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ACTIVITY OF LURBINECTEDIN AS SINGLE AGENT AND IN COMBINATION IN PATIENTS WITH ADVANCED SMALL CELL LUNG CANCER (SCLC)

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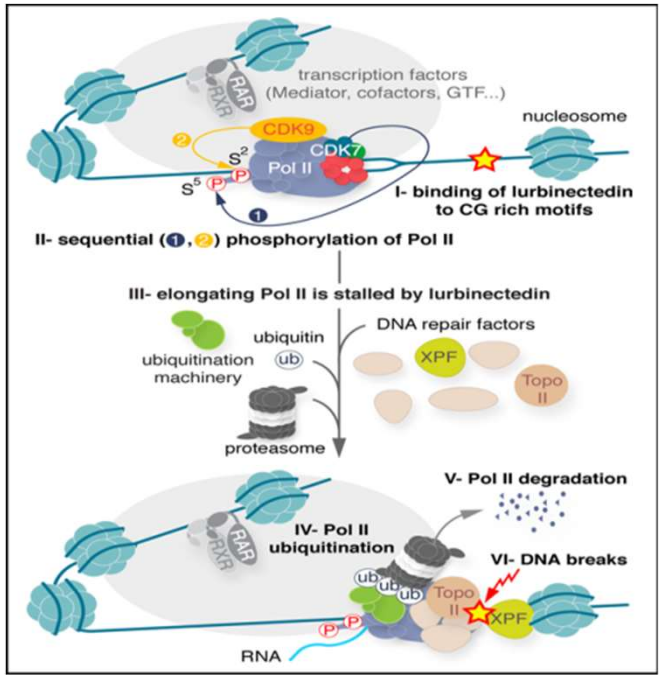
BACKGROUND

- Lurbinectedin (PM01183, L) is a novel anticancer drug that inhibits activated transcription, induces DNA double-strand breaks generating apoptosis, and modulates tumor microenvironment.



Inhibition of active transcription

I- Binding of PM1183 to the DNA

(Cytosine Guanine-rich motifs)

II- Phosphorylation of Pol II

III- Stalling of elongating Pol II

IV- Recruitment of the ubiquitin-

proteasome machinery

V- RNA Pol II degradation

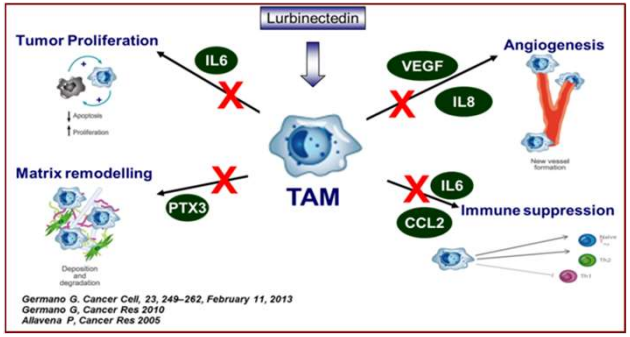
VI- Recruitment of XPF and

Generation of DNA breaks

VII- Induction of apoptosis

Tumor Microenvironment Effect

Inhibition of Tumor Associated Macrophages (TAM)



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METHODS

- Safety and efficacy of three different clinical trials were reviewed

A.- (Lurbinectedin +DOX)

- Phase Ib dose escalation followed by dose expansion at RD in selected diseases, including **SCLC**.
- Less than 3 prior chemotherapy lines for advanced disease

Treatment Schedule

- **Cohort A: doxorubicin 50 mg/m^2 + L 3-5 mg flat dose (FD)** Day 1 q3w and cont. with **L** 7 mg FD after DOX cumulative dose of 450 mg/m^2
- **RD doxorubicin 50 mg/m^2+ PM1183 2 mg/m^2 q3w**
- **Cohort B: doxorubicin 40 mg/m^2+ L 2 mg/m^2** Day 1 q3w and cont. with **L** 4 mg/m2 after DOX cumulative dose of 450 mg/m^2

B.- (Lurbinectedin +TAX)

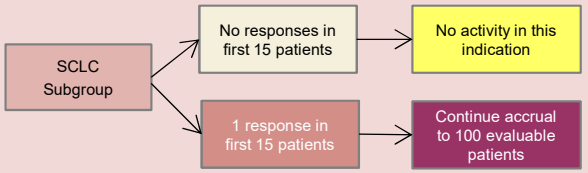
- Phase I dose escalation followed by dose expansion at RD in selected diseases including **SCLC**.
- Less than 3 prior chemotherapy lines for advanced disease

Treatment Schedule

- L day 1 q3w+ Paclitaxel weekly for 18w continued with PM1183 alone
- **RD Paclitaxel 80mg/m^2 D1 and 8 + L 2.2 mg/m^2 q3w**

C.- (Lurbinectedin single-agent)

- Phase II Multicenter, open-label, exploratory, Basket trial
- Less than 2 prior chemotherapy lines for advanced disease
- Primary objective: Response rate
- Sample size: initially 15 patients to be recruited



Treatment Schedule:

- **PM1183 3.2 mg/m^2, 1h iv infusion, q3wks**

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BASELINE CHARACTERISTICS

		L+Dox		L+TAX	L single-agent
		Cohort A (n=21)	Cohort B (n=27)	(n=7)	(n=36)
Age (years)	Median (range)	62 (48-73)	64 (49-77)	55 (48-68)	63 (40-83)
ECOG	0	9 (43%)	9 (32%)	3 (43%)	10 (36%)
	1	12 (57%)	18 (68%)	4 (57%)	22 (61%)
	2	-	-	-	4 (8%)
Previous PCI	Yes	43%	54%	57%	50%
	No	57%	46%	43%	50%
Known CNS involvement	Yes	33%	4%	14%	3%
	No	67%	96%	86%	97%
Visceral metastasis	Yes	71%	68%	86%	92%
	No	29%	32%	14%	8%
Median number of metastatic sites	Range	3 (1-5)	3 (1-5)	3 (1-4)	3 (1-5)
Bulky disease (>50mm)	Yes	62%	75%	71%	69%
	No	38%	25%	29%	31%
Median CTFI months	Range	3.1 (0.5-10.6)	3.4 (0-15.9)	2.3 (0.5-10.3)	3.5 (0.07-7.9)
CTFI < 3 months	%	48%	36%	57%	50%
CTFI > 3 months	%	52%	64%	43%	47%*
CTFI > 30 d	n (%)	16 (76%)	21 (78%)	5 (72%)	29 (81%)

* CTFI (chemotherapy-free interval) unknown in one patient

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RESULTS

Response Evaluable patients	Lurbinectedin+DOX (q3wk)		Lurbinectedin +TAX (q3wk)	Lurbinectedin single-agent (q3wk)
	Cohort A L 3-5 mg FD D1 + DOX 50 mg/m^2 D1 (n=21)	Cohort B L 2 mg/m^2 D1 + DOX 40 mg/m^2 D1 (n=27)	L 2.2 mg/m^2 D1 + TAX 80 mg/m^2 D1 & D8 (n=7)	L 3.2 mg/m^2 D1 (n=36)
CR	2 (10%)	1 (4%)	1 (14%)	-
PR	12(57%)	9 (33%)	4 (57%)	13 (36%)
ORR	**14 (67%)**	**10 (37%)**	**5 (71%)**	**13 (36%)**
SD	3 (14%)	9 (33%)	-	14 (39%)
PD	4 (19%)	8 (30%)	2 (29%)	9(25%)
DCR	17 (81%)	19 (70%)	5 (71%)	27 (75%)
DOR (mo)	**4.5**	**5.2**	**2.3**	**6.2+**
PFS (mo) CTFI >30d*	4.7	5.3	3.9	3.1+
PFS (mo) Platinum-sensitive	**5.8**	**6.2**	**3.9**	**4.6+**

D, day; DCR, disease control rate; DOR, duration of response; FD, flat dose; mo, months; q3wk, every 3 weeks; CTFI, chemotherapy free interval.

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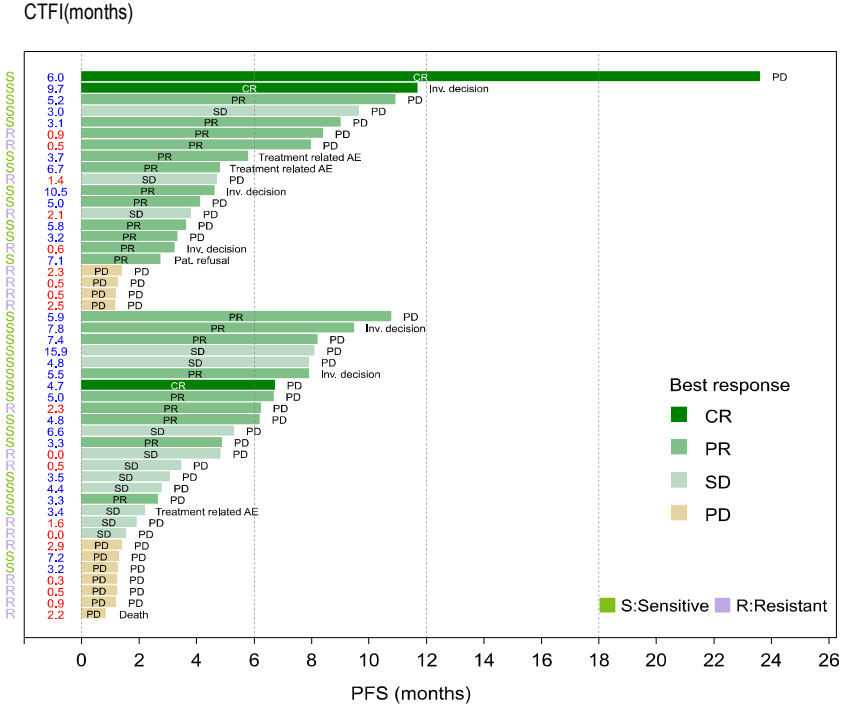
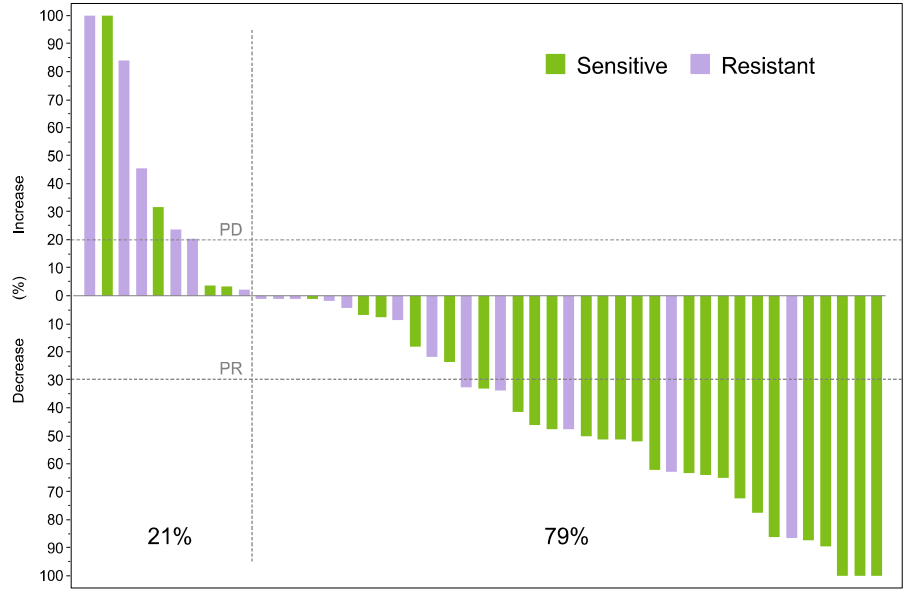
RESULTS

Lurbinectedin+DOX





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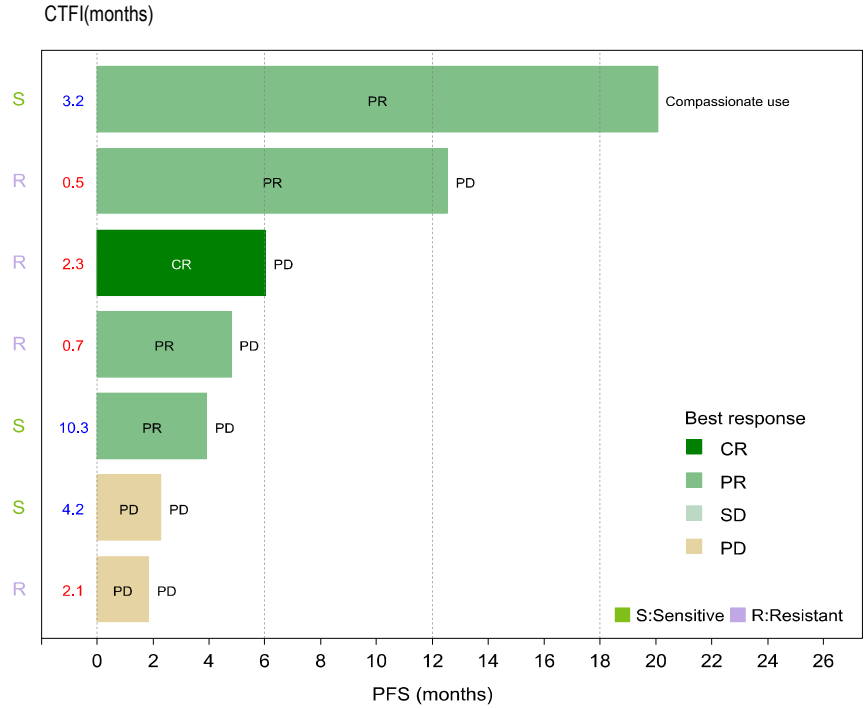
RESULTS

Lurbinectedin+TAX



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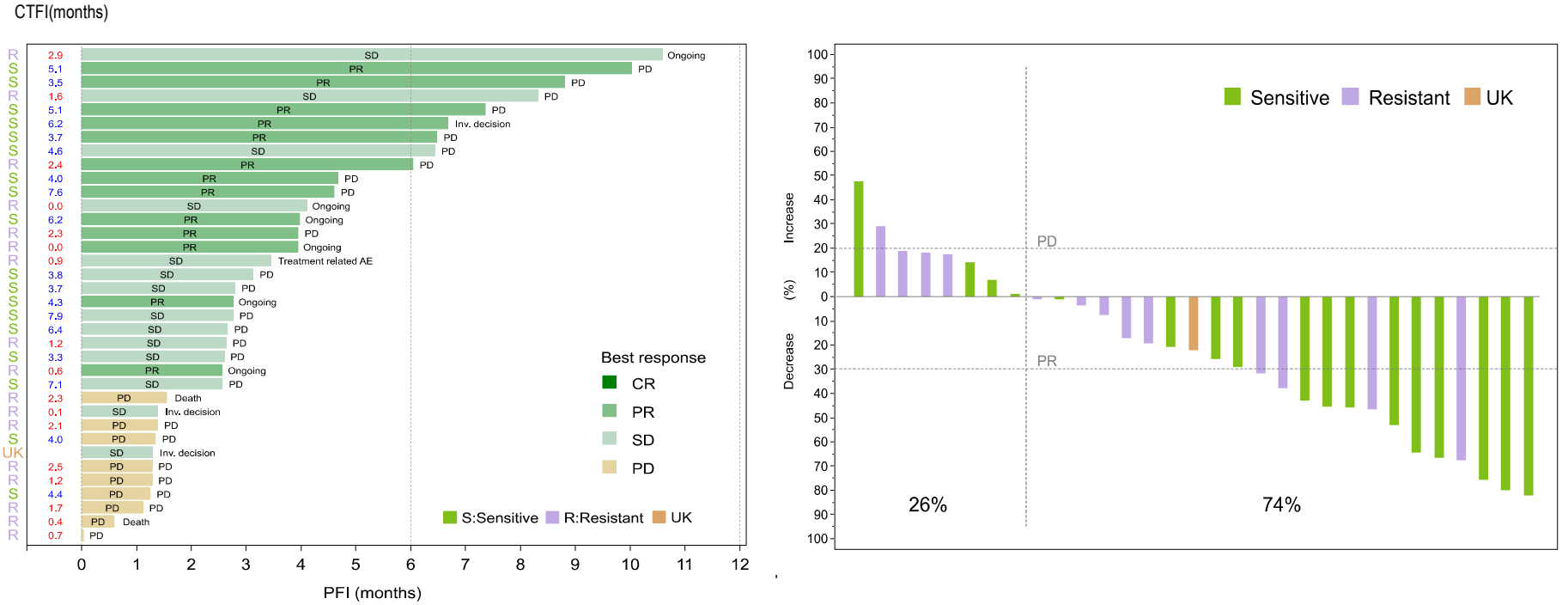
RESULTS

Lurbinectedin single-agent



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SAFETY

CTC grade v4.0	Study							
	L+DOX				L+TAX		L alone	
	Cohort A (n=21)		Cohort B (n=27)		(n=7)		(n=36)	
	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Fatigue	15 (68.2)	3 (13.6)	15 (53.6)	7 (25.0)	4 (57.1)	-	18 (50.0)	2 (5.6)
Nausea	12 (54.5)	3 (13.6)	17 (60,7)	2 (7.1)	3 (42.9)	-	11 (30.6)	1 (2.8)
Vomiting	5 (22.7)	-	11 (39.3)	-	1 (14.3)	-	7 (19.4)	-
Diarrhea	4 (18.2)	-	2 (7.1)	-	3 (42.9)	-	-	-
Constipation	5 (22.7)	-	5 (17.9)	-	1 (14.3)	-	6 (16.7)	-
Neutropenic infection	-	1 (4.5)	-	1 (3.6)	-	-	-	-
FN	-	8 (36.4)	-	4 (14.3)	-	1 (14.3)	-	4 (11.1)
Anemia*	11 (50.0)	10 (45.5)	20 (71.4)	7 (25.0)	5 (71.4)	2 (28.6)	28 (77.8)	5 (13.9)
Neutropenia*	1 (4.5)	21 (95.5)	1 (3.26)	26 (92.9)	-	6 (85.7)	13 (36.1)	14 (38.9)
Thrombocytopenia*	13 (59,1)	7 (31.8)	12 (42.9)	6 (21.4)	2 (28.6)	-	11 (30.6)	4 (11.1)
ALT*	12 (54.5)	3 (13.6)	11 (39.3)	1 (3.6)	-	-	22 (61.1)	3 (8.3)
AST*	8 (36.4)	1 (4.5)	8 (28.6)	1 (3.6)	-	-	11 (30.6)	-

Laboratory abnormalities (regardless of relationship*) and treatment-related adverse events (≥ 10% of patients or grade ≥3).

L+DOX combination Cohort A: Use of G-CSF 71%, dose reductions 33%, dose delays 38%

L+DOX combination Cohort B: use of G-CSF 43%, dose reductions 21%, dose delays 39%

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CONCLUSION

- Lurbinectedin shows remarkable activity in a dramatic scenario as platinum-progressed SCLC.
- Strong activity shown as a single-agent and in combination.
- Results are noteworthy in terms of DOR, PFS and DCR, especially in platinum-sensitive SCLC.
- Toxicity mainly consisted of transient myelosuppression, which was manageable with dose reductions and G-CSF use.