# Integrated Exposure-Response Analysis of Efficacy and Safety of Lurbinectedin to Support the Dose Regimen in Small Cell Lung Cancer

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**Short title**: Lurbinectedin exposure-response in SCLC

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# Supplementary Information

**Supplementary Table S1** Characteristics of the clinical trials included in the integrated E-R analysis of lurbinectedin

| Study | Dose level | Tumor types | Patients treated | Patients with ORR data | Patients with PK and safety data | ANC/platelets sampling schedule |
|---|---|---|---|---|---|---|
| PM1183-A-001-08 NCT00877474 [1] | 0.02–6.9 mg/m² (D1) | Advanced solid tumors | 33 | NA | 31 | D1, D8, D15, and D22 of every cycle, and on screening, end of treatment, and follow-up |
| PM1183-A-002-10[a] NCT01314599 [2] | 3.5–7.0 mg FD (D1,8) | Hematological malignancies | 24 | NA | 23 | NA |
| | 1.0–3.0 mg FD (D1-3) | | 18 | NA | 18 | |
| PM1183-A-005-11[a] NCT01405391 | 3.0–5.0 mg FD (D1,8) | Advanced solid tumors | 21 | NA | 21 | NA |
| PM1183-B-001-10 | 7.0 mg FD (D1) | Pancreatic cancer | 45 | NA | 44 | D8 and D15 of cycle 1, D1 and D10 of further cycles, and on screening and end of treatment |
| PM1183-B-002-10 [4] | 7.0 mg FD (D1) | Ovarian cancer | 52 | NA | 22 | D8 and D15 of cycle 1, D1 and D10 of further cycles, and on screening and end of treatment |
| PM1183-B-003-11 NCT01525589 [5] | 7.0 mg FD (D1) | Breast cancer | 109 | NA | 38 | D8 and D15 of cycle 1, D1 and D10 of cycle 2, D1 of further cycles, and on screening and end of treatment. From cycle 2 onwards, D10 only if toxicity |
| PM1183-B-004-13 NCT01951157 | 7.0 mg FD & 3.2 mg/m² (D1) | NSCLC | 21 | NA | 21 | D8 and D15 of cycle 1, D1 and D8 of further cycles, and on screening and end of treatment |
| PM1183-B-005-14 NCT02454972 [6] | 3.2 mg/m² (D1) | Selected solid tumors | 335[b] | 96 | 333 | D1, D8, and 15 during cycles 1 and 2, D1 of further cycles, and screening and end of treatment. From cycle 2 onwards, D8 and D15 only if toxicity |

| | | | | | | |
|---|---|---|---|---|---|---|
| PM1183-C-004-14<br>NCT02421588 [7] | 3.2 mg/m²<br>(D1) | Ovarian cancer | 219 | NA | 204 | Screening and D8 of cycle 1, D1 and D8 of cycle 2, and D1 of further cycles. |

ANC, absolute neutrophil count; D, day; E-R, exposure-response; FD, flat dose; NA, not applicable; NSCLC, non–small cell lung cancer; ORR, objective response rate; PK, pharmacokinetics.

[a]Included in pool of population PK analysis. [b]SCLC cohort in B-005 study included 105 patients.

**Supplementary Table S1 References**


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**Supplementary Table S2** Summary of pharmacokinetic parameters in final model and bootstrap results

| Parameter | Final model estimate (RSE%) | Non-parametric bootstrap (n=400) | |
|---|---|---|---|
| | | Median (RSE%) | 95% CI |
| Typical parameter | | | |
| $V_1$ (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 |
| $V_3$ (L) | 454 (2.26) | 447 (3.16) | 424–480 |
| $Q_3$ (L/h) | 16.0 (2.05) | 15.9 (2.36) | 15.2–16.7 |
| $V_2$ (L) | 37.5 (2.50) | 37.0 (2.24) | 35.5–38.7 |
| $Q_2$ (L/h) | 31.8 (2.38) | 31.7 (3.13) | 29.9–33.9 |
| Residual variability (CV%) | | | |
| RV | 31.7 (2.52) | 30.9 (2.39) | 29.4–32.5 |
| Inter-individual variability (CV%) | | | |
| η $V_1$ | 34.6 (13.2) | 31.7 (31.2) | 21.7–41.3 |
| η CL | 49.9 (3.96) | 50.0 (9.42) | 45.7–54.4 |
| η $V_3$ | 39.1 (5.33) | 37.2 (31.2) | 31.5–45.5 |
| η $Q_3$ | 27.2 (6.54) | 27.0 (19.1) | 24.2–30.1 |
| η $V_2$ | 33.4 (7.78) | 30.7 (15.7) | 25.6–35.0 |
| η RV | 59.2 (3.42) | 59.6 (15.7) | 55.0–63.6 |
| η $AAG_{C004}$ | 54.2 (13.6) | 47.1 (27.7) | 35.7–60.3 |
| Inter-individual variability correlation (%) | | | |
| η $Q_3$ – η $V_3$ | 77.0 (6.42) | 75.7 (13.2) | 77.5–72.4 |
| Typical covariate parameters | | | |
| $CL_{AAG}$ | -0.627 (8.36) | -0.727 (10.3) | -0.858 to -0.568 |
| $CL_{ALB}$ | 0.746 (19.6) | 0.633 (28.2) | 0.261–0.979 |
| $CL_{INH}$ | -0.408 (12.2) | -0.407 (14.6) | -0.517 to -0.275 |
| $Q_{3,AAG}$ | -0.578 (8.57) | -0.603 (8.18) | -0.697 to -0.504 |
| $Q_{3,BSA}$ | 0.990 (14.2) | 0.964 (15.3) | 0.658–1.227 |
| $Q_{3,SEXF}$ | -0.195 (14.4) | -0.198 (16.3) | -0.254 to -0.13 |
| $V_{1,AAG}$ | -0.992 (9.78) | -1.032 (9.83) | -1.233 to -0.839 |
| $V_{2,AAG}$ | -0.653 (10.6) | -0.675 (9.99) | -0.803 to -0.541 |
| $V_{2,BSA}$ | 0.423 (25.6) | 0.390 (28.5) | 0.188– 0.630 |
| $V_{3,AAG}$ | -0.517 (11.8) | -0.600 (17.7) | -0.758 to -0.319 |
| $V_{3,BSA}$ | 1.915 (8.70) | 1.802 (10.1) | 1.474–2.174 |
| $V_{3,SEXF}$ | -0.244 (13.1) | -0.245 (15.1) | -0.312 to -0.174 |
| $V_{1,BSA}$ | 0.748 (21.3) | 0.744 (23.1) | 0.436–1.129 |
| $AAG_{C004}$ | 260 (7.53) | 230 (9.42) | 201–280 |

AAG, α-1-acid glycoprotein; $AAG_{C004}$, AAG in study C-004 CORAIL; ALB, albumin; BSA, body surface area; 95% CI, 95% confidence interval; CL, clearance; $CL_{AAG}$, relationship between CL and AAG; $CL_{ALB}$, relationship between CL and albumin; $CL_{INH}$, relationship between CL and CYP3A inhibitors; CV, coefficient of variation; INH, CYP3A inhibitor; $Q_2$, intercompartmental clearance for shallow compartment; $Q_3$, intercompartmental clearance for deep compartment; $Q_{3,AAG}$, relationship between $Q_3$ and AAG; $Q_{3,BSA}$, relationship between $Q_3$ and BSA; $Q_{3,SEXF}$, relationship between $Q_3$ and gender; RSE, relative standard error; RV, residual variability; SEXF, gender; $V_1$,

apparent volume of distribution of central compartment; $V_2$, apparent volume of distribution of shallow peripheral compartment; $V_3$, apparent volume of distribution of deep peripheral compartment; $V_{1,AAG}$, relationship between $V_1$ and AAG; $V_{1,BSA}$, relationship between $V_1$ and BSA; $V_{2,AAG}$, relationship between $V_2$ and AAG; $V_{2,BSA}$, relationship between $V_2$ and BSA; $V_{3,AAG}$, relationship between $V_3$ and AAG; $V_{3,BSA}$, relationship between $V_3$ and BSA; $V_{3,SEXF}$, relationship between $V_3$ and gender.

**Supplementary Table S3** ORR of topotecan in clinical trials in patients with second-line SCLC

| Study | Resistant (CTFI < 90 days) | | | Sensitive (CTFI ≥ 90 days) | | |
|---|---|---|---|---|---|---|
| | Responders (n) | Total patients (n) | ORR (%) (95% CI) | Responders (n) | Total patients (n) | ORR (%) (95% CI) |
| von Pawel (1999) [1] | 3 | 22 | 13.64 | 0 | 0 | 0 |
| O'Brien (2006) [2] | 4 | 41 | 9.76 | 1 | 30 | 3.33 |
| von Pawel (2014) [3] | 9 | 96 | 9.38 | 25 | 117 | 21.37 |
| Evans (2015) [4] | 3 | 37 | 8.11 | 5 | 42 | 11.9 |
| Ardizzoni (1997) [5] | 3 | 47 | 6.38 | 17 | 45 | 37.78 |
| Depierre (1997) [6] | 1 | 41 | 2.44 | 8 | 57 | 14.04 |
| Eckardt (1996) [7] | 1 | 38 | 2.63 | 7 | 36 | 19.44 |
| Total | 24 | 322 | 7.45 (4.83–10.89) | 63 | 327 | 19.27 (15.13–23.96) |

CI, confidence interval; CTFI, chemotherapy-free interval; ORR, objective response rate; SCLC, small cell lung cancer.

**Supplementary Table S3 References**


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