Overall survival with lurbinectedin plus doxorubicin in relapsed SCLC. Results from an expansion cohort of a phase Ib trial.

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Background: Lurbinectedin (PM01183, L) is a new anticancer drug that binds to DNA, inhibits transactivated transcription and modulates tumor microenvironment. Preclinical evidence of synergism was observed for PM01183 in combination with doxorubicin (DOX).

Methods: This multicenter, phase Ib clinical trial found impressive activity in second-line SCLC patients (ORR 67%) leading to an expansion cohort with a reduced dose (L 2mg/m^2+ DOX 40mg/m^2) implemented to improve safety. SCLC patients <75 years with ECOG performance status (PS) 0-1 and pretreated with no more than one chemotherapy line were included. Stable brain metastases were allowed. DOX was interrupted after 10 cycles and PM01183 could be continued as single-agent. Primary G-CSF prophylaxis was not mandatory.

Results: 27 patients were treated. Males: 75%; median age: 64 (49-77) years; ECOG PS 0-1: 32%-68%; known central nervous system involvement: 4%; bulky disease (>50 mm): 75%. 88% responded to 1st line (CR in 4%). Median chemotherapy-free interval (CTFI) was 3.5 months (m). 22% were refractory (CTFI <30 days), 15% were resistant (R) (CTFI 30-90 days) and 63% sensitive (S) (CTFI>90 days). Overall confirmed ORR was 37% (95%CI, 19-58%) (CR in 4%), and 53% (95% CI: 28-77) (CR in 6%) in S patients. Overall median PFS was 3.4 m (95% CI, 1.5-6.2), being 1.5 m (95%CI, 0.8-3.4) in R pts, and 5.7 m (95%CI 2.6-7.9) in S patients. Overall survival (OS) data are summarized in the following table.

OS	Overall	Resistant	Sensitive
Overall (n=27)	7.9 m (95% CI: 4.9-11.5)	4.9 m (95% CI: 2.3-6.7)	11.5 m (95% CI: 6.0-16.6)
Excluding CTFI<30days (n= 21)	10.2 m (95% CI: 6.0-12.1)	6.7 m (95% CI: 5.1-8.4)	11.5 m (95% CI: 6.0-16.6)

Data shown are median and 95% CI.

Grade 4 neutropenia, anemia or thrombocytopenia appeared in 64%/0%/7% of patients, respectively, and febrile neutropenia (G3/4) occurred in 10%. Non-hematological toxicity was mild and mainly due to fatigue (G3=18%) and nausea (G3=7%).

Conclusion: Lurbinectedin/DOX combination showed remarkable activity as second line in SCLC, especially in sensitive patients (CTFI>90 days). Activity is higher than that reported for CAV or topotecan. OS shows an outstanding improvement in this second-line setting, especially when excluding refractory pts. A phase III clinical trial (ATLANTIS, NCT02566993) is currently ongoing evaluating this combination in relapsed SCLC patients