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Multicenter phase I trial of trastuzumab emtansine in combination with non-pegylated liposomal doxorubicin in HER2-positive metastatic breast cancer. THELMA Study.

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BACKGROUND

- EMILIA[1], TH3RESA[2], and KAMILLA[3] phase III trials showed that trastuzumab emtansine (T-DM1) is highly active and safe as single-agent in human epidermal growth factor receptor 2 (HER2)-positive [+] metastatic breast cancer (MBC) patients (pts).
- T-DM1 and non-pegylated liposomal doxorubicin (NPLD) may be safely combined to increase antitumor effect compared to each agent alone.
- The aim of this trial is to determine the dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) of T-DM1 combined with NPLD in HER2[+] MBC (*ClinicalTrials.gov* identifier NCT03809988).

OBJECTIVES

- **PRIMARY OBJECTIVE**

  To determine the MTD of the combination of T-DM1 and NPLD in HER2[+] MBC pts previously treated with taxane and trastuzumab-based therapy.

- **Primary Endpoint:**
  - MTD is defined as the highest dose level at which 0/3 pts or ≤1/6 pts experienced DLT during the first 2 cycles of study treatment.
    * DLT is defined as any of the drug-related adverse events (AEs) described in the **Table 1**, occurring during the first 2 cycles of study treatment.

Table 1. Summary of Dose-Limiting Toxicities (DLTs)

Hematological toxicities:	Cardiac toxicity:	Hepatic toxicity:	Other non-hematological toxicities
>7 days of G4 neutropenia; or ≥G3 febrile neutropenia.	Sudden death.	AST or ALT increased >5x.	G≥ 3 preventing the start of the third cycle on Day 42.
Uncomplicated G4 thrombocytopenia not recovered to G1 before next planned dose.	Heart failure NYHA criteria class III-IV and LVEF decline with absolute drop ≥10% and final LVEF <50%.	Total bilirubin value increased > 3x ULN.	G≥ 2 requiring interruption of treatment for > 21 days.
G≥1 thrombocytopenia with clinically significant bleeding.		Hy's Law [4].	Patient not able to receive 100% of the dose level going into Cycle 3, Day 1.

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; G: Grade; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association; ULN: Upper limit of normal (ULN).

- **SECONDARY OBJECTIVES**
  - Objective response rate (ORR) and clinical benefit rate (CBR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
  - Number and rate of patients with progressive disease (PD) and death.
  - AEs assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.4.
  - The extent of exposure to T-DM1 and NPLD.
  - The pharmacokinetics (PK) profile of T-DM1, NPLD, and each one's metabolites.
  - The relationship between efficacy (ORR, CBR, and PD) and PK systemic exposure (Cmax and AUCinf) to T-DM1 and metabolites.

TRIAL DESIGN

- This is a multi-center, open-label, 3+3 dose-escalation phase I clinical trial.
- The initial dose of T-DM1 was 3.6 mg/kg intravenously (IV) and NPLD 45 mg/m² IV on Day 1, every three weeks for up to 6 cycles of NPLD (cohort 1).
- In the next dose levels, only the NPLD dose was increased to 50 mg/m² (cohort 2) and 60 mg/m² (cohort 3).
- Six additional pts were enrolled at the MTD.
- T-DM1 treatment was continued as a single-agent until PD or intolerable toxicity.

KEY SELECTION CRITERIA

- Main selection criteria were:
  1. Women with HER2[+] MBC ≥ 18 years (yrs) relapsed or progressed on or after taxanes and trastuzumab-based therapy;
  2. No prior treatment with T-DM1 or anthracyclines;
  3. Measurable or non-measurable disease with litic bone lesions;
  4. Eastern Cooperative Oncology Group (ECOG) performance status ≤1.

RESULTS

Table 2. Patient characteristics (N=15)

	Cohort 1, N=3 NPLD (45 mg/m²)	Cohort 2, N=3 NPLD (50 mg/m²)	Cohort 3, N=9 NPLD (60 mg/m²)	Total (N=15)
Age, Median (range), years	50 (39, 62)	58 (57, 61)	42 (31, 62)	50 (31, 62)
Caucasian, n (%)	3 (100%)	3 (100%)	9 (100%)	15 (100%)
ECOG 0, n (%)	3 (100%)	3(100%)	7 (77.8%)	13 (86.7%)
ER[+], n (%)	2 (66.7%)	3 (100%)	6 (66.7%)	11 (73.5)
PgR[+], n (%)	1 (33.3%)	2 (66.7%)	4 (44.4%)	7 (46.7%)
MBC at initial diagnostic, n (%)	3 (100%)	3 (100%)	3 (33.3%)	9 (60.0%)
≥2L MBC, n (%)	3 (100%)	0 (0%)	1 (11.1%)	4 (26.7%)
Previous trastuzumab plus pertuzumab, n (%)	1 (33.3%)	3 (100%)	8 (88.9%)	12 (80%)
Visceral involvement, n (%)	0 (0%)	3 (100%)	8 (88.9%)	11 (77.3%)
Brain involvement, n (%)	1 (33.3%)	0 (0%)	1 (11.1%)	2 (13.3%)
Bone involvement, n (%)	3 (100%)	3 (100%)	4 (44.4%)	10 (66.7%)

2L: Second line; ECOG: Eastern Cooperative Oncology Group; ER: Estrogen receptor; MBC: Metastatic breast cancer; NPLD: non-pegylated liposomal doxorubicin; PgR: Progesterone receptor.

SAFETY

- The only DLT was in the cohort 3 (neutrophil count <0.5x10⁹/L lasted 13 days). **The dose of cohort 3 (NPLD 60 mg/m²) was the MTD** (Table 3).
- Median relative dose intensity for TDM-1 and NPLD were 90.6% and 85.9%, respectively. Median duration in months for TDM-1 and NPLD were 6.3 and 3.7 months, respectively. No≥ G3 cardiac AEs occurred.

Table 3. Patients with DLTs

	Cohort 1, (N=3)	Cohort 2, (N=3)	Cohort 3, (N=9)	Total (N=15)
Pts with DLTs	0 (100%)	0 (100%)	1 (11.1%)	1 (6.7%)

DLT: Dose limiting toxicity; Pts: patients.

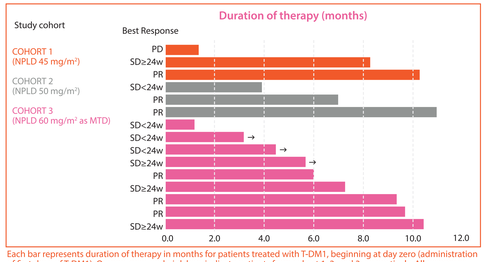
Table 4. Drug-related Adverse Events with Grade ≥3

	Cohort 1, (N=3)	Cohort 2, (N=3)	Cohort 3, (N=9)	Total (N=15)
Hematological				
Neutropenia	0 (0.0%)	2 (66.7%)	6 (66.7%)	8 (53.3%)
Thrombocytopenia	0 (0.0%)	0 (0.0%)	2 (22.2%)	2 (13.3%)
Leukopenia	0 (0.0%)	1 (33.3%)	1 (11.1%)	2 (13.3%)
Lymphopenia	0 (0.0%)	1 (33.3%)	1 (11.1%)	2 (13.3%)
Non-hematological				
AST increased	0 (0.0%)	0 (0.0%)	2 (22.2%)	2 (13.3%)
Fatigue	0 (0.0%)	0 (0.0%)	1 (11.1%)	1 (6.7%)

AST: Aspartate aminotransferase.

EFFICACY

Figure 1. Duration of T-DM1 treatment and best tumor response



Each bar represents duration of therapy in months for patients treated with T-DM1, beginning at day zero (administration of first dose of T-DM1). Orange, gray, and pink bars indicate patients from cohort 1, 2, and 3, respectively. All responses were confirmed at 6 or 9 weeks.
→ :patients continue under treatment with T-DM1; SD<24w: stable disease duration lasting < 24 weeks; SD≥24w: stable disease duration lasting ≥ 24 weeks; PD: progressive disease; PR: partial response.

Table 5. Tumor response and evaluation of clinical benefit

	Cohort 1, (N=3)	Cohort 2, (N=3)	Cohort 3, (N=9)	Total (N=15)
ORR*, n (%)	1 (33.3%)	2 (66.7%)	3 (33.3%)	6 (40%)
CBR**, n (%)	2 (66.7%)	2 (66.7%)	6 (66.7%)	10 (66.7%)
PFS events, n (%)	3 (100%)	2 (66.6%)	7 (77.8%)	12 (80%)
PD, n (%)	2 (66.6%)	2 (66.6%)	7 (77.8%)	11 (73.3%)
Deaths***, n (%)	1 (33.3%)	1 (33.3%)	0 (0%)	2 (13.3%)
Median PFS in months (95%CI)	-	-	7.2 (4.5 to 9.6)	7.2 (4.5 to 9.6)

CBR: Clinical benefit rate; CI: Confidence interval; CR: Complete response; ORR: Overall response rate; PD: Progressive disease; PFS: Progression-free survival.
* All responders showed partial response (PR). All PR were radiologically confirmed after initial observation.
**CR or PR or stable disease for 24 weeks or longer.
***Deaths were due to PD.

PHARMACOKINETICS (PK) CONCENTRATIONS

Following IV dose administration of T-DM1 with NPLD the mean concentrations for:

- Serum T-DM1, trastuzumab, and plasma DM1 declined in an exponential manner.
- Plasma NPLD declined quickly, whereas mean doxorubicinol concentrations gradually declined in a mono-exponential manner.

PK EXPOSURE AND EFFICACY

- We do not observe a significant relationship of efficacy (ORR, CBR, and PFS) to PK systemic exposure (Cmax and AUCinf) to T-DM1 and the individual active compounds trastuzumab and DM1.

CONCLUSIONS

- T-DM1 plus NPLD is a safe and active combination for pts with previously treated HER2[+] MBC.
- T-DM1 and NPLD systemic exposure estimates generally agreed with previously reported data[5,6]. These suggest minimal influence of doxorubicin on T-DM1 pharmacokinetics and vice versa.
- We did not observe a clear positive or negative correlation between efficacy and PK systemic exposure to T-DM1. Likely the small sample size limited the analysis.

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Conflicts of interest: https://medsir.org/thelma/

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