OVERALL SURVIVAL WITH LURBINECTEDIN PLUS DOXORUBICIN IN RELAPSED SCLC. RESULTS FROM AN EXPANSION COHORT OF A PHASE Ib TRIAL.

Martin Forster[1], Víctor Moreno[2], Emiliano Calvo[3] María Eugenia Olmedo[4], María Pilar López Criado[5], José Antonio López-Vilariño[6], Rafael Núñez[6], Carmen Kahatt[6].

[1] University College of London Hospital and UCL Cancer Institute, London, UK. [2] START Madrid – FJD (Hospital Fundación Jiménez Díaz), Madrid, Spain. [3] START Madrid - HM CIOCC, Hospital Madrid Norte Sanchinarro, Madrid, Spain. [4] Hospital Ramon y Cajal, Madrid, Spain.
[5] M.D. Anderson Cancer Center, Madrid, Spain. [6] Pharma Mar, S.A., Colmenar Viejo, Madrid, Spain.

BACKGROUND

Lurbinectedin (Zepsyre®, PM1183, L) is a new investigational drug that is *thought to block trans-activated* a selective inhibitor of active transcription of protein-encoding genes.
In transcriptionally-addicted tumor cells, like SCLC [1,2], L causes a detachment of transcription factors from their promoters inhibiting its trans-activating activity [3,4].

Preclinical
L has cytotoxic activity against a number of platinum resistant cell lines *in vitro* and in xenograft animal models. An improved (additive or synergistic) in vivo antitumor activity was found after the treatment with L plus doxorubicin (DOX) of mice bearing SCLC xenografted tumors.

Clinical
Cohort A: Phase Ib 3+3 dose escalation (L 3-5 mg FD+DOX 50mg/m²) followed by dose expansion at RD in selected diseases, including SCLC with less than 3 prior chemotherapy lines for advanced disease
Activity in cohort A showed an ORR 67% (57% PR; 10% CR, 95% CI: 43-85%), especially remarkable in sensitive patients (CTFI>90 days) with an ORR 100% (n=11, PR 82%, CR 18%, 95% CI: 71.5-100%) [5] .
Cohort B: An expansion cohort with a reduced dose was implemented in endometrial and SCLC to determine the safety and efficacy of the combination. Results from this cohort are presented in this poster.

METHODS

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.
Treatment Schedule

- **Cohort B: DOX 40 mg/m² + L 2 mg/m² Day 1 q3w and continue with L at 4 mg/m² after DOX cumulative dose of 450 mg/m² reached.**

RESULTS

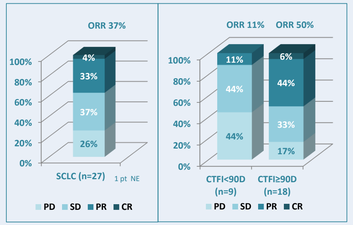
	Cohort B (n=28)
Median age in years (range)	64 (49-77)
Gender (M / F)	75% / 25%
ECOG PS (0 / 1)	32% / 68%
BSA Mean/ Median in m² (range)	1.9 / 1.9 (1.5 - 2.3)
Median prior therapy lines (range)	1 (1 - 2*)
Previous platinum	100%
Previous PCI	50%
Known CNS involvement	4%
Visceral metastases	93%
Median number of metastatic sites (range)	3 (1 - 4)
Bulky disease (>50 mm)	75%
Median CTFI in months (range)	3.4 (0 - 15.9)
CTFI < 90 days (Resistant)	36%
CTFI ≥ 90 days (Sensitive)	64%
Median TTP to 1st line platinum-based combination in months (range)	6.8 (1.4 - 18.9)

CNS, central nervous system; CTFI, chemotherapy-free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; F, female; M, male; PCI, prophylactic cranial irradiation; TTP, time-to-progression.
* Prior nivolumab 1 pt

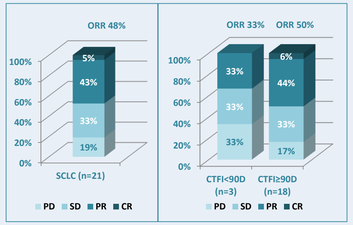
(1) Bradner et al. Cell 2017; 168: 629-643
(2) Aubert et al. Cancer Cell 2014; 26:783-784
(3) Di Giandomenico et al. Oncogene 2014; 33:5201-5210
(4) Harlow et al. Cancer Res 2016; 76(22):6657-6668
(5) Activity and Safety of the Combination of L and Doxorubicin in Relapsed SCLC. Final Results of a Phase Ib Trial". Emiliano Calvo et al. WCLC 2017 18th World Conference on Lung Cancer. Yokohama. October 2017.

RESULTS

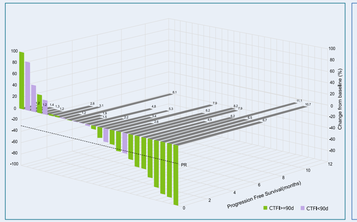
Cohort B: Objective responses in SCLC and according to Chemotherapy-free interval (CTFI) (sensitive vs resistant)



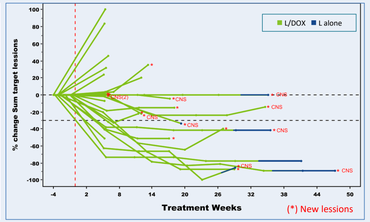
Cohort B: Objective responses in SCLC excluding pts with CTFI <30 days and according to Chemotherapy-free interval (CTFI) (sensitive vs resistant)



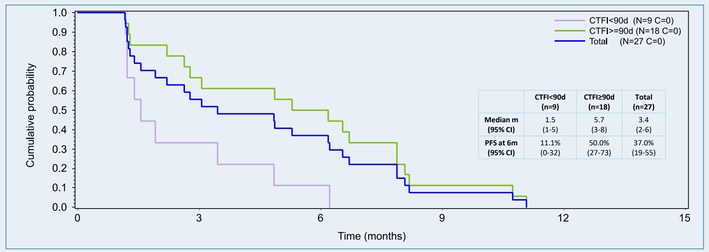
Waterfall 3D Cohort B, showing maximal tumor variation in size according to CTFI and PFS (n=27)



Spider plot showing tumor variation over time during treatment with L/DOX and L alone in cohort B patients (n=27)

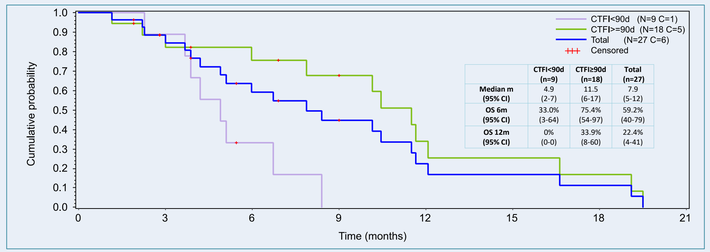


PFS by CTFI cohort B



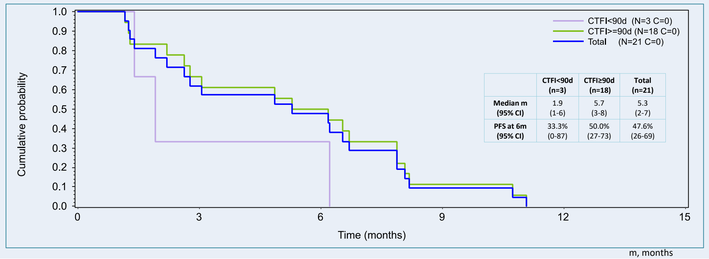
	CTFI<90d (n=9)	CTFI≥90d (n=18)	Total (n=27)
Median m (95% CI)	1.5 (1-5)	5.7 (3-8)	3.4 (2-6)
PFS at 6m (95% CI)	11.1% (0-32)	50.0% (27-73)	37.0% (19-55)

OS by CTFI cohort B



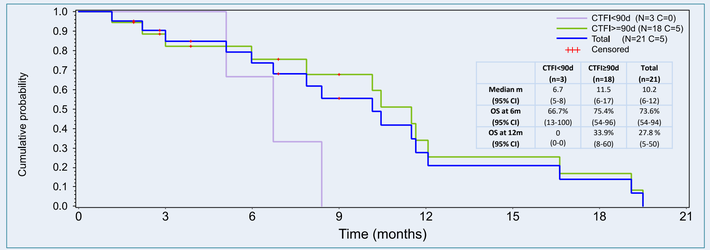
	CTFI<90d (n=9)	CTFI≥90d (n=18)	Total (n=27)
Median m (95% CI)	4.9 (2-7)	11.5 (6-17)	7.9 (5-12)
OS 6m (95% CI)	33.0% (3-64)	75.4% (54-97)	59.2% (40-79)
OS 12m (95% CI)	0% (0-0)	33.9% (8-60)	22.4% (4-41)

PFS by CTFI excluding CTFI < 30 days



	CTFI<90d (n=3)	CTFI≥90d (n=18)	Total (n=21)
Median m (95% CI)	1.9 (1-6)	5.7 (3-8)	5.3 (2-7)
PFS at 6m (95% CI)	33.3% (0-87)	50.0% (27-73)	47.6% (26-69)

OS by CTFI excluding CTFI < 30 days



	CTFI<90d (n=3)	CTFI≥90d (n=18)	Total (n=21)
Median m (95% CI)	6.7 (5-8)	11.5 (6-17)	10.2 (6-12)
OS at 6m (95% CI)	66.7% (13-100)	75.4% (54-96)	73.6% (54-94)
OS at 12m (95% CI)	0 (0-0)	33.9% (8-60)	27.8 % (5-50)

m, months

Safety: L/DOX(n=28)

	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	25%	50%	21%	-
Neutropenia	4%	-	25%	68%
Febrile Neutropenia	-	-	7%	7%
Thrombocytopenia	36%	7%	7%	11%
ALT	29%	-	4%	-
AST	29%	-	-	4%
Anorexia	21%	18%	4%	-
Fatigue	14%	50%	14%	-
Nausea/Vomiting	50%	14%	7%	-
Diarrhea	4%	-	-	-
Alopecia	11%	14%	-	-
Mucositis	11%	7%	-	-

CONCLUSIONS

- L/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 a remarkable improvement in this second-line setting, especially when excluding refractory pts. (CTFI<30 days)
- Main hematological toxicity was myelosuppression well-managed with G-CSF and dose reductions.
- A phase III clinical trial (ATLANTIS, NCT02566993) evaluating this combination in relapsed SCLC patients has recently completed recruitment

ACKNOWLEDGEMENTS

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