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PHASE I MULTICENTER CLINICAL TRIAL EVALUATING THE COMBINATION OF TRASTUZUMAB EMTANSINE (T-DM1) AND NON-PEGYLATED LIPOSOMAL DOXORUBICIN (NPLD) IN HER2-POSITIVE METASTATIC BREAST CANCER (MBC) (MEDOPP038 STUDY).

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BACKGROUND

- T-DM1, for the treatment of HER2-positive MBC, has been assessed for both clinical efficacy and safety in several phase II and III trials and is now considered the standard of care in taxane-and trastuzumab-progressing patients [1,2].
- However, although T-DM1 has shown encouraging antitumor activity in the advanced setting, several strategies to improve T-DM1 efficacy are currently being evaluated.
- Here, we evaluate the combination of T-DM1 and non-pegylated liposomal doxorubicin (NPLD), taking into consideration that:
  - i) doxorubicin is one of the most active chemotherapeutic agents against HER2-positive breast cancer,
  - ii) the combination of doxorubicin and trastuzumab induces synergistic antitumor activity in HER2-overexpressing preclinical models, and
  - iii) liposomal formulations of doxorubicin have a shown a reduced risk of developing cardiac toxicity.

OBJECTIVES

- **The primary objective** of this trial is to determine the maximum tolerated dose (MTD) of the combination of T-DM1 and NPLD in anthracycline-naïve, HER2-positive MBC patients previously treated with trastuzumab and a taxane.

- MTD is defined as the highest dose level at which 0 of 3 pts or ≤1 of 6 pts experience dose-limiting toxicity (DLT) during the first two cycles of treatment (Table 1).

- **The secondary objectives include**:
  1) Safety, with special emphasis on cardiac safety evaluated by left ventricular ejection fraction, high-sensitivity troponin I and B-type natriuretic peptide (BNP) levels.
  2) Pharmacokinetics.
  3) Antitumor activity.
  4) Role of single nucleotide polymorphisms of HER2 gene in developing cardiotoxicity.

TABLE 1. DOSE-LIMITING TOXICITIES (DLT) DEFINITIONS

DLT: Defined by the occurrence of any of the following adverse events assessed as related to study treatment (T-DM1 plus NPLD) within the 1st and 2nd cycles (first 42 days) of treatment.

Hematological:

- G4 neutropenia ≥ 7 days.
- Febrile neutropenia.
- G4 thrombocytopenia not recovered before next planned dose.
- Thrombocytopenia (any grade) with bleeding that requires medical intervention (platelet transfusion or cauterization).*

Non-hematological:

- G≥3 preventing the start of the 3rd cycle.
- G2 requiring interruption of treatment for > 21 days.
- Not able to receive 100% of the dose level going into Cycle 3, Day 1.

Cardiac toxicity (Level I):

- Sudden death within 24 hours of treatment.
- Heart failure NYHA class III-IV and LVEF absolute drop ≥10% with a final LVEF <50%.

Hepatic toxicity:

- Increase in AST/ALT values to >5x ULN.
- Increase in total bilirubin value to > 3xULN.
- Hy's Law criteria.

Grade ≥ 3 non-hematological not considered as DLTs (exceptions):

- G≥3 diarrhea recovered to G ≤ 2 after 24 hours of antidiarrheal treatment.
- G3 nausea, vomiting or diarrhea without appropriate treatment.
- G≥3 nausea or anorexia resolved to G1 prior to next cycle.
- Infusion-related reactions (IRR).
- G3≥ laboratory values toxicities not clinically significant.

* G1 or G2 epistaxis may have cauterization and this should not be considered as a DLT

TRIAL DESIGN

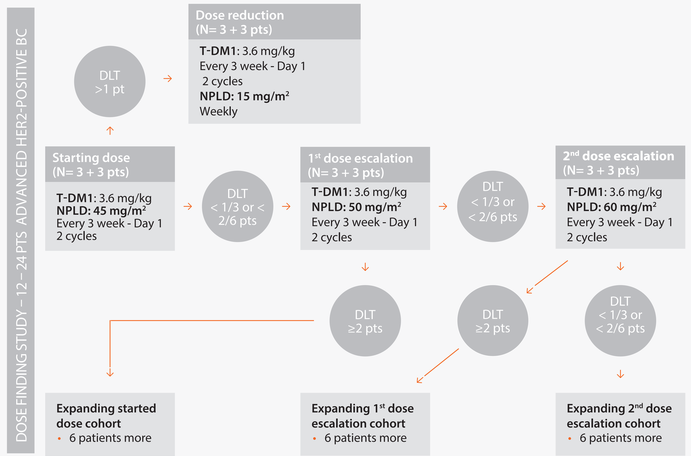
- This is a dose-finding, open-label, non-randomized and multicenter phase I clinical trial of T-DM1 at a fixed dose of 3.6 mg/kg IV in combination with three different dose levels (DL) of NPLD (45, 50, and 60 mg/m2) IV administered on Day 1 every three weeks.

- The trial follows a modified dose escalation scheme with a 3+3 design (Figure 1).

- Any patient who does not complete the DLT assessment (at end of cycle 2 or pre-dose at cycle 3 day 1) will be replaced, except for patients who reach end of study due to any DLT that does not allow to start cycle 2.

- Key eligibility criteria are described in tables 2A and 2B.

FIGURE 1. DESIGN OF STUDY COHORTS



BC: Breast cancer; DLT: Dose limiting toxicities; NPLD: Non-pegylated Liposomal Doxorubicin; T-MD1:Trastuzumab emtansine.

TABLE 2A. INCLUSION CRITERIA

1	Women ≥ 18 years with histologically or cytological confirmed locally advanced or metastatic HER2-positive breast cancer.
2	Anthracycline-naïve patients with to 2 prior chemotherapy regimens in the advanced setting.
3	Progressed or relapsed on after taxane and trastuzumab-based therapy.
4	Pts must have measurable (according to RECIST 1.1) or non-measurable disease with these exceptions: - Pts with only blastic bone lesions - Pts with only pleural, peritoneal or cardiac effusion, or meningeal carcinomatosis
5	ECOG performance status<2.
6	Grade ≤ 1 toxicities, except for alopecia.
7	LVEF ≥ 55% as assessed by echocardiography.
8	Adequate bone marrow and organ function.
9	Written informed consent.

TABLE 2B. EXCLUSION CRITERIA

1	Previous treatment with T-DM1 or anthracyclines, either in the (neo) adjuvant or in the metastatic setting.
2	>2 chemotherapeutic regimens for locally advanced incurable disease or metastatic disease.
3	Patients who have received prior anti-cancer treatment within 3 weeks.
4	Clinical significant impairment in cardiopulmonary function.
5	Patients with CNS involvement clinically unstable, receiving steroid therapy or who have received radiotherapy ≤ 4 weeks prior to starting study.
6	G≥3 Peripheral neuropathy, per the NCI CTCAE, v4.0.
7	Current known active infection with HIV, hepatitis B, and/or hepatitis C virus.
8	Women who are pregnant or breast-feeding.

ACCRUAL

- A total of 12-24 patients will be enrolled at four sites in Spain and France.
- Accrual was opened on September 2015.
- To date, six patients have been enrolled.

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