



# ANNUAL MEETING ON WOMENS' CANCER®

**BUILDING BRIDGES // BREAKING BARRIERS**

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# Updated Results From the Phase 1b Expansion Study of Upifitamab Rilsodotin (UpRi; XMT-1536), a NaPi2b-directed Dolaflexin Antibody Drug Conjugate (ADC) in Ovarian Cancer

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# Financial Disclosures

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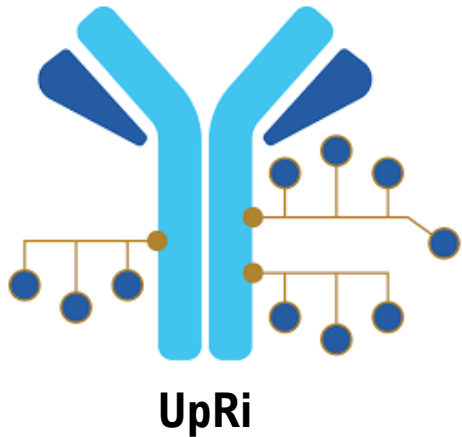
- I have the following financial relationships with ACCME-defined ineligible companies to report over the past 24 months:
  - Consulting for Mersana, AstraZeneca, GlaxoSmithKline

# Unlabeled/Investigational Uses

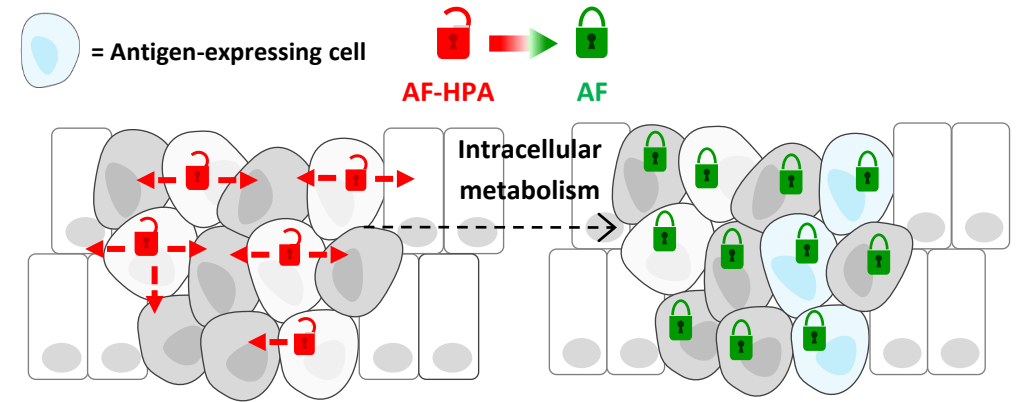
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- I will be discussing unlabeled or investigational uses of pharmaceutical products or medical devices
  - This is a presentation of a clinical trial of upifitamab rilsodotin (UpRi, XMT-1536), which is not FDA-approved

# Upfitamab Rilsodotin (UpRi) – First-in-Class ADC Targeting NaPi2b

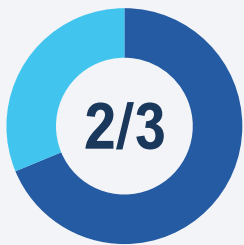


- Antibody:** Humanized monoclonal anti-NaPi2b<sup>1</sup>
- Linker:** Polymer scaffold; cleavable ester linker<sup>2</sup>
- Payload:** AF-HPA (DolaLock-controlled bystander effect)<sup>1</sup>
- Drug-to-Antibody Ratio:** ~10

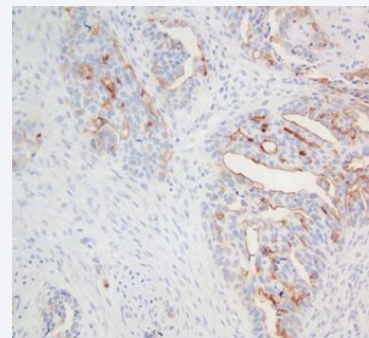


Upon ADC internalization into tumor cells and efficient release of payload, AF-HPA payload is metabolized to AF that remains highly potent but loses the ability to cross the cell membrane, locking it in the tumor, controlling the bystander effect, and consequently limiting impact on adjacent healthy cells<sup>2,3</sup>

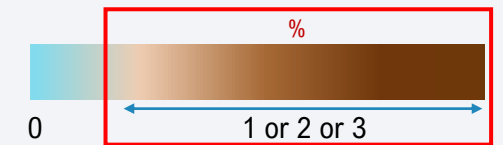
## NaPi2b Is a Sodium-Dependent Phosphate Transporter Broadly Expressed in Ovarian Cancer With Limited Expression in Healthy Tissues<sup>4</sup>



- NaPi2b expressed by tumor cells in two-thirds of patients with high-grade serous ovarian cancer<sup>2</sup>
- NaPi2b is a lineage antigen (not an oncogene)<sup>1</sup>



**NaPi2b IHC assay in development** – an optimal diagnostic assay would be robust, predictive, reproducible, easily able to distinguish a wide range of expression using **TPS scoring method**<sup>2</sup>



# UpRi Phase 1b Study – Ovarian Cancer Expansion Cohort Study Design

## Study Closed for Enrollment

**Patient Population:** HGSOC<sup>a</sup> progressing after standard treatments; measurable disease per RECIST v1.1; ECOG PS 0 or 1

### Ovarian Cancer Cohort

- 1–3 prior lines in platinum-resistant
- 4 prior lines regardless of platinum status
- High-grade serous histology
- Archived tumor and fresh biopsy (if medically feasible) for NaPi2b
- Exclusion: Primary platinum-refractory disease

UpRi IV Q4W until disease progression or unacceptable toxicity

36 mg/m<sup>2</sup> cohort initiated in August 2019

43 mg/m<sup>2</sup> to a max of ~80 mg cohort initiated in December 2019

### Primary Objectives

- Evaluate safety and tolerability of MTD or RP2D
- Assess preliminary efficacy (ORR, DCR)

### Secondary Objectives

- Association of tumor NaPi2b expression and objective tumor response using an IHC assay with a broad dynamic range to distinguish tumors with high and low NaPi2b expression
- Further assessment of preliminary anti-neoplastic activity (DoR)

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

<sup>a</sup> HGSOC including fallopian tube and primary peritoneal cancer.

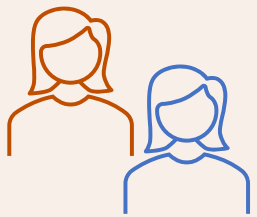
CT, computed tomography; DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HGSOC, high-grade serous ovarian cancer; IHC, immunohistochemistry; IV, intravenous; MRI, magnetic resonance imaging; MTD, maximum tolerated dose; NaPi2b, sodium-dependent phosphate transport protein 2B; ORR, overall response rate; PS, performance score; Q4W, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; UpRi, upifitamab rilsodotin.

1. Tolcher AW et al. ASCO Annual Meeting 2019; Abstract 3010. 2. Richardson DL et al. SGO Annual Meeting 2020; LBA8. 3. Hamilton E et al. ESMO Virtual Congress 2020; Abstract 2365.

# Expansion Cohort Experience Across a Range of Doses Allowed for Further Optimization of UpRi Profile

## Updated Analysis of Phase 1b PROC Expansion Cohort to Evaluate Safety and ORR Based on UpRi Dose Levels<sup>a</sup>

### Dose Group 36 (33–38 mg/m<sup>2</sup>) (n=29)

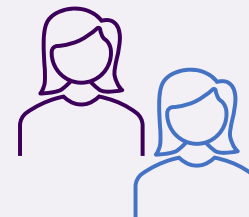


12 patients at **36 mg/m<sup>2</sup>** starting dose  
(all BSA levels)

+

17 patients at ~80 mg starting dose  
with BSA ≥1.8 who received an actual  
dose of **33 to 38 mg/m<sup>2</sup>**

### Dose Group 43 (>38–43 mg/m<sup>2</sup>) (n=66)



39 patients at **43 mg/m<sup>2</sup>** starting dose  
with BSA <1.8

+

27 patients at ~80 mg starting dose  
with BSA ≥1.8 who received an actual  
dose of **>38 mg/m<sup>2</sup>**

# Patient Demographics and Disease Characteristics

## Phase 1b Expansion Study in Ovarian Cancer Included 97 Patients in Safety Analysis Set

		All Dose Levels (N=97)	Dose Group 36 (n=29)	Dose Group 43 (n=66)
<b>Median Age, years (range)</b>		68 (33, 87)	66 (33, 85)	69 (38, 87)
<b>Baseline ECOG PS, n (%)</b>	0	33 (34)	6 (21)	27 (41)
	1	64 (66)	23 (79)	39 (59)
<b>Median Baseline BSA, m<sup>2</sup> (range)</b>		1.82 (1.34, 2.78)	2.12 (1.58, 2.30)	1.77 (1.34, 2.02)
<b>Primary Tumor Type, n (%)</b>	Ovarian	72 (74)	22 (76)	48 (73)
	Fallopian Tube	15 (15)	2 (7)	13 (20)
	Primary Peritoneal	8 (8)	5 (17)	3 (5)
<b>Prior Lines of Therapy, n (%)</b>	1–3	65 (67)	21 (72)	42 (64)
	4+ <sup>a</sup>	32 (33)	8 (28)	24 (36)
<b>Prior Therapy, n (%)</b>	Bevacizumab	68 (70)	17 (59)	49 (74)
	PARPi	57 (59)	13 (45)	43 (65)
<b>Platinum-free Interval,<sup>b</sup> n (%)</b>	0–3 mos	34 (35)	11 (38)	22 (33)
	>3–6 mos	46 (47)	14 (48)	31 (47)
	>6 mos <sup>c</sup>	10 (10)	2 (7)	8 (12)
	Unknown <sup>d</sup>	7 (7)	2 (7)	5 (8)
<b>BRCA1/2 Mutation, n (%)</b>	Yes	15 (15)	3 (10)	11 (17)
	No	65 (67)	21 (72)	43 (65)
	Unknown <sup>e</sup>	17 (18)	5 (17)	12 (18)
<b>NaPi2b Expression by TPS, n (%)</b>	Determined	78 (80)	24 (83)	52 (79)
	High (TPS ≥75)	50 (64)	18 (75)	32 (62)
	Low (TPS <75)	28 (36)	6 (25)	20 (38)
	Not Yet Determined <sup>f</sup>	19 (20)	5 (17)	14 (21)

Data cut: June 10, 2021. Two patients received <30 mg/m<sup>2</sup> and therefore were not included in either dose group.

<sup>a</sup> Three patients enrolled with 5 prior lines of systemic therapy. <sup>b</sup> 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. <sup>c</sup> All patients had received 4 or 5 lines of prior therapy. <sup>d</sup> Treatment dates missing/not provided; unable to determine. <sup>e</sup> BRCA1/2 mutation status not available/not reported. <sup>f</sup> NaPi2b expression not yet determined or tissue unavailable.

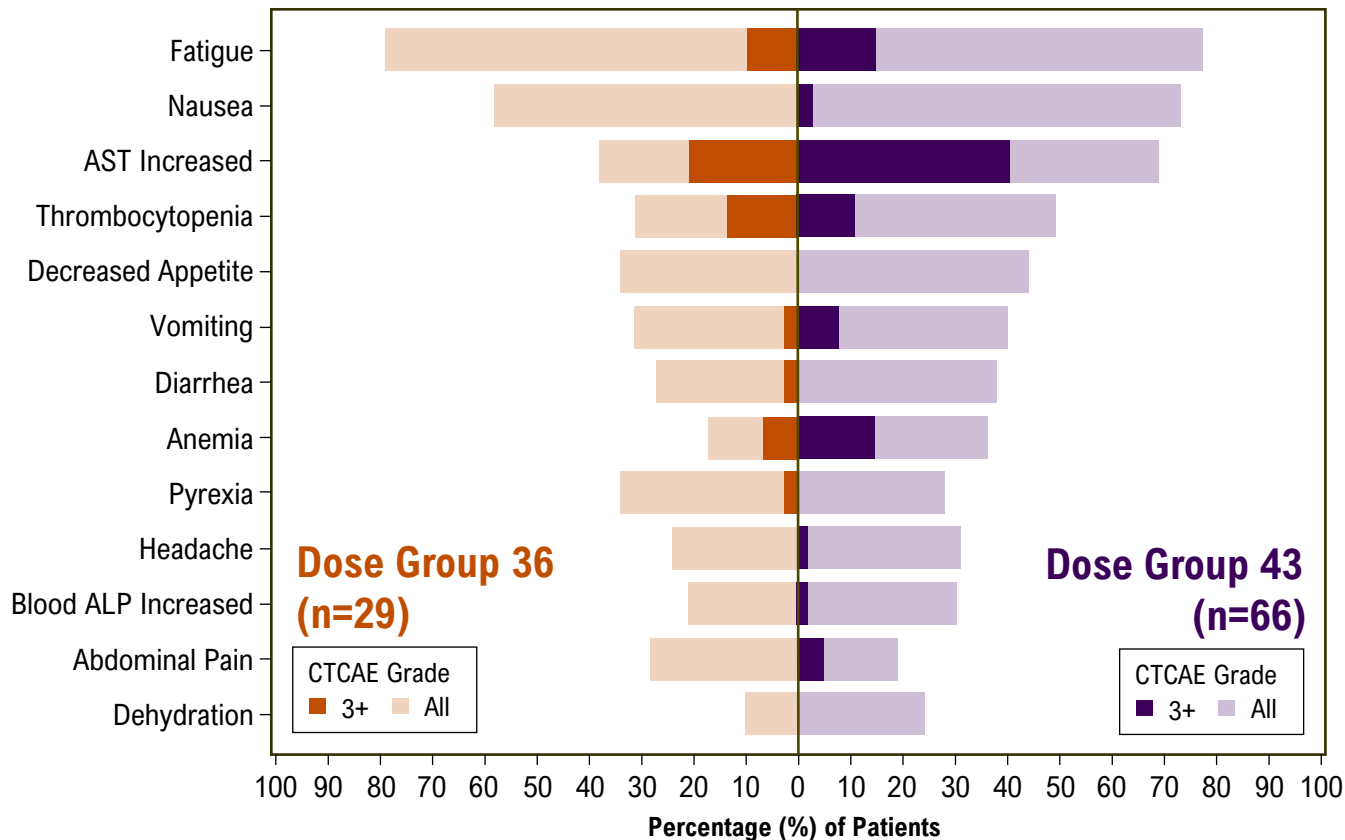
BSA, body surface area; BRCA1/2, breast cancer susceptibility gene 1 or 2; ECOG, Eastern Cooperative Oncology Group; NaPi2b, sodium-dependent phosphate transport protein 2B; PARPi, poly (ADP-ribose) polymerase inhibitor; PS, performance status; TPS, tumor proportion score.



# Treatment-Related AEs by UpRi Dose Group

## Dose Group 36 Had a More Favorable Safety Profile Compared to Dose Group 43

### TRAEs $\geq 20\%$



- No severe ocular toxicity, neutropenia, or peripheral neuropathy in either dose group
- 4 (14%) patients had treatment-related SAEs in Dose Group 36 vs 18 (27%) in Dose Group 43
- Lower frequencies and lower grade pneumonitis occurred in Dose Group 36 (with no Grade 3+) vs Dose Group 43<sup>a</sup>

Data cut: June 10, 2021. Analysis with 95 patients. Two patients received  $<30$  mg/m<sup>2</sup> and therefore were not included in either dose group.

<sup>a</sup> Dose Group 36 pneumonitis: Grade 1–2 (n=2), Grade 3+ (n=0); Dose Group 43 pneumonitis: Grade 1–2 (n=5), Grade 3+ (n=4).

AE, adverse event; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event; TRAE, treatment-related adverse event; UpRi, upifitamab rilsodotin.

# Dose Modification by UpRi Dose Group

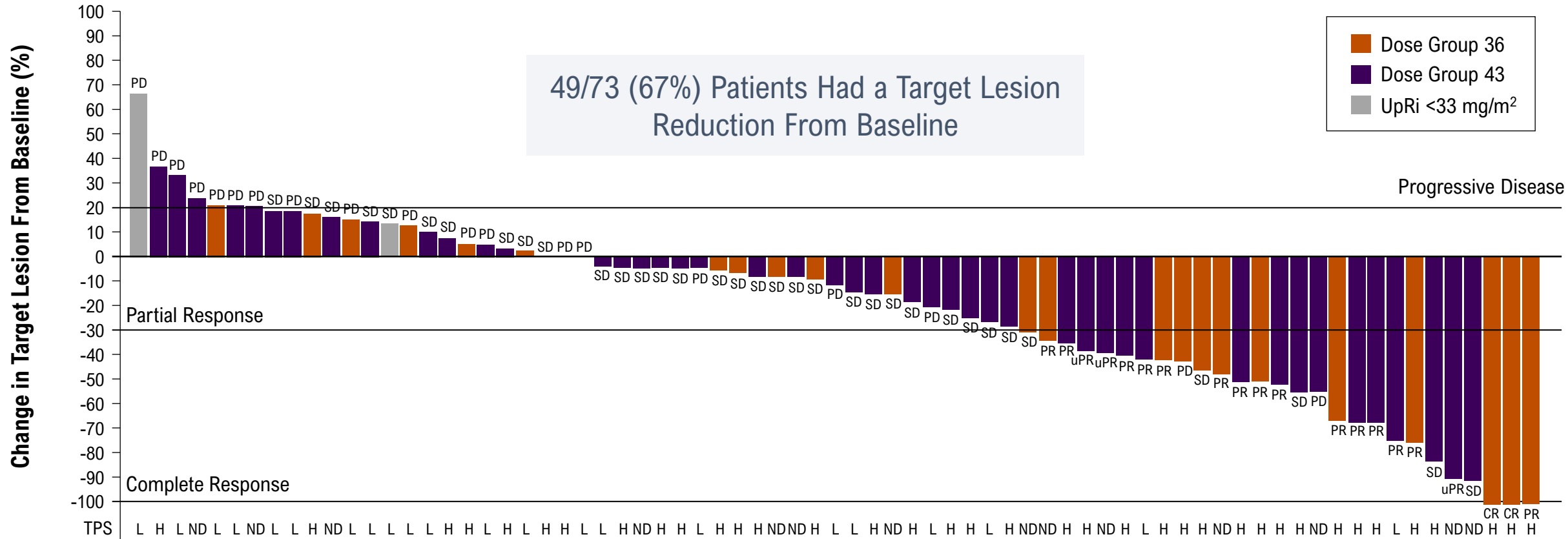
## Dose Group 36 Had Fewer Treatment-Related Dose Modifications and Treatment Discontinuations Compared to Dose Group 43

	Dose Group 36 (n=29)	Dose Group 43 (n=66)
<b>Any Dose Modification d/t TRAE (Reduction, Delay, Discontinuation), n (%)</b>	<b>10 (34)</b>	<b>32 (48)</b>
Dose Reduction d/t TRAE, n (%)	6 (21)	20 (30)
Dose Delay d/t TRAE, n (%)	4 (14)	12 (18)
Dose Discontinuation d/t TRAE, n (%)	2 (7)	8 (12)

Data cut: June 10, 2021. Analysis with 95 patients. Two patients received <30 mg/m<sup>2</sup> and therefore were not included in either dose group. d/t, due to; TRAE, treatment-related adverse event; UpRi, upifitamab rilsodotin.

# Best Response by UpRi Dose Group

Similar Tumor Reduction in Both Dose Groups: Two-thirds of Patients Had Reductions in Target Tumor Lesions by RECIST 1.1



Data cut: June 10, 2021. Analysis with 73 evaluable patients. Two patients excluded as post-baseline tumor measurement shows “Not Measurable”, yet “PD” was assigned by investigator in response dataset. There were 22 unevaluable patients: 4 in Dose Group 36, 2 patient withdrawals (1 enrolled in hospice), 2 patient deaths; 18 in Dose Group 43, 5 patient withdrawals, 1 clinical progression, 3 due to adverse events, 8 deaths, 1 had not reached first scan.

CR, complete response; H, high; L, low; ND, not yet determined; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TPS, tumor proportion score; uPR, unconfirmed partial response; UpRi, upifitamab rilsodotin.

# Confirmed ORR by UpRi Dose Group and NaPi2b Level, Duration of Response

## 44% ORR in Dose Group 36 for Patients With NaPi2b-High Ovarian Cancer

		All Dose Levels	Dose Group 36	Dose Group 43
<b>NaPi2b-High (TPS ≥75)</b>	N	38	16	22
	<b>ORR, n (%)</b>	<b>13 (34)</b>	<b>7 (44)</b>	<b>6 (27)</b>
	CR, n (%)	2 (5)	2 (13)	0
	PR, n (%)	11 (29)	5 (31)	6 (27)
	DCR, n (%)	33 (87)	12 (75)	21 (95)
<b>All NaPi2b Levels</b>	N	75	25	48
	<b>ORR, n (%)</b>	<b>17 (23)</b>	<b>9 (36)</b>	<b>8 (17)</b>
	CR, n (%)	2 (3)	2 (8)	0
	PR, n (%)	15 (20)	7 (28)	8 (17)
	DCR, n (%)	54 (72)	18 (72)	35 (73)

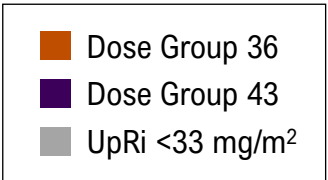
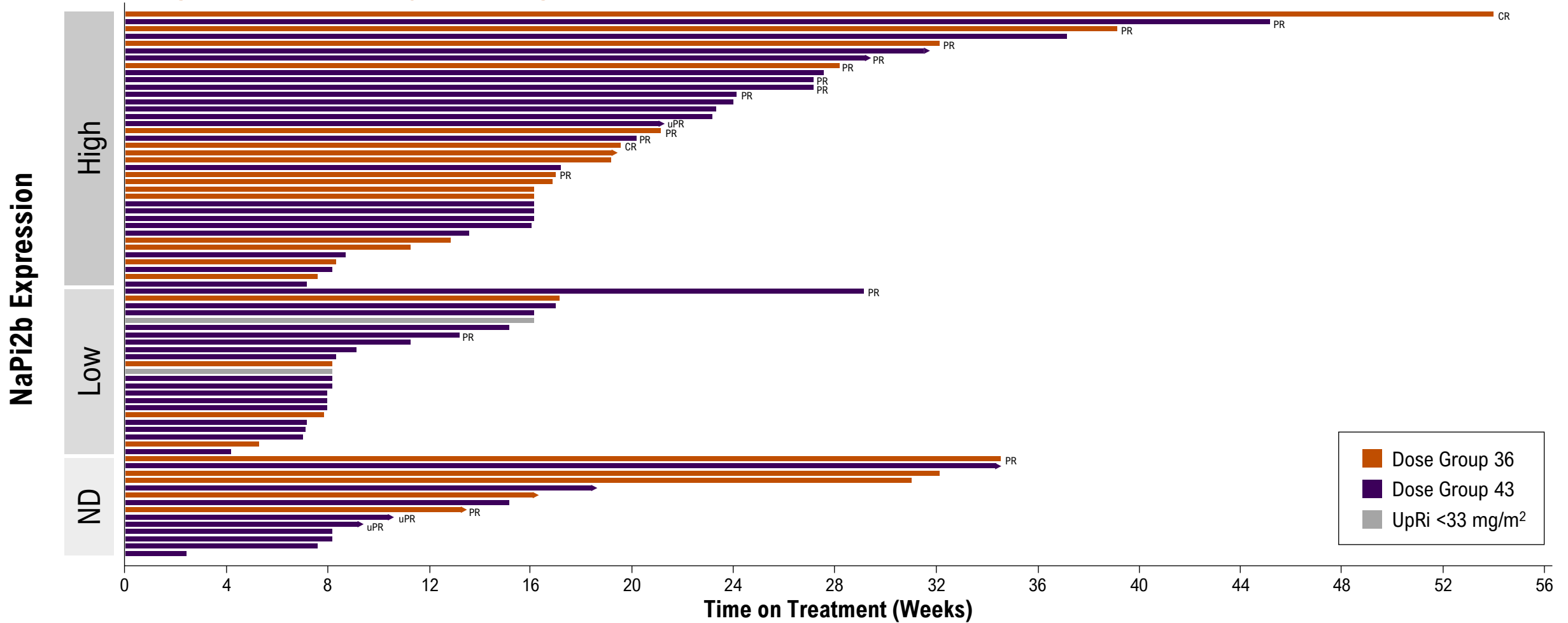
- **Median DoR in patients (all dose levels) with NaPi2b-high ovarian cancer (n=13): 5 months**
- No obvious difference in median DoR observed between Dose Groups 36 and 43

Data cut: June 10, 2021. Two patients received <30 mg/m<sup>2</sup> and therefore were not included in either dose group. All responses are confirmed. There were 75 evaluable patients. There were 22 unevaluable patients: 4 in Dose Group 36, 2 patient withdrawals (1 enrolled in hospice), 2 patient deaths; 18 in Dose Group 43, 5 patient withdrawals, 1 clinical progression, 3 due to adverse events, 8 deaths, 1 had not reached first scan. Of 4 unevaluable patients in Dose Group 36, 2 were NaPi2b-high; of 18 unevaluable in Dose Group 43, 10 were NaPi2b-high.

CR, complete response; DCR, disease control rate; DoR, duration of response; NaPi2b, sodium-dependent phosphate transport protein 2B; ORR, overall response rate; PR, partial response; TPS, tumor proportion score; UpRi, upifitamab rilsodotin.

# Time on UpRi Study in Evaluable Patients

## Trend to Longer Time on Study With High NaPi2b Expression



# UPLIFT (ENGOT-ov67 / GOG-3048)

## UpRi Single-Arm Registrational Trial in Platinum-Resistant Ovarian Cancer



Global  
US, Europe, Australia, Canada

**Patient Population:** HGSOCA progressing after standard treatments; measurable disease per RECIST v1.1; ECOG PS 0 or 1; enrolling regardless of NaPi2b expression

### Key Inclusion Criteria

- Platinum-resistant ovarian cancer (PROC)
- 1–4 prior lines of therapy
- Grade  $\leq 2$  peripheral neuropathy
- Archival or fresh tissue required for biomarker evaluation

### Key Exclusion Criteria

- 1–2 prior lines bevacizumab-naive
- Primary platinum-refractory disease

UpRi 36 mg/m<sup>2</sup> up to  
max 80 mg; IV Q4W

### Primary Endpoint

- Confirmed ORR in NaPi2b-high (N = ~100)

### Secondary Endpoint

- Confirmed ORR in overall population (N = up to ~180 including 100 NaPi2b-high)

### Other Secondary Endpoints

- DoR
- Safety

Prospectively-defined retrospective analysis to validate NaPi2b biomarker cutoff

**NCT03319628: Trial Currently Enrolling Patients**

<sup>a</sup> HGSOCA including fallopian tube and primary peritoneal cancer.

HGSOCA, high-grade serous ovarian cancer; IV, intravenous; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; FPD, first patient dosed; NaPi2b, sodium-dependent phosphate transport protein 2B; ORR, overall response rate; PROC, platinum-resistant ovarian cancer; PS, performance score; Q4W, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; UpRi, upifitamab rilsodotin.

# UP-NEXT (GOG-3049 / ENGOT-OV71-NSGO-CTU)

## Phase 3 Study of UpRi Monotherapy Maintenance vs Placebo in Recurrent Platinum-Sensitive Ovarian Cancer

### Key Enrollment Criteria

- CR, PR, or SD as best response following platinum in recurrent disease
- 2–4 prior lines of platinum (including the immediately preceding platinum)
- NaPi2b-high (TPS  $\geq 75$ )
- Prior PARPi therapy only required for *BRCAMut*

Randomize  
2:1  
N=350

UpRi IV Q4W

Placebo

### Primary Endpoint

- PFS by BICR

### Secondary Endpoints

- PFS by Investigator
- ORR
- OS

**Informed by FDA Feedback and CHMP Scientific Advice; Plans to Initiate in 2022**

# Conclusions

- UpRi, a first-in-class ADC targeting NaPi2b, showed clinically meaningful activity in a population of heavily pre-treated patients with ovarian cancer, without severe ocular toxicity, neutropenia, or neuropathy
- UpRi had notable activity in patients with NaPi2b-high tumors
- Based on analysis of reported UpRi expansion data, Dose Group 36 had a more favorable safety profile while maintaining similar efficacy compared to Dose Group 43
- At the optimized dose of 36 mg/m<sup>2</sup>, UpRi demonstrated robust clinical activity with a differentiated safety profile
- These data support the design of UPLIFT and UP-NEXT registrational studies



# Acknowledgements

## We Thank the Patients, Their Families, and Caregivers for Their Contribution to This Study

### UNITED STATES

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### CANADA

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British Columbia Cancer Agency, Vancouver

### AUSTRALIA

Lifeshouse Australia as trustee for the Lifeshouse Australia Trust, Camperdown  
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Austin Health, Heidelberg, Victoria