# HERMIONE: A Phase 2, Randomized, Open Label Trial Comparing MM-302 Plus Trastuzumab With Chemotherapy of Physician's Choice Plus Trastuzumab, In Anthracycline Naïve HER2-positive, Locally Advanced/Metastatic Breast Cancer Patients, Previously Treated With Pertuzumab And Ado-trastuzumab emtansine (T-DM1)

Kathy Miller[1], Javier Cortes[2], Sara A. Huvitz[3], Ian E. Krop[4], Debu Tripathy[5], Sunil Verma[6], Michelle Dionne[7], Karen Campbell[7], Joseph Reynolds[7], Thomas Wickham[7], Istvan Molnar[7], Denise Yardley[8,9]

[1]Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN; [2]Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [3]University of California Los Angeles, Los Angeles, CA; [4]Dana-Farber Cancer Institute, Boston, MA; [5]MD Anderson Cancer Centre, Houston, TX; [6]Sunnybrook Odette Cancer Center, Toronto, Canada; [7]Merrimack Pharmaceuticals, Cambridge, MA; [8]Sarah Cannon Research Institute, Nashville, TN; [9]Tennessee Oncology, PLLC, Nashville, TN

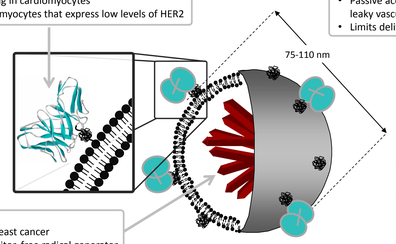
## Background

- Despite improvements in treatment with newly approved HER2-targeted therapies such as pertuzumab and ado-trastuzumab emtansine (T-DM1), HER2-positive metastatic breast cancer (MBC) remains a serious and life-threatening disease
- Historically anthracyclines have been broadly used in breast cancer, irrespective of disease state, however their use is decreasing due to the recognition of associated cardiac toxicity and development of agents with similar efficacy (*Giordano et al., J. Clin Oncol. 2012, 30(18)*).
- MM-302 is an HER2-targeted antibody-liposomal doxorubicin conjugate. MM-302 is designed to bring a potentially safer and more effective anthracycline treatment to a growing population of anthracycline naïve HER2-positive MBC patients
- A Phase 1 study in heavily pretreated HER2-positive MBC patients evaluated the safety of MM-302 alone, in combination with trastuzumab and in combination with trastuzumab and cyclophosphamide (*LoRusso et al., AACR 2015, April 20, 2015*).
  - MM-302 appears to be well tolerated and anthracycline naïve patients appear to have higher response rate and longer progression free survival (PFS) than anthracycline exposed patients
- The HERMIONE trial is a Phase 2/3, registration directed study designed to address an unmet medical need in HER2-positive anthracycline naïve locally advanced breast cancer (LABC)/MBC patients following progression on pertuzumab and ado-trastuzumab emtansine

## MM-302 and Mechanism of Action

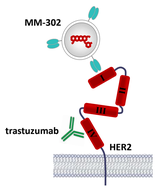
**Anti-HER2 scFv antibody (F5)-PEG-DSPE conjugate**
- Targets liposome to HER2-overexpressing cells
- Promotes internalization into HER2-overexpressing tumor cells
- Does not inhibit HER2 signaling in cardiomyocytes
- Little or no uptake into cardiomyocytes that express low levels of HER2

**Liposome**
- Provides extended half-life and circulation time
- Stably encapsulates doxorubicin
- Passive accumulation in tissues possessing leaky vasculature (such as tumors)
- Limits delivery to cardiac tissue

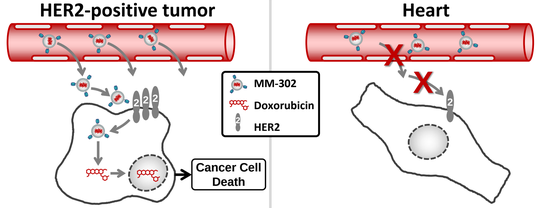



**Doxorubicin crystals**
- Effective cytotoxic agent in breast cancer
- DNA intercalator, TOP2A inhibitor, free radical generator

Schematic of MM-302, a HER2-targeted PEGylated liposomal doxorubicin. MM-302 consists of three principal components:
- anti-HER2 antibodies
- liposome
- doxorubicin




- MM-302 binds to extracellular subdomain I of HER2
- Trastuzumab binds to extracellular subdomain IV of HER2




- MM-302 accumulates in tumors via leaky vasculature
- Once in the tumor microenvironment, MM-302 binds to tumor cells that overexpress HER2
- After internalization MM-302 releases doxorubicin inside the cell




- Intact vasculature in the heart prevents extravasation
- Cardiomyocytes express HER2 below the threshold required for MM-302 uptake (*Reynolds et al., Toxicol Appl Pharmacol. 2012, 262(1); Hendriks et al., Mol Cancer Ther, 2013, 12(9)*)

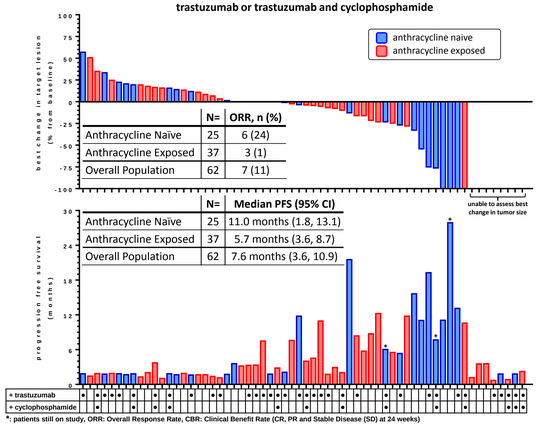
## MM-302 Phase 1

- A Phase 1 study has been conducted in HER2-positive MBC patients

| | MM-302 monotherapy | MM-302 + trastuzumab | MM-302 + trastuzumab + cyclophosphamide |
|---|---|---|---|
| n= | 34 | 22 | 13 |

- Median of 4 prior regimens for MBC
- Neutropenia was the most common grade 3/4 adverse event and occurred in 7 patients
- Adverse events observed in >20% of the population included fatigue, nausea, constipation, decreased appetite, vomiting, cough, diarrhea, neutropenia, stomatitis and dyspnea
- Cardiac events have been infrequent and none were symptomatic or serious adverse events
  - *6 out of 69 patients (6%) experienced declines in ejection fraction*
    - *4 patients had reversible declines*
    - *1 patient had a decline to 47% noted at off study assessment*
    - *1 patient twice had a decline to 45-50% (Grade 1 heart failure)*
- 11 patients have had cumulative anthracycline exposure exceeding 550 mg/m$^2$ without a reduction in left ventricular ejection fraction
- Alopecia observed in ~10% and hand foot syndrome in ~4% of patients

**Patients treated with ≥30 mg/m$^2$ MM-302 alone, in combination with trastuzumab or trastuzumab and cyclophosphamide**




| | N= | ORR, n (%) |
|---|---|---|
| Anthracycline Naïve | 25 | 6 (24) |
| Anthracycline Exposed | 37 | 3 (1) |
| Overall Population | 62 | 7 (11) |

| | N= | Median PFS (95% CI) |
|---|---|---|
| Anthracycline Naïve | 25 | 11.0 months (1.8, 13.1) |
| Anthracycline Exposed | 37 | 5.7 months (3.6, 8.7) |
| Overall Population | 62 | 7.6 months (3.6, 10.9) |

*: patients still on study, ORR: Overall Response Rate, CBR: Clinical Benefit Rate (CR, PR and Stable Disease (SD) at 24 weeks)

*Data presented by Patricia LoRusso at AACR 2015 (April 20, 2015 in Philadelphia Pennsylvania*

## HERMIONE Study Design

**The HERMIONE trial (NCT02213744) is a Phase 2, registration directed, randomized 2-arm, multicenter, multinational, open-label study**

At randomization, patients will be stratified by:
- Geographic regions (*North America/Western Europe/Other*)
- Presence of visceral disease (*Yes/No*)
- Number of prior anti-cancer regimens for metastatic disease (*≤3/≥4*)

**250 patients** → **randomized 1:1**

**Arm A (Experimental Arm)**
6 mg/kg trastuzumab*, Q3W
+ 30 mg/m$^2$ MM-302, Q3W

**Arm B (Control Arm)**
6 mg/kg trastuzumab*, Q3W
+ Chemotherapy of Physician's Choice
(capecitabine, gemcitabine or vinorelbine)

**: 8 mg/kg loading dose of trastuzumab*

The study will use two independent committees for safety assessment:
- The Data Safety Management Board (DSMB) will monitor accumulating patient safety data
- The Cardiac Review Committee (CRC) will adjudicate cardiac toxicity and other cardiac events

## Key Eligibility

**Inclusion Criteria**:
- Patients must have HER2-positive breast cancer as defined by ASCO/CAP 2013 guidelines that is confirmed by a central laboratory
- Patients must have been previously treated with trastuzumab in any setting
- Patients must have progressed on, or be intolerant to, treatment with the following therapies:
  - Pertuzumab in the LABC/MBC setting or development of disease recurrence within 12 months of neoadjuvant/adjuvant treatment
  - Ado-trastuzumab emtansine in the LABC/MBC setting
- Patients must have an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1
- Patients must have a left ventricular ejection fraction >50%

**Exclusion Criteria**:
- Patients previously treated with doxorubicin, liposomal doxorubicin, epirubicin, mitoxantrone or any other anthracycline derivative
- Subjects with central nervous system (CNS) metastases, unless they have been treated and are stable without symptoms for 4 weeks after completion of treatment and must be off steroids for at least 4 weeks prior to treatment
- Patients with any class NYHA congestive heart failure (CHF) or heart failure with preserved ejection fraction (HFPEF)

**There is no limit on number of prior lines of therapy**

## Primary Objective

- To determine whether the combination of MM-302 plus trastuzumab is more effective than chemotherapy of physician's choice (CPC) plus trastuzumab based on progression free survival (PFS) as assessed by an independent blinded review of tumor assessments

## Exploratory Objectives

- To explore the correlation between biomarkers from tumor tissue and and/or blood samples and clinical outcome in those patients that opt to consent
- Quality of Life (QoL) between the two arms
- To determine the population PK of MM-302 and to estimate the typical values for inter-patient variability of PK parameters (including covariate effects on inter-patient variability in this patient population
- To compare the rate of development/time to development of CNS progression and development of new CNS metastases

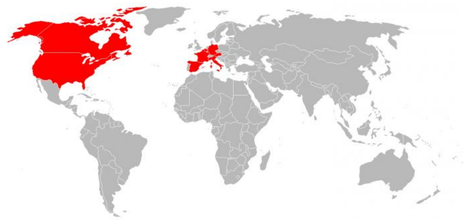
## Secondary Objectives

- Investigator assessed PFS
- Overall Survival (OS)
- Landmark overall survival rate (6 months and 1 year)
- Time to Treatment Failure (TTF)
- Objective Response Rate (ORR) based on both independent and investigator review of tumor assessments
- Duration of Response (DoR) based on both independent and investigator review of tumor assessments

## Statistical Methods

- A total of 191 events is required for at least 90% power to detect a 60% improvement in PFS (Hazard Ratio 0.625)
- Hypothesis testing for the primary endpoint will be conducted at a two sided 0.05 significant level using a stratified log rank test

**The study will occur in approximately 110 sites**



| North America (~75): | Western Europe (~35): | |
|---|---|---|
| Canada | Austria | Germany |
| United States | Belgium | Italy |
| | France | Spain |

For more information please visit www.hermionetrial.com or www.merrimack.com