# Abstract 2365: Safety and Efficacy of XMT-1536 in Ovarian Cancer: A Subgroup Analysis from the Phase I Expansion Study of XMT-1536, a NaPi2b Antibody-Drug Conjugate

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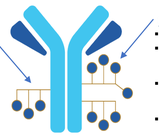
## INTRODUCTION

- There is a significant unmet medical need for effective therapies for patients with platinum-resistant ovarian cancer (OC)
- 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]
- XMT-1536 **(Figure 1)** is a first-in-class ADC targeting NaPi2b (SLC34A2), the sodium-dependent phosphate transport protein, broadly expressed in solid tumors such as serous epithelial OC and non-small cell lung adenocarcinoma (NSCLC)[4]
- XMT-1536 is being evaluated in patients with ovarian cancer and non-small cell lung adenocarcinoma in a Phase I study (NCT03319628) and has shown a favorable safety profile and evidence of clinical activity[5,6,7]
- Here, we report on the interim safety and efficacy of XMT-1536 in patients with ovarian cancer in the expansion (EXP) portion of the ongoing Phase I study

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

**Hydrophilic Polymer Scaffold**

- High drug-to-antibody ratio (DAR) with ~10-12 payloads
- Excellent drug-like properties
- Highly stable in circulation
- Dose-proportional exposure
- Very low exposure of free payload



**DolaLock Payload with Controlled Bystander Effect**

- Selectively toxic to rapidly dividing cells
- Initially released payload (Auristatin F-HPA) freely cell permeable and bystander killing capable
- Intracellular conversion to Auristatin F diminishes permeability and controls bystander effect
- Accumulates in tumor, not a PgP substrate
- Induces immunogenic cell death *in vitro*

## METHODS

**Figure 2. XMT-1536 Phase 1b Expansion Study Design**

**Ovarian Cancer Cohort**
- 1-3 prior lines in platinum-resistant
- 4 prior lines regardless of platinum status
- High grade serous histology
- *Exclusion: primary platinum-resistant defined as lack of response or disease progression within 3 mos after completing front-line platinum containing therapy*

**NSCLC Cohort**
- Prior treatment with platinum doublet and PD-1/L1 inhibitor
- Prior TKIs if targetable mutation
- Up to 2 prior lines of cytotoxic therapy
- Adenocarcinoma histology

**XMT-1536**
36 or 43 mg/m$^2$ IV once every 4 weeks until disease progression or unacceptable toxicity

**Assessments**: Tumor imaging (MRI or CT): baseline and every 2nd cycle; response assessed per RECIST v1.1

***Patient population:*** High grade serous ovarian cancer (including fallopian tube and primary peritoneal) and NSCLC adenocarcinoma progressing after standard treatments **(Figure 2)**
- Measurable disease per RECIST v1.1
- ECOG Performance Status 0 or 1
- Archived tissue and fresh tissue, when medically feasible, for retrospective assessment of NaPi2b expression

***Dosing:*** IV every 4 weeks until disease progression or unacceptable toxicity
- 36 mg/m$^2$ cohort initiated in August 2019 and enrollment closed
- 43 mg/m$^2$ cohort initiated in December 2019; current dose evaluated in EXP

***Primary Objectives:***
- Safety and tolerability of the MTD of XMT-1536
- Preliminary anti-neoplastic activity (ORR, DCR)

***Secondary Objectives:***
- 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 previously reported[5,6])
- Further assessment of preliminary anti-neoplastic activity (DOR)

*The following data are for the 47 patients with ovarian cancer enrolled in EXP and include available data from assessments completed by 18 August 2020*

Abbreviations: mos = months; PD-1/L1 = programmed cell death protein 1/programmed death-ligand-1; TKIs = tyrosine kinase inhibitors; EXP = expansion; NSCLC = non-small cell lung cancer; RECIST = Response Evaluation Criteria in Solid Tumors; ECOG = Eastern Cooperative Oncology Group; MTD = maximum tolerated dose; ORR = objective response rate; DCR = disease control rate; DOR = duration of response

## RESULTS

### *Patient Demographics and Disease Characteristics*

**Table 1. Baseline Characteristics in Patients with OC (N=47)**

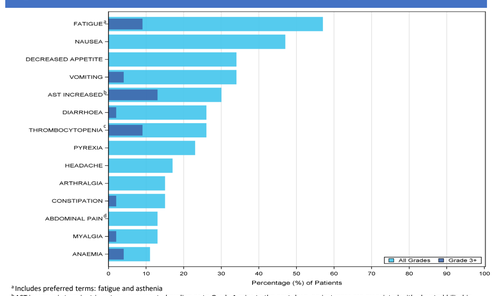
| | | |
|---|---|---|
| **Age; years** | Median (range) | 69 (37, 85) |
| **ECOG Performance Status; n (%)** | 0 | 16 (34) |
| | 1 | 31 (66) |
| **Primary Tumor Type[a]; n (%)** | Ovarian | 34 (72) |
| | Fallopian Tube | 7 (15) |
| | Primary Peritoneal | 6 (13) |
| **Prior Lines of Therapy; n (%)** | 1-3 | 28 (60) |
| | 4+[b] | 19 (40) |
| **Prior Therapy; n (%)** | Bevacizumab | 33 (70) |
| | PARP inhibitor | 25 (53) |
| **Platinum-free Interval[c]; n (%)** | 0-3 mos | 14 (30) |
| | >3-6 mos | 27 (57) |
| | >6 mos[d] | 5 (11) |
| | Unknown[e] | 1 (2) |
| **BRCA1/2 Mutation; n (%)** | Yes | 6 (13) |
| | No | 37 (79) |
| | Unknown[f] | 4 (9) |
| **NaPi2b H-score[g]; n (%)** | Higher | 26 (55) |
| | Lower | 15 (32) |
| | Not Determined (ND) | 6 (13) |

[a] Includes 1 Endometrioid, 1 Low Grade, 1 Serous / Endometroid, and 1 Carcinosarcoma histology
[b] Two patients enrolled with 5 prior lines of systemic therapy
[c] Platinum-free interval defined as the time between the last cycle of most recent platinum-containing regimen and evidence of disease progression; determined from treatment dates and/or clinic notes
[d] All patients are platinum-sensitive and had received 4 or 5 lines of prior therapy
[e] Treatment dates missing/not provided; unable to determine
[f] BRCA1/2 mutation status not available/not reported
[g] Higher NaPi2b Expression: as defined in dose escalation as at / above lowest H-score at which response observed (≥110); Lower NaPi2b Expression: as defined in dose escalation as below the lowest H-score at which response observed (<110); ND = Hypocellular specimen/indeterminate for H-score or not determined yet

### *Treatment-related Adverse Events in Patients with OC*

- 38 (81%) patients reported at least 1 treatment-related adverse event (TRAE)
- No ≥Grade 3 (severe) TRAEs of neutropenia, peripheral neuropathy, or ocular toxicity have been reported

**Figure 3. TRAEs Reported in ≥10% of Patients with OC (N=47)**




[a] Includes preferred terms: fatigue and asthenia
[b] AST increase is transient in nature, recovers to baseline or to Grade 1 prior to the next dose, no instances are associated with elevated bilirubin or cases of Hy's law
[c] Includes preferred terms: thrombocytopenia and platelet count decrease. 1 patient with Grade 4 thrombocytopenia on C1D8 recovered within 3 days
[d] Includes preferred terms: abdominal pain, abdominal pain upper
Abbreviation: TRAEs = treatment-related adverse events; AST = Aspartate aminotransferase

### *Safety Summary of XMT-1536 in Patients with OC*

- Of the 47 EXP patients with OC, 11 (23%) patients had a dose reduction, delay, and/or discontinuation due to a TRAE
- Dose reductions due to TRAE occurred in 7 (15%) patients
- Dose delays due to TRAE occurred in 4 (9%) patients
- Dose discontinuation due to TRAE occurred in 2 (4%) patients
  - Most frequent TRAEs leading to dose reductions were: AST increase [2 patients]; thrombocytopenia [3 patients]
- 17 Serious adverse events (SAE) occurred in 11 (23%) patients
- SAEs reported in ≥2 (4%) patients included:
  - Abdominal pain [2 patients]
  - Cerebrovascular accident/transient ischemic attack [2 patients]
  - Pneumonia [2 patients]
  - Respiratory failure [2 patients]
- 2 of the 17 SAEs were deemed by the Investigator to be treatment-related: pneumonitis (Grade 2) and vomiting (Grade 3)

### *Outcome Response for Evaluable Patients with OC*

- Response observed within 2 cycles in 70 % of patients (7 of 10)
- Response observed within 4 cycles in 100% of patients (10 of 10)

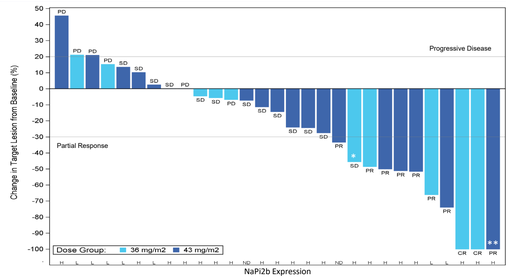
**Table 2. Efficacy Results in Evaluable Patients with OC (n=29)**

| Endpoint | All Patients (n = 29) | Higher NaPi2b (n = 20) | Lower NaPi2b (n = 7) | NaPi2b ND (n = 2) |
|---|---|---|---|---|
| CR; n(%) | 2 (7) | 2 (10) | 0 | 0 |
| PR; n (%) | 8 (28) | 5 (25) | 2 (29) | 1 (50) |
| SD; n (%) | 13 (45) | 10 (50) | 2 (29) | 1 (50) |
| PD; n (%) | 6 (21) | 3 (15) | 3 (43) | 0 |
| ORR [CR + PR]; n (%) | 10 (34) | 7 (35) | 2 (29) | 1 (50) |
| DCR [CR + PR + SD]; n (%) | 23 (79) | 17 (85) | 4 (57) | 2 (100) |

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; ORR = objective response rate; DCR = disease control rate; ND = not determined (i.e., Hypocellular specimen/indeterminate for H-score or not determined yet)

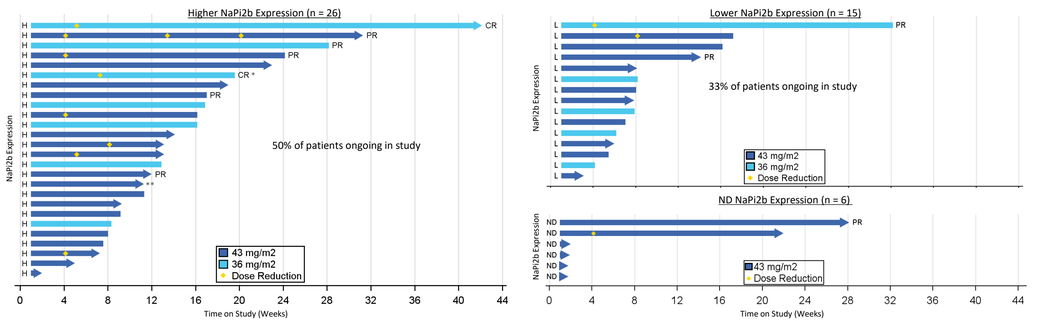
- Of the 47 patients with OC, 29 were evaluable at the time of data cut
- 18 patients were not evaluable for RECIST response
  - 15 patients did not have RECIST assessment as of data cut
  - 3 patients discontinued prior to receiving the first scan (1 clinical progression [lower NaPi2b expression]; 1 withdrew consent [lower NaPi2b expression]; 1 unrelated Grade 5 SAE [lower NaPi2b expression])

**Figure 4. Maximum % Change from Baseline in Target Lesions in Patients with OC**



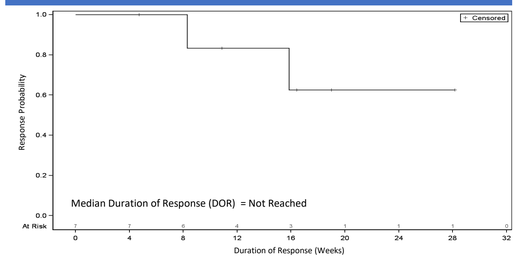

* Following PR next scan showed new lesions, BOR per RECIST v1.1 is SD
** CR of target lesions and non-CR/non-PD of non-target lesions, BOR per RECIST v1.1 is PR
Abbreviations: PD = progressive disease; SD = stable disease; PR = partial response; CR = complete response; H = Higher NaPi2b Expression; L = Lower NaPi2b Expression; ND = not determined (i.e., Hypocellular specimen/indeterminate for H-score or not determined yet)

**Time on XMT-1536 Study in Patients with OC (n = 47)**



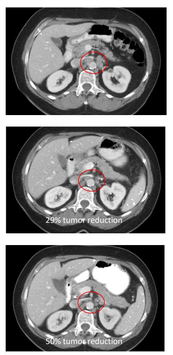

* Scans at 28-weeks confirmed ongoing CR in this patient
** Patient previously reported as unconfirmed PR at ASCO 2020; patient discontinued study after 1 Cycle and confirmatory scans not completed; patient off study for 3.5 months, with disease progression and study treatment re-initiated; plot is shown from re-initiation of study treatment
Abbreviations: CR = complete response; PR = partial response; H = Higher NaPi2b Expression; L = Lower NaPi2b Expression; ND = not determined (i.e., Hypocellular specimen/indeterminate for H-score or not determined yet)

**Figure 6. Durability of Response in Patients with OC and Higher NaPi2b (n = 7)**

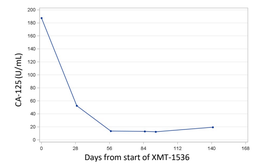



- Median duration of response (DOR) not reached in Higher NaPi2b (n = 7) subgroup
- 2 patients with Lower NaPi2b with DOR of 4.1 week and 16.1 weeks, respectively
- 1 patient with NaPi2b ND with DOR 16.1 weeks
- Longest DOR in a patient with Higher NaPi2b is ongoing at 28.1+ weeks and the patient continues on study at 42.1 weeks
- Data support NaPi2b as a proposed biomarker of response to XMT-1536

**Figure 7. Partial Response in a Patient with Platinum-resistant OC**




- 61-year old BRCA1/2 negative patient with platinum-resistant high grade serous ovarian cancer
- Prior systemic therapies included carboplatin/paclitaxel; carboplatin/liposomal doxorubicin; bevacizumab and maintenance therapy with PARPi
- Initiated XMT-1536 at 43 mg/m$^2$; dose reductions to 20 mg/m$^2$ (current dose)
- Confirmed PR by RECIST v1.1 after Cycle 4 of treatment
- Remains on study treatment at 31 weeks




## CONCLUSIONS

- In this subgroup analysis of patients with ovarian cancer, XMT-1536 continued to be well tolerated with a favorable safety profile – no severe neutropenia, peripheral neuropathy, or ocular toxicity
- Antitumor activity is observed with XMT-1536, as previously reported, including patients previously treated with bevacizumab and PARPi
  - Complete response observed in 2 patients with platinum-resistant OC; one patient ongoing on study at 42.1 weeks with DOR ongoing at 28.1 weeks
  - ORR of 34% in patients with OC with a DCR of 79%
- Median DOR was not reached in patients with OC with higher NaPi2b, supporting the continued development of NaPi2b companion diagnostic
- These data support the continued development of XMT-1536 for the treatment of patients with platinum-resistant high-grade serous ovarian cancer who have received up to three prior lines of systemic therapy or patients who have received four prior lines of systemic therapy regardless of platinum status
- XMT-1536 granted FDA Fast Track Designation on August 11, 2020

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## DISCLOSURES

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