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Results From the Phase 1 Dose Escalation Study of XMT-1592, a Dolasynthen NaPi2b-Directed Antibody-Drug Conjugate (ADC)

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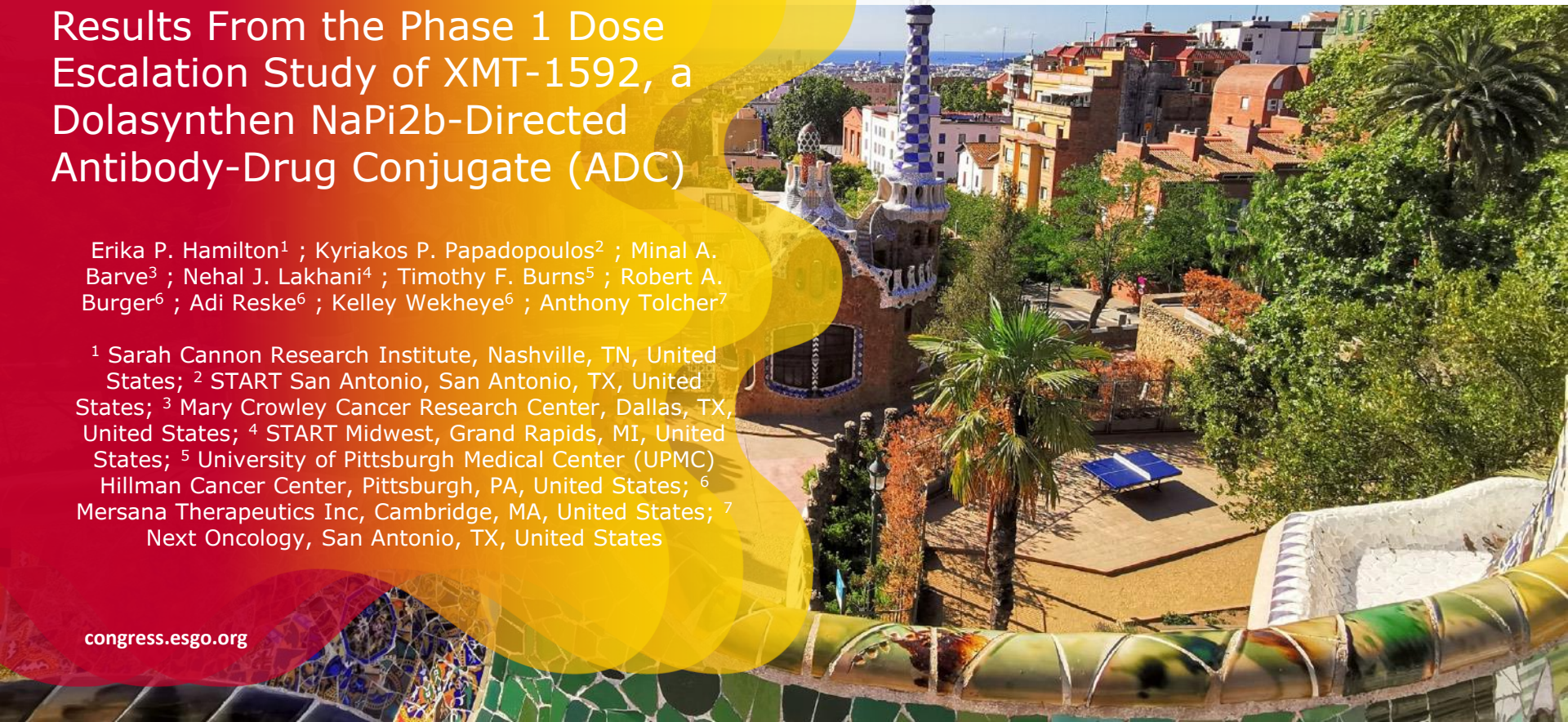

Introduction

- ADCs have provided substantial benefits to patients; nonetheless, observed platform toxicities and payload resistance limit their use
- NaPi2b is a sodium-dependent phosphate transporter broadly expressed in ovarian cancer (OC), non-small cell lung cancer (NSCLC) and in healthy Type II pneumocytes in the lung, but with limited expression in other healthy tissue (Table 1)[1]
- ADCs targeting NaPi2b have demonstrated clinical activity in platinum-resistant OC, but have been associated with both target-related toxicities (ILD/pneumonitis) and platform-related toxicities, including AST increase, thrombocytopenia/platelet count decrease (observed with XMT-1536)[2] , and neutropenia and neuropathy (observed with lifatuzumab vedotin)[3]
- Dolasynthen is a next-generation platform designed to produce homogeneous ADCs with precise control of the drug-to-antibody ratio and site-specific bioconjugation with the goal of improving efficacy and reducing platform-related toxicities[4]
  - Improvements in PK, in vivo efficacy and tolerability were observed preclinically with XMT-1592 when compared with an earlier NaPi2b-targeted ADC, XMT-1536 (UpRi; data on file)

NaPi2b Highly Expressed in Normal Lung and Ovarian Cancer Tissues[1]

Type of tissue	IHC Score[a]			
	0	1	2	3
Normal breast (n=4)	0	0	1	3
Breast cancer (n=10)	8	2	0	0
Normal lung (n=9)	0	0	1	8
Lung cancer (n=11)	5	5	0	1
Normal uterus (n=3)	0	0	1	2
Normal oviduct (n=2)	0	0	0	2
Normal ovary (n=5)	5	0	0	0
Ovarian cancer (n=10)	0	1	1	8

Table 1: Semi-Quantitative Scoring of IHC Staining for NaPi2b (MX35) in a Panel of Normal and Cancer Tissues

- NaPi2b is highly expressed in normal lung tissue at a cumulative IHC score comparable to that for OCs[1]
- Type II pneumocytes in the lungs may be proliferating and thus susceptible to a microtubule inhibitor

Here we report Phase 1 dose escalation data for XMT-1592, a Dolasynthen NaPi2b-directed ADC in patients with OC and NSCLC

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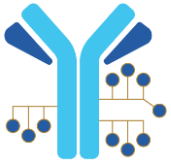
1. Kiyamova R, et al. Exp Oncol. 2011;33(3):157_161; 2. Richardson D, et al. Gynecol Oncol Rep. 2022;44(2):S16-S17; 3. Banjeree S, et al. Ann Oncol. 2018;29(4):917_923; 4. Fessler S, et al. Can Res. 2020;80(suppl 16):2894.
[a]IHC labeling intensity: 1+ = weak; 2+ = moderate; 3+ = strong. ADC, antibody drug conjugates; NaPi2b, sodium-dependent phosphate transporter 2b; ILD, interstitial lung disease; AST, aspartate aminotransferase; PK, pharmacokinetics; IHC, immunohistochemistry

Leveraging Learnings to Develop an Improved Cytotoxic ADC Platform

Dolaflexin
(First-generation cytotoxic ADC platform)



- AF-HPA payload with controlled bystander effect; highly potent anti-tubulin inhibitor selectively toxic to rapidly dividing cells designed to avoid dose-limiting neuropathy or neutropenia
- Stochastic (random) bioconjugation
- Heterogeneous DAR ~10
- Fully preserved Fcγ receptor interaction; could lead to non-target uptake

Goals for Next-Generation Platform

- DAR customization for target
- Antibody-like PK
- Enhance tumor payload delivery
- Increase efficacy
- Reduce platform toxicity
- Expand therapeutic index

Dolasynthen
(Next-generation cytotoxic ADC platform)

- AF-HPA payload with controlled bystander effect; highly potent anti-tubulin inhibitor selectively toxic to rapidly dividing cells designed to avoid dose-limiting neuropathy or neutropenia
- Site-specific conjugation
- Homogeneous DAR 6
- Significantly reduced Fcγ binding

ADC, antibody-drug conjugate; AF-HPA, Auristatin F hydroxypropyl amide; DAR, drug-to-antibody ratio; Fcγ, fragment crystallizable gamma receptor

Preclinical Studies: Dolasynthen Outperforms Dolaflexin at Equal Payload Doses

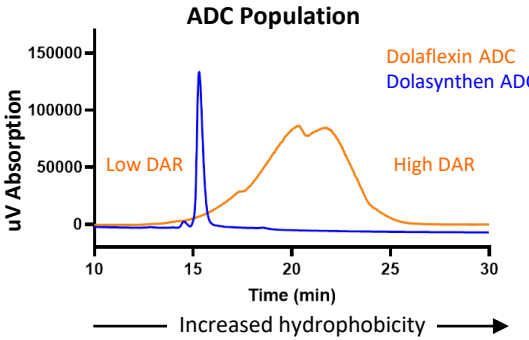


Figure 1: Heterogeneous Population vs Homogeneous Population. As measured by hydrophobic interaction chromatography, 280 nanometers

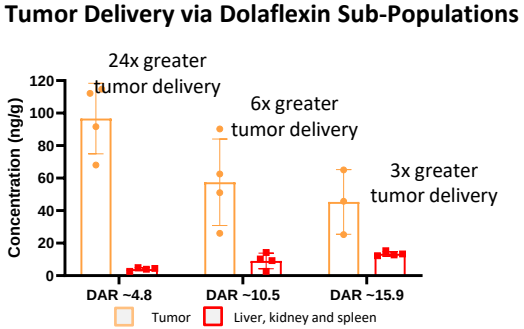


Figure 2: Dolaflexin High-DAR Subpopulations Show Reduced Tumor-Specific Delivery (Total payload/DAR)

- Dolasynthen platform enables the creation of single-species ADCs that outperform Dolaflexin's heterogeneous ADC population in preclinical models

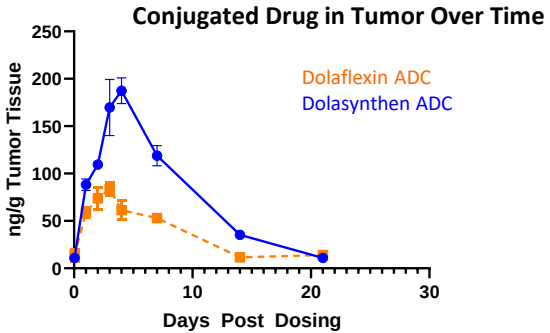


Figure 3: Higher Payload Exposure in Tumor With Dolasynthen
0.05 mg/kg payload (mouse)

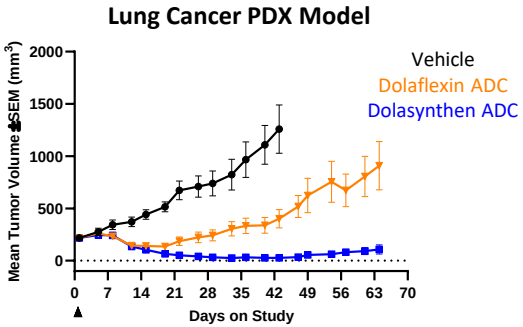


Figure 4: Enhanced Efficacy With Dolasynthen
Time of administration, single-dose IV, 0.1 mg/kg payload

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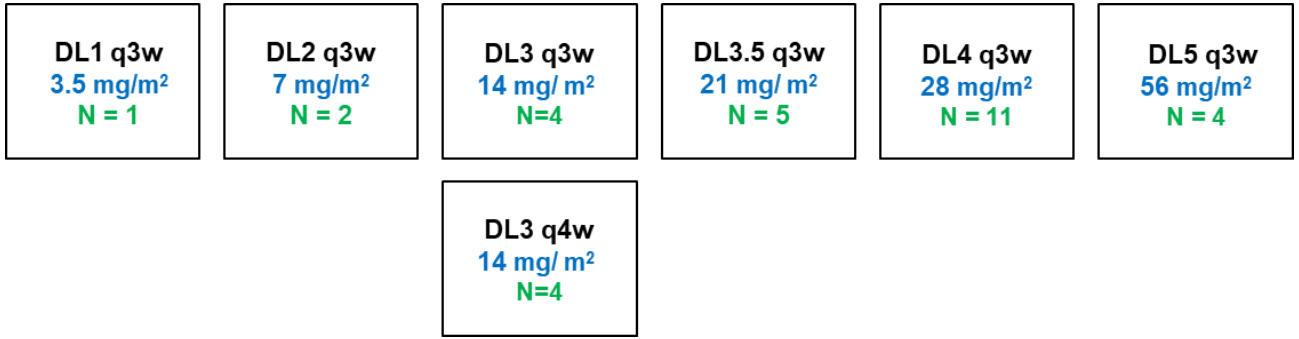
ADC, antibody-drug conjugate; DAR, drug to antibody ratio; PDX, patient-derived xenograft; UV, ultraviolet.

Methods: XMT-1592 Phase 1 Dose Escalation Trial Design

- Enrolled patients with OC with histological diagnosis of high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancers; non-squamous NSCLC
  - Measurable disease by RECIST 1.1
  - ECOG performance status 0 or 1
  - Available archival tumor tissue blocks, or freshly cut tissue slides for retrospective NaPi2b testing
- Dosing: XMT-1592 administered IV every 3 or 4 weeks
- Primary objectives: MTD or RP2D; safety and tolerability
- Escalation design: Modified version of the Simon accelerated titration design



DL, dose level; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; MTD, maximum tolerated dose; NaPi2b, sodium-dependent phosphate transporter 2b; NSCLC, non-small cell lung cancer; OC, ovarian cancer; qw, every week; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose

Results *(Data cutoff: November 1, 2022)*

Patient Demographics and Disease Characteristics

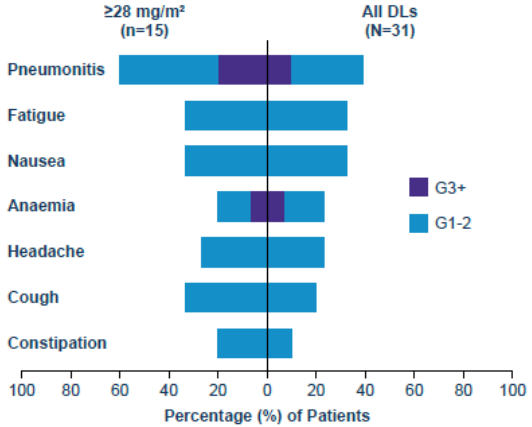
Safety Analysis Set (N=31)	
Median age (range), years	68 (47,82)
ECOG PS, n (%) 0 1	4 (12.9) 27 (87.1)
Primary tumor type, n (%) NSCLC[b] OC	3 (9.7) 28 (90.3)
Prior Lines of Therapy, n (%) 1-3 ≥4	13 (41.9) 18 (58.1)
Prior Therapy, n (%) Bevacizumab PARP inhibitor	16 (51.6) 18 (58.1)
Platinum-Free Interval, n (%) 0-3 Months >3-6 Months >6 Months Unknown	11 (35.5) 9 (29.0) 7 (22.6) 4 (12.9)
NaPi2b H-Score, n (%) Determined High (H-score ≥110) Low (H-score <110) Not determined	25 (80.6) 12 (48) 13 (52) 6 (19.4)

[b] Adenocarcinoma

ECOG PS, Eastern Cooperative Oncology Group performance status; NaPi2b, sodium-dependent phosphate transporter 2b; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PARP, poly-ADP ribose polymerase

Results *(Data cutoff: November 1, 2022)*

Safety – TRAEs in ≥15% of Patients



- TRAEs were mostly low grade
- Pneumonitis observed (including 1 G5) likely an on-target toxicity based on NaPi2b expression in Type II pneumocytes
- No severe peripheral neuropathy, neutropenia, or ocular toxicity
- No thrombocytopenia or treatment-related bleeding events
- XMT-1592 half-life: 7.5-10.3 days

Platform Toxicities Appear to be Greatly Reduced with Next-Generation Dolasynthen Platform[c]

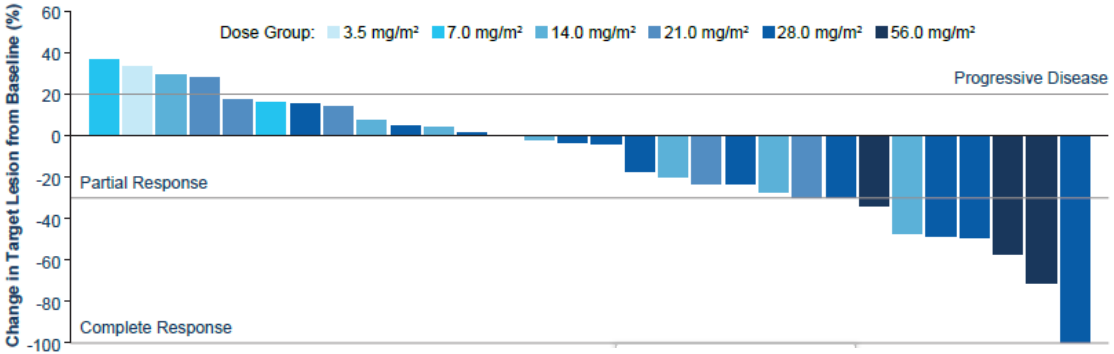
	TRAEs	First-Generation XMT-1536 (n=268)[d] 36mg/m² N (%)		Next-Generation XMT-1592 (n=31) All DLs N (%)	
		All grades	Grade ≥3	All grades	Grade ≥3
Presumed off-target platform toxicities	AST Elevation, n (%)	185 (69.0)	124 (46.3)	3 (9.7)	0
	Platelet Count Decrease/ thrombocytopenia, n (%)	133 (49.6)	32 (11.9)	0	0
	Nausea, n (%)	139 (51.9)	6 (2.2)	10 (32.3)	0
	Fatigue, n (%)	118 (44.0)	26 (9.7)	10 (32.3)	0
Presumed on-target toxicity	Pneumonitis, n (%)	26 (9.7)	2 (<1)	12 (38.7)	3 (9.7)

- Observed pneumonitis believed to be due to target-dependent uptake of the ADC by the Type II pneumocytes in the lungs expressing NaPi2b
- Histologic findings in Type II pneumocytes in animal models have not been seen with multiple other Dolasynthen ADCs directed towards other targets (data on file)

[c] Based on two independent studies. [d] Data cut: May 31, 2023 (UPLIFT: Phase 2 trial).
ADC, antibody-drug conjugate; AST, aspartate aminotransferase; DL, dose level; G, grade; NaPi2b, sodium-dependent phosphate transporter 2b; TRAE, treatment-related adverse event

Results *(Data cutoff: November 1, 2022)*

Efficacy – Best Percent Change from Baseline in Target Lesions (N=30, all dose-levels)[e]



Waterfall Plot of Evaluable Patients Regardless of NaPi2b Expression

	All Patients All DLs	Ovarian Cancer ≥28 mg/m²
Patients, N	30[e]	13[e]
ORR, n (%)	5 (17%)	4 (31%)
SD, n (%)	19 (63%)	7 (54%)
DCR, n (%)	24 (80%)	11 (85%)
Median DOR, months	7.9	7.9

Confirmed Best Overall Response of Evaluable Patients Regardless of NaPi2b Expression

e Evaluable patients; excludes one patient at 56 mg/m2 who was non-evaluable by RECIST due to withdrawal of consent before first scan.
CR, complete response; DCR, disease control rate; DL, dose level; DOR, duration of response; NaPi2b, sodium-dependent phosphate transporter 2b; ORR, objective response rate; SD, stable disease

Conclusions

- XMT-1592 is a NaPi2b-directed Dolasynthen ADC evaluated in a Phase 1 dose escalation trial in patients with platinum-resistant OC and non-squamous NSCLC
- Platform-associated off-target toxicity with XMT-1592 appeared to be reduced relative to first-generation NaPi2b-directed ADCs. Fatigue, nausea, thrombocytopenia, and AST elevation occurred at a lower frequency and severity with XMT-1592 as compared to XMT-1536. No treatment-related bleeding events were reported with XMT-1592
- Pneumonitis was the most common TRAE with XMT-1592 and is believed to be an on-target toxicity due to NaPi2b expression in Type II pneumocytes. Histologic findings in Type II pneumocytes in animal models have not been seen with multiple other Dolasynthen ADCs directed towards other targets
- Responses were observed with XMT-1592 treatment in heavily pretreated patients, including one CR. In evaluable OC patients regardless of NaPi2b expression treated with 28 mg/m^2 or 56 mg/m^2, ORR was 31% with median DOR of 7.9 months
- Development of XMT-1592 was discontinued by the sponsor before completing the Phase 1 dose escalation due to portfolio reprioritization considerations

ADC, antibody-drug conjugate; CR, complete response; DOR, duration of response; NaPi2b, sodium-dependent phosphate transporter 2b; NSCLC, non-small cell lung cancer; OC, ovarian cancer; ORR, objective response rate; TRAE, treatment-related adverse event

Acknowledgments

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