

Table S5. Cardiac toxicity and clinical efficacy associated to liposomal doxorubicin in breast cancer trials

STUDY Author (Ref) Design	N	Setting	Antracycline	Schedule	HE R2	Median age	Cardiac assessment	Cardiotoxicity	Efficacy
<i>O'Brien (12) Phase III</i>	509	1 st line MBC	PLD vs DOX	Monotherapy	No	58.5	LEVF at baseline, one during treatment after 300 and 400mg/m2 LVEF	DOX > PLD (HR = 3.16; 95%CI 1.58–6.31; <i>P</i> <0.001)	PFS 6.9 vs 7.8 m HR 1 (95%CI 0.82-1.22) OS 21 vs 22m HR 0.94; (95%CI 0.74–1.19)
<i>Rafiyath (13) Metanalysis</i>	222 0	1 st line MBC	Liposomal vs conventional antracyclines	Monotherapy	No	Patients with median ages between 37 and 59	Congestive cardiac failure and mean percentage change in LVEF from baseline	Conventional > Liposomal OR 0.34 (95%CI 0.24-0.47)	Not evaluated
<i>Overmoyer (22) Phase II</i>	51	1 st line MBC	PLD 30mg/m2/3w	Plus CPM 600mg/m2	No	54	LEVF at baseline, accumulative dose of 300mg/m2, each 100 mg/m2 thereafter and at the end.	LVEF decrease (G1) in 15% All asymptomatic	ORR 50%, CR 8%, PR: 43%, CB: 86%.
<i>Trudeau (23) Phase II</i>	70	1 st line MBC	PLD 35 mg/m2	Plus CPM 600mg/m2/3w	No	55	LEVF at baseline every 2 cycles	1.4% pts had > 15% in LVEF drop 7.14% pts had > 10% LVEF drop at the end of treatment. All asymptomatic	ORR 38%. BC: 71% PD: 29% TTP: 12.2 m OS: 16.5 m.
<i>Rau (24) Phase II</i>	45	2 nd line MBC	PLD 40mg/m2/3w	Plus CPM 500mg/m2 5FU 500mg/m2/3w	No	52.5	LVEF at baseline at the end of treatment	No decrease in LVEF	ORR: 80%; PD 15.6% PFS 8.2m OS 36.6m
<i>Vorobiof (25) Phase II</i>	34	1 st line MBC	PLD 30mg/m2/3w	Plus paclitaxel 175mg/m2	No	55	LEVF at baseline and at the end.	LVEF decrease > 20% (G2) in 3% LVEF decrease >10% (G1) in 20%. All asymptomatic	ORR 73%, CR 21% PR 53% PD 3%.
<i>Rigatos (26) Phase II</i>	23	1 st line MBC	PLD 30mg/m2/3w	Plus paclitaxel 175mg/m2	No	59	LEVF at baseline, and at the end of treatment	Significant drop in LVEF in one pts and one arrhythmia (8.7%). All asymptomatic	ORR: 69.57%. CR 8.70% PR 60.87%. TTP: 7 m, OS: 10 m.
<i>Dong (30) Phase II matched 1:2</i>	43/8 6	NAC	PLD 35mg/m2/3w vs epirubicin 100mg/m2/3w	Plus taxanes	No	51	LEVF was measured at baseline, and during treatment	Non-significant differences in LVEF drop rate>10% (p=0.463)	ORR PLD 76.6% epirubicin 75.7% PD both 2.3% pCR: 16.3% vs 11.6%

<i>Gogas (28) Phase II</i>	35	NAC	PLD 35 mg/m ² /3w	Plus paclitaxel 175mg/m ²	No	54	LEVF was measured at baseline and during treatment	No significant changes during treatment.	ORR 71% CR 17%, PR: 54% PD 6% pCR:8.5%
<i>Schmid (27) Phase II</i>	44	NAC	Non peylated liposomal DOX 60mg/m ² /3w	Plus docetaxel 75mg/m ² and gemcitabine 350mg/m ² /3w	No	45	LEVF at baseline and every 2 cycles. Serial ECG	No cases of cardiac failure	ORR: 73%. CR: 23% PR 50% PD: 2.5% pCR: 16%
<i>García Mata (31) Phase II</i>	74	NAC	Non-pegylated liposomal DOX 60m/m ² /3w	Docetaxel 75mg/m ² and CPM 600mg/m ²	No	46	LEVF at baseline, and during treatment	No significant changes in LVEF	ORR: 75%, PD: 2% pCR 24%
<i>Gil-Gil (14)</i>	50	NAC	PLD 35 mg/m ² /4w	Plus CPM 600mg/m ² /4w followed paclitaxel 80 /w	No	73	LEVF at baseline, 9, 6 and 18 w and during 5 years	No significant changes in LVEF	ORR 26%; pCR 32%, 5y RFS 54.4%, 5y OS 56%and 5y BCSS 67,7%

Abbreviations: CB, Clinical Benefit; CI, Confidence Interval; CPM, Cyclophosphamide; CR, Complete Response; DOX, Doxorubicin; m, months; ECG, Electrocardiogram; G, Grade; HR, Hazard Ratio; LVEF, Left ventricular ejection fraction; N, number; NAC; Neoadjuvan chemotherapy, MBC, Metastatic Breast Cancer, ORR, Overall Response Rate; OS, Overall Survival; pCR, Pathological Complete Response; PD, Progression; PFS, Progression Free Survival; PLD, Pegylated liposomal doxorubicin; Pts, Patients; PR, Partial Response; Ref, Reference, TTP, Median time to progression; w, weeks; y, year

