XMT-1660: A Phase 1b Trial of a B7-H4–targeting Antibody-Drug Conjugate (ADC) in Endometrial, Ovarian, and Breast Cancers

Hamilton, Erika[1]; Chaudhry, Arvind[2]; Spira, Alexander[3]; Adams, Sylvia[4]; Abuhadra, Nour[5]; Giordano, Antonio[6]; Parajuli, Ritesh[7]; Han, Hyo[8]; Weise, Amy[9]; Collins, Scott D[10]; Li, Fu[10]; Marchesani, Aubri[10]; Josephs, Kate[10]; Im, Ellie[10]; Kalinsky, Kevin[11]

[1]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [2]Summit Cancer Centers, Spokane Valley, WA; [3]Virginia Cancer Specialists, Fairfax, VA; [4]NYU Langone Health, New York, NY; [5]Memorial Sloan Kettering Cancer Center, New York, NY; [6]Dana-Farber Cancer Institute, Boston, MA; [7] University of California Irvine, Orange, CA; [8]Moffitt Cancer Center, Tampa, FL; [9]Henry Ford Health, Detroit, MI; [10]Mersana Therapeutics, Inc., Cambridge, MA; [11]Winship Cancer Institute at Emory University, Atlanta, GA

BACKGROUND

Unmet Medical Need in Gynecologic and Breast Cancers

- Patients with advanced/recurrent endometrial cancer (EC) have a poor prognosis and limited existing therapeutic options[1]
  - A subset of patients may be eligible for treatment with PD-1 inhibitors and/or targeted therapies,[1] but reported OS remains low (17–18 months pembrolizumab plus lenvatinib vs 11–12 months chemotherapy) and rates of dose reduction (66.5%) and treatment discontinuation (33.0%) are high[2]
- Ovarian cancer (OC) is the second most common gynecologic malignancy, and the majority of patients are diagnosed at an advanced stage.[3,4] The standard of care (SOC) is platinum-based therapy, and nearly all patients will progress; less than half will survive for ≥5 years from diagnosis[4-6]
- Breast cancer (BC) is the most common cancer diagnosed in women[3]; ~70% of patients are diagnosed with HR+/HER2- disease, and 10–15% of patients are diagnosed with triple-negative disease (TNBC)[7,8]
  - Among BC subtypes, patients with TNBC have the poorest prognosis and survival
- Despite some recent therapeutic advances, there is still a large unmet medical need for patients with advanced endometrial, ovarian, and breast cancers, as there is no clear treatment algorithm for the majority of patients who progress on the current SOC[9-12]

XMT-1660: An Investigational B7-H4–targeting Dolasynthen ADC

- B7-H4 is part of the CD28/B7 family of immune co-stimulatory and co-inhibitory molecules, and it promotes tumorigenesis by suppressing anti-tumor immunity[13]
- B7-H4 is broadly expressed in endometrial, ovarian, and breast cancers (Fig 1)[14]; protein expression is limited in healthy/normal tissue[15]
- XMT-1660 is a B7-H4–directed Dolasynthen ADC with a precise, target-optimized drug-to-antibody ratio (DAR) and clinically validated DolaLock microtubule inhibitor payload with controlled bystander effect

XMT-1660

Antibody: Monoclonal anti–B7-H4

Linker: Polymer scaffold; cleavable ester linker

Payload: AF-HPA (DolaLock-controlled bystander effect)

DAR: 6 (Dolasynthen platform)

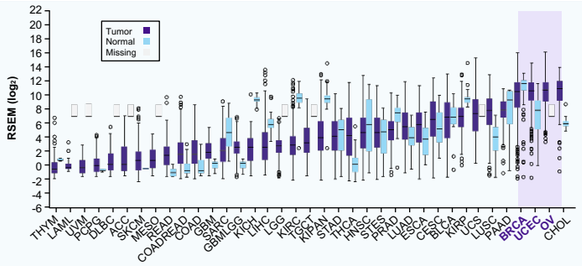

Figure 1: B7-H4 differential plot using FIREBrowse[14]; BRCA, breast invasive carcinoma; OV, ovarian; UCEC, uterine corpus endometrial carcinoma

Preclinical Data

- In vivo anti-tumor activity of XMT-1660 has been demonstrated in endometrial, ovarian, and breast PDX models (Fig 2, Fig 3), providing rationale for clinical investigation

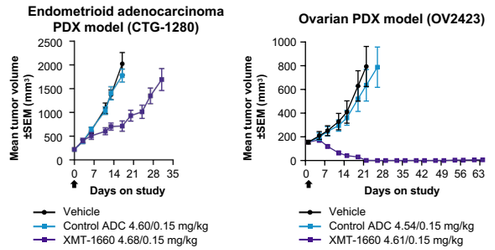

Figure 2: In vivo anti-tumor activity of XMT-1660 in endometrial and ovarian PDX models[a]

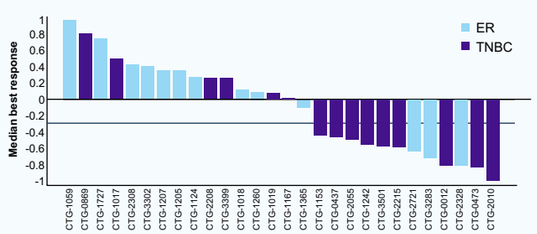

Figure 3: Anti-tumor effect of XMT-1660 in an unselected panel of patient-derived xenograft models of BC (n=28) following a single dose of XMT-1660 at 4.71/0.15 mg/kg (mAb/payload).[16]
A single dose of XMT-1660 elicits a range of anti-tumor activity in models of human BC and shows anti-tumor activity in both TNBC and ER-positive models, including in models derived from previously treated tumors. A relationship is seen between XMT-1660 efficacy and B7-H4 expression; stronger anti-tumor activity of XMT-1660 tends to be more frequent in models with higher B7-H4 expression.

METHODS

Study Design and Eligibility

- This Phase 1, first-in-human trial will examine XMT-1660 safety and efficacy in both dose escalation (DES) and expansion (EXP) phases in patients with endometrial, ovarian, and breast cancers following progression on SOC therapies
- Patients are not selected by B7-H4 status, but baseline tumor samples are collected for retrospective analysis

Key Enrollment Criteria for Both DES and EXP Phases Include:

- Recurrent or advanced/metastatic disease
- Measurable disease as defined by RECIST v1.1
- ECOG PS 0–1
- Recovered to Grade ≤1 toxicity from previous therapies, with exception of Grade 2 peripheral neuropathy, alopecia

Dose Escalation (N=~42)

Key Enrollment Criteria

- **EC:** 1+ LoT in advanced/metastatic setting
- **OC:** 2+ LoT in advanced/metastatic setting
- **TNBC:** 2+ LoT in advanced/metastatic setting
- **HR+/HER2- BC:** 1+ LoT in advanced/metastatic setting, which must have included CDK4/6i plus ET

BOIN Design

- DL1
- DL2
- DL3
- DL4
- DL5
- DL6
- DL7

IV dosing q21 days

Tumor assessment q2 cycles

Primary Endpoints

- RP2D
- Safety and tolerability

Secondary Endpoints

- ORR
- DOR

Dose Expansion – Patients will be divided into 3 cohorts

Key Enrollment Criteria

- **EC/OC (N=35):**
  - **EC:** confirmed endometrial carcinoma, 1+ lines of platinum-doublet therapy; no more than 3 LoT for recurrent/metastatic disease (not including hormonal therapy)
  - **OC:** confirmed HGSOC, platinum-resistant disease; 1–4 prior LoT including at least 1 platinum-containing regimen
- **TNBC (N=30):** 1–3 prior lines of CT in the metastatic setting[b]
- **HR+/HER2- BC (N=35):** ≤2 prior lines of CT for A/MBC; must have received CDK4/6i plus ET[b]

RP2D

IV dosing q21 days

Tumor assessment q2 cycles

Primary Endpoints

- Safety and tolerability
- ORR
- DOR

Secondary Endpoints

- PK
- ADA
- B7-H4 expression
- PD-L1 expression
- Additional biomarkers

Statistical Considerations

- BOIN design will be used in the DES to determine the RP2D
- Additional patients may be enrolled in both the DES and EXP based on emerging data

CONCLUSIONS

- XMT-1660 is a novel, investigational ADC targeting B7-H4, an immune co-inhibitory molecule
- DES and EXP phases of this first-in-human, Phase 1 study will evaluate the preliminary safety and efficacy of XMT-1660 monotherapy in EC, OC, TNBC, and HR+/HER2- BC
  - Primary endpoint of DES is to establish the RP2D and assess safety
  - Primary endpoint of EXP is to assess preliminary efficacy and safety at the RP2D
- Targeted therapeutic options for patients with endometrial, ovarian, and breast cancers that progress on the SOC therapies are needed, as current options are limited for this patient population
- ClinicalTrials.gov registry: NCT05377996

ACKNOWLEDGMENTS

We would like to thank the patients, their families, and the site staff for making this study possible.

This study is sponsored by Mersana Therapeutics, Inc.

Editorial support for this poster was provided by BluPrint Oncology.

REFERENCES

1. Marth C et al. *Int J Gynecol Cancer*. 2022;32(1):93–100. **2.** Makker V et al. *N Engl J Med*. 2022;386(5):437–448. **3.** American Cancer Society. *Cancer Facts & Figures 2022*. Atlanta, GA: American Cancer Society; 2022. **4.** National Cancer Institute. Cancer stat facts: ovarian cancer. Accessed August 2, 2022. https://seer.cancer.gov/statfacts/html/ovary.html **5.** NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Ovarian Cancer V.3.2022. Published July 25, 2022. Accessed August 11, 2022. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf **6.** Hanker LC et al. *Ann Oncol*. 2012;23(10):2605–2612. **7.** National Cancer Institute. Cancer stat facts: female breast cancer subtypes. Accessed August 2, 2022. https://seer.cancer.gov/statfacts/html/breast-subtypes.html **8.** American Cancer Society. Triple-negative breast cancer. Accessed August 2, 2022. https://www.cancer.org/cancer/breast-cancer/about/types-of-breast-cancer/triple-negative.html **9.** Gupta G et al. *Ann Breast Cancer Ther*. 2020;4(1):48–57. **10.** Qui H et al. *Front Oncol*. 2022;12:887773. **11.** Makker V et al. *Nat Rev Dis Primers*. 2021;7(1):88. **12.** Vanacker H et al. *Cancer Treat Rev*. 2021;99:102255. **13.** Leung J, Suh W-K. *Immune Netw*. 2014;14(6):265–276. **14.** FIREBrowse. Accessed August 2, 2022. http://firebrowse.org/viewGene.html?gene=vtcn1 **15.** Liang L et al. *Hum Pathol*. 2016;57:1–6. **16.** Collins SD et al. AACR Annual Meeting 2022; Abstract 1756.

ADDITIONAL INFORMATION

Downloadable PDF copies of this poster obtained through Quick Response (QR) code are for personal use only and may not be reproduced without permission from IGCS and the author of this poster.

For more information on this study, visit ClinicalTrials.gov page NCT05377996 via QR code provided or contact medicalinformation@mersana.com

[a] ADC dose levels are shown as mAb/payload mg/kg. [b] PARPi is allowed for patients with a *BRCA* mutation, and this is not counted toward an LoT.

ADA, anti-drug antibody; ADC, antibody-drug conjugate; AF-HPA, auristatin F-hydroxypropylamide; A/MBC, advanced or metastatic breast cancer; BC, breast cancer; BOIN, Bayesian optimal interval; *BRCA*, BRCA DNA repair associated gene; CD, cluster of differentiation; CT, chemotherapy; DAR, drug-to-antibody ratio; DES, dose escalation; DL, dose level; DOR, duration of response; EC, endometrial cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; ET, endocrine-based therapy; EXP, dose expansion; HER2, human epidermal growth factor receptor 2; HGSOC, high-grade serous ovarian cancer; HR, hormone receptor; IV, intravenous; LoT, line of treatment; mAb, monoclonal antibody; OC, ovarian cancer; ORR, objective response rate; OS, overall survival; OV, ovarian; PARPi, poly (ADP-ribose) polymerase inhibitor; PD-1, programmed death receptor 1; PD-L1, programmed death receptor-ligand 1; PDX, patient-derived xenograft; PK, pharmacokinetics; q, every; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended Phase 2 dose; RSEM, relative standard of the mean; SEM, standard error of the mean; SOC, standard of care; TNBC, triple-negative breast cancer; UCEC, uterine corpus endometrial carcinoma.

IGCS 2022 ANNUAL GLOBAL MEETING NEW YORK CITY

TiP Abstract 1420