Phase 1 dose escalation of XMT-1522, a novel HER2-targeting antibody-drug conjugate (ADC), in patients with HER2-expressing breast, lung and gastric tumors

Erika Paige Hamilton1; Minal A. Barve2; Aditya Bardia3; Muralidhar Beeram4; Johanna C. Bendell1; W. Jeffrey Edenfield5; Anne Noonan6; Rebecca Mosher7; Eric Hailman7; Donald Alan Bergstrom7; Howard A. Burris III1; Hatem Hussein Soliman8

Sarah Cannon Research Institute and Tennessee Oncology, PLLC, Nashville, TN
2 Mary Crowley Cancer Research Institute, Dallas, TX
3 Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA
4 Southwest Texas Accelerated Research Therapeutics, San Antonio, TX
5 University of South Carolina, Greenville, SC
6 The Ohio State University, Comprehensive Cancer Center, Columbus, OH
7 Mersana Therapeutics, Cambridge, MA
8 Moffitt Cancer Center, Tampa, FL

Introduction

• There is current medical need for effective therapies for patients with HER2-positive breast cancer after treatment with trastuzumab, pertuzumab and T-DM1, and for HER2-positive gastric cancer after treatment with trastuzumab.
• There are no approved HER2-directed therapies for HER2-low (HER2 NC 0-1+) or HER2-negative (HER2 0) gastric cancer or for HER2-expressing RCC.

XMT-1522 is a patient HER2-targeting ADC with a high drug-to-antibody ratio and a controlled bystander effect.

• Preliminary safety and efficacy results are available from ongoing dose escalation in patients with HER2-expressing breast, gastric or lung cancer.

Methodology

• Patients with HER2-expressing (by local assessment) breast, gastric, or lung tumors.
• XMT-1522 dosed IV every 3 weeks in 21-day cycles until disease progression or unacceptable toxicity.
• Dose escalation: +1 dose with optional 4th patient at each dose level.
• Intertreatment dose escalation allowed.

Phase 1a Dose Escalation and Dose Expansion

Objectives – Dose Escalation

• Assess safety and tolerability of XMT-1522 administered IV every 3 weeks with standard anti-HER2-directed treatment.
• Assess pharmacokinetics of XMT-1522 and its metabolites.
• Assess preliminary efficacy of XMT-1522.
• Assess development of confirmed or progressive disease criteria.

• Retrospectively evaluate the relationship of tumor response with HER2 expression, expression of other target genes, and patient demographics.

Key Dose Escalation Eligibility Criteria

• Advanced HER2-expressing tumors – by local assessment.
• Breast cancer: HER2 NC 2 or 3+.
• RCC: IMDC PC, M, or I+ in all subgroups.
• GC: GC, MC, or I+ in all subgroups.
• Patients must have progressive disease after standard of care therapies.
• Adequate organ function at baseline.
• Measurable disease per RECIST 1.1.
• ECOG performance status 0–1.
• LVEF ≥ 50% or normal and no history of significant cardiac disease.

Dose-Limiting Toxicity (DLT) Criteria

• DLTs are defined as Grade 3 or higher drug-related adverse event occurring during Cycle 1, with exceptions of detailed criteria for gastrointestinal events, liver enzyme elevations, changes in electrolytes, neutropenia, and thrombocytopenia.

• Adverse events, concurrent medications, PK, and laboratory, echocardiography, OOP
• Toxicity can be dose limiting if REDUCT 1.1.

Assessments

• Disease: PD on cycle 1 + DLT criteria.

• Study Design

• Treatment Related Adverse Events Occurring in >10% of Patients Through D6L (N = 22)

• TRAEs in <10% of Patients Through D6L (N = 22)

• Pharmacodynamic Analysis (Cycle 1)

• Pharmacodynamic analysis of time-dependent and rate-dependent toxicities.

• Grade 3 Treatment-Related Adverse Events (Through D6L)

• Pharmacodynamics Cycle 1

• Conclusions

• XMT-1522 is the first ADC on the Dollysafe platform to enter the clinic.
• Treatment has been well-tolerated, with most AEs being low grade and manageable; the most common treatment-related AEs were fatigue, diarrhea, nausea, vomiting, anemia, and transient elevations of AST and ALT.
• Preliminary safety of XMT-1522 has been seen at doses 1x 16 mg/m2 with overall best response of SD or better in 11 of 15 patients and one confirmed PR at D6L (21.3 mg/m2).
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