ESGO
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UPLIFT (ENGOT-ov67/GOG-3048): Results from the Phase 2 Trial of Upifitamab Rilsodotin (UpRi; XMT-1536), a NaPi2b-Directed Dolaflexin Antibody-Drug Conjugate (ADC) in Platinum-Resistant Ovarian Cancer (PROC)

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Declaration of Interest

Consulting/Advisory: ImmunoGen, Seagen, Akesobio, EISAI, GSK, AstraZeneca, Mersana Therapeutics, eTheRNA immunotherapies NV, Kartos

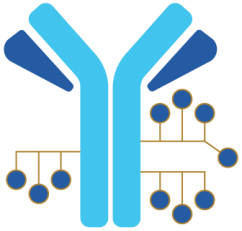
Travel Expenses: Roche, Genmab, Amgen

Educational fees: Kartos, MSD, Medscape Oncology, TouchIME

Functions in societies: President of ESGO; Chair of ENGOT Early Drug Development Network

Background

- Effective and well-tolerated treatments for Platinum-Resistant Ovarian Cancer (PROC) remain an unmet medical need
- Standard of care single-agent chemotherapy has limited efficacy, with response rates at ~12%[1]
- NaPi2b is broadly expressed in solid tumors, including high-grade serous epithelial ovarian cancer*, with expression on healthy type II pneumocytes in the lung, but limited expression in other healthy tissue[2,3]
- **Upifitamab rilsodotin (UpRi; XMT-1536)** is a NaPi2b-directed Dolaflexin ADC designed to minimize the common toxicities associated with ADCs (peripheral neuropathy, neutropenia, ocular toxicity)



Antibody: Humanized monoclonal anti-SLC34A2 (NaPi2b)

Linker: Polymer scaffold; Stochastic cysteine conjugation

Payload: AF-HPA - controlled bystander effect; highly potent anti-tubulin inhibitor selectively toxic to rapidly dividing cells

Drug-to-Antibody Ratio: Heterogeneous; ~10

UPLIFT (ENGOT-ov67 / GOG-3048) was a global, single-arm Phase 2 Trial evaluating UpRi in adult patients with platinum-resistant high-grade serous epithelial ovarian, primary peritoneal, or fallopian tube cancers

1. Richardson et al., JAMA Oncol, 2023; 2. *Lin et al., Clin Cancer Res 2015; 3. Kiyamova et al. Exp Oncol. 2011*
* Includes fallopian tube and primary peritoneal cancers; NaPi2b, sodium dependent phosphate transport protein; ADC, antibody drug conjugate

UPLIFT (ENGOT-ov67/GOG-3048): Study Design

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[b] ovarian cancer
- 1–4 prior lines of therapy
- Grade ≤2 peripheral neuropathy
- Available archived or fresh tissue for retrospective NaPi2b evaluation

Key Exclusion Criteria

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

UpRi 36 mg/m2 up to max 80 mg; IV Q4W

Primary Endpoint

- Confirmed INV-assessed ORR in NaPi2b-positive (TPS ≥75)

Secondary Endpoints

- Confirmed INV-assessed ORR in overall population
- Confirmed ORR by BICR in the NaPi2b positive and in the ITT population
- INV-assessed DOR in the NaPi2b positive population
- Safety

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[a] HGSOC including fallopian tube and primary peritoneal cancer. [b] Platinum-resistant is defined as disease that has progressed within 6 months of last dose of platinum.
DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HGSOC, high-grade serous ovarian cancer; IV, intravenous;
NaPi2b, sodium-dependent phosphate transport protein 2B; ORR, overall response rate; q4w, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; UpRi, upifitamab rilsodotin; TPS, Tumor Proportion Score.

Patient Demographics and Disease Characteristics

		NaPi2b Positive (N=141)	ITT Population (N=268)
Median Age (years)		60.0	61.5
Median Baseline BSA, m^2 (min, max)		1.740 (1.38, 2.43)	1.740 (1.38, 2.43)
Baseline ECOG Performance Status	0	73 (51.8%)	154 (57.5%)
	1	68 (48.2%)	114 (42.5%)
Central NaPi2b Expression TPS	Negative [TPS<75]	0	123 (45.9%)
	Positive [TPS≥75]	141 (100.0%)	141 (52.6%)
	ND[a]	0	4 (1.5%)
Median Time Since Initial Diagnosis (mos)		32.88	35.38
Prior Lines of Anti-Cancer Therapy	1-2	46 (32.6%)	72 (26.9%)
	3	47 (33.3%)	113 (42.2%)
	4	48 (34.0%)	83 (31.0%)
Number of Lines of Prior Therapy in a Platinum-Resistant Setting	0	66 (46.8%)	125 (46.6%)
	1-2	70 (49.6%)	137 (51.1%)
	3	5 (3.5%)	6 (2.2%)
Patients with Prior Bev/Bev Biosimilar		117 (83.0%)	224 (83.6%)
Patients with Prior PARPi		97 (68.8%)	184 (68.7%)
Median Duration of Most Recent PFI[b] (mos)		3.52	3.48

- 52.6% (N=141) of patients determined to be NaPi2b positive (TPS≥75)
- Approximately 1/3 of patients had 4 prior lines of therapy
- More than half of patients had at least 1 prior therapy in the PROC setting
- 83% and 69% of patients had prior bev or prior PARPi, respectively

[a] NaPi2b expression not determined; [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

BSA, body surface area; ECOG, Eastern Cooperative Oncology Group; NaPi2b, sodium-dependent phosphate transport protein 2B; TPS, tumor proportion score; PARPi, poly (ADP-ribose) polymerase inhibitor

Investigator-Assessed Objective Response Rate in NaPi2b Positive, NaPi2b Negative and ITT Population

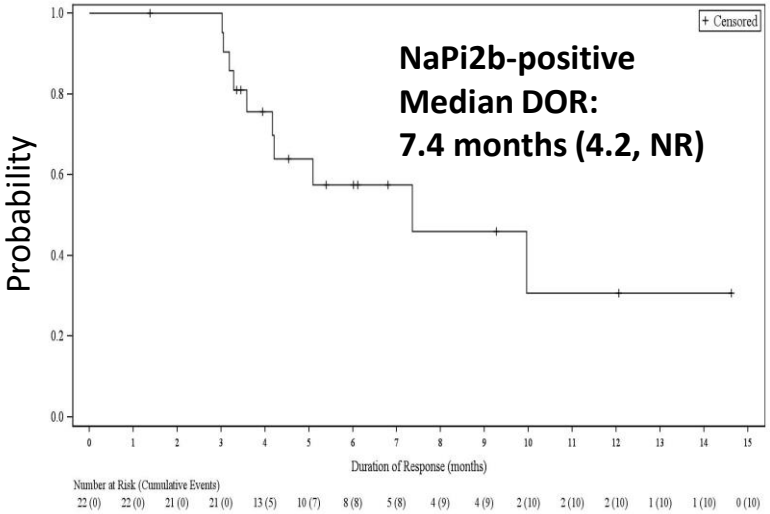
	NaPi2-Positive Population (TPS ≥75)	NaPi2b-low Population (TPS <75)	ITT Population
N	141	127	268
ORR[a], n (%); Two-sided 95% CI	22 (15.6%) 10.0%, 22.7%	13 (10.2%) 5.6%, 16.9%	35 (13.1%) 9.3%, 17.7%
CR, n (%)	2 (1.4%)	1 (0.8%)	3 (1.1%)
PR, n (%)	20 (14.2%)	12 (9.4%)	32 (11.9%)
DCR[b]	93 (66.0%)	64 (50.4%)	157 (58.6%)

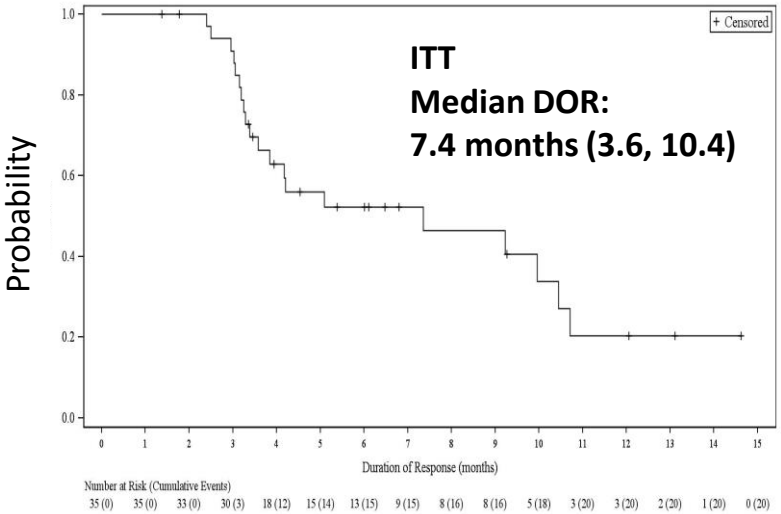
Biomarker did not appear to enrich for response

Data cut: May 31, 2023

[a]ORR is determined by investigator radiologic review and defined as the proportion of patients who achieve a confirmed CR or PR per RECIST v1.1.The exact two-sided 95% CI is calculated based on binomial distribution using the Clopper-Pearson method; [b]DCR is defined as the proportion of patients who achieve a confirmed CR, PR, or SD

Investigator-Assessed Duration of Response: NaPi2b-Positive Population (N=22) and ITT (N=35)





Data cut: May 31, 2023

DOR, duration of response; NaPi2b, sodium-dependent phosphate transport protein 2B; NR, not reached; ITT, intent to treat

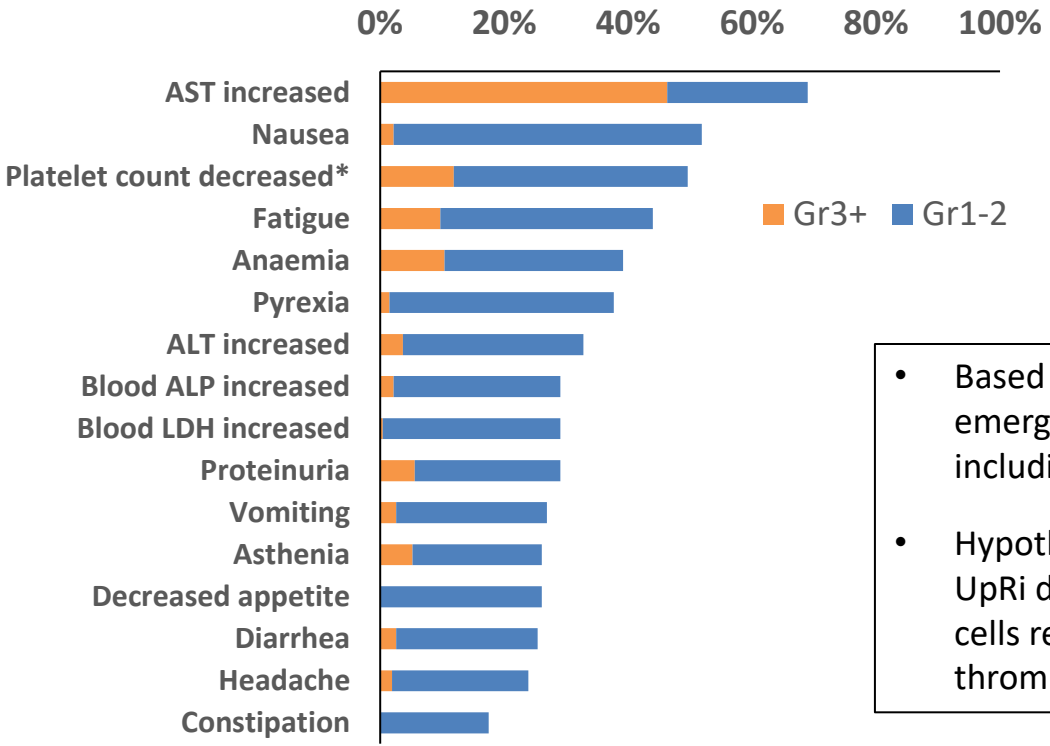
Overall Summary of TEAEs Leading to Discontinuation/Delay/Hold

	UPLIFT Safety Population (ITT; N=268)
N	268
Any TEAE Leading to Drug Discontinuation	70 (26.1%)
Any TEAE Leading to Dose Delay/Hold	110 (41.0%)
Any TEAE Leading to Dose Reduction	72 (26.9%)
Any TEAE Leading to Death[a]	15 (5.6%)

Data cut: May 31, 2023

[a]TEAEs leading to death: Intracranial hemorrhage (N=3); sepsis (N=3), sudden death (N=2), and following events were seen in one participant each: tumor hemorrhage, pulmonary hemorrhage, acute MI, acute pulmonary edema, lymphangitic carcinomatosis, peritoneal perforation, circulatory shock

TRAEs Observed in ≥15% of Patients (N=268)



Data cut: May 31, 2023

* Includes thrombocytopenia

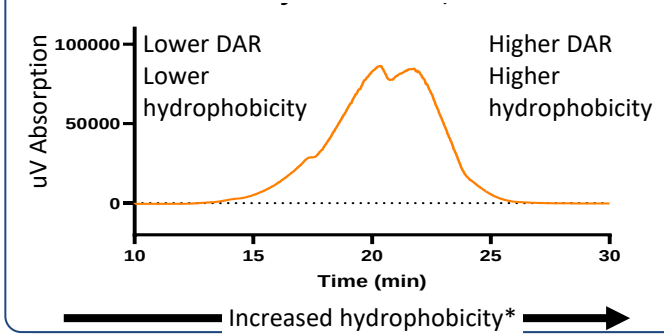
- G3 peripheral neuropathy and neutropenia occurred in <1%; no G3+ ocular toxicity
- Pneumonitis occurred in 9.7% of patients, 0.7% G3 (no G4 or G5); believed to be on-target toxicity due to NaPi2b expression on Type II pneumocytes in the lungs

- Based on aggregate analysis of bleeding cases, treatment emergent G3+ hemorrhage occurred in 5.6% of patients, including 5 G5 (fatal) cases
- Hypothesize that the high-DAR sub-population within UpRi disproportionately delivered payload to endothelial cells resulting in off-target toxicities, including thrombocytopenia and bleeding

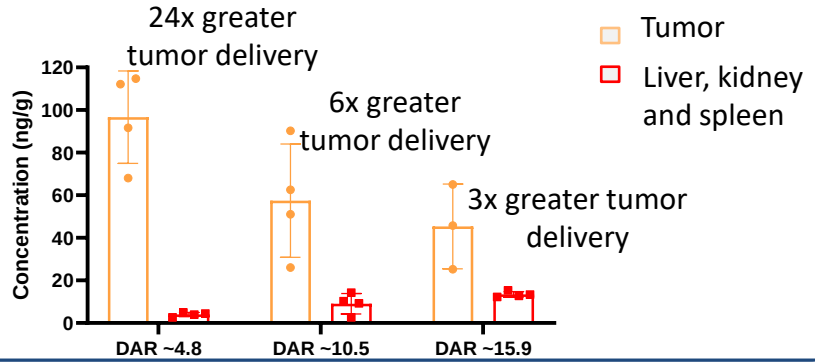
TRAE, Treatment related adverse events

Dolaflexin's Heterogeneity and High-DAR Sub-Populations are Believed to Have Contributed to Off-Target Toxicities

Dolaflexin Heterogeneous ADC population – an ADC sub-population mixture



Dolaflexin High-DAR Sub-Populations Show Reduced Tumor-Specific Delivery



- A heterogeneous ADC mixture, UpRi is composed of ADCs with a wide range of DARs that average a DAR of ~10
- Sub-population fractionation of a Dolaflexin ADC (upper right) suggests reduced tumor-specific delivery at the higher DAR compared to lower DAR
- Hypothesized that the high-DAR subpopulation may have reduced UpRi's efficacy while also increasing toxicity, including potentially thrombocytopenia and bleeding

* As measured by hydrophobic interaction chromatography, 280 nanometers

Conclusion

UPLIFT failed to meet its primary endpoint, confirmed ORR in NaPi2b-positive patients, criterion (lower limit of 95% CI >12%)

Investigator-assessed efficacy showed modest anti-tumor activity:

- Observed ORR in NaPI2b-positive was 15.6% (95% CI 10.0, 22.7)
- Observed ORR in ITT was 13.1% (95% CI 9.3, 17.7)
- Biomarker did not appear to enrich for response
- Durable response observed in NaPi2b positive responders: DOR 7.4 months (95% CI 4.2, NR)

Safety:

- Most common TRAEs included transient AST increase, nausea, platelet count decrease/thrombocytopenia, fatigue, and anemia
- G3+ bleeding, including fatal cases observed; hypothesize that UpRi's high-DAR sub-populations disproportionately delivered payload to endothelial cells, resulting in off-target toxicities
- Generally low grade pneumonitis observed; believed to be on-target toxicity due to NaPi2b expression on Type II pneumocytes in the lungs

Based on the efficacy not meeting prespecified primary endpoint criterion, the sponsor discontinued the development of UpRi

Acknowledgments

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