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Original Research

Lurbinectedin shows clinical activity and immune-modulatory functions in patients with pre-treated small cell lung cancer and malignant pleural mesothelioma☆

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KEYWORDS
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immunotherapy;
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Abstract ***Purpose:*** Lurbinectedin is a promising new drug being investigated in pre-treated patients with small cell lung cancer (SCLC) or malignant pleural mesothelioma (MPM). Its clinical activity in the real-world setting has not been investigated yet.
Patients and methods: Clinical data of patients with SCLC and MPM who were treated with lurbinectedin were prospectively collected. Comprehensive immune cell profiling by flow cytometry was performed on screening and treating peripheral blood samples.
Results: A total of 95 patients (43 SCLC and 52 MPM) were treated, mostly as ≥3-line of therapy. In the SCLC cohort, a median progression-free survival (mPFS) was 1.5 months (95% CI: 1.4–3.0), and median overall survival was 7.0 months (95% CI: 4.7–not reached). Objective radiological response and disease control rate after 12 weeks were 16% and 28%, respectively. In the MPM cohort, median progression-free survival was 2.8 months (95% CI: 1.4–4.2), and median overall survival was 7.2 months (95% CI: 5.9–not reached). Disease control rate after 12 weeks was 29%, whereas no partial responses were registered. No new safety signals were

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observed. Lurbinectedin treatment was significantly associated with the depletion of circulating classical monocytes, which correlated with a better PFS in patients with SCLC. Lurbinectedin increased the proliferation of $CD4^+$ and $CD8^+$ T cells (SCLC) and natural killer and natural killer T cells (SCLC and MPM) and altered co-stimulatory and co-inhibitory receptor expression on circulating lymphocytes.

Conclusion: Lurbinectedin has a manageable safety profile and shows clinical activity in pre-treated patients with SCLC and MPM. Its immune-modulatory functions make lurbinectedin a potential platform for immunotherapy combinations.

1. Introduction

Small cell lung cancer (SCLC) and malignant pleural mesothelioma (MPM) are both aggressive thoracic malignancies with a dismal prognosis. Despite the addition of immune checkpoint inhibitors to the treatment armamentarium [1–3], overall survival (OS) remains poor, and there is a lack of treatment options after first-line treatment failure [4,5]. Thus, the identification of new effective treatment strategies for both diseases represents an utmost clinical challenge.

Lurbinectedin (Zepzelca®) is a promising new agent that is currently being investigated in patients with SCLC or MM after the failure of at least first-line systemic therapy [6–8]. Lurbinectedin recognises specific sequences within the promoters of actively transcribed genes, blocks the binding of oncogenic transcription factors to their target sequences and promotes the irreversible proteasomal degradation of RNA polymerase II [9,10]. As a consequence of its mechanism of action, lurbinectedin induces double-strand breaks in the DNA, triggers an extended delay in the transition through the S phase of the cell cycle with an arrest in the G2/M phase and finally leads to tumour cell death by apoptosis [11]. Apart from its direct cytotoxic effect on the tumour cells, lurbinectedin presents a marked effect on the tumour microenvironment by inhibiting the transcription and secretion of tumour-growth promoting cytokines by tumour associated macrophages (TAMs) [12]. TAMs are responsible for an immune-suppressive tumour microenvironment and their reduction may lead to a more effective anti-tumour immune response [13]. Based on a phase 2 basket trial with 105 patients with stage IV SCLC pre-treated with one chemotherapy regimen (immunotherapy was allowed, combined with chemotherapy or alone), in 2019, the EMA granted orphan designation. Subsequently, in 2020, the FDA granted accelerated approval to lurbinectedin for patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy [6].

In another phase 2 trial, 42 patients with progressive MPM were treated with lurbinectedin in 2nd line. Although this trial met its primary end-point, progression-free survival (PFS) at 12 weeks, this did not lead to registration for this indication [8,14].

As far as we know, no real-world data on the efficacy of lurbinectedin have been published. Lurbinectedin has previously been reported to deplete monocytes (specifically $Ly6c^{high}CD11b^+CD115^+$ monocytes) in mice [12], but whether this occurs in patients with SCLC and MPM remains largely unknown. Here, we present real-world data of two large cohorts of patients with SCLC or MPM treated with lurbinectedin in a Dutch tertiary referral university medical cancer centre on a named patient program. We also report on the immune-modulatory effect of lurbinectedin, as determined by the circulating immune profile of these patients.

2. Methods

2.1. Study design and procedures

Data from patients with SCLC or MPM treated with lurbinectedin intravenously at a dose of 3·2 mg/m^2 every 3 weeks, as part of a named patient program in Erasmus Medical Centre (Rotterdam, the Netherlands), were prospectively collected. A detailed description of eligibility criteria and procedures of the clinical study is provided in the **Data Supplement**. The database lock for the current analysis was 19th March 2021. All patients with a follow-up shorter of 3 months before data cut-off were excluded except when progression was established before data cut-off or death. Of all included patients, blood samples were collected for immune monitoring analysis. All study procedures were conducted in accordance with the Declaration of Helsinki. Blood samples were obtained after patient's informed consent. According to national guidelines, no ethical committee approval was needed for the prospective collection of the clinical data.

The primary objective was to describe the real-world efficacy of lurbinectedin in patients with SCLC and MPM. Secondary and exploratory objectives were to investigate safety and immune-modulatory properties of lurbinectedin. A detailed description of the outcome measurements is provided in the **Data Supplement**.

The statistical analysis is described in the **Data Supplement**.

3. Results

3.1. Patient characteristics

From 29th November 2019 to 22nd December 2020, a total of 95 patients (43 patients with SCLC and 52 patients with MPM) started treatment with lurbinectedin. Patients had a median age of 67 years (range: 40–82), and 75 patients (90%) had a good Eastern Cooperative Oncology Group performance status score of 0/1 at the start of treatment. All patients with SCLC and 81% of patients with MPM had received at least two previous lines of treatment (Table 1).

3.2. Clinical outcomes and safety of lurbinectedin in the real-world setting

Patients with SCLC received a median number of lurbinectedin cycles of 2 (range: 1–12), whereas those with MPM received a median of 3 cycles (range: 1–13) with 12 (28%) and 8 (15%) patients receiving ≥6 cycles, respectively.

In the SCLC cohort, with a median follow-up time of 7.2 months, 39/43 patients had progression of disease and 23/43 died. Median PFS was 1.5 months (95% CI: 1.4–3.0) (Fig. 1A), and median OS was 7.0 months (95% CI: 4.7 – not reached) (Fig. 1B). The 6-month PFS rate

Table 1
Patient and disease baseline characteristics.

Characteristic	SCLC (n = 43)	MPM (n = 52)
Median age, years (range)	62 (40–77)	71 (52–82)
Gender, male, No. (%)	19 (44)	46 (87)
Median time from diagnosis to start of lurbinectedin, months (IQR)	15.2 (9·9–22·0)	18·7 (12·8–27·1)
Smoking status, No. (%)		
Former/current	31 (72)	29 (55)
Never	2 (5)	13 (26)
Unknown	10 (23)	10 (19)
ECOG PS at start of lurbinectedin, No. (%)		
0	5 (12)	10 (19)
1	34 (79)	26 (50)
≥2	3 (6)	5 (10)
Unknown	1 (3)	11 (21)
Histological subtype, No. (%)		
Epithelioid	NA	41 (79)
Mixed/Sarcomatoid	NA	9 (17)
Peritoneal mesothelioma (epithelioid)	NA	2 (4)
Previous line(s) of treatment, No. (%)		
1	0 (0)	10 (19)
2	21 (48)	25 (48)
≥3	22 (52)	17 (33)
Median previous line(s) of therapy (range)	2 (2–6)	2 (1–8)
Prior chemotherapy, No. (%)	43 (100)	52 (100)
Prior immunotherapy, No. (%)	8 (19)	43 (83)
Time since last cycle of systemic treatment, months (range)	1·9 (0·8–10·8)	1·6 (0·5–21·2)
<90 days	31 (72)	36 (69)
≥90 days	10 (23)	16 (31)
Unknown	2 (5)	0 (0)
Type of last systemic treatment, No. (%)		
Chemotherapy	43 (100)	17 (33)
Immunotherapy	0 (0)	35 (67)
Best response to last line of systemic treatment, No. (%)		
PD	24 (54)	19 (37)
SD	8 (19)	21 (40)
PR/CR	10 (22)	12 (23)
Unknown	2 (5)	0 (0)
Median albumin, g/l (range)	39 (28–46)	35 (22–45)
Median LDH, U/L (range)	277 (150–1537)	184 (125–370)

Abbreviations: SCLC, small cell lung cancer; MPM, malignant pleural mesothelioma; IQR, Interquartile range; ECOG PS, Eastern Cooperative Oncology Group performance score; PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response; LDH, lactate dehydrogenase.

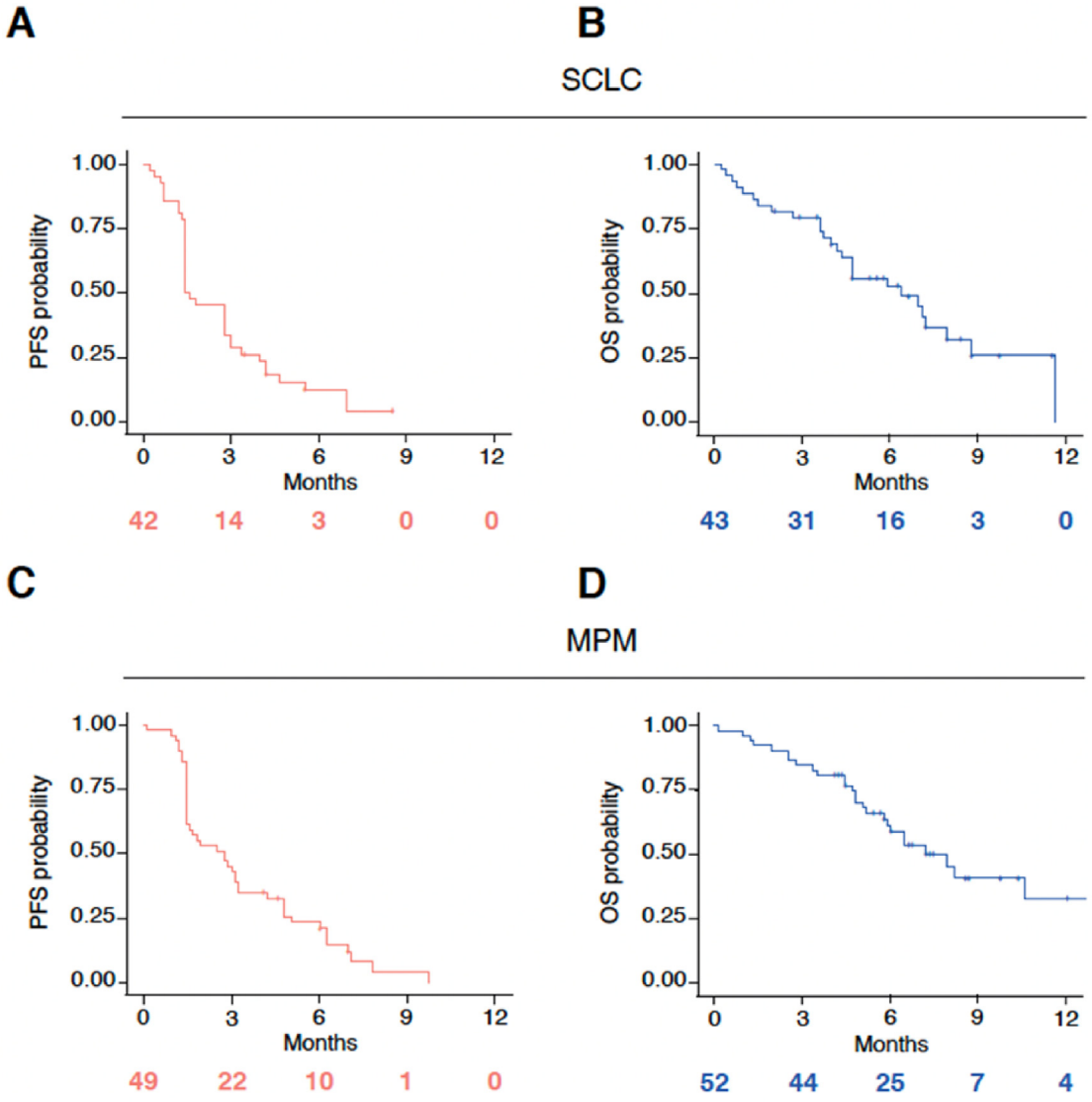

Fig. 1. Kaplan–Meier analyses in patients with small cell lung cancer (SCLC) and malignant pleural mesothelioma (MPM). **(A)** Progression-free survival of patients with SCLC (entire cohort). **(B)** Overall survival of patients with SCLC (entire cohort). **(C)** Progression-free survival of patients with MPM (entire cohort). **(D)** Overall survival of patients with MPM (entire cohort).

was 12% (95% CI: 5–28%) and the 6-month OS rate was 57% (95% CI: 43–75%). Regarding the overall lurbinectedin activity, 7/43 patients had a tumour response (16.3% ORR) and five (11.6%) had stable disease as the best result after 12 weeks of treatment, resulting in a disease control rate of 27.9%.

Univariable Cox proportional hazard regression analysis in patients with SCLC revealed no major clinical parameters able to predict the outcome, outside known prognostic factors (Data Supplement Table 2).

In the MPM cohort, the median follow-up time was 7.3 months. Forty-four out of 52 patients had progression of disease and 28/52 died. Median PFS was 2.8 months (95% CI: 1.4–4.2) (Fig. 1C), and median OS was 7.2 months (95% CI: 5.9–not reached) (Fig. 1D). The 6-month PFS rate was 20% (95% CI: 11–36%) and the 6-month OS rate was 58% (95% CI: 46–74%). No tumour responses were registered, and 15/52 patients obtained stable disease after 12 weeks of treatment for a disease control rate of 28.8%.

Univariable Cox proportional hazard regression analysis in patients with MPM revealed no major clinical parameters able to predict the outcome, outside known prognostic factors (Data Supplement Table 3).

The treatment safety profile was consistent with previous studies, and no new safety signals were reported (Table 2). Lurbinectedin-related adverse events (AEs) of any grade were observed in 83/95 pts (87.4%) and grade 3/4 AEs in 25/95 patients (26.3%). The most common grade 3/4 AEs were neutropenia (11% SCLC,

Table 2
Treatment-related adverse events (SCLC n = 45; MPM, n = 52).

	Grade 3	Grade 4
Any	20 (21)	5 (5)
Anemia	2 (2)	0
Neutropenia	8 (8)	5 (5)
Thrombocytopenia	1 (1)	1 (1)
Creatinine increased	0	0
Alanine aminotransferase increased	0	2 (2)
Aspartate aminotransferase increased	2 (2)	0
γ-glutamyl transferase increased	2 (2)	0
Alkaline phosphatase increased	0	0
Fatigue	4 (4)	0
Nausea	0	0
Dysgeusia	0	0
Vomiting	0	0
Diarrhea	1 (1)	0
Constipation	0	0
Febrile neutropenia	2 (2)	0
Hiccups	1 (1)	0
Dyspnea	2 (2)	0
Mucositis	1 (1)	0
Rash	0	0

16% MM) and fatigue (2% SCLC, 6% MM). Febrile neutropenia was documented in two patients (4%) with MPM. There was no association between chemotherapy-free interval and neutropenia onset in the whole cohort ($P = 0.30$, Wilcoxon signed-rank test).

Dose reductions were performed in 27% of patients and were mainly due to haematologic toxicity and fatigue. Two patients stopped the treatment due to AEs; one due to persisting thrombocytopaenia, the other one due to persisting neutropenia. Treatment delays occurred at least once in 6 patients with SCLC (14%) and 17 patients with MM (33%) (Data Supplement Table 4).

3.3. Immunological phenotyping

Major baseline characteristics and clinical outcome of the patients of whom peripheral blood samples were collected (SCLC n = 20 and MPM n = 19) did not differ from the whole group of patients. (Data Supplement Table 5, Data Supplement Fig. 2).

Although the relative proportion of the total monocyte population did not change significantly during therapy (Fig. 2A), lurbinectedin significantly reduced the proportions of $HLADR^{+}CD56^{-}CD14^{+}CD16^{-}$ classical monocytes within the total monocyte population, in patients with both SCLC and MPM (Fig. 2B and C; see for gating: Supplementary Fig. 2). This decrease of classical monocyte frequencies was paraleled by a significant relative increase of intermediate monocytes in both SCLC (Fig. 2B) and MPM (Fig. 2C). Interestingly, we found that patients with SCLC and with lower frequencies of classical monocytes before treatment with lurbinectedin had a longer PFS (Data Supplement Fig. 3).

We subsequently analysed whether treatment with lurbinectedin also affected lymphocytes. The treatment did not result in changes in the proportions of $CD4^{+}$ and $CD8^{+}$ T cells, natural killer (NK) cells and natural killer T (NKT) cells within the lymphocyte compartment in patients with both SCLC and MPM (data not shown). Next, proliferation was assessed by Ki67 expression, a cell cycle marker expressed by dividing or recently divided cells. Lurbinectedin increased the frequencies of $Ki67^{+}$ proliferating cells within the $CD4^{+}$ and $CD8^{+}$ T cell populations specifically in patients with SCLC (Fig. 3A) and of NK and NKT cells in both SCLC and MPM (Fig. 3B). This increase in proliferation was independent of clinical response (Data Supplement Fig. 4A and B). We also examined whether differences in the proliferation of $CD8^{+}$ T cells prior to treatment could help identify patients with longer PFS under lurbinectedin. Log rank test revealed that patients with SCLC and with a higher proportion of $CD8^{+}$ proliferating T cells (cut-off based on the median proportion) at screening had a significantly longer PFS upon lurbinectedin (median PFS: 4.7 versus 2.1 months, p = 0.04) (Data Supplement Fig. 4C).

We also investigated different T cell subsets (Data Supplement Fig. 5A and 5B). Even though proliferating $CD4^{+}$ and $CD8^{+}$ T cells and T_{EM} cells were increasing upon treatment in SCLC, no correlation was noted between the decrease of classical monocytes and the increase of proliferating $CD8^{+}$ total, $CD8^{+}$ T_{EM}, $CD4^{+}$ total or $CD4^{+}$ T_{EM} cells in SCLC (Data Supplement Fig. 6).

In addition to T cell proliferation, we assessed the expression of a variety of co-stimulatory and -inhibitory receptors on circulating T cells (Fig. 3C). The frequency of both $CD4^{+}$ and $CD8^{+}$ T cells that expressed the co-receptor CD28 slightly, but significantly, increased upon treatment in patients with SCLC, indicating that lurbinectedin-induced T cell activation. Contrary to CTLA-4 which was significantly increased upon treatment in $CD4^{+}$ T cells in patients with MPM only, the inhibitory receptor TIM-3 changed with similar dynamics both on $CD4^{+}$ and $CD8^{+}$ T cells and both in SCLC and MPM (Fig. 3C). These findings suggest that lurbinectedin induced a two-side alteration of the circulating T cell phenotype, with upregulation of co-stimulatory receptors being counterbalanced by the contemporary upregulation of co-inhibitory markers. These findings should help the implementation of rational combination therapies.

4. Discussion

To the best of our knowledge, this is the first prospective real-world dataset from patients with SCLC and MM treated with lurbinectedin mostly as third or further-line treatment.

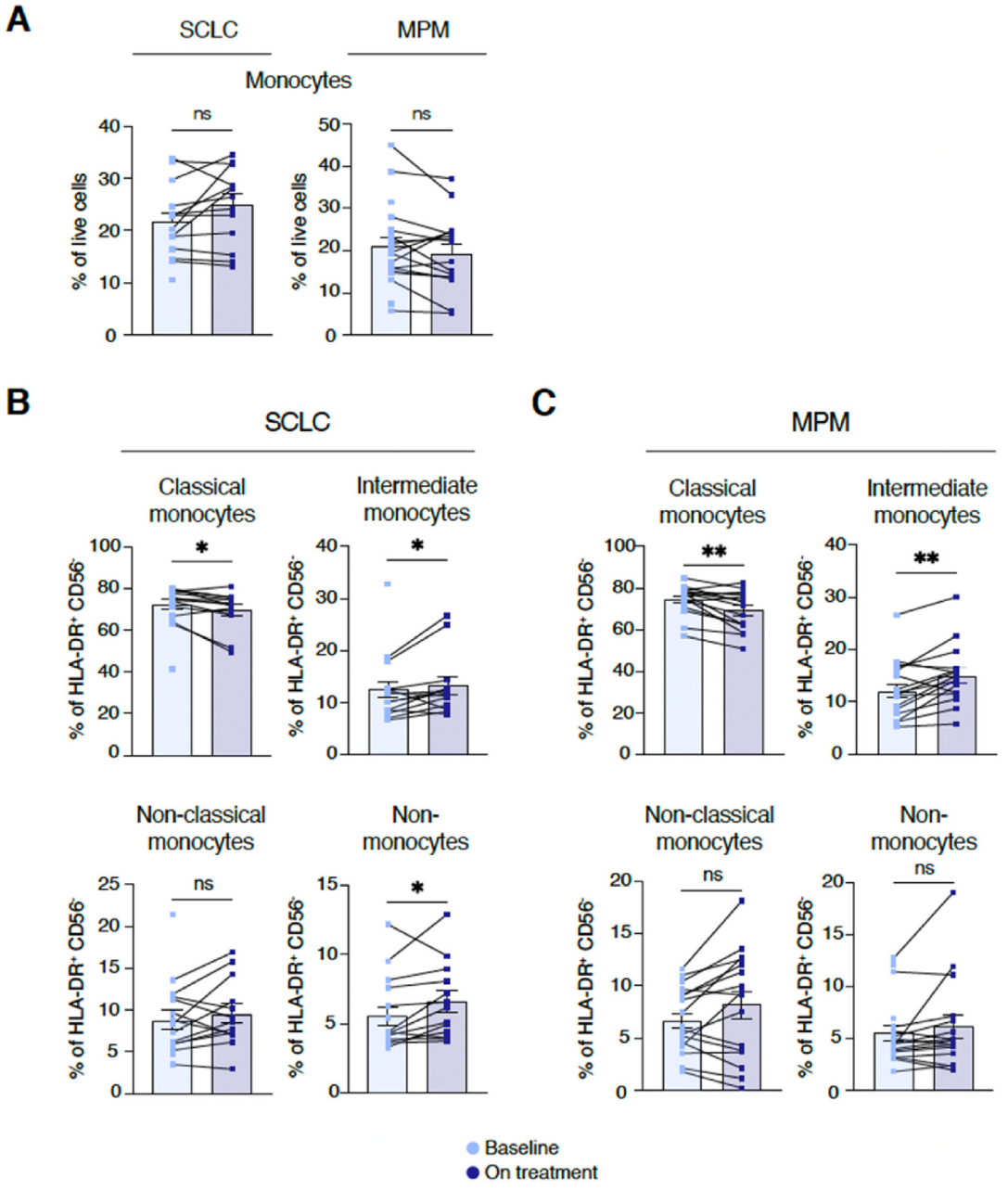

Fig. 2. Lurbinectedin treatment is associated with depletion of the classical monocyte subset. **(A)** Percentage of monocytes ($CD14^{+}$ $CD16^{+/-}$ and $CD14^{-}$ $CD16^{+}$) at screening (pale blue) and on-treatment (light violet) time points in patients with small cell lung cancer (SCLC) (left) and patients with malignant pleural mesothelioma (MPM). **(B)** Percentage of human leucocyte antigen - DR-isotype $(HLA\text{-}DR)^{+}$ $CD56^{-}$ cell subsets, at screening and on-treatment time points in patients with small cell lung cancer (SCLC). **(C)** Percentage of $HLA\text{-}DR^{+}$ $CD56^{-}$ cell subsets, at screening and on-treatment time points in patients with malignant pleural mesothelioma (MPM). Wilcoxon matched-pairs signed-rank tests or Student's t-tests were performed to calculate statistical significance. Paired samples are shown connected by black lines. Bars depict mean values with standard error of the mean. A total of 29 patients had data available at both time points and were included in the analysis (n = 13 SCLC; n = 16 MPM). ns = not significant, * = $p < 0.05$, ** = $p < 0.01$.

When comparing our real-world data to the clinical trials in SCLC and MM, our results are inferior (Table 3) [6,8,14]. This result is expected considering that our unselected and heterogeneous patient cohort represented more frail and more heavily pre-treated population.

Comparing the results of lurbinectedin in our real-world SCLC cohort with those obtained with topotecan, which is the standard of care according to the guidelines after the failure of first-line chemotherapy [15], we found a promising ORR of 16% in our cohort compared to 5% (for chemotherapy-refractory disease) and 17% (for

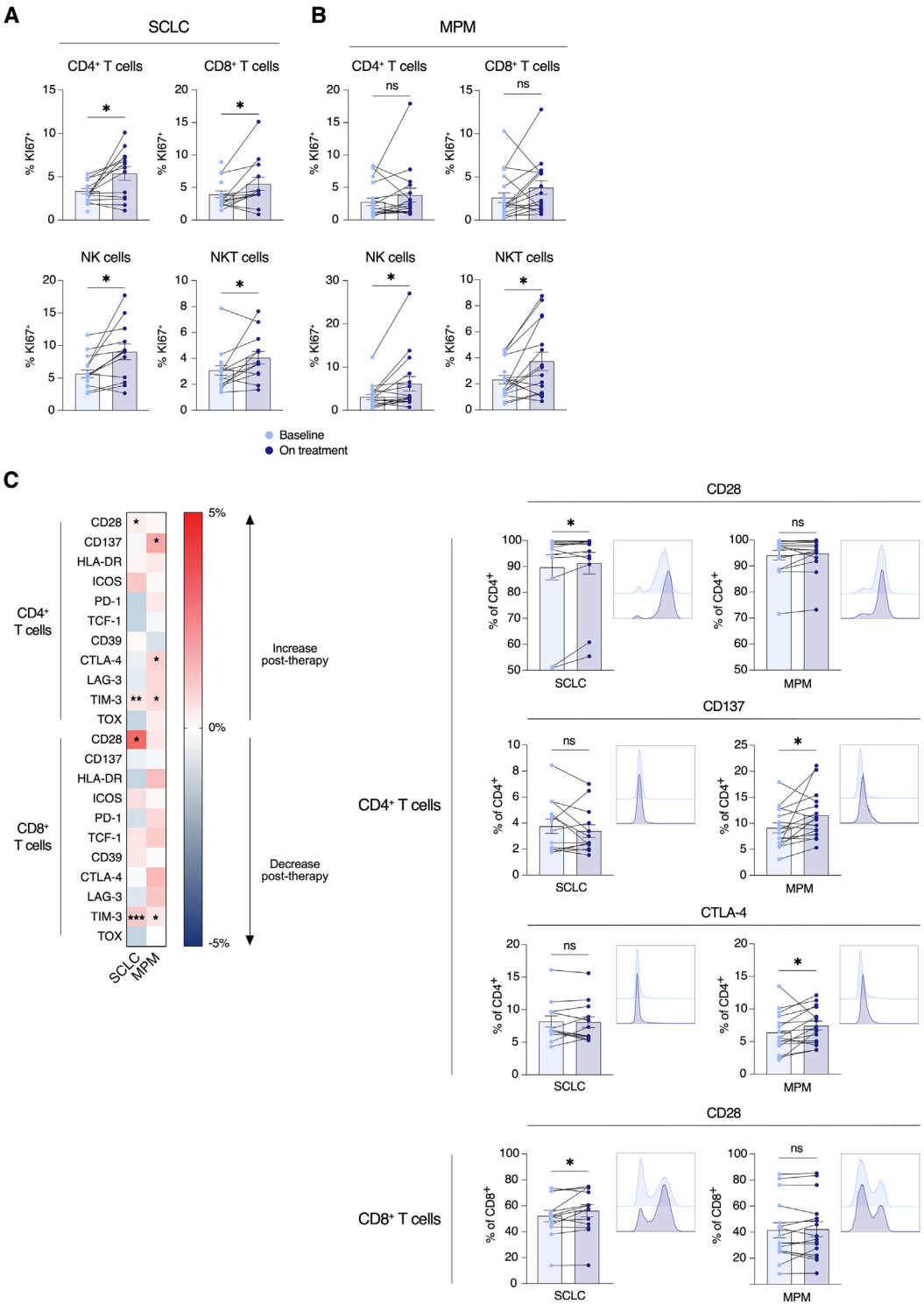

Fig. 3. Lurbinectedin modulates proliferation and alters phenotype of circulating lymphocyte subsets. **(A)** Percentage of Ki67$^+$ CD4$^+$ T cells, CD8$^+$ T cells, NK and NKT cells, at screening (pale blue) and on-treatment (light violet) time points in patients with small cell lung cancer (SCLC). **(B)** Percentage of Ki67$^+$ CD4$^+$ T cells, CD8$^+$ T cells, NK and NKT cells, at screening and on-treatment time points in patients with malignant pleural mesothelioma (MPM). **(C)** Heatmap, graphs and (representative) histograms showing mean percentage of change and paired analyses of co-stimulatory and co-inhibitory receptor expression during lurbinectedin in patients with SCLC and MPM. Wilcoxon matched-pairs signed-rank tests or Student's *t-tests* were performed to calculate statistical significance. Paired samples are shown connected by black lines. Bars depict mean values with standard error of the mean. A total of 29 patients had data available at both time points and were included in the analysis (n = 13 SCLC; n = 16 MPM). ns = not significant, * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$. NK, natural killer; NKT, natural killer T.

Table 3
Main efficacy outcomes in SCLC and MPM patients treated with lurbinectedin monotherapy in the context of phase 2 trials and in the Erasmus MC real-world experience.

	Trigo *et al.* (SCLC)	Dumoulin *et al.* (SCLC)	Metaxas *et al.*/Mark *et al.* (MPM)	Dumoulin *et al.* (MPM)
Patient number	105	43	42	52
Treatment line	2–3	3–4	2–3	2–3
Median follow-up	17.1 months	7.2 months	32.8	7.3 months
Median pts CFI	3.5 months	1.9 months	Unknown	1.6 months
DCR 12 weeks	68%	28%	52%	29%
ORR 12 weeks	35%	16%	4%	0%
Median PFS	3.5 months	1.5 months	4.1 months	2.8 months
Median OS	9.3 months	7.0 months	11.5 months	7.2 months

Abbreviations: CFI, chemotherapy-free interval; DCR, disease control rate; ORR, overall response rate, PFS, progression-free survival; OS, overall survival.

chemotherapy-sensitive disease) with topotecan. Of note, this relatively high response rate in our patients was seen despite the fact that the patients were heavily pre-treated and largely being pre-treated with topotecan as second-line treatment.

Recently, in the randomised phase 3 ATLANTIS study, the combination of lurbinectedin (at a 2 mg/m2 dosage) with doxorubicin as second-line treatment for SCLC did not improve OS when compared to topotecan or cyclophosphamide/doxorubicin/vincristine [16]. However, the safety profile of lurbinectedin was better and a model developed by investigators (based on exposure-response analysis) predicted that the usage of single-agent lurbinectedin at 3.2 mg/m^2 (approved dose) would have yielded significantly higher response rates and significantly longer survival. In this context, our real-world clinical data offer further support for the efficacy of lurbinectedin in thoracic neoplasms.

The combinations of lurbinectedin with other cytotoxic agents or immune checkpoint inhibitors are being explored based on the hypothesised the immunological effects of lurbinectedin (NCT04358237, NCT04610658, NCT04253145 and NCT02611024). We further explored this immune modulating effect in patients. Our study, by using comprehensive immune monitoring, demonstrated that lurbinectedin induces a relative reduction of circulating classical monocytes. These effects on the myeloid compartment have not been previously reported in patients and further deepen previous pre-clinical observations showing that lurbinectedin induces a dose- and time-dependent death in cultured monocytes and monocytic myeloid-derived suppressor cells [17]. Our study showed that despite lurbinectedin-mediated depletion of classical monocytes, only patients with SCLC with lower frequencies of classical monocytes prior to start of treatment seem to benefit, while patients with MPM seemed not to be affected, to signify that different (immunological) mechanisms might also play a role in response to lurbinectedin.

Looking at modulation of the lymphoid subset, in this study, lurbinectedin was found to increase the proliferation of CD4$^+$ and CD8$^+$ T cells specifically in patients with SCLC, and of NK and NKT cells in both SCLC and MPM. This proliferation was irrespective of clinical response, which can be ascribed to a number of mechanisms, but open the field of research by combining lurbinectedin with other immune modulating agents. This is supported by the effect found on the circulating T cell phenotype, with both activation (CD28 on CD4$^+$ T cells in SCLC) and inhibitory markers (CTLA-4 on CD4$^+$ T cells in MPM and TIM-3 on CD4$^+$ and CD8$^+$ T cells in both SCLC and MPM) being upregulated upon treatment. The increased expression of these markers on lymphocytes following lurbinectedin suggests that the combination of lurbinectedin with immunotherapy might be efficacious [18]. In our study, the alteration of T cell phenotype involved different markers and was dependent on tumour type, suggesting that the development of future combinational therapy should come along with in-depth immune monitoring investigations.

Noteworthy, neither T cell proliferation nor the activation phenotype related to monocytes frequencies. These findings are in line with previous observations from our group showing that the depletion of TAM is not sufficient *per se* to enhance CD8$^+$ T cell proliferation and effector phenotype, and combination with other type of immunotherapies such as dendritic cell vaccination is needed to improve T cell memory responses and consequentially survival [13].

Apart from this, the observed increase of T cell proliferation (T_{EM} cells specifically) may be an indirect result of the cytotoxic effect from lurbinectedin on tumour cells (probably involving an increased release of tumour-derived antigens) rather than a direct drug-mediated modulation of immune cells.

Despite its prospective design and the use of an extensive cohort of SCLC and MPM for the immune monitoring analysis, this study has some limitations. As this study is not a randomised controlled trial, there is no control group. The absence of a control group precludes formal conclusions to be made on the immune-modulatory functions of lurbinectedin that should be considered exploratory and need confirmation in the

context of larger randomised trial. However, most of the immune-related changes were observed early on treatment (6 weeks), making tumour response/progression less likely responsible for the observed modifications.

Furthermore, the widespread effects of lurbinectedin on a variety of immune cells *in vivo*, the absence of available tissue sample and the lack of functional *in vitro* data, precludes us to provide clear mechanistic insights into how lurbinectedin may modulate the anti-tumour immune response.

Nonetheless, our real-world data confirmed the activity of lurbinectedin in a cohort of patients with heavily pre-treated SCLC and MPM. Lurbinectedin monotherapy appears to be an alternative therapeutic option of interest for these patients with a dismal prognosis of which the efficacy might be positively influenced by the combination with other agents, based on the results of our exploratory study. In fact, our study suggests that lurbinectedin might have immune-modulatory functions by promoting proliferation and phenotype shifting of anti-tumour immune cell populations, making lurbinectedin an interesting chemotherapy backbone on which to build better immunotherapy combination options for patients with SCLC and MPM.

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This study was not funded. Lurbinectedin was provided free of charge by Pharmamar. All authors had full access to the data in the study and had final responsibility for the decision to submit for publication. Pharmamar was not involved in the study design, data collection, data analysis and interpretation of the data. Pharmamar has read the manuscript and approved the final version for submission.

Author contributions

Conception and design: Daphne W. Dumoulin, Luca Cantini, Marcella Willemsen, Joachim G.J.V. Aerts. **Collection and assembly of data:** Daphne W. Dumoulin, Luca Cantini, Marcella Willemsen, Robin Cornelissen, Madelief Vink, Larissa Klaase, Kick Sloof, Nura Tebayna, Joanne M. Mankor. **Data analysis and interpretation:** Daphne W. Dumoulin, Luca Cantini, Robin Cornelissen, Joanne M. Mankor, Sara J. Baart, Rudi Hendriks, Anne-Marie C. Dingemans, Marcella Willemsen, Joachim G.J.V. Aerts. **Manuscript writing:** All authors. **Final approval of manuscript:** All authors. **Accountable for all aspects of the work:** All authors.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors declare no relevant conflict of interest related to the published manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.06.020.

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