

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

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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

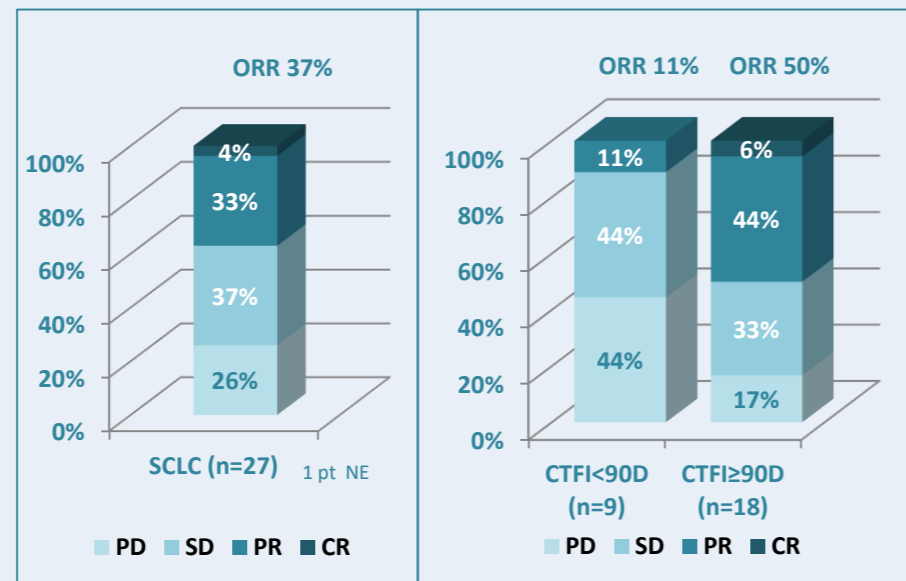
	Cohort B (n=28)
Median age in years (range)	64 (49-77)
Gender (M / F)	75% / 25%
ECOG PS (0 / 1)	32% / 68%
BSA Mean/ Median in m ² (range)	1.9 / 1.9 (1.5 - 2.3)
Median prior therapy lines (range)	1 (1 - 2*)
Previous platinum	100%
Previous PCI	50%
Known CNS involvement	4%
Visceral metastases	93%
Median 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 1 st 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

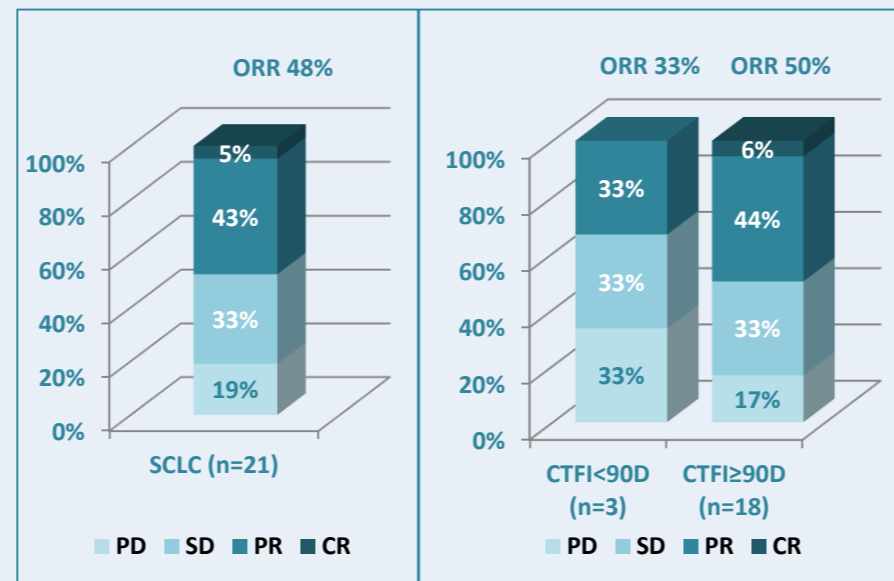
(1) Bradner et al. Cell 2017; 168: 629-643
(2) Aubert et al. Cancer Cell 2014; 26:783-784
(3) Di Giandomenico et al. Oncogene 2014; 33:5201-5210
(4) Harlow et al. Cancer Res 2016; 76(22):6657-6668
(5) Activity and Safety of the Combination of L and Doxorubicin in Relapsed SCLC. Final Results of a Phase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

RESULTS

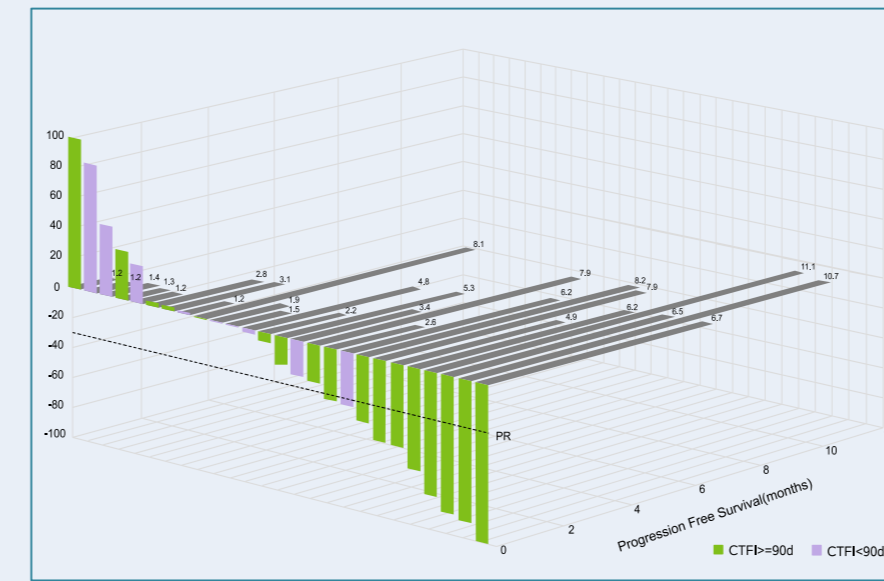
Cohort B: Objective responses in SCLC and according to Chemotherapy-free interval (CTFI) (sensitive vs resistant)



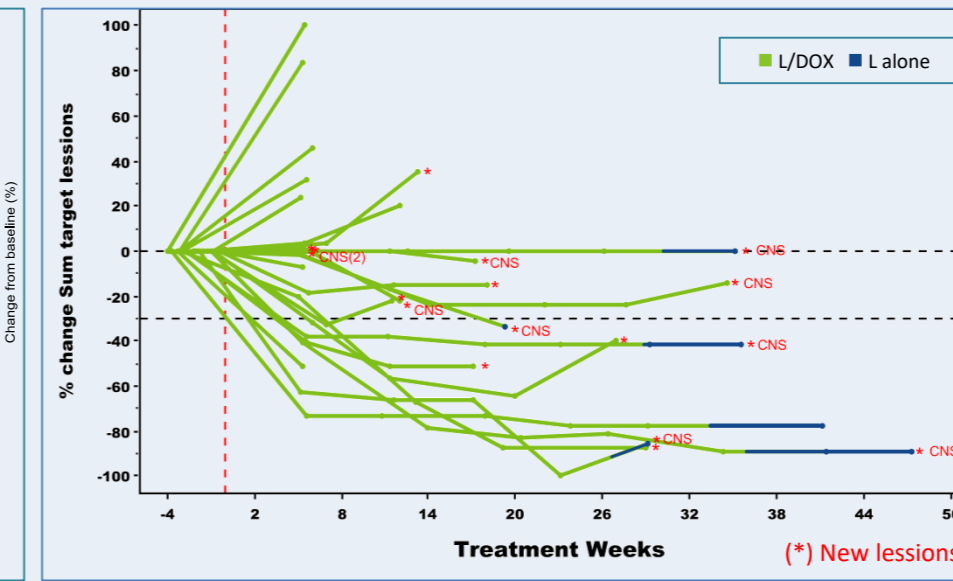
Cohort B: Objective responses in SCLC excluding pts with CTFI < 30 days and according to Chemotherapy-free interval (CTFI) (sensitive vs resistant)



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)



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%	-	-

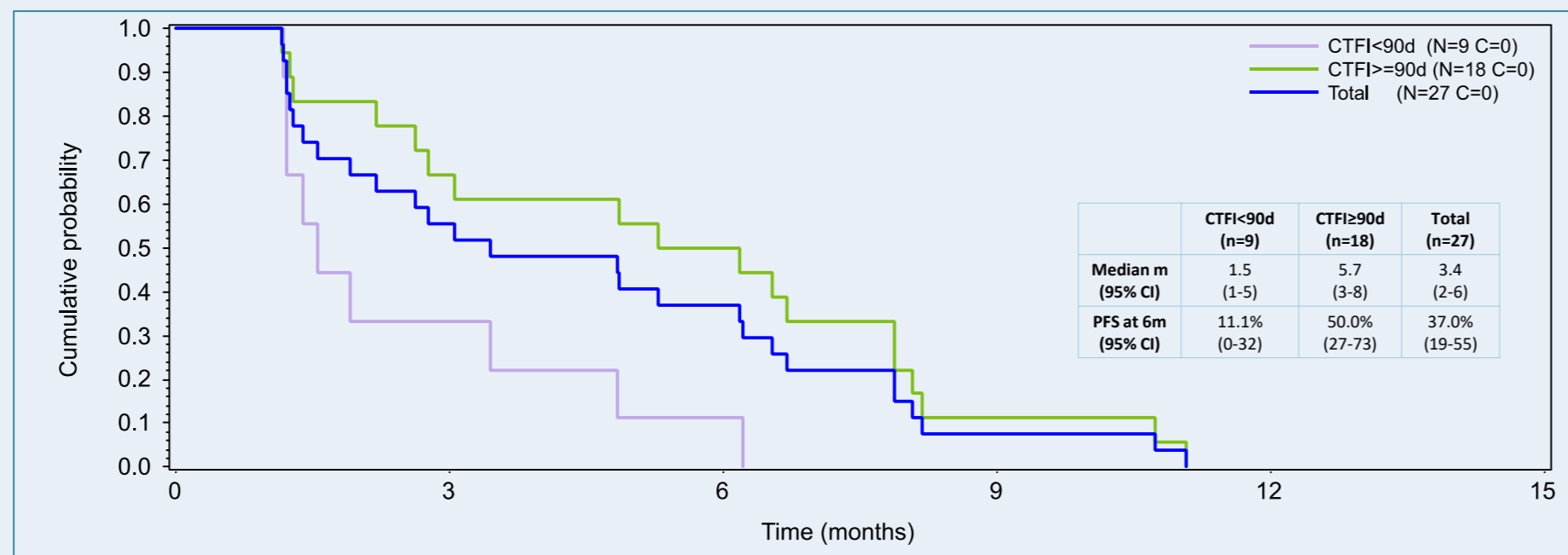
CONCLUSIONS

- ❖ 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

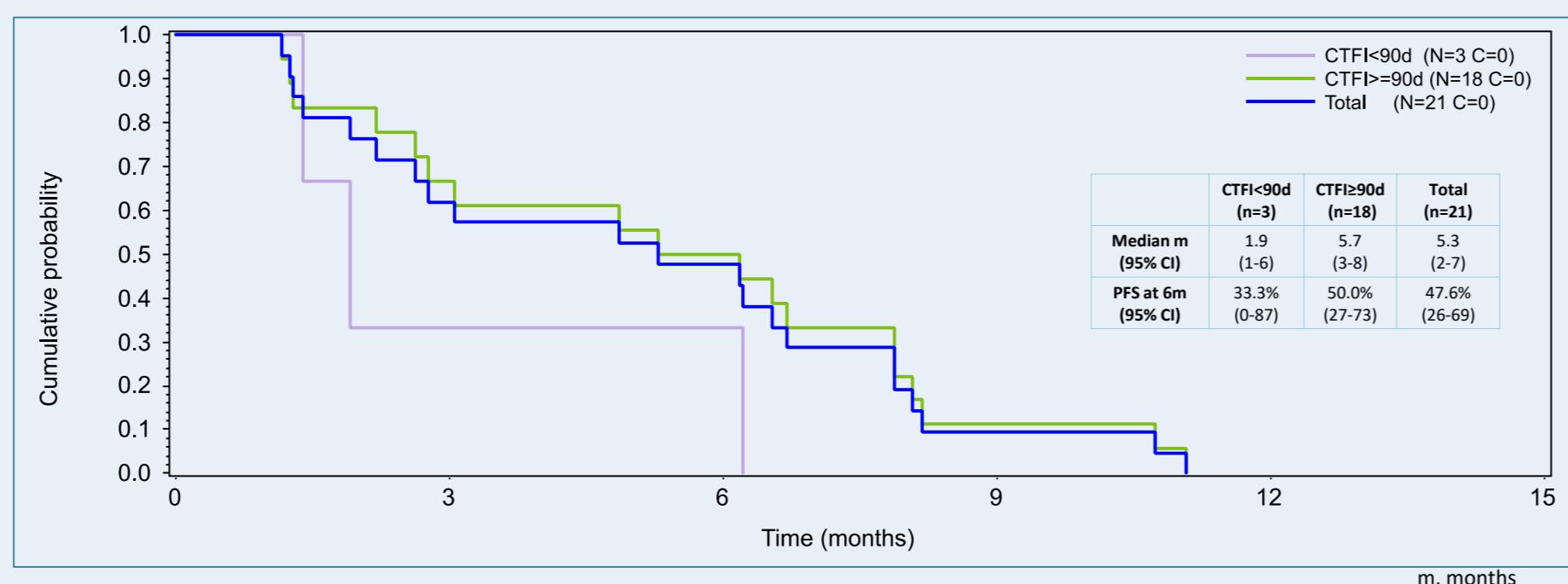
ACKNOWLEDGEMENTS

- ❖ To all the patients and their families
- ❖ To all the investigators involved in this trial
- ❖ To Ana García Salas and Mariano Sigüero for their help and support

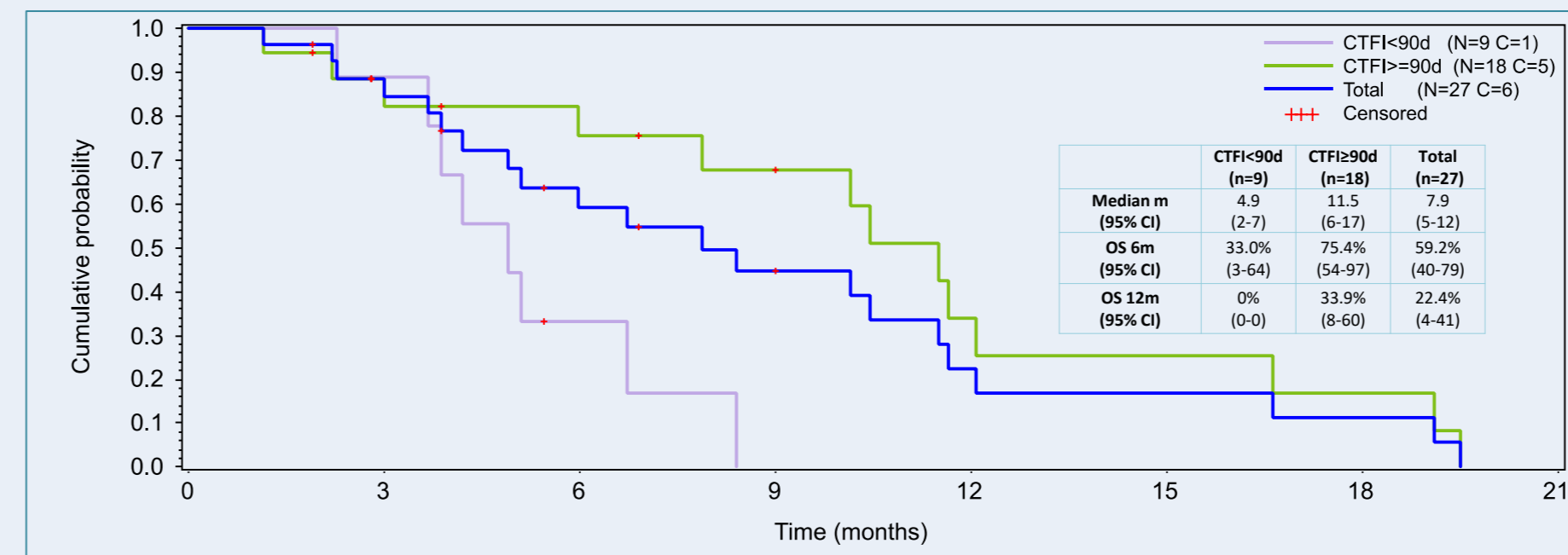
PFS by CTFI cohort B



PFS by CTFI excluding CTFI < 30 days



OS by CTFI cohort B



OS by CTFI excluding CTFI < 30 days

