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

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BACKGROUND

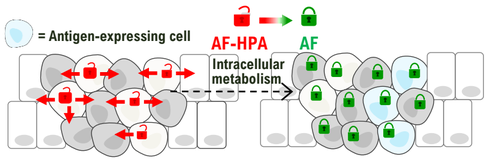
High Unmet Need in Recurrent Ovarian Cancer With Low Activity of Single-Agent Chemotherapy[1–3]

- There remains a high unmet medical need for women with ovarian cancer who have received multiple lines of therapy and are no longer responsive to platinum-based regimens
- Current standard of care is single-agent chemotherapy which has limited efficacy, with ORR of ≤12%, mPFS of only 3–4 months, and mOS of <12 months
- Adverse events associated with chemotherapies include nausea, fatigue, hematologic toxicities, mucositis, alopecia, and peripheral neuropathy

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

Antibody: Humanized monoclonal anti-NaPi2b[4]
Linker: Polymer scaffold; cleavable ester linker[5]
Payload: AF-HPA (DolaLock-controlled bystander effect)[4]
Drug-to-Antibody Ratio (DAR): ~10

Most ADCs have a DAR of 3–4
Higher DAR increases payload delivery per internalization and is expected to increase the therapeutic index[4]

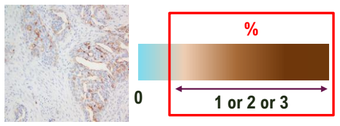


Upon ADC internalization into tumor cells and efficient release of payload, AF-HPA payload is metabolized to AF that remains highly potent but loses the ability to cross the cell membrane, locking it in the tumor, controlling the bystander effect, and, consequently, limiting impact on adjacent healthy cells[5,6]

NaPi2b Is a Sodium-Dependent Phosphate Transporter Broadly Expressed in Ovarian Cancer With Limited Expression in Healthy Tissues[7]

- NaPi2b expressed by tumor cells in two-thirds of patients with high-grade serous ovarian cancer[5]
- NaPi2b is a lineage antigen (not an oncogene product)[4]

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***[5]



METHODS

Study Design[6,8,9]

Patient Population: HGSOC[a] 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/m² cohort initiated in August 2019
43 mg/m² to a max of ~80 mg cohort initiated in December 2019

NCT03319628: Study Closed to Enrollment

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

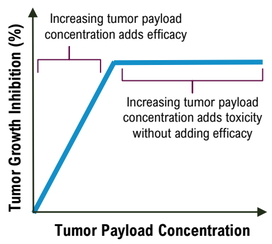
[a] HGSOC including fallopian tube and primary peritoneal cancer.

Analyses Data Sets

- Primary endpoint was investigator-determined ORR defined as the proportion of patients who achieve a confirmed PR or CR per RECIST v1.1
- Efficacy endpoints were analyzed using efficacy response evaluable analysis set, that is, patients for whom baseline response assessment and at least 1 post-baseline response assessment were available
- Safety analyses were conducted on all patients receiving 1 dose of treatment

METHODS (CONT'D)

Correlation of ADC Efficacy and Tumor Payload Concentration: Increasing Dose Beyond the Optimal Threshold May Add Incremental Toxicity Without Incremental Efficacy[10]



- Further analysis utilizing population PK models confirmed efficacy and safety findings showing association between increasing exposure and Grade 3+ AEs
- Preclinically, ADCs have a well-characterized exposure/response relationship
  - ADC efficacy increases with payload tumor concentration up to a plateau
  - Beyond this plateau, additional drug can decrease tolerability without improving efficacy

Dose that optimizes therapeutic index may not be MTD

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

Dose Group 36 (33–38 mg/m²) (n=29)
- 12 patients at **36 mg/m²** 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/m²**

Dose Group 43 (>38–43 mg/m²) (n=66)
- 39 patients at **43 mg/m²** 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/m²**

Two patients received <30 mg/m² and therefore were not included in either dose group.

RESULTS

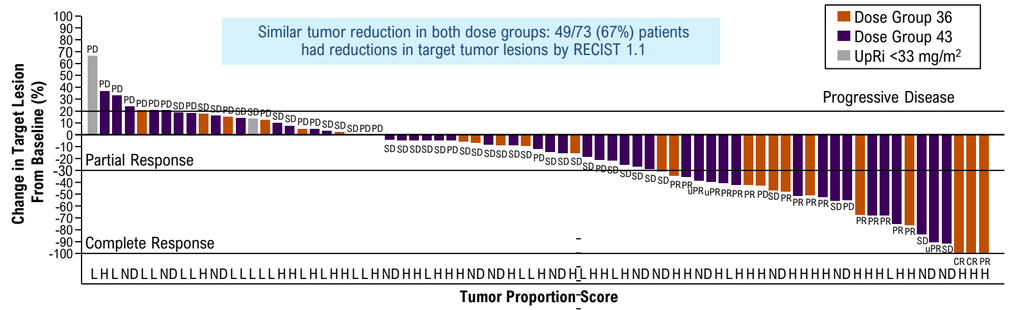
Patient Demographics and Disease Characteristics

		All Dose Levels (N=97)	Dose Group 36 (n=29)	Dose Group 43 (n=66)
Median Age, years (range)		68 (33, 87)	66 (33, 85)	69 (38, 87)
Baseline ECOG PS, n (%)	0	33 (34)	6 (21)	27 (41)
	1	64 (66)	23 (79)	39 (59)
Median Baseline BSA, m² (range)		1.82 (1.34, 2.78)	2.12 (1.58, 2.30)	1.77 (1.34, 2.02)
Primary Tumor Type, n (%)	Ovarian	72 (74)	22 (76)	48 (73)
	Fallopian Tube	15 (15)	2 (7)	13 (20)
	Primary Peritoneal	8 (8)	5 (17)	3 (5)
Prior Lines of Therapy, n (%)	1–3	65 (67)	21 (72)	42 (64)
	4+[a]	32 (33)	8 (28)	24 (36)
Prior Therapy, n (%)	Bevacizumab	68 (70)	17 (59)	49 (74)
	PARPi	57 (59)	13 (45)	43 (65)
Platinum-free Interval,[b] n (%)	0–3 mos	34 (35)	11 (38)	22 (33)
	>3–6 mos	46 (47)	14 (48)	31 (47)
	>6 mos[c]	10 (10)	2 (7)	8 (12)
	Unknown[d]	7 (7)	2 (7)	5 (8)
***BRCA1/2* Mutation, n (%)**	Yes	15 (15)	3 (10)	11 (17)
	No	65 (67)	21 (72)	43 (65)
	Unknown[e]	17 (18)	5 (17)	12 (18)
NaPi2b Expression by TPS, n (%)	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)
	ND[f]	19 (20)	5 (17)	14 (21)

Data cut: June 10, 2021. Two patients received <30 mg/m² and therefore were not included in either dose group. [a] Three patients enrolled with 5 prior lines of systemic therapy. [b] 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. [c] All patients had received 4 or 5 lines of prior therapy. [d] Treatment dates missing/not provided; unable to determine. [e] *BRCA1/2* mutation status not available/not reported. [f] NaPi2b expression not yet determined or tissue unavailable.

RESULTS (CONT'D)

Response by UpRi Dose Group



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.

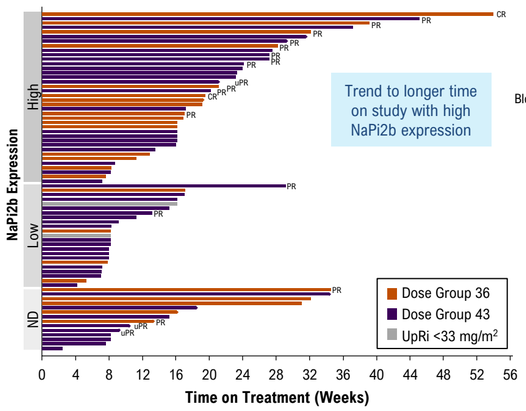
Confirmed ORR by UpRi Dose Group and NaPi2b Level, DoR

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

Data cut: June 10, 2021. Two patients received <30 mg/m² 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.

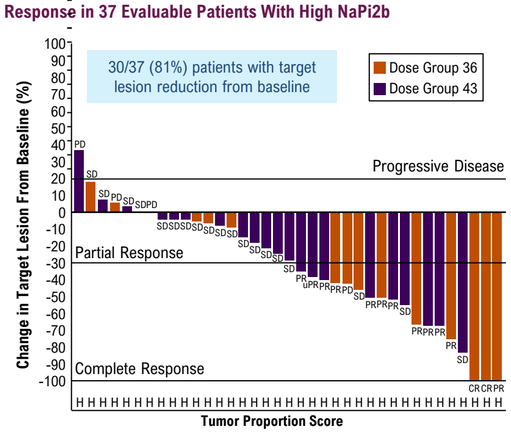
- 23% ORR for patients treated with UpRi at all dose levels across all NaPi2b expression levels
- 44% ORR in Dose Group 36 for patients with NaPi2b-high ovarian cancer
- **Median DoR in patients (all dose levels) with NaPi2b-high ovarian cancer (n=13): 5 months**
- No obvious difference in median DoR observed between Dose Groups 36 and 43

Time on UpRi Study in Evaluable Patients (n=75)



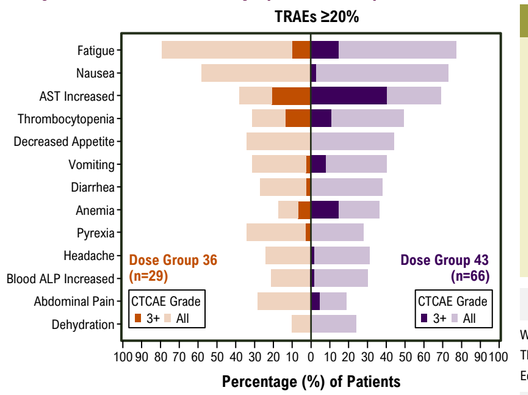
Data cut: June 10, 2021. Median follow-up time for all patients was 21.3 weeks.

Response in 37 Evaluable Patients With High NaPi2b



Data cut: June 10, 2021.

Safety: Treatment-Related AEs by UpRi Dose Group



- **Dose Group 36 had a more favorable safety profile compared to Dose Group 43**
- 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[a]

Data cut: June 10, 2021. Analysis with 95 patients. Two patients received <30 mg/m² and therefore were not included in either dose group. [a] 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).

Safety: Dose Modification by UpRi Dose Group

	Dose Group 36 (n=29)	Dose Group 43 (n=66)
Any Dose Modification d/t TRAE (Reduction, Delay, Discontinuation), n (%)	**10 (34)**	**32 (48)**
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/m² and therefore were not included in either dose group.

- Dose Group 36 had fewer treatment-related dose modifications and treatment discontinuations compared to Dose Group 43

ONGOING / UPCOMING STUDIES

UPLIFT (ENGOT-ov67 / GOG-3048)

Global: US, Europe, Australia, Canada

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

Patient Population: HGSOC[a] 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
- 1–4 prior lines of therapy
- Grade ≤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/m² 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

[a] HGSOC including fallopian tube and primary peritoneal cancer.

NCT03319628: Trial Currently Enrolling Patients

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 ≥75)
- Prior PARPi therapy only required for *BRCA*mut

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
- Therapeutic activity was positively associated with NaPi2b expression
- 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/m², UpRi demonstrated robust clinical activity with a differentiated safety profile
- These data support the design of UPLIFT registrational study

ACKNOWLEDGEMENTS

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ADDITIONAL INFORMATION

Abbreviations: ADC, antibody drug conjugate; AE, adverse event; AF, auristatin F; AF-HPA, auristatin F hydroxypropylamide; ALP, alkaline phosphatase; AST, aspartate transaminase; BICR, blinded independent central review; *BRCA*, breast cancer susceptibility gene; *BRCA*mut, *BRCA* mutated; BSA, body surface area; CHMP, Committee for Medicinal Products for Human Use; CR, complete response; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; DAR, drug-to-antibody ratio; DCR, disease control rate; DoR, duration of response; d/t, due to; ECOG, Eastern Cooperative Oncology Group; FDA, Food and Drug Administration; Gr, Grade; H, high; HGSOC, high-grade serous ovarian cancer; HRD, homologous recombination deficiency; IHC, immunohistochemistry; IV, intravenous; L, low; mOS, median overall survival; mPFS, median progression-free survival; MRI, magnetic resonance imaging; MTD, maximum tolerated dose; NaPi2b, sodium-dependent phosphate transport protein 2B; ND, not yet determined; ORR, overall response rate; PARPi, poly (ADP-ribose) polymerase inhibitor; PD, pharmacodynamic; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; PS, performance score; Q4W, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; SAE, serious adverse event; SD, stable disease; TPS, tumor proportion score; TRAE, treatment-related adverse event; uPR, unconfirmed PR; UpRi, upifitamab rilsodotin.