164P: Immune modulatory functions of lurbinectedin in small cell lung cancer and malignant pleural mesothelioma patients

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Background/Methods:

- Lurbinectedin (Lur) is currently investigated in pre-treated patients (pts) with small cell lung cancer (SCLC) or malignant pleural mesothelioma (MPM). According to pre-clinical models, lur is able to induce anticancer immune responses. The **immune-modulatory functions** of lur in thoracic cancer pts have not been investigated yet.

- **SCLC and MPM** pts treated with lurbinectedin in the context of a named patient program at the Erasmus Medical Center, Rotterdam, NL were prospectively included. Comprehensive **immune cell profiling** by multicolor flow-cytometry was performed on screening and on treatment (after 2 cycles) peripheral blood samples.

Results:

- In total, 95 pts (43 SCLC and 52 MPM) were treated, mainly as ≥3-line of therapy. In the **SCLC** cohort, median (m) PFS was 1.5 months (95% CI: 1.4–3.0), and **mOS was 7.0 months** (95% CI: 4.7–not reached). In the **MPM** cohort, mPFS was 2.8 months (95% CI: 1.4–4.2), and **mOS was 7.2 months** (95% CI: 5.9–not reached).

- Immunological phenotyping was performed on 39 pts. Lur significantly reduced HLADR+CD56-CD14+CD16- cell frequencies, the **classical monocyte subset**, in both SCLC and MPM pts (*Figure 1*). SCLC pts with lower frequencies of classical monocytes before treatment also had a longer PFS.

- Lur significantly increased **proliferation of CD4+, CD8+ T-cells** (SCLC), and NK- and NKT-cells (SCLC and MPM) (*Figure 2AB*). Treatment increased the proliferation of CD4+ central memory (TCM) and effector memory (TEM) T-cells and of CD8+ TEM cells among SCLC. In MPM, treatment increased more specifically the proliferation of CD4+ TEM cells, while CD8+ T-cells were not affected.

***Lurbinectedin** represents a potential chemotherapy backbone for future **immunotherapy combinations** in SCLC and MPM*

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Figure 2. Lurbinectedin modulates proliferation and alters phenotype of circulating lymphocyte subsets. **A-B:** Percentage of Ki67+ CD4+ T cells, CD8+ T cells, NK and NKT cells, at screening and on-treatment in SCLC (**A**) and MPM (**B**) patients. **C**: Heatmap showing mean percentage of change and paired analyses of co-stimulatory and co-inhibitory receptor expression during lurbinectedin.

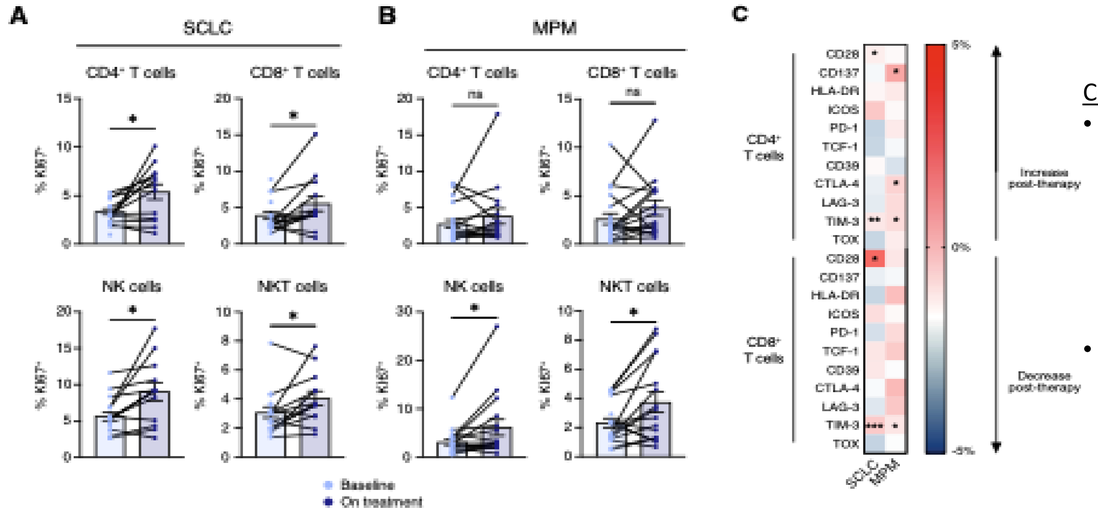
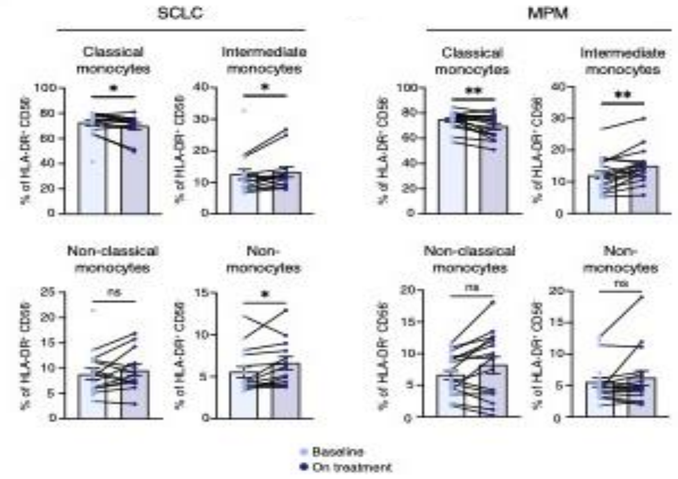


Figure 1. Lurbinectedin treatment is associated with depletion of the classical monocyte subset. Percentage of HLA-DR+ CD56- cell subsets, at screening and on-treatment time points in SCLC and MPM patients.



Results:

- Finally, lur induced a two-side alteration of the **circulating T-cell phenotype**, with upregulation of co-stimulatory receptors being counterbalanced by upregulation of co-inhibitory markers (*Figure 2C*).

Conclusions:

- Lur confirms **clinical activity** in pre-treated SCLC and MPM pts. Our exploratory immunomonitoring study also shows that lur might have **immune-modulatory functions** through depletion of the classical monocyte subset, promotion of proliferation and phenotype shifting of anti-tumor immune cell populations.

- Therefore, lur might represent an interesting chemotherapy **backbone for future immunotherapy combinations** in SCLC and MPM.

The first and presenting author has no conflicts of interest to declare.