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Original Research

Pooled Safety Analysis of Single-Agent Lurbinectedin in Patients With Advanced Solid Tumours

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Abstract ***Background:*** Lurbinectedin was approved by FDA and other health regulatory agencies for treating adults with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy. Safety profile at approved dose (3.2 mg/m^2 every 3 weeks) was acceptable and manageable in 105 adult SCLC patients from a phase II basket trial. This study analyses safety data from several solid tumours treated at the lurbinectedin-approved dose.
Methods: Data were pooled from 554 patients: 335 from all nine tumour-specific cohorts of the phase II basket trial and 219 from a randomised phase III trial (CORAIL) in platinum-resistant ovarian cancer. Events and laboratory abnormalities were graded using NCI-CTCAE v.4.
Results: Most common tumours were ovarian (n = 219, 40%), SCLC (n = 105, 19%) and endometrial (n = 73, 13%). Transient haematological laboratory abnormalities were the most

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frequent grade 3 or more events: neutropenia (41%), leukopenia (30%), anaemia (17%) and thrombocytopenia (10%). Most common treatment-emergent non-haematological events (any grade) were transient transaminase increases (alanine aminotransferase [66%], aspartate aminotransferase [53%]), fatigue (63%), nausea (57%), constipation (32%), vomiting (30%) and decreased appetite (25%). Dose reductions were mostly due to haematological toxicities, but most patients (79%) remained on full lurbinectedin dose. Serious events mostly consisted of haematological disorders. Eighteen treatment discontinuations (3%) and seven deaths (1%) were due to treatment-related events.

Conclusions: This analysis confirms a manageable safety profile for lurbinectedin in patients with advanced solid tumours. Findings are consistent with those reported in patients with relapsed SCLC, Ewing sarcoma, germline *BRCA1/2* metastatic breast cancer, neuroendocrine tumours and ovarian cancer.

1. Introduction

Lurbinectedin (Zepzelca) is a synthetic tetrahydroisoquinoline alkaloid structurally related to trabectedin that inhibits oncogenic transcription primarily through binding to the exocyclic amino group of guanine-rich DNA sequences around gene promoters, thereby altering the three-dimensional DNA structure and evicting oncogenic transcription factors from their binding sites [1–3]. Lurbinectedin adducts may also inhibit messenger RNA synthesis and induce the ubiquitination and degradation of RNA polymerase II [4] and trick the nucleotide excision repair system, thereby favouring the formation of DNA double-strand breaks and triggering apoptotic cell death [5].

A previous report described the anti-tumour activity and safety profile of lurbinectedin in 105 patients with small cell lung cancer (SCLC) after failure of platinum-based chemotherapy [6]. These patients were included in one of nine tumour-specific cohorts of an open-label, phase II basket trial that evaluated lurbinectedin at 3.2 mg/m^2 administered as a 1-h intravenous (i.v.) infusion on day 1 every 3 weeks (q3wk) [7]. In this previous analysis, lurbinectedin at this dose and schedule resulted in an overall response rate of 35.2% and showed an acceptable and manageable safety profile in the 105 patients treated, with haematological abnormalities being the most common grade 3 or 4 adverse events (AEs). Based on the results in the SCLC cohort of the phase II basket trial [6], approval of lurbinectedin for the treatment of adults with metastatic SCLC with disease progression on or after platinum-based chemotherapy was obtained first in the United States [8] and later in other countries (Canada, Australia, Singapore, the United Arab Emirates, Qatar, South Korea, Ecuador, Mexico, Israel and Switzerland). Recently, the results of other cohorts of this basket trial have shown anti-tumour activity in relapsed Ewing sarcoma, leading to inclusion in the National Comprehensive Cancer Network guidelines in the United States [9], and in pretreated germline *BRCA1/2* metastatic breast cancer [10].

To date, two clinical trials have evaluated lurbinectedin at the approved dose and schedule (3.2 mg/m^2 on day 1 q3wk): the aforementioned basket trial in selected advanced solid tumours and an open-label, randomised, controlled phase III trial comparing lurbinectedin versus pegylated liposomal doxorubicin or topotecan in platinum-resistant ovarian cancer (CORAIL study) [11]. This report describes a detailed post hoc assessment of the safety profile of lurbinectedin monotherapy at the approved dose based on pooled patient-level data from these two studies.

2. Materials and methods

Patients

This pooled analysis includes safety data from all patients treated with at least one dose of lurbinectedin 3.2 mg/m^2 as a 1-h i.v. infusion on day 1 q3wk in an open-label, single-arm, phase II basket trial in nine cohorts of adult patients with selected, difficult-to-treat, advanced solid tumours (ClinicalTrials.gov identifier: NCT02454972; n = 335 patients) and an open-label, two-arm, randomised phase III trial in adult patients with platinum-resistant ovarian cancer (CORAIL; ClinicalTrials.gov identifier: NCT02421588; n = 219 patients). Detailed information on the design, eligibility criteria, study treatment and safety assessments of these two trials is provided as Supplemental Data.

Both trials were conducted at sites in Europe and the United States in compliance with the International Conference on Harmonisation Good Clinical Practice guidelines. The protocols were approved by the centres' Research Ethics Committees. Signed written informed consent was obtained for each patient before any study-specific procedures.

Treatment was administered until disease progression, unacceptable toxicity, treatment delay > 3 weeks (except if clear clinical benefit), requirement of > 2 dose reductions, intercurrent illness precluding study continuation

and patient refusal and/or non-compliance with study requirements. Standard antiemetic prophylaxis (dexamethasone 8 mg and ondansetron 8 mg or equivalent) was given before each lurbinectedin infusion. Secondary prophylaxis with granulocyte colony-stimulating factor (G-CSF) was allowed; however, primary prophylaxis with G-CSF was not allowed.

Study assessments

All pooled safety analyses were based on the assessment of AEs and laboratory abnormalities. Safety was monitored throughout treatment and up to 30 d after the last lurbinectedin infusion or start of a new anti-tumour therapy, whichever occurred first. Any lurbinectedin-related AE was followed until recovery to grade 1 or less or stabilisation of symptoms or until start of a new anti-tumour therapy, whichever occurred first. Laboratory assessments were conducted weekly in the phase II basket trial and on day 1 and day 8 of each cycle in the phase III trial during the first two cycles and every 3 weeks or whenever indicated in subsequent cycles in both trials. AEs and laboratory abnormalities were coded using the Medical Dictionary for Regulatory Activities (MedDRA) v.21.0 and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v.4 [12].

Statistical analysis

Frequency tables were prepared for categorical variables. Continuous variables were described using summary tables with the median and range for each variable. Non-continuous variables were described using frequency tables with counts and percentages. SAS v.9.4 was used for all analyses.

Data sharing statement

Individual participant data are not publicly available since this requirement was not anticipated in the study protocols, considering that both trials started patient enrolment in 2015. Clinical trial summary results were placed at ClinicalTrials.gov (https://www.clinicaltrials.gov).

3. Results

Characteristics of patients

The baseline characteristics of the 554 patients treated with lurbinectedin and included in this pooled analysis are summarised in Table 1. Most patients (n = 408, 74%) were female, with an Eastern Cooperative Oncology Group performance status score ≥1 (n = 303, 55%) and a median age of 61 years (range, 18–85 years); 207 patients (37%) were aged ≥65 years. Most common tumour types were ovarian cancer (n = 219, 40%), SCLC (n = 105, 19%) and endometrial carcinoma (n = 73, 13%). Overall, 194 patients (35%) had liver metastases, and 238 (43%) had lung metastases at baseline; only two patients had central nervous system metastases at baseline (protocol deviations). The median number of prior chemotherapy lines per patient was 1 (range, 1–8 lines).

Treatment exposure

Exposure to lurbinectedin among the 554 treated patients is presented in Table 2. The median number of cycles per patient was 4 (range, 1–52 cycles), with 215 patients (39%) and 69 patients (13%) receiving ≥6 cycles and ≥12 cycles each. Patients were on treatment for a median of 13.3 weeks (range, 1.1–162.3 weeks). The median relative dose intensity was 97.7% (range, 53.2–157.5%). Most treatment discontinuations (n = 436, 79%) were due to disease progression.

Incidence of AEs

An overview of the pooled incidence of AEs reported among the 554 treated patients is provided in Table 3. Pooled incidences of haematological and biochemical abnormalities (regardless of relationship), treatment-emergent AEs (TEAEs), and AEs related to treatment or with unknown relationship are presented in Table 4.

Treatment-emergent AEs

The most common treatment-emergent non-haematological AEs of any grade reported during treatment were fatigue (63%), gastrointestinal disorders (nausea [57%], constipation [32%] and vomiting [30%]) and decreased appetite (25%; Table 4). Most of these AEs were grade 1 or 2, and grade 3 or more AEs comprised fatigue (10%) and nausea and vomiting (4% each). Only four patients had musculoskeletal events that occurred concomitantly with increased creatine phosphokinase levels; these four events were grade 1 or 2, were managed with cycle delays but did not require dose modification and resolved after a median of 7.5 d. Of note, no episodes of rhabdomyolysis were reported.

Treatment-related AEs

The most frequent non-haematological AEs of any grade that were related to treatment (or with unknown relationship) were fatigue (53%), gastrointestinal disorders (nausea [51%], vomiting [25%], constipation [17%] and diarrhoea [13%]) and decreased appetite (17%; Table 4). The most relevant of these AEs are shown in Fig. 1. The most common of these events to reach grade 3 or more were fatigue (7%), nausea and

Table 1
Baseline characteristics of treated patients.

	Phase II basket (n = 335)	Phase III CORAIL (n = 219)	Pooled (n = 554)
Gender, n (%)			
Female	189 (56)	219 (100)	408 (74)
Male	146 (44)	0	146 (26)
Age (years), median (range)	60 (18–83)	63 (25–85)	61 (18–85)
≥65 years	113 (34)	94 (43)	207 (37)
ECOG performance status, n (%)			
0	127 (38)	124 (57)	251 (45)
1	188 (56)	87 (40)	275 (50)
2	20 (6)	8 (4)	28 (5)
Albumin (g/dl), median (range)	4.0 (2.7–5.1)	4.0 (2.0–4.9)	4.0 (2.0–5.1)
BSA (m^2), median (range)	1.8 (1.3–2.6)	1.7 (1.3–2.4)	1.8 (1.3–2.6)
BMI (kg/m^2), median (range)	25.7 (16.2–52.5)	25.2 (15.0–47.9)	25.5 (15.0–52.5)
Tumour type (cohort), n (%)			
Ovarian cancer	0	219 (100)	219 (40)
Small cell lung cancer	105 (31)	0	105 (19)
Endometrial carcinoma	73 (22)	0	73 (13)
Neuroendocrine tumours	32 (10)	0	32 (6)
Ewing family of tumours	28 (8)	0	28 (5)
Germ cell tumours	23 (7)	0	23 (4)
BRCA1/2-associated metastatic breast cancer	21 (6)	0	21 (4)
Biliary tract carcinoma	19 (6)	0	19 (3)
Carcinoma of unknown primary site	19 (6)	0	19 (3)
Head and neck carcinoma	15 (5)	0	15 (3)
Number of tumour sites at baseline, median (range)	3 (1–7)	2 (1–5)	2 (1–7)
Liver metastases, n (%)	137 (41)	57 (26)	194 (35)
Lung metastases, n (%)	212 (63)	26 (12)	238 (43)
CNS metastases, n (%)	2 (< 1)	0	2 (< 1)
Bulky disease (one lesion > 50 mm), n (%)	113 (34)	77 (35)	190 (34)
Prior surgery, n (%)	194 (58)	215 (98)	409 (74)
Prior radiotherapy, n (%)	190 (57)	6 (3)	196 (35)
Number of prior systemic therapy lines, median (range)	1 (1–8)	2 (1–4)	2 (1–8)
Number of prior chemotherapy lines, median (range)	1 (1–8)	2 (1–3)	1 (1–8)

BMI, body mass index; BSA, body surface area; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group.

Table 2
Exposure to lurbinectedin and reasons for treatment discontinuation.

	Phase II basket (n = 335)	Phase III CORAIL (n = 219)	Pooled (n = 554)
Number of cycles administered per patient, median (range)	4 (1–36)	5 (1–52)	4 (1–52)
Patients treated with			
≥6 cycles	120 (36)	95 (43)	215 (39)
≥12 cycles	45 (13)	24 (11)	69 (13)
Time on treatment (weeks), median (range)	12.0 (1.1–110.3)	16.3 (3.3–162.3)	13.3 (1.1–162.3)
Cumulative dose (mg/m^2), median (range)	10.0 (3.1–114.2)	15.8 (3.1–167.1)	12.6 (3.1–167.1)
Relative dose intensity (%), median (range)	98.4 (53.2–123.8)	96.7 (53.8–157.5)	97.7 (53.2–157.5)
Patients who discontinued treatment, n (%)	333 (99)	219 (100)	552 (99)
Reasons for treatment discontinuation, n (%)			
Progressive disease	284 (85)	152 (69)	436 (79)
Patient refusal	16 (5)	14 (6)	30 (5)
Investigator's decision	11 (3)	8 (4)	19 (3)
Death	8 (2)	11 (5)	19 (3)
Death related to treatment	1 (< 1)	2 (< 1)	3 (< 1)
Treatment-related AE	8 (2)	10 (5)	18 (3)
Non-treatment–related AE	5 (2)	8 (4)	13 (2)
Symptomatic deterioration	0	13 (6)	13 (2)
Other	1 (< 1)	3 (1)	4 (< 1)
Patients still on treatment, n (%)	2 (< 1)	0	2 (< 1)

AE, adverse event.

Table 3
Overview of adverse events and support requirement during lurbinectedin treatment.

Patients with	Phase II basket (n = 335), n (%)	Phase III CORAIL (n = 219), n (%)	Pooled (n = 554), n (%)
TEAEs, any grade	331 (99)	214 (98)	545 (98)
Grade 3 or more	216 (64)	137 (63)	353 (64)
Grade 4 or more	87 (26)	52 (24)	139 (25)
Treatment-related AEs, any grade[a]	293 (87)	201 (92)	494 (89)
Grade 3 or more	139 (41)	105 (48)	244 (44)
Grade 4 or more	71 (21)	42 (19)	113 (20)
Serious TEAEs, any grade	134 (40)	92 (42)	226 (41)
Serious treatment-related AEs, any grade[a]	44 (13)	45 (21)	89 (16)
Dose reductions associated with AEs			
TEAEs	79 (24)	38 (17)	117 (21)
Treatment-related AEs[a]	79 (24)	36 (16)	115 (21)
Deaths associated with AEs			
TEAEs	14 (4)	6 (3)	20 (4)
Treatment-related AEs[a]	4 (1)	3 (1)	7 (1)
Treatment discontinuations associated with AEs			
TEAEs	34 (10)	18 (8)	52 (9)
Treatment-related AEs[a]	8 (2)	10 (5)	18 (3)
G-CSF support	79 (24)	54 (25)	133 (24)
Secondary prophylaxis	44 (13)	38 (17)	82 (15)
Therapeutic support	50 (15)	31 (14)	81 (15)
RBC transfusions	52 (16)	40 (18)	92 (17)
Platelet transfusions	11 (3)	7 (3)	18 (3)
Erythropoiesis-stimulating agent use	4 (1)	4 (2)	8 (1)

AE, adverse event; G-CSF,granulocyte colony-stimulating factor; RBC, red blood cells; TEAE, treatment-emergentadverse event.
[a] Includes AEs related to treatment or with unknown relationship.

vomiting (3%). In addition, episodes of treatment-related febrile neutropenia occurred in 6% of patients.

Haematological laboratory abnormalities

The most common grade 3 or more events reported during treatment were haematological laboratory abnormalities (Table 4). The most relevant of these abnormalities are shown in Fig. 1. Grade 3 or more neutropenia (41% of patients, grade 4 in 22%) lasted a median of 7 d (range, 1–48 d) and was mostly afebrile; the reported incidence of severe treatment-emergent febrile neutropenia was 7%. Grade 3 or more anaemia (17%, grade 4 in < 1%) occurred mostly among patients who already had anaemia at baseline; of note, the single case of grade 4 anaemia was observed following an episode of disease-related grade 3 gastrointestinal haemorrhage. Grade 3 or more thrombocytopenia (10%, grade 4 in 5%) lasted a median of 7 d (range, 1–40 d) and was not associated with bleeding episodes. The incidence of grade 3 or more haematological abnormalities was higher within the first two treatment cycles than in subsequent cycles (Fig. 2). Haematological toxicities were the most common AEs, leading to lurbinectedin dose reduction, including neutropenia (11% of patients), febrile neutropenia (3%) and thrombocytopenia (3%); however, only five treatment discontinuations (< 1% of patients) occurred due to haematological toxicities.

Overall, 133 patients (24%) required G-CSF support during lurbinectedin treatment: 82 patients (15%) as secondary prophylaxis and 81 (15%) as therapeutic support (primary G-CSF prophylaxis was not allowed). Ninety-two patients (17%) were given red blood cell transfusions, 18 (3%) received platelet transfusions and eight (1%) were given erythropoiesis-stimulating agents.

Hepatobiliary laboratory abnormalities

Grade 3 or more transaminase increases were the most common severe laboratory biochemical abnormalities regardless of relationship reported during treatment (Table 4 and Fig. 1). Grade 3 or more alanine aminotransferase (ALT) increases (6% of patients) lasted a median of 7 d (range, 2–32 d). Grade 3 or more aspartate aminotransferase (AST) increases (3% of patients) lasted a median of 5 d (range, 1–39 d). About 35% of patients with grade 3 or more transaminase increases while on lurbinectedin already had high transaminase levels at baseline. Grade 3 or more bilirubin increases (2% of patients) were observed only in patients with liver metastases or biliary tract tumours. No cases meeting the criteria for Hy's Law [13] were found.

Serious AEs, treatment discontinuations and deaths

Serious TEAEs (any grade) were reported in 226 patients (41%; Table 3); the most common were haematological

Table 4
Most common laboratory abnormalities, treatment-emergent adverse events and treatment-related adverse events during lurbinectedin treatment.

Patients with	Phase II basket (n = 335)		Phase III CORAIL (n = 219)		Pooled (n = 554)	
NCI-CTCAE grade	≥1	≥3	≥1	≥3	≥1	≥3
TEAEs (≥10% of patients)						
Fatigue	64	11	62	9	63	10
Nausea	47	2	73	8	57	4
Constipation	31	< 1	34	< 1	32	< 1
Vomiting	22	2	43	8	30	4
Decreased appetite	26	< 1	23	2	25	1
Abdominal pain	14	3	26	3	19	3
Diarrhoea	18	2	21	1	19	2
Dyspnoea	18	3	13	1	16	3
Pyrexia	15	< 1	11	.	13	< 1
Cough	12	< 1	8	.	10	< 1
Treatment-related AEs (≥5% of patients)[a]						
Fatigue	51	7	54	7	53	7
Nausea	42	1	64	6	51	3
Vomiting	18	< 1	36	5	25	3
Constipation	14	< 1	21	< 1	17	< 1
Decreased appetite	18	.	16	.	17	.
Diarrhoea	12	< 1	15	< 1	13	< 1
Febrile neutropenia	7	7	5	5	6	6
Mucosal inflammation	5	.	6	< 1	5	< 1
Abdominal pain	3	< 1	9	.	5	< 1
Haematological laboratory abnormalities						
Anaemia	93	16	90	19	92	17
Leukopenia	79	33	65	24	73	30
Neutropenia	69	46	58	32	64	41
Thrombocytopenia	51	10	47	9	49	10
Biochemical laboratory abnormalities						
Creatinine increased	86	2	81	2	84	2
ALT increased	68	6	62	7	66	6
AST increased	53	3	52	3	53	3
AP increased	49	6	41	3	46	5
Bilirubin increased	15	3	6	1	12	2
CPK increased	10	< 1	9	.	9	< 1

Data are % of patients.
Haematological and biochemical abnormalities are shown regardless of relationship to treatment.
AE, adverse event; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; TEAEs, treatment-emergent adverse events.
[a] Includes AEs related to treatment or with unknown relationship.

disorders (febrile and afebrile neutropenia and thrombocytopenia). The overall rate of treatment discontinuation due to any grade AEs was 6% (n = 31 patients; treatment related or with unknown relationship n = 18, 3%; non-treatment–related n = 13, 2%; Table 3). Deaths related to treatment or with unknown relationship occurred in seven patients (1%) and were due to pneumonia (n = 2), sepsis (n = 2), lung infection, cardiorespiratory arrest (unknown causality) and pulmonary arterial hypertension (unknown causality). Their tumour types were ovarian cancer (n = 3 patients), endometrial carcinoma (n = 2) and neuroendocrine tumours (NET; n = 2). Five of these seven patients had grade 4 neutropenia at the time of death.

AEs by age and drug exposure

An overview of the pooled incidence of AEs in the 554 treated patients according to age and duration of drug exposure is presented in Table 5. Neither age < 65 years nor exposure to lurbinectedin for ≥12 cycles had relevant effects on the overall safety profile of the drug.

4. Discussion

The current report, which is based on pooled data from tumour-specific cohorts of a phase II basket trial and from a randomised phase III trial, represents the largest and most comprehensive analysis of the safety profile of lurbinectedin monotherapy at the approved dose and schedule of 3.2 mg/m^2 i.v. on day 1 q3wk in patients with advanced solid tumours.

Transient and reversible myelosuppression was the most frequent toxicity found among patients treated with lurbinectedin in the pooled trials. Neutropenia was the most common severe haematological abnormality reported; it was generally managed with dose reductions or growth factor support and resulted in few treatment

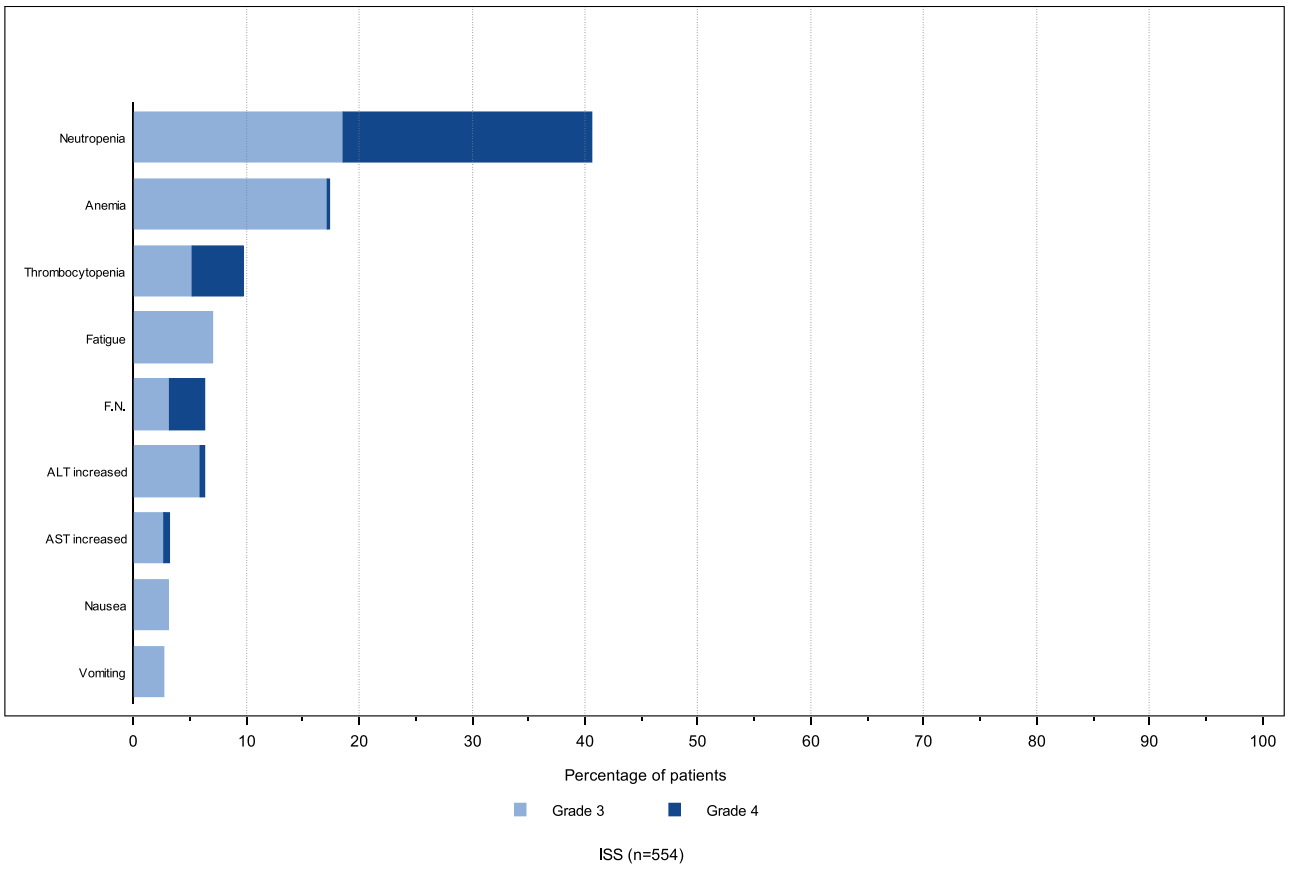

Fig. 1. Most relevant grade 3 or more treatment-related adverse events and laboratory abnormalities regardless of relationship reported in the pooled population of 554 patients during lurbinectedin treatment. ALT, alanine aminotransferase; AST, aspartate aminotransferase; FN, febrile neutropenia.

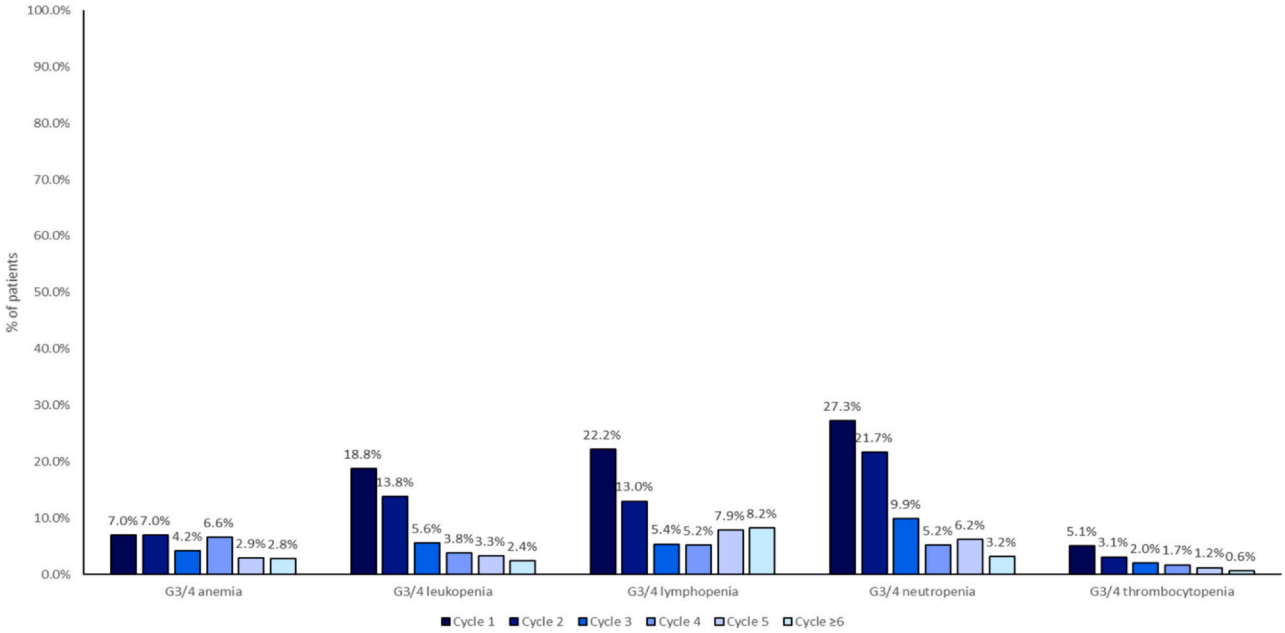

Fig. 2. Grade 3 or more haematological abnormalities in the pooled population of 554 patients during lurbinectedin treatment. Incidence is shown during cycle 1 (n = 554 cycles), cycle 2 (n = 493 cycles), cycle 3 (n = 363 cycles), cycle 4 (n = 292 cycles), cycle 5 (n = 243 cycles) and cycle 6 and subsequent cycles (n = 1267 cycles). G, grade.

Table 5
Overview of adverse events during lurbinectedin treatment according to patient age and duration of drug exposure.

	Age (years)		Drug exposure (cycles)	
Patients with	< 65 (n = 347)	≥65 (n = 207)	< 12 (n = 485)	≥12 (n = 69)
TEAEs, any grade	339 (98)	206 (99)	477 (98)	68 (99)
Grade 3 or more	206 (59)	147 (71)	311 (64)	42 (61)
Grade 4 or more	76 (22)	63 (30)	122 (25)	17 (25)
Treatment-related AEs, any grade[a]	301 (87)	193 (93)	428 (88)	66 (96)
Grade 3 or more	134 (39)	110 (53)	210 (43)	34 (49)
Grade 4 or more	63 (18)	50 (24)	98 (20)	15 (22)
Serious TEAEs, any grade	129 (37)	97 (47)	207 (43)	19 (28)
Serious treatment-related AEs, any grade[a]	46 (13)	43 (21)	81 (17)	8 (12)
Dose reductions associated with AEs				
TEAEs	71 (20)	46 (22)	89 (18)	28 (41)
Treatment-related AEs[a]	71 (20)	44 (21)	87 (18)	28 (41)
Deaths associated with AEs				
TEAEs	10 (3)	10 (5)	19 (4)	1 (1)
Treatment-related AEs[a]	3 (< 1)	4 (2)	6 (1)	1 (1)
Treatment discontinuations associated with AEs				
TEAEs	22 (6)	30 (14)	50 (10)	2 (3)
Treatment-related AEs[a]	7 (2)	11 (5)	17 (4)	1 (1)

Data are n (%) of patients.
AE, adverse event; TEAE, treatment-emergent adverse event.
[a] Includes AEs related to treatment or with unknown relationship.

discontinuations. The incidence of severe haematological abnormalities decreased after the second treatment cycle. Transaminase increases, fatigue, gastrointestinal disorders and decreased appetite were the non-haematological abnormalities and toxicities most commonly found during lurbinectedin treatment; most episodes of these events were mild or moderate. Patients treated with lurbinectedin for < 12 cycles showed no relevant differences in the drug's safety profile compared to patients treated for longer periods, thereby supporting the non-cumulative nature of lurbinectedin adverse effects.

Severe events reported during lurbinectedin treatment were mostly managed with cycle delays and dose reductions. Few patients required secondary therapeutic support with G-CSF or transfusions. Furthermore, low rates of treatment-related discontinuations (3%) and treatment-related deaths (1%) were observed.

The vast majority of treated patients (79%) did not require dose modification and remained on the full lurbinectedin dose of 3.2 mg/m^2 on day 1 q3wk throughout treatment, thereby achieving a high median relative dose intensity (97.7%). These findings suggest that toxicities associated with lurbinectedin were well managed. Recommendations on the management of cycle delays and dose modifications in the event of lurbinectedin toxicities are available to treating physicians [14]. Lurbinectedin was well tolerated in the population of elderly patients (aged ≥65 years).

Consistency was observed between the safety profile of lurbinectedin in the pooled population of 554 patients described herein and the profiles previously reported in single cohorts from the phase II basket trial in patients with relapsed SCLC [6], Ewing sarcoma [9], breast cancer [10] and NET [15] and in the phase III trial in patients with relapsed ovarian cancer [11]. For instance, compared with the SCLC cohort, the pooled population showed similar rates of severe haematological abnormalities (neutropenia 41% versus 46%; thrombocytopenia, 10% versus 7%), treatment-related febrile neutropenia (6% versus 5%) and requirement of G-CSF support (24% versus 22%). Similar rates were also observed for severe transaminase increases (ALT, 6% versus 5%; AST, 3% versus 2%) and for treatment-related fatigue (63% versus 58%) and decreased appetite (25% versus 21%) of any grade. The pooled population showed higher rates of some treatment-related gastrointestinal disorders of any grade, including nausea (57% versus 32%), vomiting (30% versus 18%) and abdominal pain (19% versus < 10%); these may be due to more than half of the pooled population consisting of patients with ovarian cancer (40%) and endometrial carcinoma (13%), tumour types that frequently have peritoneal carcinomatosis as co-morbidity.

In conclusion, this pooled analysis confirms that single-agent lurbinectedin 3.2 mg/m^2 on day 1 q3wk has a manageable safety profile in patients with advanced solid tumours, with the most common toxicity being transient and reversible myelosuppression. The profile is consistent with that reported previously in tumour-specific cohorts.

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Alexandra Leary: Investigation, Resources, Writing – review & editing. **Ana Oaknin:** Investigation, Resources,

Writing – review & editing. **José Manuel Trigo:** Investigation, Resources, Writing – review & editing. **Victor Moreno:** Investigation, Resources, Writing – review & editing. **Jean-Pierre Delord:** Investigation, Resources, Writing – review & editing. **Valentina Boni:** Investigation, Resources, Writing – review & editing. **Irene Braña:** Investigation, Resources, Writing – review & editing. **Cristian Fernández:** Methodology, Formal analysis, Writing – review & editing. **Carmen Kahatt:** Conceptualisation, Methodology, Supervision, Writing – review & editing. **Antonio Nieto:** Formal analysis, Methodology, Writing – review & editing. **Martin Cullell-Young:** Methodology, Writing – original draft, Writing – review & editing. **Ali Zeaiter:** Methodology, Supervision, writing – review and editing. **Vivek Subbiah:** Conceptualisation, Investigation, Resources, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.113259.

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