3549: Phase 1 expansion study of XMT-1536, a novel NaPi2b-targeting antibody-drug conjugate (ADC): Preliminary efficacy, safety, and biomarker results in patients with previously treated metastatic ovarian cancer (OC) or non-small cell lung cancer (NSCLC)

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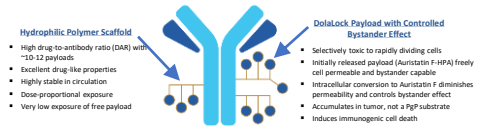
INTRODUCTION

- There is a significant unmet medical need for effective therapies for patients with platinum-resistant ovarian cancer (OC) and for patients with non-small cell lung cancer (NSCLC) adenocarcinoma after disease progression with current standard of care therapies
- In patients with platinum-resistant OC, standard of care treatment such as single-agent pegylated liposomal doxorubicin and topotecan have limited efficacy with response rates of 4% to 12% and median progression-free survival of 3 to 4 months[1,2,3]
- In patients with NSCLC adenocarcinoma, despite advances in treatment options, clinical outcomes remain poor with response rates of 12% to 20% for second- and subsequent- line chemotherapy[4,5,6]

Background

- NaPi2b is a sodium-dependent phosphate transporter with broad expression observed in OC and NSCLC adenocarcinoma and limited expression in normal tissue

Figure 1. XMT-1536, a first-in-class Dolaflexin Antibody-Drug Conjugate Targeting NaPi2b

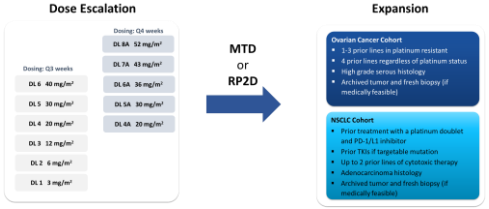


METHODS

Dose Escalation (DES):

- The DES phase is complete (data previously presented at ASCO 2019[7], SGO 2020 [webinar][8]); the MTD was determined to be 43 mg/m^2

Figure 2. XMT-1536 Phase 1b Study Design



Dose Expansion (EXP):

- Expansion dose of 36 mg/m^2 every 4 weeks (q4w) initiated in Aug-2019; 43 mg/m^2 q4w initiated in Dec-2019 (current dose evaluated in EXP)

Primary Objective (EXP):

- Safety and tolerability of MTD/RP2D XMT-1536
- Preliminary anti-neoplastic activity

Secondary Objectives (EXP):

- Association of tumor NaPi2b expression and objective tumor response using an immunohistochemistry (IHC) assay with a broad dynamic range to distinguish tumors with higher and lower NaPi2b expression (as determined in the DES)

The following data are for the 34 patients enrolled in the EXP and include available data from assessments completed by 01 May 2020.

RESULTS

Patient Demographics and Disease Characteristics

Table 1. Patient Demographics, EXP Patients (N=34)

Age; years	Median (range)	67 (53, 85)
Sex; n (%)	Female	31 (91)
	Male	3 (9)
ECOG performance Status; n (%)	0	11 (32)
	1	23 (68)
Primary Tumor Type; n (%)	OC[a,b]	27 (79)
	NSCLC, adenocarcinoma	7 (21)
Prior lines of Therapy; Median (range)	Ovarian[c]	3 (1, 5)
	NSCLC, adenocarcinoma[d]	2 (1, 3)
Prior Therapies OC; n (%)	Platinum	27 (100)
	Taxane	27 (100)
	Bevacizumab	17 (63)
	PARP inhib.	14 (52)
Prior Therapies NSCLC; n (%)	Platinum	7 (100)
	Pemetrexed	7 (100)
	Immune checkpoint inhib.	7 (100)
	Taxane	3 (43)

a. Includes fallopian tube and primary peritoneal
b. Includes 1 Endometrioid, 1 Low Grade, 1 Serous / Endometroid, and 1 Carcinosarcoma
c. 2 patients with OC enrolled with 5 lines of systemic therapy
d. For NSCLC, patients may have had up to 2 chemotherapies and 1 immune checkpoint inhibitor

Treatment-related Adverse Events

- 28 (82%) patients reported at least 1 treatment-related adverse event (TRAE)
- No Grade 4 or Grade 5 TRAEs have been reported
- No ≥Grade 3 (severe) TRAEs of neutropenia, peripheral neuropathy, or ocular toxicity have been reported

Figure 3. TRAEs Reported in ≥10% of Patients (N=34)

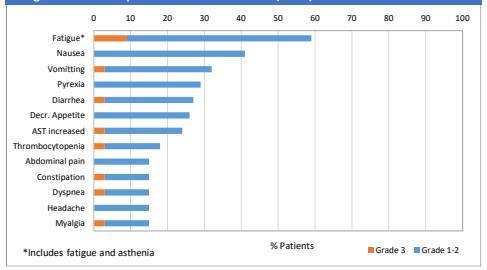


Table 2. TRAEs Reported in ≥10% of Patients Overall, by Dose and Severity

Preferred Term (MedDRA); n (%)	EXP 36 mg/m^2 (n=15)			EXP 43 mg/m^2 (n=19)			All Pts (N=34)
	Gr1	Gr2	Gr3	Gr1	Gr2	Gr3	
Fatigue [a]	1 (7)	8 (53)	1 (7)	6 (32)	2 (11)	2 (11)	20 (59)
Nausea	1 (7)	4 (27)	0	4 (21)	5 (26)	0	14 (41)
Vomiting	3 (20)	1 (7)	1 (7)	3 (16)	3 (16)	0	11 (32)
Pyrexia	5 (33)	0	0	5 (26)	0	0	10 (29)
Decr. appetite	2 (13)	2 (13)	0	4 (21)	1 (5)	0	9 (26)
Diarrhea	2 (13)	1 (7)	1 (7)	4 (21)	1 (5)	0	9 (26)
AST increased [b]	0	2 (13)	1 (7)	1 (5)	4 (21)	0	8 (24)
Thrombocytopenia	0	3 (20)	0	2 (11)	0	1 (5)	6 (18)
Abdominal pain	2 (13)	2 (13)	0	1 (5)	0	0	5 (15)
Constipation	1 (7)	1 (7)	1 (7)	1 (5)	1 (5)	0	5 (15)
Dyspnea	1 (7)	2 (13)	0	1 (5)	0	1 (5)	5 (15)
Headache	0	2 (13)	0	2 (11)	1 (5)	0	5 (15)
Myalgia	1 (7)	1 (7)	0	1 (5)	1 (5)	1 (5)	5 (15)

a. Includes fatigue and asthenia
b. AST increased is transient in nature, recovers to baseline or to Grade 1 prior to the next dose, none are associated with cases of Hy's law

- Of the 34 EXP patients, 7 (21%) patients had a dose delay, reduction, and/or discontinuation due to a TRAE
- Dose delays due to TRAEs occurred in 3 (9%) patients
- Dose reductions due to TRAEs occurred in 7 (21%) patients
- Dose discontinuation due to TRAEs occurred in 4 (12%) patients

Serious Adverse Events

- 18 SAEs have been reported in 10 (29%) patients
- SAEs reported in ≥2 (6%) patients included:
  - Infection (3 pts [9%]; pneumonia and lung infection)
  - Cerebral vascular accident/transient ischemic attack (3 pts [9%])
  - Pulmonary embolism/deep vein thrombosis (2 pts [6%])
  - Respiratory failure (2 pts [6%]; acute resp failure and resp failure)
- 2 of the 18 SAEs were deemed by the Investigator to be treatment-related: cerebral vascular accident and pneumonitis (both Grade 2)

Preferred terms were coded using MedDRA v20.1

OVARIAN CANCER

Ovarian Cancer: Outcome Response for Evaluable Patients

- Of the 27 patients with OC, 20 were evaluable at the time of data cut (7 patients were not evaluable: 1 withdrew consent [lower NaPi2b expression]; 1 with unrelated SAE leading to discontinuation and death [lower NaPi2b expression]; 5 have not yet received a scan)

Table 3. Ovarian Cancer: Response per RECIST v1.1 (N=20)

	All Patients	Higher[a] NaPi2b	Lower[b] NaPi2b	NaPi2b ND[c]
N	20	14	4	2
CR [n (%)]	2 (10)	2 (14)	0	0
PR [n (%)]	5 (25)	2 (14)	1 (25)	2 (100)
uPR[d] [n (%)]	1 (5)	1 (7)	0	0
SD [n (%)]	8 (40)	7 (50)	1 (25)	0
PD [n (%)]	4 (20)	2 (14)	2 (50)	0

a. Higher NaPi2b Expression: defined in DES as at / above lowest H-score at which response observed (≥110)
b. Lower NaPi2b Expression: defined in DES as below the lowest H-score at which response observed (<110)
c. NaPi2b Expression not yet determined
d. uPR=1 patient with unconfirmed PR; confirmatory scan pending at the time of data cut

Figure 4. Ovarian Cancer: Best % Change from Baseline in Target Lesions

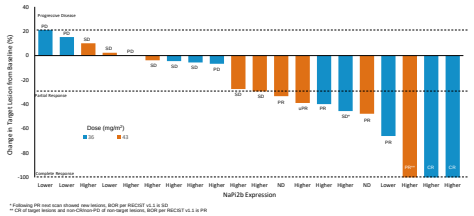
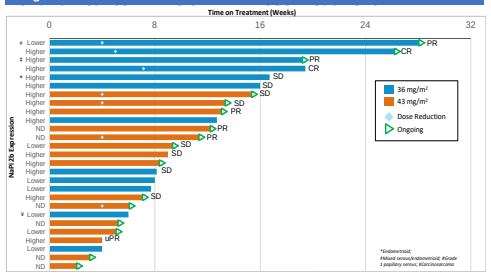


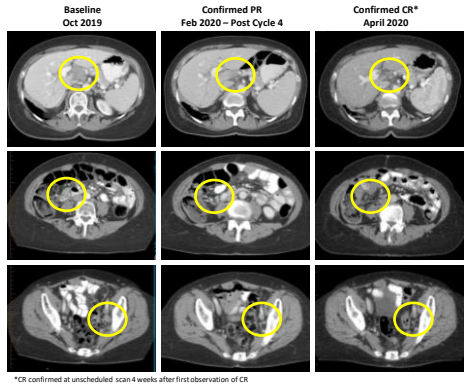
Figure 5. Ovarian Cancer: Time on XMT-1536 Treatment



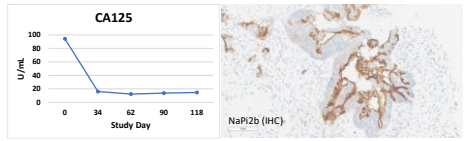
Ovarian Cancer Patient With Complete Response

- 70-yr-old woman with platinum-resistant high-grade serous OC previously treated with carboplatin/paclitaxel; carboplatin/gemcitabine; bevacizumab; niraparib; investigational anti-PD1
- Treated with 36 mg/m^2 q4w (with dose reduction to 30 mg/m^2 at Cycle 2); first PR observed after approx. 7 weeks of treatment with XMT-1536 (end of Cycle 2) which was confirmed with the following scan (end of Cycle 4); best overall response of CR
- Patient remains disease free and on study for >6 months

Figure 6. Ovarian Cancer: Patient With Complete Response



*CR confirmed at unscheduled scan 4 weeks after first observation of CR

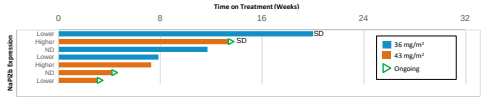


NSCLC ADENOCARCINOMA

NSCLC Adenocarcinoma: Outcome Response for Evaluable Patients

- Of the 7 NSCLC patients, 4 were evaluable at the time of data cut (3 patients were not evaluable: 2 have not yet received a scan; 1 discontinued for disease progression with ND NaPi2b expression and no scan done prior to 01 May 2020)

Figure 7. NSCLC Adenocarcinoma: Time on XMT-1536 Treatment



CONCLUSIONS

- XMT-1536 is a first-in-class Dolaflexin ADC targeting the sodium-dependent phosphate transport protein NaPi2b
- The MTD was determined to be 43 mg/m^2 and this is the current dose being evaluated in expansion
- XMT-1536 has a favorable safety profile
  - Most TRAEs were Grade 1 or 2
  - Fatigue, nausea, vomiting, pyrexia, decreased appetite, diarrhea, AST increased (transient) were the most frequently (≥20%) reported TRAEs
  - No ≥Grade 3 (severe) neutropenia, peripheral neuropathy, or ocular toxicity
- Antitumor activity is observed with XMT-1536 in patients with platinum-resistant OC
  - CR observed in 2 (10%) patients with platinum-resistant OC
  - ORR of 35% in patients with platinum-resistant OC (excludes 1 patient with an unconfirmed PR) with a DCR of 80%
- There is a trend toward response in patients with ovarian cancer with higher NaPi2b expression
- More data in patients with NSCLC are needed to assess antitumor activity
- More data are needed before a biomarker cut-off point can be declared and used to prospectively select patients likely to respond to XMT-1536
- These data support the continued evaluation of XMT-1536 in the ongoing Phase 1b study (NCT03319628) in patients with OC and NSCLC adenocarcinoma

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Abbreviations: AST=aspartate aminotransferase; CR=complete response; DES=dose expansion phase; ECOG=Eastern Cooperative Oncology Group; EXP=dose expansion phase; IHC=immunohistochemistry; MedDRA=Medical Dictionary for Regulatory Activities; MTD=maximum tolerated dose; NSCLC=non-small cell lung cancer; OC=ovarian cancer; BOR=best overall response; PD=progressive disease; PR=partial response; uPR=unconfirmed partial response; q4w=every 4 weeks dosing; RP2D=recommended Phase 2 dose; SAE=serious adverse event; TRAE=treatment-related adverse event; Decr.=decreased; Inhib.=inhibitor