ISV, CV% (RSE%)
MTT (h)	126 (0.84)	8.93 (14.6)
EC50 (µg/L)	4.93 (5.73)	47.3 (8.78)
β	0.329 (3.93)	-
γ	0.512 (2.93)	-
Hill	5.71 (8.59)	-
Pooled PLT (x10^9/L)	87.2 (6.88)	-
RV (CV%)	21.3 (1.87)	-
Covariate parameters		
EC_{50}AAG (x10^{-3})	0.907 (12.8)	
EC_{50}BSA	0.481 (43.2)	
EC_{50}SENS	-0.235 (25.5)	

MTT, Mean maturation time; EC50, concentration at 50% of maximum effect; β, MTT feedback; γ, proliferative feedback; RV, residual variability; EC50AAG, relationship between EC50 and AAG; EC50BSA, relationship between EC50 and BSA; EC50SENS, relationship between sensitive subjects (pancreatic and ovarian cancer subjects) and EC50.

For a typical patient, the decrease of platelets started 5 days after the lurbinectedin infusion, with nadir between Day 9 and 10, and recover to baseline on Day 15.

Among the covariates included into the model, AAG levels increased EC_{50}. The next relevant covariate was BPLT, being a strong predictor of the grade of thrombocytopenia. Subjects with BPLT lower than 189 x 109/L had a large risk of grade 4 thrombocytopenia. Other covariates that affected the grade of thrombocytopenia, such as CYP3A inhibitors, albumin or CRP, were in fact related to changes in lurbinectedin exposure, while subjects with ovarian or pancreatic tumour types were more sensitive to develop thrombocytopenia, as shown by lower EC_{50} values.

In the stochastic simulations, the dose of 3.2 mg/m² q3wk showed an approximately 49% and 81% lower incidence of grade 3-4 thrombocytopenia (2.2% vs. 4.3%) and grade 4 thrombocytopenia (0.035% vs. 0.18%), compared to the dose of 7.0 mg FD, respectively.

BSA-dosing produced similar thrombocytopenia to all subjects regardless of BSA, while FD

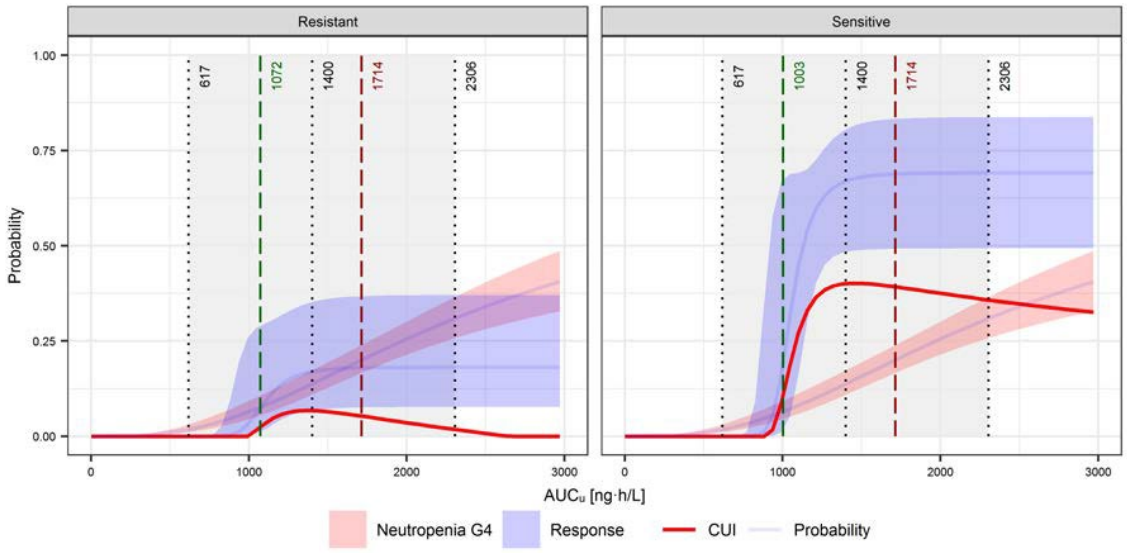
administration produced higher thrombocytopenia for subjects with lower BSA.

The dose of 3.2 mg/m² q3wk was associated to a significant reduction in the incidence of grade 3-4 and grade 4 thrombocytopenia.

5.2.5. Dose selection and therapeutic window

Lurbinectedin unbound exposure higher than 1714 ng·h/L resulted in more than 20% incidence of grade 4 neutropenia. Therefore, exposures between 1072 or 1003 and 1714 ng·h/L provided the best benefit/risk ratio for lurbinectedin, and the recommended dosing regimen, with a median unbound exposure of 1400 ng·h/L, maximizes the proportion of patients within this lurbinectedin target exposure range. The figure below displays the Clinical Utility Index (CUI), defined as the difference between the probability of ORR and the probability of G4 neutropenia (2:1 ratio), as a function of lurbinectedin AUCu, stratified by sensitive and resistant SCLC patients. The CUI indicated that lowering the dose resulted in reduced efficacy, whereas increasing the dose increased the incidence of severe haematological toxicity without improvement of efficacy.

Figure 11 Clinical utility index with AUCu in resistant (left panel) and sensitive (right panel) SCLC patients



Dashed green vertical line is the lurbinectedin AUCu providing an ORR of 7.5% (resistant) and 19.3% (sensitive), which are the ORR corresponding to topotecan. Dashed dark red vertical line is the AUCu at which the probability of grade 4 neutropenia is 20%. The grey shaded area represents the 95% prediction interval of the observed AUCu in SCLC patients. Black dotted vertical lines are percentile 5, 50 and 95 of AUCu.

Relative to the equivalent lurbinectedin fixed dose, the lurbinectedin BSA-based dosing at 3.2 mg/m² provides similar ORR and similar incidence of neutropenia and thrombocytopenia in the entire population. For subjects with BSA >1.65 m², both the BSA-based dosing at 3.2 mg/m² and the fixed-dose at 5.6 mg are associated with less than 20% and 5% incidence of severe neutropenia and thrombocytopenia, respectively; however, in subjects with BSA >1.95 m², a 10% increase in ORR is expected with BSA-based dosing, relative to flat dosing.

For subjects at the lower quartile of BSA (<1.65 m²), the BSA-based dosing at 3.2 mg/m² provides a 16% and 18% reduction in the incidence of severe thrombocytopenia and neutropenia, while only have a 12% reduction in the ORR relative to fixed dose.

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

Bioanalytical methods

In total, three plasma and two urine bioanalytical methods were developed for lurbinectedin and validated in accordance with ICH M10.

The initially used plasma method (Method A, UPLC MS/MS), used in the FIH phase I study (A-001) for plasma and urine was subsequently deemed inadequate due to incurred sample reanalysis (ISR) failure (only 60% within ±20%) and identified stability issues; consequently, PK results from this study are not considered reliable.

These issues were addressed through the development of two new methods: Method B (plasma) and Method C (plasma and urine), both based on LC-MS/MS with supported liquid extraction. Method B was validated at two independent laboratories with successful cross-validation. It was used for the studies IMforte, B-005, C-004, A-017, A-018, A-19, to measure lurbinectedin in plasma. Additionally, it was also applied for unbound lurbinectedin determination following revalidation of extended long-term stability in studies A-017, A018 and A019. Method C was used in the human mass balance study (A-015). Both methods met predefined acceptance criteria and are considered suitable for their intended use.

In the IMforte study, 5.23% of samples underwent ISR, with 89.3% meeting acceptance criteria. Although this is below guideline recommendations, this deviation is considered acceptable given the high ISR success rate.

In addition, validated methods were also developed for lurbinectedin metabolites M1 and M4 for use in the drug-drug interaction (DDI) studies with itraconazole and bosentan (studies A-018 and A-019, respectively) and the hepatic impairment study (study A-017). All samples were analysed within demonstrated stability, and analytical runs met predefined criteria.

For atezolizumab, previously submitted bioanalytical methods were used (EMEA/H/C/004143/0000, EMEA/H/C/004143/II/0007/G, EMEA/H/C/004143/II/0018, EMEA/H/C/004143/II/0019, EMEA/H/C/004143/X/0017, EMEA/H/C/004143/X/0076), as the commercial formulation was used in the pivotal study and comparability with the phase III formulation was demonstrated; this approach is acceptable.

Overall, the bioanalytical methods used for the pivotal studies are compliant with ICH M10 and are considered acceptable.

Pharmacokinetic data analysis

The pharmacokinetic data analysis methods were applied appropriately. Population pharmacokinetic (PopPK) estimates were generally consistent with the results obtained from non-compartmental analysis (NCA).

Population PK model

The Pop PK models was mainly used to describe PK in the target population and to provide information regarding covariate effects in SmPC section 5.2. Individual predicted lurbinectedin concentrations were derived to be used subsequently in the exposure-response analysis. The overall regulatory impact of the model is considered low.

Several covariates were retained in the final model: BSA, ALB, AAG, CRP, GEM and INH.

The final popPK model consisted of total 7896 plasma obtained from three phase 1 clinical studies (PM1183-A-001-08, PM1183-A-002-10 and PM1183-A-005-11), five phase 2 clinical studies (PM1183-B-001-10, PM1183-B-002-11, PM1183-B-003-11, PM1183-B-004-13 and PM1183-B-005-14) and one phase 3 trial (PM1183-C-004-14 CORAIL). Data exclusions were appropriately justified; preinfusion samples collected before treatment start (677, 7.38%), BLQ samples (568, 6.19%) and aberrant samples (35, 0.38%). No data points in the analysis dataset were identified as outliers.

Base model that described PK lurbinectedin was best described by 3-compartment disposition model parameterized in terms of CL, V1, V2, V3 and two intercompartmental distribution flows (Q2 and Q3). An exponential-error model, with between-subject variability, was used to quantify the residual unexplained variability of the lurbinectedin total plasma concentrations. All parameters were estimated with good precision as RSE values were below 30%. Goodness of fit plots indicate adequate fit of the mode.

In the final model, the following covariates were retained: BSA on Q3, V1, V2, and V3; AAG on CL, Q3, V1, V2, and V3; ALB on CL; co-medication with a CYP3A inhibitor on CL; and sex on Q3 and V3. The exploration of covariate effects was performed for PK parameters AUC, AUCu, CL, CLu, V1, Cmax and Cmin after a single 1-h infusion lurbinectedin dose of 3.2 mg/m² or 5.6 mg FD (equivalent to a 3.2 mg/m² for a BSA of 1.75 m²). Although covariates such as serum albumin and AAG, BSA were significant, their clinical relevance is of low value as the geometric mean ratio values of PK exposure (AUCu) remained within or overlapped with the 0.8 to 1.25 reference bounds. In this context, a BSA-based dosing helps in minimizing the differences in the maximum lurbinectedin concentration achieved at the end of the infusion, although it has no impact on the area under lurbinectedin concentration - time curve.

The intrinsic factors (i.e., age, height, weight, race, ascites, liver metastasis, performance status, left ventricular ejection fraction [LVEF], alanine aminotransferase [ALT], alkaline phosphatase [AP], creatinine, CrCL, CRP, haemoglobin, total proteins, total bilirubin) did not impact lurbinectedin PK.

PBPK

Enzyme CYP3A4 is the main enzyme included in metabolism of lurbinectedin. A dedicated drug-drug interaction clinical trial with a strong CYP3A4 inhibitor (itraconazole) was conducted, and a Physiologically Based Pharmacokinetic (PBPK) model was developed to evaluate the impact of moderate CYP3A4 inhibitors on lurbinectedin PK. The PBPK model was based on sufficient amount of i*n vitro*, as well as *in vivo* clinical data. Uncertainty associated with model predictions was not reported. However, dedicated clinical study have been conducted with strong CYP3A4 inhibitor (itraconazole), which is considered more reliable. PBPK mostly concerns use for interpolation scenarios (weaker CYP3A4 inhibitors), thus it can be regarded as supportive only.

PK

The pharmacokinetics of lurbinectedin were assessed in a First-in-Human study (A-001) involving patients with advanced solid tumours. A subsequent mass balance/ADME study (A-015) provided further insight into the metabolism and elimination of lurbinectedin. To evaluate the impact of intrinsic factors such as hepatic impairment and race/ethnicity on lurbinectedin PK parameters, studies were conducted in Japanese patients (A-013) and in patients with hepatic impairment (A-017). To assess the influence of extrinsic factors and potential drug–drug interactions (DDIs), studies A-018 (effect of a strong CYP3A inhibitor) and A-019 (effect of a strong CYP3A inducer) were performed.

Absorption

Lurbinectedin is administered intravenously; therefore, Tmax is achieved immediately upon completion of the 60-minute infusion. No bioavailability or food-effect studies were conducted, which is acceptable

given that lurbinectedin is administered parenterally.

Distribution

Lurbinectedin is highly protein bound (>99%) and primarily found in plasma. The blood-to-plasma partitioning ratio was calculated to be 0.68. A total volume of distribution of 504 L, corresponding to 7.2 L/kg for an average body weight of 70 kg, was estimated from the PopPK model. This relatively large volume of distribution is consistent with the lipophilic properties of lurbinectedin and aligns with findings from nonclinical tissue distribution studies. Lurbinectedin is not expected to cross the blood brain barrier and penetrate into the central nervous system in a clinically relevant manner.

Elimination

Lurbinectedin clearance (11 L/h) and half-life (51 h) were estimated from the reference PopPK model and were found to be generally consistent with the results obtained from NCA analysis.

In the mass balance study, lurbinectedin was given to patients with advanced solid tumours as a single 5.0 mg [^{14}C]-labelled IV dose, followed by non-radiolabelled lurbinectedin 3.2 mg/m² as a 1-hour infusion, consistent with the proposed dosing regimen.

The recovery in the mass balance study was adequate (~94%) with majority of the radioactivity (~83% of the dose) excreted in faeces. Due to the low extraction efficiency (28.5%) and the high proportion of unaccounted faecal radioactivity (78.4%), the EMA DDI guideline requirement to identify ≥80% of recovered radioactivity was not met. Nonetheless, the limited characterisation was largely attributable to redundant metabolism of metabolites in faeces, resulting in numerous low-abundance radioactive components. Therefore, it is reasonable to conclude that no individual faecal metabolite accounts for more than 10% of total faecal excretion. Hence, this issue will not be pursuit further.

Metabolism

The elimination pathway proposed by the Applicant is plausible: lurbinectedin is primarily metabolised by CYP3A4 to form five active metabolites (M1, M2, M3, M4 and M5) which are mainly excreted in faeces (89% of the administered dose). In the mass balance study, M1, M2, M3, and M4 were quantified in plasma, while M5 was detected but not quantified.

The major human metabolites, M1 (14% of parent) and M4 (10% of parent), were also observed in animal species. In rats, M4 exposure exceeded that in humans, whereas M1 exposure in non-human primates (NHPs) was approximately half of that observed in patients. Although M1 was not present at equal or higher exposure levels in animals, further risk assessment is not considered necessary given the proposed indication in advanced cancer (see Non-clinical Assessment 4.5.).

The Applicant measured the major metabolites M1 and M4 in a DDI study involving both induction and inhibition of the primary metabolic enzyme CYP3A4, as well as in a clinical study involving patients with hepatic impairment. As expected, the formation of metabolites M1 and M4 was markedly reduced following administration of a strong CYP3A4 inhibitor itraconazole. Conversely, CYP3A4 induction using the moderate inducer bosentan resulted in an increased conversion to metabolite M1, but not M4. Relevant information on CYP3A4 inducers and inhibitors has been adequately reflected in the SmPC.

In the dedicated hepatic impairment study, patients with moderate and severe hepatic impairment showed significantly higher dose-normalized Cmax and AUC metabolic parent ratios (MPRs) for metabolite M1 compared to those with mild hepatic impairment. For metabolite M4, the differences were not statistically significant, although a trend toward decreased exposure was observed. The Applicant hypothesised that the increased M1/parent lurbinectedin Cmax and AUC ratios may result from CYP3A4 inducibility compensating for hepatic impairment, thereby limiting the impact on parent lurbinectedin metabolism. In contrast, M4 appears to be influenced by hepatic impairment, suggesting

metabolism through a less inducible pathway than CYP3A4 or direct biliary excretion. These results, and their clinical implications, are reflected in the SmPC recommendations for use in hepatic impairment.

Lurbinectedin is produced as a single enantiomer. The Applicant did not address potential *in vivo* interconversion; however, as major metabolites are not formed at chiral centres, this is not considered relevant.

Dose proportionality

The systemic exposure of lurbinectedin is dose-proportional over the dose range of 0.02 to 6.9 mg/m2. All drug-drug interaction (DDI) studies used lurbinectedin dose in the dose proportional range of exposure.

Time dependency

Pharmacokinetics are not time-dependent. No accumulation in plasma lurbinectedin concentrations was observed after repeated doses.

Variability

In the PopPK model, variability in the PK of lurbinectedin was moderate. The inter-individual variability for typical CL was estimated at 50%, while variability in the volumes of distribution, V1, V2, and V3, was 35%, 33%, and 39%, respectively. These findings are generally consistent with the moderate to high inter-patient variability observed in the NCA-derived parameters, where CL and Vss showed coefficients of variation (CV) of 61.3% and 74.4%, respectively.

Intra-patient variability was calculated in study B-005 with the NCA-derived CL and Vss being moderate for CL (33%), and large for Vss (59%). Based on the available data, no additional dose adjustments are considered necessary.

PK in target population

In Study B-005, the total plasma PK of lurbinectedin were similar when NCA was conducted in both the overall population of patients with selected advanced solid tumours and the subpopulation with SCLC, indicating comparable PK profiles between patients with solid tumours and target population.

Therapeutic window

In the FIH study the Applicant identified MTD and the RD for the subsequent Phase II study. In the Phase II study, the dose of 3.2 mg/m2 administered as an 1h IV infusion was confirmed as a dose with improved safety and further used as a dose in following Phase III trials. Hepatic impairment study and DDI inhibition studies were conducted with half of the recommended dose at 1.6 mg/m² of lurbinectedin

Special population

Renal impairment

No dedicated renal impairment study is available since only a minor fraction of lurbinectedin (6% of administered dose) is excreted via kidneys; therefore, renal impairment is not expected to significantly affect the elimination of lurbinectedin. In the population PK dataset, there were 41% of patients categorized as normal renal function, 41% as mild renal impairment, and 18% as moderate renal impairment. Only one patient had severe renal impairment, however 46.4% of patients were not included in popPK analysis due to missing CRCL values.

Overall, population PK analysis did not identify a clinically meaningful difference in lurbinectedin exposure in patients with mild or moderate renal impairment compared to patients with normal renal

function. The effects of severe renal impairment or end-stage renal disease on lurbinectedin exposure have not been studied in sufficient number of patients to estimate the risk; therefore, it should not be administered to these patients. No dose adjustment is recommended on basis of mild and moderate renal impairment, which is found acceptable.

Hepatic impairment

A dedicated study on hepatic impairment was conducted including patients with mild (n=11), moderate (n=8) and severe (n=6) hepatic impairment. Hepatic function was graded according to the NCI-ODWG and Child-Pugh classification criteria, consistent with the recommendations for use in specific patient subgroups described in the SmPC. Mild hepatic impairment had no effect on the pharmacokinetics of lurbinectedin; therefore, based on safety and PK data, no dose adjustment is recommended for patients with mild hepatic impairment. However, due to the potential increase in M1 exposure at 3.2 mg/m² (see the discussion on metabolism above), treatment of these patients at the full dose is not recommended. Patients with moderate hepatic impairment should instead be treated with 50% of the recommended dose (1.6 mg/m² q3wk), and, as a precautionary measure, treatment of patients with severe hepatic impairment should be avoided. If the treatment is deemed necessary, the recommended dose is 1.6 mg/m² q3wk and patients should be monitored for increased adverse reactions (see sections 4.2 and 5.2 of the SmPC).

Ethnic factors

Race as covariate has been evaluated in popPK model. The majority of patients, 76%, were categorized as White, 0.8% as Black, 1.2% as Asian, and for 22% patients' data were missing. However, if missing values are removed from calculation, 97% of patients were White. Given the limited number of Black and Asian race, race as covariate in popPK model is not expected to be identified as significant.

Phase I study (A-013) was conducted in Japanese patients (n=26) treated with lurbinectedin at doses ranging from 1.5 to 3.5 mg/m2. Based on available clinical data, no differences in lurbinectedin PK have been observed between Japanese and non-Japanese patients, and none are expected on the basis of ethnicity. However, the limited number of Asian and Black patients treated with lurbinectedin, together with the moderate inter-subject PK variability, precludes definitive conclusions regarding potential differences. Nevertheless, no recommendations on dosage adjustments are considered necessary based on ethnicity.

Weight

Body weight as covariate was analysed using popPK model. In the data set, median weight was 70 kg with a range from 39-154 kg. Body weight was not found to be statistically significant.

Another covariate related to body weight, was body surface area (BSA) that was analysed in popPK model. In the data set, median BSA was 1.76 m^2 with a range from 1.29-2.65 m^2. BSA was found to be statistically significant, and was retained in that final model. However, further simulation showed that all volumes of distribution increase with BSA increase but not related to total or unbound clearance. Thus, BSA was not considered clinically relevant. However, recommended dosing is 3.2 mg/m^2, and discussion on dosing is provided in appropriate section.

Elderly

The median (range) age in the popPK data set was 61 (18- 85) years and 37% of the patients were above 65 years. In the PopPK analyses, age was not a significant predictor of exposure. Overall, no dose adjustment is required based on age.

Gender

In the PopPK analysis, gender was not statistically significant. In the population PK dataset, 67% of patients were female and 33% were male. Gender retained in the model as significant covariate on intercompartmental clearance for deep compartment (Q3) and apparent volume of distribution of deep peripheral compartment (V3). Females had 19.5% and 24.4% lower V3 and Q3 than males. However, there was no clinically meaningful difference between male and female regrading CL and CLu, thus no dose adjustment is needed.

DDI

In vitro

In vitro, lurbinectedin is predominantly metabolized by CYP3A4, with potential but undetermined role of CYP2D6 and CYP2C19. Lurbinectedin was identified as an *in vitro* inhibitor of CYP2B6, CYP2C8, and CYP3A4 however, these findings are not considered to be clinically relevant.

In vitro CYP induction study RPT02094 was performed in 2008 and therefore was not performed in accordance with CPMP/EWP/560/95/Rev. 1 Corr. 2** Guideline on the investigation of drug interactions. A new CYP induction study compliant with the requirements of ICH M12 is requested as a post-marketing commitment. An update to the SmPC should be implemented upon availability of the results from this study.

Lurbinectedin is a substrate of P-glycoprotein (P-gp, MDR1) however, clinically relevant interactions with P-gp modulators are not expected due to its rapid metabolism via CYP3A4. Lurbinectedin is not a substrate of BCRP and is unlikely to be a substrate of OATP1B1, OATP1B3, OCT1, or MATE1. Other transporters were not investigated, which is acceptable given the minor role of renal elimination (OAT1/OAT3, OCT2, MATE2-K) and the negligible contribution of MRP2 to lurbinectedin disposition.

Lurbinectedin did not inhibit any tested transporter at clinically relevant concentrations.

In silico

Potential effects of co-administration of atezolizumab on lurbinectedin PK and vice versa were explored using popPK modelling.

To explore whether lurbinectedin have an impact on atezolizumab, popPK model publicly available for atezolizumab have been used. Using data as external validation for IMforte study showed adequate performance of the model. Results of the simulation have shown no difference in atezolizumab concentration when taken with lurbinectedin.

To explore whether atezolizumab has an impact on lurbinectedin PK, the reference popPK model was used. Data from IMforte study that were used for external validation of the reference popPK model showed adequate performance of the model. Results of the simulation have shown no difference in lurbinectedin concentration when taken with atezolizumab.

Given that atezolizumab is a monoclonal antibody results of performed popPK models are found clinically plausible and acceptable.

In vivo

The applicant conducted two clinical drug-drug interaction (DDI) studies to evaluate the impact of itraconazole, a strong CYP3A4 inhibitor (Study PM1183-A-018-20), and bosentan, a moderate CYP3A4 inducer (Study PM1183-A-019-20), on the pharmacokinetics (PK) of lurbinectedin, which was evaluated as the victim drug. A lack of a study on the influence of a proton pump inhibitor on lurbinectedin PK is supported since lurbinectedin is administered intravenously. Additionally, a lack of clinical studies with lurbinectedin as a perpetrator of DDI interactions is supported since the risk of clinically important interactions is considered to be negligible.

Co-administration of lurbinectedin with multiple oral doses of itraconazole, a strong CYP3A4 inhibitor, increased total plasma Cmax by 15% and AUCinf by 2.7-fold compared to lurbinectedin administered alone (3.2 mg/m^2, 1-hour i.v. infusion). Unbound lurbinectedin AUCinf increased by 2.4-fold. In addition, the formation of metabolite M1 was almost completely inhibited, and the formation of metabolite M4 was reduced by 69%. Based on these findings, co-administration with strong or moderate CYP3A inhibitors is expected to increase lurbinectedin exposure and should be avoided where possible. If co-administration cannot be avoided, a dose reduction of 50% is recommended.

Co-administration of lurbinectedin with multiple oral doses of bosentan, a moderate CYP3A4 inducer, decreased total plasma lurbinectedin AUCinf by 20% with no statistically significant effect on unbound lurbinectedin exposure. Total plasma clearance increased by approximately 25%, primarily due to increased formation of metabolite M1. These changes are not considered clinically relevant, and co-administration with moderate CYP3A inducers is not expected to have a meaningful impact on lurbinectedin exposure.

Pharmacodynamics

Lurbinectedin (ZEPZELCA) selectively inhibits the oncogenic transcription process leading to subsequent cell cycle arrest and tumour cell apoptosis (for further details please see Non-clinical assessment).

Primary pharmacology

No dedicated clinical studies assessing pharmacodynamic (PD) endpoints in patients have been conducted.

As part of the pharmacodynamic assessment, the applicant conducted exposure–response analyses for both safety and efficacy to support the proposed lurbinectedin dosage regimen of 3.2 mg/m² every three weeks, evaluating the magnitude of the treatment effect on ORR and OS while also taking into account the patient's chemotherapy-free interval (CTFI) status (sensitive vs. resistant). These analyses are considered relevant for the evaluation of the therapeutic effects.

In patients receiving lurbinectedin + atezolizumab (IMforte study), a trend towards lower atezolizumab exposure and faster clearance was observed in ADA-positive participants. Nevertheless, the majority of IMforte participants, irrespective of ADA status, maintained atezolizumab concentrations above the target efficacious threshold of 6 µg/mL and therefore this finding was not considered clinically meaningful.

Secondary pharmacology

The potential for QTc prolongation with lurbinectedin was evaluated in 39 patients with advanced cancer. Large effects (>10 ms) on the QTc interval were not detected with lurbinectedin dosed at 3.2 mg/m² every 21 days.

Pharmacodynamic interactions with other medicinal products or substances

In general, no pharmacodynamic interactions have been identified, and none are anticipated between lurbinectedin and atezolizumab, given their distinct mechanisms of action (cytotoxic DNA disruption and immune checkpoint inhibition). Plasma protein displacement interactions are also not expected, as lurbinectedin plasma concentrations are comparatively low relative to the physiological levels of albumin and AAG.

Relationship between plasma concentration and effect and safety

Exposure-response was performed to characterise the relationship between lurbinectedin exposure and both the efficacy (objective response rate (ORR), duration of response (DoR), and overall survival

(OS)) and safety outcomes (incidence of G4 neutropenia and G≥3 thrombocytopenia), in order to justify dose of 3.2 mg/m2 qwk. Efficacy data were obtained from pivotal study B-005, while safety data were taken from all other clinical studies in which lurbinectedin was administered as single agent.

Regarding efficacy endpoints, positive correlation have been found between lurbinectedin and ORR and OS. In both efficacy endpoints analysis, significant difference have been found in patients categorized as resistant or sensitive.

For sensitive patients, the maximal ORR and median OS were estimated to be 69.1% (95% CI: 49.3-83.8) if lurbinectedin AUCu>1400 ng·h/mL and 15.9 (95% CI: 10.9-19.3) months if lurbinectedin AUCu>1000 ng·h/mL. However, for resistant patients, the maximal ORR and median OS were estimated to be 18.1% (95% CI: 7.7-37.1) if lurbinectedin AUCu>1400 ng·h/mL and 6.2 months (95% CI: 4.3-8.1) if lurbinectedin AUCu>1000 ng·h/mL.

Regarding safety endpoint, as expected, the incidence of neutropenia and thrombocytopenia had a positive and statistically significant relationship with lurbinectedin AUCu, and the magnitude of the association was strongest with the incidence of G4 neutropenia. Lurbinectedin AUCu higher than approximately 1714 ng·h/L resulted in more than 20% increase in the G4 neutropenia incidence, a threshold to initiate primary prophylaxis with G-CSF or have a dose reduction.

Furthermore, the applicant performed additional two exposure-response analysis to explore atezolizumab and lurbinectedin for safety and efficacy in IMforte, a Phase III, randomized study of lurbinectedin in combination with atezolizumab as maintenance therapy in patients with ES-SCLC.

Safety endpoints for lurbinectedin Grade 4 neutropenia and Grade ≥3 thrombocytopenia were found to be statistically significant with increase of lurbinectedin exposure. Other analysed safety endpoints with lurbinectedin (Grade ≥3 AEs, AESI) and atezolizumab (Adverse events of Grades 3 to 5 (AEG35) and AESI) were not found to be statistically significant with exposure increase. This finding is consistent with observed clinical data and only support that there is no higher incidence for safety concern when lurbinectedin is co-administered with atezolizumab.

Overall submitted exposure-response analyses are found supportive as safety and efficacy endpoint were assessed in more detail in dedicated clinical study. Thus, it is not considered as high regulatory impact.

PK/PD Models

Throughout clinical studies, neutropenia and thrombocytopenia were common toxicity which required dose delays, dose reductions or the use of granulocyte colony stimulating factor (GCSF). Thus the applicant used two semi-mechanistic PKPD model to describe the time course of absolute neutrophil counts (ANC) and platelets (PLT) following intravenous administration of lurbinectedin as single agent from two phase I and three phase II trials, in which patients were administered with doses ranging from 0.02 to 6.9 mg/m2 on Day 1 or Days 1 and 8 every three weeks.

Both, thrombocytopenia and neutropenia were found to be reversible, and noncumulative.

Both semi-mechanistic models were found supportive only. Overall, they support the recommendation in SmPC section 4.2 that lurbinectedin can only be administered to patients having ANC count equal or above ≥1.5 x 10^9/L and platelet count ≥ 100 x 10^9/L . Furthermore, the ANC and PLT models were also found supportive in management of neutropenia and thrombocytopenia, notably the dose suspension and reduction described in section 4.2 and 4.4 of the SmPC. See also the section 5.4.12.1. Discussion on clinical safety.

Dose justification

The proposed dose administration of lurbinectedin is 3.2 mg/m^2 by intravenous infusion over 60

minutes repeated every 21 days. Throughout clinical development lurbinectedin has been administered as a single agent in doses ranging from 0.02 to 5.0 mg/m².

Several exposure-response (E-R) and PK/PD model have been performed to justify dosage recommendation. The E-R analyses demonstrate that lurbinectedin exposure was significantly associated with efficacy (ORR and OS) and safety (incidence of G4 neutropenia and G≥3 thrombocytopenia) outcomes. Exposure levels that were found acceptable to reach maximum effect and less toxicity was between 1700 ng·h/L and 1000 ng·h/L. Proposed dosage regimen of 3.2 mg/m2 provides median lurbinectedin AUC_u to be around 1400 ng/ml.

Results of the models indicate better response and lower incidence of toxicity with proposed dosage regimen compared to other dosage regimen (such as a flat dose).

5.2.6.2. Conclusions

A comprehensive clinical pharmacology package has been submitted to support the approval of lurbinectedin. The data are considered adequate to support the proposed indication and dosing recommendations.

5.3. Clinical efficacy

5.3.1. Dose response studies

No dedicated dose-response studies were performed within this application (see clinical pharmacology).

5.3.2. Main study

5.3.2.1. Study GO43104 (IMforte)

5.3.2.1.1. Study GO43104 (IMforte): A Phase III, randomized, open-label, multicenter study of lurbinectedin in combination with atezolizumab compared with atezolizumab as maintenance therapy in participants with extensive-stage small cell lung cancer (ES SCLC) following first-line induction therapy with carboplatin, etoposide and atezolizumab

5.3.2.1.2. Study design

Study GO43104 is a Phase III, randomized, open-label, multicenter study of lurbinectedin in combination with atezolizumab compared with atezolizumab alone administered as maintenance therapy in participants with ES-SCLC after first-line induction therapy with carboplatin, etoposide, and atezolizumab. Participants are required to have an ongoing response or SD per the Response Evaluation Criteria in Solid Tumor (RECIST) v1.1 after completion of 4 cycles of carboplatin, etoposide, and atezolizumab induction treatment in order to be considered for eligibility screening for the maintenance phase. Enrolment was planned for 690 participants, with 450 participants randomised (225 participants per each treatment group).

STUDY TREATMENT IN THE INDUCTION PHASE

Participants eligible for the induction phase were enrolled to receive exactly 4 cycles of standard of

care treatment with carboplatin, etoposide and atezolizumab unless unacceptable toxicity, disease progression or a participant's decision to discontinue occurred, with each cycle being 3 weeks (21 days) in length. All participants were to receive a fixed dose of 1200 mg atezolizumab administered by IV infusion on Day 1 of each 21-day cycle.

STUDY TREATMENT IN THE MAINTENANCE PHASE

Arm A: atezolizumab 1200 mg IV then lurbinectedin 3.2 mg/m2 IV on Day 1 of each 21-day cycle. The lurbinectedin dose is dependent on body surface area (BSA). Prophylactic anti-emetic medication and primary prophylaxis with pegylated G-CSF were administered at the discretion of the treating physician.

All participants received a fixed dose of atezolizumab 1200 mg IV on Day 1 of each 21-day cycle, continued until disease progression (per RECIST v1.1), unacceptable toxicity, or another discontinuation criterion. The atezolizumab dose was not weight or BSA-based, and no dose reductions were permitted, temporary suspensions were allowed for adverse event management.

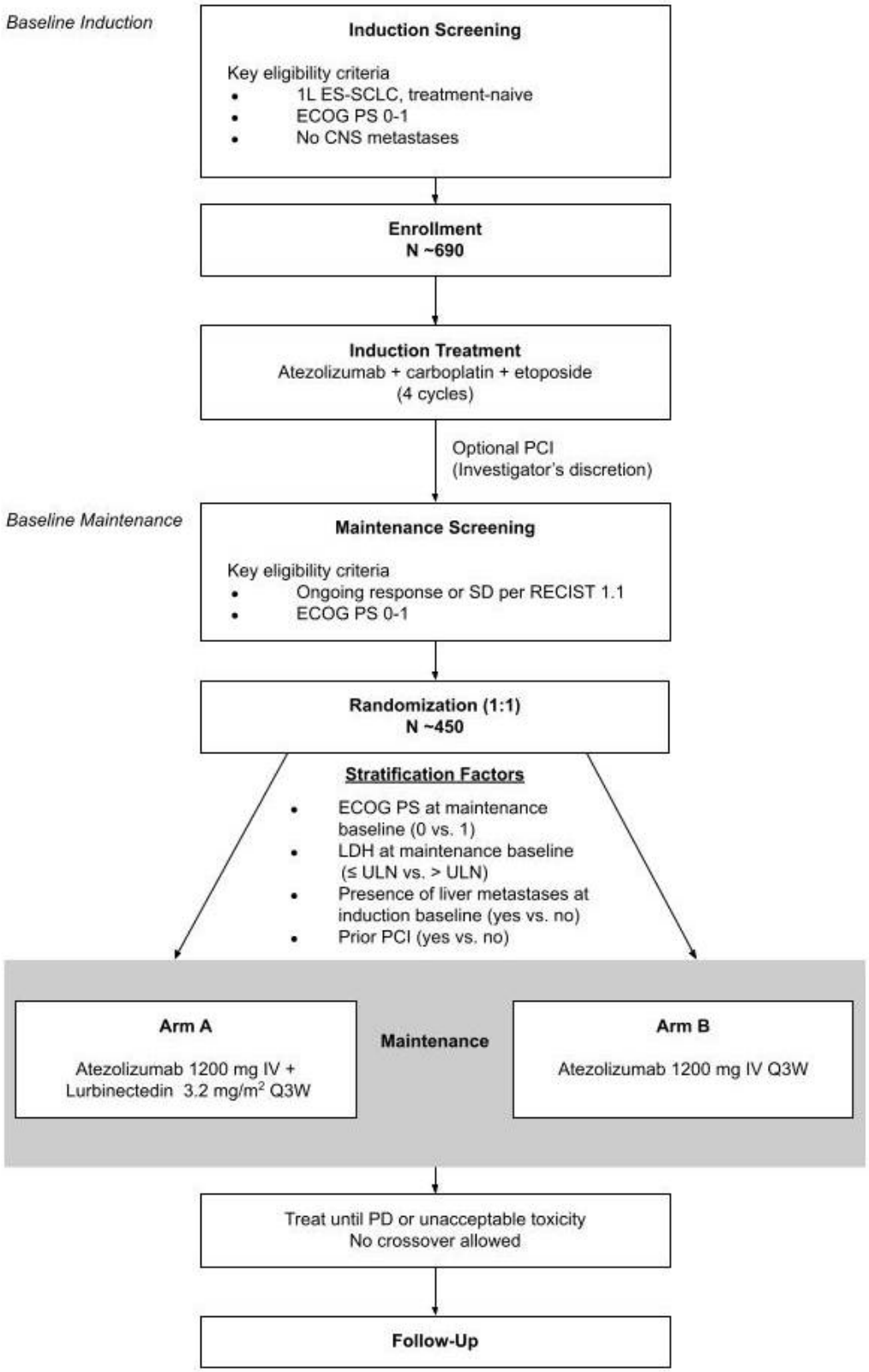
Lurbinectedin dosing allowed up to two reductions: first to 2.6 mg/m² and then to 2.0 mg/m² Q3W. Once reduced, the dose was not allowed to be re-escalated. If toxicity occurred at the 2.0 mg/m² dose, lurbinectedin had to be permanently discontinued.

Atezolizumab and lurbinectedin could be interrupted or discontinued independently, based on the nature and suspected cause of the toxicity. If either lurbinectedin or atezolizumab was delayed due to toxicity, administration should resume with both drugs synchronised.

Arm B: Atezolizumab

Atezolizumab 1200 mg IV on Day 1 of each 21-day cycle.

Figure 12 Study schema for Phase III GO43104 (IMforte)



1L = first-line; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ES-SCLC = extensive-stage small-cell lung cancer; PCI = prophylactic cranial irradiation; PD = progressive disease; Q3W = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; ULN = upper limit of normal.

Randomisation and blinding

The study was a randomized, open-label study. Randomised treatment assignments were concealed from Sponsor personnel (including the medical monitor, statistician, and data manager) to prevent bias in analyses prior to pre-specified efficacy evaluations.

PFS and OS were reviewed by an independent review facility (IRF) through a centralised, review of images, and other clinical data prior to the efficacy analyses. The IRF had no knowledge of randomised treatment assignment.

Randomisation was stratified by:

- Eastern Cooperative Oncology Group (ECOG) performance status (PS) at maintenance baseline (0 vs. 1)
- Lactate dehydrogenase (LDH) at maintenance baseline (≤ upper limit normal ULN vs > ULN) via local laboratory test.
- Presence of liver metastases at induction baseline (yes vs. no).
- Prior receipt of prophylactic cranial irradiation (PCI) (yes vs. no).

Safety oversight was conducted by an independent Data Monitoring Committee (iDMC), with periodic review of unblinded safety data beginning after approximately 24 participants completed 2 maintenance cycles or 6 months from the first maintenance randomization, and every 6 months thereafter. iDMC analyses were prepared by an independent Data Coordinating Center, with final decisions resting with the Sponsor, and any study-impacting outcomes communicated to investigators for IRB/EC notification.

Patient population

This study was conducted at 96 centres in 13 countries: Turkey (17 centres), United States (15), Germany (11), Korea (8), Spain (7), Belgium (6), Poland (6), United Kingdom (6), Greece (5), Italy (5), Hungary (4), Taiwan (4), Mexico (2).

Key Inclusion Criteria – Induction Phase

- ≥18 years at the time of signing the Informed Consent Form.
- ECOG Performance Status of 0 or 1.
- Histologically or cytologically confirmed extensive-stage small-cell lung cancer (ES-SCLC) per the Veterans Administration Lung Study Group (VALG) staging system.
- No prior systemic treatment for ES-SCLC.
  Participants who have received prior chemoradiotherapy for limited-stage SCLC are eligible if:
    - Treatment was given with curative intent, and
    - There is a treatment-free interval of ≥6 months between the last dose of chemotherapy, thoracic radiotherapy, or chemoradiotherapy and the diagnosis of ES-SCLC.
- Adequate Hematologic and End-Organ Function (within 14 days prior to enrolment):
    - ANC ≥1.5 × 10^9/L (1500/μL) for participants of non-African descent, or ≥1.3 × 10^9/L (1300/μL) for participants of African descent without G-CSF support

    - Lymphocyte count ≥0.5 × 10^9/L (500/μL)
    - Platelet count ≥100 × 10^9/L (100,000/μL) without transfusion
    - Haemoglobin ≥90 g/L (9 g/dL); transfusion allowed to meet this criterion
- **Measurable Disease** defined per RECIST v1.1. Previously irradiated lesions were acceptable only if:
  (1) progression has been clearly documented at the site since radiation therapy, and
  (2) the lesion is not the only site of measurable disease.

Key Inclusion Criteria – Maintenance Phase

- ECOG Performance Status of 0 or 1.
- Received **exactly 4 cycles** of induction treatment with carboplatin, etoposide, and atezolizumab.
- Must have achieved CR, PR, or SD by RECIST v1.1 based on radiographic assessment within 28 days prior to randomization.
- Must be randomized:
    - Within 35 days from the last dose of atezolizumab, carboplatin, or etoposide (whichever is latest), or
    - Within 63 days from the last induction dose if prophylactic cranial irradiation (PCI) was administered.
- Maintenance treatment must not begin:
    - <3 weeks (21 days) from Cycle 4 Day 1 of induction, or
    - <2 weeks (14 days) from the last radiotherapy dose
- Adequate hematologic and organ function (same parameters as induction), documented within 7 days prior to randomization.

Key Exclusion Criteria – Induction Phase

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 7 months after the last dose of study treatment.
    - Female participants of childbearing potential must have a negative serum pregnancy test within 14 days prior to enrolment.
- Known or suspected CNS metastases.
    - A contrast-enhanced brain CT or MRI is required at screening; MRI is preferred.
    - Spinal cord compression not definitively treated with surgery and/or radiotherapy, or previously treated but not clinically stable for ≥1 week prior to enrolment.
    - Leptomeningeal disease.
- Participants for whom consolidative thoracic radiotherapy is planned are not eligible.
- Uncontrolled tumour-related pain
- History of autoimmune disease or immune deficiency, including but not limited to:

    - Myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus (SLE), rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, granulomatosis with polyangiitis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis.
- History or evidence of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or active pneumonitis on screening CT, radiation pneumonitis confined to the radiation field (fibrosis) is permitted.
- Cardiovascular Disease
    - Clinically significant cardiovascular conditions within 3 months prior to enrolment:
    - NYHA Class II–IV heart failure
    - Myocardial infarction
    - Stroke or cerebrovascular accident
    - Unstable arrhythmia or angina
    - Participants with stable CAD, CHF (EF ≥50%), or well-controlled conditions may be eligible with cardiologist clearance.
- Prior therapy with:
    - CD137 agonists
    - Immune checkpoint inhibitors (e.g., anti–PD-1, anti–PD-L1, anti–CTLA-4)
    - Lurbinectedin or trabectedin
    - Systemic immunostimulatory agents (e.g., interferons, IL-2) within 4 weeks or 5 half-lives (whichever is longer).
    - Systemic immunosuppressive medications within 1 week prior to enrolment, with exceptions
- Known allergy or hypersensitivity to any component of lurbinectedin or atezolizumab formulations.
- Prior allogeneic stem cell or solid organ transplantation.
- History of malignancy other than SCLC within 5 years prior to enrolment
- Receipt of live, attenuated vaccines within 4 weeks prior to enrolment, or planned during the study and up to:
    - 5 months after the final dose of atezolizumab, or
    - 2 weeks after the last dose of lurbinectedin (whichever is later)

Key Exclusion Criteria – Maintenance Phase

- Uncontrolled pain.
- Lesions (e.g., bone or nerve-impinging metastases) requiring palliative radiotherapy.
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring drainage ≥ once per month.
    - Indwelling catheters are allowed.

- Uncontrolled or symptomatic hypercalcemia (ionized calcium >1.5 mmol/L, calcium >12 mg/dL, or corrected calcium >ULN).
- Major surgery (other than diagnostic) within 4 weeks prior to randomization, or anticipated need during the study.
- Severe infection within 2 weeks prior to randomization, including:
- Use of therapeutic oral or IV antibiotics at the time of randomization is exclusionary, except:

  Prophylactic antibiotics (e.g., for UTI or COPD) are allowed.

5.3.2.1.3. Objectives and estimands

Primary objective

To evaluate the efficacy of lurbinectedin in combination with atezolizumab compared with atezolizumab monotherapy in participants with ES-SCLC, who have an ongoing response or SD after completion of 4 cycles of carboplatin, etoposide, and atezolizumab induction treatment on the basis of IRF-assessed PFS according to RECIST v1.1 and OS.

Estimands for the primary objective

Table 25: Estimands for primary objective

Population	individuals with ES-SCLC who have ongoing CR, PR, or SD after completion of 4 cycles of carboplatin, etoposide, and atezolizumab first-line induction treatment, as defined through the inclusion and exclusion criteria for the maintenance phase
Treatment conditions	Experimental arm: atezolizumab 1200 mg IV + lurbinectedin 3.2 mg/m2 IV on Day 1 of each 21-day cycle Control arm: atezolizumab 1200 mg IV on Day 1 of each 21-day cycle
Endpoint (variable)	• IRF-assessed PFS after randomisation, defined as the time from randomisation to the date of first documented disease progression (as assessed by the IRF according to RECIST v1.1) or death, whichever occurs first • OS after randomisation, defined as the time from randomisation to the date of death from any cause
Population-level summary	• hazard ratio for IRF-assessed PFS • hazard ratio for OS
Intercurrent events and strategy to handle them	
Early discontinuation from study treatment for any reason	treatment policy strategy
Start of non-protocol anti-cancer therapy prior to the	treatment policy strategy

respective event of interest	

The clinical question of interest is:

Is there a difference in overall survival and/or progression-free survival in patients who did not progress after induction therapy consisting of atezolizumab, carboplatin and etoposide, between patients treated with atezolizumab as a maintenance therapy and patients treated with atezolizumab and lurbinectedin as maintenance therapy, regardless of early discontinuation from study treatment for any reason and start of non-protocol anti-cancer therapy prior to the respective event of interest?

Two intercurrent events were considered for both endpoints - early discontinuation from study treatment and start of non-protocol anti-cancer therapy (NPT) prior to the event of interest and for both treatment-policy strategy was applied.

Statistical methods for estimation and sensitivity analysis on primary estimands

The participant analysis sets for the purposes of analyses are:

- Full analysis set (FAS) - All participants randomized into the maintenance phase regardless of whether or not the assigned study treatment is received: participants will be included in the analyses according to the treatment to which they were assigned by IxRS at randomisation
- Safety analysis set (SAS) - All participants who are randomized into the maintenance phase and receive at least 1 dose of atezolizumab or lurbinectedin: participants will be analysed according to the treatment that they received, i.e., participants who receive lurbinectedin in error will be analysed in Arm A for the SAS
- Enrolled analysis set - All participants who are enrolled in the induction phase, regardless of whether or not they receive induction treatment and regardless of whether they are subsequently randomised
- Enrolled SAS - All enrolled participants, who receive at least 1 dose of atezolizumab or carboplatin or etoposide, regardless of whether or not they are subsequently randomised.

Unless otherwise specified, all efficacy analyses were performed in the FAS.

Primary endpoints

Each of the primary endpoints will be compared between two treatment arms based on the stratified log-rank test. The HR will be estimated with use of a stratified Cox regression model, including two-sided 95% confidence intervals (CIs). The stratification factors will be those used for randomisation. The Kaplan-Meier methodology will be used to estimate the median IRF-assessed PFS and median OS for each treatment arm, and Kaplan-Meier curves will be constructed to provide a visual description of the difference between treatment arms. The Brookmeyer-Crowley methodology will be used to construct the 95% CIs for the median IRF-assessed PFS and median OS for each treatment arm. Results from an unstratified analysis will also be provided.

Supplementary and sensitivity analyses are triggered if the threshold percentage of participants is reached for identified intercurrent events or missing data.

For **PFS**:
As a sensitivity analysis, if >5% of participants missed two or more consecutive assessments scheduled immediately prior to the date of disease progression per RECIST v1.1 or the data cut-off in any treatment arm, the following analysis for PFS was to be performed: participants who missed two or more

consecutive scheduled assessments immediately prior to the date of disease progression per RECIST v1.1 or death were to be censored at the last tumour assessment prior to the missed visit.

As a supplementary analysis, if >5% of participants received NPT prior to a PFS event in either treatment arm, a hypothetical strategy was to be employed where participants who start an NPT before a PFS event would be censored at the time of the last tumour assessment before the initiation of NPT.

For **OS**:
As a sensitivity analysis, if >5% of participants were lost to follow-up for OS in either treatment arm, a sensitivity analysis was to be performed for the comparisons between two treatment arms in which participants who are lost to follow-up would be considered as having died at the last date they were known to be alive.

As a supplementary analysis, if >10% of participants received NPT in either treatment arm, hypothetical strategy was to be employed, where for the participants who received non-protocol cancer therapy the duration from initiation of NPT to death or censoring date would be discounted by 10, 20 or 30 % for OS analysis to account for potential survival benefit provided by the supplemental therapy.

Sample size determination

Approximately 920 participants were planned to be screened to achieve the enrolment of 690 participants into the induction phase. Approximately 450 participants were planned to be randomized into this study for an estimated total of 225 participants per treatment group.

The sample size determination was based on the number of events required to demonstrate efficacy with regard to OS in the FAS. The estimate of the number of events required was based on the following assumptions:

- 1:1 randomization ratio
- Two-sided significance level of 0.049 for the comparison of OS
- Approximately 85% power to detect an HR=0.71 in OS, corresponding to an improvement in median OS from 12.5 months to 17.6 months in the FAS
- One planned interim analysis for OS at approximately 68% of the information fraction, with the stopping boundary determined by the Hwang-Shih-DeCani alpha spending function with the gamma parameter of -1.5
- Dropout rate of 5% over 24 months for each treatment arm for OS

With these assumptions, the final OS analysis was to occur when approximately 323 deaths (72% of 450 randomized participants) have been observed in the FAS. With these assumptions, the minimum detectable difference in HR was approximately 0.793 for the final OS analysis. The final OS analysis was expected to occur approximately 41 months after the first participant is randomized.

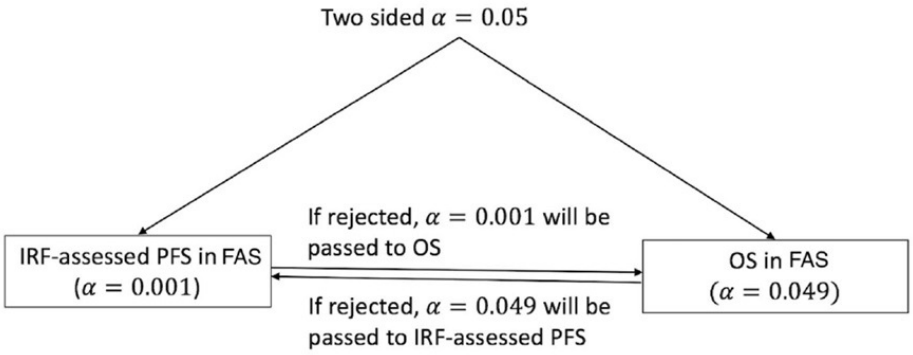
Multiplicity

The overall type I error (α) for this study was 0.05 (2-sided) and was controlled for the primary endpoints of OS and IRF-assessed PFS according to RECIST v1.1 in the FAS with use of a group sequential weighted Holm procedure. A 2-sided α=0.049 and a 2-sided α=0.001 were allocated to OS and IRF-assessed PFS, respectively.

An alpha recycling from IRF-assessed PFS to OS was planned as follows: if the IRF-assessed PFS comparison was not statistically significant at a 2-sided α=0.001, the primary comparison of OS was to be tested at a 2-sided α=0.049; if the IRF-assessed PFS comparison was statistically significant at the

2-sided α=0.001, OS was to be tested at a 2- sided α=0.05. Additionally, if OS was statistically significant at the 2-sided α=0.049, IRF-assessed PFS was to be tested at a 2-sided α=0.05. The overview of the type I error rate control strategy is shown in Figure 13.

Figure 13: Type 1 Error Rate Control Strategy



FAS = Full Analysis Set; IRF-assessed PFS = Independent Review Facility- assessed progression-free survival; OS = overall survival.

Censoring rules for time-to-event endpoints were as follows:

- OS - participants who are not reported as having died by the clinical cutoff date were censored at the date when they were last known to be alive. Participants who do not have information after baseline were censored at the date of randomisation. Participants who are lost to follow-up were censored at the last date they were known to be alive for the primary analysis of OS.
- PFS - participants who have not experienced disease progression and have not died by the clinical cutoff date were censored at the time of the last tumour assessment. Participants who have no tumour assessment after baseline and have not died by the clinical cutoff date were censored at the date of randomisation
- DOR - participants who have not progressed and who have not died at the time of analysis were censored at the time of the last tumour assessment date
- TTCD - data for participants were censored at the last time when they completed an assessment if they have not experienced a confirmed clinically meaningful deterioration at the clinical cutoff date. If no baseline or postbaseline assessment is performed, participants were censored at the randomisation date. According to the while-on-treatment/while-alive strategy, participants who died before reporting any clinically meaningful deterioration were censored at the last time they completed an assessment.

Interim analysis

One interim analysis was planned for OS at approximately 68% of the information fraction, with the stopping boundary determined by the Hwang-Shih-DeCani alpha spending function with the gamma parameter of -1.5.

The primary IRF-assessed PFS analysis was planned to be conducted at the time of the OS interim analysis when approximately 219 deaths have been observed in the FAS or when the minimum follow-up has been completed, whichever occurs later. The minimum follow-up was defined as 5 months after the target sample size of 450 participants has been randomized, or 5 months after the last participant has been randomised in case the final sample size is lower than 450 participants. At the time of the OS interim analysis, it was estimated that approximately 392 PFS events in the FAS will have occurred.

This number of events provides more than 99% power to detect an HR=0.5 in IRF-assessed PFS at a 2-sided significance level of 0.001, based on the following assumptions:

- 1:1 randomisation ratio
- Median PFS of 2.6 months in atezolizumab arm and 5.2 months in the atezolizumab + lurbinectedin arm (corresponding to a target HR=0.5)
- Dropout rate of 5% over 12 months for PFS
- No interim analysis for PFS

With these assumptions, the minimum detectable difference in HR was approximately 0.72 for the IRF-assessed PFS analysis in the FAS.

Projected analysis timing and stopping boundaries for interim and final analysis of OS are given in the Table 26.

Table 26: Analysis timing and stopping boundaries for interim and final analysis of OS

Analysis	Estimated Time from FPI (months)	Information Fraction (Number of Events)	Stopping boundary in 2-sided p-value (HR)	
			If IRF-assessed PFS is not statistically significant	If IRF-assessed PFS is statistically significant
OS IA	*27*	*68*% (219)	p≤*0.0248* (HR≤*0.738*)	p≤*0.0253* (HR≤*0.739*)
OS FA	*41*	100% (*323*)	p≤*0.0372* (HR≤*0.793*)	p≤*0.0380* (HR≤*0.794*)

FA=final analysis; FPI = first participant in the maintenance phase; HR=hazard ratio; IA=interim analysis; IRF-assessed PFS=Independent Review Facility-assessed progression-free survival; OS=overall survival.

Changes from protocol-specified analyses

With Clinical Study Protocol (CSP) version 7 (27 November 2023), substantial changes in the assumptions for sample size calculation, required number of events for the OS analysis and follow-up time duration were introduced.

Rationale for the key changes in the CSP

The change of the statistical testing boundary from O'Brien-Fleming (in v6) to Hwang-Shih-DeCani with the gamma parameter of -1.5 (in v7) was justified by the need to mitigate the potential impact of non-protocol anti-cancer treatments following discontinuation of study treatment on overall survival.

The required number of OS events at the final overall survival analysis has been increased from 313 (event-patient-ratio [EPR] 70%) to 323 (EPR 72%) to maintain the same overall power for overall survival despite the change in the statistical testing boundary.

A minimum follow-up of 5 months from the time of reaching the target sample size of 450 randomized participants has been added to determine the timing of the OS interim analysis in addition to the required target number of 219 OS events. This was done to ensure sufficient minimum follow-up at the time of the interim overall survival analysis.

Secondary objectives

Table 27: Secondary and Exploratory objectives and endpoints for randomized participants

Secondary Objectives	**Endpoints**
To evaluate the efficacy of lurbinectedin in combination with atezolizumab compared with atezolizumab	Investigator-assessed PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first
	Confirmed ORR, defined as the proportion of randomized participants with a CR or PR on two consecutive occasions ≥4 weeks apart after randomization, as determined by the IRF and investigator according to RECIST v1.1
	DOR in participants with measurable disease at baseline, defined as the time from the first occurrence of a documented confirmed objective response after randomization until disease progression as determined by the IRF and investigator according to RECIST v1.1, or death from any cause, whichever occurs first
	PFS rates at 6 months and 12 months, defined as the proportion of participants who have not experienced disease progression or death from any cause at 6 months and 12 months after randomization, as determined by the IRF and investigator according to RECIST v1.1
	OS rates at 12 months and 24 months, defined as the proportion of participants who have not experienced death from any cause at 12 months and 24 months after randomization
To evaluate the safety of lurbinectedin in combination with atezolizumab compared with atezolizumab	Incidence and severity of adverse events, including serious adverse events and adverse events of special interest, with severity determined according to NCI CTCAE v5.0
To evaluate the immunogenicity of atezolizumab with and without lurbinectedin	Prevalence of ADAs to atezolizumab at induction phase baseline and incidence of ADAs to atezolizumab after drug administration
To evaluate the health-related quality of life of participants treated with lurbinectedin in combination with atezolizumab compared with atezolizumab	TTCD from randomization in participant-reported physical functioning and global health status as measured by the EORTC QLQ-C30
Exploratory Objectives	
Objective	**Endpoints**
To evaluate the safety and tolerability of lurbinectedin in combination with atezolizumab compared with atezolizumab	Change from baseline in targeted vital signs, Change from baseline in targeted clinical laboratory test results
To evaluate the tolerability of lurbinectedin in combination with atezolizumab compared	Presence, frequency of occurrence, severity, and/or degree of interference with daily function of symptomatic treatment toxicities as assessed through

with atezolizumab from the participant's perspective	use of the NCI PRO-CTCAE, Change from baseline in severity of selected symptomatic treatment toxicities as assessed by the NCI PRO-CTCAE
To evaluate the health-related quality of life of participants treated with lurbinectedin in combination with atezolizumab compared with atezolizumab	Change from baseline in PROS of HRQOL, physical functioning and global health status as assessed by the EORTC QLQ-C30, Change from baseline in lung cancer-related symptoms as assessed by the EORTC QLQ-LC13, Frequency of response by arm and by time point of the EORTC IL46 single item for bothered by treatment effects
To characterize the PK profile of lurbinectedin and atezolizumab	Plasma concentration of lurbinectedin at specified timepoints, Serum concentration of atezolizumab at specified timepoints
To evaluate the potential effects of atezolizumab immunogenicity	Relationship between atezolizumab ADA status and efficacy, safety, or PK endpoints

Abbreviations: PFS: Progression-Free Survival, ORR: Overall Response Rate, DOR: Duration of Response, OS: Overall Survival, ADAs: Anti-Drug Antibodies, TTCD: Time To Deterioration, EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30, IRF: Independent Review Facility, NCI CTCAE v5.0: National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0, RECIST v1.1: Response Evaluation Criteria in Solid Tumors version 1.1

Estimands for the secondary objectives

Estimands for secondary objectives and endpoints were not explicitly presented in the study protocol or SAP, i.e. possible intercurrent events and strategy to handle them were not listed.

Table 28: Secondary and Exploratory objectives and endpoints for randomized participants

Secondary Objectives	Estimands
To evaluate the efficacy of lurbinectedin in combination with atezolizumab compared with atezolizumab	Population: The same as for primary objective Treatment conditions: The same as for primary objective Endpoint (variable): Investigator-assessed PFS Population-level summary: hazard ratio (HR)
	Population: individuals with ES-SCLC who have ongoing CR, PR, or SD and measurable disease after completion of 4 cycles of carboplatin, etoposide, and atezolizumab first-line induction treatment, as defined through the inclusion and exclusion criteria for the maintenance phase Treatment conditions: The same as for primary objective Endpoint (variable): Confirmed ORR as determined by the IRF and investigator Population-level summary: • difference in IRF-assessed ORR • difference in investigator-assessed ORR

	Population: individuals with ES-SCLC who have ongoing CR, PR, or SD and measurable disease after completion of 4 cycles of carboplatin, etoposide, and atezolizumab first-line induction treatment, as defined through the inclusion and exclusion criteria for the maintenance phase and who had a confirmed objective response in the maintenance phase Treatment conditions: The same as for primary objective Endpoint (variable): Duration of response (DOR) as determined by the IRF and investigator Population-level summary: • hazard ratio for IRF-assessed DOR • hazard ratio for investigator-assessed DOR
	Population: The same as for primary objective Treatment conditions: The same as for primary objective Endpoint (variable): PFS rate Population-level summary: • difference in PFS at 6 months • difference in PFS at 12 months
	Population: The same as for primary objective Treatment conditions: The same as for primary objective Endpoint (variable): OS rates Population-level summary: • difference in OS at 12 months • difference in OS at 24 months
To evaluate the health-related quality of life of participants treated with lurbinectedin in combination with atezolizumab compared with atezolizumab	Population: The same as for primary objective Treatment conditions: The same as for primary objective Endpoint (variable): • TTCD in Physical Functioning • TTCD in Global Health Status/Quality of Life Population-level summary: • hazard ratio for TTCD in Physical Functioning • hazard ratio for TTCD in Global Health Status/Quality of Life

Statistical methods for estimation and sensitivity analysis on the secondary estimands

Secondary efficacy endpoints

Investigator-assessed **PFS** has the same censoring rules and will be analysed through use of the same methods as the IRF-assessed PFS.

The analysis set for confirmed objective response rate (**ORR**) was the FAS with measurable disease at baseline. All participants not meeting the criteria for confirmed objective response, including participants without any post-baseline tumour assessment, were considered non-responders. An estimate of confirmed ORR and its 95% CI was calculated with use of the Clopper-Pearson method for each treatment arm. Confidence intervals for the difference in confirmed ORRs between the two treatment arms was determined with use of the normal approximation to the binomial distribution.

Duration of response (**DOR**) was assessed in participants who had a confirmed objective response according to RECIST v1.1 in the FAS. Participants who had not progressed and who had not died at the time of analysis were censored at the time of the last tumour assessment date. Duration of response is based on a non-randomised subset of participants (specifically, participants who achieved a confirmed objective response); therefore, formal hypothesis testing was not performed for this endpoint. Comparisons between treatment arms was made for descriptive purposes. The same methodology described for other time-to event endpoints was used.

The IRF-assessed and investigator-assessed **PFS rates at 6 months** and at **12 months** after randomisation and the **OS rates at 12 months** and **24 months** after randomisation were estimated with use of the Kaplan-Meier methodology for each treatment arm, along with 95% CIs calculated with use of the standard error derived from Greenwood's formula. The 95% CI for the difference in PFS/OS rates between the two treatment arms was estimated with use of the normal approximation method.

Secondary endpoint assessing the health-related quality of life

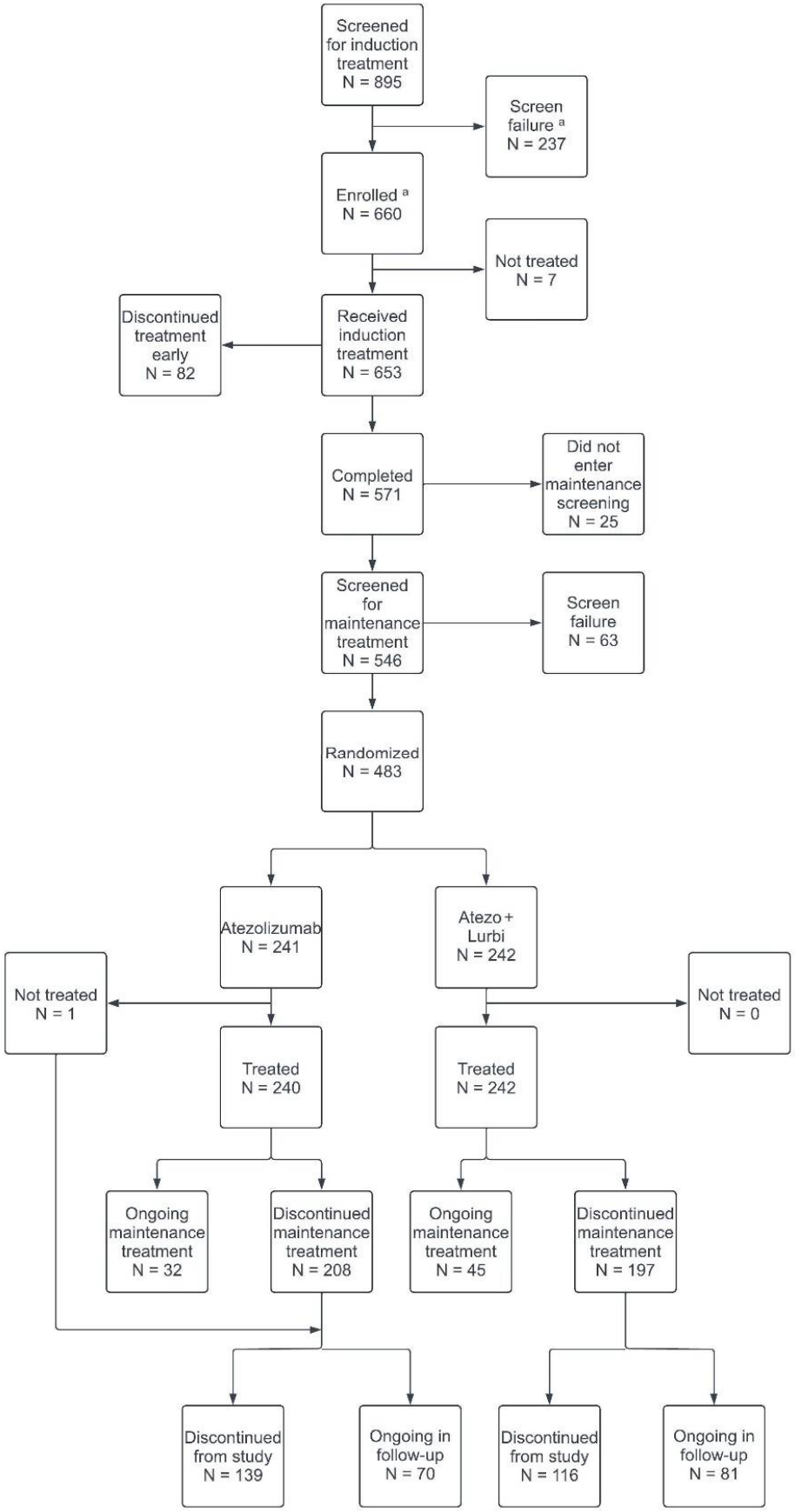
Confirmed clinically meaningful deterioration for physical functioning and Global Health Status (GHS)/Quality of Life (QoL)was defined as a clinically meaningful decrease from baseline in the physical functioning or GHS/QoL scores (a score change of ≥ 10-point change in GHS/QoL and functional subscale scores) that must be held for at least two consecutive assessments or an initial clinically meaningful decrease above baseline followed by death attributable to cancer progression within 6 weeks of the last deteriorated PRO assessment. For time to confirmed deterioration (**TTCD**), data for participants were censored at the last time when they completed an assessment if they had not experienced a confirmed clinically meaningful deterioration at the clinical cutoff date. If no baseline or postbaseline assessment was performed, participants were censored at the randomisation date. According to the while-on-treatment/while-alive strategy, participants who died before reporting any clinically meaningful deterioration were censored at the last time they completed an assessment. Time to confirmed deterioration using the EORTC scale was analysed with use of the same methods as for PFS.

5.3.2.1.4. Results

Participant flow and numbers analysed

The first participant was enrolled on 17 November 2021, and the last participant was enrolled on 11 January 2024. Data cut-off date for the interim analysis: 29 July 2024. Data cut-off date for the updated OS analysis: 12 February 2025.

Figure 14: Participant flow (DCO date: 29 July 2024)



A total of 546 participants were screened for the randomised phase of the study. 63 participants failed screening; based on information collected on the interactive voice or Web-based response system (IxRS), mainly due to "non-completion of induction phase or disease progression".

Table 29: Summary of Participants Who Discontinued from Treatment in the Randomised Phase (Safety Analysis Set)

	Atezolizumab (N=240)	Atezolizumab+Lurbinectedin (N=242)	
	Atezolizumab	Atezolizumab	Lurbinectedin
Treatment Status	240	242	242
Ongoing	32 (13.3%)	45 (18.6%)	44 (18.2%)
Discontinued Maintenance Treatment	208 (86.7%)	197 (81.4%)	198 (81.8%)
Reason for Discontinuation of Maintenance Treatment			
Progressive Disease	185 (88.9%)	160 (81.2%)	155 (78.3%)
Death	6 (2.9%)	16 (8.1%)	16 (8.1%)
Adverse Event	9 (4.3%)	6 (3.0%)	13 (6.6%)
Withdrawal by Subject	2 (1.0%)	9 (4.6%)	8 (4.0%)
Symptomatic Deterioration	5 (2.4%)	5 (2.5%)	5 (2.5%)
Physician Decision	1 (0.5%)	1 (0.5%)	1 (0.5%)

Data Cutoff: 29JUL2024; Rave Data Extracted: 01OCT2024.

Table 30: Disposition of participants in randomised phase (Full Analysis Set)

	Atezolizumab (N=241)	Atezolizumab+ Lurbinectedin (N=242)	All Patients (N=483)
Received Maintenance Treatment	240 (99.6%)	242 (100%)	482 (99.8%)
Randomization Phase Status	241 (100%)	242 (100%)	483 (100%)
Ongoing	102 (42.3%)	126 (52.1%)	228 (47.2%)
Discontinued	139 (57.7%)	116 (47.9%)	255 (52.8%)
Reason for Discontinuation from Randomization Phase	139 (57.7%)	116 (47.9%)	255 (52.8%)
Death	135 (56.0%)	112 (46.3%)	247 (51.1%)
Withdrawal by Subject	1 (0.4%)	3 (1.2%)	4 (0.8%)
Lost to Follow-up	1 (0.4%)	1 (0.4%)	2 (0.4%)
Progressive Disease	2 (0.8%)	0	2 (0.4%)

Data Cutoff: 29JUL2024; Rave Data Extracted: 01OCT2024.

Table 31: Summary of intercurrent events for primary endpoints, Full Analysis Set

	Progression-Free Survival per IRF		**Overall Survival**	
	Atezolizumab (N=241)	**Atezolizumab + Lurbinectedin (N=242)**	**Atezolizumab (N=241)**	**Atezolizumab + Lurbinectedin (N=242)**
Early discontinuation from any study treatment for any reason	208 (86.3%)	199 (82.2%)	208 (86.3%)	199 (82.2%)
Start of non-protocol systemic anticancer therapy	6 (2.5%)	14 (5.8%)	76 (31.5%)	55 (22.7%)

IRF, Independent Review Facility.

Table 32: Summary of analysis population

	Atezolizumab (N=241)	Atezolizumab+ Lurbinectedin (N=242)	All Patients (N=483)
Full analysis set (FAS)	241	242	483
Safety analysis set (SAS)	240	242	482
Randomized Atezo PK evaluable set	233	234	467
Lurbi PK evaluable set	0	234	234
Randomized Atezo ADA evaluable set	239	242	481

Data Cutoff: 29JUL2024; Rave Data Extracted: 01OCT2024.

Deviations from study plan

Changes in the planned conduct of the study

The first version of the protocol was issued on 11 August 2021. Thereafter, the protocol was globally amended six times, with Version 7 in effect at the time of clinical cut-off date (CCOD; 29 July 2024).

Key changes included:

Version 2 (22 September 2021)

- The safety management guidelines for atezolizumab were updated to no longer allow temporarily interrupting treatment with atezolizumab for Grade 2 immune-mediated myocarditis and treatment with atezolizumab must be permanently discontinued for immune-mediated myocarditis Grade ≥2.
- The safety management guidelines were also updated to include management guidelines for symptomatic hyperthyroidism.
- It was clarified that atezolizumab must be permanently discontinued if the adverse event for which atezolizumab had been interrupted does not improve or resolve to Grade ≤1 within 12 weeks of initiating steroids or for inability to reduce prednisone to ≤10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Version 3 (3 December 2021)

- Laboratory test values defining the adequate hematologic and end-organ function required to be eligible to enter the enrolment phase of the study were added to the inclusion criteria to align with the eligibility criteria of the maintenance phase.
- Exclusion criteria from the enrolment phase that may start after enrolment and that may not be covered by exclusions through prohibited therapies or mandated treatment discontinuations due to toxicity or progressive disease have been added to the list of exclusion criteria for the maintenance phase.

Version 4 (18 February 2022)

- The safety management guidelines for atezolizumab were updated to align with atezolizumab Investigator's Brochure Version 18.
- It was clarified that the number of enrolled participants will be adjusted in accordance with the actual screen failure rate observed during maintenance screening to achieve the required sample size of the maintenance population (450 participants).

- The inclusion criteria for the induction study phase were updated to allow participants with lesions (e.g., bone metastases or metastases causing nerve impingement) requiring palliative radiotherapy in the induction study phase to be eligible for the study to broaden eligibility for the study and the list of permitted therapies was updated accordingly.

Version 5 (19 September 2022)

- Rhabdomyolysis was added as a risk associated with lurbinectedin and safety information was revised accordingly.
- The list of identified risks for atezolizumab was revised to include pericardial disorders.
- The adverse event management guidelines were updated to align with the atezolizumab Investigator's Brochure Version 19.
- In order to reduce the risk of extravasation during a lurbinectedin infusion, a recommendation was added to use a central venous catheter, particularly in participants with limited venous access. Additionally, details on the risk of infusion site reactions and their management were added.

Version 6 (23 February 2023)

- The list of adverse events of special interest and list of identified risks for atezolizumab were revised to include myelitis and facial paresis.
- Hemophagocytic lymphohistiocytosis was updated from a potential risk to an identified risk associated with atezolizumab and language was revised accordingly.
- The adverse event management guidelines were updated to align with the Addendum 1 and Addendum 2 to the atezolizumab Investigator's Brochure Version 19.

Version 7 (27 November 2023)

- To mitigate the potential impact of non-protocol anti-cancer treatments following discontinuation of study treatment on overall survival, the statistical testing boundary was changed from O'Brien-Fleming to Hwang-Shih-DeCani with the gamma parameter of -1.5.
- The required number of OS events at the final overall survival analysis has been increased from 313 (EPR 70%) to 323 (EPR 72%) to maintain the same overall power for overall survival despite the change in the statistical testing boundary.
- To ensure sufficient minimum follow-up at the time of the interim overall survival analysis, a minimum follow-up of 5 months from the time of reaching the target sample size of 450 randomised participants was added to determine the timing of the OS interim analysis in addition to the required target number of 219 OS events. If the final number of randomised participants is below 450, the minimum follow-up would be 5 months from the randomisation of the last participant.
- The adverse event management guidelines were updated to align with the atezolizumab Investigator's Brochure Version 20.

No audits were conducted for this study. A serious GCP non-compliance (SNC) has been reported as detailed below:

One site in the UK failed to timely inform participants of updates to the atezolizumab safety information of pericardial disorder. Such information was initially communicated to sites via Dear Investigator Letter (DIL) by the sponsor and was classified by the MHRA as an Urgent Safety Measure DIL on 01 August 2022. On 10 August 2022, the site was requested to verbally inform all of their

participants of the risks and record willingness to continue in the study prior to their next dose of atezolizumab; however, participants were not verbally informed of the new safety information according to these requirements and there were delays in re-consenting participants to the updated ICF containing the updated safety information. This issue was reported for assessment as a potential SNC on 18 April 2024. On 25 April 2024, GCP council determined this issue met the criteria of an SNC due to the impact on patient safety and patient rights. The MHRA was notified on 25 April 2024.

Protocol deviations

Table 33: Summary of major protocol deviations (FAS)

	Atezolizumab (N=241)	Atezolizumab+ Lurbinectedin (N=242)	All Patients (N=483)
Total number of patients with at least one major deviation	87 (36.1%)	99 (40.9%)	186 (38.5%)
Overall total number of major deviations	131	163	294
Inclusion criteria			
Total number of patients with at least one major deviation	22 (9.1%)	28 (11.6%)	50 (10.4%)
Overall total number of major deviations	22	30	52
Adequate hematologic and end organ function	0	2 (0.8%)	2 (0.4%)
Inclusion-related test not done	13 (5.4%)	13 (5.4%)	26 (5.4%)
Missed tumor assessment during induction or maintenance screening	4 (1.7%)	9 (3.7%)	13 (2.7%)
Procedural, i.e., inclusion-related test done out of window	4 (1.7%)	5 (2.1%)	9 (1.9%)
Submission of pre-induction tumor sample	1 (0.4%)	1 (0.4%)	2 (0.4%)
Exclusion criteria			
Total number of patients with at least one major deviation	2 (0.8%)	2 (0.8%)	4 (0.8%)
Overall total number of major deviations	2	2	4
Randomization of patient with disease progression following induction therapy	2 (0.8%)	2 (0.8%)	4 (0.8%)
Medication			
Total number of patients with at least one major deviation	5 (2.1%)	10 (4.1%)	15 (3.1%)
Overall total number of major deviations	7	10	17
Administration of commercial atezolizumab or lurbinectedin	1 (0.4%)	0	1 (0.2%)
Continuation of study drug beyond discontinuation criteria	2 (0.8%)	1 (0.4%)	3 (0.6%)
Dose missed or administered outside the protocol-allowed window (excludes protocol allowed delays)	2 (0.8%)	9 (3.7%)	11 (2.3%)
Dosing error resulting in a dose deviation by more than 10% from planned dose	1 (0.4%)	0	1 (0.2%)
Procedural			
Total number of patients with at least one major deviation	69 (28.6%)	80 (33.1%)	149 (30.8%)
Overall total number of major deviations	100	121	221
Breach of patient confidentiality	1 (0.4%)	0	1 (0.2%)
Error with stratification	17 (7.1%)	25 (10.3%)	42 (8.7%)
Failure to report SAE or pregnancy within 24 hours of learning of the event	7 (2.9%)	5 (2.1%)	12 (2.5%)
ICF - Late re-consent to an updated ICF describing new safety risks	4 (1.7%)	7 (2.9%)	11 (2.3%)
ICF - other procedural issues	0	1 (0.4%)	1 (0.2%)
Missing maintenance BASELINE PRO assessment	18 (7.5%)	13 (5.4%)	31 (6.4%)
Omission of significant safety-related lab test within 4 days prior to study drug administration	27 (11.2%)	27 (11.2%)	54 (11.2%)
Tumor assessment omitted or performed outside of the protocol-specified window	17 (7.1%)	20 (8.3%)	37 (7.7%)

Percentages are of the total number of patients in the analysis population, as given in the column headings.
For frequency counts by deviation, multiple occurrences of the same deviation in an individual are counted only once.
For the total number of deviations, multiple occurrences of the same deviation in an individual are counted separately.
Includes major protocol deviations after the last dose of induction treatment in the Enrollment Phase.
Note that the subcategory of 'Failure to report SAE or pregnancy within 24 hours of learning of the event' only displays deviations regarding to late SAE reporting given that there were no pregnancies on the study (see Section 5.2.3.3)
Data Cutoff: 29JUL2024; Rave Data Extracted: 01OCT2024.

Baseline data

Table 34: Summary of Demographics and Baseline Characteristics (FAS)

	Atezolizumab (N=241)	Atezolizumab+ Lurbinectedin (N=242)	All Patients (N=483)
Age (years) at Randomization			
n	241	242	483
Mean (SD)	66.0 (8.0)	65.1 (7.6)	65.5 (7.8)
Median	67.0	65.0	66.0
Min - Max	35 - 85	38 - 85	35 - 85
Age Group at Randomization			
n	241	242	483
<65	90 (37.3%)	118 (48.8%)	208 (43.1%)
>=65	151 (62.7%)	124 (51.2%)	275 (56.9%)
Region			
n	241	242	483
Asia-Pacific	31 (12.9%)	30 (12.4%)	61 (12.6%)
Europe and Middle East	190 (78.8%)	194 (80.2%)	384 (79.5%)
North America	17 (7.1%)	14 (5.8%)	31 (6.4%)
Central and South America	3 (1.2%)	4 (1.7%)	7 (1.4%)
Sex			
n	241	242	483
Male	151 (62.7%)	151 (62.4%)	302 (62.5%)
Female	90 (37.3%)	91 (37.6%)	181 (37.5%)
Race			
n	241	242	483
American Indian or Alaska Native	0	1 (0.4%)	1 (0.2%)
Asian	31 (12.9%)	31 (12.8%)	62 (12.8%)
Black or African American	1 (0.4%)	3 (1.2%)	4 (0.8%)
White	199 (82.6%)	195 (80.6%)	394 (81.6%)
Not Reported	10 (4.1%)	12 (5.0%)	22 (4.6%)
Ethnicity			
n	241	242	483
Hispanic or Latino	16 (6.6%)	16 (6.6%)	32 (6.6%)
Not Hispanic or Latino	210 (87.1%)	206 (85.1%)	416 (86.1%)
Not Reported	15 (6.2%)	20 (8.3%)	35 (7.2%)
Weight (kg) at Randomization			
n	240	239	479
Mean (SD)	74.6 (16.3)	75.8 (16.8)	75.2 (16.6)
Median	72.8	74.2	73.3
Min - Max	42 - 155	41 - 169	41 - 169
Tobacco Use History			
n	241	242	483
Never	5 (2.1%)	7 (2.9%)	12 (2.5%)
Current	73 (30.3%)	88 (36.4%)	161 (33.3%)
Previous	163 (67.6%)	147 (60.7%)	310 (64.2%)
ECOG PS at Enrollment			
n	241	242	483
0	93 (38.6%)	101 (41.7%)	194 (40.2%)
1	148 (61.4%)	141 (58.3%)	289 (59.8%)
ECOG PS at Randomization (eCRF)			
n	241	242	483
0	102 (42.3%)	105 (43.4%)	207 (42.9%)
1	139 (57.7%)	137 (56.6%)	276 (57.1%)
ECOG PS at Randomization (IxRS)			
n	241	242	483
0	102 (42.3%)	103 (42.6%)	205 (42.4%)
1	139 (57.7%)	139 (57.4%)	278 (57.6%)
LDH at Randomization (eCRF)			
n	241	242	483
<=ULN	179 (74.3%)	176 (72.7%)	355 (73.5%)
>ULN	62 (25.7%)	66 (27.3%)	128 (26.5%)

	Atezolizumab (N=241)	Atezolizumab+ Lurbinectedin (N=242)	All Patients (N=483)
LDH at Randomization (IxRS)			
n	241	242	483
<=ULN	177 (73.4%)	180 (74.4%)	357 (73.9%)
>ULN	64 (26.6%)	62 (25.6%)	126 (26.1%)
Liver Metastases at Enrollment (eCRF)			
n	241	242	483
Yes	94 (39.0%)	100 (41.3%)	194 (40.2%)
No	147 (61.0%)	142 (58.7%)	289 (59.8%)
Liver Metastases at Enrollment (IxRS)			
n	241	242	483
Yes	87 (36.1%)	88 (36.4%)	175 (36.2%)
No	154 (63.9%)	154 (63.6%)	308 (63.8%)
Prior Receipt of PCI (eCRF)			
n	241	242	483
Yes	37 (15.4%)	34 (14.0%)	71 (14.7%)
No	204 (84.6%)	208 (86.0%)	412 (85.3%)
Prior Receipt of PCI (IxRS)			
n	241	242	483
Yes	35 (14.5%)	34 (14.0%)	69 (14.3%)
No	206 (85.5%)	208 (86.0%)	414 (85.7%)

Data Cutoff: 29JUL2024; Rave Data Extracted: 01OCT2024.

Table 35: Summary of Baseline Disease Characteristics (FAS)

	Atezolizumab (N=241)	Atezolizumab+ Lurbinectedin (N=242)	All Patients (N=483)
Initially diagnosed with LS-SCLC prior to progressing to ES-SCLC			
n	241	242	483
Yes	17 (7.1%)	15 (6.2%)	32 (6.6%)
No	222 (92.1%)	220 (90.9%)	442 (91.5%)
Unknown	2 (0.8%)	7 (2.9%)	9 (1.9%)
Staging Type at Time of ES-SCLC			
n	241	242	483
Clinical	98 (40.7%)	107 (44.2%)	205 (42.4%)
Pathological	143 (59.3%)	135 (55.8%)	278 (57.6%)
Primary Tumor Stage at Enrollment			
n	238	242	480
TX	14 (5.9%)	11 (4.5%)	25 (5.2%)
T1	21 (8.8%)	19 (7.9%)	40 (8.3%)
T2	31 (13.0%)	31 (12.8%)	62 (12.9%)
T3	32 (13.4%)	58 (24.0%)	90 (18.8%)
T4	140 (58.8%)	123 (50.8%)	263 (54.8%)
Regional Lymph Node			
n	239	242	481
NX	10 (4.2%)	6 (2.5%)	16 (3.3%)
N0	9 (3.8%)	8 (3.3%)	17 (3.5%)
N1	15 (6.3%)	12 (5.0%)	27 (5.6%)
N2	96 (40.2%)	103 (42.6%)	199 (41.4%)
N3	109 (45.6%)	113 (46.7%)	222 (46.2%)
Distant Metastases			
n	241	242	483
M0	16 (6.6%)	12 (5.0%)	28 (5.8%)
M1A	45 (18.7%)	69 (28.5%)	114 (23.6%)
M1B	38 (15.8%)	46 (19.0%)	84 (17.4%)
M1C	142 (58.9%)	115 (47.5%)	257 (53.2%)
Time to Enroll from LS-SCLC Dx (months)			
n	12	6	18
Mean (SD)	13.8 (7.2)	17.0 (9.0)	14.9 (7.7)
Median	14.8	16.3	14.8
Min - Max	2 - 24	4 - 30	2 - 30
Time to Enroll from ES-SCLC Dx (months)			
n	229	237	466
Mean (SD)	0.8 (0.6)	0.8 (0.6)	0.8 (0.6)
Median	0.6	0.7	0.7
Min - Max	0 - 5	0 - 3	0 - 5
Time to Rand from LS-SCLC Dx (months)			
n	12	6	18
Mean (SD)	17.1 (7.3)	20.0 (9.1)	18.1 (7.8)
Median	18.1	19.3	18.1
Min - Max	4 - 27	7 - 34	4 - 34
Time to Rand from ES-SCLC Dx (months)			
n	229	237	466
Mean (SD)	4.0 (0.8)	4.0 (0.7)	4.0 (0.7)
Median	3.9	3.9	3.9
Min - Max	3 - 8	3 - 6	3 - 8
Lung Metastases at Enrollment			
n	241	242	483
Yes	224 (92.9%)	221 (91.3%)	445 (92.1%)
No	17 (7.1%)	21 (8.7%)	38 (7.9%)
Response to induction treatment			
n	240	236	476
CR/PR	213 (88.8%)	206 (87.3%)	419 (88.0%)
SD	25 (10.4%)	28 (11.9%)	53 (11.1%)
PD	2 (0.8%)	2 (0.8%)	4 (0.8%)

Data Cutoff: 29JUL2024; Rave Data Extracted: 01OCT2024.

Table 36 Summary of baseline disease characteristics per IRF, Full Analysis Set

	Atezolizumab (N=241)	Atezolizumab+ Lurbinectedin (N=242)	All Patients (N=483)
Number of Metastatic Sites at Maintenance Baseline per IRF			
n	211	208	419
Mean (SD)	2.15 (1.15)	2.08 (1.03)	2.11 (1.09)
Median	2.00	2.00	2.00
Min - Max	1.0 - 7.0	1.0 - 5.0	1.0 - 7.0
Sum of Diameters (mm) at Maintenance Baseline per IRF			
n	182	175	357
Mean (SD)	58.48 (43.59)	52.34 (37.52)	55.47 (40.78)
Median	46.00	42.00	44.00
Min - Max	11.0 - 270.0	13.0 - 272.0	11.0 - 272.0
Measurable Disease at Maintenance Baseline per IRF			
N	59 (24.5%)	67 (27.7%)	126 (26.1%)
Y	182 (75.5%)	175 (72.3%)	357 (73.9%)

Multiple lesions in the same site in one individual are counted only once.
Data Cutoff: 29JUL2024; Rave Data Extracted: 01OCT2024.

Table 37: Summary of Prior Cancer Therapy (FAS)

	Atezolizumab (N=241)	Atezolizumab+ Lurbinectedin (N=242)	All Patients (N=483)
Total number of patients with at least one therapy	12 (5.0%)	8 (3.3%)	20 (4.1%)
Total number of therapies	23	18	41
Therapy Type			
Chemotherapy	11 (4.6%)	8 (3.3%)	19 (3.9%)
Targeted therapy	0	1 (0.4%)	1 (0.2%)
Other	1 (0.4%)	0	1 (0.2%)

Investigator text for medications is encoded using WHODrug Global B3 Format dictionary (version March 1, 2024).
Data Cutoff: 29JUL2024; Rave Data Extracted: 01OCT2024.

In the FAS, 9.5% of participants underwent cancer surgery prior to enrolment into the induction treatment phase with the most common procedure being a biopsy of the lung (2.9%). Moreover, 7.9% of participants had received radiotherapy before enrolment into the induction treatment phase. Overall, 14.7% of randomized participants had received prophylactic cranial irradiation (PCI) prior to randomization.

On-study and follow-up non-protocol local and systemic anti-cancer therapies

In the FAS as of the DCO date of 12 February 2025, a small number of participants received radiotherapy during the randomised phase (2 participants in the atezolizumab + lurbinectedin arm and 5 participants in the atezolizumab arm). Overall, 34.4% of randomised participants in the FAS received follow-up radiotherapy. The most commonly irradiated site was the brain. Compared with the atezolizumab arm, in the atezolizumab + lurbinectedin arm, a higher proportion of participants received radiotherapy to the brain and a lower proportion received radiotherapy to the lung. Moreover, no participants in the atezolizumab + lurbinectedin arm and 3 participants in the atezolizumab arm had at least one on-study cancer surgical procedure during the randomized phase. Overall, in the FAS as of the DCO date of 12 February 2025, 5 participants in the atezolizumab + lurbinectedin arm and 2 participants in the atezolizumab arm had at least one follow-up cancer surgical procedure after discontinuation of study treatment.

In the FAS as of the DCO date of 12 February 2025, a lower proportion of participants in the atezolizumab + lurbinectedin arm received follow-up non-protocol systemic anti-cancer therapy than in the atezolizumab arm (53.7% vs. 60.6%, respectively), with the difference driven by follow-up chemotherapy (44.2% and 56.0%, respectively). No participants in the atezolizumab + lurbinectedin arm received lurbinectedin as follow-up therapy whereas 9.1% of participants in the atezolizumab arm did. Follow-up immunotherapy was received by 13.3% of all participants with no notable difference between arms (14.5% and 12.0%, respectively).

Table 38: Summary of Follow-up Non-Protocol Systemic Anti-Cancer Treatments (Full Analysis Set)

Type of Therapy Regimen Name	Atezolizumab (N=241)	Atezolizumab+ Lurbinectedin (N=242)	All Patients (N=483)
Total number of patients with at least one non-protocol systemic anti-cancer treatment	132 (54.8%)	108 (44.6%)	240 (49.7%)
Total number of treatments	303	253	556
Chemotherapy			
Total number of patients with at least one treatment	119 (49.4%)	89 (36.8%)	208 (43.1%)
Total number of treatments	268	212	480
CARBOPLATIN	27 (11.2%)	39 (16.1%)	66 (13.7%)
TOPOTECAN / TOPOTECAN HYDROCHLORIDE	38 (15.8%)	25 (10.3%)	63 (13.0%)
ETOPOSIDE	23 (9.5%)	34 (14.0%)	57 (11.8%)
IRINOTECAN / IRINOTECAN HYDROCHLORIDE / IRINOTECAN HYDROCHLORIDE TRIHYDRATE	34 (14.1%)	23 (9.5%)	57 (11.8%)
CYCLOPHOSPHAMIDE	21 (8.7%)	18 (7.4%)	39 (8.1%)
VINCRISTINE / VINCRISTINE SULFATE	21 (8.7%)	17 (7.0%)	38 (7.9%)
DOXORUBICIN / DOXORUBICIN HYDROCHLORIDE	14 (5.8%)	14 (5.8%)	28 (5.8%)
PACLITAXEL	17 (7.1%)	9 (3.7%)	26 (5.4%)
CISPLATIN	16 (6.6%)	9 (3.7%)	25 (5.2%)
LURBINECTEDIN	22 (9.1%)	0	22 (4.6%)
EPIRUBICIN	5 (2.1%)	2 (0.8%)	7 (1.4%)
DOCETAXEL	3 (1.2%)	3 (1.2%)	6 (1.2%)
IFOSFAMIDE	1 (0.4%)	2 (0.8%)	3 (0.6%)
TEMOZOLOMIDE	0	3 (1.2%)	3 (0.6%)
BELOTECAN	0	2 (0.8%)	2 (0.4%)
GEMCITABINE	2 (0.8%)	0	2 (0.4%)
VINORELBINE / VINORELBINE TARTRATE	2 (0.8%)	0	2 (0.4%)
DACTINOMYCIN	1 (0.4%)	0	1 (0.2%)
OTHER ANTINEOPLASTIC AGENTS	0	1 (0.4%)	1 (0.2%)
Targeted therapy			
Total number of patients with at least one treatment	2 (0.8%)	3 (1.2%)	5 (1.0%)
Total number of treatments	3	5	8
BEVACIZUMAB	1 (0.4%)	1 (0.4%)	2 (0.4%)
SACITUZUMAB GOVITECAN	1 (0.4%)	1 (0.4%)	2 (0.4%)
DS 7300A	0	1 (0.4%)	1 (0.2%)
Immunotherapy			
Total number of patients with at least one treatment	20 (8.3%)	25 (10.3%)	45 (9.3%)
Total number of treatments	28	32	60
ATEZOLIZUMAB	9 (3.7%)	20 (8.3%)	29 (6.0%)
TARLATAMAB	8 (3.3%)	4 (1.7%)	12 (2.5%)
DURVALUMAB	3 (1.2%)	0	3 (0.6%)
IPILIMUMAB	0	1 (0.4%)	1 (0.2%)
MAGROLIMAB	0	1 (0.4%)	1 (0.2%)
NIVOLUMAB	0	1 (0.4%)	1 (0.2%)
Other			
Total number of patients with at least one treatment	3 (1.2%)	3 (1.2%)	6 (1.2%)
Total number of treatments	4	4	8
OTHER MONOCLONAL ANTIBODIES AND ANTIBODY DRUG CONJUGATES	2 (0.8%)	1 (0.4%)	3 (0.6%)
ALL OTHER THERAPEUTIC PRODUCTS	1 (0.4%)	1 (0.4%)	2 (0.4%)
TALAZOPARIB	0	1 (0.4%)	1 (0.2%)

Investigator text for medications is encoded using WHO Drug Global B3 Format dictionary (version March 1, 2024).
Multiple cases within a specific line of therapy and regimen for a patient were counted once for the frequency of line of therapy or regimen name.
A patient was counted more than once if received more than one therapy type or regimen name.
Data Cutoff: 29JUL2024; Rave Data Extracted: 01OCT2024.

Outcomes and estimation

Unless otherwise specified, all efficacy analyses are presented per the data cut-off date of the primary analysis, 29 July 2024.

Primary endpoints

- IRF-assessed PFS

In the FAS, the median duration of survival follow-up for both arms combined was 14.95 months (range: 0.2-26.1 months, with the range minimum being a censored observation) and was comparable between both arms, with 14.78 months in the atezolizumab + lurbinectedin arm and 15.18 months in the atezolizumab arm.

Table 39: Time to Event Summary for IRF-Assessed Progression-Free Survival (FAS)

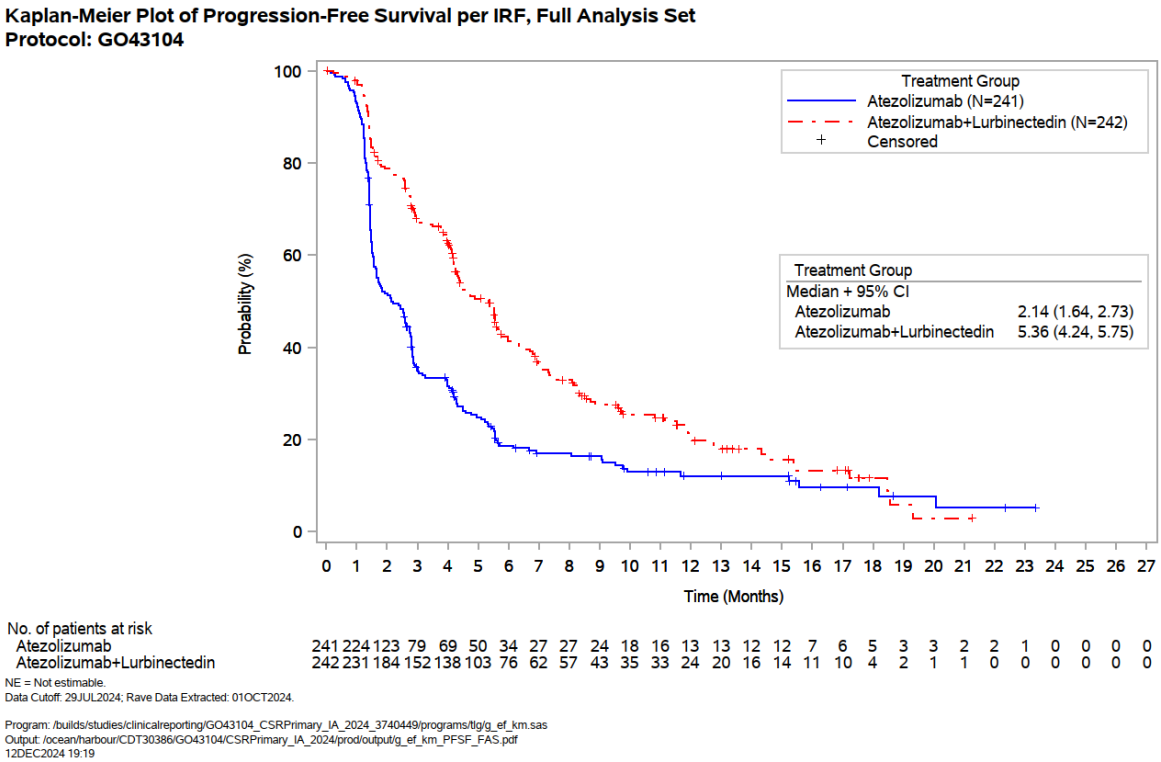
	Atezolizumab (n=241)	**Atezolizumab + Lurbinectedin** (n=242)
Patients with event (%)	202 (83.8%)	174 (71.9%)
Earliest contributing event		
Death	19	31
Disease progression	183	143
Patients without event (%)	39 (16.2%)	68 (28.1%)
Time to event (months)		
Median (95% CI)	2.14 (1.64-2.73)	5.36 (4.24-5.75)
25% and 75%-percentiles	1.41-4.96	2.60-10.81
Range	0.13 to 23.36 [a]	0.03 [a] to 21.26 [a]
Unstratified analysis p-value (log-rank)	<.0001	
Hazard ratio (95% CI)	0.56 (0.46-0.69)	
Stratified analysis p-value (log-rank)	<.0001	
Hazard ratio (95% CI)	0.54 (0.43-0.67)	
Time point analysis - 6 months		
Patients remaining at risk	34	76
Event-free rate (%) (95% CI)	18.66 (13.45-23.87)	41.22 (34.58-47.86)
Difference in event-free rate (95% CI)	22.56 (14.12-31.00)	
Time point analysis - 12 months		
Patients remaining at risk	13	24
Event-free rate (%) (95% CI)	12.03 (7.27-16.80)	20.54 (14.37-26.72)
Difference in event-free rate (95% CI)	8.51 (0.72-16.31)	

[a] Censored observation.

Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. The stratification factors are ECOG PS at randomisation (0 *vs.* 1), LDH at randomisation (≤ULN *vs.* >ULN) via local laboratory test, presence of liver metastases at enrolment (yes *vs.* no), and prior receipt of PCI (yes *vs.* no).

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PCI, prophylactic cranial irradiation; PS, performance status; ULN, upper limit of normal.

Figure 15: Kaplan-Meier Plot for IRF-assessed progression-free survival (FAS)



- OS

Table 40: Time-to-event summary for overall survival (FAS)

	Atezolizumab (n=241)	**Atezolizumab + Lurbinectedin** (n=242)
Patients with event (%)	136 (56.4%)	113 (46.7%)
Earliest contributing event		
Death	136	113
Patients without event (%)	105 (43.6%)	129 (53.3%)
Time to event (months)		
Median (95% CI)	10.64 (9.49-12.16)	13.24 (11.89-16.36)
25% and 75%-percentiles	5.98-18.20	7.66-NE
Range	0.62 to 23.69 [a]	0.23 to 26.09 [a]
Unstratified analysis p-value (log-rank)	0.0203	
Hazard ratio (95% CI)	0.74 (0.58-0.96)	
Stratified analysis p-value (log-rank)	0.0174	
Hazard ratio (95% CI)	0.73 (0.57-0.95)	
Time point analysis - 12 months		
Patients remaining at risk	69	81
Event-free rate (%) (95% CI)	44.10 (37.00-51.21)	56.25 (48.97-63.53)
Difference in event-free rate (95% CI)	12.14 (1.97-22.31)	
Time point analysis - 24 months		
Patients remaining at risk	0	1
Event-free rate (%) (95% CI)	NE (NE)	28.32 (19.28-37.36)
Difference in event-free rate (95% CI)	NE (NE)	

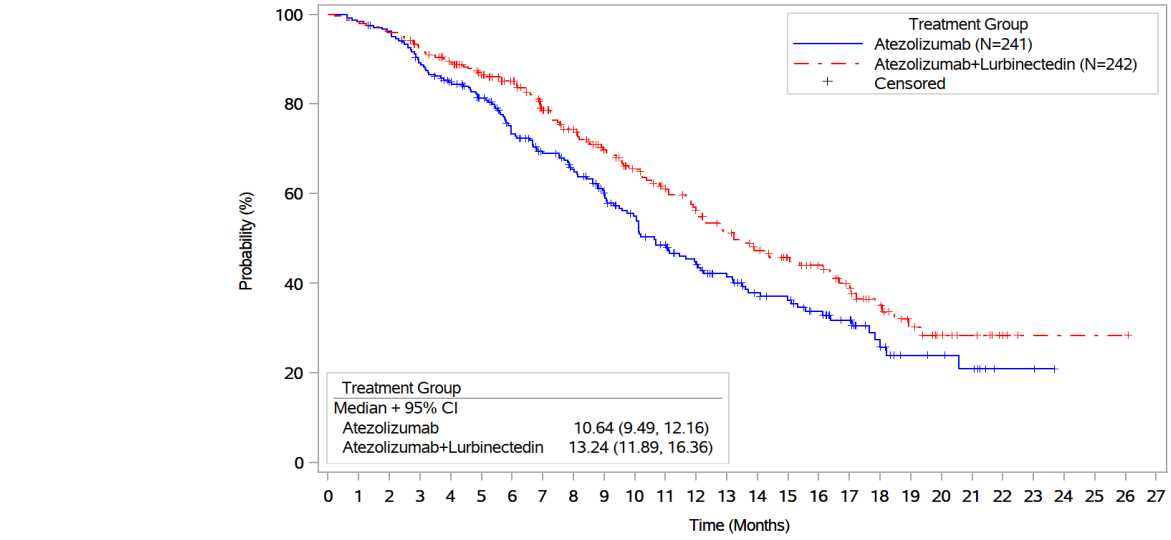
[a] Censored observation.

Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. The stratification factors are ECOG PS at randomisation (0 *vs.* 1), LDH at randomisation (≤ULN *vs.* >ULN) via local laboratory test, presence of liver metastases at enrolment (yes *vs.* no), and prior receipt of PCI (yes *vs.* no).

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; NE, not estimable; PCI, prophylactic cranial irradiation; PS, performance status; ULN, upper limit of normal.

Figure 16: Kaplan-Meier Plot for overall survival (FAS)

Kaplan-Meier Plot of Overall Survival, Full Analysis Set
Protocol: GO43104



No. of patients at risk

Atezolizumab	241	237	230	211	196	179	154	138	126	111	94	81	69	60	49	45	37	29	17	10	9	7	2	2	0	0	0	0
Atezolizumab+Lurbinectedin	242	238	232	221	209	191	174	151	136	118	104	93	81	69	60	52	46	36	25	17	11	8	4	1	1	1	1	0

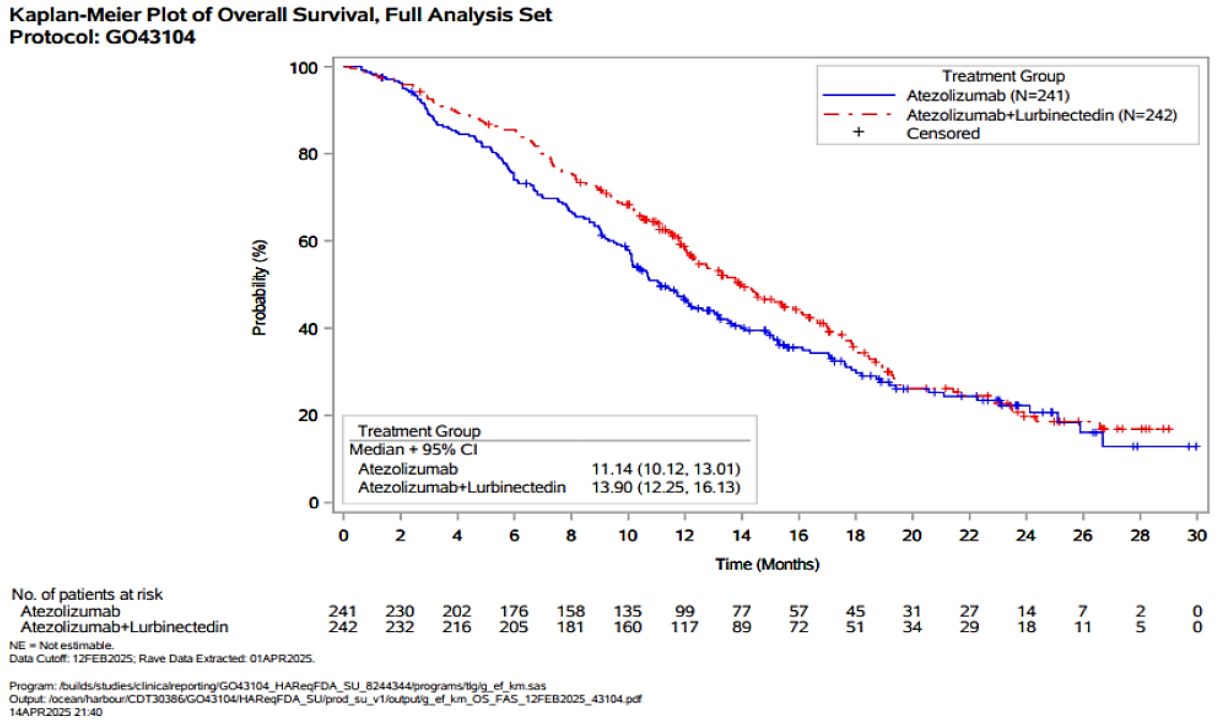
NE = Not estimable.
Data Cutoff: 29JUL2024; Rave Data Extracted: 01OCT2024.

Program: /builds/studies/clinicalreporting/GO43104_CSRPrimary_IA_2024_3740449/programs/tlg/g_ef_km.sas
Output: /ocean/harbour/CDT30386/GO43104/CSRPrimary_IA_2024/prod/output/g_ef_km_OS_FAS.pdf
12DEC2024 19:18

Table 41: Updated Overall Survival Analysis (FAS) DCO 12 February 2025

OS	Atezolizumab N=241	Atezolizumab+Lurbinectedin N=242
Number of deaths (%)	169 (70.1%)	159 (65.7%)
Median, months	11.14	13.90
Stratified HR (95% CI)	0.81 (0.65, 1.01)	

Figure 17: Updated Kaplan-Meier Plot for Overall Survival (FAS) DCO 12 February 2025



Secondary endpoints

- Investigator-assessed PFS

Table 42: Time-to-event summary for investigator-assessed progression-free survival (FAS)

	Atezolizumab (n=241)	**Atezolizumab + Lurbinectedin** (n=242)
Patients with event (%)	206 (85.5%)	178 (73.6%)
Earliest contributing event		
Death	15	27
Disease progression	191	151
Patients without event (%)	35 (14.5%)	64 (26.4%)
Time to event (months)		
Median (95% CI)	2.73 (2.53-2.83)	5.36 (4.30-6.57)
25% and 75%-percentiles	1.45-5.55	2.69-9.76
Range	0.13 to 23.36 [a]	0.03 [a] to 22.97
Unstratified analysis p-value (log-rank)	<.0001	
Hazard ratio (95% CI)	0.59 (0.48-0.72)	
Stratified analysis p-value (log-rank)	<.0001	
Hazard ratio (95% CI)	0.55 (0.45-0.68)	
Time point analysis - 6 months		
Patients remaining at risk	45	89
Event-free rate (%) (95% CI)	22.56 (17.12-28.00)	46.21 (39.60-52.81)
Difference in event-free rate (95% CI)	23.65 (15.09-32.20)	
Time point analysis - 12 months		
Patients remaining at risk	15	26
Event-free rate (%) (95% CI)	12.80 (8.07-17.52)	20.32 (14.33-26.32)
Difference in event-free rate (95% CI)	7.53 (-0.11–15.16)	

	Atezolizumab (n=241)	**Atezolizumab + Lurbinectedin** (n=242)

[a] Censored observation.

Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. The stratification factors are ECOG PS at randomisation (0 *vs.* 1), LDH at randomisation (≤ULN *vs.* >ULN) via local laboratory test, presence of liver metastases at enrolment (yes *vs.* no), and prior receipt of PCI (yes *vs.* no).

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PCI, prophylactic cranial irradiation; PS, performance status; ULN, upper limit of normal.

- IRF- and Investigator-assessed ORR confirmed ORR

Table 43: Overview of IRF-assessed confirmed objective response rate (FAS with measurable disease at baseline)

	Atezolizumab (n=182)	**Atezolizumab + Lurbinectedin** (n=175)
Responders (%)	19 (10.4%)	34 (19.4%)
Non-responders (%)	163 (89.6%)	141 (80.6%)
95% CI for response rate	6.40-15.82	13.85-26.08
Unstratified analysis		
Difference in ORR (95% CI)	8.99 (1.07-16.90)	
p-value (Chi-square with Schouten correction)	0.0208	
Stratified analysis		
Difference in ORR (95% CI)	8.99 (1.07-16.90)	
p-value (Chi-square with Schouten correction)	0.0206	
Complete response (CR) **(95% CI)**	1 (0.5%) (0.01-3.02)	4 (2.3%) (0.63-5.75)
Partial response (PR) **(95% CI)**	18 (9.9%) (5.97-15.18)	30 (17.1%) (11.88-23.56)
Stable disease (SD) **(95% CI)**	68 (37.4%) (30.32-44.83)	96 (54.9%) (47.17-62.38)
Progressive disease (PD) **(95% CI)**	87 (47.8%) (40.36-55.32)	34 (19.4%) (13.85-26.08)
Not evaluable (NE)	1 (0.5%)	0
Missing	7 (3.8%)	11 (6.3%)

95% CI for rate was constructed using the Clopper-Pearson method. 95% CI for difference in rate was constructed using the normal approximation to the binomial distribution (Wald) with continuity correction. Patients were classified as non-responders if no post-baseline response assessments. The stratification factors are ECOG PS at randomisation (0 *vs.* 1), LDH at randomisation (≤ULN *vs.* >ULN) via local laboratory test, presence of liver metastases at enrolment (yes *vs.* no), and prior receipt of PCI (yes *vs.* no).

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; NE; not evaluable; ORR, objective response rate; PCI, prophylactic cranial irradiation; PS, performance status; ULN, upper limit of normal..

Table 44: Overview of investigator-assessed confirmed objective response rate (FAS with measurable disease at baseline)

	Atezolizumab (n=205)	**Atezolizumab + Lurbinectedin** (n=205)
Responders (%)	27 (13.2%)	35 (17.1%)
Non-responders (%)	178 (86.8%)	170 (82.9%)
95% CI for response rate	8.86-18.58	12.19-22.94
Unstratified analysis		
Difference in ORR (95% CI)	3.90 (-3.51 – 11.32)	
p-value (Chi-square with Schouten correction)	0.3018	
Stratified analysis		
Difference in ORR (95% CI)	3.90 (-3.51 – 11.32)	
p-value (Chi-square with Schouten correction)	0.3217	
Complete response (CR) **(95% CI)**	2 (1.0%) (0.12-3.48)	1 (0.5%) (0.01-2.69)
Partial response (PR) **(95% CI)**	25 (12.2%) (8.05-17.47)	34 (16.6%) (11.77-22.40)

	Atezolizumab (n=205)	**Atezolizumab + Lurbinectedin** (n=205)
Stable disease (SD) **(95% CI)**	86 (42.0%) (35.11-49.03)	118 (57.6%) (50.48-64.42)
Progressive disease (PD) **(95% CI)**	85 (41.5%) (34.64-48.53)	35 (17.1%) (12.19-22.94)
Not evaluable (NE)	0	0
Missing	7 (3.4%)	17 (8.3%)

95% CI for rate was constructed using the Clopper-Pearson method. 95% CI for difference in rate was constructed using the normal approximation to the binomial distribution (Wald) with continuity correction. Patients were classified as non-responders if no post-baseline response assessments. The stratification factors are ECOG PS at randomisation (0 *vs.* 1), LDH at randomisation (≤ULN *vs.* >ULN) via local laboratory test, presence of liver metastases at enrolment (yes *vs.* no), and prior receipt of PCI (yes *vs.* no).

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; NE, not evaluable; ORR, objective response rate; PCI, prophylactic cranial irradiation; PS, performance status; ULN, upper limit of normal.

- IRF- and Investigator-assessed DOR

Table 45: Overview of IRF-assessed duration of response (FAS)

	Atezolizumab (n=19)	**Atezolizumab + Lurbinectedin** (n=34)
Patients with event (%)	11 (57.9%)	14 (41.2%)
Earliest contributing event		
Death	2	1
Disease progression	9	13
Patients without event (%)	8 (42.1%)	20 (58.8%)
Time to event (months)		
Median (95% CI)	5.62 (4.17-NE)	9.00 (5.52-NE)
25% and 75%-percentiles	2.83-14.19	4.21-16.07
Range	1.64 to 15.51	1.38 [a] to 16.07

[a] Censored observation.

Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley.

CI, confidence interval; NE, not estimable.

Table 46: Overview of investigator-assessed duration of response (FAS)

	Atezolizumab (n=27)	**Atezolizumab + Lurbinectedin** (n=35)
Patients with event (%)	9 (33.3%)	21 (60.0%)
Earliest contributing event		
Death	2	3
Disease progression	7	18
Patients without event (%)	18 (66.7%)	14 (40.0%)
Time to event (months)		
Median (95% CI)	11.93 (8.38-NE)	5.75 (4.17-11.10)
25% and 75%-percentiles	8.34-NE	3.98-14.65
Range	1.12 [a] to 22.34 [a]	1.38 [a] to 15.90 [a]

[a] Censored observation.

Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley.

CI, confidence interval; NE, not estimable.

- Landmark IRF-assessed PFS and OS Rates

Table 47: Landmark time point analysis for progression-free survival

	Atezolizumab (n=241)	**Atezolizumab + Lurbinectedin** (n=242)
IRF-assessed PFS		

	Atezolizumab (n=241)	**Atezolizumab + Lurbinectedin** (n=242)
6 months		
Participants remaining at risk	34	76
Event-free rate, % (95% CI)	18.66 (13.45-23.87)	41.22 (34.58-47.86)
Difference in event-free rate (95% CI)	22.56 (14.12-31.00)	
12 months		
Participants remaining at risk	13	24
Event-free rate, % (95% CI)	12.03 (7.27-16.80)	20.54 (14.37-26.72)
Difference in event-free rate (95% CI)	8.51 (0.72-16.31)	
Investigator-assessed PFS		
6 months		
Participants remaining at risk	45	89
Event-free rate, % (95% CI)	22.56 (17.12-28.00)	46.21 (39.60-52.81)
Difference in event-free rate (95% CI)	23.65 (15.09-32.20)	
12 months		
Participants remaining at risk	15	26
Event-free rate, % (95% CI)	12.80 (8.07-17.52)	20.32 (14.33-26.32)
Difference in event-free rate (95% CI)	7.53 (-0.11-15.16)	

CI, confidence interval; IRF, independent review facility.

Table 48: Landmark Time point Analysis for Overall Survival at Interim and Updated Overall Survival Analysis

Parameter	Interim OS Analysis (CCOD 29 July 2024)		Updated OS Analysis (CCOD 12 February 2025)	
	Atezolizumab N=241	Atezolizumab+Lurbinectedin N=242	Atezolizumab N=241	Atezolizumab+Lurbinectedin N=242
12 months				
Participants remaining at risk	69	81	99	117
Event Free Rate, % (95% CI)	44.10 (37.00, 51.21)	56.25 (48.97, 63.53)	46.40 (39.99, 52.81)	58.25 (51.89, 64.61)
Difference in Event Free Rate (95% CI)	12.14 (1.97, 22.31)		11.85 (2.82, 20.88)	
24 months				
Participants remaining at risk	0	1	14	18
Event Free Rate, % (95% CI)	NE	28.32 (19.28, 37.36)	22.25 (15.79, 28.71)	19.73 (13.15, 26.30)
Difference in Event Free Rate (95% CI)	NE		−2.53 (−11.74, 6.69)	

CCOD=clinical cutoff date; CI=confidence interval; NE=not estimable; OS=overall survival.

Source: t_ef_tte_OS_FAS, t_ef_tte_OS_FAS_12FEB2025_43104

- HRQoL

Table 49: Summary of time to confirmed deterioration in physical functioning (FAS)

	Atezolizumab (n=241)	**Atezolizumab + Lurbinectedin** (n=242)
Patients with event (%)	47 (19.5%)	75 (31.0%)
Earliest contributing event		
Confirmed deterioration-two consecutive deterioration records	38	69
Confirmed deterioration-deterioration followed by death	9	6
Patients without event (%)	194 (80.5%)	167 (69.0%)
Time to event (months)		
Median (95% CI)	NE (NE)	15.9 (11.0-NE)
25% and 75%-percentiles	6.9-NE	3.0-NE

	Atezolizumab (n=241)	Atezolizumab + Lurbinectedin (n=242)
Range	0 [a] to 23 [a]	0 [a] to 22 [a]
Stratified analysis p-value (log-rank)	0.0208	
Hazard ratio (95% CI)	1.55 (1.07-2.25)	
Unstratified analysis p-value (log-rank)	0.0234	
Hazard ratio (95% CI)	1.52 (1.06-2.20)	

[a] Censored observation.

Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. The stratification factors are ECOG PS at randomisation (0 *vs.* 1), LDH at randomisation (≤ULN *vs.* >ULN) via local laboratory test, presence of liver metastases at enrolment (yes *vs.* no), and prior receipt of PCI (yes *vs.* no).

The physical functioning scale is derived from items 1-5 of the EORTC QLQ-C30.

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; NE, not estimable; PCI, prophylactic cranial irradiation; PS, performance status; ULN, upper limit of normal.

Table 50: Summary of time to confirmed deterioration in Global Health Status/Quality of Life (FAS)

	Atezolizumab (n=241)	Atezolizumab + Lurbinectedin (n=242)
Patients with event (%)	71 (29.5%)	92 (38.0%)
Earliest contributing event		
Confirmed deterioration-two consecutive deterioration records	60	84
Confirmed deterioration-deterioration followed by death	11	8
Patients without event (%)	170 (70.5%)	150 (62.0%)
Time to event (months)		
Median (95% CI)	12.9 (11.6-NE)	10.8 (7.6-NE)
25% and 75%-percentiles	2.2-NE	1.4-NE
Range	0 [a] to 23 [a]	0 [a] to 22 [a]
Stratified analysis p-value (log-rank)	0.1887	
Hazard ratio (95% CI)	1.24 (0.90-1.71)	
Unstratified analysis p-value (log-rank)	0.2011	
Hazard ratio (95% CI)	1.23 (0.90-1.68)	

[a] Censored observation.

Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. The stratification factors are ECOG PS at randomisation (0 *vs.* 1), LDH at randomisation (≤ULN *vs.* >ULN) via local laboratory test, presence of liver metastases at enrolment (yes *vs.* no), and prior receipt of PCI (yes *vs.* no).

The global health status/QoL scale is derived from items 29 and 30 of the EORTC QLQ-C30.

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; NE, not estimable; PCI, prophylactic cranial irradiation; PS, performance status; QoL, quality of life; ULN, upper limit of normal.

Exploratory efficacy endpoints

There were no differences observed between treatment arms in GHS/QoL, functional domains, or symptom items during maintenance therapy as measured by the EORTC QLQ-C30 and the QLQ-LC13, with the exception of the TTCD analysis.

Tolerability was assessed via select items of the PRO-CTCAE. A transient worsening was reported in 8 of the 12 patient-reportable symptoms and side effects with atezolizumab + lurbinectedin treatment, which subsequently returned to randomisation baseline levels between Cycle 3 to Cycle 6, the last timepoint during maintenance treatment with a sufficient number of participants (>25%) remaining on study treatment in both arms for meaningful data interpretation.

The majority of participants treated with atezolizumab + lurbinectedin (>85%) reported little to no bother from treatment side effects during maintenance therapy, as measured by EORTC IL46.

Pre-defined and post-hoc subgroup analyses

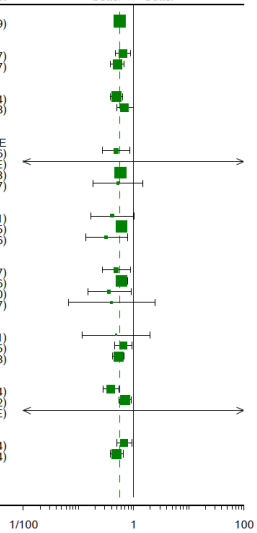
Subgroup analysis of IRF-assessed PFS

Figure

18: Subgroup analysis of IRF-assessed progression-free survival (FAS)

Forest Plot of Progression-Free Survival per IRF by Subgroups, Full Analysis Set
Protocol: GO43104

Baseline Risk Factors	Total n	Atezolizumab (N=241) n	Events	Median (Months)	Atezolizumab+ Lurbinectedin (N=242) n	Events	Median (Months)	Hazard Ratio	95% Wald CI
All Patients	483	241	202	2.1	242	174	5.4	0.56	(0.46, 0.69)
Age group (years)									
<65	208	90	73	1.8	118	86	5.4	0.64	(0.46, 0.87)
>=65	275	151	129	2.5	124	88	5.5	0.51	(0.38, 0.67)
Sex									
Male	302	151	131	1.8	151	110	5.5	0.49	(0.38, 0.64)
Female	181	90	71	2.7	91	64	4.3	0.69	(0.49, 0.98)
Race									
American Indian or Alaska Native	1				1	1	8.3	NE	NE
Asian	62	31	26	1.8	31	22	6.3	0.48	(0.27, 0.86)
Black or African American	4	1	1	1.4	3	3	8.3	<0.01	(0.00, NE)
White	394	199	167	2.1	195	140	4.7	0.58	(0.46, 0.73)
Not Reported	22	10	8	2.8	12	8	3.8	0.52	(0.18, 1.47)
Ethnicity									
Hispanic or Latino	32	16	13	2.6	16	8	6.8	0.41	(0.17, 1.01)
Not Hispanic or Latino	416	210	176	2.1	206	153	4.9	0.60	(0.48, 0.75)
Not Reported	35	15	13	1.8	20	13	5.4	0.32	(0.14, 0.76)
Region									
Asia-Pacific	61	31	26	1.8	30	21	6.3	0.48	(0.27, 0.87)
Europe and Middle East	384	190	157	2.4	194	140	5.4	0.60	(0.48, 0.76)
North America	31	17	16	2.1	14	10	3.1	0.36	(0.15, 0.90)
Central and South America	7	3	3	1.5	4	3	5.1	0.40	(0.06, 2.47)
Tobacco Use History									
Never	12	5	4	1.4	7	6	5.8	0.49	(0.12, 2.01)
Current	161	73	57	2.5	88	61	4.7	0.65	(0.45, 0.95)
Previous	310	163	141	2.1	147	107	5.5	0.53	(0.41, 0.68)
LDH at Enrollment									
<=ULN	200	94	80	2.2	106	65	6.3	0.39	(0.28, 0.54)
>ULN	280	145	120	2.1	135	108	4.3	0.71	(0.54, 0.92)
Unknown	3	2	2	3.6	1	1	8.5	<0.01	(0.00, NE)
ECOG at Enrollment									
0	194	93	73	2.6	101	76	4.4	0.68	(0.49, 0.94)
1	289	148	129	2.1	141	98	5.6	0.49	(0.37, 0.64)



Hazard ratios and the associated Wald confidence intervals were estimated using unstratified Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
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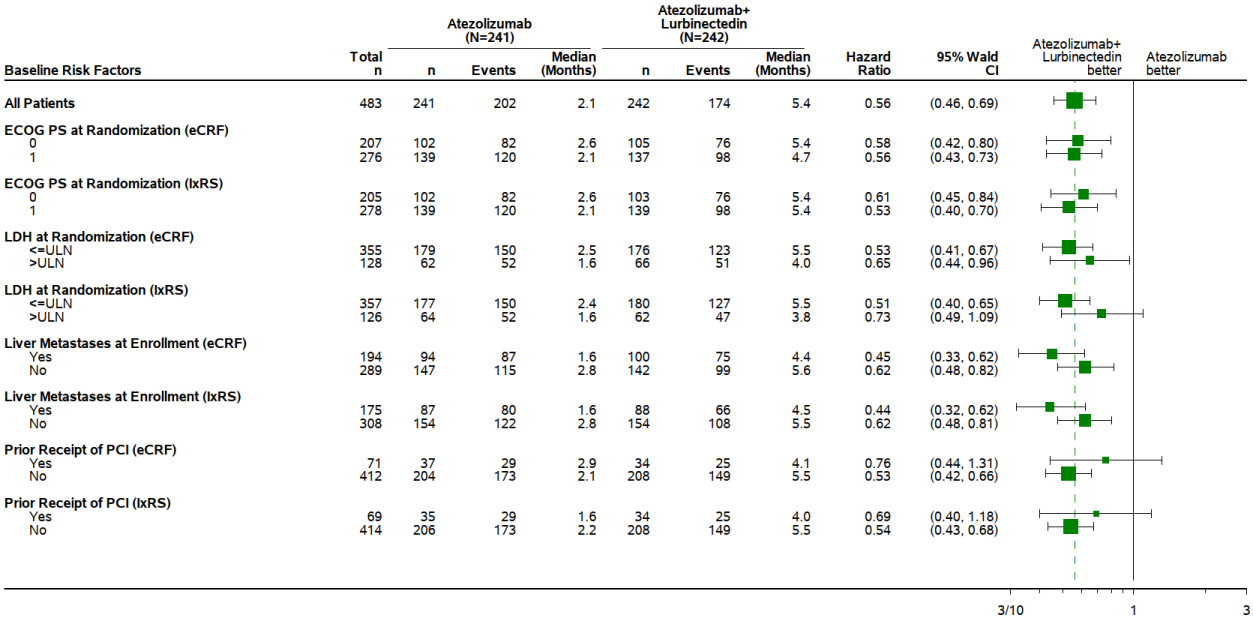
Forest Plot of Progression-Free Survival per IRF by Subgroups, Full Analysis Set
Protocol: GO43104



Hazard ratios and the associated Wald confidence intervals were estimated using unstratified Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
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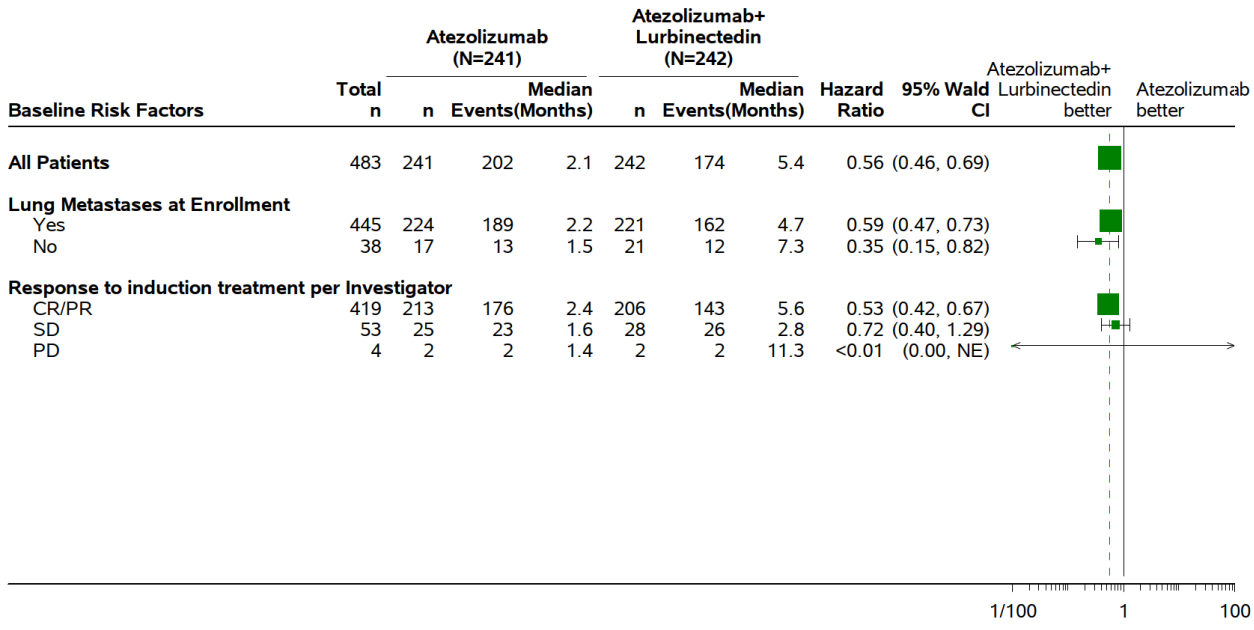
Forest Plot of Progression-Free Survival per IRF by Subgroups, Full Analysis Set
Protocol: GO43104



Hazard ratios and the associated Wald confidence intervals were estimated using unstratified Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
Data Cutoff: 29JUL2024; Rave Data Extracted: 01OCT2024.
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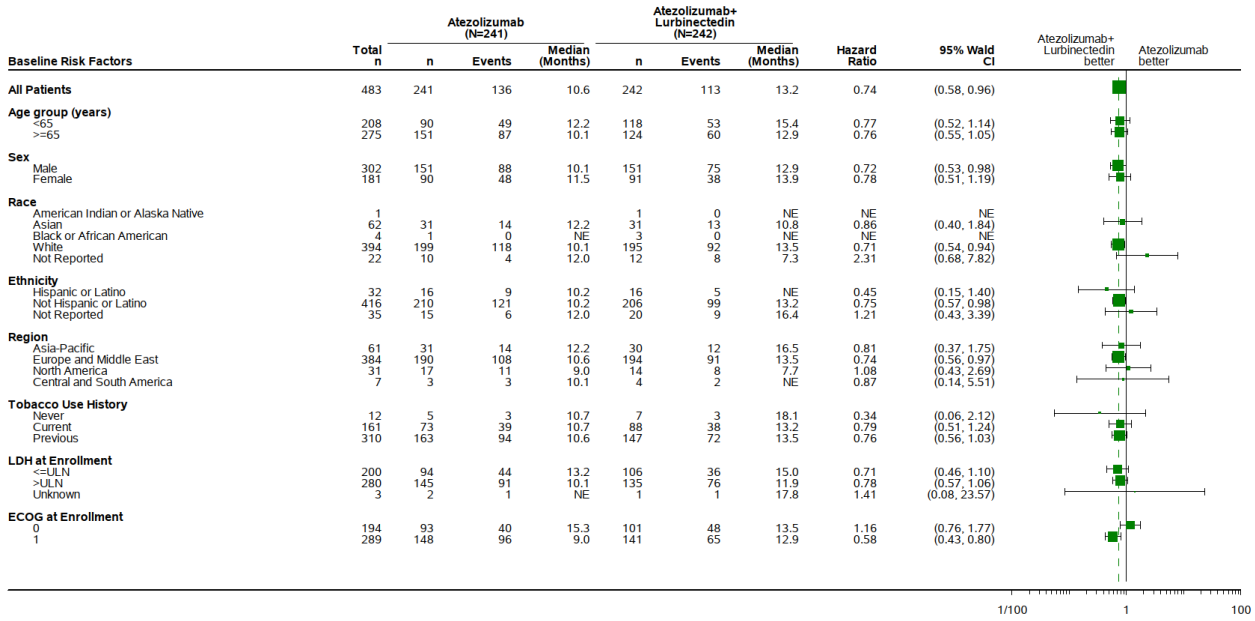
Subgroup analysis of OS

Figure 19: Subgroup analysis of overall survival (FAS)

Forest Plot of Overall Survival by Subgroups, Full Analysis Set
Protocol: GO43104



Baseline Risk Factors	Total n	Atezolizumab (N=241) n	Events	Median (Months)	Atezolizumab+ Lurbinectedin (N=242) n	Events	Median (Months)	Hazard Ratio	95% Wald CI
All Patients	483	241	136	10.6	242	113	13.2	0.74	(0.58, 0.96)
Age group (years)									
<65	208	90	49	12.2	118	53	15.4	0.77	(0.52, 1.14)
>=65	275	151	87	10.1	124	60	12.9	0.76	(0.55, 1.05)
Sex									
Male	302	151	88	10.1	151	75	12.9	0.72	(0.53, 0.98)
Female	181	90	48	11.5	91	38	13.9	0.78	(0.51, 1.19)
Race									
American Indian or Alaska Native	1				1	0	NE	NE	NE
Asian	62	31	14	12.2	31	13	10.8	0.86	(0.40, 1.84)
Black or African American	4	1	0	NE	3	0	NE	NE	NE
White	394	199	118	10.1	195	92	13.5	0.71	(0.54, 0.94)
Not Reported	22	10	4	12.0	12	8	7.3	2.31	(0.68, 7.82)
Ethnicity									
Hispanic or Latino	32	16	9	10.2	16	5	NE	0.45	(0.15, 1.40)
Not Hispanic or Latino	416	210	121	10.2	206	99	13.2	0.75	(0.57, 0.98)
Not Reported	35	15	6	12.0	20	9	16.4	1.21	(0.43, 3.39)
Region									
Asia-Pacific	61	31	14	12.2	30	12	16.5	0.81	(0.37, 1.75)
Europe and Middle East	384	190	108	10.6	194	91	13.5	0.74	(0.56, 0.97)
North America	31	17	11	9.0	14	8	7.7	1.08	(0.43, 2.69)
Central and South America	7	3	3	10.1	4	2	NE	0.87	(0.14, 5.51)
Tobacco Use History									
Never	12	5	3	10.7	7	3	18.1	0.34	(0.06, 2.12)
Current	161	73	39	10.7	88	38	13.2	0.79	(0.51, 1.24)
Previous	310	163	94	10.6	147	72	13.5	0.76	(0.56, 1.03)
LDH at Enrollment									
<=ULN	200	94	44	13.2	106	36	15.0	0.71	(0.46, 1.10)
>ULN	280	145	91	10.1	135	76	11.9	0.78	(0.57, 1.06)
Unknown	3	2	1	NE	1	1	17.8	1.41	(0.08, 23.57)
ECOG at Enrollment									
0	194	93	40	15.3	101	48	13.5	1.16	(0.76, 1.77)
1	289	148	96	9.0	141	65	12.9	0.58	(0.43, 0.80)

Hazard ratios and the associated Wald confidence intervals were estimated using unstratified Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
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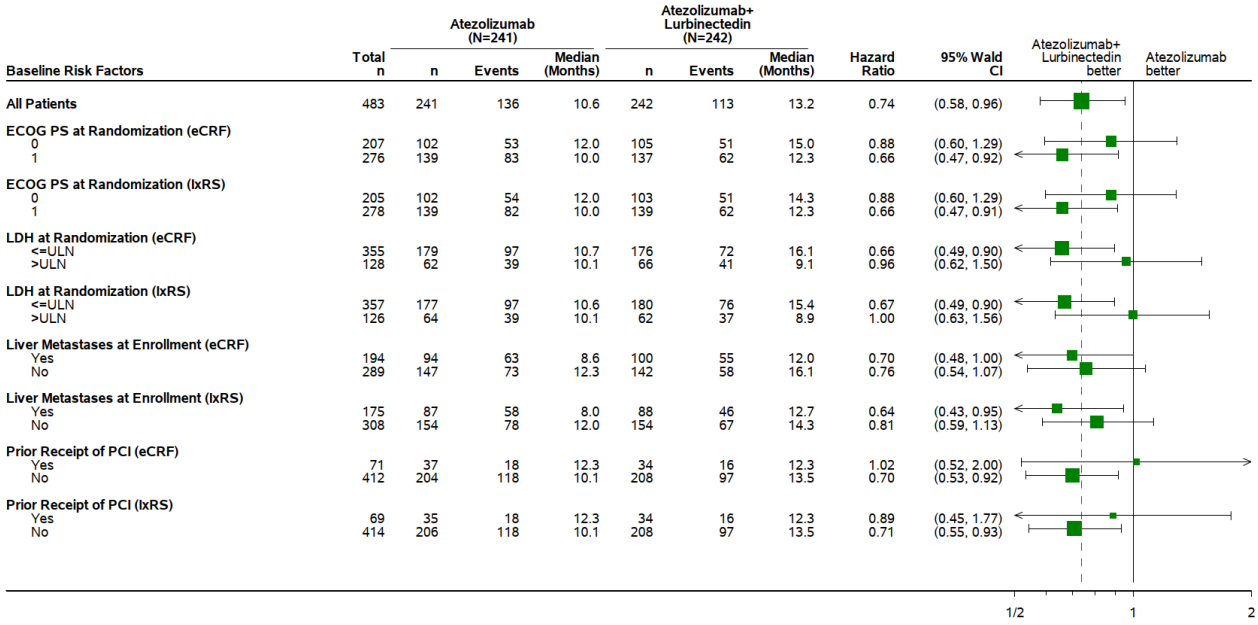
Forest Plot of Overall Survival by Subgroups, Full Analysis Set
Protocol: GO43104



Baseline Risk Factors	Total n	Atezolizumab (N=241) n	Events	Median (Months)	Atezolizumab+ Lurbinectedin (N=242) n	Events	Median (Months)	Hazard Ratio	95% Wald CI
All Patients	483	241	136	10.6	242	113	13.2	0.74	(0.58, 0.96)
ECOG PS at Randomization (eCRF)									
0	207	102	53	12.0	105	51	15.0	0.88	(0.60, 1.29)
1	276	139	83	10.0	137	62	12.3	0.66	(0.47, 0.92)
ECOG PS at Randomization (IxRS)									
0	205	102	54	12.0	103	51	14.3	0.88	(0.60, 1.29)
1	278	139	82	10.0	139	62	12.3	0.66	(0.47, 0.91)
LDH at Randomization (eCRF)									
<=ULN	355	179	97	10.7	176	72	16.1	0.66	(0.49, 0.90)
>ULN	128	62	39	10.1	66	41	9.1	0.96	(0.62, 1.50)
LDH at Randomization (IxRS)									
<=ULN	357	177	97	10.6	180	76	15.4	0.67	(0.49, 0.90)
>ULN	126	64	39	10.1	62	37	8.9	1.00	(0.63, 1.56)
Liver Metastases at Enrollment (eCRF)									
Yes	194	94	63	8.6	100	55	12.0	0.70	(0.48, 1.00)
No	289	147	73	12.3	142	58	16.1	0.76	(0.54, 1.07)
Liver Metastases at Enrollment (IxRS)									
Yes	175	87	58	8.0	88	46	12.7	0.64	(0.43, 0.95)
No	308	154	78	12.0	154	67	14.3	0.81	(0.59, 1.13)
Prior Receipt of PCI (eCRF)									
Yes	71	37	18	12.3	34	16	12.3	1.02	(0.52, 2.00)
No	412	204	118	10.1	208	97	13.5	0.70	(0.53, 0.92)
Prior Receipt of PCI (IxRS)									
Yes	69	35	18	12.3	34	16	12.3	0.89	(0.45, 1.77)
No	414	206	118	10.1	208	97	13.5	0.71	(0.55, 0.93)

Hazard ratios and the associated Wald confidence intervals were estimated using unstratified Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
Data Cutoff: 29JUL2024; Rave Data Extracted: 01OCT2024.
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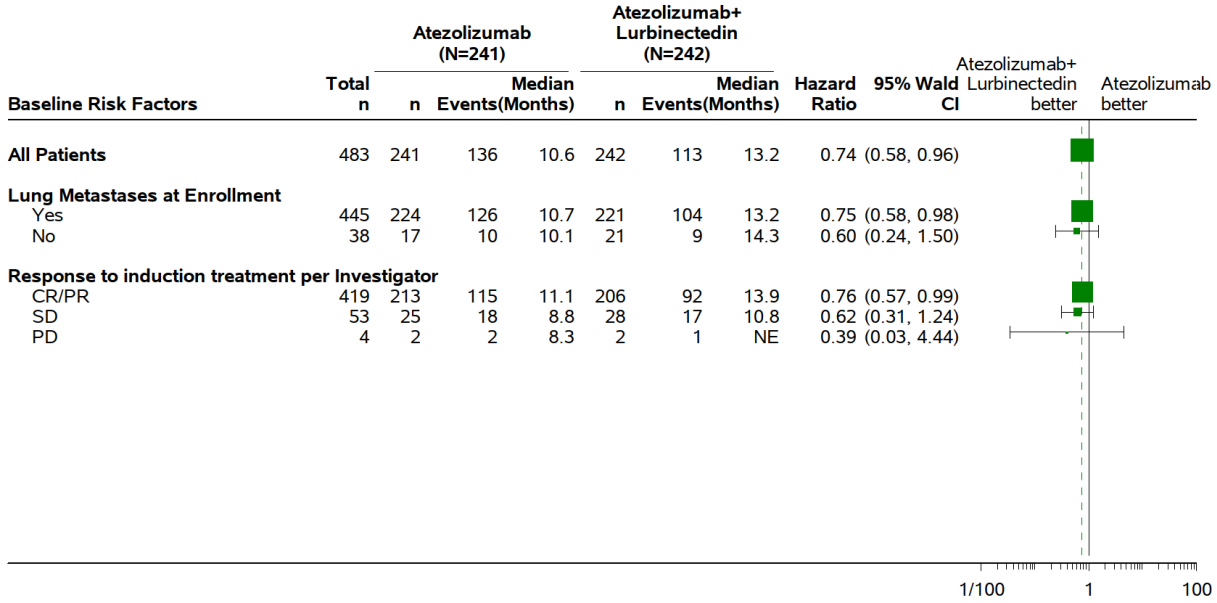
Forest Plot of Overall Survival by Subgroups, Full Analysis Set
Protocol: GO43104



Hazard ratios and the associated Wald confidence intervals were estimated using unstratified Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
Data Cutoff: 29JUL2024; Rave Data Extracted: 01OCT2024.
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Pre-defined and post-hoc sensitivity analyses

Sensitivity analysis of IRF-assessed PFS

Table 51: Impact of two or more consecutively missed scheduled tumour assessments prior to an IRF-assessed progression-free survival event (FAS)

	Atezolizumab (n=241)	**Atezolizumab + Lurbinectedin** (n=242)
Patients with event (%)	194 (80.5%)	158 (65.3%)
Earliest contributing event		
Death	11	16
Disease progression	183	142
Patients without event (%)	47 (19.5%)	84 (34.7%)
Time to event (months)		
Median (95% CI)	2.14 (1.64-2.73)	4.73 (4.24-5.68)
25% and 75%-percentiles	1.41-4.50	2.60-9.76
Range	0.03 [a] to 23.36 [a]	0.03 [a] to 21.26 [a]
Unstratified analysis p-value (log-rank)	<.0001	
Hazard ratio (95% CI)	0.53 (0.43-0.66)	
Stratified analysis p-value (log-rank)	<.0001	
Hazard ratio (95% CI)	0.50 (0.40-0.63)	
Time point analysis - 6 months		
Patients remaining at risk	28	66
Event-free rate (%) (95% CI)	17.21 (11.98-22.45)	40.14 (33.27-47.02)
Difference in event-free rate (95% CI)	22.93 (14.29-31.58)	
Time point analysis - 12 months		
Patients remaining at risk	11	20
Event-free rate (%) (95% CI)	12.74 (7.77-17.72)	21.20 (14.65-27.74)
Difference in event-free rate (95% CI)	8.46 (0.24-16.68)	

	Atezolizumab (n=241)	**Atezolizumab + Lurbinectedin** (n=242)

[a] Censored observation.

Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. The stratification factors are ECOG PS at randomisation (0 vs. 1), LDH at randomisation (≤ULN vs. >ULN) via local laboratory test, presence of liver metastases at enrolment (yes vs. no), and prior receipt of PCI (yes vs. no).

Participants who missed two or more consecutive scheduled assessments immediately prior to the date of disease progression per RECIST v.1.1 or death censored at the last tumour assessment prior to the missed visit.

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PCI, prophylactic cranial irradiation; PS, performance status; ULN, upper limit of normal.

Ancillary analyses

Supplementary analysis of IRF-assessed PFS

Table 52: Impact of non-protocol therapy prior to an IRF-assessed progression-free survival event (FAS)

	Atezolizumab (n=241)	**Atezolizumab + Lurbinectedin** (n=242)
Patients with event (%)	196 (81.3%)	160 (66.1%)
Earliest contributing event		
Death	15	19
Disease progression	181	141
Patients without event (%)	45 (18.7%)	82 (33.9%)
Time to event (months)		
Median (95% CI)	2.14 (1.64-2.73)	5.36 (4.24-5.75)
25% and 75%-percentiles	1.41-4.60	2.60-9.69
Range	0.03 [a] to 23.36 [a]	0.03 [a] to 21.26 [a]
Unstratified analysis p-value (log-rank)	<.0001	
Hazard ratio (95% CI)	0.55 (0.44-0.68)	
Stratified analysis p-value (log-rank)	<.0001	
Hazard ratio (95% CI)	0.52 (0.42-0.65)	
Time point analysis - 6 months		
Patients remaining at risk	31	69
Event-free rate (%) (95% CI)	17.98 (12.74-23.22)	41.05 (34.17-47.93)
Difference in event-free rate (95% CI)	23.07 (14.42-31.72)	
Time point analysis - 12 months		
Patients remaining at risk	12	21
Event-free rate (%) (95% CI)	12.51 (7.65-17.36)	21.31 (14.83-27.79)
Difference in event-free rate (95% CI)	8.80 (0.70-16.90)	

[a] Censored observation.

Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. The stratification factors are ECOG PS at randomisation (0 vs. 1), LDH at randomisation (≤ULN vs. >ULN) via local laboratory test, presence of liver metastases at enrolment (yes vs. no), and prior receipt of PCI (yes vs. no).

Participants who start an NPT before a PFS event will be censored at the time of the last tumour assessment before the initiation of NPT.

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; NPT, non-protocol systemic anticancer therapy; PCI, prophylactic cranial irradiation; PS, performance status; ULN, upper limit of normal.

Supplementary analysis of OS

Table 53: Impact of non-protocol anticancer therapy on overall survival (FAS)

	Overall survival stratified hazard ratio (95% CI)
Discounting for NPT with 10% benefit reduction	0.71 (0.55, 0.92)
Discounting for NPT with 20% benefit reduction	0.72 (0.55, 0.93)

	Overall survival stratified hazard ratio (95% CI)
Discounting for NPT with 30% benefit reduction	0.71 (0.55, 0.92)

NPT, non-protocol anticancer therapy.

Immunogenicity impact on primary efficacy endpoints

Table 54: Overall Efficacy in the Randomized Phase by Atezolizumab ADA Status

	Atezolizumab (N=239)		Atezolizumab+ Lurbinectedin (N=242)	
	Atezo ADA- (N=219)	Atezo ADA+ (N=20)	Atezo ADA- (N=223)	Atezo ADA+ (N=19)
Overall Survival				
Patients with event (%)	125 (57.1%)	9 (45.0%)	106 (47.5%)	7 (36.8%)
Patients without event (%)	94 (42.9%)	11 (55.0%)	117 (52.5%)	12 (63.2%)
Time to event (months)				
Median	10.64	16.39	13.47	12.32
95% CI	(9.30, 12.25)	(5.62, NE)	(11.89, 16.46)	(9.56, NE)
25% and 75%-ile	5.98, 18.00	5.62, NE	7.56, NE	9.56, NE
Range	0.6 to 23.7*	1.1 to 21.7*	0.2 to 26.1*	2.7* to 17.5*
Progression Free Survival per IRF				
Patients with event (%)	184 (84.0%)	16 (80.0%)	163 (73.1%)	11 (57.9%)
Patients without event (%)	35 (16.0%)	4 (20.0%)	60 (26.9%)	8 (42.1%)
Time to event (months)				
Median	2.14	2.83	4.90	5.78
95% CI	(1.61, 2.73)	(1.48, 4.21)	(4.21, 5.65)	(2.99, 9.69)
25% and 75%-ile	1.41, 5.09	1.48, 4.30	2.60, 11.14	2.99, 8.08
Range	0.1 to 23.4*	1.1 to 20.1	0.0* to 21.3*	0.0* to 9.8*

* Censored observation; NE = Not estimable.
Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley.
ADA = Anti-Drug Antibodies (is also referred to as ATA, or Anti-Therapeutic Antibodies); ADA- = Without treatment enhanced/induced; ADA+ = With treatment enhanced/induced.
Data Cutoff: 29JUL2024; Rave Data Extracted: 01OCT2024.

Clinical studies in special populations

Table 55: Clinical studies in special populations

	Controlled Trials	***Non-controlled trials***
Renal impairment* patients (Subjects number /total number)	2 (CKD stage 3b)/482	
Hepatic impairment** patients (Subjects number /total number)	0	14/32
Paediatric patients <18 years (Subjects number /total number)	0	
Older patients; Age 65-74 (Subjects number /total number)	211/482	
Age 75-84 (Subjects number /total number)	61/482	
Age 85+ (Subjects number /total number)	2/482	

* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)
** Hepatic impairment by the NCI-ODWG classification criteria; analysis by the Child-Pugh classification was secondary

Refer to section 5.2.2.10. of this assessment report for information on the effect of organ impairment

on the exposure to lurbinectedin.

5.3.3. In vitro biomarker test for patient selection for efficacy

Not applicable

5.3.4. Supportive study

Study B-005 was a multicentre, open-label, non-comparative, phase II study designed to assess lurbinectedin anticancer activity in nine difficult-to-treat tumour types: SCLC, head and neck carcinoma, neuroendocrine tumours, biliary tract carcinoma, endometrial carcinoma, BRCA 1/2-associated metastatic breast carcinoma, carcinoma of unknown primary site, germ cell tumours and Ewing's family of tumours. Patients with each tumour type were treated in separate cohorts (one cohort per tumour type) with lurbinectedin 3.2 mg/m^2 as a 1-hour i.v. q3wk infusion.

For the SCLC cohort, eligible subjects were SCLC patients with ECOG PS ≤ 2 treated with only one prior platinum-containing chemotherapy line (other therapies such as immunotherapy could have been previously administered as a second line). Patients with CNS involvement were excluded. No restriction according to previous chemotherapy-free interval (CTFI) was included in the eligibility criteria; therefore, patients with both resistant (CTFI<90 days) or sensitive disease (CTFI≥90 days) were treated.

The primary efficacy endpoint was confirmed ORR per RECIST v.1.1 according to the investigator assessment (IA). Secondary endpoints were DOR, clinical benefit rate (objective response or stable disease ≥4 months), disease control rate (objective response or stable disease), PFS, OS, and evaluation of safety. An independent blinded review of tumour response by an Independent Review Committee (IRC) was incorporated as a secondary objective for the SCLC cohort to confirm the investigator's assessment as well as to minimise the data interpretation bias. Tumour assessments were performed every two cycles until Cycle 6 and every three cycles thereafter. Objective responses were confirmed by the same method at least four weeks after the date of the first documentation of response.

The SCLC cohort in study B-005 included 105 patients treated at 26 investigational sites in the USA (N=11 patients) and Europe, including Spain (N=59), France (N=20), Switzerland (N=7), Belgium (N=3), United Kingdom (N=3) and Italy (N=2).

Overall, patient selection criteria were chosen such that the population evaluated in this study reflected the target population of SCLC patients treated in the second-line setting. The majority were male (60.0%) with a median age (60 years) typical of this disease, including 35.2% ≥ 65 years. Among the patients treated, 92.4% were current or former smokers, 45.2% had abnormal LDH values, and 41% had liver metastases at baseline, with a median of three disease sites. Most of patients (93.3%) received lurbinectedin as second-line following a platinum-based first-line regimen. The study protocol allowed patients with prior immunotherapy: eight patients had received this type of agent as first or second-line SCLC therapy.

Overall, 74.3% of patients had responded to first-line platinum-based therapy. Of 105 patients, 45 (42.9%) had CTFI<90 days (resistant disease) and 60 (57.1%) had CTFI≥90 days (sensitive disease). Of note, 20% of patients had CTFI<30 days, a population with poor prognosis and usually not included in clinical trials.

Table 56: Summary of efficacy results in the overall population (All Treated Patients, B-005, SCLC cohort; end-of-study analysis)

Parameter	Overall (n=105)	
	IA [a]	IRC [a,b]
ORR, % (95% CI)	36.2 (27.0, 46.1)	29.5 (21.0, 39.2)
Median DOR, months (95% CI)	5.3 (4.1, 6.2)	5.3 (4.9, 5.9)
DOR at 6 months, % (95% CI)	37.8 (22.2, 53.5)	32.5 (15.1, 49.8)
Disease control rate (CR+PR+SD), % (95% CI)	68.6 (58.8, 77.3)	64.8 (54.8, 73.8)
Median PFS, months (95% CI)	3.7 (2.6, 4.3)	3.4 (2.6, 4.1)
Median OS, months (95% CI)	8.1 (6.5, 10.9)	

a Agreement between objective response reported by IA and IRC in all treated patients was 73.7%. An ad-hoc analysis measuring the concordance between IA and IRC assessment shows a Weighted Kappa Coefficient of 0.7374 (p≤0.0001).

b Five patients were not evaluable by IRC.

CI, confidence interval; CR, complete response; DOR, duration of response; IA, Investigator assessment; IRC, Independent Review Committee; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.

Table 57: Survival outcomes in responding patients by Investigator assessment (B-005, SCLC cohort; end-of-study analysis)

	Overall (n=38)	**Resistant (CTFI<90 days)** (n=10)	**Sensitive (CTFI≥90 days)** (n=28)
Overall survival (OS) in responding patients			
Number of events, n (%)	35 (92.1)	10 (100.0%)	25 (89.3%)
Median OS, months (95% CI)	13.7 (10.2-16.0)	10.0 (6.3-14.0)	15.3 (10.8-19.5)
OS at 12 months, % (95% CI)	55.3 (39.5-71.1)	40.0 (9.6-70.4%)	60.7 (42.6-78.8)
OS at 24 months, % (95% CI)	21.1 (8.1-34.0)	-	28.6 (11.8-45.3)

CI, confidence interval; CTFI, chemotherapy-free interval; OS, overall survival.

5.3.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

5.3.6. Overall discussion and conclusions on clinical efficacy

5.3.6.1. Discussion

Design and conduct of the clinical studies

Dose considerations

The recommended dose of lurbinectedin is 3.2 mg/m² by intravenous infusion every 21 days until disease progression or unacceptable toxicity, including in combination with atezolizumab. In the first-in-human study A-001 (N=31), q3wk doses from 0.02 to 5.0 mg/m² were evaluated and 4.0 mg/m² was proposed; a flat dose of 7.0 mg (≈4.0 mg/m² for BSA 1.75 m²) q3wk was subsequently explored

(N=9) and recommended for further studies.

However, later Phase 1/2 data and population PK/PD and exposure–response analyses supported a BSA-based regimen of 3.2 mg/m² IV q3wk, reducing toxicity while maintaining exposures in the target range. This dose was used in study B-005 and the pivotal IMforte trial and received preliminary support at scientific advice with a recommendation for close monitoring of haematological toxicity. Population modelling supported efficacy with manageable toxicity; no significant exposure–response with PFS or OS was demonstrated, although higher exposures were associated with numerically longer survival. In IMforte, pharmacokinetics was comparable in combination with atezolizumab, and the safety profile was consistent with the individual medicinal products. Hematologic toxicity was confirmed as exposure-related, but overall, the dose is considered justified. For further details, please refer to the clinical pharmacology section.

Study design and population

Pivotal study GO43104 is a Phase 3, randomized, open-label, multicentre study of lurbinectedin in combination with atezolizumab compared with atezolizumab alone administered as maintenance therapy in participants with ES-SCLC after first-line induction therapy with carboplatin, etoposide, and atezolizumab. Participants were required to have an ongoing response or SD per RECIST v1.1 after completion of 4 cycles of carboplatin, etoposide, and atezolizumab induction treatment in order to be considered for eligibility screening for the maintenance phase. Enrolment was planned for 690 participants in the induction phase, with 450 participants randomised in the maintenance phase (225 per treatment group).

Overall, the induction phase enrolled treatment-naïve patients with newly diagnosed ES-SCLC, who met general safety and biomarker collection requirements in line with previous studies with atezolizumab (IMpower133), while the maintenance phase selected a responder-rich, fitter population that both tolerated and benefited from induction treatment, requiring closer timing and recovery criteria before continued therapy. Exclusion criteria largely overlap between phases but are more stringent for the maintenance phase regarding recovery from toxicity, timing of infections, and need for stable disease control. The main patient characteristics are reflected in section 5.1 of the SmPC. Additional information is provided in section 4.4 mentioning that lurbinectedin in combination with atezolizumab should be used with caution in patients with ECOG performance status ≥2; central nervous system (CNS) metastases, a history of autoimmune disease, or administration of systemic immunosuppressive medicinal products within 1 week prior to treatment initiation, due to the absence of data. While this approach provides a more homogeneous setting for evaluating maintenance treatment, it excluded those with early progression, treatment-limiting toxicity, or delayed recovery.

The regimen and comparator align with ESMO 2021 ES-SCLC guidelines. Prophylactic cranial irradiation was allowed per investigator decision.

Premedication with G-CSF and anti-emetics was mandatory for participants assigned to the lurbinectedin arm and this is reflected in the SmPC accordingly; however, not all participants in the lurbinectedin arm received premedication. The reasons for omission of prophylaxis were not collected, which is acceptable. Concomitant medication uses reflected protocol requirements: in the randomized phase, prophylactic G-CSF was administered to 83.9% of patients in the combination arm versus 10.0% in the atezolizumab arm. Prophylactic antiemetics and corticosteroids were also substantially more frequent with the combination (77.7% and 72.7%) than with atezolizumab alone (23.7% and 14.5%).

Tumour assessment criteria applied in this study are largely consistent with RECIST version 1.1, including the definitions of measurable and non-measurable lesions, size thresholds and measurement methods with some adaptations in maintenance and follow-up. Lesions could be reassigned at

maintenance screening, especially for patients with CR but residual disease; patients with no radiographic evidence of disease at maintenance baseline were considered progressed at the appearance of any new lesion. These adaptations are considered acceptable but should be acknowledged as deviations from standard RECIST.

Randomisation was carried out after induction therapy**.** Randomization was stratified by ECOG PS at maintenance baseline (0 vs 1), LDH at maintenance baseline (≤ULN vs >ULN), presence of liver metastases at induction baseline (yes vs no), and prior PCI (yes vs no). ECOG, LDH, and liver metastases were agreed in the EMA Scientific Advice procedure (EMA/SA/0000053581).

The study was open-label due to the required pre-medication in the lurbinectedin arm and the distinct safety profile. To minimise bias tumour assessments were conducted at the same frequency in both arms using RECIST v1.1 criteria and PFS was assessed as a primary endpoint by a blinded independent review facility (IRF).

The primary objective of the study was to evaluate the efficacy of lurbinectedin in combination with atezolizumab compared with atezolizumab monotherapy in participants with ES-SCLC, with ongoing response or SD after completion of 4 cycles of carboplatin, etoposide, and atezolizumab induction treatment based on IRF-assessed PFS according to RECIST v1.1 and OS as dual primary endpoints.

In Scientific Advice (EMA/SA/0000053581), OS as a fully objective endpoint, was recommended by CHMP as the only primary endpoint in this poor prognosis setting, with concerns on clinical relevance of PFS and potential bias due to the open-label design. PFS was recommended as a secondary endpoint; however, if retained, independent review, sensitivity analyses, and bias minimisation measures were advised. In this context, the use of IRF-assessed PFS alongside OS as dual primary endpoints is acceptable.

The secondary and exploratory endpoints are appropriate and clinically relevant for patients with ES-SCLC. While investigator assessed PFS is of limited value in an open-label study, it supplements IRF-assessed PFS and the concordance of two outcomes makes the results more reliable. The same applies for inv-ORR and inv-DOR. PROs are also of limited value, due to missing data and open-label nature of study, but nevertheless, they are needed in order to capture data on patient safety and tolerance of therapy.

The applicant confirmed that the same intercurrent events defined for the primary objectives apply to the secondary efficacy objectives and the same treatment policy strategy was used for secondary endpoints.

The planned statistical methods for the analysis of the primary and secondary endpoints are standard and well-suited for the data types in this trial. The presented censoring rules for time-to-event endpoints appear acceptable.

The use of a group sequential weighted Holm procedure to control overall type I error (α) of 0.05 (2-sided) for the primary endpoints of OS (2-sided α=0.049) and IRF-assessed PFS (a 2-sided α=0.001) is acceptable. The study sample size was calculated according to OS, which is supported. The study has power of 85 % to detect hazard ratio of 0.71, corresponding to prolongation of median survival time from 12.5 to 17.6 months. The calculations generally appear appropriate considering assumptions used.

However, late changes in the Study protocol, which include change in the α-spending function and which also affected assumptions for sample size calculation, were of concern.

Namely, with CSP version 7 (27 November 2023), substantial changes in the assumptions for sample size calculation, required number of events for the OS analysis and follow-up time duration were introduced. Compared with CSP v6, the assumptions that PFS and OS follow exponential distributions

were removed, the interim OS boundary was changed from O'Brien–Fleming boundary to Hwang–Shih–DeCani alpha spending function with gamma -1.5 and a minimum follow-up of 5 months from randomization of the target sample size of 450 patients was added in addition to the required 219 OS events. This increased the required OS events at final analysis from 313 (EPR 70%) to 323 (EPR 72%) to maintain the same overall power. The γ value of -1.5 was chosen to allow spending more alpha earlier while minimizing impact on the minimum detectable difference (MDD 0.793 vs 0.8 in v6); however, the MDD at interim analysis was not stated, so its clinical relevance cannot be discussed. The change of α-spending function was justified by potential impact of non-protocol systemic anti-cancer therapy, specifically cross-over to lurbinectedin after progression, with approximately 25% of control patients anticipated to receive lurbinectedin (unexplained approximation). This justification is not methodologically standard, as treatment switching is typically addressed via sensitivity analyses rather than adjustment of the alpha-spending function.

Initially, the enrolment was projected at ~18 months with a 65% conversion rate, actual enrolment and randomization lasted approximately 26 and 23 months, with an observed conversion rate of 73%. The minimum 5-month follow-up was introduced to achieve an estimated median follow-up of ~16 months at interim, close to the target median OS of 17.6 months, although no details were provided on how this estimate was derived. At 249 events (minimum 5-month follow-up), the OS analysis was statistically significant (p=0.0174) under both Hwang–Shih–DeCani (boundary 0.0313) and O'Brien–Fleming (boundary 0.0214). A tipping point analysis showed that even with a more conservative gamma value (−4.5), slightly more conservative than O'Brien–Fleming, statistical significance would have been retained. However, the originally planned interim analysis was negative, approximately half of patients had not yet experienced an OS event at IA and long-term survival estimates were based on limited numbers at risk with reduced minimum exposure. Although median follow-up is close to the expected median survival, maturity of data should be judged in the context of how events are distributed over time, extent of censoring, and consistency of the estimated treatment effect. When a substantial proportion of patients are enrolled late and contribute limited follow-up, the trial may accumulate the required number of events yet still lack meaningful long-term observation. In this setting, even if the median follow-up appears adequate from a mathematical standpoint, the reduced minimum exposure remains a key source of uncertainty in the IMforte findings. Although amendments were operational and not data-driven, they facilitated earlier alpha spending and increased the likelihood of statistical success at IA.

Therefore, although use of a more liberal alpha spending function is not considered acceptable to address cross-over of patients from control arm to lurbinectedin, this change did not affect the study results.

Efficacy data and additional analyses

Overall, 483 participants were randomized to the maintenance phase of the study, with balanced allocation across treatment arms (242 participants in the atezolizumab + lurbinectedin arm and 241 participants in the atezolizumab arm; FAS). One participant randomized into the atezolizumab arm did not receive study treatment and was excluded from the SAS. The percentage of screen failures for maintenance treatment was 11.5%. The main reasons for not meeting eligibility criteria were non-completion of induction phase and disease progression, which may have an impact on generalizability.

In general, baseline demographic and disease characteristics were well balanced between the treatment arms. Participants were predominantly White (81.6%) and male (62.5%). The median age was 66 years (range: 35–85), with 51.2% of participants ≥65 years in the atezo + lurbi arm versus 62.7% in the atezolizumab arm; 30 participants in the combination arm and 33 in the control arm were ≥75 years. The majority of participants were from Europe and the Middle East (79.5%) with a history of tobacco use (97.5%). As per protocol requirement, all participants had a high functional

status (ECOG PS 0 or 1), had LDH levels at or below the ULN at randomization (73.5%), did not have liver metastases at enrolment (59.8%) and had not previously received PCI at randomization (85.3%).

The majority of participants randomized to receive maintenance treatment were initially diagnosed with ES-SCLC (91.5%). The median time from diagnosis of ES-SCLC to study enrolment was 0.7 months. Overall, 88.0% of randomized participants had achieved a CR or PR to induction treatment, 11.1% had achieved SD, and 4 participants (0.8%) were randomized despite having experienced disease progression and were reported as major protocol deviations. At induction baseline, median tumour burden was similar between arms (atezolizumab: 123.4 mm; atezolizumab + lurbinectedin: 120.5 mm). After induction, 88.8% vs. 87.3% of patients achieved an objective response and 10.4% vs. 11.9% had stable disease; 0.8% in both arms had progressed. At maintenance baseline, median tumour burden had decreased (46.0 mm vs. 42.0 mm), median number of metastatic sites was 2 in each arm, and measurable disease rates were balanced (75.5% vs. 72.3%). Complete response occurred in 9 patients (7 in the combination arm, 2 in the control arm).

Some imbalances were noted, including metastatic subcategories (M1A: +24 patients in the combination arm; M1C: +27 patients in the control arm), and tumour stage T4 (123 [50.8%] in combination arm vs 140 [58.8%] in control arm), potentially favouring the combination arm. However, adjusted analyses showed that hazard ratios and confidence intervals remained largely unchanged. The incidence of major protocol deviations was 40.9% in the atezo + lurbi arm and 36.1% in the atezolizumab arm, but these are considered unlikely to impact the study validity.

At the time of the primary analysis of IRF-assessed PFS and interim analysis of OS (data cut-off 29 July 2024), when 249 events occurred, the study met its primary endpoints.

At the time of primary analysis of IRF-assessed PFS, 71.9% of patients in the atezo + lurbi arm experienced an event compared to 83.8% in the atezo arm. The primary endpoint IRF-assessed PFS was statistically significantly improved in the atezo + lurbi arm compared to atezo arm (median PFS 5.36 vs 2.14 months; stratified HR 0.54 [95% CI: 0.43, 0.67], $p < 0.0001$). Participants in the atezo + lurbi arm had a 46% reduction in the risk of disease progression or death. The separation of Kaplan-Meier curves was evident from approximately 1.5 months.

At the time of interim analysis of OS, 46.7% of patients in the atezo + lurbi arm had died compared to 56.4% in the atezo arm. OS was statistically significantly improved (median OS 13.24 vs 10.64 months; HR 0.73 [95% CI: 0.57, 0.95], $p = 0.0174$), corresponding to a 27% reduction in the risk of death. The separation of Kaplan-Meier curves was evident from approximately 2.5 months.

At the updated OS analysis (data cut-off 12 February 2025), 65.7% of patients in the atezo + lurbi arm had died compared to 70.1% in the atezo arm (~68% events). OS was not statistically tested, but the HR favoured the combination (median OS 13.90 vs 11.14 months; HR 0.81 [95% CI: 0.65–1.01]) and is considered descriptive.

The applicant also provided results per CSP version 6 (data cut-off 13 May 2024). These were consistent for PFS (HR 0.52; $p < 0.0001$), while OS was not statistically significant (HR 0.78; $p = 0.0706$) and remained immature.

Handling of non-protocol anticancer therapy (NPT) prior to IRF-PFS events was described. NPT use occurred in 14/242 (5.8%) patients in the atezolizumab + lurbinectedin arm and 6/241 (2.5%) patients in the atezolizumab arm. For most of these patients (15/20: 10 in the combination arm, 5 in the control arm, data not shown), NPT was initiated after assessment of disease progression by the investigator (11 patients) or withdrawal of consent (4 patients), minimizing potential PFS bias. For the remaining 5 patients, narratives were provided to clarify reasons for NPT initiation.

A sensitivity analysis counting NPT initiation prior to IRF-PFS as a progression event confirmed robustness (stratified HR 0.55 [95% CI 0.45–0.68] vs primary IRF-PFS HR 0.54 [95% CI 0.43–0.67]), see Table 52. For OS, a supplementary analysis assessing the impact of NPT was consistent with the interim OS analysis (Table 53).

No multiplicity control was foreseen for secondary endpoints. The investigator-assessed PFS was improved in the atezo + lurbi arm (median PFS 5.36 vs 2.73 months; HR 0.55 [95% CI: 0.45–0.68]), and consistent with the IRF-PFS. The IRF-assessed ORR favoured the combination (19.4% vs 10.4%), and the investigator-assessed ORR also favoured the combination (17.1% vs 13.2%), although interpretation is limited due to discrepancies in analysis sets.

The DOR results were inconsistent between IRF and investigator assessments (IRF median DOR: 9.00 vs 5.62 months; investigator median DOR: 11.93 vs 5.75 months) and are of limited interpretability. Overall, IRF-based results are considered more robust and less susceptible to bias.

Pre-specified sensitivity and supplementary analyses of IRF-assessed PFS, including handling of missed assessments and NPT, were consistent with the primary analysis (HR 0.50–0.58). Subgroup analyses were generally consistent with FAS analyses, including by age (<65 vs ≥65 years). Analyses by measurable vs non-measurable disease showed consistent PFS and OS benefit (measurable: median PFS 4.50 vs 1.71 months, median OS 12.25 vs 10.12 months; non-measurable: median PFS 7.29 vs 2.83 months, median OS 16.36 vs 12.16 months). Landmark analyses showed numerically higher PFS and OS rates in the combination arm, though gains declined over time.

Censoring rules and handling of intercurrent events were acceptable. Censoring occurred in 63 patients (26.0%) at the last tumour assessment and 5 (2.1%) at randomization in the atezo + lurbi arm vs 39 patients (16.2%) in the atezo arm (all at last tumour assessment). A higher proportion of censored participants in the combination arm likely reflects fewer PFS events and improved disease control.

Some imbalances in subsequent therapies and progression patterns were observed, including higher proportion of brain radiotherapy in the combination arm (DCO 12 February 2025: 24.0% vs 14.5%) and first progression in the brain (27.3% vs 10.4%). However, time to first progression in the brain was longer in the combination arm (median 4.30 vs 2.76 months), with no evidence of faster progression.

Discrepancies between IRF and investigator assessments of measurable disease (IRF: 357; investigator: 410) and ORR populations were noted but attributed to study design rather than missing data. Overall, these factors are not considered to meaningfully impact the robustness or interpretation of the efficacy results.

There was no evidence that atezo ADA positivity had an impact on the IRF-assessed PFS and OS, but interpretation is hampered by a low number of atezo ADA-positive patients.

Indirect comparison to approved treatments and its effects is not straightforward due to different study designs, baseline population characteristics and comparators. It is additionally complicated as lurbinectedin add-on treatment is intended for maintenance treatment only after initial response to induction with atezo + chemotherapy, while previously approved products are indicated for 1L treatment of ES-SCLC (as induction + maintenance treatment).

SCLC cohort of the Phase 2, basket, open-label, non-comparative, multicentre study (B-005) is submitted as **supportive evidence**. Supportive study data showed lurbinectedin activity in 2L SCLC. Thus, the supportive study is of limited relevance for the 1L indication.

5.3.6.2. Conclusions on the clinical efficacy

Pivotal study GO43104 is a randomised, open-label, Phase 3 trial assessing maintenance atezolizumab and lurbinectedin in responders with ES-SCLC after first-line induction. The maintenance setting isolates the effect of continued therapy.

The study met its dual primary endpoints. Median OS was prolonged by ~2.5–2.8 months with lurbinectedin, corresponding to a 27% reduction in risk of death. Median PFS was prolonged by ~3 months, with a 46% reduction in risk of progression or death. Pre-specified sensitivity, supplementary, and subgroup analyses support the robustness of findings.

Late protocol changes affecting OS assumptions and α-spending raise some uncertainty, and final OS data remain exploratory. Overall, atezolizumab + lurbinectedin demonstrated clinically meaningful improvement in OS (~12% 12-month gain) and PFS, supporting a favourable benefit–risk profile in selected ES-SCLC patients.

5.4. Clinical safety

Please refer to the table of studies in section 5.1.2. .

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse drug reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

Table 58: Summaries for safety data collection

The following data were to be summarized for enrolled patients during the induction phase in tabular format:	The following data were to be summarized by treatment arm for randomized patients during the maintenance phase in tabular format:	The following listings from the clinical database will be available for enrolled patients during the induction phase and for randomized patients during the maintenance phase if requested in the closed reports:
• Patient disposition • Exposure to study treatment	• Demographics and maintenance baseline characteristics	• Serious adverse events

• Deaths and causes of death • All adverse events • Serious adverse events • NCI CTCAE Grades ≥ 3 adverse events	• Major protocol deviations • Patient disposition • Exposure to study treatment • Deaths and causes of death • Adverse events summary • All adverse events • Serious adverse events • NCI CTCAE Grade ≥ 3 adverse events • Adverse events leading to discontinuation of any study treatment • Treatment-related adverse events • Adverse events of special interest • Clinically relevant laboratory shifts from baseline	• NCI CTCAE Grade ≥ 3 adverse events • Adverse events leading to discontinuation of study treatment • Listing of deaths

Safety data from the atezolizumab + lurbinectedin arm and atezolizumab arm of the IMforte study based on the safety analysis set (SAS) are summarised and displayed side by side with the pooled Atezo Mono population (N = 3178) and the pooled Lurbi Mono population (N = 554). Caution should be exercised when analysing the data as these pooled data are not intended for a direct comparison to the IMforte data due to the variation in sample sizes, disease stages, line of therapies, treatment durations, and indications.

Table 59: Overview of pooling strategy for the Lurbi Mono population

Study	No. of patients receiving lurbinectedin
B-005	335
C-004	219
Total	**554**

Table 60: Overview of pooling strategy for the Atezo Mono population

Study	No. of patients receiving atezolizumab
OAK	609
POPLAR	142
BIRCH	659
FIR	137
IMvigor211	459
IMvigor210	429
IMmotion150	103
PCD4989g	640
Total	**3178**

The safety data collection and reporting methodology of each study that comprises the safety dataset is summarised below.

Table 61: Per protocol adverse event collection for studies in Summary of Clinical Safety

Study	Up to 30 days from last dose [a]	Up to 90 days from last dose [a]	After the AE reporting period
Pivotal study			
IMforte	All AEs regardless of relationship	All SAEs and AESIs [c] regardless of relationship	All SAEs or AESIs considered to be related to prior treatment with study drug
Atezolizumab monotherapy studies			

OAK	All AEs regardless of relationship	N/A	Non-PD deaths, regardless of relationship to study drug, and SAEs or other AEs of concern considered related to prior treatment with study drug
POPLAR	N/A	All AEs regardless of relationship	Non-PD deaths, regardless of relationship to study drug, and SAEs or other AEs of concern considered related to prior treatment with study drug
BIRCH	All AEs regardless of relationship	N/A	All SAEs or other AEs of concern considered to be related to prior treatment with study drug
FIR	N/A	All AEs regardless of relationship	All SAEs or other AEs of concern considered to be related to prior treatment with study drug
IMvigor211 [b]	All AEs regardless of relationship	All SAEs and AESIs regardless of relationship	All SAEs or other AEs of concern considered to be related to prior treatment with study drug
IMvigor210	All AEs regardless of relationship	N/A	All SAEs considered to be related to prior treatment with study drug
IMmotion150	All AEs regardless of relationship	All SAEs and AESIs regardless of relationship	All SAEs or other AEs of concern considered to be related to prior treatment with study drug
PCD4989g	N/A	All AEs regardless of relationship	All SAEs considered to be related to prior treatment with study drug
Lurbinectedin monotherapy studies			
B-005	All AEs regardless of relationship	N/A	All SAEs considered to be related to prior treatment with study drug
C-004	All AEs regardless of relationship	N/A	All SAEs considered to be related to prior treatment with study drug

[a] Or until initiation of another non-protocol systemic anti-cancer therapy, whichever occurs first.

[b] Note that SAEs and AESIs in this study have different reporting requirements.

[c] Note that AESIs for IMforte and atezolizumab monotherapy studies refer to AESIs for atezolizumab.

AE, adverse event; AESI, adverse event of special interest; N/A, not applicable; PD, progressive disease; SAE, serious adverse event.

Verbatim descriptions of AEs were mapped to the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms. MedDRA v.27.0 was used for the IMforte study and the pooled Atezo Mono and pooled Lurbi Mono populations.

Per the IMforte study protocol, the schedule of activities included safety monitoring at every study visit. For participants at participating sites who have signed Informed Consent to take part in mobile nursing visits, this assessment or procedure may be performed by a trained nursing professional at the participant's home or another suitable location. The investigator recorded all relevant adverse event or serious adverse event information on the eCRF, and assessed severity using NCI CTCAE v5.0 grading scale, and ASTCT Grading Scale for Cytokine Release Syndrome.

5.4.2. Patient exposure

Table 62: Summary of studies contributing to safety evaluation

Study No.	Study design	Population	No. of patients evaluable for safety	Dose, route, and regimen	Data cutoff date
Pivotal study					

Study No.	Study design	Population	No. of patients evaluable for safety	Dose, route, and regimen	Data cutoff date
IMforte (GO43104)	Phase III, global, open-label, multicentre, randomised study	Patients with ES-SCLC whose disease had not progressed after first-line induction therapy with atezolizumab, carboplatin, and etoposide. Patients were stratified by ECOG PS at maintenance baseline (0 *vs.* 1), LDH at maintenance baseline (≤ ULN *vs.* >ULN), presence of liver metastases at induction baseline (yes *vs.* no), and prior receipt of PCI (yes *vs.* no)	242 patients treated with atezolizumab + lurbinectedin, 240 patients treated with atezolizumab monotherapy	Atezolizumab 1200 mg i.v. q3wk Lurbinectedin 3.2 mg/m^2 i.v. q3w	Primary analysis: 29 July 2024
Atezolizumab monotherapy studies					
OAK (GO28915)	Phase III, global, open-label, multicentre, randomised study	Patients with locally advanced, metastatic, or recurrent non-squamous or squamous NSCLC who have failed a prior platinum-containing regimen (second-line and third-line). Patients were stratified by PD-L1 status (IC0 *vs.* IC1 *vs.* IC2 *vs.* IC3), number of prior chemotherapy regimens (1 *vs.* 2), and histology (non-squamous *vs.* squamous)	609 patients treated with atezolizumab monotherapy	Atezolizumab 1200 mg i.v. q3wk	Primary analysis: 7 July 2016
POPLAR (GO28753)	Phase II, global, multicentre, open-label, randomised, controlled trial	Patients with locally advanced, metastatic, or recurrent non-squamous or squamous NSCLC who have failed a prior platinum-containing regimen (second-line and third-line). Patients were stratified by PD-L1 status (IC0 *vs.* IC1 *vs.* IC2 *vs.* IC3), number of prior chemotherapy regimens (1 *vs.* 2), and histology (non-squamous *vs.* squamous)	142 patients treated with atezolizumab monotherapy	Atezolizumab 1200 mg i.v. q3wk	Updated analysis: 1 December 2015
BIRCH (GO28754)	Phase II, global, multicentre, three-cohort, single-arm trial	Patients with locally advanced or metastatic NSCLC who were treatment-naive in the metastatic setting (first-line), or had progressed during or following treatment with one platinum-based regimen (second-line), or had progressed during or following at least two regimens (third-line or beyond), one of which had to have been a platinum-containing regimen for advanced disease. Patients were PD-L1 selected (TC2/3 or IC2/3)	659 patients treated with atezolizumab monotherapy: Cohort 1 (first-line) = 139 Cohort 2 (second-line) = 268 Cohort 3 (third-line or beyond) = 252	Atezolizumab 1200 mg i.v. q3wk	Updated analysis: 1 December 2015
FIR (GO28625)	Phase II, global, multicentre, three-cohort, single-arm trial	Patients with locally advanced or metastatic NSCLC who were treatment-naive in metastatic setting (first-line, Cohort 1) or progressed during or following a prior platinum-based chemotherapy regimen without restriction to the maximum number of prior therapies (i.e., second-line or beyond; Cohort 2), or second-line or beyond patients with previously treated brain metastases (Cohort 3). Patients were PD-L1 selected (TC2/3 or IC2/3)	137 patients treated with atezolizumab monotherapy: Cohort 1 (first-line) = 31 Cohort 2 (second-line or beyond) = 93 Cohort 3 (second-line or beyond with brain metastases) = 13	Atezolizumab 1200 mg i.v. q3wk	Primary analysis: 7 January 2015
IMvigor 211 (GO29294)	Phase III, global, open-label, multicentre, randomised study	Patients with locally advanced or metastatic UC who have progressed during or following a platinum-containing regimen (second-line/third-line). Patients were stratified by chemotherapy (vinflunine *vs.* taxane), PD-L1 status (IC0/1 *vs.* IC2/3), number of risk factors, and presence of liver metastases	459 patients treated with atezolizumab monotherapy	Atezolizumab 1200 mg i.v. q3wk	Primary analysis: 13 March 2017

Study No.	Study design	Population	No. of patients evaluable for safety	Dose, route, and regimen	Data cutoff date
IMvigor 210 (GO29293)	Phase II, global, multicentre, two-cohort, single-arm trial	Patients with locally advanced or first-line metastatic UC (no prior chemotherapy in the metastatic setting and ineligible for cisplatin-based chemotherapy) or second-line or more patients with locally advanced or metastatic UC (patients who failed a prior platinum-based therapy or progressed within 12 months of a platinum-containing treatment administered in the neoadjuvant or adjuvant setting). Approximately 30% of the patient population was planned to be PD-L1 selected (IC2/3)	429 patients treated with atezolizumab monotherapy: Cohort 1 (first-line) = 119 Cohort 2 (second-line) = 310	Atezolizumab 1200 mg i.v. q3wk	Updated analysis: 4 July 2016
IMmotion150 (WO29074)	Phase II, multicentre, randomised, open-label study	Patients with histologically confirmed, inoperable, locally advanced or metastatic RCC who have not received prior systemic therapy either in the adjuvant or metastatic setting	103 patients treated with atezolizumab monotherapy	Atezolizumab 1200 mg i.v. q3wk	Primary analysis: 17 October 2016
PCD4989g (GO27831)	Phase I, open-label, dose-escalation and dose-expansion stages	Patients with locally advanced or metastatic solid tumours (including UC and NSCLC) and haematologic malignancies	640 patients treated with atezolizumab monotherapy: UC = 95, NSCLC = 89, Non-UC + Non NSCLC = 456	Atezolizumab ≤ 1, 3, 10, 15, 20 mg/kg and 1200 mg q3wk	Interim analysis: 31 March 2016
Lurbinectedin monotherapy studies					
B-005 [a]	Phase II	Previously treated patients with the following advanced solid tumours: SCLC, head and neck carcinoma, neuroendocrine tumours, biliary tract carcinoma, endometrial carcinoma, BRCA 1/2-associated metastatic breast carcinoma, carcinoma of unknown primary site, germ cell tumours, and Ewing's family of tumours.	335 (All cohorts)	Lurbinectedin 3.2 mg/m^2 i.v. q3wk	16 November 2020
C-004 [a] **(CORAIL)**	Phase III	Patients with platinum-resistant ovarian cancer.	219 (Arm A)	Lurbinectedin 3.2 mg/m^2 i.v. q3wk	12 October 2018

[a] For the sake of simplicity, the lurbinectedin study codes are abbreviated in this document as follows: B-005 instead of PM1183-B-005-14, and C-004 instead of PM1183-C-004-14.

BRCA, BReast CAncer gene; ECOG, Eastern Cooperative Oncology Group; ES-SCLC, extensive-stage small cell lung cancer; IC, tumour-infiltrating immune cell; i.v., intravenous; LDH, lactate dehydrogenase; NSCLC, non-small cell lung cancer; PCI, prophylactic cranial irradiation; PD-L1, programmed death-ligand 1; PS, performance status; q3wk, every three weeks; RCC, renal cell carcinoma; SCLC, small cell lung cancer; TC, tumour cell; UC, urothelial carcinoma; ULN, upper limit of normal.

For the IMforte study, the clinical cut-off date (CCOD) of the primary analysis was 29 July 2024 and the updated CCOD was 12 February 2025 (i.e. providing approximately an additional 6.5 months of data since the primary analysis).

Table 63: Duration of safety follow-up (Safety-Evaluable Population)

	IMforte		Pooled population	
	Atezolizumab (n=240)	**Atezolizumab + Lurbinectedin** (n=242)	**Atezo Mono** (n=3178)	**Lurbi Mono** (n=554)
Duration of safety follow-up (months)				
n	240	242	3178	554
Mean (SDev)	5.91 (3.90)	7.39 (4.37)	8.61 (7.18)	4.5 (4.2)
Median	5.06	6.44	6.01	3.1
Min - Max	0.6-23.9	0.2-25.5	0.0-53.0	0.3-37.3

	IMforte		Pooled population	
	Atezolizumab (n=240)	**Atezolizumab + Lurbinectedin** (n=242)	**Atezo Mono** (n=3178)	**Lurbi Mono** (n=554)

Max, maximum; Min, minimum; SDev, standard deviation.

Table 64: Duration of safety follow-up (Safety Analysis Set, Study GO43104, DCO 12 Feb 2025)

	Atezolizumab (N=240)	Atezolizumab+ Lurbinectedin (N=242)	All Patients (N=482)
Duration of Safety Follow-up (months)			
n	240	242	482
Mean (SD)	6.8 (5.3)	8.7 (5.5)	7.8 (5.5)
Median	5.1	7.6	5.7
Q1 - Q3	3.7 - 8.0	4.6 - 11.6	3.9 - 10.3
Min - Max	1 - 30	0 - 29	0 - 30

Duration is defined as time from the start of study treatment to the earliest of the end of study date, the treatment end date + 90 days, or the clinical cut-off date.
Data Cutoff: 12FEB2025; Rave Data Extracted: 01APR2025.

The safety follow-up lasted for 90 days following the last dose of study drug for the IMforte and Atezo Mono populations, and for 30 days following the last dose of study drug for the Lurbi Mono population.

Table 65: Exposure to Atezolizumab and Lurbinectedin, Safety Analysis Set (DCO: 29 Jul 2024)

Study Treatment Exposure, Randomization Phase, Safety Analysis Set
Protocol: GO43104

	Atezolizumab (N=240)	Atezolizumab+ Lurbinectedin (N=242)	
	Atezolizumab	Atezolizumab	Lurbinectedin
Treatment duration (months)			
n	240	242	242
Mean (SD)	3.6 (4.3)	5.2 (4.6)	5.2 (4.6)
Median	2.1	4.2	4.1
Min - Max	0 - 24	0 - 23	0 - 23
Treatment duration			
n	240	242	242
0 to <=3 months	159 (66.3%)	94 (38.8%)	96 (39.7%)
>3 months to <= 6 months	39 (16.3%)	66 (27.3%)	65 (26.9%)
>6 months to <= 12 months	26 (10.8%)	63 (26.0%)	62 (25.6%)
>12 months	16 (6.7%)	19 (7.9%)	19 (7.9%)
Dose intensity (%)			
n	240	242	242
Mean (SD)	97.9 (6.4)	96.3 (6.4)	93.7 (9.2)
Median	100.0	99.4	97.6
Min - Max	59 - 108	60 - 102	60 - 111
Number of doses received			
n	240	242	242
Mean (SD)	6.1 (6.1)	8.2 (6.2)	8.1 (6.3)
Median	4.0	7.0	6.5
Min - Max	1 - 35	1 - 32	1 - 32
Total cumulative dose (mg)			
n	240	242	242
Mean (SD)	7260.0 (7324.2)	9798.3 (7471.0)	46.1 (35.8)
Median	4800.0	8400.0	38.4
Min - Max	1200 - 42000	1200 - 38400	4 - 175

Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.
Dose intensity is the total number of doses administered divided by the total number of doses scheduled to be administered.
Data Cutoff: 29JUL2024; Rave Data Extracted: 01OCT2024.

Table 66: Exposure to Atezolizumab and Lurbinectedin (Safety Analysis Set, Study GO43104, DCO 12 Feb 2025)

	Atezolizumab (N=240)	Atezolizumab+ Lurbinectedin (N=242)	
	Atezolizumab	Atezolizumab	Lurbinectedin
Treatment duration (months)			
n	240	242	242
Mean (SD)	4.4 (5.7)	6.3 (5.7)	6.2 (5.7)
Median	2.1	4.8	4.4
Min - Max	0 - 30	0 - 28	0 - 28
Treatment duration			
n	240	242	242
0 to <=3 months	158 (65.8%)	90 (37.2%)	92 (38.0%)
>3 months to <= 6 months	31 (12.9%)	51 (21.1%)	50 (20.7%)
>6 months to <= 12 months	24 (10.0%)	68 (28.1%)	68 (28.1%)
>12 months to <= 18 months	15 (6.3%)	22 (9.1%)	21 (8.7%)
>18 months	12 (5.0%)	11 (4.5%)	11 (4.5%)
Dose intensity (%)			
n	240	242	242
Mean (SD)	98.0 (5.9)	96.0 (6.8)	94.1 (14.7)
Median	100.0	99.0	97.4
Min - Max	59 - 108	56 - 102	56 - 266
Number of doses received			
n	240	242	242
Mean (SD)	7.1 (8.1)	9.5 (7.8)	9.4 (7.9)
Median	4.0	7.5	7.0
Min - Max	1 - 44	1 - 40	1 - 40
Total cumulative dose (mg)			
n	240	242	242
Mean (SD)	8506.1 (9704.4)	11421.0 (9399.7)	54.3 (48.8)
Median	4800.0	9000.0	43.0
Min - Max	1200 - 52800	1200 - 48000	4 - 375

Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.
Dose intensity is the total number of doses administered divided by the total number of doses scheduled to be administered.
Data Cutoff: 12FEB2025; Rave Data Extracted: 01APR2025.

5.4.3. Adverse events

Information in this section is presented through a side by side summary of safety data with clinical cut-off dates (CCOD) of 29 July 2024 and/or of 12 February 2025 where updated data sets were submitted. Data was presented by the applicant through the Safety Analysis Set (safety data accumulated through the Randomisation Phase i.e. maintenance period treatment with lurbinectedin) and through a Safety-Evaluable Population Set with the pooling strategy as mentioned in section 5.4.1.

Safety Analysis Set (Randomization Phase) – CCOD 12 February 2025

Table 67: Adverse events with an incidence rate of at least 10% in any treatment arm by system organ class and Preferred Term, Randomization Phase, Safety Analysis Set

MedDRA System Organ Class	MedDRA Preferred Term	Atezolizumab (N=240)	Lurbinectedin (N=242)
Gastrointestinal disorders	Nausea	11 (4.6%)	91 (37.6%)
	Diarrhoea	20 (8.3%)	38 (15.7%)
	Vomiting	6 (2.5%)	36 (14.9%)
	Constipation	15 (6.3%)	31 (12.8%)
	Fatigue	20 (8.3%)	51 (21.1%)

General disorders and administration site conditions	Asthenia	16 (6.7%)	34 (14.0%)
Blood and lymphatic system disorders	Anaemia	17 (7.1%)	82 (33.9%)
	Thrombocytopenia	4 (1.7%)	31 (12.8%)
	Neutropenia	4 (1.7%)	30 (12.4%)
Investigations	Platelet count decreased	7 (2.9%)	37 (15.3%)
	Neutrophil count decreased	3 (1.3%)	32 (13.2%)
Metabolism and nutrition disorders	Decreased appetite	16 (6.7%)	44 (18.2%)
Respiratory, thoracic and mediastinal disorders	Dyspnoea	20 (8.3%)	26 (10.7%)

Notes: Data cutoff-12FEB2025, for frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. AEs included are those occurring on or after the start of atezolizumab or lurbinectedin during the Randomisation Phase. AEs were encoded using MedDRA version 27.1.

Table 68: Adverse Events with a Difference of at Least 5% between treatment arms by preferred term (Safety Analysis Set)

MedDRA Preferred Term	Atezolizumab (N=240)	Atezolizumab + Lurbinectedin (N=242)
Nausea	11 (4.6%)	91 (37.6%)
Anaemia	17 (7.1%)	82 (33.9%)
Fatigue	20 (8.3%)	51 (21.1%)
Decreased appetite	16 (6.7%)	44 (18.2%)
Diarrhoea	20 (8.3%)	38 (15.7%)
Asthenia	16 (6.7%)	34 (14.0%)
Constipation	15 (6.3%)	31 (12.8%)
Platelet count decreased	7 (2.9%)	37 (15.3%)
Vomiting	6 (2.5%)	36 (14.9%)
Neutrophil count decreased	3 (1.3%)	32 (13.2%)
Thrombocytopenia	4 (1.7%)	31 (12.8%)
Neutropenia	4 (1.7%)	30 (12.4%)
Dizziness	5 (2.1%)	19 (7.9%)
White blood cell count decreased	5 (2.1%)	19 (7.9%)
COVID-19	4 (1.7%)	17 (7.0%)
Phlebitis	0	17 (7.0%)

Notes: Data cutoff-12FEB2025

Safety-Evaluable Population Set – CCOD 29 July 2024

Table 69: Adverse events by preferred term with an incidence rate of at least 10% in any treatment group (Safety-Evaluable Population)

MedDRA PT	IMforte		Pooled population	
	Atezolizumab (n=240)	Atezolizumab + Lurbinectedin (n=242)	Atezo Mono (n=3178)	Lurbi Mono (n=554)
Fatigue	19 (7.9%)	49 (20.2%)	1142 (35.9%)	350 (63.2%)[a]
Nausea	10 (4.2%)	88 (36.4%)	747 (23.5%)	317 (57.2%)

Anaemia	16 (6.7%)	77 (31.8%)	505 (15.9%)	119 (21.5%)
Decreased appetite	16 (6.7%)	41 (16.9%)	810 (25.5%)	139 (25.1%)
Platelet count decreased	7 (2.9%)	37 (15.3%)	37 (1.2%)	11 (2.0%)
Diarrhoea	18 (7.5%)	34 (14.0%)	624 (19.6%)	105 (19.0%)
Vomiting	6 (2.5%)	33 (13.6%)	477 (15.0%)	168 (30.3%)
Asthenia	15 (6.3%)	31 (12.8%)	461 (14.5%)	0[a]
Thrombocytopenia	4 (1.7%)	31 (12.8%)	82 (2.6%)	36 (6.5%)
Neutrophil count decreased	3 (1.3%)	31 (12.8%)	5 (0.2%)	29 (5.2%)
Constipation	15 (6.3%)	29 (12.0%)	652 (20.5%)	179 (32.3%)
Neutropenia	4 (1.7%)	26 (10.7%)	36 (1.1%)	160 (28.9%)
Dyspnoea	18 (7.5%)	24 (9.9%)	651 (20.5%)	87 (15.7%)
Cough	16 (6.7%)	23 (9.5%)	660 (20.8%)	57 (10.3%)
Arthralgia	12 (5.0%)	20 (8.3%)	580 (18.3%)	37 (6.7%)
Pruritus	17 (7.1%)	18 (7.4%)	406 (12.8%)	11 (2.0%)
Headache	6 (2.5%)	15 (6.2%)	352 (11.1%)	50 (9.0%)
Pyrexia	2 (0.8%)	13 (5.4%)	639 (20.1%)	74 (13.4%)
Back pain	9 (3.8%)	13 (5.4%)	481 (15.1%)	55 (9.9%)
Urinary tract infection	4 (1.7%)	12 (5.0%)	338 (10.6%)	26 (4.7%)
Oedema peripheral	4 (1.7%)	12 (5.0%)	332 (10.4%)	52 (9.4%)
Abdominal pain	4 (1.7%)	12 (5.0%)	268 (8.4%)	104 (18.8%)
Rash	6 (2.5%)	8 (3.3%)	358 (11.3%)	15 (2.7%)

ISS, Integrated Summary of Safety; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term. The frequencies of adverse reactions included in Table 3 of Section 4.8 of the SmPC are based on all-cause AE frequencies identified in the IMforte clinical trial (Preferred Terms merged in this table have been reflected in its footnote; a Fatigue and asthenia were reported together in the ISS for lurbinectedin.

Table 70: Adverse Event Summary (Safety-Evaluable Population)

	IMforte		**Pooled population**	
	Atezolizumab (n=240)	**Atezolizumab + Lurbinectedin** (n=242)	**Atezo Mono** (n=3178)	**Lurbi Mono** (n=554)
Total number of patients with at least one AE	194 (80.8%)	235 (97.1%)	3051 (96.0%)	545 (98.4%)
Total number of events	828	1912	33374	12686
Total number of patients with at least one				
Treatment-related AE	96 (40.0%)	202 (83.5%)	2167 (68.2%)	494 (89.2%)
Grade 3/4 AE	53 (22.1%)	92 (38.0%)	1482 (46.6%)	336 (60.6%)
Treatment-related grade 3/4 AE	14 (5.8%)	62 (25.6%)	496 (15.6%)	239 (43.1%)
Grade 5 AE	**6 (2.5%)**	**12 (5.0%)**	**119 (3.7%)**	**18 (3.2%)[a]**
Treatment-related grade 5 AE	1 (0.4%)	2 (0.8%)	11 (0.3%)	6 (1.1%)
SAE	41 (17.1%)	75 (31.0%)	1309 (41.2%)	225 (40.6%)
Treatment-related SAE	9 (3.8%)	28 (11.6%)	353 (11.1%)	88 (15.9%)
AE leading to treatment discontinuation	8 (3.3%)	15 (6.2%)	226 (7.1%)	52 (9.4%)
AE leading to treatment modification / interruption	33 (13.8%)	92 (38.0%)	881 (27.7%)	219 (39.5%)[b]

a Nine patients had primary cause of death recorded as progressive disease, eight patients had primary cause of death as adverse event, and one patient had primary cause of death recorded as other. b Only actual interruption/modifications are counted. Patients without further cycles of dose administration were excluded.

Table 71: Adverse Event Summary (Enrolled Safety Analysis Set) – Induction phase

	Atezolizumab+Carboplatin+Etoposide (N=653)
Total number of patients with at least one AE	611 (93.6%)
Total number of events	3512
Total number of patients with at least one Treatment-related AE	
Any Treatment	530 (81.2%)
Atezolizumab	270 (41.3%)
Carboplatin	494 (75.7%)
Etoposide	494 (75.7%)
Grade 3-4 AE	307 (47.0%)
Related to Any Treatment	259 (39.7%)
Related to Atezolizumab	63 (9.6%)
Related to Carboplatin	238 (36.4%)
Related to Etoposide	236 (36.1%)
Grade 5 AE	31 (4.7%)
Related to Any Treatment	10 (1.5%)
Related to Atezolizumab	3 (0.5%)
Related to Carboplatin	10 (1.5%)
Related to Etoposide	10 (1.5%)
Serious AE	181 (27.7%)
Related to Any Treatment	97 (14.9%)
Related to Atezolizumab	29 (4.4%)
Related to Carboplatin	78 (11.9%)
Related to Etoposide	80 (12.3%)
AE leading to withdrawal from treatment	
Any Treatment	31 (4.7%)
Atezolizumab	31 (4.7%)
Carboplatin	19 (2.9%)
Etoposide	19 (2.9%)
Total number of patients with at least one AE leading to any dose modification/interruption	
Any treatment	245 (37.5%)
Atezolizumab	181 (27.7%)
Carboplatin	210 (32.2%)
Etoposide	222 (34.0%)

Investigator text for AEs encoded using MedDRA version 27.0. Percentages are based on N in the column headings.

The Applicant provided listings for adverse events related to carboplatin and/or etoposide by System Organ Class, Preferred Term and Highest NCI CTCAE Grade. No apparent unexpected AEs occurred during chemo+azetolizumab.

Table 72: Adverse Reactions and Grade Summary in the Randomized Phase (Safety Analysis Set)

	Primary Analysis		Safety Update	
	Atezolizumab (N=240)	Atezolizumab+ Lurbinectedin (N=242)	Atezolizumab (N=240)	Atezolizumab+ Lurbinectedin (N=242)
Total number of patients with at least one adverse event	194 (80.8%)	235 (97.1%)	196 (81.7%)	235 (97.1%)
Total number of events	828	1912	927	2081
Total number of patients with at least one:				
Treatment-related AE	96 (40.0%)	202 (83.5%)	97 (40.4%)	205 (84.7%)
Atezolizumab-related AE	88 (36.7%)	136 (56.2%)	90 (37.5%)	141 (58.3%)
Lurbinectedin-related AE	0	190 (78.5%)	0	195 (80.6%)
Carboplatin-related AE	31 (12.9%)	35 (14.5%)	32 (13.3%)	36 (14.9%)
Etoposide-related AE	28 (11.7%)	35 (14.5%)	29 (12.1%)	36 (14.9%)
Grade 3-4 AE	53 (22.1%)	92 (38.0%)	59 (24.6%)	100 (41.3%)
Treatment-related Grade 3-4 AE	14 (5.8%)	62 (25.6%)	16 (6.7%)	71 (29.3%)
Atezolizumab-related Grade 3-4 AE	14 (5.8%)	33 (13.6%)	16 (6.7%)	37 (15.3%)
Lurbinectedin-related Grade 3-4 AE	0	56 (23.1%)	0	63 (26.0%)
Carboplatin-related Grade 3-4 AE	1 (0.4%)	8 (3.3%)	2 (0.8%)	8 (3.3%)
Etoposide-related Grade 3-4 AE	1 (0.4%)	8 (3.3%)	2 (0.8%)	8 (3.3%)
Grade 5 AE	6 (2.5%)	12 (5.0%)	6 (2.5%)	12 (5.0%)
Treatment-related Grade 5 AE	1 (0.4%)	2 (0.8%)	1 (0.4%)	2 (0.8%)
Atezolizumab-related Grade 5 AE	1 (0.4%)	0	1 (0.4%)	0
Lurbinectedin-related Grade 5 AE	0	2 (0.8%)	0	2 (0.8%)
Carboplatin-related Grade 5 AE	0	0	0	0
Etoposide-related Grade 5 AE	0	0	0	0
Total number of patients with at least one:				
Serious AE	41 (17.1%)	75 (31.0%)	43 (17.9%)	83 (34.3%)
Treatment-related SAE	9 (3.8%)	28 (11.6%)	9 (3.8%)	32 (13.2%)
Atezolizumab-related SAE	9 (3.8%)	20 (8.3%)	9 (3.8%)	22 (9.1%)
Lurbinectedin-related SAE	0	24 (9.9%)	0	27 (11.2%)
Carboplatin-related SAE	0	2 (0.8%)	0	2 (0.8%)
Etoposide-related SAE	0	3 (1.2%)	0	3 (1.2%)
AE leading to any study treatment withdrawal	8 (3.3%)	15 (6.2%)	10 (4.2%)	17 (7.0%)
AE leading to atezolizumab withdrawal	8 (3.3%)	6 (2.5%)	10 (4.2%)	7 (2.9%)
AE leading to lurbinectedin withdrawal	0	12 (5.0%)	0	14 (5.8%)
AE leading to any dose modification/interruption	33 (13.8%)	92 (38.0%)	38 (15.8%)	100 (41.3%)
AE leading to atezolizumab interruption	33 (13.8%)	69 (28.5%)	38 (15.8%)	79 (32.6%)
AE leading to lurbinectedin modification/interruption	0	83 (34.3%)	0	90 (37.2%)

Table 73: TEAEs of increased frequency related to any study treatment (assessor's table)

System Organ Class	MedDRA Preferred Term	Atezolizumab (N=240)	Atezolizumab + Lurbinectedin (N=242)	All Patients (N=482)
Gastrointestinal disorders	Nausea	6 (2.5%)	78 (32.2%)	84 (17.4%)
	Diarrhoea	11 (4.6%)	25 (10.3%)	36 (7.5%)
	Vomiting	1 (0.4%)	29 (12.0%)	30 (6.2%)
	Constipation	4 (1.7%)	18 (7.4%)	22 (4.6%)

	Dry mouth	7 (2.9%)	3 (1.2%)	10 (2.1%)
	Colitis	3 (1.3%)	3 (1.2%)	6 (1.2%)
	Stomatitis	1 (0.4%)	5 (2.1%)	6 (1.2%)
Blood and lymphatic system disorders	Anaemia	6 (2.5%)	73 (30.2%)	79 (16.4%)
	Thrombocytopenia	2 (0.8%)	30 (12.4%)	32 (6.6%)
	Neutropenia	2 (0.8%)	27 (11.2%)	29 (6.0%)
	Leukopenia	0	10 (4.1%)	10 (2.1%)
General disorders and administration site conditions	Fatigue	8 (3.3%)	35 (14.5%)	43 (8.9%)
	Asthenia	8 (3.3%)	26 (10.7%)	34 (7.1%)
Investigations	Platelet count decreased	5 (2.1%)	35 (14.5%)	40 (8.3%)
	Neutrophil count decreased	1 (0.4%)	31 (12.8%)	32 (6.6%)
	WBC count decreased	1 (0.4%)	16 (6.6%)	17 (3.5%)
Metabolism and nutrition disorders	Decreased appetite	9 (3.8%)	30 (12.4%)	39 (8.1%)
	Hypomagnesaemia	3 (1.3%)	7 (2.9%)	10 (2.1%)
	Hyponatraemia	2 (0.8%)	7 (2.9%)	9 (1.9%)
Skin and subcutaneous tissue disorders	Pruritus	13 (5.4%)	15 (6.2%)	28 (5.8%)
	Dry skin	7 (2.9%)	3 (1.2%)	10 (2.1%)
	Rash	5 (2.1%)	4 (1.7%)	9 (1.9%)
Endocrine disorders	Hypothyroidism	17 (7.1%)	19 (7.9%)	36 (7.5%)
	Hyperthyroidism	7 (2.9%)	8 (3.3%)	15 (3.1%)
Nervous system disorders	Neuropathy peripheral	4 (1.7%)	7 (2.9%)	11 (2.3%)
	Dysgeusia	1 (0.4%)	5 (2.1%)	6 (1.2%)
Respiratory, thoracic and mediastinal disorders	Pneumonitis	3 (1.3%)	9 (3.7%)	12 (2.5%)
	Dyspnoea	3 (1.3%)	4 (1.7%)	7 (1.5%)
Vascular disorders	Phlebitis	0	11 (4.5%)	11 (2.3%)
	Thrombophlebitis	0	9 (3.7%)	9 (1.9%)
Infections and infestations	Pneumonia	3 (1.3%)	0	3 (0.6%)
	Herpes zoster	1 (0.4%)	1 (0.4%)	2 (0.4%)
	Sepsis	1 (0.4%)	1 (0.4%)	2 (0.4%)
Musculoskeletal and connective tissue disorders	Arthralgia	4 (1.7%)	3 (1.2%)	7 (1.5%)
	Myalgia	1 (0.4%)	6 (2.5%)	7 (1.5%)
Renal and urinary disorders	Immune-mediated nephritis	1 (0.4%)	3 (1.2%)	4 (0.8%)
Hepatobiliary disorders	Cholestasis	0	2 (0.8%)	2 (0.4%)
Neoplasms (benign, malignant, etc.)	Acute myeloid leukaemia	0	1 (0.4%)	1 (0.2%)

There were no treatment-related AEs by PT with the proportion in the atezolizumab arm exceeding the proportion in the atezolizumab + lurbinectedin arm by at least 5%.

Atezolizumab vs Lurbinectedin treatment related AEs

Table 74: Differences in TEAEs of increased frequency between atezolizumab related vs lurbinectedin related as determined by investigator, Randomization Phase, Safety Analysis Set

MedDRA System Organ Class	MedDRA Preferred Term	Atezolizumab related (N=240)	Lurbinectedin related (N=242)	All Patients (N=482)
Gastrointestinal disorders	Nausea	4 (1.7%)	30 (12.4%)	34 (7.1%)
	Diarrhoea	11 (4.6%)	17 (7.0%)	28 (5.8%)
General disorders and administration site conditions	Fatigue	7 (2.9%)	33 (13.6%)	40 (8.3%)
Blood and lymphatic system disorders	Anaemia	4 (1.7%)	66 (27.3%)	70 (14.5%)
	Neutropenia	1 (0.4%)	26 (10.7%)	27 (5.6%)
Metabolism and nutrition disorders	Decreased appetite	8 (3.3%)	29 (12.0%)	37 (7.7%)
Skin and subcutaneous tissue disorders	Pruritus	13 (5.4%)	6 (2.5%)	19 (3.9%)
Endocrine disorders	Hypothyroidism	16 (6.7%)	4 (1.7%)	20 (4.1%)
Respiratory, thoracic and mediastinal disorders	Pneumonitis	3 (1.3%)	3 (1.2%)	6 (1.2%)
Nervous system disorders	Neuropathy peripheral	2 (0.8%)	5 (2.1%)	7 (1.5%)

Only skin and subcutaneous tissue disorders like pruritus (5.4% vs 2.5%) as well as endocrine disorders like hypothyroidism were more common with atezolizumab (6.7% vs 1.7%), all other events were more attributed to the combination arm with lurbinectedin.

Adverse event summary from the Induction phase (Enrolled Safety Analysis Set).

In the atezolizumab + carboplatin + etoposide arm (N=653), serious adverse events (SAEs) occurred in 181 patients (27.7%), with a total of 279 events reported. The most frequently observed SAEs were infections (9.2%), including pneumonia, sepsis, neutropenic sepsis, and COVID-19, consistent with immunosuppressive effects of cytotoxic chemotherapy. Hematologic toxicities were also common, affecting 53 patients (8.1%), predominantly anaemia and febrile neutropenia, possibly reflecting the expected myelosuppressive profile of platinum–etoposide. Other less frequent SAEs involved metabolic (2.9%), gastrointestinal (2.6%), respiratory (2.3%), cardiac (1.4%), and neurologic (1.2%) systems, as well as isolated events across vascular, musculoskeletal, renal, endocrine, psychiatric, and hepatobiliary categories. Overall, the pattern, frequency, and distribution of SAEs are consistent with the known safety profile of platinum–etoposide chemotherapy in patients with extensive-stage SCLC, and no new or unexpected safety signals were identified.

In the atezolizumab + carboplatin + etoposide arm (N=653), **Grade 5 adverse events occurred in 31 patients (4.7%)**, consistent with the known safety profile of platinum–etoposide chemotherapy in patients with extensive-stage SCLC. The majority of fatal events were infections (19 patients; 2.9%), including sepsis, pneumonia, neutropenic sepsis, and septic shock, reflecting the immunosuppressive effects of cytotoxic therapy. Other reasons for death were across cardiovascular (n=2; 0.3%), respiratory (n=3; 0.5%), vascular (n=2; 0.3%), and general disorder categories (n=4; 0.6%), with sudden cardiac death or acute cardiopulmonary events noted in a small number of patients. Overall,

the pattern and frequency of fatal events are consistent with expectations for this patient population and treatment regimen, with no new safety signals identified beyond the established toxicity profile of chemotherapy in ES-SCLC.

5.4.3.1. Adverse drug reactions

In accordance with Appendix 3 to the Guideline on the clinical evaluation of anticancer medicinal products, the frequencies of adverse reactions in section 4.8 of the SmPC are based on all-cause AE frequencies identified in patients exposed to lurbinectedin in combination with atezolizumab in the IMforte study (N= 242).The Applicant performed a comprehensive review of the adverse drug reactions (ADRs) observed in the pivotal IMforte study, focusing specifically on those for which the absolute difference in incidence between the lurbinectedin plus atezolizumab arm and the atezolizumab monotherapy arm was ≥2% with additional selected ADRs of clinical relevance. Additional adverse reactions with a rare frequency (rhabdomyolysis and tumour lysis syndrome) reported in post-marketing have also been added in section 4.8 of the SmPC. The Preferred Terms for adverse reactions included in section 4.8 of the SmPC are merged as follows:

- Upper respiratory tract infection: includes upper respiratory tract infection, nasopharyngitis, pharyngitis, viral upper respiratory tract infection, catarrh.
- Covid-19: includes COVID-19, COVID-19 pneumonia.
- Respiratory tract infection: includes respiratory tract infection, bronchitis, influenza.
- Urinary tract infection: includes urinary tract infection cystitis.
- Thrombocytopenia: includes platelet count decreased, thrombocytopenia.
- Neutropenia: includes neutropenia, neutrophil count decreased.
- Leukopenia: includes leukopenia, white blood cell count decreased.
- Lymphopenia: includes lymphocyte count decreased, lymphopenia.
- Hypomagnesaemia: includes blood magnesium decreased, hypomagnesaemia.
- Neuropathy peripheral: includes hypoesthesia, neuropathy peripheral, paraesthesia, peripheral sensory neuropathy.
- Abdominal pain: includes abdominal discomfort, abdominal distension, abdominal pain, abdominal pain upper.
- Musculoskeletal pain: includes back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, pain in extremity.
- Fatigue: includes asthenia, fatigue.
- Oedema: includes oedema, oedema peripheral.
- Transaminase increase: includes alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased.

Table 75: ADRs proposed for inclusion in the SmPC

Frequency category (any grade)	Adverse Reaction by System Organ Class	Any grade (%)	Grade ≥3 (%)
Infections and infestations			
Common	Pneumonia	5.4	3.3

Frequency category (any grade)	Adverse Reaction by System Organ Class	Any grade (%)	Grade ≥3 (%)
	Urinary tract infection[a]	5.4	0.4
	Infection	3.3	1.2
	Skin infection[b]	2.1	0.4
Uncommon	Sepsis	0.4	0.4
Blood and lymphatic system disorders			
Very common	Anaemia	33.9	9.5
	Thrombocytopenia	27.7	11.2
	Neutropenia	25.2	12.4
	Leukopenia	12.4	2.9
Common	Lymphopenia	5.4	2.1
	Febrile neutropenia	1.7	1.7
Uncommon	Pancytopenia	0.4	0.4
Endocrine disorders			
Common	Hypothyroidism	7.9	0
Metabolism and nutrition disorders			
Very common	Decreased appetite	18.2	0.8
Common	Hypomagnesaemia	5.4	0.4
	Hypocalcaemia	4.5	0.8
Very rare	Tumour Lysis Syndrome[c]	frequency not known	-
Nervous system disorders			
Common	Neuropathy peripheral[d]	8.3	0.8
	Headache	6.6	0
	Dysgeusia	2.9	0
Vascular disorders			
Common	Phlebitis	7.0	0
	Thrombophlebitis	4.5	0.4
Respiratory, thoracic and mediastinal disorders			
Very common	Dyspnoea	10.7	2.5
Common	Cough	9.9	0
	Pneumonitis	4.5	0.8
	Productive cough	4.1	0
Gastrointestinal disorders			
Very common	Nausea	37.6	2.9
	Diarrhoea	15.7	0.4
	Vomiting	14.9	0.8
	Constipation	12.8	0
Common	Abdominal pain[e]	9.9	0.4
	Dyspesia	4.5	0
	Stomatitis	2.5	0
Skin and subcutaneous tissue disorders			
Common	Pruritus	7.9	0.4
	Rash	5.8	0
Musculoskeletal and connective tissue disorders			
Very common	Musculoskeletal pain[f]	15.7	0.8
Common	Arthralgia	8.3	1.2
Rare	Rhabdomyolysis[c]	frequency not known	-
General disorders and administration site conditions			
Very common	Fatigue[g]	34.3	5.0
Common	Oedema[h]	6.2	0.4
	Pyrexia	5.4	0
	Peripheral swelling	4.5	0.4
	Extravasation[i]	3.3	0

Frequency category (any grade)	Adverse Reaction by System Organ Class	Any grade (%)	Grade ≥3 (%)
	Mucosal inflammation	2.5	0
Investigations			
Common	Transaminases increased[j]	9.1	2.9
	Blood creatinine increased	5.4	0
	Gamma-glutamyltransferase increased	3.3	0.8
	Blood creatine phosphokinase increased	2.1	0.4
	Weight decreased	3.3	0

[a] including, Urinary tract infection, Cystitis
[b] including Skin infection, Cellulitis
[c] reported in port-marketing setting (information related to grade not available).
[d] including Hypoesthesia, Neuropathy peripheral, Paraesthesia, Peripheral sensory neuropathy.
[eb] including Abdominal discomfort, Abdominal distension, Abdominal pain, Abdominal pain upper.
[f] including Back pain, Musculoskeletal chest pain, Musculoskeletal pain, Myalgia, Neck pain, Pain in extremity
[gd] including Asthenia, Fatigue.
[h] including Oedema, Oedema peripheral
[i] in few cases tissue necrosis was reported
[j] including Alanine aminotransferase increased, Aspartate aminotransferase increased, Transaminases increased
Additional adverse reactions were reported post-marketing with rare frequency: Rhabdomyolysis and Tumour lysis syndrome.

In IMforte, 25.2% of patients experienced neutropenia (all grades), 12.4% experienced Grade 3/4 neutropenia, and 1.7% experienced febrile neutropenia and 0.4% sepsis. The median time to first onset of neutropenia (all grade) was 10 (range: 7-29) days. The median duration was 11 (range: 1-196) days. Neutropenia* led to dose reduction or interruption in 1.7% or 5.4% of patients, respectively. Treatment was permanently discontinued in 1.7% of patients.

Serious adverse reactions occurred in 34.3% of patients receiving ZEPZELCA with atezolizumab. The most frequent serious adverse reactions were thrombocytopenia (2.9%), pneumonia (3.7%), respiratory tract infection (2.5%) and dyspnoea (2.1%). Fatal adverse reactions occurred in 5% of patients receiving ZEPZELCA with atezolizumab, in most cases due to pneumonia and other lung infections.

5.4.4. Adverse events of special interest, serious adverse events and deaths, other significant events

Adverse events of special interest

AESIs for the purpose of expedited reporting were pre-defined in the protocol based on the known mechanism of action for atezolizumab and concerns reported with other immune checkpoint inhibitors.

For the purpose of atezolizumab AESI analysis, a set of comprehensive definitions using standardized MedDRA queries (SMQs), High-Level Terms (HLTs) and Sponsor-defined adverse event grouped terms (AEGTs) were used to identify and summarize AESIs from the clinical database by medical concept. The medical concepts included atezolizumab-associated important identified risks and potential risks, and class effects reported with other immune checkpoint inhibitors.

AESI requiring systemic corticosteroid treatment included AEs per all the following criteria:

- Date of systemic corticosteroid initiation was on or up to 30 days after the AE onset date;
- Date of systemic corticosteroid initiation was before the AE resolution date.

Table 76: Overview of Adverse Events of Special Interest for Atezolizumab (Safety Analysis Set)

	Primary Analysis		Safety Update	
	Atezolizumab (N=240)	Atezolizumab+ Lurbinectedin (N=242)	Atezolizumab (N=240)	Atezolizumab+ Lurbinectedin (N=242)
Total number of patients with at least one AESI	54 (22.5%)	76 (31.4%)	58 (24.2%)	86 (35.5%)
Total number of events	97	132	110	148
Total number of patients with at least one				
Treatment-related AESI	42 (17.5%)	58 (24.0%)	44 (18.3%)	66 (27.3%)
Atezolizumab-related AESI	41 (17.1%)	51 (21.1%)	42 (17.5%)	59 (24.4%)
Lurbinectedin-related AESI	0	29 (12.0%)	0	33 (13.6%)
Grade 3–4 AESI	8 (3.3%)	15 (6.2%)	8 (3.3%)	16 (6.6%)
Treatment-related Grade 3-4 AESI	6 (2.5%)	12 (5.0%)	6 (2.5%)	13 (5.4%)
Atezolizumab-related Grade 3-4 AESI	6 (2.5%)	9 (3.7%)	6 (2.5%)	10 (4.1%)
Lurbinectedin-related Grade 3-4 AESI	0	7 (2.9%)	0	7 (2.9%)
Grade 5 AESI	0	0	0	0
Treatment-related Grade 5 AESI	0	0	0	0
Atezolizumab-related Grade 5 AESI	0	0	0	0
Lurbinectedin-related Grade 5 AESI	0	0	0	0
Serious AESIs	5 (2.1%)	10 (4.1%)	5 (2.1%)	12 (5.0%)
Treatment-related serious AESIs	4 (1.7%)	9 (3.7%)	4 (1.7%)	10 (4.1%)
Atezolizumab-related serious AESI	4 (1.7%)	9 (3.7%)	4 (1.7%)	10 (4.1%)
Lurbinectedin-related serious AESI	0	4 (1.7%)	0	4 (1.7%)
Total number of patients with at least one				
AESIs leading to any study treatment withdrawal	1 (0.4%)	3 (1.2%)	1 (0.4%)	4 (1.7%)
AESIs leading to atezolizumab withdrawal	1 (0.4%)	3 (1.2%)	1 (0.4%)	4 (1.7%)
AESIs leading to lurbinectedin withdrawal	0	0	0	0
AESIs leading to any dose modification/interruption	7 (2.9%)	17 (7.0%)	9 (3.8%)	20 (8.3%)
AESIs leading to atezolizumab interruption	7 (2.9%)	15 (6.2%)	9 (3.8%)	17 (7.0%)
AESIs leading to lurbinectedin modification/interruption	0	12 (5.0%)	0	14 (5.8%)
Medical Concepts: patients with at least one				
Immune-mediated adrenal insufficiency	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.4%)
Immune-mediated colitis	4 (1.7%)	3 (1.2%)	4 (1.7%)	3 (1.2%)
Immune-mediated diabetes mellitus	2 (0.8%)	4 (1.7%)	2 (0.8%)	4 (1.7%)
Immune-mediated encephalitis	1 (0.4%)	0	1 (0.4%)	1 (0.4%)
Immune-mediated hepatitis (diagnosis and lab abnormalities)	14 (5.8%)	25 (10.3%)	17 (7.1%)	27 (11.2%)
Immune-mediated hepatitis (diagnosis)	0	1 (0.4%)	0	1 (0.4%)
Immune-mediated hepatitis (lab abnormalities)	14 (5.8%)	24 (9.9%)	17 (7.1%)	26 (10.7%)

Medical Concepts: patients with at least one				
Immune-mediated hyperthyroidism	8 (3.3%)	8 (3.3%)	8 (3.3%)	8 (3.3%)
Immune-mediated hypothyroidism	18 (7.5%)	17 (7.0%)	18 (7.5%)	19 (7.9%)
Immune-mediated meningoencephalitis	1 (0.4%)	0	1 (0.4%)	1 (0.4%)
Immune-mediated myositis	0	0	0	1 (0.4%)
Immune-mediated myositis (myositis and rhabdomyolysis)	0	0	0	1 (0.4%)
Immune-mediated nephritis	0	3 (1.2%)	1 (0.4%)	3 (1.2%)
Immune-mediated ocular inflammatory toxicity	0	1 (0.4%)	0	1 (0.4%)
Immune-mediated pancreatitis	2 (0.8%)	2 (0.8%)	2 (0.8%)	2 (0.8%)
Immune-mediated pericardial disorders	0	1 (0.4%)	0	1 (0.4%)
Immune-mediated pneumonitis	4 (1.7%)	10 (4.1%)	4 (1.7%)	13 (5.4%)
Immune-mediated rash	18 (7.5%)	14 (5.8%)	20 (8.3%)	19 (7.9%)
Immune-mediated severe cutaneous reaction	1 (0.4%)	1 (0.4%)	1 (0.4%)	2 (0.8%)
Immune-mediated vasculitis	0	1 (0.4%)	0	1 (0.4%)
Infusion-related reactions [a]	0	1 (0.4%)	0	1 (0.4%)

Note: Investigator text for AEs was encoded using MedDRA version 27.0 in the SCS and MedDRA version 27.1 in the Safety Update.
a Infusion-related reactions search strategy was expanded to include anaphylactic reactions in the Safety Update.

AESIs for the purpose of analysis were pre-defined medical concepts based on the known mechanism of action for lurbinectedin. A set of comprehensive definitions using MedDRA preferred terms and System Organ Class (SOC) were used to identify and summarize lurbinectedin AESIs from the clinical database by medical concept. The medical concepts were acute myeloid leukaemia/myelodysplasia and infection with and without concomitant neutropenia.

Table 77: Overview of Adverse Events of Special Interest for Lurbinectedin (Safety Analysis)

	Primary Analysis		Safety Update	
	Atezolizumab (N=240)	Atezolizumab+ Lurbinectedin (N=242)	Atezolizumab (N=240)	Atezolizumab+ Lurbinectedin (N=242)
Total number of patients with at least one AESI	62 (25.8%)	93 (38.4%)	65 (27.1%)	100 (41.3%)
Total number of events	85	131	95	151
Total number of patients with at least one				
Treatment-related AESI	10 (4.2%)	19 (7.9%)	11 (4.6%)	21 (8.7%)
Atezolizumab-related AESI	9 (3.8%)	10 (4.1%)	10 (4.2%)	12 (5.0%)
Lurbinectedin-related AESI	0	17 (7.0%)	0	18 (7.4%)
Grade 3–4 AESI	12 (5.0%)	18 (7.4%)	12 (5.0%)	20 (8.3%)
Treatment-related Grade 3-4 AESI	1 (0.4%)	5 (2.1%)	1 (0.4%)	6 (2.5%)
Atezolizumab-related Grade 3-4 AESI	1 (0.4%)	2 (0.8%)	1 (0.4%)	3 (1.2%)
Lurbinectedin-related Grade 3-4 AESI	0	5 (2.1%)	0	5 (2.1%)
Grade 5 AESI	4 (1.7%)	7 (2.9%)	4 (1.7%	6 (2.5%)
Treatment-related Grade 5 AESI	1 (0.4%)	2 (0.8%)	1 (0.4%)	2 (0.8%)
Atezolizumab-related Grade 5 AESI	1 (0.4%)	0	1 (0.4%)	0
Lurbinectedin-related Grade 5 AESI	0	2 (0.8%)	0	2 (0.8%)
Serious AESIs	16 (6.7%)	28 (11.6%)	16 (6.7%)	32 (13.2%)
Treatment-related serious AESIs	2 (0.8%)	8 (3.3%)	2 (0.8%)	9 (3.7%)
Atezolizumab-related serious AESI	2 (0.8%)	3 (1.2%)	2 (0.8%)	4 (1.7%)
Lurbinectedin-related serious AESI	0	8 (3.3%)	0	8 (3.3%)
AESIs leading to any study treatment withdrawal	1 (0.4%)	0	1 (0.4%)	1 (0.4%)
AESIs leading to atezolizumab withdrawal	1 (0.4%)	0	1 (0.4%)	1 (0.4%)
AESIs leading to lurbinectedin withdrawal	0	0	0	0
Total number of patients with at least one				
AESIs leading to any dose modification/interruption	11 (4.6%)	23 (9.5%)	14 (5.8%)	25 (10.3%)
AESIs leading to atezolizumab interruption	11 (4.6%)	21 (8.7%)	14 (5.8%)	23 (9.5%)
AESIs leading to lurbinectedin modification/interruption	0	20 (8.3%)	0	22 (9.1%)
Medical Concepts: patients with at least one				
Acute myeloid leukaemia/Myelodysplasia	0	1 (0.4%)	0	1 (0.4%)
Infection with and without concomitant neutropenia	62 (25.8%)	93 (38.4%)	65 (27.1%)	100 (41.3%)
Infection with concomitant neutropenia	3 (1.3%)	9 (3.7%)	5 (2.1%)	12 (5.0%)
Infection without concomitant neutropenia	59 (24.6%)	87 (36.0%)	60 (25.0%)	94 (38.8%)

Serious adverse events

Table 78: Serious adverse events with an incidence rate of at least 1% in any treatment group (Safety-Evaluable Population)

MedDRA SOC **MedDRA PT**	**IMforte**	
	Atezolizumab (n=240)	**Atezolizumab + Lurbinectedin** (n=242)
Total number of patients with at least one SAE	43 (17.9)	83 (34.3%)
Blood and lymphatic system disorders		
Febrile neutropenia	0	4 (1.7%)
Cardiac disorders		
Myocardial infarction	0	3 (1.2%)
Infections and infestations		
Pneumonia	6 (2.5%)	7 (2.9%)
Respiratory tract infection	1 (0.4%)	5 (2.1%)
Infection	0	3 (1.2%)
Vascular device infection	0	3 (1.2%)
Investigations		
Platelet count decreased	0	5 (2.1%)
Neutrophil count decreased	0	3 (1.2%)

Metabolism and nutrition disorders		
Hyponatraemia	3 (1.3%)	2 (0.8%)
Renal and urinary disorders		
Renal failure	0	3 (1.2%)
Respiratory, thoracic, and mediastinal disorders		
Dyspnoea	4 (1.7%)	5 (2.1%)
Pulmonary embolism	0	3 (1.2%)
Pneumonitis	0	3 (1.2%)
One patient with pyrexia as SAE in the CCOD 29 July 2024 has been recodified as atypical pneumonia in the CCOD 12 February 2025, reducing the incidence rate of pyrexia to 0.8%. MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SAE, serious adverse event; SOC, system organ class.		

Deaths

Table 79: All deaths and primary cause of death (Safety-Evaluable Population)

Primary cause of death	IMforte		Safety Update		Pooled population	
	Atezolizumab (n= 240)	**Atezolizumab + Lurbinectedin** (n= 242)	**Atezolizumab (N=240)**	**Atezolizumab + Lurbinectedin (N=242)**	**Atezo Mono** (n= 3178)	**Lurbi Mono** (n= 554)
Total number of deaths	135 (56.3%)	113 (46.7%)	168 (70.0%)	159 (65.7%)	1898 (59.7%)	431 (77.8%)
Adverse event	6 (2.5%)	12 (5.0%)	6 (3.6%)	12 (7.5%)	120 (3.8%)	8 (1.4%)
Progressive disease	117 (48.8%)	90 (37.2%)	149 (88.7%)	132 (83.0%)	1476 (46.4%)	409 (73.8%)
Other[a]	12 (5.0%)	11 (4.5%)	13 (7.7%)	15 (9.4%)	302 (9.5%)	14 (2.5%)

Notes: [a] Deaths listed under the category of Other are deaths that occurred outside the protocol defined adverse event reporting period and were not considered related to disease progression.

Based on the provided narratives, the investigators generally considered the causes of death to be unrelated to the study treatments (atezolizumab, carboplatin, etoposide, and lurbinectedin) and more often related to the disease under study, other causes (unspecified), or concurrent illnesses.

Table 80: *Grade 5* Adverse Events by System Organ Class and Preferred Term, Randomization Phase, Safety Analysis Set)

MedDRA System Organ Class MedDRA Preferred Term	Atezolizumab (N=240)	Atezolizumab+ Lurbinectedin (N=242)	All Patients (N=482)
Total number of patients with at least one adverse event	6 (2.5%)	12 (5.0%)	18 (3.7%)
Overall total number of events	6	12	18
Infections and infestations			
Total number of patients with at least one adverse event	4 (1.7%)	6 (2.5%)	10 (2.1%)
Total number of events	4	6	10
Pneumonia	2 (0.8%)	1 (0.4%)	3 (0.6%)
Sepsis	1 (0.4%)	1 (0.4%)	2 (0.4%)
Abscess intestinal	1 (0.4%)	0	1 (0.2%)
COVID-19 pneumonia	0	1 (0.4%)	1 (0.2%)
Pneumonia viral	0	1 (0.4%)	1 (0.2%)
Septic shock	0	1 (0.4%)	1 (0.2%)
Vascular device infection	0	1 (0.4%)	1 (0.2%)
Cardiac disorders			
Total number of patients with at least one adverse event	0	4 (1.7%)	4 (0.8%)
Total number of events	0	4	4
Cardio-respiratory arrest	0	2 (0.8%)	2 (0.4%)
Myocardial infarction	0	2 (0.8%)	2 (0.4%)
Blood and lymphatic system disorders			
Total number of patients with at least one adverse event	0	1 (0.4%)	1 (0.2%)
Total number of events	0	1	1
Febrile neutropenia	0	1 (0.4%)	1 (0.2%)
General disorders and administration site conditions			
Total number of patients with at least one adverse event	1 (0.4%)	0	1 (0.2%)
Total number of events	1	0	1
Death	1 (0.4%)	0	1 (0.2%)
Nervous system disorders			
Total number of patients with at least one adverse event	1 (0.4%)	0	1 (0.2%)
Total number of events	1	0	1
Cerebrovascular accident	1 (0.4%)	0	1 (0.2%)
Psychiatric disorders			
Total number of patients with at least one adverse event	0	1 (0.4%)	1 (0.2%)
Total number of events	0	1	1
Completed suicide	0	1 (0.4%)	1 (0.2%)

Investigator text for AEs encoded using MedDRA version 27.0. Percentages are based on N in the column headings. Only treatment emergent AEs are displayed. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately. Data Cutoff: 29JUL2024;

Due to a change in the verbatim term of one Grade 5 event in the atezolizumab+lurbinectedin arm, the PT changed from septic shock to neutropenia at the CCOD of 12 February 2025. Grade 5 AEs were reported in 12 participants (5.0%) in the atezolizumab + lurbinectedin arm and 6 participants (2.5%) in the atezolizumab arm. The majority of grade 5 AEs reported in both arms by SOC were infections and infestations.

There were two grade 5 AEs (sepsis and febrile neutropenia) in the atezolizumab + lurbinectedin arm that were considered as related to lurbinectedin. One grade 5 AE of sepsis in the atezolizumab arm was considered as related to atezolizumab.

Safety-Evaluable Population Set – Death summaries pooled for Lurbinectedin, Atezolizumab

Table 81: Death and cause of death: Lurbinectedin pool (safety-evaluable population)

Protocols: PM1183-B-005-14 (All Cohorts), PM1183-C-004-14(CORAIL Arm A)

Reason*	Lurbi Mono Pool (N = 554)
All deaths	431 (77.8)
Primary cause of death	
n	431 (77.8)
Malignant disease	409 (73.8)
Adverse event	8 (1.4)
Other	14 (2.5)
Death due to other cause	
Other	14 (2.5)
Aplastic crisis	1 (0.2)
Cardiac arrest	1 (0.2)
Cardiorespiratory arrest	2 (0.4)
Cariopulmonary arrest	1 (0.2)
Cerebral ischemia	1 (0.2)
Not reported in source documents	1 (0.2)
Pneumonia	1 (0.2)
Precapillary pulmonary arterial hypertension	1 (0.2)
Unknown	5 (0.9)

Lurbi = Lurbinectedin; Lurbi Mono = PM1183-B-005-14 (All Cohorts), PM1183-C-004-14(CORAIL Arm A). Malignant disease refers to progressive disease Note: For the safety-evaluable population, it is assumed that all deaths are treatment-emergent. Clinical cut-off dates: PM1183-B-005-14: 16NOV2020, PM1183-C-004-14: 12OCT2018.

Table 82: Death and Other cause of death: Atezolizumab pool (safety-evaluable population)

	IMFORTE		Pooled Population
	Atezolizumab (N=240)	Atezolizumab + Lurbinectedin (N=242)	Atezo Mono (N=3178)
Primary cause of death			
n	135 (56.3%)	113 (46.7%)	1898 (59.7%)
ADVERSE EVENT	6 (2.5%)	12 (5.0%)	120 (3.8%)
PROGRESSIVE DISEASE	117 (48.8%)	90 (37.2%)	1476 (46.4%)
OTHER	12 (5.0%)	11 (4.5%)	302 (9.5%)
Other cause of death			
n	12	11	301
DEATH DURING FOLLOW-UP	0	0	269
DEAD	0	0	8
DEATH DUE TO UNKNOWN	2	2	4
DEATH DUE TO NOT KNOWN	0	0	3
POST STUDY REPORTING OF DEATH	1	1	0
DEATH	0	0	1
DEATH DUE TO 14/AUG/2023 ADMITTED TO THE OUTSIDE HOSPITAL DUE TO FEAVER. CAUSE OF DEATH UNKNOWN	1	0	0
DEATH DUE TO CAN NOT BE DETERMINED	0	1	0
DEATH DUE TO CARDIAC ARREST	0	0	1
DEATH DUE TO CEREBRAL INFARCTION	0	0	1
DEATH DUE TO CHOK SEPTIC	1	0	0
DEATH DUE TO DEATH AFTER ORTHOPAEDIC ACCIDENT AND OPERATION	1	0	0
DEATH DUE TO DEATH DURING FOLLOW UP	0	0	1
DEATH DUE TO DEATH IN FOLLOW UP	0	0	1
DEATH DUE TO DEATH OCCURRED DURING FOLLOW UP AND REASON UNKNOWN.	0	0	1
DEATH DUE TO DEATH OCCURRED DURING FOLLOW-UP AND NO FURTHER DETAILS WERE PROVIDED IN SOURCE.	0	0	1
DEATH DUE TO DISPNE	1	0	0
DEATH DUE TO DURING NEXT LINE TREATMENT. SUDDEN DEATH.	1	0	0
DEATH DUE TO EUTHANASIA	0	0	1
DEATH DUE TO FEBRILE NEUTROPENIA	1	0	0
DEATH DUE TO FUNGAL PNEUMONIA DURING FOLLOW FOLLOW UP PERIOD	0	0	1
DEATH DUE TO HEART ATTACK	1	0	0
DEATH DUE TO ILEUS (PATIENT REFUSED TREATMENT)	0	0	1
DEATH DUE TO INTRACEREBRAL HEMORRHAGE	1	0	0
DEATH DUE TO INTRACRANIAL BLEED	0	0	1
DEATH DUE TO NOT FOLLOWED, PATIENT WENT BACK TO PAKISTAN. REASON OF DEATH UNKNOWN	0	0	1
DEATH DUE TO PATIENT HAD A FALL ON 30 DEC 15 SUFFERING INTRACEREBRAL HAEMORRHAGE WITH INTRAVENTRICULAR HAEMORRHAGE. PATIENT PASSED AWAY 17 JAN 16	0	0	1
DEATH DUE TO PNEUMONIA	0	1	0
DEATH DUE TO RENAL FAILURE	0	0	1
DEATH DUE TO SEPSIS	0	1	0
DEATH DUE TO SEPSIS OF UNKNOWN ORIGIN	0	0	1
DEATH DUE TO SEPTIC SHOCK	0	1	0
DEATH DUE TO SEPTICEMIA	0	1	0
DEATH DUE TO SPINAL CORD COMPRESSION	1	0	0
DEATH DUE TO THE CAUSE OF DEATH IS UNKNOWN. THE DEATH EPICRISIS REPORT WAS REQUESTED FROM THE PATIENT'S RELATIVE. IT DID NOT REACH US.	0	1	0
DEATH DUE TO THE PATIENT PASSED AWAY ON JUNE 19. WHEN THE PATIENT WAS CALLED FOR A SURVIVAL VISIT, THE PATIENT'S RELATIVE REPORTED THAT THE PATIENT HAD PASSED AWAY.	0	1	0
DEATH DUE TO UNKNOWN CAUSE OF DEATH - SUSPECTED THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) AND DISSEMINATED INTRAVASCULAR COAGULATION (DIC) MULTIPLE FACTORS AND CANNOT DETERMINE CAUSE OF DEATH	0	0	1
DEATH DUE TO UNKNOWN, DIED IN HOSPIZ	0	1	0
DEATH RECORDED AS PER PUBLIC RECORDS	0	0	1

Atezo = Atezolizumab. Atezo Mono: GO27831(PCD4989g All Cohorts) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211) + WO29074 (IMMOTION150 Arm B prior to crossover). Note: The safety population from IMforte reflects safety evaluable patients from the randomized phase of the study. Other cause of death is displayed verbatim. Grade 5 Adverse Events of Disease Progression Coded as DISEASE RECURRENCE/PROGRESSIVE. A patient in GO29293 had missing data for Other cause of death. For IMforte, includes deaths occurring on or after the start of Atezolizumab or Lurbinectedin during the Randomization Phase.

5.4.5. Discontinuation due to adverse events

Discontinuation due to adverse events

Table 83: Patients discontinued from atezolizumab or lurbinectedin treatment (Safety-Evaluable Population)

	IMforte			Pooled population	
	Atezolizumab (n=240)	Atezolizumab + Lurbinectedin (n=242)		Atezo Mono (n=3178)	Lurbi Mono (n=554)
Patients discontinued from treatment					
Study drug	**Atezolizumab**	**Atezolizumab**	**Lurbinectedin**	**Atezolizumab**	**Lurbinectedin**
All reasons	208 (86.7%)	197 (81.4%)	198 (81.8%)	2627 (82.7%)	554 (100%)
Progressive disease	185 (77.1%)	160 (66.1%)	155 (64.0%)	2233 (70.3%)	436 (78.7%)
Adverse event	9 (3.8%)	6 (2.5%)	13 (5.4%)	213 (6.7%)	31 (5.6%)
Withdrawal by subject	2 (0.8%)	9 (3.7%)	8 (3.3%)	94 (3.0%)	30 (5.4%)
Death	6 (2.5%)	16 (6.6%)	16 (6.6%)	15 (0.5%)	19 (3.4%)
Physician decision	1 (0.4%)	1 (0.4%)	1 (0.4%)	34 (1.1%)	19 (3.4%)
Protocol violation	0	0	0	14 (0.4%)	0
Symptomatic deterioration	5 (2.1%)	5 (2.1%)	5 (2.1%)	4 (0.1%)	13 (2.3%)
Other	0	0	0	10 (0.3%)	6 (1.1%)
Non-compliance	0	0	0	8 (0.3%)	0
Lost to follow-up	0	0	0	2 (<0.1%)	0

Table 84: Participants Discontinued from Maintenance Treatment (Safety Analysis Set, Study GO43104, DCO 12 Feb 2025)

	Atezolizumab (N=240)	Atezolizumab+Lurbinectedin (N=242)	
	Atezolizumab	Atezolizumab	Lurbinectedin
Treatment Status	240	242	242
Ongoing	21 (8.8%)	27 (11.2%)	27 (11.2%)
Discontinued Maintenance Treatment	219 (91.3%)	215 (88.8%)	215 (88.8%)
Reason for Discontinuation of Maintenance Treatment			
Progressive Disease	194 (88.6%)	176 (81.9%)	171 (79.5%)
Death	6 (2.7%)	16 (7.4%)	16 (7.4%)
Adverse Event	11 (5.0%)	7 (3.3%)	14 (6.5%)
Withdrawal by Subject	2 (0.9%)	10 (4.7%)	8 (3.7%)
Symptomatic Deterioration	5 (2.3%)	5 (2.3%)	5 (2.3%)
Physician Decision	1 (0.5%)	1 (0.5%)	1 (0.5%)

Data Cutoff: 12FEB2025; Rave Data Extracted: 01APR2025.

Table 85: Adverse Events Leading to Any Study Treatment Discontinuation, IMforte study, Safety Analysis Set

MedDRA System Organ Class MedDRA Preferred Term	Atezolizumab (N=240)	Atezolizumab+ Lurbinectedin (N=242)	All Patients (N=482)
Total number of patients with at least one adverse event	8 (3.3%)	15 (6.2%)	23 (4.8%)
Overall total number of events	11	24	35
Nervous system disorders			
Total number of patients with at least one adverse event	4 (1.7%)	1 (0.4%)	5 (1.0%)
Total number of events	6	1	7
Neuropathy peripheral	1 (0.4%)	1 (0.4%)	2 (0.4%)
Lethargy	1 (0.4%)	0	1 (0.2%)
Peripheral motor neuropathy	1 (0.4%)	0	1 (0.2%)
Peripheral sensory neuropathy	1 (0.4%)	0	1 (0.2%)
Seizure	1 (0.4%)	0	1 (0.2%)
Trigeminal neuropathy	1 (0.4%)	0	1 (0.2%)
Blood and lymphatic system disorders			
Total number of patients with at least one adverse event	0	3 (1.2%)	3 (0.6%)
Total number of events	0	5	5
Anaemia	0	3 (1.2%)	3 (0.6%)
Neutropenia	0	1 (0.4%)	1 (0.2%)
Thrombocytopenia	0	1 (0.4%)	1 (0.2%)
General disorders and administration site conditions			
Total number of patients with at least one adverse event	0	3 (1.2%)	3 (0.6%)
Total number of events	0	3	3
Fatigue	0	1 (0.4%)	1 (0.2%)
Malaise	0	1 (0.4%)	1 (0.2%)
Peripheral swelling	0	1 (0.4%)	1 (0.2%)
Investigations			
Total number of patients with at least one adverse event	0	3 (1.2%)	3 (0.6%)
Total number of events	0	7	7
Neutrophil count decreased	0	3 (1.2%)	3 (0.6%)
Platelet count decreased	0	2 (0.8%)	2 (0.4%)
White blood cell count decreased	0	1 (0.4%)	1 (0.2%)
Renal and urinary disorders			
Total number of patients with at least one adverse event	0	3 (1.2%)	3 (0.6%)
Total number of events	0	3	3
Immune-mediated nephritis	0	2 (0.8%)	2 (0.4%)
Nephropathy	0	1 (0.4%)	1 (0.2%)
Gastrointestinal disorders			
Total number of patients with at least one adverse event	1 (0.4%)	1 (0.4%)	2 (0.4%)
Total number of events	1	1	2
Gastrointestinal haemorrhage	1 (0.4%)	0	1 (0.2%)
Nausea	0	1 (0.4%)	1 (0.2%)
Musculoskeletal and connective tissue disorders			
Total number of patients with at least one adverse event	1 (0.4%)	1 (0.4%)	2 (0.4%)
Total number of events	1	1	2
Joint swelling	0	1 (0.4%)	1 (0.2%)
Psoriatic arthropathy	1 (0.4%)	0	1 (0.2%)
Respiratory, thoracic and mediastinal disorders			
Total number of patients with at least one adverse event	1 (0.4%)	1 (0.4%)	2 (0.4%)
Total number of events	2	1	3
Pneumonitis	1 (0.4%)	1 (0.4%)	2 (0.4%)
Dyspnoea	1 (0.4%)	0	1 (0.2%)
Vascular disorders			
Total number of patients with at least one adverse event	0	2 (0.8%)	2 (0.4%)
Total number of events	0	2	2
Phlebitis	0	2 (0.8%)	2 (0.4%)
Infections and infestations			
Total number of patients with at least one adverse event	1 (0.4%)	0	1 (0.2%)
Total number of events	1	0	1
Pneumonia	1 (0.4%)	0	1 (0.2%)

Investigator text for AEs encoded using MedDRA version 27.0. Percentages are based on N in the column headings.
Only treatment emergent AEs are displayed. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately.
Data Cutoff: 29JUL2024; Rave Data Extracted: 01OCT2024.

Dose modifications due to adverse events

In the atezolizumab + lurbinectedin arm, 39 participants (16.1%) experienced AEs leading to lurbinectedin dose modification (reduction).

In contrast to lurbinectedin, dose modifications (reductions) of atezolizumab were not permitted. Interruptions or delays of drug administration were allowed for both drugs.

The proportion of participants who experienced AEs leading to any study treatment modification or interruption in the atezolizumab + lurbinectedin arm (38.0%) was higher than that of the atezolizumab arm (13.8%). The proportion of participants who experienced AEs leading to lurbinectedin and/or atezolizumab interruption was higher in the atezolizumab + lurbinectedin arm (31.0%) than in the atezolizumab arm (13.8%). In the atezolizumab + lurbinectedin arm, 37 participants (15.3%) experienced AEs leading to lurbinectedin dose modification (reduction).

The most frequent AEs by PT (≥5% of participants in either arm) that led to any study treatment modification or interruption were: platelet count decreased (5.0% and 0%) and anaemia (6.2% and 0.8%).

The AEs leading to dose modification or interruption of any study treatment experienced with a ≥2% difference between treatment arms by PT were: platelet count decreased (5.0% and 0%), neutrophil count decreased (3.7% and 0%), anaemia (6.2% and 0.8%), asthenia (3.7% and 0.4%), vomiting (2.1% and 0%), and decreased appetite (2.1% and 0%).

5.4.6. Safety in special populations

Table 86: Adverse events by age range.

	Atezolizumab				Atezolizumab + lurbinectedin			
MedDRA Terms	<65 n (%)	65-74 n (%)	75-84 n (%)	≥85 n (%)	<65 n (%)	65-74 n (%)	75-84 n (%)	≥85 n (%)
Number of patients	90	117	32	1	118	94	29	1
Total AEs	76 (84.4)	94 (80.3)	25 (78.1)	1 (100)	112 (94.9)	93 (98.9)	29 (100)	1 (100)
Serious AEs – Total	14 (15.6)	19 (16.2)	10 (31.3)	-	34 (28.8)	40 (42.6)	9 (31.0)	-
- Fatal	2 (2.2)	4 (3.4)	-	-	7 (5.9)	3 (3.2)	2 (6.9)	-
- Hospitalization/prolong existing hospitalization	14 (15.6)	17 (14.5)	10 (31.3)	-	32 (27.1)	38 (40.4)	7 (24.1)	-
- Life-threatening	-	3 (2.6)	1 (3.1)	-	4 (3.4)	3 (3.2)	1 (3.4)	-
- Disability/incapacity	1 (1.1)	-	-	-	1 (0.8)	-	-	-
- Other (medically significant)	-	1 (0.9)	-	-	2 (1.7)	2 (2.1)	-	-
AE leading to drop-out	2 (2.2)	5 (4.3)	3 (9.4)	-	2 (1.7)	12 (12.8)	3 (10.3)	-
Psychiatric disorders[1]	3 (3.3)	5 (4.3)	2 (6.3)	-	9 (7.6)	10 (10.6)	5 (17.2)	-
Nervous system disorders[1]	15 (16.7)	17 (14.5)	6 (18.8)	-	28 (23.7)	24 (25.5)	9 (31.0)	1 (100)
Accidents and injuries[2]	2 (2.2)	6 (5.1)	1 (3.1)	-	6 (5.1)	8 (8.5)	1 (3.4)	-
Cardiac disorders[1]	2 (2.2)	2 (1.7)	-	-	6 (5.1)	5 (5.3)	3 (10.3)	-
Vascular disorders[1]	5 (5.6)	8 (6.8)	-	-	27 (22.9)	18 (19.1)	3 (10.3)	-
Cerebrovascular disorders[3]	-	1 (0.9)	-	-	-	-	1 (3.4)	-
Infections and infestations[1]	21 (23.3)	33 (28.2)	10 (31.3)	-	44 (37.3)	41 (43.6)	13 (44.8)	1 (100)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[4]	2 (2.2)	7 (6.0)	2 (6.3)	-	10 (8.5)	11 (11.7)	3 (10.3)	1 (100)

Clinical cutoff date (CCOD): 12 February 2025
The following PTs were not observed in the study: Anticholinergic syndrome and Quality of life decreased.
[1]Determined by SOC
[2] Determined by SOC: Injury, poisoning and procedural complications
[3] Determined by PTs: Cerebrovascular accident and Brain oedema
[4] Determined by PTs: Hypotension; Fall; Syncope; Dizziness; Ankle fracture; Hip fracture; Humerus fracture; Femur fracture and Spinal fracture

There was a higher percentage of participants aged 65 and over with grade 3–4 drug-related AEs (37.1%) than participants aged under 65 (21.2%) in the atezolizumab + lurbinectedin arm. Of the 37.1% of participants aged 65 years and over with severe drug-related adverse events (AEs) in the atezolizumab + lurbinectedin arm, most were Grade 3 (27.4%) vs. Grade 4 (8.9%). While individual Grade 3-4 AEs were mostly comparable between age groups and across study arms, haematotoxicity-associated AEs drove the observed discrepancy in participants aged ≥65 years in the atezolizumab + lurbinectedin arm vs. the control arm, including anaemia (9.7% vs. 0), neutropenia (4.8% vs. 0), febrile neutropenia (1.6% vs. 0), thrombocytopenia (4.8% vs. 0), and the corresponding investigation AEs of platelet count decreased (8.1% vs. 0) and neutrophil count decreased (8.1% vs. 0). It is important to note that Grade 3–4 haematological AEs in this age group were less frequent than in the lurbinectedin mono pool (anaemia 17.0%, neutropenia 22.0%, thrombocytopenia 4.9%). Conversely, these rates were higher than the corresponding "Investigation" AEs (platelet count decreased 1.4%, neutrophil count decreased 4.2%) reported in the lurbinectedin mono pool. It should be noted that the AE Preferred Term is derived based on the investigator-reported verbatim term and the corresponding MedDRA mapping for these similar medical concepts.

A higher proportion of participants with AEs leading to treatment withdrawal were observed in participants aged ≥65 years (12.1%) than in participants aged <65 years (1.7%) in the atezolizumab + lurbinectedin arm. While these were mostly isolated individual PTs, prevalent AEs observed in participants aged ≥65 years in the atezolizumab + lurbinectedin arm included anaemia (2.4%), neutrophil count decreased (2.4%), neutropenia (1.6%), platelet count decreased (1.6%), and immune-mediated nephritis (1.6%).

Intrinsic factors

Table 87 Overview of safety by age (Safety-Evaluable Population)

	Atezolizumab (N=240)					Atezolizumab+ Lurbinectedin (N=242)				
	<65 (N=90)	>=65 (N=150)	65 - 74 (N=117)	75 - 84 (N=32)	>=85 (N=1)	<65 (N=118)	>=65 (N=124)	65 - 74 (N=94)	75 - 84 (N=29)	>=85 (N=1)
Total number of patients with at least one AE	76 (84.4%)	120 (80.0%)	94 (80.3%)	25 (78.1%)	1 (100%)	112 (94.9%)	123 (99.2%)	93 (98.9%)	29 (100%)	1 (100%)
Total number of events	367	560	425	132	3	1005	1076	842	230	4
Total number of patients with at least one										
Treatment-related AE										
Any Treatment	43 (47.8%)	54 (36.0%)	41 (35.0%)	12 (37.5%)	1 (100%)	96 (81.4%)	109 (87.9%)	83 (88.3%)	26 (89.7%)	0
Atezolizumab	38 (42.2%)	52 (34.7%)	40 (34.2%)	12 (37.5%)	0	67 (56.8%)	74 (59.7%)	59 (62.8%)	15 (51.7%)	0
Lurbinectedin	0	0	0	0	0	90 (76.3%)	105 (84.7%)	80 (85.1%)	25 (86.2%)	0
Carboplatin	16 (17.8%)	16 (10.7%)	12 (10.3%)	3 (9.4%)	1 (100%)	20 (16.9%)	16 (12.9%)	14 (14.9%)	2 (6.9%)	0
Etoposide	14 (15.6%)	15 (10.0%)	11 (9.4%)	3 (9.4%)	1 (100%)	22 (18.6%)	14 (11.3%)	12 (12.8%)	2 (6.9%)	0
Grade 3-4 AE	21 (23.3%)	38 (25.3%)	27 (23.1%)	11 (34.4%)	0	38 (32.2%)	62 (50.0%)	49 (52.1%)	13 (44.8%)	0
Related to Any Treatment	6 (6.7%)	10 (6.7%)	9 (7.7%)	1 (3.1%)	0	25 (21.2%)	46 (37.1%)	36 (38.3%)	10 (34.5%)	0
Related to Atezolizumab	6 (6.7%)	10 (6.7%)	9 (7.7%)	1 (3.1%)	0	16 (13.6%)	21 (16.9%)	16 (17.0%)	5 (17.2%)	0
Related to Lurbinectedin	0	0	0	0	0	25 (21.2%)	38 (30.6%)	31 (33.0%)	7 (24.1%)	0
Related to Carboplatin	1 (1.1%)	1 (0.7%)	1 (0.9%)	0	0	5 (4.2%)	3 (2.4%)	3 (3.2%)	0	0
Related to Etoposide	1 (1.1%)	1 (0.7%)	1 (0.9%)	0	0	5 (4.2%)	3 (2.4%)	3 (3.2%)	0	0
Grade 5 AE	2 (2.2%)	4 (2.7%)	4 (3.4%)	0	0	7 (5.9%)	5 (4.0%)	3 (3.2%)	2 (6.9%)	0
Related to Any Treatment	1 (1.1%)	0	0	0	0	2 (1.7%)	0	0	0	0
Related to Atezolizumab	1 (1.1%)	0	0	0	0	0	0	0	0	0
Related to Lurbinectedin	0	0	0	0	0	2 (1.7%)	0	0	0	0
Related to Carboplatin	0	0	0	0	0	0	0	0	0	0
Related to Etoposide	0	0	0	0	0	0	0	0	0	0
Total number of patients with at least one										
Serious AE	14 (15.6%)	29 (19.3%)	19 (16.2%)	10 (31.3%)	0	34 (28.8%)	49 (39.5%)	40 (42.6%)	9 (31.0%)	0
Related to Any Treatment	4 (4.4%)	5 (3.3%)	4 (3.4%)	1 (3.1%)	0	13 (11.0%)	19 (15.3%)	18 (19.1%)	1 (3.4%)	0
Related to Atezolizumab	4 (4.4%)	5 (3.3%)	4 (3.4%)	1 (3.1%)	0	8 (6.8%)	14 (11.3%)	13 (13.8%)	1 (3.4%)	0
Related to Lurbinectedin	0	0	0	0	0	13 (11.0%)	14 (11.3%)	13 (13.8%)	1 (3.4%)	0
Related to Carboplatin	0	0	0	0	0	2 (1.7%)	0	0	0	0
Related to Etoposide	0	0	0	0	0	3 (2.5%)	0	0	0	0
AE leading to withdrawal from treatment										
Any Treatment	2 (2.2%)	8 (5.3%)	5 (4.3%)	3 (9.4%)	0	2 (1.7%)	15 (12.1%)	12 (12.8%)	3 (10.3%)	0
Atezolizumab	2 (2.2%)	8 (5.3%)	5 (4.3%)	3 (9.4%)	0	0	7 (5.6%)	5 (5.3%)	2 (6.9%)	0
Lurbinectedin	0	0	0	0	0	2 (1.7%)	12 (9.7%)	11 (11.7%)	1 (3.4%)	0
AE leading to any dose modification/interruption										
Any treatment	9 (10.0%)	29 (19.3%)	23 (19.7%)	6 (18.8%)	0	45 (38.1%)	55 (44.4%)	41 (43.6%)	14 (48.3%)	0
Atezolizumab	9 (10.0%)	29 (19.3%)	23 (19.7%)	6 (18.8%)	0	34 (28.8%)	45 (36.3%)	36 (38.3%)	9 (31.0%)	0
Lurbinectedin	0	0	0	0	0	41 (34.7%)	49 (39.5%)	37 (39.4%)	12 (41.4%)	0

For related AE parameters, carboplatin and etoposide data are presented to account for adverse events with onset during the randomized phase and assessed as related to either one or both of the enrollment phase chemotherapy drugs by the PI.
Investigator text for AEs encoded using MedDRA version 27.1. Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of AEs' row in which multiple occurrences of the same AE are counted separately.
Includes adverse events occurring on or after the start of Atezolizumab or Lurbinectedin during the Randomization Phase.
Data Cutoff: 12FEB2025; Rave Data Extracted: 01APR2025.

Table 88: Overview of safety by sex (Safety-Evaluable Population)

	Atezolizumab (N=240)		Atezolizumab+ Lurbinectedin (N=242)	
	Female (N=90)	Male (N=150)	Female (N=91)	Male (N=151)
Total number of patients with at least one AE	75 (83.3%)	121 (80.7%)	88 (96.7%)	147 (97.4%)
Total number of events	360	567	674	1407
Total number of patients with at least one Treatment-related AE				
Any Treatment	36 (40.0%)	61 (40.7%)	72 (79.1%)	133 (88.1%)
Atezolizumab	34 (37.8%)	56 (37.3%)	47 (51.6%)	94 (62.3%)
Lurbinectedin	0	0	68 (74.7%)	127 (84.1%)
Carboplatin	9 (10.0%)	23 (15.3%)	13 (14.3%)	23 (15.2%)
Etoposide	8 (8.9%)	21 (14.0%)	9 (9.9%)	27 (17.9%)
Grade 3-4 AE	24 (26.7%)	35 (23.3%)	36 (39.6%)	64 (42.4%)
Related to Any Treatment	6 (6.7%)	10 (6.7%)	22 (24.2%)	49 (32.5%)
Related to Atezolizumab	6 (6.7%)	10 (6.7%)	13 (14.3%)	24 (15.9%)
Related to Lurbinectedin	0	0	17 (18.7%)	46 (30.5%)
Related to Carboplatin	1 (1.1%)	1 (0.7%)	4 (4.4%)	4 (2.6%)
Related to Etoposide	1 (1.1%)	1 (0.7%)	3 (3.3%)	5 (3.3%)
Grade 5 AE	2 (2.2%)	4 (2.7%)	2 (2.2%)	10 (6.6%)
Related to Any Treatment	0	1 (0.7%)	1 (1.1%)	1 (0.7%)
Related to Atezolizumab	0	1 (0.7%)	0	0
Related to Lurbinectedin	0	0	1 (1.1%)	1 (0.7%)
Related to Carboplatin	0	0	0	0
Related to Etoposide	0	0	0	0
Total number of patients with at least one Serious AE	16 (17.8%)	27 (18.0%)	27 (29.7%)	56 (37.1%)
Related to Any Treatment	2 (2.2%)	7 (4.7%)	9 (9.9%)	23 (15.2%)
Related to Atezolizumab	2 (2.2%)	7 (4.7%)	5 (5.5%)	17 (11.3%)
Related to Lurbinectedin	0	0	8 (8.8%)	19 (12.6%)
Related to Carboplatin	0	0	1 (1.1%)	1 (0.7%)
Related to Etoposide	0	0	1 (1.1%)	2 (1.3%)
AE leading to withdrawal from treatment				
Any Treatment	5 (5.6%)	5 (3.3%)	6 (6.6%)	11 (7.3%)
Atezolizumab	5 (5.6%)	5 (3.3%)	3 (3.3%)	4 (2.6%)
Lurbinectedin	0	0	4 (4.4%)	10 (6.6%)
AE leading to any dose modification/interruption				
Any treatment	20 (22.2%)	18 (12.0%)	33 (36.3%)	67 (44.4%)
Atezolizumab	20 (22.2%)	18 (12.0%)	28 (30.8%)	51 (33.8%)
Lurbinectedin	0	0	29 (31.9%)	61 (40.4%)

For related AE parameters, carboplatin and etoposide data are presented to account for adverse events with onset during the randomized phase and assessed as related to either one or both of the enrollment phase chemotherapy drugs by the PI.
Investigator text for AEs encoded using MedDRA version 27.1. Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of AEs' row in which multiple occurrences of the same AE are counted separately.
Includes adverse events occurring on or after the start of Atezolizumab or Lurbinectedin during the Randomization Phase.
Data Cutoff: 12FEB2025; Rave Data Extracted: 01APR2025.

Table 89 : Overview of safety by race (Safety-Evaluable Population)

	Atezolizumab (n=240)				Atezolizumab + Lurbinectedin (n=242)			
	White (n=199)	Black (n=1)	Asian (n=30)	Other (n=10)	White (n=195)	Black (n=3)	Asian (n=31)	Other (n=13)
Total number of patients with at least one AE	160 (80.4%)	1 (100%)	25 (83.3%)	8 (80.0%)	188 (96.4%)	3 (100%)	31 (100%)	13 (100%)
Total number of events	706	3	89	30	1546	40	232	94
Total number of patients with at least one								
Treatment-related AE								

	Atezolizumab (n=240)				Atezolizumab + Lurbinectedin (n=242)			
	White (n=199)	**Black** (n=1)	**Asian** (n=30)	**Other** (n=10)	**White** (n=195)	**Black** (n=3)	**Asian** (n=31)	**Other** (n=13)
Any treatment	85 (42.7%)	0	7 (23.3%)	4 (40.0%)	159 (81.5%)	3 (100%)	28 (90.3%)	12 (92.3%)
Atezolizumab	77 (38.7%)	0	7 (23.3%)	4 (40.0%)	117 (60.0%)	3 (100%)	12 (38.7%)	4 (30.8%)
Lurbinectedin	0	0	0	0	147 (75.4%)	3 (100%)	28 (90.3%)	12 (92.3%)
Carboplatin	31 (15.6%)	0	0	0	33 (16.9%)	0	1 (3.2%)	1 (7.7%)
Etoposide	28 (14.1%)	0	0	0	31 (15.9%)	0	2 (6.5%)	2 (15.4%)
Grade 3/4 AE	43 (21.6%)	0	8 (26.7%)	2 (20.0%)	67 (34.4%)	1 (33.3%)	18 (58.1%)	6 (46.2%)
Related to any treatment	13 (6.5%)	0	1 (3.3%)	0	44 (22.6%)	0	14 (45.2%)	4 (30.8%)
Related to atezolizumab	13 (6.5%)	0	1 (3.3%)	0	29 (14.9%)	0	3 (9.7%)	1 (7.7%)
Related to lurbinectedin	0	0	0	0	38 (19.5%)	0	14 (45.2%)	4 (30.8%)
Related to carboplatin	1 (0.5%)	0	0	0	8 (4.1%)	0	0	0
Related to etoposide	1 (0.5%)	0	0	0	8 (4.1%)	0	0	0
Grade 5 AE	5 (2.5%)	0	1 (3.3%)	0	11 (5.6%)	0	0	1 (7.7%)
Related to any treatment	1 (0.5%)	0	0	0	2 (1.0%)	0	0	0
Related to atezolizumab	1 (0.5%)	0	0	0	0	0	0	0
Related to lurbinectedin	0	0	0	0	2 (1.0%)	0	0	0
Related to carboplatin	0	0	0	0	0	0	0	0
Related to etoposide	0	0	0	0	0	0	0	0
SAE	33 (16.6%)	0	6 (20.0%)	2 (20.0%)	60 (30.8%)	1 (33.3%)	11 (35.5%)	3 (23.1%)
Related to any treatment	8 (4.0%)	0	1 (3.3%)	0	23 (11.8%)	0	4 (12.9%)	1 (7.7%)
Related to atezolizumab	8 (4.0%)	0	1 (3.3%)	0	16 (8.2%)	0	3 (9.7%)	1 (7.7%)
Related to lurbinectedin	0	0	0	0	19 (9.7%)	0	4 (12.9%)	1 (7.7%)
Related to carboplatin	0	0	0	0	2 (1.0%)	0	0	0
Related to etoposide	0	0	0	0	3 (1.5%)	0	0	0
AE leading to withdrawal from treatment								
Any treatment	7 (3.5%)	0	1 (3.3%)	0	12 (6.2%)	0	2 (6.5%)	1 (7.7%)
Atezolizumab	7 (3.5%)	0	1 (3.3%)	0	6 (3.1%)	0	0	0
Lurbinectedin	0	0	0	0	9 (4.6%)	0	2 (6.5%)	1 (7.7%)
AE leading to any dose modification/interruption								
Any treatment	29 (14.6%)	0	4 (13.3%)	0	70 (35.9%)	2 (66.7%)	14 (45.2%)	6 (46.2%)
Atezolizumab	29 (14.6%)	0	4 (13.3%)	0	55 (28.2%)	2 (66.7%)	10 (32.3%)	2 (15.4%)
Lurbinectedin	0	0	0	0	64 (32.8%)	1 (33.3%)	14 (45.2%)	4 (30.8%)

	Atezolizumab (n=240)				Atezolizumab + Lurbinectedin (n=242)			
	White (n=199)	Black (n=1)	Asian (n=30)	Other (n=10)	White (n=195)	Black (n=3)	Asian (n=31)	Other (n=13)

For related AE parameters, carboplatin and etoposide data are presented to account for adverse events with onset during the randomised phase and assessed as related to either one or both of the enrolment phase chemotherapy drugs by the investigator.

AE, adverse event; SAE, serious adverse event.

Table 90: Overview of safety by Eastern Cooperative Oncology Group performance status score (Safety-Evaluable Population)

	Atezolizumab (N=240)		Atezolizumab+ Lurbinectedin (N=242)	
	0 (N=102)	1 (N=138)	0 (N=105)	1 (N=137)
Total number of patients with at least one AE	85 (83.3%)	111 (80.4%)	100 (95.2%)	135 (98.5%)
Total number of events	471	456	992	1089
Total number of patients with at least one Treatment-related AE				
Any Treatment	46 (45.1%)	51 (37.0%)	90 (85.7%)	115 (83.9%)
Atezolizumab	42 (41.2%)	48 (34.8%)	56 (53.3%)	85 (62.0%)
Lurbinectedin	0	0	87 (82.9%)	108 (78.8%)
Carboplatin	17 (16.7%)	15 (10.9%)	21 (20.0%)	15 (10.9%)
Etoposide	16 (15.7%)	13 (9.4%)	23 (21.9%)	13 (9.5%)
Grade 3-4 AE	26 (25.5%)	33 (23.9%)	36 (34.3%)	64 (46.7%)
Related to Any Treatment	10 (9.8%)	6 (4.3%)	29 (27.6%)	42 (30.7%)
Related to Atezolizumab	10 (9.8%)	6 (4.3%)	17 (16.2%)	20 (14.6%)
Related to Lurbinectedin	0	0	27 (25.7%)	36 (26.3%)
Related to Carboplatin	1 (1.0%)	1 (0.7%)	5 (4.8%)	3 (2.2%)
Related to Etoposide	1 (1.0%)	1 (0.7%)	5 (4.8%)	3 (2.2%)
Grade 5 AE	4 (3.9%)	2 (1.4%)	9 (8.6%)	3 (2.2%)
Related to Any Treatment	1 (1.0%)	0	2 (1.9%)	0
Related to Atezolizumab	1 (1.0%)	0	0	0
Related to Lurbinectedin	0	0	2 (1.9%)	0
Related to Carboplatin	0	0	0	0
Related to Etoposide	0	0	0	0
Total number of patients with at least one Serious AE	17 (16.7%)	26 (18.8%)	33 (31.4%)	50 (36.5%)
Related to Any Treatment	5 (4.9%)	4 (2.9%)	14 (13.3%)	18 (13.1%)
Related to Atezolizumab	5 (4.9%)	4 (2.9%)	9 (8.6%)	13 (9.5%)
Related to Lurbinectedin	0	0	13 (12.4%)	14 (10.2%)
Related to Carboplatin	0	0	2 (1.9%)	0
Related to Etoposide	0	0	2 (1.9%)	1 (0.7%)
AE leading to withdrawal from treatment				
Any Treatment	5 (4.9%)	5 (3.6%)	5 (4.8%)	12 (8.8%)
Atezolizumab	5 (4.9%)	5 (3.6%)	3 (2.9%)	4 (2.9%)
Lurbinectedin	0	0	4 (3.8%)	10 (7.3%)
AE leading to any dose modification/interruption				
Any treatment	15 (14.7%)	23 (16.7%)	39 (37.1%)	61 (44.5%)
Atezolizumab	15 (14.7%)	23 (16.7%)	27 (25.7%)	52 (38.0%)
Lurbinectedin	0	0	38 (36.2%)	52 (38.0%)

For related AE parameters, carboplatin and etoposide data are presented to account for adverse events with onset during the randomized phase and assessed as related to either one or both of the enrollment phase chemotherapy drugs by the PI.
Investigator text for AEs encoded using MedDRA version 27.1. Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of AEs' row in which multiple occurrences of the same AE are counted separately.
Includes adverse events occurring on or after the start of Atezolizumab or Lurbinectedin during the Randomization Phase.
Data Cutoff: 12FEB2025; Rave Data Extracted: 01APR2025.

No patients with baseline hepatic impairment (defined as having Child-Pugh score B or C) were included in the IMforte study.

Table 91: Summary of adverse events with single-agent lurbinectedin in study PM1183-A-017-20

	Study cohort			
	Normal hepatic function [c]	**Mild hepatic impairment**	**Moderate hepatic impairment**	**Severe hepatic impairment**
	Single-agent lurbinectedin dose			
	3.2 mg/m² (n=7)	**3.2 mg/m²** (n=11)	**1.6 mg/m²** (n=8)	**1.6 mg/m²** (n=6)
Total number of patients with at least one: [a]				
TEAE [b] regardless of relationship	7 (100.0%)	10 (90.9%)	8 (100.0%)	6 (100.0%)
Treatment-related AE [c,d]	4 (57.1%)	10 (90.9%)	3 (37.5%)	2 (33.3%)
Grade ≥ 3 TEAE [b]	2 (28.6%)	8 (72.7%)	7 (87.5%)	4 (66.7%)
Grade ≥ 4 TEAE [b]	0	4 (36.4%)	0	1 (16.7%)
Grade ≥ 3 treatment-related AE	0	4 (36.4%)	0	2 (33.3%)
Grade ≥ 4 treatment-related AE	0	2 (18.2%)	0	0
Treatment-emergent [b] SAE	2 (28.6%)	5 (45.5%)	4 (50.0%)	4 (66.7%)
Treatment-related SAE [d]	0	2 (18.2%)	0	1 (16.7%)
Grade ≥ 3 treatment-emergent SAE	2 (28.6%)	4 (36.4%)	4 (50.0%)	3 (50.0%)
Grade ≥ 4 treatment-emergent SAE	0	3 (27.3%)	0	1 (16.7%)
Grade ≥ 3 treatment-related SAE	0	1 (9.1%)	0	1 (16.7%)
Grade ≥ 4 treatment-related SAE	0	1 (9.1%)	0	0
Death associated with TEAEs [b]	0	2 (18.2%)	0	0
Death associated with treatment-related AEs [d]	0	0	0	0
Dose delay associated with TEAEs [b]	0	1 (9.1%)	0	0
Dose delay associated with treatment-related AEs [d]	0	0	0	0
Dose reduction associated with TEAEs [b]	0	1 (9.1%)	0	0
Dose reductions associated with treatment-related AEs [d]	0	1 (9.1%)	0	0
TEAE [b] leading to treatment discontinuation	1 (14.3%)	1 (9.1%)	1 (12.5%)	1 (16.7%)
Treatment-related AEs leading to treatment discontinuation [d]	0	0	0	0

Data shown are n (%) of patients.
[a] These figures include events related to laboratory values; these events are discussed in a separate section of the Clinical Study Report.
[b] TEAEs were defined as any adverse event aggravated in severity from baseline or having their onset between the first dose of the study drug and 31-day (±10 days) after the last treatment dose, death or date of further therapy, whichever came first. AEs related to the study treatment or with unknown relationship occurring more than 31 days after the last dose were also considered as TEAEs.
[c] One patient had grade 2 infusion-related reaction that resulted in a lurbinectedin infusion interruption due to a treatment-related AE.
[d] Includes events with unknown relationship.
AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Two patients included in the IMforte study had baseline renal impairment (chronic kidney disease stage 3b): one in the Atezo arm and one in the lurbinectedin + atezolizumab arm.

Extrinsic factors

Table 92: Overview of safety by region (Safety-Evaluable Population)

	Atezolizumab (n=240)				Atezolizumab + Lurbinectedin (n=242)			
	Asia-Pacific (n=30)	**Central and South America** (n=3)	**Europe and Middle East** (n=190)	**North America** (n=17)	**Asia-Pacific** (n=30)	**Central and South America** (n=4)	**Europe and Middle East** (n=194)	**North America** (n=14)
Total number of patients with at least one AE	25 (83.3%)	2 (66.7%)	152 (80.0%)	15 (88.2%)	30 (100%)	4 (100%)	187 (96.4%)	14 (100%)
Total number of events	89	42	649	48	228	48	1527	109
Total number of patients with at least one								
Treatment-related AE								
Any treatment	7 (23.3%)	1 (33.3%)	79 (41.6%)	9 (52.9%)	27 (90.0%)	4 (100%)	157 (80.9%)	14 (100%)
Atezolizumab	7 (23.3%)	1 (33.3%)	72 (37.9%)	8 (47.1%)	12 (40.0%)	1 (25.0%)	112 (57.7%)	11 (78.6%)
Lurbinectedin	0	0	0	0	27 (90.0%)	4 (100%)	146 (75.3%)	13 (92.9%)
Carboplatin	0	0	29 (15.3%)	2 (11.8%)	1 (3.3%)	0	34 (17.5%)	0
Etoposide	0	0	26 (13.7%)	2 (11.8%)	2 (6.7%)	0	33 (17.0%)	0
Grade 3/4 AE	8 (26.7%)	2 (66.7%)	41 (21.6%)	2 (11.8%)	17 (56.7%)	3 (75.0%)	66 (34.0%)	6 (42.9%)
Related to any treatment	1 (3.3%)	1 (33.3%)	11 (5.8%)	1 (5.9%)	13 (43.3%)	2 (50.0%)	44 (22.7%)	3 (21.4%)
Related to atezolizumab	1 (3.3%)	1 (33.3%)	11 (5.8%)	1 (5.9%)	3 (10.0%)	1 (25.0%)	28 (14.4%)	1 (7.1%)
Related to lurbinectedin	0	0	0	0	13 (43.3%)	2 (50.0%)	38 (19.6%)	3 (21.4%)
Related to carboplatin	0	0	1 (0.5%)	0	0	0	8 (4.1%)	0
Related to etoposide	0	0	1 (0.5%)	0	0	0	8 (4.1%)	0
Grade 5 AE	1 (3.3%)	0	5 (2.6%)	0	0	0	12 (6.2%)	0
Related to any treatment	0	0	1 (0.5%)	0	0	0	2 (1.0%)	0
Related to atezolizumab	0	0	1 (0.5%)	0	0	0	0	0
Related to lurbinectedin	0	0	0	0	0	0	2 (1.0%)	0
Related to carboplatin	0	0	0	0	0	0	0	0
Related to etoposide	0	0	0	0	0	0	0	0
SAE	6 (20.0%)	1 (33.3%)	33 (17.4%)	1 (5.9%)	11 (36.7%)	1 (25.0%)	59 (30.4%)	4 (28.6%)
Related to any treatment	1 (3.3%)	0	8 (4.2%)	0	4 (13.3%)	1 (25.0%)	22 (11.3%)	1 (7.1%)
Related to atezolizumab	1 (3.3%)	0	8 (4.2%)	0	3 (10.0%)	1 (25.0%)	15 (7.7%)	1 (7.1%)
Related to lurbinectedin	0	0	0	0	4 (13.3%)	1 (25.0%)	18 (9.3%)	1 (7.1%)
Related to carboplatin	0	0	0	0	0	0	2 (1.0%)	0
Related to etoposide	0	0	0	0	0	0	3 (1.5%)	0
AE leading to withdrawal from treatment								

	Atezolizumab (n=240)				Atezolizumab + Lurbinectedin (n=242)			
	Asia-Pacific (n=30)	**Central and South America** (n=3)	**Europe and Middle East** (n=190)	**North America** (n=17)	**Asia-Pacific** (n=30)	**Central and South America** (n=4)	**Europe and Middle East** (n=194)	**North America** (n=14)
Any treatment	1 (3.3%)	1 (33.3%)	6 (3.2%)	0	2 (6.7%)	0	13 (6.7%)	0
Atezolizumab	1 (3.3%)	1 (33.3%)	6 (3.2%)	0	0	0	6 (3.1%)	0
Lurbinectedin	0	0	0	0	2 (6.7%)	0	10 (5.2%)	0
AE leading to any dose modification/interruption								
Any treatment	4 (13.3%)	1 (33.3%)	27 (14.2%)	1 (5.9%)	13 (43.3%)	3 (75.0%)	69 (35.6%)	7 (50.0%)
Atezolizumab	4 (13.3%)	1 (33.3%)	27 (14.2%)	1 (5.9%)	9 (30.0%)	1 (25.0%)	55 (28.4%)	4 (28.6%)
Lurbinectedin	0	0	0	0	13 (43.3%)	2 (50.0%)	64 (33.0%)	4 (28.6%)

For related AE parameters, carboplatin and etoposide data are presented to account for adverse events with onset during the randomised phase and assessed as related to either one or both of the enrolment phase chemotherapy drugs by the investigator.

AE, adverse event; SAE, serious adverse event.

Table 93: Overview of safety by tobacco use history (Safety-Evaluable Population)

	Atezolizumab (N=240)			Atezolizumab+ Lurbinectedin (N=242)		
	Never (N=5)	Current (N=72)	Previous (N=163)	Never (N=7)	Current (N=88)	Previous (N=147)
Total number of patients with at least one AE	5 (100%)	60 (83.3%)	131 (80.4%)	7 (100%)	86 (97.7%)	142 (96.6%)
Total number of events	20	268	639	78	682	1321
Total number of patients with at least one Treatment-related AE						
Any Treatment	2 (40.0%)	29 (40.3%)	66 (40.5%)	7 (100%)	70 (79.5%)	128 (87.1%)
Atezolizumab	2 (40.0%)	29 (40.3%)	59 (36.2%)	4 (57.1%)	50 (56.8%)	87 (59.2%)
Lurbinectedin	0	0	0	7 (100%)	65 (73.9%)	123 (83.7%)
Carboplatin	0	8 (11.1%)	24 (14.7%)	0	17 (19.3%)	19 (12.9%)
Etoposide	0	7 (9.7%)	22 (13.5%)	0	18 (20.5%)	18 (12.2%)
Grade 3-4 AE	2 (40.0%)	14 (19.4%)	43 (26.4%)	3 (42.9%)	29 (33.0%)	68 (46.3%)
Related to Any Treatment	0	5 (6.9%)	11 (6.7%)	2 (28.6%)	18 (20.5%)	51 (34.7%)
Related to Atezolizumab	0	5 (6.9%)	11 (6.7%)	0	10 (11.4%)	27 (18.4%)
Related to Lurbinectedin	0	0	0	2 (28.6%)	15 (17.0%)	46 (31.3%)
Related to Carboplatin	0	0	2 (1.2%)	0	4 (4.5%)	4 (2.7%)
Related to Etoposide	0	0	2 (1.2%)	0	3 (3.4%)	5 (3.4%)
Grade 5 AE	0	2 (2.8%)	4 (2.5%)	0	3 (3.4%)	9 (6.1%)
Related to Any Treatment	0	0	1 (0.6%)	0	0	2 (1.4%)
Related to Atezolizumab	0	0	1 (0.6%)	0	0	0
Related to Lurbinectedin	0	0	0	0	0	2 (1.4%)
Related to Carboplatin	0	0	0	0	0	0
Related to Etoposide	0	0	0	0	0	0
Total number of patients with at least one Serious AE	2 (40.0%)	12 (16.7%)	29 (17.8%)	3 (42.9%)	29 (33.0%)	51 (34.7%)
Related to Any Treatment	0	5 (6.9%)	4 (2.5%)	1 (14.3%)	7 (8.0%)	24 (16.3%)
Related to Atezolizumab	0	5 (6.9%)	4 (2.5%)	0	4 (4.5%)	18 (12.2%)
Related to Lurbinectedin	0	0	0	1 (14.3%)	5 (5.7%)	21 (14.3%)
Related to Carboplatin	0	0	0	0	0	2 (1.4%)
Related to Etoposide	0	0	0	0	0	3 (2.0%)
AE leading to withdrawal from treatment						
Any Treatment	0	3 (4.2%)	7 (4.3%)	0	5 (5.7%)	12 (8.2%)
Atezolizumab	0	3 (4.2%)	7 (4.3%)	0	1 (1.1%)	6 (4.1%)
Lurbinectedin	0	0	0	0	5 (5.7%)	9 (6.1%)
AE leading to any dose modification/interruption						
Any treatment	0	12 (16.7%)	26 (16.0%)	4 (57.1%)	32 (36.4%)	64 (43.5%)
Atezolizumab	0	12 (16.7%)	26 (16.0%)	4 (57.1%)	25 (28.4%)	50 (34.0%)
Lurbinectedin	0	0	0	4 (57.1%)	29 (33.0%)	57 (38.8%)

For related AE parameters, carboplatin and etoposide data are presented to account for adverse events with onset during the randomized phase and assessed as related to either one or both of the enrollment phase chemotherapy drugs by the PI.
Investigator text for AEs encoded using MedDRA version 27.1. Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of AEs' row in which multiple occurrences of the same AE are counted separately.
Includes adverse events occurring on or after the start of Atezolizumab or Lurbinectedin during the Randomization Phase.
Data Cutoff: 12FEB2025; Rave Data Extracted: 01APR2025.

5.4.7. Immunological events

An analysis of the safety data by ADA status in the randomized phase did not show a clinically meaningful difference in the safety profile between ADA subgroups in both arms.

5.4.8. Safety related to drug-drug interactions and other interactions

Please refer to the assessment of clinical pharmacology.

5.4.9. Vital signs and laboratory findings

Table 94 : Shift table for laboratory abnormalities worsening from baseline occurring in ≥10% of treated patients in the IMforte study and Lurbi Mono population (Safety-Evaluable Population)

		IMforte		Pooled population
		Atezolizumab (n=240)	**Atezolizumab + Lurbinectedin** (n=242)	**Lurbi Mono** (n=554)
Lymphocyte count (10^9/L), decreased	n	239	241	554
	All grades	73 (30.5%)	133 (55.2%)	392 (70.8%)
	Grade 3/4	26 (10.9%)	42 (17.4%)	180 (32.5%)
Platelet count (10^9/L), decreased	n	234	240	554
	All grades	35 (15.0%)	130 (54.2%)	249 (44.9%)
	Grade 3/4	6 (2.6%)	35 (14.6%)	54 (9.7%)
Haemoglobin (g/dL), decreased	n	239	241	553
	All grades	28 (11.7%)	122 (50.6%)	399 (72.2%)
	Grade 3/4	6 (2.5%)	31 (12.9%)	71 (12.8%)
Leukocyte count (10^9/L), decreased	n	239	241	554
	All grades	24 (10.0%)	96 (39.8%)	399 (72.0%)
	Grade 3/4	4 (1.7%)	26 (10.8%)	164 (29.6%)
Neutrophil count (10^9/L), decreased	n	228	230	554
	All grades	17 (7.5%)	82 (35.7%)	354 (63.9%)
	Grade 3/4	8 (3.5%)	41 (17.8%)	226 (40.8%)
AP (U/L), increased	n	236	238	550
	All grades	34 (14.4%)	69 (29.0%)	164 (29.8%)
	Grade 3/4	0	2 (0.8%)	25 (4.5%)
Sodium (mmol/L), decreased	n	237	241	552
	All grades	70 (29.5%)	64 (26.6%)	201 (36.4%)
	Grade 3/4	12 (5.1%)	10 (4.1%)	57 (10.3%)
ALT (U/L), increased	n	236	241	550
	All grades	43 (18.2%)	61 (25.3%)	337 (61.3%)
	Grade 3/4	4 (1.7%)	8 (3.3%)	35 (6.4%)
AST (U/L), increased	n	235	240	548
	All grades	51 (21.7%)	58 (24.2%)	230 (42.0%)
	Grade 3/4	2 (0.9%)	6 (2.5%)	18 (3.3%)
Calcium (mmol/L), decreased	n	235	238	305
	All grades	19 (8.1%)	56 (23.5%)	26 (8.5%)
	Grade 3/4	2 (0.9%)	8 (3.4%)	2 (0.7%)

		IMforte		Pooled population
		Atezolizumab (n=240)	**Atezolizumab + Lurbinectedin** (n=242)	**Lurbi Mono** (n=554)
Creatinine (µmol/L), increased	n	236	240	552
	All grades	32 (13.6%)	50 (20.8%)	416 (75.4%)
	Grade 3/4	0	6 (2.5%)	9 (1.6%)
Magnesium (mmol/L), decreased	n	237	238	
	All grades	34 (14.3%)	46 (19.3%)	
	Grade 3/4	0	3 (1.3%)	
Albumin (g/L), decreased	n	236	239	534
	All grades	33 (14.0%)	46 (19.2%)	192 (36%)
	Grade 3/4	3 (1.3%)	3 (1.3%)	12 (2.2%)
Potassium (mmol/L), increased	n	237	240	552
	All grades	24 (10.1%)	40 (16.7%)	88 (15.9%)
	Grade 3/4	7 (3.0%)	4 (1.7%)	9 (1.6%)
Potassium (mmol/L), decreased	n	237	240	552
	All grades	28 (11.8%)	36 (15.0%)	117 (21.2%)
	Grade 3/4	7 (3.0%)	6 (2.5%)	22 (4.0%)
International Normalised Ratio (fraction of 1), increased	n	161	139	
	All grades	9 (5.6%)	14 (10.1%)	
	Grade 3/4	0	5 (3.6%)	
Calcium (mmol/L), increased	n	235	238	305
	All grades	26 (11.1%)	21 (8.8%)	30 (9.8%)
	Grade 3/4	3 (1.3%)	7 (2.9%)	1 (0.3%)
CPK, enzyme activity (U/L), increased	n	232	235	536
	All grades	37 (15.9%)	20 (8.5%)	42 (7.8%)
	Grade 3/4	2 (0.9%)	0	2 (0.4%)

Since the primary analysis, one participant in the atezolizumab + lurbinectedin arm had corresponding laboratory results that fulfilled the laboratory criteria suggestive for Hy's law (post-baseline ALT or AST >3 x upper limit of normal [ULN] in combination with an elevated total bilirubin >2 x ULN). No AE was reported in association with the abnormal laboratory results and the participant experienced disease progression as per investigator's assessment proximal to the date of the reported abnormal laboratory values.

Consistent with the primary analysis, the number of treatment-emergent TSH laboratory abnormalities (defined as normal at baseline and abnormal at post-baseline) continued to be comparable between the atezolizumab + lurbinectedin arm and the atezolizumab arm (low: 11.6% and 8.8%; high: 11.2% and 11.3%). Hyperthyroidism was reported in 3.3% of participants in each arm and hypothyroidism was reported in 7.9% and 7.1% of participants in the atezolizumab + lurbinectedin arm and atezolizumab arm, respectively. All events were Grade 1-2 in severity.

Table 95: Vital Sign Abnormalities (Safety Analysis Set Study GO43104, DCO 29 July 2024)

Protocol: GO43104

Assessment	Direction of Abnormality	Atezolizumab (N=240)	Atezolizumab+ Lurbinectedin (N=242)
Diastolic Blood Pressure	Low	31/223 (13.9%)	64/226 (28.3%)
	High	94/190 (49.5%)	99/181 (54.7%)
Systolic Blood Pressure	Low	4/239 (1.7%)	10/241 (4.1%)
	High	91/170 (53.5%)	100/175 (57.1%)
Pulse Rate	Low	25/229 (10.9%)	22/232 (9.5%)
	High	31/215 (14.4%)	53/232 (22.8%)
Respiratory Rate	Low	0/240	0/242
	High	29/222 (13.1%)	40/222 (18.0%)
Temperature	Low	77/ 97 (79.4%)	96/113 (85.0%)
	High	2/240 (0.8%)	3/242 (1.2%)

Abnormalities are based on normal ranges: Diastolic Blood Pressure 60-80 mmHg; Pulse Rate 60-100 beats/min; Respiratory Rate: 8-20 breaths/min; Systolic Blood Pressure: 90-123 mmHg; Temperature: 36.5-37.3 C
Table entries provide the number of patients with a on-treatment assessment abnormality in the direction specified among patients without abnormality at baseline or with missing baseline values. Baseline is the patient's last observation prior to initiation of study drug.
Data Cutoff: 29JUL2024; Rave Data Extracted: 01OCT2024.

Program: /builds/studies/clinicalreporting/GO43104_OtherReg_HA_IA_2024_1343114/programs/tlg/t_vs_abn2.sas
Output: /ocean/harbour/CDT30386/GO43104/OtherReg_HA_IA_2024/prod_ema_v2/output/t_vs_abn2_VSMNTP_SE.out

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Table 96: Vital Sign Abnormalities (Safety Analysis Set, Study GO43104, DCO 12 Feb 2025)

Assessment	Direction of Abnormality	Atezolizumab (N=240)	Atezolizumab+ Lurbinectedin (N=242)
Diastolic Blood Pressure	Low	34/223 (15.2%)	65/226 (28.8%)
	High	98/190 (51.6%)	106/181 (58.6%)
Systolic Blood Pressure	Low	5/239 (2.1%)	11/241 (4.6%)
	High	94/170 (55.3%)	105/175 (60.0%)
Pulse Rate	Low	28/229 (12.2%)	25/232 (10.8%)
	High	33/215 (15.3%)	57/232 (24.6%)
Respiratory Rate	Low	0/240	0/242
	High	29/222 (13.1%)	40/222 (18.0%)
Temperature	Low	78/ 97 (80.4%)	96/113 (85.0%)
	High	2/240 (0.8%)	4/242 (1.7%)

Abnormalities are based on normal ranges: Diastolic Blood Pressure 60-80 mmHg; Pulse Rate 60-100 beats/min; Respiratory Rate: 8-20 breaths/min; Systolic Blood Pressure: 90-123 mmHg; Temperature: 36.5-37.3 C
Table entries provide the number of patients with a on-treatment assessment abnormality in the direction specified among patients without abnormality at baseline or with missing baseline values. Baseline is the patient's last observation prior to initiation of study drug.
Data Cutoff: 12FEB2025; Rave Data Extracted: 01APR2025.

At baseline, there was one participant in each arm with clinically significant ECG abnormalities. Post-baseline, there were five participants (one with grade 5 myocardial infarction and one with grade 3 atrial fibrillation) and two participants with clinically significant ECG abnormalities reported in the atezolizumab + lurbinectedin arm and the atezolizumab arm, respectively.

Since the primary analysis, one additional participant with clinically significant ECG abnormalities at baseline was reported in the atezolizumab + lurbinectedin arm.

5.4.10. Post-marketing experience

Zepzelca was first approved by the US FDA on 15 June 2020 (International Birth Date (IBD)) and since then has been approved in several countries worldwide. Since the IBD through 14 December 2024, an estimated cumulative total of 31,355 patients have received lurbinectedin from marketing experience (North America N=29,728; South America N=12; Europe N=348; Oceania N=223; Asia N=1,044).

Furthermore, at the same cut-off date, a total of 6,406 patients have been exposed to lurbinectedin through compassionate use (North America N= 898; South America N= 2; Europe N= 4,776; Oceania N= 190; Asia N= 540) (Periodic Benefit Risk Evaluation Report, PBRER, Report No. 9).Three ADRs have been included in section 4.8 of the SmPC based on the post-marketing experience: extravasation including tissue necrosis (uncommon), CPK elevations including rhabdomyolysis (frequency not known), and tumour lysis syndrome (TLS) (frequency not known). Fatal cases of rhabdomyolysis were not reported in the concerned setting. After providing additional details, it is concluded that extravasation including tissue necrosis, CPK elevations including rhabdomyolysis are considered ADRs. TLS has not been reported in the SCLC setting, but due to the risk it is deemed appropriate to include information in the PI.

5.4.11. In vitro biomarker test for patient selection for safety

Not applicable.

5.4.12. Overall discussion and conclusions on clinical safety

5.4.12.1. Discussion

5.4.12.1.1. Overall assessment of available safety data

Safety datasets and exposure

The **safety database** is comprised of the IMforte data including the atezolizumab + lurbinectedin arm (N=242) and the atezolizumab arm (N=240). IMforte safety data with a DCO date of 29 July 2024 are displayed side by side with the pooled Atezo Mono population (N=3178) and the pooled Lurbi Mono population (N=554; including 105 patients with SCLC). These pooled populations are not intended for a direct comparison to the IMforte data set due to different indications, populations, disease stages etc. Safety data from the pooled lurbinectedin mono population appear similar to the pivotal study safety data.

Additionally, updated safety data with a DCO date of 12 February 2025 are presented separately. Where applicable, the updated safety data is presented and discussed in the assessment report. The updated safety data are consistent with the primary safety analysis. Patients were exposed to the proposed dose regimen of lurbinectedin. The safety follow-up lasted for 90 days following the last dose of study drug for the IMforte and Atezo Mono populations, and for 30 days following the last dose of study drug for the Lurbi Mono population.

Overall, the available safety database and lurbinectedin exposures are considered acceptable and of sufficient size to reflect the safety of the product. Exposure to chemotherapy during the induction phase was comparable in the subsequently randomised groups in the maintenance phase in the IMforte study. The median **duration of lurbinectedin treatment** was longer in the atezolizumab + lurbinectedin arm (4.4 months) of the IMforte study compared with the Lurbi Mono population and the atezolizumab arm of the IMforte study (2.1 months). The median number of doses administered was 7.0 for lurbinectedin and 7.5 for atezolizumab in the atezolizumab + lurbinectedin arm in the IMforte study, 4.0 in the atezolizumab arm, and 4.0 in the Lurbi Mono population. Treatment durations of lurbinectedin in the atezolizumab + lurbinectedin arm in the IMforte study were: 38.0% ≤3 mo, 20.7% >3-6 mo, 28.1% >6-12 mo, 8.7% >12-18, 4.5% >18-24 mo. Treatment duration per month for lurbinectedin is reflective of the disease burden.

Adverse events

The combination of atezolizumab with lurbinectedin was associated with a substantially higher incidence of treatment-emergent adverse events (TEAEs) compared to atezolizumab monotherapy. Overall, 84.7% of patients in the combination arm experienced at least one TEAE versus 40.4% in the monotherapy arm, with a corresponding increase in the total number of events (2081 vs. 927). This indicates a significant additive toxicity burden with the combination regimen.

The **AEs by PT related to any study treatment** experienced by a greater proportion **(≥5% difference**) of participants in the atezolizumab + lurbinectedin arm than in the atezolizumab arm were: nausea (30.6% and 2.1%), diarrhoea (9.9% vs. 4.2%), vomiting (11.6% and 0.4%), anaemia (28.9% and 2.1%), thrombocytopenia (12.4% and 0.8%), neutropenia (9.9% and 0.8%), fatigue (14.5% and 3.3%), asthenia (11.2% and 3.3%), platelet count decreased (14.5% and 2.1%), neutrophil count decreased (12.4% and 0.4%), white blood cell count decreased (6.6% and 0.4%), and decreased appetite (12.0% and 3.8%).

There were no treatment-related AEs by PT with the proportion in the atezolizumab arm exceeding the proportion in the atezolizumab + lurbinectedin arm by at least 5%.

In terms of differences of relatedness to each drug, only skin and subcutaneous tissue disorders like pruritus (5.4% vs 2.5%) as well as endocrine disorders like hypothyroidism were more common with atezolizumab (6.7% vs 1.7%), all other events were more commonly attributed to lurbinectedin in the combination arm. The largest difference between the combination arm and the monotherapy arm was observed in hematologic toxicities. This included marked increases in anaemia (30.2% vs. 2.5%), thrombocytopenia (12.4% vs. 0.8%), neutropenia (11.2% vs. 0.8%) and leukopenia (4.1% vs. 0). Febrile neutropenia occurred exclusively in the combination arm (1.7%), which is expected due to the myelosuppressive effects of lurbinectedin even though G-CSF was administered. These findings were further supported by laboratory investigations, where reductions in platelet count (14.5% vs. 2.1%), neutrophil count (12.8% vs. 0.4%) and WBC count decreased (6.6% vs. 0.4%) were substantially more frequent with the combination.

Gastrointestinal disorders also notably increased with the combination therapy compared to the atezolizumab monotherapy. Nausea (32.2% vs. 2.5%), vomiting (12.0% vs. 0.4%), and diarrhoea (10.3% vs. 4.6%) were the most common, which is not unexpected due to previous chemotherapy treatment and what is known from experience with lurbinectedin.

General disorders and administration site conditions, particularly fatigue and asthenia were more common with added lurbinectedin (32.6% vs. 8.3%) compared to atezolizumab monotherapy. Fatigue occurred in 14.5% of patients in the combination arm and asthenia in 10.7%, compared to 3.3% each in the monotherapy group, highlighting a greater burden on physical function with a higher degree of treatment-related debilitation compared to monotherapy atezolizumab.

This demonstrates a pronounced impact on patients' daily functioning and overall tolerability.

Endocrine disorders, including immune-mediated hypothyroidism and hyperthyroidism, were observed at similar rates between arms. Hypothyroidism affected 7.9% of patients in the combination arm and 7.1% in the monotherapy arm; hyperthyroidism was reported in 3.3% in the combination arm vs. 2.9% in the monotherapy arm. These events are consistent with the known immune-related profile of atezolizumab and do not appear to be exacerbated by the addition of lurbinectedin.

Conversely, metabolic and nutritional disorders were more prevalent in the combination arm than in the monotherapy arm (20.7% vs. 7.1%). Most frequent events included decreased appetite (12.4% vs. 3.8%) and electrolyte imbalances such as hypomagnesemia, hyponatremia, and hypocalcaemia, occurring in 2–3% of patients with the combination, but rarely with monotherapy.

Respiratory events, particularly pneumonitis, were more common with the combination. The most commonly reported event was dyspnoea, occurring in 2.5% of patients in the combination arm versus 1.7% with atezolizumab alone and cough (1.2% vs. 0%). Events such as pulmonary embolism (1.2%), haemoptysis (0.8%), and respiratory failure (0.4%) were rare but only observed in the combination arm, suggesting a potential increase in respiratory-related toxicity with the addition of lurbinectedin. Other respiratory AEs such as respiratory failure, immune-mediated lung disease, and interstitial lung disease were rare with no discernible pattern.

As a consequence, pulmonary toxicity with the combination therapy is reflected in section 4.8 of the SmPC.

Infections and infestations were reported in 7.0% of patients treated with the combination and in 4.2% of patients with monotherapy. Opportunistic and fungal infections (e.g. candidiasis, Pneumocystis jirovecii pneumonia) occurred exclusively in the combination arm but in low instances. This aligns with the known immunosuppressive effects of lurbinectedin.

Vascular disorders, notably phlebitis and thrombophlebitis, occurred in 11.6% of combination-treated patients versus just 0.4% with atezolizumab alone. Since these events were entirely absent in the monotherapy arm, a vascular toxicity signal could be attributable to lurbinectedin. Recently published research with lurbinectedin used in 2nd line and above showed that the two cohorts had different incidences of phlebitis, where thromboembolic events were more probable with lower use of a central venous catheter (Scattolin et al 2025). Thus, further investigations and validations are needed to explore whether a more widespread use of central venous catheter in patients receiving lurbinectedin may help to reduce the occurrence of thrombophlebitis from the site of injection. The use of a central venous catheter should be considered to reduce the risk of extravasation and thrombophlebitis, particularly in patients with limited venous access as per section 4.2 of the SmPC.

Skin and subcutaneous tissue disorders were relatively balanced across arms (11.2% vs. 13.3%), with pruritus and rash being the most common events. While the events were generally low-grade and manageable, several rare dermatoses, including toxic skin eruptions and vitiligo were reported in both groups.

Neurologic toxicities were somewhat higher in the combination arm (9.9% vs. 6.3%), with increased reports of peripheral neuropathy, dysgeusia, and somnolence.

Finally, cardiac events were reported only in the combination arm (1.7%), including atrial fibrillation and myocardial infarction. Cardiac disorders were reported in 14.1% of patients in the atezolizumab arm and 20.2% in the atezolizumab + lurbinectedin arm during the induction phase. The most common conditions were atrial fibrillation (2.5% vs 5.0%), coronary artery disease (3.3% vs 2.5%), and myocardial ischaemia (1.2% vs 2.9%). Other cardiac events occurred at low frequencies (~1%). Four fatal cardiac events occurred in the atezolizumab + lurbinectedin arm: two cases of cardiorespiratory arrest and two cases of myocardial infarction. All four patients were older males (61–77 years), three with ECOG 0 and one with ECOG 1, all past smokers. Investigators assessed all fatal events as unrelated to study treatment and attributable to underlying disease or other non-treatment causes. No autopsies were performed, and limited data was available. Reasoning about connection to previous atherosclerotic disease rather than treatment related cardiotoxicity was provided for the two fatal myocardial infarction cases. The two cardiorespiratory arrest cases were more plausibly explained by a non-cardiac cause, e.g., respiratory failure, infection, metabolic disturbances, and it was stated that cardiorespiratory arrest often is used as a non-specific term to describe sudden death when no definitive cause can be identified. Smoking is considered a major background cardiovascular risk factor in the IMforte study population. The numerically higher number of cardiac events in the combination arm was plausibly explained by random variation superimposed on a background of substantial pre-existing cardiovascular risk, rather than by any treatment related effect.

Moreover, non-clinical data were discussed in the light of cardiac findings and non-specificity of the findings was explained. Non-clinical findings were not considered relevant as no consistency in pattern nor signal of cumulative cardiotoxicity was observed, and those were not observed in the clinical setting.

In conclusion it can be agreed that a possible relation to study treatment with cardiac toxicity cannot be convincingly substantiated.‘

TAEs of special interest

The safety profile of atezolizumab plus lurbinectedin combination demonstrates two distinct domains of concern in terms of **AESIs**: a quantitatively increased burden of immune-mediated adverse events, largely attributable to PD-L1 inhibitor atezolizumab, and substantial elevation in infection-related toxicities, more associated with myelosuppressive properties of lurbinectedin.

Key categories included immune-mediated hepatitis, thyroid disorders (hypo- and hyperthyroidism), pancreatitis, diabetes mellitus, myositis, nephritis, rash, adrenal insufficiency, pneumonitis, colitis, and various neurologic and inflammatory syndromes such as Guillain-Barré, myasthenia gravis, meningitis, and encephalitis. Additional AESIs encompassed infusion-related reactions, ocular inflammation, vasculitis, hypophysitis, myocarditis, severe cutaneous reactions, and autoimmune haemolytic anaemia. These categories reflect known immune-related toxicities associated with checkpoint inhibitors and were identified using a combination of narrow SMQs, HLTs, and sponsor-defined groupings.

In line with the known immunotoxicity profile of checkpoint inhibitors, immune-mediated AESIs observed with the combination therapy generally mirrored those previously associated with atezolizumab monotherapy. At the time of the safety update provided during the evaluation, the overall frequency of AESIs was again higher with the combination: 35.5% of patients experienced at least one AESI with atezolizumab + lurbinectedin, compared to 24.2% with atezolizumab alone. Similarly, treatment-related AESIs occurred in 27.3% versus 18.3%, and serious AESIs in 5.0% vs. 2.1%, respectively.

The rate of **Grade 3–4 AESIs** was also greater in the combination arm (16 patients; 6.6%) versus monotherapy (8 patients; 3.3%), with lurbinectedin contributing Grade 3–4 treatment-related AESIs in 2.9% of patients. Of note, no Grade 5 (fatal) immune-mediated AESIs were reported in either group. The combination was associated with higher corticosteroid use (16.5% vs. 7.5%). Particularly higher were immune-mediated hepatitis (reported in 11.2% vs. 7.1%) and pneumonitis (5.4% vs. 1.7%), potentially indicating more severe or persistent events. These findings may suggest an additive or synergistic effect of lurbinectedin on hepatic and pulmonary immune activation.

In parallel, a clinically meaningful and consistently higher burden of **infection-related AESIs** was observed with the combination therapy. In the safety update, 41.3% of patients in the atezolizumab + lurbinectedin group experienced infection-related AESIs, compared to 27.1% in the monotherapy group. Grade 3–4 infections were reported in 8.3% vs. 5.0%, and Grade 5 (fatal) infections in 2.5% vs. 1.7%, respectively. Infections occurred with or without concomitant neutropenia, with the most frequent being COVID-19 (5.8%), urinary tract infections (5.0%), and upper respiratory tract infections (5.0%). Infections with neutropenia occurred in 5.0% of combination-treated patients versus 2.1% with atezolizumab alone, further supporting a myelosuppressive component. Febrile neutropenia was only observed in the combination arm (1.7%), including one fatal event.

Additionally, several serious and opportunistic infections were exclusively reported in patients treated with the combination, including COVID-19 pneumonia, Pneumocystis jirovecii pneumonia, encephalitis, and sepsis, most of which were Grade 3–4. While each of these events was individually rare (≤0.4%), their collective emergence suggests a clinically meaningful compromise in host immune defence,

particularly in this setting where immunosuppressive and cytotoxic effects could be cumulative. An isolated Grade 4 case of acute myeloid leukaemia in a lurbinectedin-treated patient was also reported, although causality remains unconfirmed, and a leukemogenic potential of lurbinectedin is not established.

AESIs resulting in treatment withdrawal were low overall but more frequent in the combination group (4 patients; 1.7%) versus monotherapy (1 patient; 0.4%). Similarly, dose modification or treatment interruption due to AESIs occurred in 8.3% of patients in the combination arm, with lurbinectedin-related modifications in 5.8% findings not seen in the atezolizumab-alone arm where dose-modifications were not permitted.

SAEs

The overall incidence of **serious adverse events (SAEs)** was higher with atezolizumab plus lurbinectedin (34.3%) compared to atezolizumab alone (17.9%), though lower than in the broader monotherapy safety databases for atezolizumab (41.2%) and lurbinectedin (40.6%). While absolute event rates were generally low, reflecting the limited sample size, emerging patterns suggest that the addition of lurbinectedin may be associated with increased hematologic and infectious toxicities. Febrile neutropenia (1.7%), thrombocytopenia (0.8%), and platelet count decrease (2.1%) were observed only in the combination arm, aligning with known lurbinectedin-associated myelosuppression. Similarly, infections such as respiratory tract infections (2.1%) and pneumonia (2.9%) occurred more frequently with the combination, and selected events such as pneumonitis, pulmonary embolism, and myocardial infarction appeared exclusively in this group. These findings, although limited by small numbers, indicate an increased treatment-related toxicity with the combination regimen as mentioned earlier. Febrile neutropenia, pneumonia and sepsis are considered as ADRs in section 4.8 of the SmPC, and an appropriate warning regarding myelosuppression resulting in serious infections and sepsis is included in section 4.4 of the SmPC.

Deaths

In the IMforte study, **Grade 5 (fatal)** treatment-emergent adverse events occurred in 6 patients (2.5%) in the atezolizumab arm and 12 patients (5.0%) in the atezolizumab plus lurbinectedin arm, totalling 18 deaths (3.7%) across the safety population. Fatal infections were the most common cause of death in both arms, reported in 1.7% of patients on atezolizumab and 2.1% on the combination, with pneumonia, sepsis, and COVID-19 pneumonia among the identified causes. All cardiac-related fatal events (cardio-respiratory arrest and myocardial infarction) occurred exclusively in the combination arm (1.7%). Similarly, fatal hematologic events (febrile neutropenia and neutropenia, 0.8%), and the only reported suicide (0.4%) were reported in the combination group. Atezolizumab monotherapy was associated with isolated fatal events including cerebrovascular accident (0.4%) and death reported under general disorders (0.4%). Due to a change in the verbatim term of one Grade 5 event in the atezolizumab + lurbinectedin arm, the PT changed from septic shock to neutropenia at the CCOD of 12 February 2025.

There were two grade 5 AEs (sepsis and febrile neutropenia) in the atezolizumab + lurbinectedin arm that were considered as related to lurbinectedin. Narratives were provided. One grade 5 AE of sepsis in the atezolizumab arm was considered as related to atezolizumab.

Based on all provided narratives, the investigators generally considered the causes of death to be unrelated to the study treatments (atezolizumab, carboplatin, etoposide, and lurbinectedin) and more often related to the disease under study, other causes (unspecified), or concurrent illnesses, which is plausible.

Regarding the one case of AML related to lurbinectedin, a narrative was also provided. The patient was below 65 years of age with extensive-stage SCLC, ECOG 1, and a history of rheumatic fever,

dyslipidaemia, atrial fibrillation, arterial occlusive disorder, prior heroin use, and heavy smoking. He received induction atezolizumab + carboplatin + etoposide (4 cycles) followed by maintenance atezolizumab + lurbinectedin (Arm A). During treatment he developed multiple toxicities, including biopsy-confirmed immune-mediated nephritis and hepatitis (related to atezolizumab), pancytopenia (related to lurbinectedin), and later acute myeloid leukaemia (linked to etoposide/lurbinectedin), and several lower-grade events (neutropenia, anaemia, nausea, vomiting, asthenia). He also experienced haemoptysis attributed to disease progression, which was treated with palliative thoracic radiotherapy. The patient discontinued study therapy on Day 463 due to progression and subsequently developed AML; despite azacitidine and venetoclax treatment, he then died on Day 626 from disease progression, with AML and fatigue unresolved at death.

Discontinuations, interruptions and dose reductions due to AEs

Treatment with lurbinectedin was permanently discontinued due to adverse reactions in 5.8% of patients who were receiving lurbinectedin in combination with atezolizumab. The most frequent adverse reaction requiring permanent discontinuation was neutropenia (1.7%).

Adverse reactions leading to interruption of lurbinectedin in patients who received lurbinectedin with atezolizumab occurred in 28.9% of patients; the most common adverse reactions leading to interruption were neutropenia (5.4%), anaemia (5.0%), fatigue (4.6%) and thrombocytopenia (3.3%).

Dose reductions of lurbinectedin due to an adverse reaction in patients who received lurbinectedin with atezolizumab occurred in 16.1% of patients. The most frequent adverse reactions requiring dose reductions included thrombocytopenia (4.1%), fatigue (3.3%), nausea (2.1%) and vomiting (2.1%).

Safety in special populations

Safety in special populations have been analysed by relevant intrinsic (age, sex, race, baseline ECOG PS, hepatic impairment, renal impairment) and extrinsic factors (region, tobacco use history). In most special populations in the IMforte study no meaningful differences in the AE incidences are observed. Generally, a trend of higher AE incidences in the atezolizumab + lurbinectedin arm compared to the atezolizumab arm is observed, as expected. Participants aged over 65 had a higher percentage of grade 3–4 drug-related adverse events (AEs) than participants aged under 65 in the atezolizumab + lurbinectedin arm. Additionally, a higher proportion of AEs leading to treatment withdrawal were observed in participants aged >65 years than in participants aged <65 years in the atezolizumab + lurbinectedin arm. This may be explained due to a higher incidence of grade 3–4 haematological AEs and haematotoxicity-associated AEs in participants aged 65 years and over in this group. Furthermore, these haematological adverse events were the main reason why treatment was discontinued more frequently for subjects aged 65 and over than for younger subjects. It has been established that haematotoxicity-associated side effects have been identified as a well-characterised risk associated with lurbinectedin. The safety profile is more burdensome in patients with baseline ECOG PS 1 compared to 0, and in previous tobacco users compared to current.

No patients with baseline hepatic impairment (defined as having Child-Pugh score B or C) were included in the IMforte study. Data from a phase 1b PM1183-A-017-20 study are available. The most common AEs in all cohorts were fatigue, decreased appetite, nausea, anaemia, and peripheral oedema, pyrexia and vomiting. Most TEAEs were grade 1/2. Grade ≥3 TEAEs were mostly associated with pre-existing hepatic impairment. The safety profile in patients moderate to severe hepatic impairment with reduced dose of lurbinectedin seems manageable and broadly comparable to the one with normal hepatic function and mild impairment. Incidences of SAEs were higher in patients with moderate to severe hepatic impairment. A warning on hepatotoxicity has been included in section 4.4 of the SmPC. Two patients with renal impairment (CKD stage 3b) were enrolled in the IMforte study but no conclusions can be drawn. There are no safety data available on the use of lurbinectedin in pregnant

women, lactating women, or patients younger than 18 years of age, as these patients' categories were excluded from the clinical studies. This is, however, adequately reflected in sections 4.4 and 4.6, and 4.2 (for paediatric patients) of the SmPC.

Lurbinectedin and atezolizumab are not expected to affect each other's pharmacokinetics. Lurbinectedin is primarily metabolised by CYP3A4, and thus **DDI** are expected. Please refer to section 5.2 Clinical pharmacology.

Laboratory and other findings

Shifts in **laboratory values** with worsening from baseline and relevant difference between the two IMforte arms were presented. Higher incidences (≥5% difference) of low haemoglobin, low absolute lymphocyte count, low absolute neutrophil count, low platelet, and low total leukocyte count in the atezolizumab + lurbinectedin arm were observed. The observed differences in laboratory values are highly likely to be directly related to the use of lurbinectedin, given its mechanism of action and the available non-clinical data. Those AEs are identified as ADRs, which is supported

In IMforte, ALT increase was reported in 6.6% of patients (2.5% ≥Grade 3), while AST increase was reported in 7.0% of patients (1.2% ≥Grade 3). The median time to first onset of ALT increase (all grade) was 7 (range: 3-22) days. The median duration was 17 (range: 7-21) days. ALT increase led to dose reduction or interruption in 0.4% of patients each, respectively. The median time to first onset of AST increased (all grade) was 4 (range: 3-8) days. The median duration was 9 (range: 6-21) days. AST increased led to dose reduction in 0.8% of patients.

It is particularly important to note that the most recent safety update review submitted by the applicant identified a single case in which a participant in the atezolizumab+ lurbinectedin arm exhibited laboratory results that met the laboratory criteria suggestive for Hy's law (i.e. post-baseline ALT or AST >3 x ULN in combination with an elevated total bilirubin >2 x ULN). No AE had been reported in connection with these abnormal laboratory test results. 'transaminases increased, including alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased' are included as ADRs in section 4.8 of the SmPC.

Liver tests, including ALT, AST and bilirubin should be monitored prior to initiating lurbinectedin and periodically during treatment as clinically indicated. Dose modifications may be required.

Considering the hepatotoxicity profile of lurbinectedin, AE under the investigation SOC "Gamma-glutamyltransferase increased" (all frequency 3.31%, grade 3 and above 0.83%) is considered ADR and is also included in section 4.8 of the SmPC.

A comparable pattern is evident in instances of increased creatinine levels. While these events are not necessarily specific to organ impairment, in clinical practice they are often associated with renal impairment. There is a known risk of immune-mediated nephritis associated with atezolizumab, and renal changes have been observed during non-clinical toxicity studies of lurbinectedin. 'blood creatinine increased' is included as an ADR in section 4.8 of the SmPC.

The occurrence of infections in patients in the IMforte study was observed to be independent of their glucose levels at baseline, and no specific pattern regarding hyperglycaemia and infection was identified. It is important to note that no cases of immune-mediated diabetes mellitus were diagnosed in the absence of blood sugar level testing. A total of six cases of immune-mediated diabetes were documented, with four occurring in the lurbinectedin plus atezolizumab group and two in the atezolizumab monotherapy group. In the combination arm, two patients had a history of diabetes mellitus, which worsened during the maintenance phase. No infections were reported subsequent to the exacerbation of diabetes. The remaining two cases of new-onset diabetes occurred during maintenance, with no reported associated infection.

There were a low number of patients with **ECG abnormalities**, but two participants in the atezolizumab + lurbinectedin arm experienced Grade 5 and 3 abnormalities. Narratives of the five participants in the atezolizumab + lurbinectedin group that had clinically significant post-baseline ECG abnormalities showed no apparent causal relationship to the study drugs, as all patients had cardiac comorbidities. Of note, there is a high proportion of missing post-baseline ECG assessments (over 40%) in both treatment arms.

There were no clinically meaningful observations on the **vital sign abnormalities**.

ZEPZELCA has moderate influence on the ability to drive and use machines. Patients experiencing fatigue, dizziness, vertigo and nausea should be advised not to drive and use machines until symptoms abate.

If an overdose is suspected, monitor the patient closely for myelosuppression and hepatic enzymes and institute supportive-care measures as appropriate.

There is no known antidote for overdose with lurbinectedin.

Haemodialysis is not expected to enhance the elimination of lurbinectedin because lurbinectedin is highly bound to plasma proteins (99%), and renal excretion is negligible.

Post-marketing experience

Rhabdomyolysis

Rhabdomyolysis has been reported in patients treated with lurbinectedin in the post-marketing phase. No fatal cases have been reported.

Creatine phosphokinase (CPK) should be monitored prior to initiating lurbinectedin and periodically during treatment as clinically indicated.

If rhabdomyolysis occurs, supportive measures such as parenteral hydration, urine alkalinisation and dialysis should be promptly established, as indicated. Based on severity, ZEPZELCA treatment should be withheld, or the dose should be reduced.

Caution should be taken if medicinal products with known association with rhabdomyolysis (e.g., statins), are administered concomitantly with lurbinectedin, since the risk of rhabdomyolysis may be increased.

Extravasation resulting in tissue necrosis

Cases of extravasation with local irritation have been uncommonly reported with post-marketing use of lurbinectedin. Extravasation resulting in skin and soft tissue injury, including necrosis requiring debridement, may occur.

The use of a central venous catheter should be considered to reduce the risk of extravasation, particularly in patients with limited venous access. Patients should be monitored for signs and symptoms of extravasation during the ZEPZELCA infusion.

If extravasation occurs, the infusion should be immediately discontinued, the infusion catheter should be removed, and the patient should be monitored for signs and symptoms of tissue necrosis. The time to onset of necrosis after extravasation may vary. Supportive care should be administered and an appropriate medical specialist should be consulted as needed for management of signs and symptoms of extravasation. Subsequent infusions should be administered at a site that was not affected by extravasation.

Tumour Lysis Syndrome (TLS)

TLS, which may be fatal, has been reported with ZEPZELCA therapy in the post-marketing phase. Healthcare professionals are advised to closely monitor patients for TLS, especially those with a high tumour burden. Key precautions include preventing dehydration and managing electrolyte imbalances. If TLS develops, it should be treated promptly, and the potential need for interruption or discontinuation of treatment should be considered.

5.4.12.1.2. Adverse drug reactions (ADRs) in the SmPC

The ADRs proposed by the applicant for inclusion in the SmPC are described in section 5.4.3.1 above.

5.4.12.2. Conclusions on clinical safety

The safety database and lurbinectedin exposures are considered sufficient in the context of the concerned clinical setting, and enable characterisation of the safety profile of lurbinectedin as a part of combination treatment with atezolizumab. The main safety findings pertain to myelosuppression, gastrointestinal events, decreased appetite, fatigue, musculoskeletal pain. Hepatotoxic events and rhabdomyolysis were observed too, in the post-marketing setting. Five percent of patients had fatal adverse reactions, in most cases due to pneumonia and other lung infections.

The immune-mediated safety profile of the combination appears qualitatively consistent with that of atezolizumab monotherapy, the addition of lurbinectedin clearly amplifies the total burden of treatment-related toxicity. Although the overall safety signal remains within an expected and monitorable range, these findings underscore the need for robust risk mitigation strategies, supportive care (e.g., G-CSF, antibiotics), and early corticosteroid intervention.

Safety findings in the combination arm are consistent with the known pharmacologic effects of lurbinectedin and the need for additional safety monitoring and proactive supportive care when this regimen is administered. The safety profile remains acceptable when managed appropriately but reflects a clear additive toxicity risk compared to atezolizumab monotherapy.

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

The applicant proposed the following summary of safety concerns in the RMP:

Table 97 : Summary of safety concerns in the proposed RMP

Summary of safety concerns	
Important identified risks	None
Important potential risks	Embryo-foetal toxicity
Missing information	None

6.1.2. Discussion on proposed safety specification

Important identified risks

Myelosuppression

Myelosuppression was initially proposed to be included as an important identified risk in the RMP. It was acknowledged that there are specific clinical recommendations in the PI. However, lurbinectedin is a synthetic analog of trabectedin for which myelosuppression is also an identified risk, and which has been marketed for more than 15 years. In addition, topotecan, which was used as comparator in several lurbinectedin clinical studies, has been approved since 1996 in the EU for the treatment of patients with relapsed SCLC for whom re-treatment with the first-line regimen is not considered appropriate, and also has myelosuppression as an identified risk. Both trabectedin and topotecan have very similar specific clinical recommendations on haematologic toxicities in the PI as proposed for lurbinectedin. In addition, myelosuppression is a known ADR of atezolizumab with extensive clinical recommendations in the PI. It was acknowledged that the combination of atezolizumab with lurbinectedin was associated with a substantially higher incidence of TEAEs compared to atezolizumab monotherapy, with largest difference observed in haematologic toxicities. However, this was expected given lurbinectedin's cytotoxic and myelosuppressive properties. It should also be highlighted that, considering the nature of the proposed indication (extensive stage SCLC), it is expected that patients on this therapy will be closely monitored.

In conclusion, it is considered that proposed risk minimisation measures for myelosuppression have become established in clinical practice, and it is not expected that further characterisation will change the impact of this risk on the risk-benefit of lurbinectedin in the proposed indication. Thus, '*Myelosuppression'* should be removed from the list of safety concerns in the RMP. Nevertheless, given observed increase in haematologic toxicities in atezolizumab + lurbinectedin arm, including serious infection, sepsis and bleeding cases as clinical consequences of myelosuppression/neutropenia, the 'Serious infections, including sepsis' and 'Haemorrhage' should be included as important identified risks in the periodic safety update report (PSUR) rather than '*Myelosuppression*', in accordance with GVP module V, rev 2.

CPK elevations, including rhabdomyolysis

Data provided in section *SVII.3.1 Presentation of important identified risks and important potential risks* in the RMP is not very informative since tables mostly present cumulative number of all adverse reactions retrieved with the MedDRA SMQ '*Rhabdomyolysis/myopathy'* and the preferred term [PT] '*Myoglobin urine'* so it is not possible to identify how many of them were actually rhabdomyolysis cases. More detailed data was only presented for the ISA population and the SCLC sub-population, in which lurbinectedin was given as monotherapy, i.e. no data from the atezolizumab + lurbinectedin arm was presented nor their comparison with atezolizumab arm. In general, data on safety concerns described in the section *SVII.3.1 Presentation of important identified risks and important potential risks* in the RMP should be focused primarily on claimed indication, i.e. data from study GO43104 (IMforte).

Cases observed in the ISA population and the SCLC sub-population only reported CPK elevations, mostly Grade 1-2. No rhabdomyolysis cases were reported in those lurbinectedin mono clinical phase II and III studies. According to the provided Safety Update Report, only 5 cases (2.1%) of CPK elevations were reported in atezolizumab + lurbinectedin arm, out of which four were Grade 1 and one Grade 3. In the atezolizumab arm, 13 cases (5.4%) were reported; of these, 10 were Grade 1, and the remaining three were one case each of Grade 2, Grade 3, and Grade 4. Only 3/13 cases were considered related to atezolizumab (one case grade 1, one grade 3 and one grade 4), and 2/5 related to atezolizumab/lurbinectedin (both grade 1). Only in 1 case, CPK elevation led to lurbinectedin interruption. In the atezolizumab monotherapy arm, CPK elevation led to atezolizumab dose modification or interruption in 3 cases. Only one case in the atezolizumab arm was assessed as Treatment-Related Serious Adverse Event.

Considering *blood creatine phosphokinase increased* is a known ADR for atezolizumab (frequency uncommon), and that no indication that the combination of atezolizumab and lurbinectedin would lead to more serious and/or frequent cases of CPK elevations is observed at the moment (majority of cases were non-serious and resolved, slightly higher incidence in the atezolizumab mono arm), CPK elevations is considered to be neither an identified nor an important risk for inclusion in the list of safety concerns in the RMP.

It is noted that atezolizumab has listed immune-mediated reactions, which include myositis. In the Tecentriq (atezolizumab) RMP (version 32.1, DLP: 27 May 2025) it is stated that myositis has the capacity to lead to serious complications such as rhabdomyolysis or myocarditis. There is also a patient card in place informing patients and physicians about this risk as well as relevant monitoring instructions and management guidelines, to facilitate earlier diagnosis and timely intervention.

From data available in the submitted Safety Update Report, no case of rhabdomyolysis was seen in any arm, while one case of Grade 2 myositis was identified in the atezolizumab + lurbinectedin arm vs no case in the atezolizumab arm.

It is acknowledged that rare cases of rhabdomyolysis, including two fatal cases, have been reported with post-marketing use of lurbinectedin, and that this information is included in the US PI based on the recommendation from the FDA, following the cumulative safety update on rhabdomyolysis, dated 13 July 2021. According to the provided Periodic Benefit Risk Evaluation Report/Periodic Safety Update Report for lurbinectedin No. 9 (interval period: 15 June 2024 – 14 December 2024), 5 cases of rhabdomyolysis were reported cumulatively in the post-marketing setting, and 5 cases in the clinical trial setting (4 cases with single agent and 1 in combination

There are specific clinical recommendations for managing the risk of rhabdomyolysis in the PI.

Overall, no new data have been provided during the evaluation and available data are not considered sufficient to support the inclusion of *CPK elevations, including rhabdomyolysis* as an important identified risk in the RMP. The important identified risk *Rhabdomyolysis* should be included in the PSUR only. Analysis of this risk should include data on the effectiveness of the clinical recommendations included in the PI. Data on grade 3 or higher cases of CPK elevations could also be presented as part of this analysis in the PSUR.

Important potential risks

Capillary leak syndrome (CLS)

CLS has been originally categorized as an important potential risk for lurbinectedin because this is an important identified risk for trabectedin, which is a medicinal product of the same therapeutic class as lurbinectedin. No cases reporting the PT Capillary leak syndrome were found, and no cases were categorised as CLS because they either met only one diagnostic criterion or reported insufficient information for adequate diagnosis confirmation. Therefore, CLS has not yet been observed among patients treated with lurbinectedin.

Although CLS is an identified ADR of trabectedin (frequency uncommon), it is not an important identified risk in the trabectedin-containing medicinal products' RMP (e.g. Yondelis and Trabectedin Accord). No additional RMMs are in place either.

Only specific follow-up questionnaire for further characterisation of this risk was proposed. No information (routine RMM) on this risk is proposed in the lurbinectedin PI.

Since no case was identified in the available data, including in the post-marketing data, and the potential mechanism by which lurbinectedin may induce CLS is not known, it is considered that there is no sufficient evidence for a conclusion on a class effect at the moment. In addition, no specific clinical

recommendations are proposed in the PI. Thus, it is considered that CLS should not be included in the RMP as an important potential risk, and it could be closely monitored as an important potential risk in the PSUR.

Acute myeloid leukaemia/ Myelodysplasia

Acute myeloid leukaemia (AML) was reported in one patient receiving atezolizumab + lurbinectedin maintenance after induction with atezolizumab + carboplatin + etoposide. Given this is a single case from the IMforte study, possible contribution of etoposide (a known leukemogenic), and the clinical context of extensive-stage SCLC with short overall survival and limited treatment duration, this event does not represent a safety signal uniquely attributable to lurbinectedin. Pancytopenia observed in this patient is in line with the expected hematologic toxicity profile of cytotoxic chemotherapy.

It is acknowledged that based on its mechanism of action, lurbinectedin may potentially induce a tumourigenic effect. However, median exposure to lurbinectedin in the claimed indication is typically <6 months, which is not consistent with the prolonged cumulative exposure usually associated with therapy-related AML. Therefore, it is questionable whether it is feasible to further characterise this risk.

It is highlighted that due to the short median duration of lurbinectedin exposure (<6 months), the prolonged latency typically required for therapy-related AML, the advanced disease setting with limited life expectancy, and the presence of strong confounding risk factors, the systematic collection of sufficient, interpretable data to establish or exclude a causal association between lurbinectedin and AML occurrence is not realistically achievable, which is endorsed. Any AML cases observed during or shortly after lurbinectedin treatment were more plausibly explained by prior cytotoxic therapies, radiotherapy, underlying malignancy, or patient-related risk factors, rather than recent exposure to lurbinectedin, which is acknowledged. Consequently, "Acute myeloid leukaemia/Myelodysplasia" was removed as an important potential risk in the RMP, including the associated Follow-up Questionnaire. All parts of the RMP were updated accordingly.

Missing information

Use during pregnancy, including reproductive and development toxicity

Although it is acknowledged that there are no data on lurbinectedin use during pregnancy, it is not expected that sufficient data will be obtained due to the proposed recommendations on contraception in males and females included in the PI. In addition, lung cancer rarely occurs in patients who are younger than 45 years, and no activity for collecting more data on use during pregnancy has been proposed. Thus, the inclusion of this missing information is not supported. Nevertheless, considering available non-clinical data and lurbinectedin's mechanism of action, embryo-foetal toxicity should be included as an important potential risk in the RMP.

Overall comments on part I and part II of the RMP

It can be agreed that risks myelosuppression, CPK elevations, including rhabdomyolysis, gastrointestinal disorders, fatigue, liver enzymes increase, injection site reaction, including extravasation, and Acute myeloid leukaemia/ Myelodysplasia are not considered important for inclusion in the list of safety concerns in the RMP.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan.

Routine pharmacovigilance activities

Routine pharmacovigilance (PhV) activities include closely monitoring of case reports from both clinical trial and post-marketing settings, focusing on the collection, evaluation of the risk factors, severity, seriousness, and outcome but also the reporting to applicable competent authorities. Furthermore, ongoing evaluation of aggregate safety information from all sources from interval periods and cumulative will be performed, including trending analysis for all safety concerns in the Periodic Safety Update Report/Periodic Benefit Risk Evaluation Report (PSUR/PBRER).

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction Follow-up Questionnaires are in place for: none.

The applicant did not propose any additional pharmacovigilance activities.

6.2.2. Discussion on the pharmacovigilance plan

6.2.2.1. Routine pharmacovigilance activities

The PRAC, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

6.2.2.2. Additional pharmacovigilance activities

No additional PhV activities are proposed. Considering the data submitted, this approach is considered acceptable.

6.3. Plans for post-authorisation efficacy studies

No planned or on-going imposed post-authorisation efficacy studies are in place for lurbinectedin, this is endorsed.

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

Table 98: Planned routine risk minimisation measures

Safety concern	Routine risk minimisation activities
Embryo-foetal toxicity	**Routine risk communication:** *SmPC Section 4.4 Special warnings and precautions for use* *SmPC Section 4.6 Fertility, pregnancy and lactation* *SmPC Section 5.3 Preclinical safety data* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *SmPC Section 4.4 Special warnings and precautions for use* *Embryo-foetal toxicity* Lurbinectedin can cause fetal harm when administered to a pregnant woman. Pregnancy testing is recommended in women of childbearing potential prior to starting treatment.

Safety concern	Routine risk minimisation activities
	Female patients of childbearing potential should use highly effective contraception during treatment with lurbinectedin and for 7 months after the last dose. Male patients with female partners of childbearing potential should use condom during treatment and for 4 months after the last dose. Female partners of childbearing potential should use highly effective contraception for the same period. *SmPC Section 4.6 Fertility, pregnancy and lactation* Pregnancy testing is recommended in women of childbearing potential prior to starting treatment with lurbinectedin. Female patients of childbearing potential should use highly effective contraception during treatment and for 7 months after the last dose. Male patients with female partners of childbearing potential should use condom during treatment and for 4 months after the last dose. Female partners of childbearing potential should use highly effective contraception for the same period. *Pregnancy* There are no or limited amount of data from the use of lurbinectedin in pregnant women. Studies in animals have shown severe embryo-foetal development toxicity. Lurbinectedin should not be used during pregnancy unless the clinical condition of the woman requires treatment with lurbinectedin. Pregnant or non-pregnant women of childbearing potential should be advised of the potential risk to a foetus. If lurbinectedin is used during pregnancy, or if a patient becomes pregnant while receiving lurbinectedin, the patient should be apprised of the potential risk to the foetus. *Breast-feeding* It is unknown whether lurbinectedin/metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Lurbinectedin is contraindicated during breastfeeding. *Fertility* Although no specific studies were conducted to assess fertility with lurbinectedin, and no clear signals of toxicity of reproductive organs were observed in toxicity studies, due to the nature of the compound (cytotoxic and mutagenic) it is likely to affect the reproductive capacity. Advice on conservation of ovules or sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with lurbinectedin. Genetic counselling is also recommended for patients wishing to have children after therapy.

The applicant did not propose any additional risk minimisation measures.

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

The PRAC having considered the data submitted was of the opinion that the proposed risk minimisation

measures are sufficient to minimise the risks of the product in the proposed indication.

6.4.2.2. Additional risk minimisation measures

No additional risk minimisation measures are proposed by the applicant. Considering the data submitted, this approach is considered acceptable.

6.5. RMP summary and RMP annexes overall conclusion

The RMP Part VI and the RMP Annexes are considered acceptable.

6.6. Overall conclusion on the Risk Management Plan

The CHMP and PRAC consider that the risk management plan version 0.4 is acceptable.

7. Pharmacovigilance

7.1. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.2. Periodic safety update reports (PSURs) submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new list of Union reference dates (EURD list) entry uses the European birth date (EBD) or the international birth date (IBD) to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request an alignment of the PSUR cycle with the IBD. The IBD is 15 June 2020.

8. Product information

8.1. Summary of product characteristics (SmPC)

8.1.1. SmPC section 4.1 justification

Intended indication is: *ZEPZELCA, in combination with atezolizumab, is indicated for the maintenance treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin and etoposide.*

The indication is supported by the data provided in the dossier.

8.1.2. SmPC section 5.1 justification

Data proposed for the SmPC section 5.1 is agreed upon.

8.2. Labelling

8.2.1. Package leaflet (PL)

8.2.2. User consultation

8.2.2.1. Conclusion from the checklist for the review of user consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

8.2.3. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD group for the following reasons:

The applicant requested the use of the minimum required particulars in the immediate label of the 20mL and 30mL vials due to limited dimensions of the immediate container, resulting in significant space constraints. The request was found acceptable as the medicinal product is to be prepared and handled by healthcare professionals only.

The particulars to be omitted as per the QRD group decision described above will, however, be included in the Annexes published with the EPAR on EMA website and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

8.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Zepzelca (lurbinectedin) is included in the additional monitoring list since it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

9. Benefit-risk assessment

9.1. Therapeutic context

9.1.1. Disease or condition, proposed therapeutic indication

The intended indication is:

ZEPZELCA, in combination with atezolizumab, is indicated for the maintenance treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) whose disease has not progressed after

first-line induction therapy with atezolizumab, carboplatin and etoposide.

Small cell lung cancer (SCLC) accounts for approximately 15% of all lung cancer cases and is distinguished from non-small cell lung cancer (NSCLC) by its rapid growth rate and early development of metastatic disease, resulting in most patients being diagnosed with extensive-stage disease (Govindan et al 2006). The majority (approximately 70%) of patients with SCLC are initially diagnosed with ES-SCLC, which has poor survival prospects: median overall survival (OS) of approximately 10-12 months (Socinski et al 2009, Horn et al 2018).

9.1.2. Available therapies and unmet medical need

For a detailed description, please see section 2.1. of this document.

The current standard first-line treatment for patients with ES-SCLC is atezolizumab plus carboplatin/etoposide (CE), as induction therapy, followed by atezolizumab maintenance therapy, or durvalumab plus platinum (cisplatin or carboplatin) and etoposide as induction therapy, followed by durvalumab maintenance therapy (ESMO 2021, NCCN 2025). Recently, two other PD-L1 inhibitors have been approved in the first-line treatment of ES-SCLC. In February 2025, serplulimab in combination with CE was approved by the EMA for the first-line treatment of patients with ES-SCLC based on data from the phase 3 ASTRUM-005 trial (Cheng et al 2022). In March 2025, tislelizumab in combination with etoposide and platinum chemotherapy was approved by the EMA for the first-line treatment of adult patients with ES-SCLC based on data from the phase 3 RATIONALE-312 trial (Cheng et al 2024). Despite the available treatment options, there is still unmet medical need in the ES-SCLC setting. SCLC has a very high rate of attrition with fewer patients eligible for therapy in later lines (Armstrong et al 2019).

9.2. Main clinical studies

For a detailed description of the main clinical studies supporting this application, please refer to section 5.3.2. of this document.

Study GO43104 (IMforte) is a pivotal Phase III, randomized, open-label, multicenter trial in participants with extensive-stage small cell lung cancer (ES-SCLC). Patients with ongoing response or stable disease after 4 cycles of carboplatin, etoposide, and atezolizumab induction were randomized (planned N=690; 450 enrolled, 225 per arm) to lurbinectedin plus atezolizumab or atezolizumab alone as maintenance. The primary objective was to evaluate efficacy, with dual primary endpoints of independent review facility (IRF)-assessed progression-free survival (PFS, RECIST v1.1) and overall survival (OS). Statistical hypotheses were prospectively defined for both endpoints. Randomization was stratified by ECOG performance status, LDH, liver metastases, and prior prophylactic cranial irradiation. Treatments were administered Q3W until progression or unacceptable toxicity. Lurbinectedin dosing allowed two stepwise reductions for toxicity, while atezolizumab was fixed-dose with interruptions permitted for adverse events. Efficacy was assessed by blinded IRF review, and safety oversight was provided by an independent Data Monitoring Committee. Data cut-off for the primary analysis was 29 July 2024. A descriptive OS analysis and updated safety data was included for cut-off 12 February 2025.

9.3. Favourable effects

The primary endpoint IRF-assessed PFS was statistically significantly improved in the atezolizumab + lurbinectedin arm compared to atezolizumab arm [median PFS 5.36 vs 2.14 months; stratified HR for

PFS 0.54 (95% CI: 0.43, 0.67), p-value <0.0001]. Separation of K-M curves was evident from approximately 1.5 month after treatment initiation.

The primary endpoint OS was statistically significantly improved in the atezolizumab + lurbinectedin arm compared to atezolizumab arm (median OS 13.24 vs 10.64 months; stratified HR for OS 0.73 (95% CI: 0.57, 0.95), p-value 0.0174). Separation of K-M curves was evident from approximately 2.5 months after treatment initiation.

The updated OS (DCO date 12 February 2025) was not statistically tested, but an improvement in the atezolizumab + lurbinectedin arm compared to atezolizumab arm (median OS 13.90 vs 11.14 months; stratified HR for OS 0.81 (95% CI: 0.65, 1.01)) was still shown. Separation of K-M curves was sustained over time until approximately 19 months.

9.3.1. Uncertainties and limitations about favourable effects

Protocol amendments and statistical assumptions

For ES-SCLC, OS requires reliable estimation of treatment effect. Changes introduced in IMforte protocol Version 7, including revised assumptions for OS analyses and follow-up duration, were of concern. Although updates to enrolment and conversion estimates and introduction of a 5-month minimum follow-up were operational and intended to maintain a median follow-up of 16 months, the amendment facilitated earlier alpha spending and increased the likelihood of statistical success at IA. The justification that cross-over to lurbinectedin required modification of the statistical boundary is not methodologically standard, as treatment switching is typically addressed via sensitivity analyses rather than adjustment of the alpha-spending function. In this setting, even if the median follow-up appears adequate from a mathematical standpoint, the reduced minimum exposure remains a key source of uncertainty in the IMforte findings. Final OS data provide directional consistency of effect, albeit being exploratory.

Patient selection and positioning in the current treatment landscape

Lurbinectedin was administrated to the relatively fit patients (ECOG 0-1) with no CNS metastases and adequate response to induction treatment. It excluded those with early progression, treatment-limiting toxicity, or delayed recovery.

9.4. Unfavourable effects

The safety population comprised 242 patients in the atezolizumab plus lurbinectedin arm and 240 patients in the atezolizumab monotherapy arm of the IMforte study (GO43104). Patients received the proposed dose regimens, with median treatment durations of 4.4 months for lurbinectedin and 4.8 months for atezolizumab in the combination arm versus 2.1 months for atezolizumab in the monotherapy arm.

Key unfavourable effects are summarized below:

1. **Hematologic toxicities (anaemia, thrombocytopenia, neutropenia, febrile neutropenia)**: More frequent in the combination arm (anaemia 30.2% vs. 2.5%, thrombocytopenia 12.4% vs. 0.8%, neutropenia 11.2% vs. 0.8%, febrile neutropenia 1.7% vs. 0%) primarily attributed to lurbinectedin. Grade 3–4 events contributed to dose modifications and discontinuations.
2. **Infections**: Overall infections 7.0% vs. 4.2%; opportunistic infections occurred only in the combination arm. Grade 3–4 infections occurred in 8.3% vs. 5.0%, fatal infections 2.5% vs.

1.7%, mainly related to lurbinectedin.

3. **Gastrointestinal events (nausea, vomiting, diarrhoea)**: Nausea 32.2% vs. 2.5%, vomiting 12.0% vs. 0.4%, diarrhoea 10.3% vs. 4.6%, mainly related to lurbinectedin. Grade 3–4 events were uncommon.
4. **Fatigue and asthenia**: Fatigue 14.5% vs. 3.3%, asthenia 10.7% vs. 3.3%, primarily related to lurbinectedin, contributing to dose modifications or interruptions.
5. **Immune-mediated adverse events**: Overall AESIs 35.5% vs. 24.2%; treatment-related AESIs 27.3% vs. 18.3%; Grade 3–4 events 6.6% vs. 3.3%, primarily associated with atezolizumab.
6. **Serious adverse events and fatalities**: SAEs 31.0% vs. 17.1%. Grade 5 events 5.0% vs. 2.5%; two Grade 5 events (sepsis and febrile neutropenia) were considered related to lurbinectedin, one (sepsis) to atezolizumab.
7. **Discontinuations and dose modifications due to adverse events**: Discontinuations 6.2% vs. 3.3%, primarily for hematologic toxicities, immune-mediated nephritis, and phlebitis. Dose modifications/interruptions 38.0% vs. 13.8%, with 5.8% attributable to lurbinectedin.

Strength of Evidence: Safety findings are consistent with the known pharmacological profiles of atezolizumab and lurbinectedin, and can be supported by adequate systematic capture of onset, severity, duration, and reversibility of AEs, as well as post-marketing experience. The updated 2025 safety follow-up and exposure data further support the robustness of these findings.

9.4.1. Uncertainties and limitations about unfavourable effects

Not applicable.

9.5. Effects table

Table 99 Effects Table for ZEPZELCA 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 (data cut-off: 29 July 2024)

Effect (short description)	***Treatment*** *atezolizumab 1200 mg Q3W + lurbinectedin 3.2 mg/m2 Q3W (N=242)*	***Control*** *atezolizumab 1200 mg Q3W (N=241)*	***Uncertainties/ Strength of evidence***	***Ref***
Favourable effects				
IRF-assessed PFS (FA) defined as: months (95% CI)	5.36 (4.24-5.75)	2.14 (1.64-2.73)	**SoE:** At the time of FA, when 249 events occurred, patients had a median duration of survival follow-up of 14.95 months. Statistically significant. **Unc:** reduced minimum exposure at the IA after protocol amendment	Study GO43104 (IMforte)
	HR stratified (95% CI) 0.54 (0.43-0.67)			
OS (IA) defined as:	13.24 (11.89-16.36)	10.64 (9.49-12.16)		

Effect (short description)	Treatment atezolizumab 1200 mg Q3W + lurbinectedin 3.2 mg/m2 Q3W (N=242)	Control atezolizumab 1200 mg Q3W (N=241)	Uncertainties/ Strength of evidence	Ref
months (95% CI)	HR stratified (95% CI) 0.73 (0.57-0.95)		**SoE:** At the time of IA of OS, 46.7% of patients in the atezo + lurbi arm had died compared to 56.4% in the atezo arm. Statistically significant. **Unc:** reduced minimum exposure at the IA after protocol amendment	
Unfavourable effects				
AEs by PT with ≥10% incidence and ≥5% difference between arms no./total no. (%)				Study GO43104 (IMforte)
Grade3-4 AEs	22.1%	38%		
SAEs	34.3%	17.9%		
Nausea	37.6%	4.6%	**SoE:** Frequencies are based on all-cause adverse events identified during a median treatment duration of 4.1 months. **Unc**: likely a cumulative effect of disease burden, induction chemotherapy, immunosuppression and investigational combination with lurbinectedin	
Anaemia	33.9%	7.1%		
Neutrophil count decreased	13.2%	1.3%		
Thrombocytopenia	12.8%	1.7%		

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence; IRF: independent review facility; PFS: progression-free survival; OS: overall survival; FA: final analysis; IA: interim analysis; HR: hazard ratio; CI: confident interval. Notes: Safety data cut-off 12-Feb-2025 with median exposure of atezolizumab+ lurbinectedin 7.6 months and 5.1 months for atezolizumab monotherapy. MedDRA version 27.1. Incidences are shown as % of patients in the Safety Analysis Set.

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

The phase 3 IMforte pivotal study supporting this application had open-label design, but it is deemed that internal validity is high and one primary endpoint, OS, is objective, and the other one, PFS, was assessed by the IRF. The study met its dual primary endpoints. Pre-specified sensitivity, supplementary and subgroup analyses add to the robustness of findings. The design of the study allowed for the assessment of the contribution of components of the treatment regimen.

Median OS (IA) is prolonged for approximately 2.5 months with lurbinectedin addition. Participants in the atezolizumab + lurbinectedin arm had a 27% reduction in the risk of death compared to participants in the atezo arm. Separation of K-M curves was evident from approximately 2.5 months after treatment initiation. Since the results of the OS IA were statistically significant, the updated OS analysis is of exploratory value. Separation of K-M curves was sustained over time until approximately

19 months.

Median PFS (FA) is prolonged for approximately 3 months with lurbinectedin addition. Participants in the atezolizumab + lurbinectedin arm had a 46% reduction in the risk of disease progression or death compared to participants in the atezolizumab arm. Separation of K-M curves was evident from approximately 1.5 months after treatment initiation.

The efficacy results can be considered clinically relevant for selected patients in the ES-SCLC setting. Indirect comparison to the approved treatments in similar setting and their effects is not straightforward. The OS and PFS gains are comparable to previously approved treatments in the 1L ES-SCLC treatment, although comparators were inactive. However, the pivotal study results clearly show improvement when lurbinectedin is added to atezolizumab in the maintenance phase of 1L ES-SCLC treatment.

However, late protocol changes (CSP v7) affecting OS assumptions, event requirements, and α-spending function raised concerns about reliability of the results. As these were introduced close to study completion and after many OS events, additional information was given and sensitivity analyses were performed to exclude potential bias. In September 2023, protocol version 7 updated enrolment and conversion estimates based on observed data. Actual enrolment and randomization periods lasted approximately 26 and 23 months, respectively, with an observed conversion rate of 73%. A minimum follow-up of 5 months was introduced to maintain median follow-up of 16 months, to support data maturity. While it was demonstrated that all of these changes were operational and not data-driven, the effect of the amendment was to facilitate earlier alpha spending and increase likelihood of statistical success at the IA. The justification that cross-over to lurbinectedin as non-protocol therapy required modification of the statistical boundary is not methodologically standard, as treatment switching is typically addressed via sensitivity analyses rather than adjustment of the alpha-spending function. This did not affect the final study results, rather reduced minimum exposure at the IA.

Safety findings from adding lurbinectedin to atezolizumab in the maintenance regimen show increases of overall incidence and severity of adverse events compared with atezolizumab monotherapy. Key unfavourable effects include hematologic toxicities (anaemia, thrombocytopenia, neutropenia, febrile neutropenia), gastrointestinal events (nausea, vomiting, diarrhoea), fatigue and asthenia, vascular and metabolic effects (phlebitis, thrombophlebitis, decreased appetite, electrolyte imbalances), infections including opportunistic infections and immune-mediated toxicities (hepatitis, pneumonitis, thyroid disorders). Most hematologic, infectious, gastrointestinal, vascular, and metabolic events were primarily attributable to lurbinectedin, whereas immune-mediated toxicities were mainly associated with atezolizumab. Grade 3–4 and serious adverse events, as well as Grade 5 fatalities, were more frequent with the combination, mostly infections and hematologic complications. Two Grade 5 events were considered related to lurbinectedin and one to atezolizumab. Discontinuations and dose modifications were higher with the combination, mainly due to hematologic, immune-mediated, or vascular events.

The adverse event profile of the combination treatment is consistent with the safety profile of each medicinal product. This is likely a cumulative effect of disease burden, induction chemotherapy, immunosuppression and investigational combination with lurbinectedin. Adequate exposure, follow-up, and post-marketing data further support the robustness of the safety findings and inform the overall benefit–risk assessment.

9.6.2. Balance of benefits and risks

Although limited, the survival improvement is considered clinically relevant for the combination treatment of atezolizumab and lurbinectedin in the maintenance treatment of patients with ES-SCLC

who have a poor prognosis. Observed safety profile of the combination treatment is evidently more burdensome, but risks could be outweighed by the benefit in selected patient population. The late protocol changes (CSP v7) affecting OS assumptions raised concerns about reliability of the results, however clarifications and additional sensitivity analyses confirmed robustness of efficacy results.

Overall, lurbinectedin + atezolizumab demonstrated a clinically meaningful improvement, in 12-month OS (~12% absolute gain), with median OS improved by ~2.8 months and early separation of curves consistent with better PFS. Later attenuation likely reflects post-progression treatment and diminishing at-risk population, so no late survival detriment could be observed, supporting a favourable benefit–risk profile .

9.7. Benefit-risk conclusions

9.7.1. At Day 210 - CHMP conclusions

The benefit-risk balance for Zepzelca (lurbinectedin) is positive.