Phase 1b study of EZH1/2 inhibitor valemetostat in combination with trastuzumab deruxtecan in subjects with HER2 low/ultra-low/null metastatic breast cancer

Senthil Damodaran[1], Angela Marx[1], Toshiaki Iwase[3], Ying Yuan[2], Jangsoon Lee[3], Carlos H.Barcenas[1], Naoto T. Ueno[3]
Department of Breast Medical Oncology[1], Department of Biostatistics[2], MD Anderson Cancer Center, Houston, TX.
Translational Clinical Research Program[3], Cancer Biology Program[4], University of Hawai'i Cancer Center, Honolulu, HI.

RATIONALE AND BACKGROUND

- Trastuzumab deruxtecan (T-DXd), is an antibody-drug conjugate, composed of an anti-HER2 antibody conjugated to topoisomerase I payload
- T-DXd, is approved for clinical use in HER2-positive, HER2-low (IHC 1+ or IHC 2+/ ISH negative) and HER2-ultralow, HR-positive metastatic breast cancer (MBC).
- Valemetostat is an oral, selective dual inhibitor of enhancer of zeste homolog 1 and 2 (EZH1/2), methyltransferases that specifically methylate histone H3 lysine 27. It is currently approved in for patients with relapsed or refractory adult T-cell leukemia/lymphoma and and peripheral T-cell lymphoma (PTCL) in Japan.
- EZH2-mediated PP2A inactivation has been shown to confer resistance to HER2-targeted therapy.
- Valemetostat has been shown to upregulate Schlafen11 (SLFN11), a putative DNA/RNA helicase that regulates sensitivity to DNA damaging agents. Thus, valemetostat may epigenetically modulate sensitivity to T-DXd
- This study examines the safety and anti-tumor activity of valemetostat in combination with T-DXd in subjects with HER2 low/ultra-low/null MBC (NCT05633979).

HYPOTHESIS

- Valemetostat potentiates the anti-tumor activity of T-DXd in HER2 low/ultra-low/null metastatic breast cancer

PS5-09-22

Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from SABCS® and the author

OBJECTIVES

Primary

- To evaluate safety and determine the maximum tolerated dose (MTD)/recommended dose for expansion (RDE) of valemetostat in combination with T-DXd
- To evaluate the objective response rate (ORR) of valemetostat at the RDE in combination with T-DXd

Secondary

- To determine ORR; defined as % of subjects who achieve complete response (CR) or partial response (PR) by RECIST 1.1 criteria.
- To determine duration of response (DoR), progression free survival (PFS), and overall survival (OS).
- To determine clinical benefit rate (CBR) defined as stable disease (SD) ≥ 16 weeks + PR + CR.
- To evaluate safety of valemetostat in combination with T-DXd.
- To evaluate the pharmacokinetics (PK) of both the drugs in combination.
- To evaluate the immunogenicity of T-DXd

Exploratory

- To investigate pharmacodynamic biomarkers
- To identify predictive biomarkers of clinical benefit.

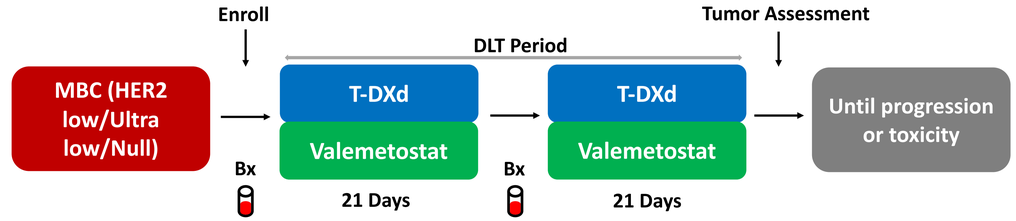
AGENTS AND DOSING

T-DXd | 5.4 | mg/kg IV Q3W

Valemetostat | 50 | 75 | 100* | 150 | 200 | mg PO QD

*Dose Level 1

TRIAL DESIGN



ELIGIBILITY

Inclusion

- Pathologically confirmed HER2 low/ultra-low/null metastatic breast cancer [Low HER2 defined as IHC1 or 2+ (ISH–ve), Ultra-low defined as IHC 0 with faint/barely perceptible incomplete staining in ≤10% tumor cells, HER2 null defined as IHC 0 without any observed tumor cell staining (Ventana 4B5 assay)]
- ECOG performance status ≤1
- Measurable disease as per RECIST 1.1
- Received at least one line of chemo in the metastatic setting
- Progressed and would no longer benefit from endocrine therapy (HR+).
- Adequate organ function

Exclusion

- Prior treatment with any anti-HER2 therapy or EZH inhibitors
- Symptomatic brain metastases or cord compression
- Uncontrolled or significant cardiovascular disease
- Interstitial lung disease
- Current use of moderate or strong CYP3A inducers

STATISTICS

Dose Escalation

Bayesian optimal interval (BOIN) design employed with conventional 3+3 design run-in to find the MTD. Target toxicity rate for MTD is 25%, with approx. 15 evaluable subjects. DLT period – first 2 cycles.

Dose Expansion

Performed at the RDE using the 2-stage Bayesian optimal dose-expansion (BOP2) design. In the first stage, 13 evaluable patients (including those treated at the RDE in the dose-escalation part) will be enrolled. If < 5 patients respond in the first stage, the study will be stopped for futility. If ≥ 5 responses are observed, 13 additional evaluable patients will be enrolled. If 11 or more responses are observed among the total of 26 patients, the treatment will be regarded as promising. This two-stage design yields 78% power under the alternative hypothesis of ORR=50% (null ORR = 30%) while controlling the one-sided type I error at 10%.

REFERENCES

- Denkert, C., et al., Clinical and molecular characteristics of HER2-low-positive breast cancer: pooled analysis of individual patient data from four prospective, neoadjuvant clinical trials. The Lancet Oncology, 2021. 22(8): p. 1151-1161
- Modi, S., et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med , 2022 387(1): 9-20.
- Bao Y, Oguz G, Lee WC, et al: EZH2-mediated PP2A inactivation confers resistance to HER2-targeted breast cancer therapy. Nat Commun 11:5878, 2020
- Gardner, E.E., et al., Chemosensitive Relapse in Small Cell Lung Cancer Proceeds through an EZH2-SLFN11 Axis. Cancer Cell, 2017. 31(2): p. 286-299.

Study Supported by Daiichi Sankyo