BACKGROUND

- T-DM1, for the treatment of HER2-positive MBC, has been assessed for both clinical efficacy and safety in several phase II/III trials. This is a dose escalation trial in breast cancer and trastuzumab-pretreated patients. 

- 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 formulations of doxorubicin have shown a reduction in the combination of doxorubicin and trastuzumab induces synergistic activity in the advanced setting, several strategies to improve T-DM1 efficacy are currently being evaluated.

OBJECTIVES

- The primary objectives of this trial are 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 2 cycles of treatment (Table 1).

- The secondary objectives include:
  1. Safety, in particular emphasis on cardiac safety evaluated by left ventricular ejection fraction, high-sensitivity troponin I, and left ventricular systolic dysfunction.
  2. Pharmacokinetics.
  3. Antitumor activity in the advanced setting, several strategies to improve T-DM1 efficacy are currently being evaluated.

MTD is defined as the highest dose level at which ≤1 of 6 pts experience dose-limiting toxicity (DLT) during the first 2 cycles of treatment (Table 1).

- Grade ≥3 non-hematological not considered as DLT.

- G1 or G2 epistaxis may have cauterization and this should not be considered a DLT.

- Infusion-related reactions (IRR).

- Grade ≥3 diarrhea recovered to ≤2 after 24 hours of anti-diarrheal treatment.

- Grade ≥3 preventing the start of the 3rd cycle.

- Grade ≥3 nausea or anorexia resolved to ≤2 prior to next cycle.

- G4 thrombocytopenia not recovered before next planned dose.

- G3 nausea, vomiting or diarrhea without appropriate treatment.

- G2 requiring interruption of treatment for ≥21 days.

- Not to receive >100% of the dose level going into Cycle 3, Day 1.

- Cardiac toxicity (Level 1):

  - Sudden death within 24 hours of treatment.

  - Heart failure WHO class III/IV and/or LVSD absolute drop ≥15% with <15% LVSD.

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- Grade ≤1 toxicities, except for alopecia.

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- Adequate bone marrow and organ function.

- Written informed consent.

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

- T-DM1 60 mg/m2

- NPLD: 3.6 mg/kg

- Expanding 1st dose escalation cohort: 1 every three weeks.

- Patients who have received prior anti-cancer treatment within 3 weeks.

- Patients with CNS involvement clinically unstable, receiving steroid therapy or who have received prior conventional radiotherapy ≤4 weeks prior to starting treatment.

- Current known active infection with HIV, hepatitis B, and or hepatitis C virus.

- Female patients who are pregnant or breast-feeding.

- MTD: March 2016; N = 32 pts. 

- NPLD: non-pegylated liposomal doxorubicin.

- Antitumor activity.

- Safety, with special emphasis on cardiac safety evaluated by left ventricular ejection fraction, high-sensitivity troponin I, and left ventricular systolic dysfunction.

- T-DM1: Trastuzumab emtansine.

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- ACCRUAL

- A total of 12-24 patients will be enrolled at four sites in Spain (Barcelona, Madrid, Valencia, and Bilbao).

- ACP: Adjuvant chemotherapy protocol.


- T-DM1: Trastuzumab emtansine.

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

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