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

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| **STUDY**  *Author (Ref)*  *Design* | **N** | **Setting** | **Antracycline** | **Schedule** | **HER2** | **Median age** | **Cardiac assessment** | **Cardiotoxicity** | **Efficacy** |
| *O’Brien (12)*  *Phase III* | 509 | 1st 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; *P* <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) |
| *Rafiyath (13)*  Metanalysis | 2220 | 1st 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 |
| *Overmoyer (22)*  *Phase II* | 51 | 1st 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%. |
| *Trudeau (23)*  *Phase II* | 70 | 1st 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. |
| *Rau (24)*  *Phase II* | 45 | 2nd 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 |
| *Vorobiof (25)*  *Phase II* | 34 | 1st 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%. |
| *Rigatos (26)*  *Phase II* | 23 | 1st 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. |
| *Dong (30) Phase II matched 1:2* | 43/86 | **NAC** | PLD 35mg/m2/3w vs epirrubicin 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% epirrubicin 75.7%  PD both 2.3%  **pCR: 16.3%** vs 11.6% |
| *Gogas (28)*  *Phase II* | 35 | **NAC** | PLD 35 mg/m2/3w | Plus paclitaxel 175mg/m2 | 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%** |
| *Schmid (27)*  *Phase II* | 44 | **NAC** | Non peylated liposomal DOX 60mg/m2/3w | Plus docetaxel 75mg/m2 and gemcitabine 350mg/m2 /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%** |
| *García Mata (31)*  *Phase II* | 74 | **NAC** | Non-pegylated liposomal DOX 60m/m2/3w | Docetaxel 75mg/m2 and CPM 600mg/m2 | No | 46 | LEVF at baseline, and during treatment | **No significant changes in LVEF** | ORR: 75**%,** PD: 2% **pCR 24%** |
| *Gil-Gil (14)* | 50 | **NAC** | PLD 35 mg/m2/4w | Plus CPM 600mg/m2/4w 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