Abstract #255157

Phase 1 dose escalation study of XMT-1536, a novel NaPi2b-targeting antibody-drug conjugate (ADC), in patients (pts) with solid tumors likely to express NaPi2b

Poster #3010

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Introduction

- There is a substantial need for effective therapies for patients with platinum-resistant ovarian cancer (PROC), and for patients with lung adenocarcinoma after progression with a platinum doublet and a PD-1/PD-L1 inhibitor
- Treatment outcome in later lines of therapy are poor in PROC and non-small cell lung cancer (NSCLC)
- Responses progressively decline with increasing numbers of treatment lines in ovarian cancer

	Ovarian Cancer*	NSCLC**
ORR	6-15%	6-20%
Median PFS	2-4 mos	3-4 mos
Median OS	5-13 mos	5-12 mos

* I.C.Hanker et al. Annals of Oncology 2012, I.Bruchim et al. EJOGRB 2012, A.N. Gordon et al. JCO 2001, J.Sehouli et al. JCO 2010, P.J Hoskins; Nhu Le Gynecologic Oncology 2005, D.G.Mutch et al. JCO 2007
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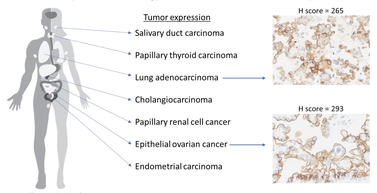
Background

- NaPi2b (SLC34A2) is a sodium-dependent phosphate transporter expressed in a high percentage of tumors from patients with epithelial ovarian cancer and lung adenocarcinoma, as well as other tumor types
- XMT-1536 is a potent NaPi2b-targeting ADC with a high drug-to-antibody ratio (DAR) and a controlled bystander effect
  - Intracellular metabolism of payload generates an active metabolite, auristatin F, which is not a Pgp substrate and not cell-permeable, effectively trapping the drug in the tumor cell
- Preliminary safety and efficacy results are available from ongoing dose escalation in patients with NaPi2b-expressing tumors

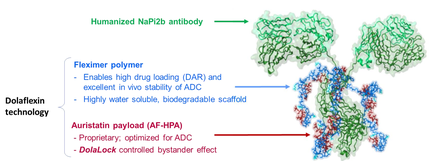
NaPi2b: An Antigen Broadly Expressed in Multiple Tumor Types

- Restricted expression in normal tissues; generally limited to apical surface of ductal structures
- ADC well-tolerated in preclinical toxicology studies in both rat and non-human primate



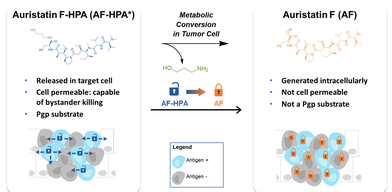
XMT-1536, a Potent, NaPi2b-targeted Dolaflexin ADC

XMT-1536 is an antibody-drug conjugate (ADC)
- Delivers novel auristatin payload specifically to NaPi2b-expressing cells
- Carries ~12 payloads per ADC molecule



DolaLock – Controlled Bystander Effect

Both AF-HPA and AF are highly potent anti-tubulin agents selectively toxic to dividing cells



*HPA = hydroxypropylamide

Methods

Dose Escalation Study Design

ClinicalTrials.gov: NCT03319628

- **Patient population**: patients with ovarian epithelial, non-squamous lung, endometrial, papillary renal, salivary duct, or papillary thyroid cancers, progressing after standard treatments
  - Measurable disease per RECIST 1.1
  - ECOG performance status 0 or 1
  - Archived tissue available for retrospective assessment of NaPi2b expression
  - LVEF ≥ 50% or lower limit of normal and no history of significant cardiac dysfunction
- **Dosing**: XMT-1536 administered IV initially every 3 weeks, amended to every 4 weeks, until disease progression or unacceptable toxicity
- **Escalation design**: single-patient cohorts for first two dose levels, followed by a standard "3 + 3" design with option for 4th patient at each dose level
- **Assessments**: standard assessments including AEs, concomitant medications, safety labs, PK, anti-drug antibodies
  - Ophthalmologic: slit lamp examination
  - Cardiovascular: LVEF (MUGA or ECHO) at baseline and after Cycle 2
  - Tumor imaging (MRI or CT): baseline and every 2nd cycle (6 weeks or 8 weeks), with response assessed per RECIST 1.1

Ongoing Dose Escalation

Planned Expansion Cohorts

MTD or RP2D

Ovarian Cancer Cohort
- High-grade serous histology
- 1-3 prior lines of therapy
- Platinum ineligible
- Archived tumor and fresh biopsy (if medically feasible)

NSCLC Cohort
- Adenocarcinoma histology
- Prior treatment with a platinum doublet and PD-1/L1 inhibitor
- No additional prior treatment with cytotoxics or immunotherapy
- Prior TKIs for patients with targetable abnormalities
- Archived tumor and fresh biopsy (if medically feasible)

Results

Safety

- Data from 37 patients as of 10 May 2019
- Treatment was generally well-tolerated; most AEs were Grade 1-2
- There were no Grade 4 or 5 treatment-related adverse events (TRAEs)
- Low rate of toxicities often associated with microtubule-targeting agents or ADCs, such as neutropenia, ocular toxicities, or peripheral neuropathy

Patient Characteristics

Patient Characteristics (N = 37)		
Age (years)	Median (range)	64 (39-93)
Sex – N (%)	Female Male	32 (86) 5 (14)
ECOG performance status – N (%)	0 1	11 (30) 26 (70)
Tumor type – N (%)	Ovarian, fallopian tube, or primary peritoneal NSCLC Endometrial Papillary renal Salivary duct	22 (59) 4 (11) 8 (22) 2 (5) 1 (3)
Prior lines of therapy for metastatic disease (N = 37)	Median (range)	4 (1-13)
Prior lines of therapy, ovarian cancer only (N = 22)	Median (range)	5 (1-11)

Treatment-Related Adverse Events in ≥10% of Patients

N = 37, data cutoff date 10 May 2019

	N (%)			
Preferred Term	Grade 1	Grade 2	Grade 3	Total
Nausea	12 (32)	2 (5)	0	14 (38)
Fatigue	4 (11)	7 (19)	0	11 (30)
Headache	5 (14)	5 (14)	0	10 (27)
Aspartate aminotransferase (AST) increased	3 (8)	2 (5)	4 (11)	9 (24)
Decreased appetite	1 (3)	6 (16)	0	7 (19)
Blood alkaline phosphatase increased	6 (16)	0	0	6 (16)
Vomiting	4 (11)	1 (3)	0	5 (14)
Gamma-glutamyltransferase (GGT) increased	3 (8)	0	1 (3)	4 (11)
Myalgia	3 (8)	1 (3)	0	4 (11)
Pyrexia	3 (8)	1 (3)	0	4 (11)

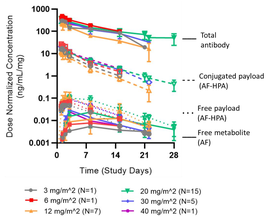
Serious Adverse Events

- SAEs occurred in 13 patients (33%)
- Two treatment-related SAEs:
  - Pyrexia, Grade 2, probably related, DL5 (30 mg/m2)
  - Cardiac failure congestive, Grade 3, possibly related, DL4 (20 mg/m^2)
    - Patient's medical history included chemo- and radiotherapy for breast cancer
- Seventeen SAEs unrelated or unlikely related to treatment occurred in 11 patients: intestinal/small intestinal obstruction (3), disease progression (2), hypoxia (2), pleural effusion (2), abdominal pain, acute blood loss anemia, cellulitis staphylococcal, cerebrovascular accident, hemorrhagic anemia, malignant ascites, pericardial effusion, subdural hematoma, and vaginal hemorrhage

Dose-Limiting Toxicities

- Dose level 6 (40 mg/m^2): Grade 3 AST elevation at Cycle 1, Day 8
  - Resolved to Grade 1 within 21 days
  - Accompanied by Grade 2 ALT elevation which resolved to Grade 1 within 8 days, and Grade 1 alkaline phosphatase elevation
  - No elevation of bilirubin
- Dose level 5A (30 mg/m^2): Grade 3 AST elevation at Cycle 1, Day 8
  - Returned to Grade 2 within 7 days and Grade 1 within 13 days
  - Accompanied by Grade 1 alkaline phosphatase elevation
  - No elevation of ALT or bilirubin

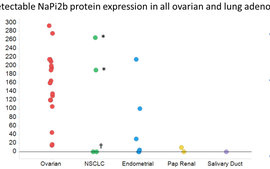
Pharmacokinetics



- PK profiles of XMT-1536 for each analyte shown, normalized to dose (available data, N=30)
- Exposure increases with increasing dose; nearly dose proportional
- PK characteristics consistent with other ADCs approved or in clinical development
- Low systemic exposure of free payload (AF-HPA) or its metabolite (AF) compared to conjugated payload
- No accumulation of free payload or metabolite after multiple doses

NaPi2b Protein Expression Measured by IHC from Archival Patient Tumor Samples

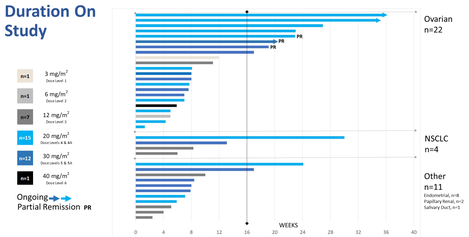
Detectable NaPi2b protein expression in all ovarian and lung adenocarcinoma samples



- Proprietary NaPi2b IHC assay formatted to show a range of NaPi2b expression in tumors
- H-Score measures number of positive tumor cells and staining intensity in NaPi2b IHC assay (H-score range 0-300)
- N=34 available tumor samples

*Confirmed lung adenocarcinoma
†One case of poorly differentiated neoplasm and one case with complex histology

Duration On Study



As of 10 May 2019

Reasons for Discontinuation for Completed Dose Levels

	DL1 3 mg/m² n=1	DL2 6 mg/m² n=1	DL3 12 mg/m² n=7	DL4 & 4A 20 mg/m² n=13	DL5 & 5A 30 mg/m² n=11	DL6 40 mg/m² n=1	Total N=34[b]
Progressive Disease per RECIST	1	1	3	7	6		18 (53%)
Clinical Progression [a]			4	2	3		9 (26%)
Patient Choice				2	1	1	4 (12%)
Physician Choice				2	1		3 (9%)

[a] Death in 3/9 patients, none related to XMT-1536
[b] 3 patients are ongoing

As of 10 May 2019

Outcome Response Evaluable Population

Outcomes in Ovarian Cancer (OC) & Non-small Cell Lung Cancer (NSCLC)	All OC	All NSCLC	OC ≥20mg/m²	NSCLC ≥20 mg/m²	OC + NSCLC ≥20 mg/m²	OC ≥30 mg/m²
N	19	3	16	2	18	7
PR*	3 (16%)	0 (0%)	3 (19%)	0 (0%)	3 (17%)	2 (28%)
SD*	8 (42%)	2 (67%)	6 (38%)	2 (100%)	8 (44%)	3 (43%)
DCR (PR + SD)	11 (58%)	2 (67%)	9 (57%)	2 (100%)	11 (61%)	5 (71%)
Treatment duration >16 wk	8 (42%)	1 (33%)	8 (50%)	1 (50%)	9 (50%)	3 (43%)
PD*	8 (42%)	1 (33%)	7 (43%)	0 (0%)	7 (39%)	2 (28%)

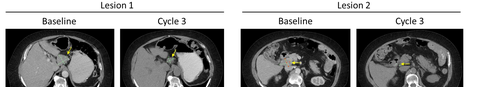
*As measured by RECIST, version 1.1

- Based on objective responses and duration of treatment, clinical activity was observed at doses of 20 mg/m^2 and higher

As of 10 May 2019

Ovarian Cancer Patient with Confirmed PR at Cycle 3

- 70-year-old woman with platinum-resistant high-grade serous ovarian cancer treated at DL 4A (20 mg/m^2)
- 11 prior lines of treatment, with progression on most recent therapy of cyclophosphamide and bevacizumab
- Target lesions of perihepatic and mid-abdominal metastases, 52 and 42 mm respectively
- Decrease of 40% in diameter of target lesions at the end of Cycle 2 (4-week cycles) and 75% at the end of Cycle 3



Conclusions

- NaPi2b, a tumor antigen targeted by XMT-1536, is broadly expressed in ovarian cancer and lung adenocarcinoma
- XMT-1536 is well tolerated at doses up to 30 mg/m^2. The most common TRAEs were Grade 1-2 nausea, fatigue, and headache, and the most frequent Grade 3 TRAE was transient AST elevation
- Objective responses have been observed at doses of 20 mg/m^2 and higher
- In ovarian cancer and lung adenocarcinoma, tumor types selected for the planned expansion phase, 3 PRs and 8 SDs have been observed (ORR 17%, SD 44%, DCR 61%), with treatment duration of >16 weeks in 10 patients (56%), at doses of ≥20 mg/m^2 (N=18)
- MTD has not been reached; enrollment in dose escalation is ongoing at 36 mg/m^2

Acknowledgments

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