

# Results From the Phase 1 Dose Escalation Study of XMT-1592, a NaPi2b-Directed Dolasynthen 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)<sup>1</sup>
- 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)<sup>2</sup>, and neutropenia and neuropathy (observed with lifituzumab vedotin)<sup>3</sup>
- 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<sup>4</sup>
  - 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)
- Here we report Phase 1 dose escalation data for XMT-1592, a Dolasynthen NaPi2b-directed ADC in patients with OC and NSCLC

## NaPi2b Highly Expressed in Normal Lung and Ovarian Cancer Tissues<sup>1</sup>

Type of tissue	IHC Score*			
	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

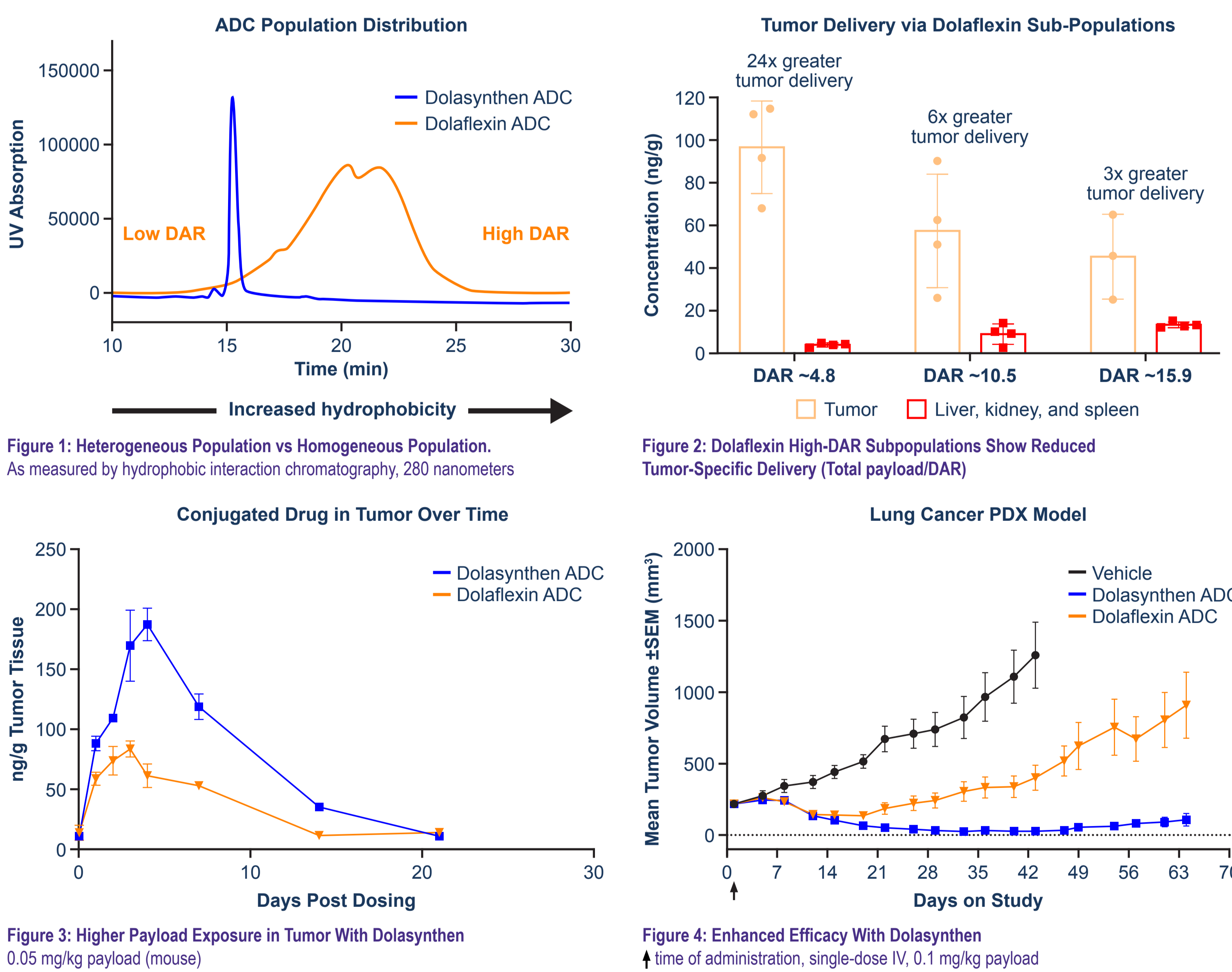
- NaPi2b is highly expressed in normal lung tissue at a cumulative IHC score comparable to that for OCs<sup>1</sup>
- Type II pneumocytes in the lungs may be proliferating and thus susceptible to a microtubule inhibitor

## Leveraging Learnings to Develop an Improved Cytotoxic ADC Platform



## Preclinical Studies: Dolasynthen Outperforms Dolaflexin at Equal Payload Doses

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



## 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

<b>DL1 q3w</b> 3.5 mg/m <sup>2</sup> n=1	<b>DL2 q3w</b> 7 mg/m <sup>2</sup> n=2	<b>DL3 q3w</b> 14 mg/m <sup>2</sup> n=4	<b>DL3.5 q3w</b> 21 mg/m <sup>2</sup> n=5	<b>DL4 q3w</b> 28 mg/m <sup>2</sup> n=11	<b>DL5 q3w</b> 56 mg/m <sup>2</sup> n=4
		<b>DL3 q4w</b> 14 mg/m <sup>2</sup> n=4			

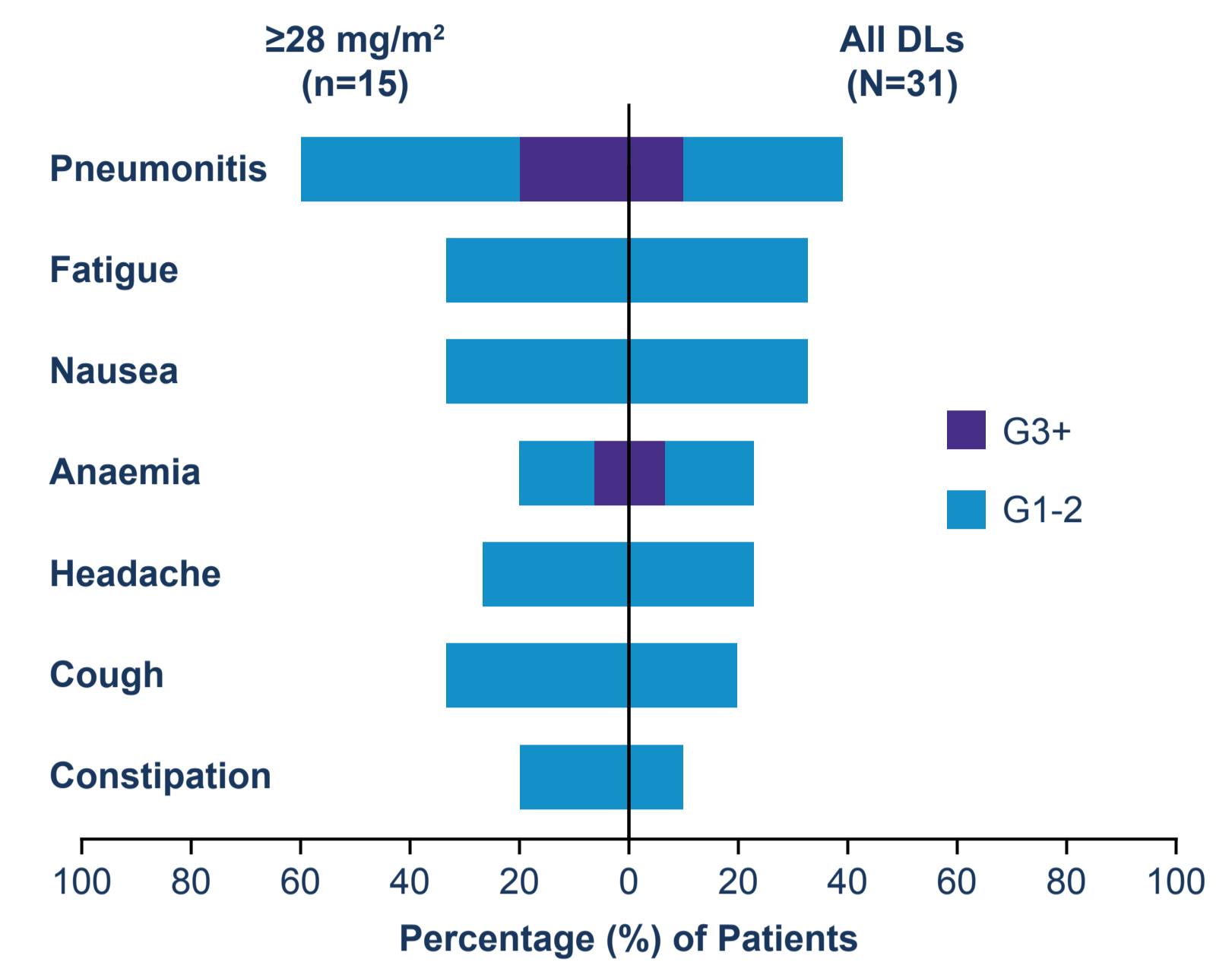
Figure 5: Dose Escalation Design

## 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	4 (12.9)
1	27 (87.1)
Primary tumor type, n (%)	
NSCLC*	3 (9.7)
OC	28 (90.3)
Prior lines of therapy, n (%)	
1-3	13 (41.9)
≥4	18 (58.1)
Prior therapy, n (%)	
Bevacizumab	16 (51.6)
PARP inhibitor	18 (58.1)
Platinum-free interval, n (%)	
0-3 Months	11 (35.5)
>3-6 Months	9 (29.0)
>6 Months	7 (22.6)
Unknown	4 (12.9)
NaPi2b H-score, n (%)	
Determined	25 (80.6)
High (H-score ≥110)	12 (48)
Low (H-score <110)	13 (52)
Not determined	6 (19.4)

### 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<sup>c</sup>

TRAEs	First-Generation XMT-1536 (N=268) <sup>a</sup> 36 mg/m <sup>2</sup> n (%)		Next-Generation XMT-1592 (N=31) All DLs n (%)	
	All grades	Grade ≥3	All grades	Grade ≥3
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
Pneumonitis, n (%)	26 (9.7)	2 (<1)	12 (38.7)	3 (9.7)

Table 2: Comparison table between XMT-1536 and XMT-1592

Based on two independent studies; select AEs

- 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)

## Efficacy

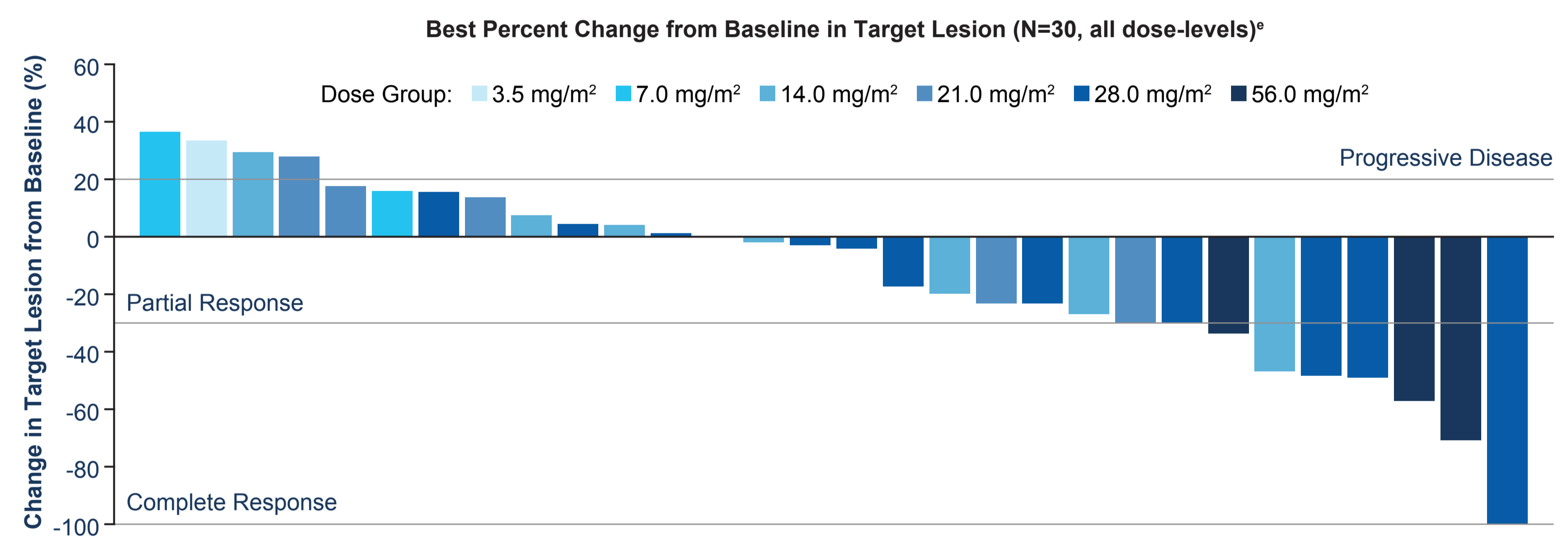


Figure 6: Waterfall Plot of Evaluable Patients Regardless of NaPi2b Expression

	All Patients All DLs	Ovarian Cancer ≥28 mg/m <sup>2</sup>
Patients, N	30 <sup>a</sup>	13 <sup>a</sup>
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

Table 3: Confirmed Best Overall Response of Evaluable Patients Regardless of NaPi2b Expression

## 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<sup>2</sup> or 56 mg/m<sup>2</sup>, 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

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