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

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BACKGROUND

Unmet Medical Need in Gynecologic and Breast Cancers

- Breast cancer (BC) is the most common cancer diagnosed in women[1]; ~70% of patients are diagnosed with HR+/HER2– disease, and 10–15% of patients are diagnosed with triple-negative disease (TNBC)[2,3]
  - Among BC subtypes, patients with TNBC have the poorest prognosis and survival
- While great advances have been made recently in recurrent endometrial cancer (EC) with immunotherapies[4,5], there still remains an unmet need for patients who may not tolerate or may not be eligible for immunotherapy based regimens
  - 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[6]
- Ovarian cancer (OC) is the second most common gynecologic malignancy, and the majority of patients are diagnosed at an advanced stage.[1,7] 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[7,8]
- Despite some recent therapeutic advances, there is still a large unmet medical need for patients with advanced breast, endometrial, and ovarian 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 cell surface immune co-stimulatory and co-inhibitory molecules, and it promotes tumorigenesis by suppressing anti-tumor immunity[13]
- B7-H4 is overexpressed 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 designed with a precise, target-optimized drug-to-antibody ratio (DAR) and proprietary 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)

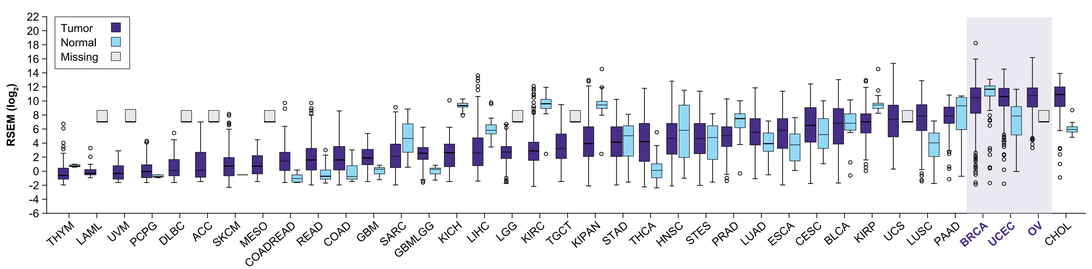

Figure 1: B7-H4 differential plot using FIREBrowse[14]; BRCA, breast invasive carcinoma; OV, ovarian; UCEC, uterine corpus endometrial carcinoma.

Preclinical Data

- In vivo anti-tumor activity of XMT-1660 has been demonstrated in endometrial, ovarian, and breast PDX models (**Fig 2, Fig 3**) without inhibiting B7-H4, providing rationale for clinical investigation

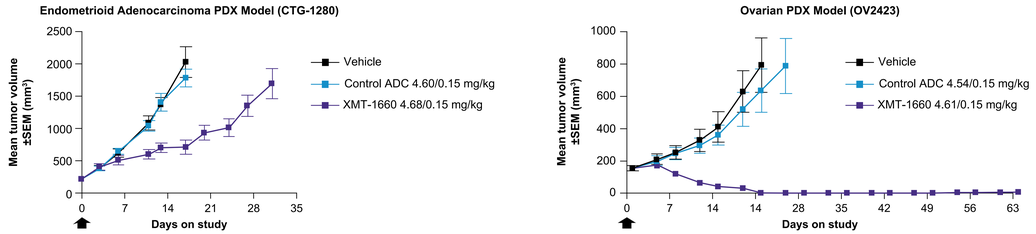

Figure 2: In vivo anti-tumor activity of XMT-1660 in endometrial and ovarian PDX models.[a]

BACKGROUND (cont'd)

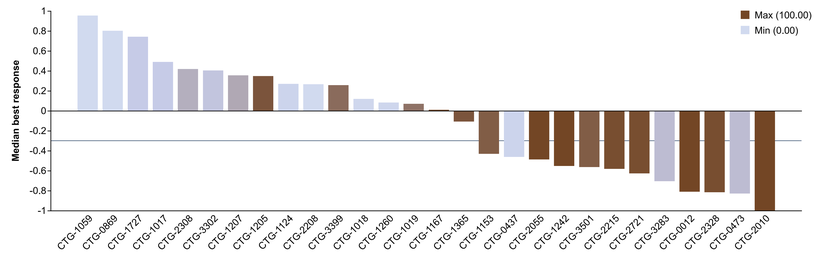

Figure 3: Relationship between B7-H4 IHC TPS score and XMT-1660 anti-tumor activity.
TPS ranged from 0–100 and was calculated based on membrane immunoreactivity. Higher B7-H4 IHC TPS values were associated with response in this sample set. Employing a cutoff, for example TPS75 (TPS high ≥75, TPS low <75), identified 75% (9/12) of responding models. Below a cutoff point of TPS75, 80% (12/15) of models were nonresponsive (MBR less than -0.3 following a single dose of XMT 1660).

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 breast, endometrial, and ovarian 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
- 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
- HR+/HER2- BC: 1+ LoT in advanced/metastatic setting, which must have included CDK4/6i plus ET
- TNBC: 2+ LoT in advanced/metastatic setting
- EC: 1+ LoT in advanced/metastatic setting
- OC: 2+ LoT in advanced/metastatic setting
- Optional backfill cohorts will enroll additional patients at a selected dose level to help determine the RP2D

BOIN Design → IV dosing q 21 days; Tumor assessment q 2 cycles

Primary Endpoints
- MTD (BOIN DES only)
- Safety and tolerability

Secondary Endpoints
- ORR, DOR, DCR
- PK, ADA, nAb

Exploratory Endpoints
- Expression of B7-H4, PD-L1
- Additional biomarkers

Dose Expansion – Patients will be divided into 3 potential cohorts

Key Enrollment Criteria
- HR+/HER2- BC (N≈35): ≤2 prior lines of CT for A/MBC; must have received CDK4/6i plus ET[b]
- TNBC (N≈30): 1–3 prior lines of CT in the metastatic setting[b]
- 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; primary platinum-resistant disease excluded

RP2D → IV dosing q 21 days; Tumor assessment q 2 cycles

Primary Endpoints
- Safety and tolerability
- ORR

Secondary Endpoints
- DOR, DCR
- PK, ADA, nAb

Exploratory Endpoints
- Expression of B7-H4, PD-L1
- Additional biomarkers

Statistical Considerations

- BOIN design will be used in the DES to determine the MTD
- 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 TNBC, HR+/HER2- BC, EC, and OC
  - Primary endpoint of DES is to establish the MTD and assess safety
  - Primary endpoint of EXP is to assess preliminary efficacy and safety at the RP2D
- Targeted therapeutic options for patients with breast, endometrial, and ovarian cancers that progress on the SOC therapies are needed, as current options are limited for this patient population
- ClinicalTrials.gov registry: NCT05377996

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[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; MTD, maximum tolerated dose; nAb, neutralizing 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.

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