SGO
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Efficacy and safety of luveltamab tazevibulin in patients with recurrent platinum-resistant ovarian cancer: results from the dose-optimization stage of the REFRαME-O1 (GOG-3086, ENGOT-79OV, and APGOT-OV9) phase 2/3 study

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Financial Disclosure for: Prof Jung-Yun Lee

I have the following financial relationships with ACCME defined ineligible companies to report over the past 24 months:

❖ Personal financial interests

- Lectures – AstraZeneca, Eisai, GSK, MSD, Roche, Takeda
- Role as Advisory board positions – AstraZeneca, CanariaBio, DS, Eisai, Genmab, GII, ImmunoGen, Merck, MSD, Seagen, Sutro, Regeneron

❖ Institutional financial interest

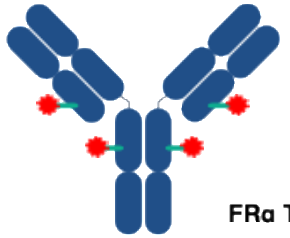
- Abbvie, Advenchen, Ascendis Pharma, Alkermes, AstraZeneca, Beigene, BergenBio, BMS, CanariaBio, Corcept, Cellid, CKD, Clovis Oncology, Daiichi Sankyo, Eisai, Genmab, Genemedicine, GII, GSK, ImmunoGen, Janssen, Kelun, Merck, Mersana, MSD, Novartis, Onconic Therapeutics, ONO, Regeneron, Roche, Seagen, Sutro, Synthon, TORL-bio, Takeda, Zymeworks

Unlabeled / Investigational Uses

I will be discussing an investigational use of a pharmaceutical product.

This presentation describes the outcomes from Phase 2 (dose optimization) of a phase 2/3 study of luveltamab tazevibulin currently under investigation for use in platinum-resistant ovarian cancer.

Background



Luvelta
FRα Targeted ADC

Luveltamab tazevibulin (luvelta) is a novel tubulin-ADC designed to target cancers with broad range of FRα expression, including recurrent PROC

Linker

Utilizes proprietary, high value conjugation site to **improve linker stability** outside the tumor

Toxic Payload "Warhead"

DAR 4 hemiasterlin
- **High potency** tubulin inhibitor
- High **ICD** & **bystander** effect
- **Low P-gp** substrate

FC Domain

FcγR-deficient ADCs mitigates off-target toxicity

- STRO-002-GM1: promising clinical efficacy with manageable safety profile
  - **ORR of 43.8% (5.2 mg/kg)** and **31.3% (4.3 mg/kg)** in patients with recurrent ovarian cancer and FRα >25% by TPS
- REFRαME-O1 is an ongoing global phase 2/3 registrational study of luvelta in patients with PROC and FRα ≥25% by TPS
- Herein, we report outcomes from the phase 2 (dose-optimization) portion of the REFRαME-O1 (NCT05870748) study

ADC, antibody-drug conjugate; DAR, drug-to-antibody ratio; FcγR, fragmented crystal-gamma receptor; FRα, folate receptor alpha; ICD, immunogenic cell death; ORR, overall response rate; P-gp, P-glycoprotein; PROC, platinum-resistant ovarian cancer; TPS, tumor proportion score.

REFRaME|O1 (GOG-3086, ENGOT-79OV, and APGOT-OV9) Study Design

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Phase 3: Currently enrolling

Eligibility

- **PROC**
- 1–3 prior lines
- ECOG PS 0–1
- FRα expression ≥25%, at any staining intensity
- Excludes primary platinum refractory

Phase 2: Dose Optimization

R 1:1

- N=25 → Luvelta dose A: 5.2 mg/kg IV Q3W + prophylactic G-CSF 4.3 mg/kg after 2 cycles
- N=25 → Luvelta dose B: 4.3 mg/kg IV Q3W

Phase 3: Randomized Trial

R 1:1

- N= ~258 → Luvelta 5.2 mg/kg IV Q3W + prophylactic G-CSF 4.3 mg/kg after 2 cycles
- N= ~258 → Investigator's choice chemotherapy

Key Endpoints

- Primary analysis
  - Primary endpoint: PFS
  - Secondary endpoints: OS, safety
  - Exploratory endpoints: ADAs, CA 125 response, PK, PROs
- Interim analysis
  - Primary endpoint: ORR
  - Secondary endpoints: DOR, safety

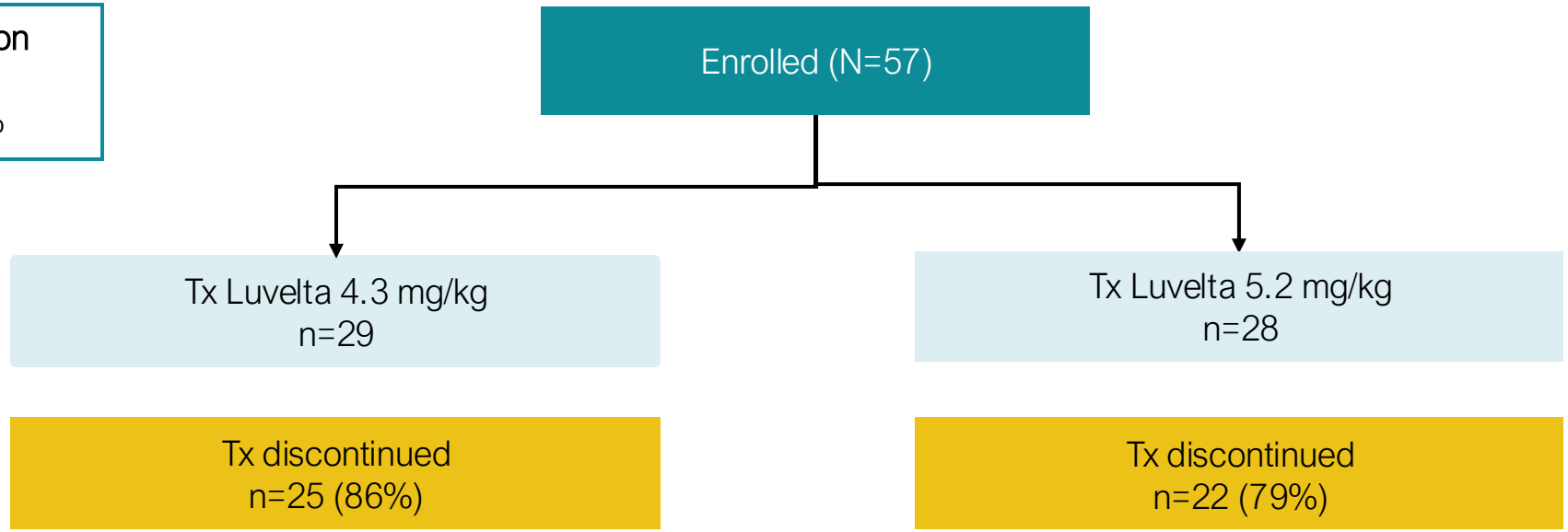
Phase 2: Dose Optimization Analyses

- **Timing:** LPI + 4 cycles (2 postbaseline imaging;12 weeks) F/U
- **Primary analysis:** safety, investigator-assessed ORR (RECIST v1.1), PK
- **Subanalyses:** ORR by FRα expression levels (PS2+ <75% vs ≥75%)
- No formal statistics

ADAs, antidrug antibodies; CA 125, cancer antigen 125; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FRα, folate receptor alpha; F/U, follow up; G-CSF, granulocyte colony-stimulating factor; IV, intravenous; LPI, last patient in; luvelta, luveltamab tazevibulin; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PROC, platinum-resistant ovarian cancer; PROs, patient-reported outcomes; PS, positive staining; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1. PK, pharmacokinetics

Phase 2 Patient Disposition

Screening FRα expression
- ≥25% by TPS: 82%
- ≥75% by PS2+: 42%



Tx discontinuation

- Progressive disease: 68.4%
  - 4.3 mg/kg: 65.5%
  - 5.2 mg/kg: 71.4%
- Adverse events: 7.0%
  - 4.3 mg/kg: 10.3%
  - 5.2 mg/kg: 3.6%

FRα, folate receptor alpha; PS, positive staining; TPS, tumor proportion score; Tx, treatment; WOC withdrawal of consent; WOC: 8.5% (4.3mg/kg: 10.3% and 5.2mg/kg: 3.6%)

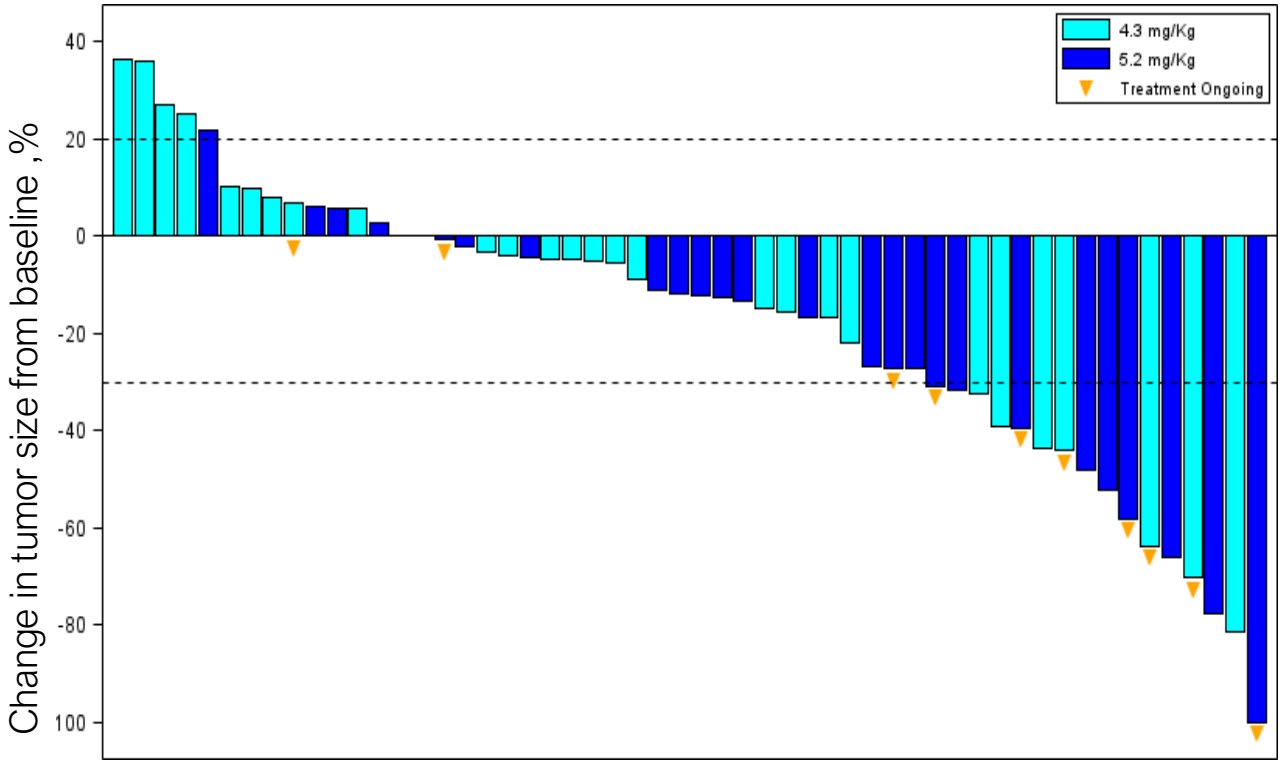
Patients: Baseline Characteristics

Characteristic	Starting dose 4.3 mg/kg N=29	Starting dose 5.2 mg/kg N=28
Median age, years (range)	59.0 (42–81)	60.5 (41–81)
ECOG PS, n (%) 0 1	 17 (58.6) 12 (41.4)	 14 (50.0) 14 (50.0)
Median lines of prior treatments (range)	2 (1–3)	2 (1–3)
Prior treatment, n (%) Bev PARPi	 23 (79.3) 16 (55.2)	 25 (89.3) 15 (53.6)
Ascites, n (%)	4 (13.8)	8 (28.6)
PS2+ status, n (%) <75% ≥75%	 11 (37.9) 18 (62.1)	 12 (42.9) 16 (57.1)

Baseline characteristics were generally balanced between the two starting doses

Bev, bevacizumab; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PARPi, poly(ADP-ribose) polymerase inhibitors; PS, positive staining.

Efficacy: Selected Dose of 5.2 mg/kg + G-CSF Followed by 4.3 mg/kg Showed Higher Response Rate

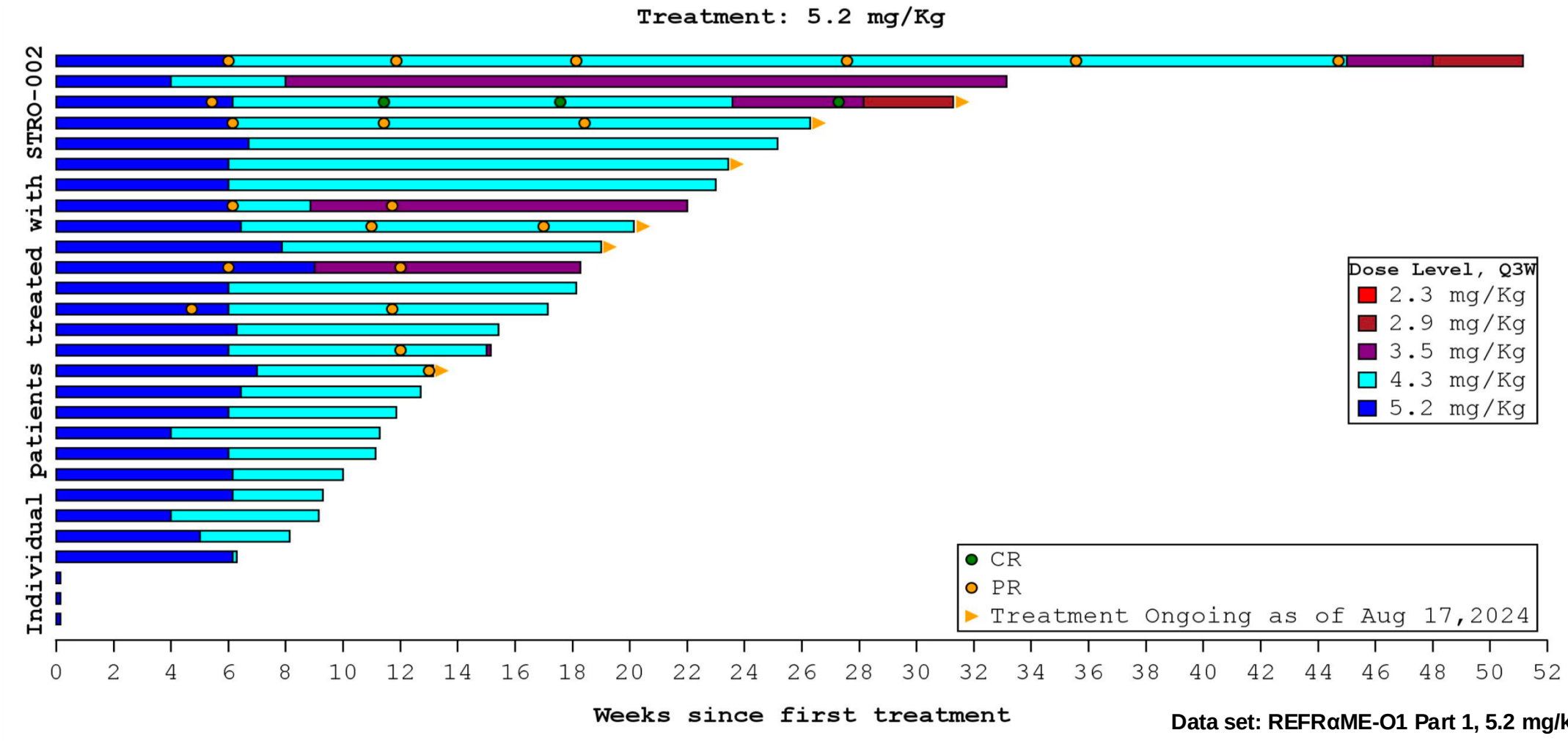


Tumor response (efficacy evaluable)*	Starting Dose 5.2 mg/kg N=25*	Starting Dose 4.3 mg/kg N=29
Best response, n (%)		
CR	1(4.0)	0
PR	7 (28.0)**	4 (13.8)
SD	17 (68.0)	16 (55.2)
PD	1 (4.0)	9 (31.0)
ORR (95% CI)	32% (17,50)**	13.8% (3.9, 32)
DCR (95% CI)	96% (80,99.9)**	69% (49,85)
Time to response, (range)	6.0 wk (4.7–11)	6.4 wk (5.4-11.9)

*Three patients were not efficacy evaluable; **After data extraction, one additional patient experienced a confirmed PR and is included in the analysis.

CI, confidence interval; CR, complete response; DCR, disease control rate; G-CSF, granulocyte colony-stimulating factor; Iuvelta, luveltamab tazevibulin; ORR, overall response rate; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; SD, stable disease.

Early Onset of Responses After 2 Cycles of 5.2mg/kg and Sustained Treatment at 4.3 mg/kg Dose



Data set: REFRαME-O1 Part 1, 5.2 mg/kg, ITT, n=28

CR, complete response; PR, partial response; Q3W, every 3 weeks.

Luvelta Demonstrated Consistent Efficacy in Patients with PROC for High and Low/Medium FRα Expression *

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Data Set (Efficacy Evaluable)	REFRαME-O1 Phase 2 (FRα ≥25% by TPS)	
Dose Cohort	**5.2 mg/kg (N=25)**	
	PS2+ ≥75% n=13	PS2+ <75% n=12
ORR (95% CI)	30.8% (9.1%, 61.4%)	33.3%** (12.3%, 60.9%)
DCR (95% CI)	100% (75.3%,100%)	91.7%** 61.5%, 99.8%)

*High is PS2+ ≥75% and Low/Medium is PS2+<75% Levels of FRα expression.
**After data extraction, one additional patient experienced a confirmed PR and is included in the analysis

CI, confidence interval; DCR, disease control rate; luvelta, luveltamab tazevibulin; ORR, overall response rate; PR, partial response; PS, positive staining.

Most Common TEAEs Were Grade 1-2 Arthralgia, Nausea, and Constipation

TEAE, n (%)	Starting dose 4.3 mg/kg N=29		Starting dose 5.2 mg/kg N=28		Total population N=57	
	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3
Patients with ≥1 TEAE	29 (100)	19 (65.5)	28 (100)	22 (78.6)	57 (100)	41 (71.9)
Arthralgia	19 (65.5)	4 (13.8)	21 (75.0)	3 (10.7)	40 (70.2)	7 (12.3)
Nausea	18 (62.1)	1 (3.4)	17 (60.7)	1 (3.6)	35 (61.4)	2 (3.5)
Constipation	19 (65.5)	1 (3.4)	12 (42.9)	3 (10.7)	31 (54.4)	4 (7.0)
Neutropenia*	14 (48.3)	8 (27.6)	12 (42.9)	8 (28.6)	26 (45.6)	16 (28.1)
Febrile Neutropenia	0	0	0	0	0	0
Fatigue	16 (55.2)	1 (3.4)	10 (35.7)	1 (3.6)	26 (45.6)	2 (3.5)
Myalgia	13 (44.8)	3 (10.3)	12 (42.9)	2 (7.1)	25 (43.9)	5 (8.8)
Abdominal pain	11 (37.9)	2 (6.9)	11 (39.3)	3 (10.7)	22 (38.6)	5 (8.8)
Neuropathy**	11 (37.9)	1 (3.4)	11 (39.3)	0	22 (38.6)	1 (1.8)
Decreased appetite	11 (37.9)	0	11 (39.3)	0	22 (38.6)	0
Vomiting	8 (27.6)	1 (3.4)	12 (42.9)	0	20 (35.1)	1 (1.8)
Insomnia	8 (27.6)	0	9 (32.1)	2 (7.1)	17 (29.8)	2 (3.5)
Alanine aminotransferase increased	7 (24.1)	1 (3.4)	8 (28.6)	2 (7.1)	15 (26.3)	3 (5.3)
Alopecia	7 (24.1)	0	7 (25.0)	0	14 (24.6)	0

*Neutropenia includes neutropenia, neutrophil count decreased, and febrile neutropenia; **Neuropathy includes neuropathy peripheral, peripheral sensory neuropathy and neurotoxicity.

The safety profile was similar between the 2 dose groups

Neutropenia occurred with less frequency than in previous trials with updated management and G-CSF prophylaxis guidelines

G-CFS, granulocyte colony-stimulating factor; TEAE, treatment-emergent adverse event.

Conclusions

- The optimized dose of luvelta was selected as 5.2 mg/kg + G-CSF x 2 cycles then 4.3 mg/kg
  - **Improved ORR, low discontinuation rate, and similar safety profile compared to 4.3 mg/kg starting dose**
- Luvelta demonstrated clinical anti-tumor activity in PROC with FRα ≥25%
  - Consistent in disease with high (PS2+ ≥75%) and low to medium (PS2+ <75%) FRα expression
- Safety was manageable and adverse events were reversible
  - Reduction of neutropenia incidence observed with the use of prophylactic G-CSF (5.2 mg/kg)
- Luvelta may provide improved patient responses compared to standard chemotherapy in PROC, importantly for patients whose tumors have low to medium FRα expression
  - ~80% of patients with PROC have FRα expression levels > 25%
- The REFRαME-O1 (GOG-3086, ENGOT-79OV, and APGOT-OV9; NCT05870748) phase 3 study is ongoing

FRα, folate receptor alpha; G-CSF, granulocyte colony-stimulating factor; luvelta, luveltamab tazevibulin; ORR, overall response rate; PROC, platinum-resistant ovarian cancer; PS, positive staining.

Acknowledgements and Disclosures

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For more information on the REFRαME-O1 study, please scan the QR code

REFRαME-O1

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