Institut de Cancérologie de l'Ouest

unicancer PAYS DE LA LOIRE

Anticorps Drogues Conjugués et Cancers de l'ovaire

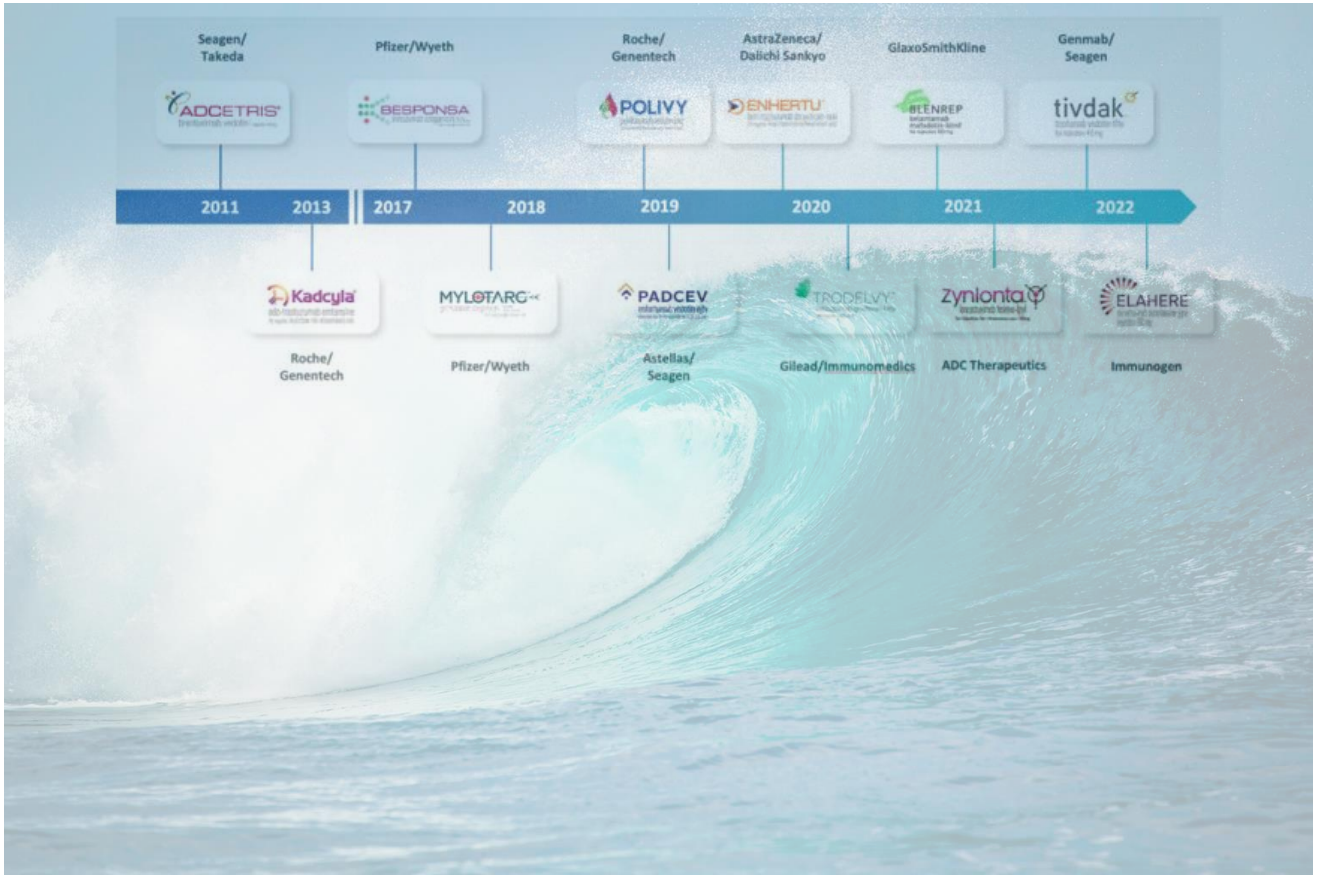
St Paul de Vence 12/01/2024

Pr Jean-Sébastien Frenel, Md, PhD.
jean-sebastien.frenel@ico.unicancer.fr

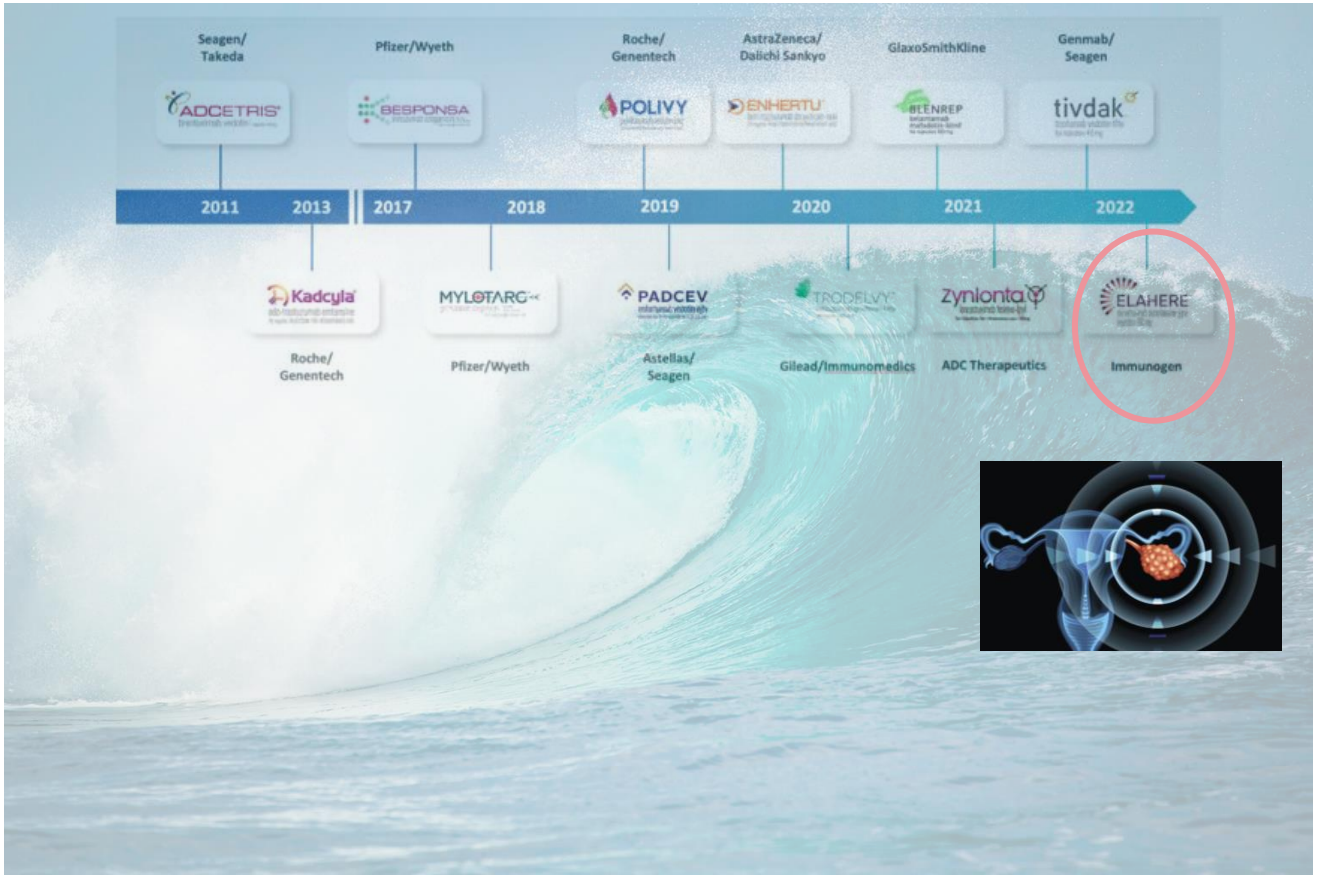
LIENS D'INTERET

	Consulting Public presentation	Travel Fee	Research Grant
Roche	x	x	
Novartis	x	x	
Lilly	x		
Astra Zeneca	x	x	
Pfizer	x	x	
Daiichi	x	x	
GSK	x		
Pierre Fabre	x		
Gilead	x	x	
Amgen	x	x	
Seagen	x	x	
MSD	x	x	
Clovis Oncology	x	x	
Menarini	x		

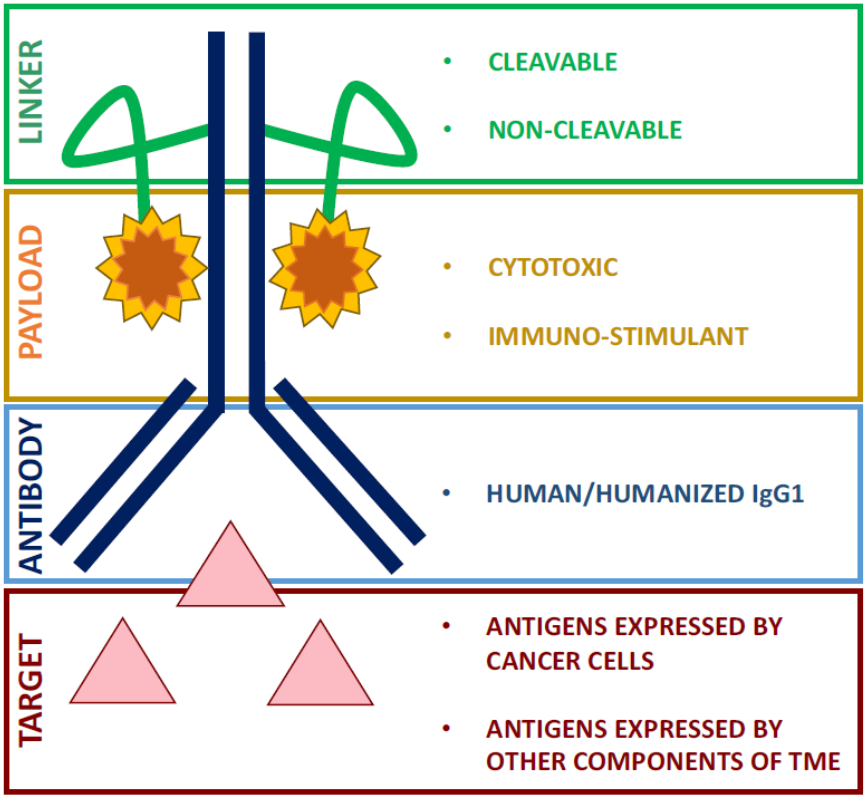
LA VAGUE ADC!


Seagen/ Takeda
ADCETRIS
2011
Pfizer/Wyeth
BESPONSA
2013
Kadcyla
Roche/ Genentech
2017
MYLOTARG
Pfizer/Wyeth
2018
Roche/ Genentech
POLIVY
2019
PADCEV
Astellas/ Seagen
AstraZeneca/ Daiichi Sankyo
ENHERTU
2020
TRODELVY
Gilead/Immunomedics
GlaxoSmithKline
BLENREP
2021
Zynlonta
ADC Therapeutics
Genmab/ Seagen
tivdak
2022
ELAHERE
Immunogen

LA VAGUE ADC!

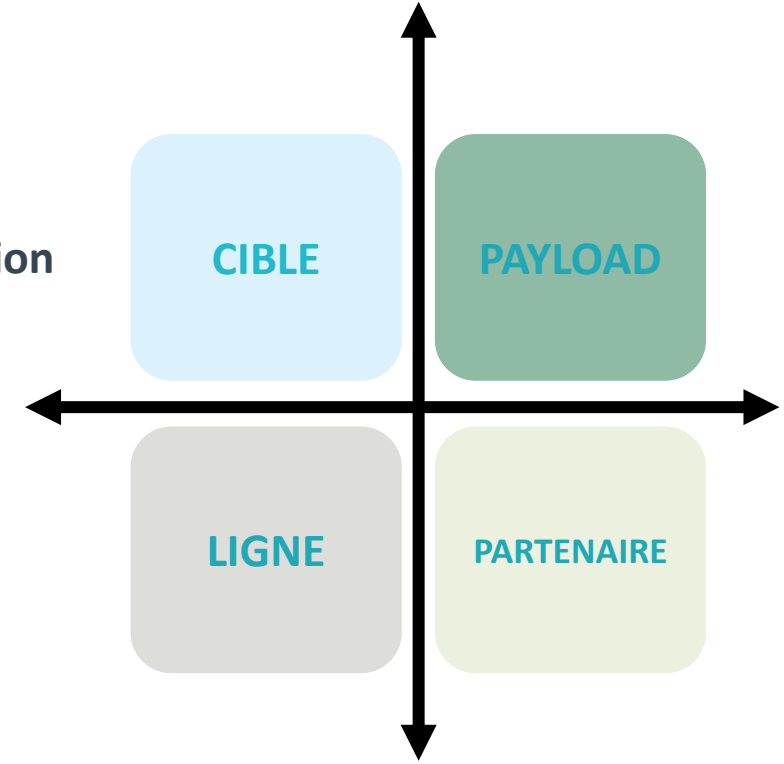

Seagen/ Takeda
ADCETRIS
2011
Pfizer/Wyeth
BESPONSA
2013
Kadcyla
Roche/ Genentech
2017
MYLOTARG
Pfizer/Wyeth
2018
Roche/ Genentech
POLIVY
2019
PADCEV
Astellas/ Seagen
AstraZeneca/ Daiichi Sankyo
ENHERTU
2020
TRODELVY
Gilead/Immunomedics
GlaxoSmithKline
BLENREP
2021
Zynlonta
ADC Therapeutics
Genmab/ Seagen
tivdak
2022
ELAHERE
Immunogen

ARCHITECTURE MOLECULAIRE DES ADC



Fuentes-Antrás J, Genta S, Vijenthira A, Siu LL. Antibody-drug conjugates: in search of partners of choice. Trends Cancer. 2023 Apr;9(4):339-354. doi: 10.1016/j.trecan.2023.01.003. Epub 2023 Feb 4. PMID: 36746689.

DEVELOPPEMENT DES ADC DANS LE CANCER OVAIRE



Meilleure cible
Niveau d'expression
Sélectivité

Effet by stander oui/non
Mécanisme d'action
Drug Antibody Ratio

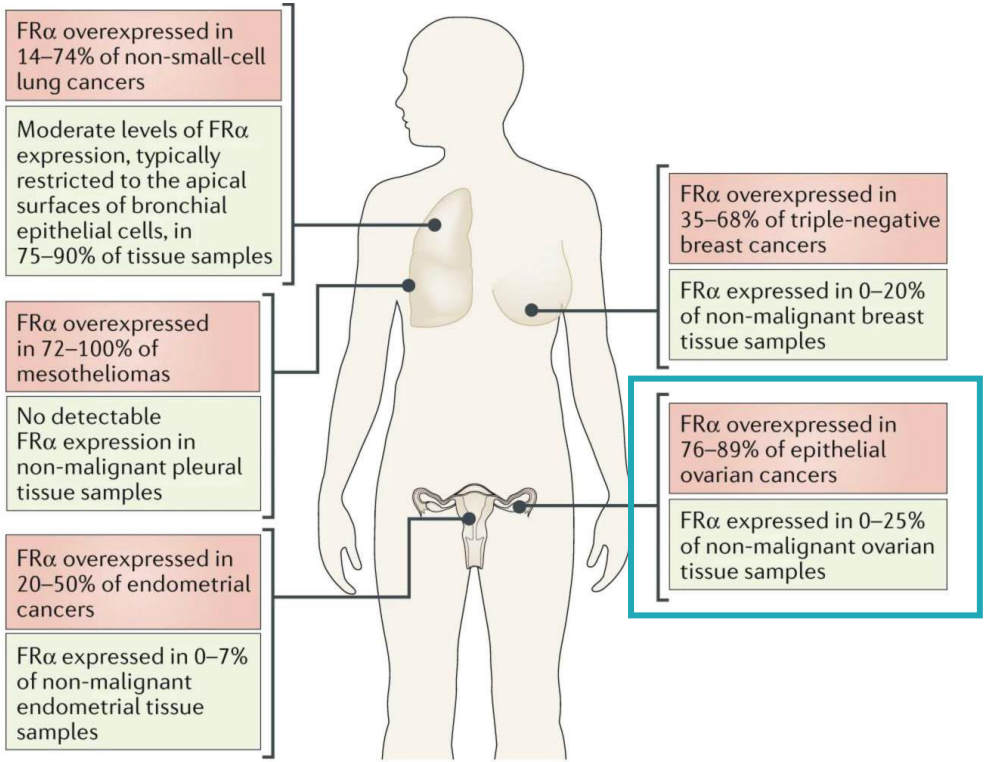
Platine résistant
Platine sensible
Maintenance

Monothérapie
Combinaison avec CT
Combinaison avec ICI

ANTIGENES CIBLES

Drug	Target	Linker	DAR	Payload	Development Stage
XB002[1,2]	Tissue factor	N-acyl sulfonamide (cleavable)	4	Auristatin	Phase 1
STRO-002	FRα	Valine-citrulline (cleavable)	4	SC239 (hemiasterlin)	Phase 1/2
Farletuzumab ecteribulin (MORAb-202)[5,6]	FRα	Val-Cit	4	Eribulin mesylate	Phase 1/2
Upifitamab rilsodotin (UpRi)	NaPi2b	Polymer scaffold (cleavable)	~10	AF-HPA/AF	**Phase 1/2; Phase 3**
XMT-1660	B7-H4	Polymer scaffold (cleavable)	6	AF-HPA/AF	Phase 1b
SGN-B7H4V	B7-H4	Protease-cleavable mc-vc linker	4	MMAE	Phase 1
AZD8205	B7-H4	Val-ala peptide linker with a PEG8 spacer	8	Topoisomerase I inhibitor	Phase 1/2a
Sacituzumab govitecan	Trop-2	Hydrolyzable linker	7.5	Topoisomerase I inhibitor (SN-38)	**Phase 2**
DS6000a	CDH6	Tetrapeptide-based linker	~8	Topoisomerase I inhibitor (Dxd)	Phase 1
SYD985	HER2	Mb-Val-Cit-PABC	2.7	Duocarmycin	**Phase 2**
DS-8201a	HER2	Peptide-based linker	7–8	Topoisomerase I inhibitor (Dxd)	**Phase 2**
DMUC-4064A	MUC-16	Protease-cleavable linker		MMAE	**Phase 1**
Anetumab ravtansine	Mesothelin	Disulfide-containing linker	3.2	DM4	**Phase 1/2**

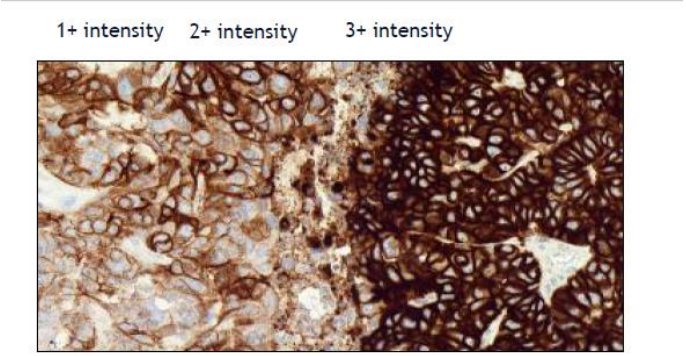
CIBLER FRα : RATIONNEL DANS LE CANCER DE L'OVAIRE



Scaranti et al., Nat Rev Clin Oncol; 2020

CIBLER FRα

- Récepteur de surface qui permet le transport intra cellulaire du folate
- Expression limitée sur les cellules normales
- Détection en immuno-histochimie/ Stable au cours du temps



ADC CIBLANT FRα

Mirvetuximab Soravtansine

- **Payload** → DM4, maytansine
- **DM4 disrupts tubulin** causing mitotic arrest and apoptosis
- DM4 diffuses through lipophilic cell membrane causing death of adjacent tumor cells via the **bystander effect**
- **More advanced in investigation** → phase III and combo

MORAb-202

- **Antibody** → farletuzumab
- **Payload** → ecteribulin
- **Bystander effect** in FRα negative cancer cells
- **Phase 1 study** (Nishio, ASCO 2022): ORR 35-50% across different FRα level (>5%, 1+ or 2+ or 3+)

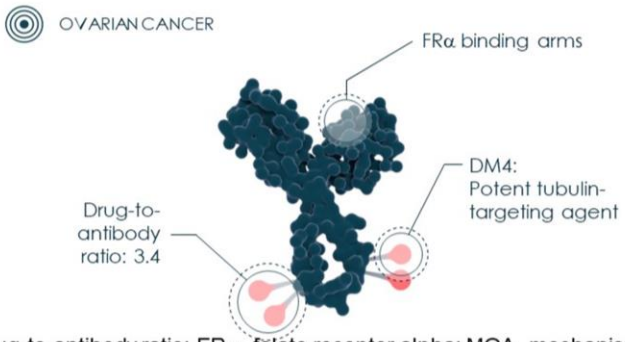
STRO-002

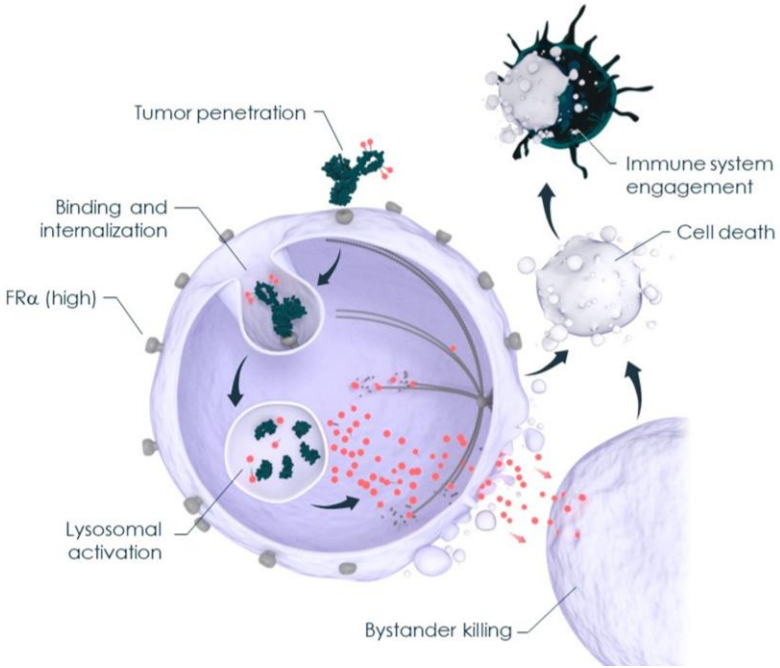
- Potential **best in class** anti FRα (homogeneous and favourable stability)
- **Payload** → hemiasterlin, antitubuline marine natural product (not a substrate of P-gP)
- **Bystander effect** in FRα negative cancer cells
- **Phase 1 ongoing** in ovarian and endometrial cancer (Naumann, ASCO 2021 and press-release): ORR 37.5%, in FRα TPS > 25%.

Fuentes-Antrás J, Genta S, Vijenthira A, Siu LL. Antibody-drug conjugates: in search of partners of choice. Trends Cancer. 2023 Apr;9(4):339-354. doi: 10.1016/j.trecan.2023.01.003. Epub 2023 Feb 4. PMID: 36746689.

MIRVETUXIMAB SORAVTANSINE

Name[1,2]: IMGN853
Antibody target: High FRα[3]
Payload: DM4[3]
Conjugation: Via lysine (random)[4]
DAR[5]: ~ 3.4
MOA: Microtubule disruption[3]
Bystander targeting: Yes[3]





DAR, drug-to-antibody ratio; FRα, folate receptor alpha; MOA, mechanism of action.

CIBLER FRα: QUEL NIVEAU D'EXPRESSION?

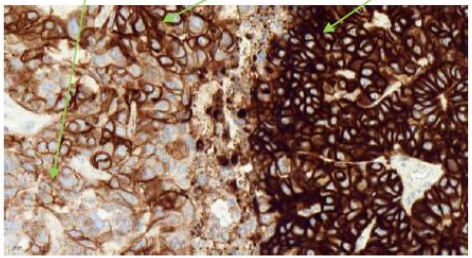
FRα SCORING IN THE MIRVETUXIMAB SORAVTANSINE PROGRAM

PS2+ Scoring

- In all prior studies, PS2+ scoring was used to assess FRα expression
- Eligibility determined by staining intensity and percentage of tumor cells staining at 0, 1+, 2+, or 3+

1+ intensity 2+ intensity 3+ intensity

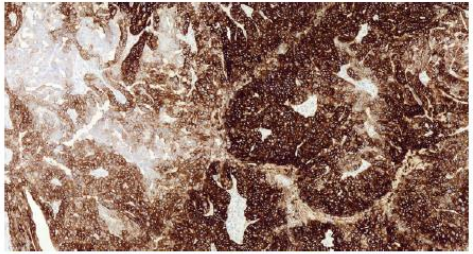
PS2+ Scoring
Positive: ≥ 50% of tumor cells with FRα membrane staining with ≥ 2+ intensity



10X Scoring

- In FORWARD I, a simplified scoring method to assess FRα expression was implemented
- Eligibility was determined by scoring just the percentage of cells with membrane staining by ≤10X magnification, without regard to intensity

10X Scoring
Positive: ≥ 50% of tumor cells with FRα membrane staining visible at 10X microscope objective



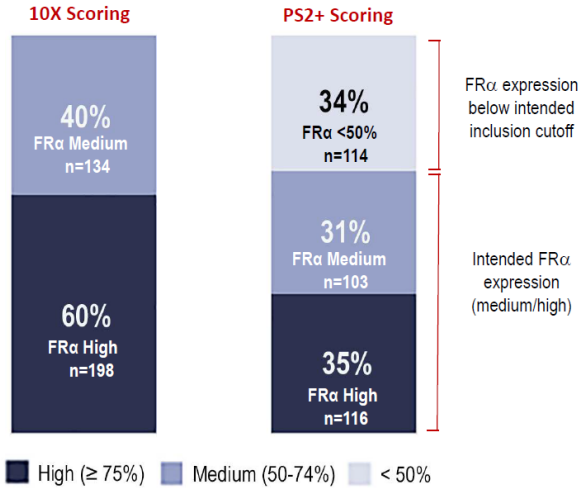
Bridging study indicated that 10X scoring was sufficient for patient selection

Exploratory analyses suggest that the change in scoring method from PS2+ to 10X introduced a population of patients into FORWARD I with lower levels of FRα expression than intended

CIBLER FRα: QUEL NIVEAU D'EXPRESSION?

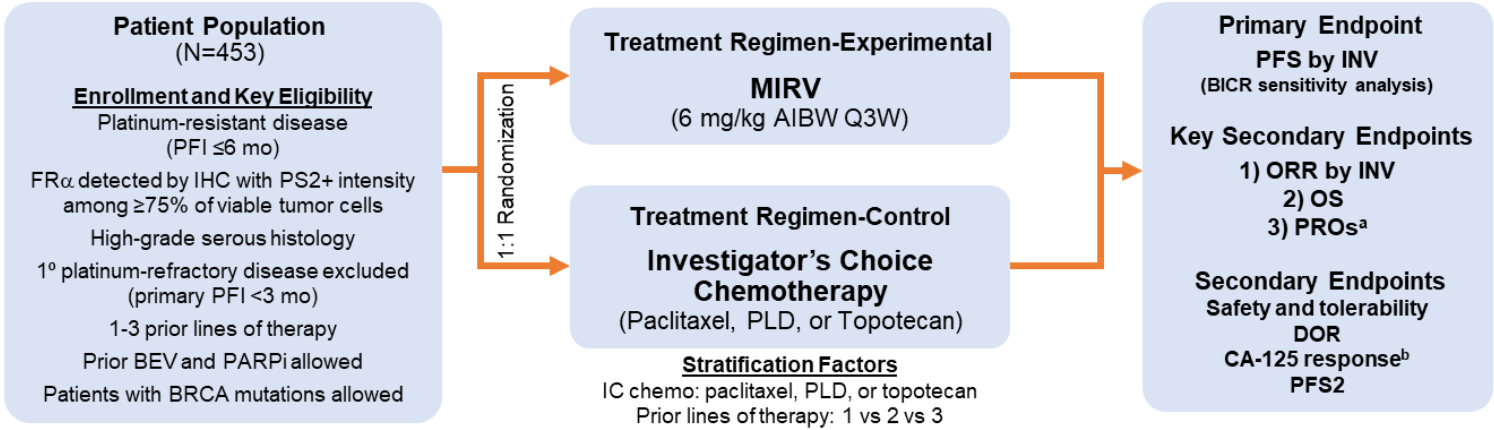
Rescoring of the FORWARD I samples using PS2+ indicates:

- 34% of patients enrolled in FORWARD I had low FRα levels that should have precluded enrollment; and
- the protocol-defined FRα high subset contained patients with a mixture of FRα expression levels



MIRVETUXIMAB SORAVTANSINE: MIRASOL

An open-label, phase 3 randomized trial of MIRV vs investigator's choice chemotherapy in patients with FRα-high platinum-resistant ovarian cancer



AIBW, adjusted ideal body weight; BEV, bevacizumab; BICR, blinded independent central review; BRCA, BReast CAncer gene; CA-125, cancer antigen 125; chemo, chemotherapy; DOR, duration of response; FRα, folate receptor alpha; IC, investigator's choice; IHC, immunohistochemistry; INV, investigator; MIRV, mirvetuximab soravtansine; ORR, objective response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitors; PFI, platinum-free interval; PFS, progression-free survival; PFS2, time from randomization until second disease progression; PLD, pegylated liposomal doxorubicin; PROs, patient-reported outcomes; PS2+, positive staining intensity ≥2; Q3W, every 3 weeks.

[a]PROs will be measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, 28-item Ovarian Cancer Module (OV28) study instrument.

[b]Gynecological Cancer InterGroup (GCIG) criteria.

1. ClinicalTrials.gov identifier: NCT04209855. Updated June 16, 2022. Accessed October 5, 2022. https://clinicaltrials.gov/ct2/show/NCT04209855

2. Moore K, et al. Presented at: 2020 American Society of Clinical Oncology Annual Meeting; May 29-31, 2020; Virtual. Abstract TPS6103.

Kathleen Moore, Associate Director of Clinical Research, Stephenson Cancer Center University of Oklahoma College of Medicine

MIRVETUXIMAB SORAVTANSINE: MIRASOL

Baseline Demographics and Stratification Factors (N=453)

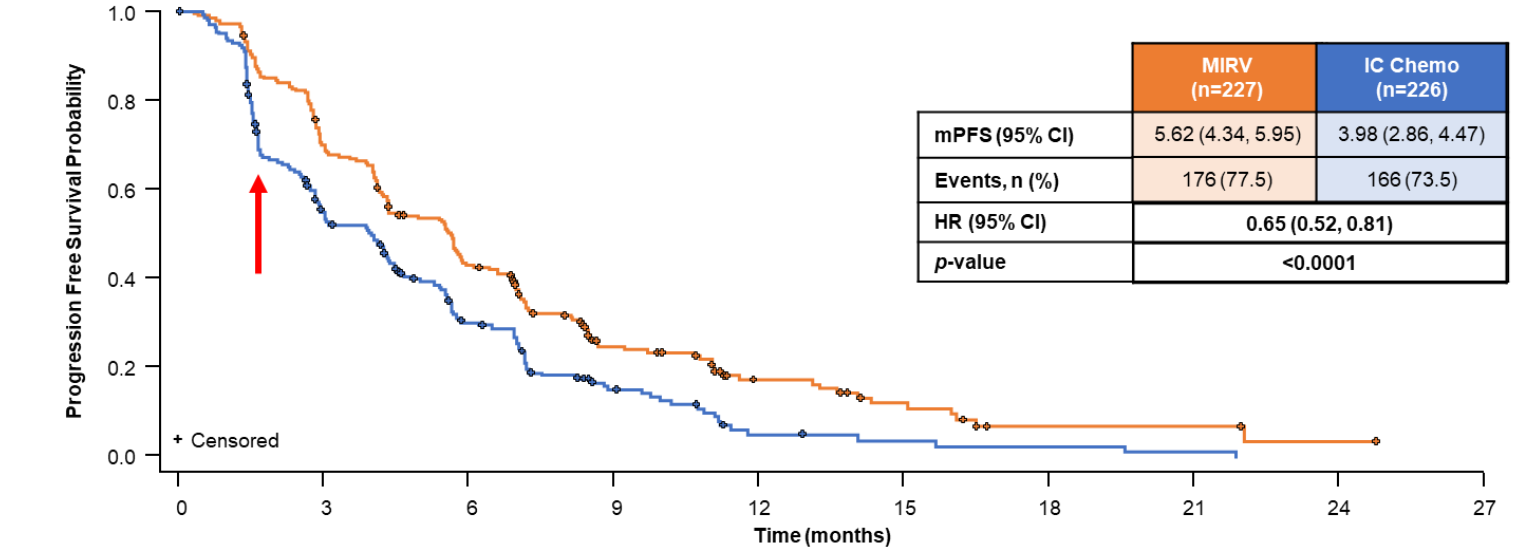
Characteristics		MIRV (n=227)	IC Chemo (n=226)
Age, median (range)	Age in years	63 (32-88)	62 (29-87)
Stage at initial diagnosis, n (%)[a]	I-II III IV	9 (4) 137 (60) 76 (33)	9 (4) 147 (65) 65 (29)
BRCA mutation, n (%)	Yes No/Unknown	29 (13) 198 (87)	36 (16) 190 (84)
Prior exposure, n (%)	Bevacizumab PARPi Taxanes	138 (61) 124 (55) 227 (100)	143 (63) 127 (56) 224 (99)
Primary platinum-free interval, n (%)[b]	≤ 12 months > 12 months	146 (64) 80 (35)	142 (63) 84 (37)
Platinum-free interval, n (%)[c]	≤ 3 months > 3 - ≤6 months	88 (39) 138 (61)	99 (44) 124 (55)
Stratification Factor **No. of prior systemic therapies, n (%)**	1 2 3	31 (14) 91 (40) 105 (46)	32 (14) 91 (40) 103 (46)
Stratification Factor **Investigator Choice of Chemotherapy**	Paclitaxel PLD Topotecan	93 (41) 82 (36) 52 (23)	92 (41) 81 (36) 53 (23)

Data cutoff: March 6, 2023. **14% of patients remain on MIRV; 3% remain on IC Chemo**
BRCA, BReast CAncer gene; PARPi, poly (ADP-ribose) polymerase inhibitors; MIRV, mirvetuximab soravtansine; IC Chemo, investigator's choice chemotherapy; PLD, pegylated liposomal doxorubicin,.
[a]Five patients (2%) in the MIRV arm and five patients in the IC chemo arm (2%) were missing information for stage at initial diagnosis. [b]One patient (<1%) in the MIRV arm was missing information on primary platinum-free interval.
[c]One patient (<1%) in the MIRV arm and 3 patients (1%) in the IC chemo arm enrolled with platinum-free interval of >6 months

Kathleen Moore, Associate Director of Clinical Research, Stephenson Cancer Center University of Oklahoma College of Medicine

MIRVETUXIMAB SORAVTANSINE: MIRASOL

Primary Endpoint: Progression-Free Survival by Investigator



	MIRV (n=227)	IC Chemo (n=226)
mPFS (95% CI)	5.62 (4.34, 5.95)	3.98 (2.86, 4.47)
Events, n (%)	176 (77.5)	166 (73.5)
HR (95% CI)	0.65 (0.52, 0.81)	
p-value	<0.0001	

No. Participants at Risk										
MIRV	227	151	89	38	18	10	3	3	1	0
IC Chemo	226	98	48	19	5	3	2	1	0	

Data cutoff: March 6, 2023
MIRV, mirvetuximab soravtansine; IC Chemo, investigator's choice chemotherapy; mPFS, median progression-free survival; CI, confidence interval; HR, hazard ratio.

Kathleen Moore, Associate Director of Clinical Research, Stephenson Cancer Center University of Oklahoma College of Medicine

MIRVETUXIMAB SORAVTANSINE: MIRASOL

Overall Response Rate by Investigator (N=453)

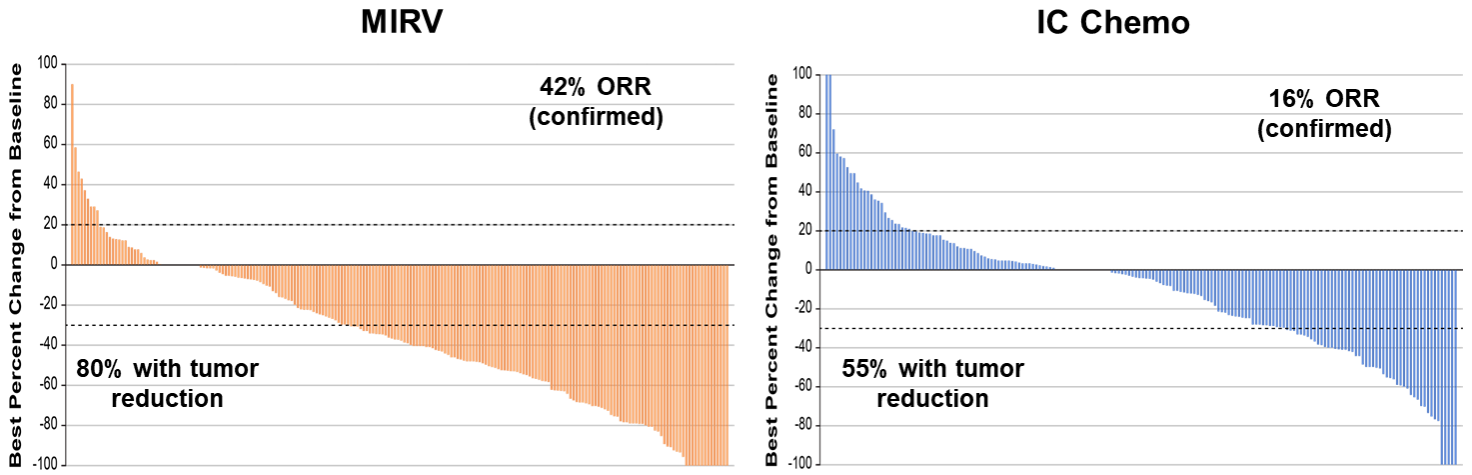
	MIRV (n=227)	IC Chemo (n=226)
ORR **n, 95% CI**	**42%** 96, (5.8, 49.0)	**16%** 36, (11.4, 21.4)
Best overall response, n (%)		
CR	12 (5%)	0
PR	84 (37%)	36 (16%)
SD	86 (38%)	91 (40%)
PD	31 (14%)	62 (27%)
Not evaluable	14 (6%)	37 (16%)

ORR Difference 26.4% (18.4, 34.4)
OR 3.81 (2.44, 5.94)
p<0.0001

Data cutoff: March 6, 2023
MIRV, mirvetuximab soravtansine; IC chemo, investigator's choice chemotherapy; ORR, objective response rate; CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OR, odds ratio.

Kathleen Moore, Associate Director of Clinical Research, Stephenson Cancer Center University of Oklahoma College of Medicine

MIRVETUXIMAB SORAVTANSINE: MIRASOL

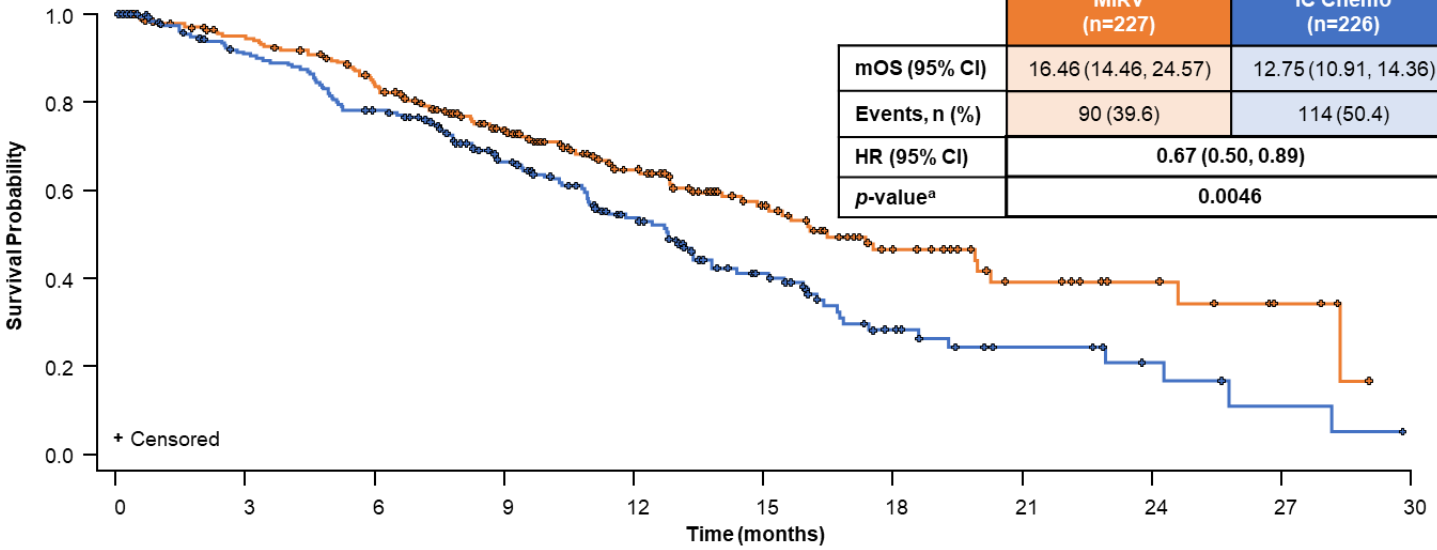


Data cutoff: March 6, 2023
MIRV, mirvetuximab soravtansine; IC chemo, investigator's choice chemotherapy; ORR, objective response rate.

Kathleen Moore, Associate Director of Clinical Research, Stephenson Cancer Center University of Oklahoma College of Medicine

MIRVETUXIMAB SORAVTANSINE: MIRASOL

Overall Survival



	MIRV (n=227)	IC Chemo (n=226)
mOS (95% CI)	16.46 (14.46, 24.57)	12.75 (10.91, 14.36)
Events, n (%)	90 (39.6)	114 (50.4)
HR (95% CI)	0.67 (0.50, 0.89)	
p-value[a]	0.0046	

No. Participants at Risk

MIRV	227	204	175	128	82	53	28	15	9	4	0
IC Chemo	226	185	157	107	68	39	18	9	5	2	0

Data cutoff: March 6, 2023; median follow-up time: 13.11 months

MIRV, mirvetuximab soravtansine; IC Chemo, investigator's choice chemotherapy; mOS, median overall survival; CI, confidence interval; HR, hazard ratio.

[a]Overall survival is statistically significant based on pre-specified boundary p-value at interim analysis = 0.01313

Kathleen Moore, Associate Director of Clinical Research, Stephenson Cancer Center University of Oklahoma College of Medicine

MIRVETUXIMAB SORAVTANSINE: MIRASOL

Progression-Free and Overall Survival in Bevacizumab-Naïve and Prior Bevacizumab-Treated Subsets by Investigator

	Bev-Naïve		Prior Bev	
	MIRV	IC Chemo	MIRV	IC Chemo
mPFS (95% CI)	7.0 (5.6, 8.4)	5.6 (3.0, 6.5)	4.4 (4.0, 5.8)	3.0 (2.5, 4.3)
Events n (%)[a]	65 (73.0)	57 (69.0)	111 (80.4)	109 (76.2)
HR (95% CI)	**0.66 (0.46, 0.94)**		**0.64 (0.49, 0.84)**	
Nominal *p*-value	0.0210		0.0011	
mOS (95% CI)	20.2 (14.8, NE)	14.4 (11.8, 16.7)	15.4 (11.3, 17.5)	10.9 (9.4, 13.3)
Events n (%)[a]	23 (25.8)	39 (47.0)	67 (48.6)	75 (52.4)
HR (95% CI)	**0.51 (0.31, 0.86)**		**0.74 (0.54, 1.04)**	
Nominal p-value	0.0099		0.0789	

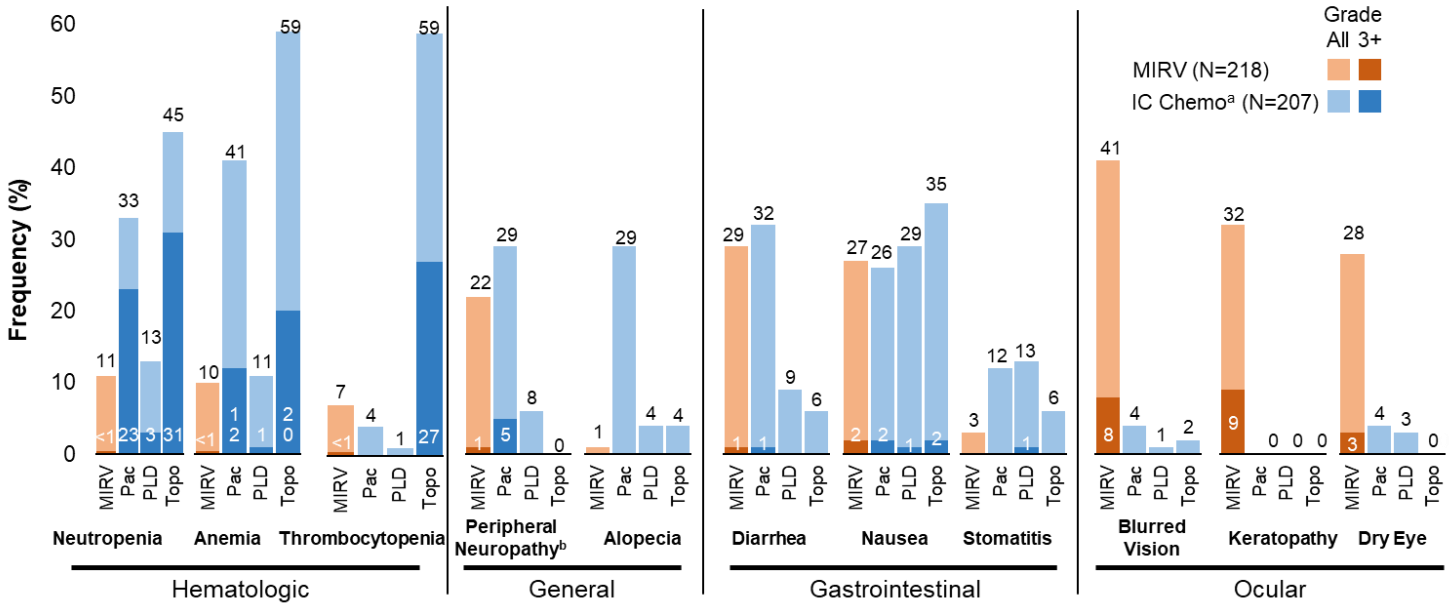
Data cutoff: March 6, 2023

[a]Percentage of events was calculated out of the total number of patients in each treatment arm: n=227 for MIRV and n=226 for IC Chemo.

mPFS, median progression-free survival; HR, hazard ratio; CI, confidence interval; mOS, median overall survival; MIRV, mirvetuximab soravtansine; Bev, bevacizumab; IC Chemo, investigator's choice chemotherapy.

MIRVETUXIMAB SORAVTANSINE: MIRASOL

Differentiated Safety Profile: Treatment-Emergent Adverse Events

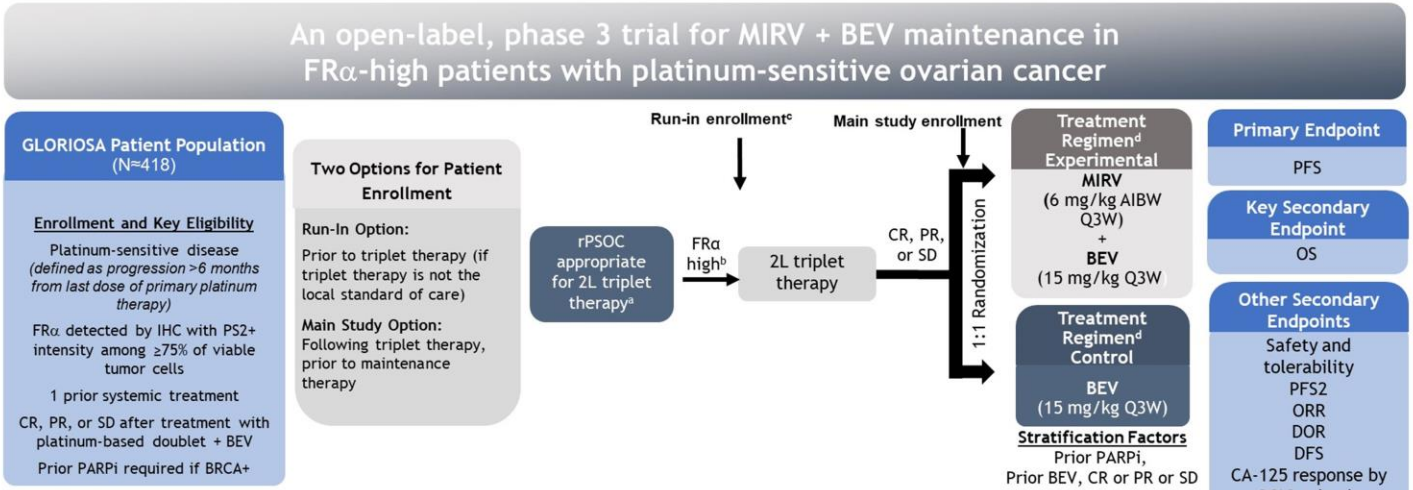


Data cutoff: March 6, 2023
MIRV, mirvetuximab soravtansine; IC Chemo: investigator's choice chemotherapy; Pac, paclitaxel; PLD, pegylated liposomal doxorubicin; Topo, topotecan.
[a]Pac n=82 (39%), PLD n=76 (37%), Topo n=49 (24%). [b]Grade 2+ peripheral neuropathy events were observed in 12% and 16% of patients that received MIRV or paclitaxel, respectively.

Kathleen Moore, Associate Director of Clinical Research, Stephenson Cancer Center University of Oklahoma College of Medicine

MIRVETUXIMAB SORAVTANSINE: DEVELOPPEMENT

GLORIOSA (NCT05445778) - Study Design[1,2]



2L, second line; AIBW; adjusted ideal body weight; BEV, bevacizumab; BRCA, BReast CAncer gene; CA-125, cancer antigen 125; CR, complete response; DFS, disease-free survival; DOR, duration of response; FRα, folate receptor alpha; GCIG, Gynecological Cancer InterGroup; IHC, immunohistochemistry; MIRV, mirvetuximab soravtansine; ORR, objective response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitors; PFS, progression-free survival; PFS2, time from randomization until second disease progression; PR, partial response; PROs, patient-reported outcomes; PS2+, positive staining intensity ≥2; Q3W, every 3 weeks; SD, stable disease; rPSOC, recurrent platinum-sensitive ovarian cancer. [a]Triplet treatment consists of platinum+chemotherapy+bevacizumab for planned 6 cycles (minimum 4 and maximum 8 cycles), including at least 3 cycles of bevacizumab. [b]Pre-screening consent must be obtained for tissue testing for FRα expression by Ventana FOLR1 Assay. [c]FRα-high patients who desire to be treated and followed while on their run-in triplet therapy must sign a run-in consent as part of the main consent form if they meet eligibility criteria as assessed by the investigator. [d]Treatment in both study arms will continue until disease progression or unacceptable toxicity. [e]PROs will be measured using the EuroQol-5 Dimension 5-level (EQ-5D-5L) and NCCN-FACT Ovarian Symptom Index (NFOSI-18) study instruments. **1.** ClinicalTrials.gov identifier: NCT05445778. Updated July 13, 2022. Accessed October 5, 2022. https://clinicaltrials.gov/ct2/show/NCT05445778 **2.** Data on file. ImmunoGen, Inc.

2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

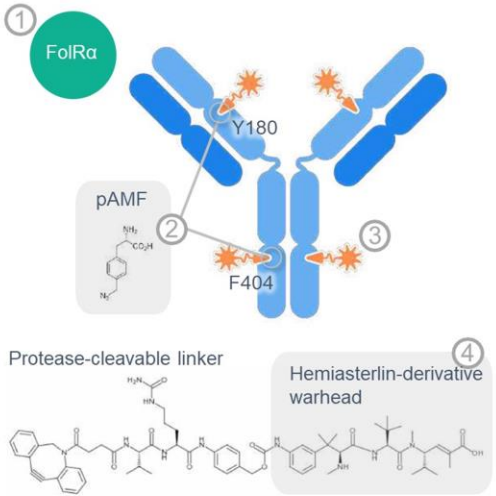
Institut de Cancérologie de l'Ouest

unicancer PAYS DE LA LOIRE

CIBLER FRα: STRO-002 Luveltamab Tazevibulin

STRO 002

STRO-002 Highly optimized ADC designed to drive efficient tumor responses across a broad range of target antigen levels



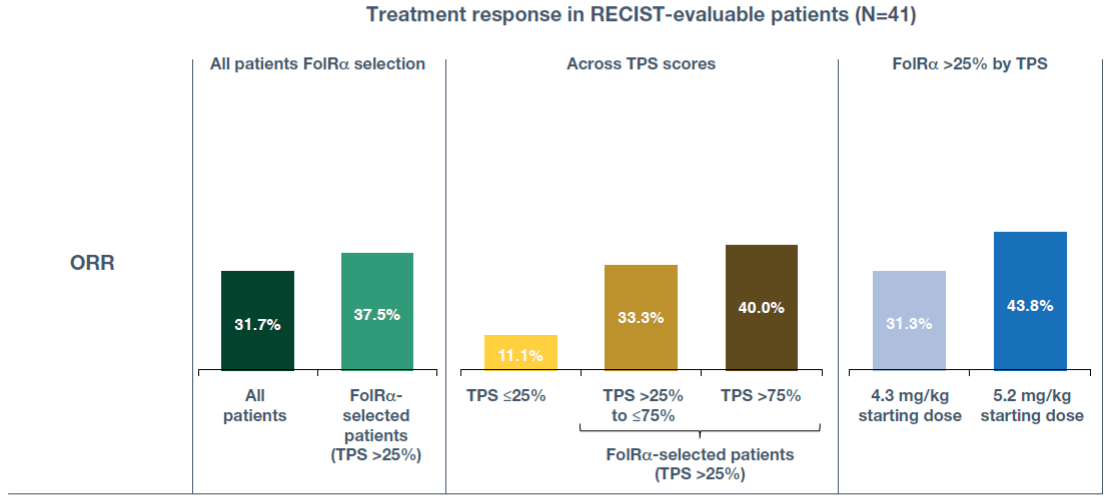
STRO-002 is a homogeneous antibody drug conjugate (ADC) with a drug-antibody ratio (DAR) of 4, targeting folate-receptor alpha (FolRα)

1. FolRα is overexpressed in certain cancers including ovarian cancer and endometrial cancer
2. Precisely positioned non-natural amino acids, p-azidomethyl-L-phenylalanine (pAMF), at positions Y180 and F404 on the heavy chain
3. Stable protease-cleavable linkers, with rapid clearance of toxic catabolite after release and cell killing
4. Warhead is hemiasterlin-derivative[1] with potentially dual mechanism against the tumor – tubulin-inhibitor cytotoxin, less sensitive to P-gp transport and induces immunogenic response upon cell death[2]

[1] Sutro-proprietary tubulin-targeting 3-aminophenol hemiasterlin warhead, SC209
[2] Based on STRO-002 pre-clinical models showing immune stimulation at site of tumor upon cell death

CIBLER FRα: STRO-002 Luveltamab Tazevibulin

Figure 1. Luveltamab demonstrated robust clinical activity in patients with recurrent ovarian cancer[4]



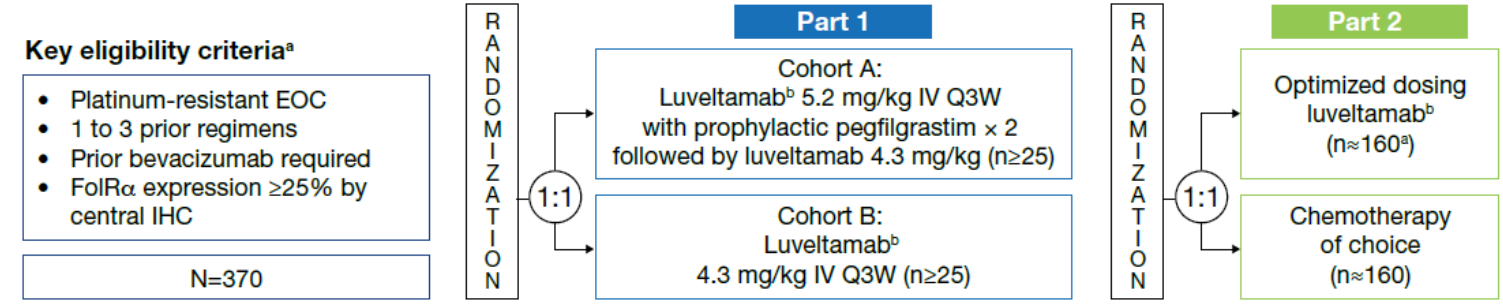
RECIST-evaluable patients	N=41	n=32	n=9	n=12	n=20	n=16	n=16
PR	13	12	1	4	8	5	7
ORR (95% CI), %	31.7 (18.1, 48.1)	37.5 (21.1, 56.3)	11.1 (0.3, 48.3)	33.3 (9.9, 65.1)	40.0 (19.1, 63.9)	31.3 (11.0, 58.7)	43.8 (19.8, 70.1)

FolRα selected defined as TPS >25%.
FolRα, folate receptor alpha; ORR, objective response rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; TPS, tumor proportion score.

CIBLER FRα: STRO-002 Luveltamab Tazevibulin

REFRaME-O1/ENGOT-OV79/GOG-3086: A Phase 2/3 Open-label Study Evaluating the Efficacy and Safety of Luveltamab Tazevibulin Versus Investigator's Choice of Chemotherapy in Women With Relapsed Platinum-resistant Epithelial Ovarian Cancer Expressing Folate Receptor Alpha

Figure 2. Study design



[a]Additional details in Table 1. [b]Patients will be treated until disease progression, unacceptable toxicity, withdrawal of consent, or end of study (study completion).
EOC, epithelial ovarian cancer; FolRα, folate receptor alpha; IHC, immunohistochemistry; IV, intravenous; Q3W, every 3 weeks.

CIBLER FRα: MORAb-202 FARLETUZUMAB ERIBULIN

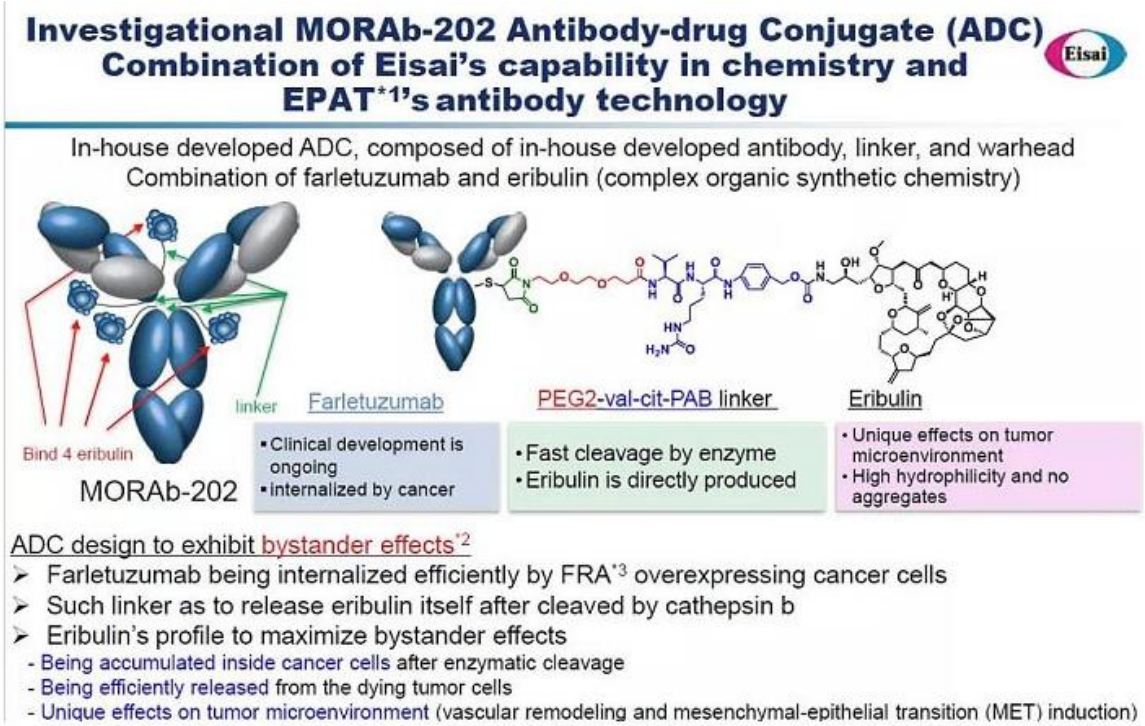


Figure 4. Structure of MORAb-202

CIBLER FRα: MORAb-202 FARLETUZUMAB ERIBULIN

Patient Baseline Characteristics and Tumor Responses

Table 1. Baseline Characteristics

Parameter	Cohort 1 (n = 24) MORAb-202 0.9 mg/kg	Cohort 2 (n = 21) MORAb-202 1.2 mg/kg)
Median age, years (range)	56 (23–74)	58 (41–76)
Female sex, n (%)	24 (100)	21 (100)
Race, n (%)		
Asian (Japanese)	24 (100)	21 (100)
ECOG PS, n (%)		
0	18 (75.0)	14 (66.7)
1	6 (25.0)	7 (33.3)
Median weight, kg (range)	52.25 (36.3–71.5)	54.30 (43.4–91.3)
Prior anticancer regimens, n (%)		
1	6 (25.0)	4 (19.0)
2	6 (25.0)	3 (14.3)
3	5 (20.8)	8 (38.1)
≥4	7 (29.2)	6 (28.6)
Regimens after platinum resistance, n (%)		
0	15 (62.5)	14 (66.7)
1	7 (29.2)	5 (23.8)
2	2 (8.3)	2 (9.5)
Cancer type, n (%)		
Fallopian tube	1 (4.2)	2 (9.5)
Ovarian	18 (75.0)	14 (66.7)
Peritoneal	5 (20.8)	5 (23.8)
FRα expression, n (%)		
<50%	6 (25.0)	2 (9.5)
≥50%	18 (75.0)	19 (90.5)

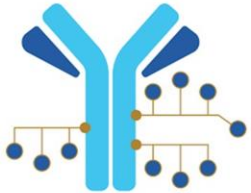
Table 2. Tumor Responses as Assessed by Investigator per RECIST v1.1

Parameter	Cohort 1 (n = 24) MORAb-202 0.9 mg/kg	Cohort 2 (n = 21) MORAb-202 1.2 mg/kg
CR, n (%)	1 (4.2)	0
PR, n (%)	5 (20.8)	11 (52.4)
SD, n (%)	10 (41.7)	9 (42.9)
PD, n (%)	8 (33.3)	1 (4.8)
ORR, n (%), (95% CI)	6 (25.0), (9.8–46.7)	11 (52.4), (29.8–74.3)
ORR by FRα status, n of n (%), (95% CI)		
FRα <50%	2 of 6 (33.3), (4.3–77.7)	1 of 2 (50.0), (1.3–98.7)
FRα ≥50%	4 of 18 (22.2), (6.4–47.6)	10 of 19 (52.6), (28.9–75.6)
ORR by HGS status, n of n (%), (95% CI)		
HGS	6 of 19 (31.6), (12.6–56.6)	10 of 20 (50.0), (27.2–72.8)
Non-HGS	0 of 5, (0)	1 of 1 (100), (2.5–100)
DCR, n (%), (95% CI)	16 (66.7), (44.7–84.4)	20 (95.2), (76.2–99.9)
Median DOR, months (95% CI)	10.6 (3.9–NE)	7.6 (4.3–10.8)

Data cutoff date: October 31, 2021.

Cibler NaPi2B: SODIUM DEPENDANT PHOSPHATE TRANSPORTER

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



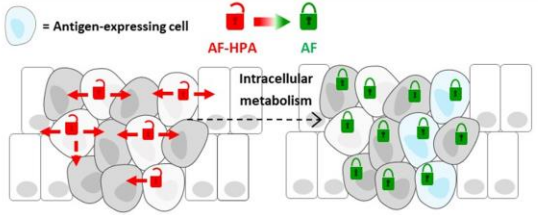
UpRi

Antibody: Humanized monoclonal anti-NaPi2b[1]

Linker: Polymer scaffold; cleavable ester linker[2]

Payload: AF-HPA (DolaLock-controlled bystander effect)[1]

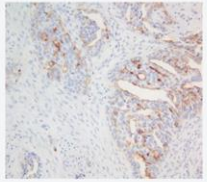
Drug-to-Antibody Ratio: ~10



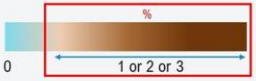
Upon ADC internalization into tumor cells and efficient release of payload, AF-HPA payload is metabolized to AF that remains highly potent but loses the ability to cross the cell membrane, locking it in the tumor, controlling the bystander effect, and consequently limiting impact on adjacent healthy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

NaPi2b Is a Sodium-Dependent Phosphate Transporter Broadly Expressed in Ovarian Cancer With Limited Expression in Healthy Tissues[4]

- NaPi2b expressed by tumor cells in majority of patients with high-grade serous ovarian cancer[2]
- NaPi2b is a lineage antigen (not an oncogene)[1]



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***[2]

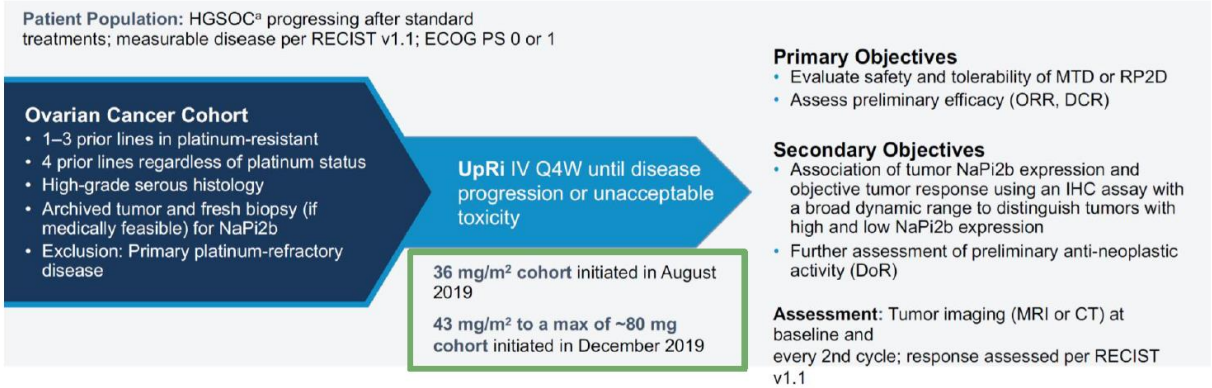


ADC, antibody drug conjugate; AF, Auristatin F; AF-HPA, auristatin F-hydroxypropylamide; IHC, immunohistochemistry; NaPi2b, sodium-dependent phosphate transport protein 2B; TPS, tumor proportion score; UpRi, upifitamab rilsodotin.

1. Bodyak ND et al. *Mol Cancer Ther*. 2021;20(5):885–895. 2. Mersana. Data on File. 2022. 3. Tolcher AW et al. ASCO Annual Meeting 2019; Abstract 3010.
4. Lin K et al. *Clin Cancer Res*. 2015;21(22):5139–5150.

Cibler NaPi2B: SODIUM DEPENDANT PHOSPHATE TRANSPORTER

UpRi – PHASE 1 STUDY – EXPANSION COHORT OVARIAN CANCER



Richardson et al, SGO 2022

Cibler NaPi2B: SODIUM DEPENDANT PHOSPHATE TRANSPORTER

UPIFITAMAB RILSODOTIN

Efficacy according NaPi2b expression and dose level

Tumor shrinkage in 67%

		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)

- **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

Richardson et al, SGO 2022

Cibler NaPi2B: DEVELOPPEMENT

PROC Space: UPLIFT (ENGOT-ov67 / GOG-3048) 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 (PROC)
- 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

Global
US, Europe, Australia, Canada

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 (FPD April 2021) – Study has completed accrual

[a] HGSOC including fallopian tube and primary peritoneal cancer.
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; PROC, platinum-resistant ovarian cancer; PS, perfon score; Q4W, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; UpRi, upifitamab ribodotin.

2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY:

GOG-3049 / ENGOT-ov71-NSGO-CTU

UP-NEXT

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

Key Enrollment Criteria
- Platinum-sensitive recurrent HGSOC[a]
- 4–6 cycles of platinum-based therapy in 2nd to 4th line setting (not all lines need to include platinum-based therapy)
- Best response to last line of treatment: NED, CR, PR, or SD[b]
- ECOG PS 0–1
- NaPi2b-positive (TPS ≥75%) tumor (archival or fresh biopsy)
- Prior PARPi required for patients with known deleterious *BRCA* mutations
- Patients who received bevacizumab in combination with their last platinum-containing regimen are excluded

Randomized 2:1 N=350

UpRi 30 mg/m² (capped at 66 mg) **IV q4w**

Placebo q4w

All patients continue until PD or unacceptable AE, or up to 18 months

Primary Endpoint
- PFS by BICR

Secondary Endpo
- PFS by Investigator
- ORR
- OS
- PROs

NCT05329545: Trial Currently Enrolling Patients

[a] HGSOC, including fallopian tube and primary peritoneal cancer. [b] For SD, no increase in disease confirmed by central review of imaging and absence of CA-125 rise >15% in 7 days prior to first dose.

AE, adverse event; BICR, blinded independent central review; *BRCA*, BRCA DNA repair associated gene; CA-125, cancer antigen 125; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HGSOC, high-grade serous ovarian cancer; IV, intravenous; NaPi2b, sodium-dependent phosphate transport protein 2B; NED, no evidence of disease; ORR, overall response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor; PD, progressive disease; PFS, progression-free survival; PR, partial response; PRO, patient reported outcomes; q4w, every 4 weeks; SD, stable disease; TPS, tumor proportion score; UpRi, upifitamab ribodotin.

ENGOT

2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY:

UPGRADE-A

Phase 1 UpRi + Carboplatin Combination in Platinum-Sensitive Ovarian Cancer

Key Enrollment Criteria
- Recurrent, platinum-sensitive,[a] high-grade serous ovarian cancer, including fallopian tube or primary peritoneal cancer
- Participant has received 1 to 3 prior lines of therapy for their ovarian cancer; a non-platinum-based chemotherapy regimen is permitted provided it is not the most recent line of therapy
- Participants not selected for NaPi2b expression
- Tissue (fresh or archival) for retrospective assessment of NaPi2b expression
- RECIST v1.1 measurable disease
- ECOG PS = 0–1

Dose Escalation (BOIN design)

UpRi IV q4w + carbo AUC 5 q4w × 6[b] → **UpRi** until PD or unacceptable AE

Expansion (N=30)

UpRi 30 mg/m² (capped at BSA 2.2 m²) **IV q4w + carbo AUC 5 q4w** × 6[b] → **UpRi** until PD or unacceptable AE

Primary Endpoint
- MTD for UpRi with carboplatin AUC 5

Secondary Endpoints
- AEs, PK for UpRi, PK for carboplatin, immunogenicity for UpRi, ORR, PFS, OS

Primary Endpoint
- Feasibility at 30mg/m² (≥60% of participants complete at least 4 cycles of the combination)

Secondary Endpoints
- AEs, PK for UpRi, PK for carboplatin, immunogenicity for UpRi, ORR, PFS, OS, efficacy by NaPi2b expression

NCT04907968: Currently Enrolling Patients to Dose Expansion Portion of Trial

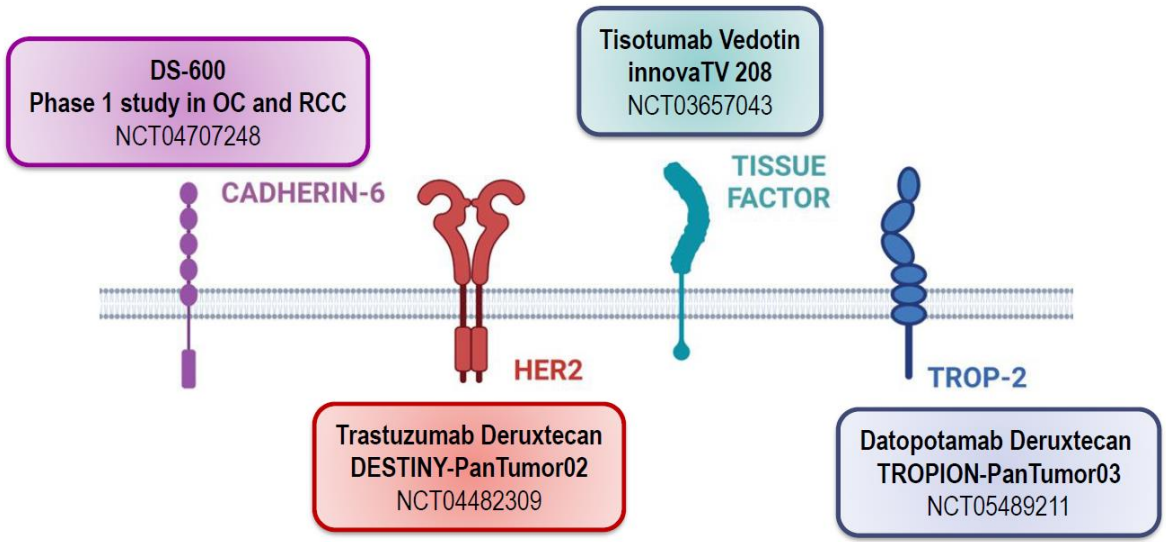
[a] Platinum-sensitive is defined as having achieved either a partial or complete response to 4 or more cycles in their last platinum-containing regimen and their disease progressing more than 6 months after completion of the last dose of platinum-containing therapy. [b] Up to 6 cycles.

AE, adverse event; AUC, area under the curve; BOIN, Bayesian Optimal Interval; carbo, carboplatin; BSA, body surface area; ECOG, Eastern Cooperative Oncology Group; MTD, maximum tolerated dose; NaPi2b, sodium-dependent phosphate transport protein 2B; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; PS, performance score; q4w, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; UpRi, upifitamab ribodotin.

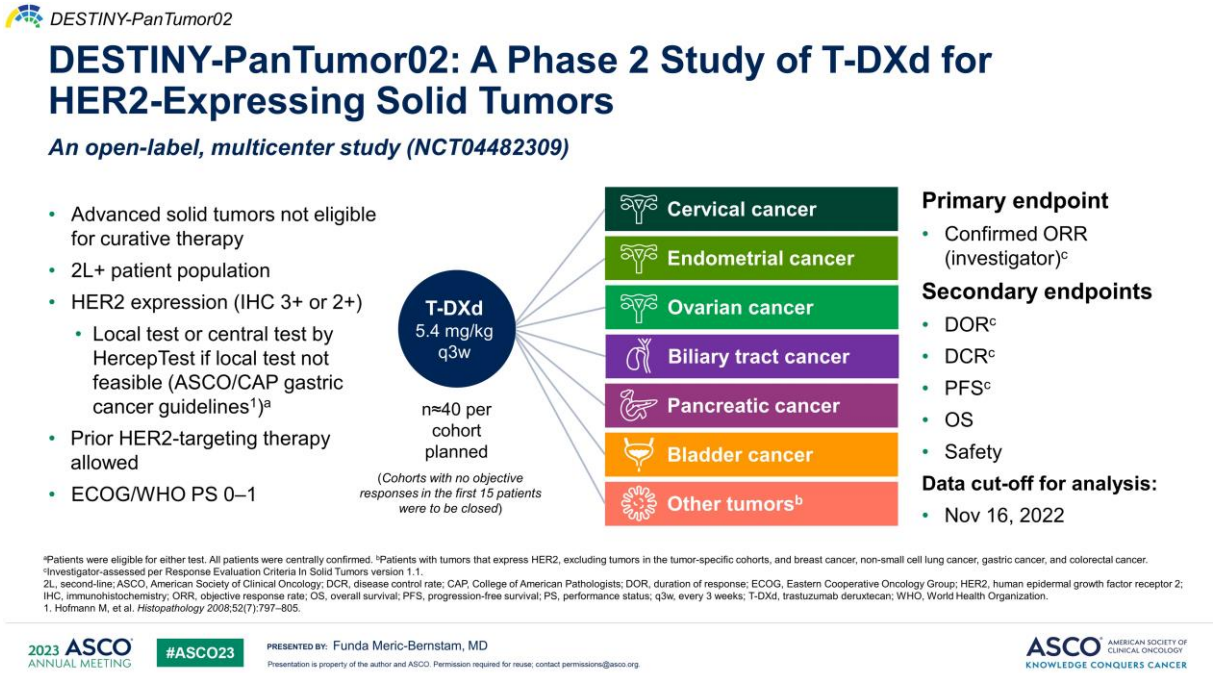
2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY:

ASCO KNOWLEDGE CONQUERS CANCER

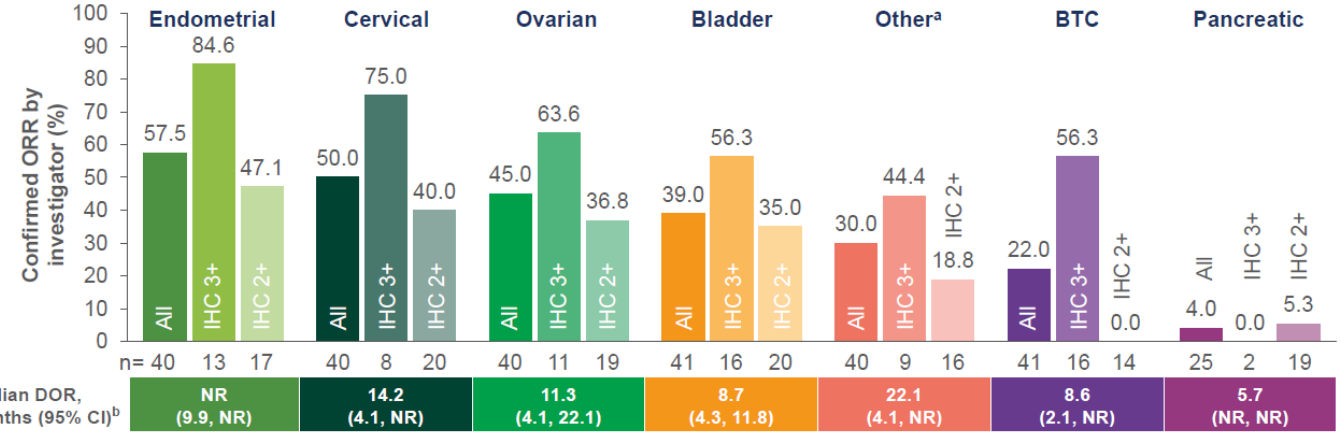
CIBLES PROMETTEUSES



HER2 and TdX-D



Objective response and duration of response



	All patients (N=267)	IHC 3+ (n=75)	IHC 2+ (n=125)
ORR, % (95% CI)	37.1 (31.3, 43.2)	61.3 (49.4, 72.4)	27.2 (19.6, 35.9)
Median DOR, months (95% CI)[b]	11.3 (9.6, 17.8)	22.1 (9.6, NR)	9.8 (4.3, 12.6)

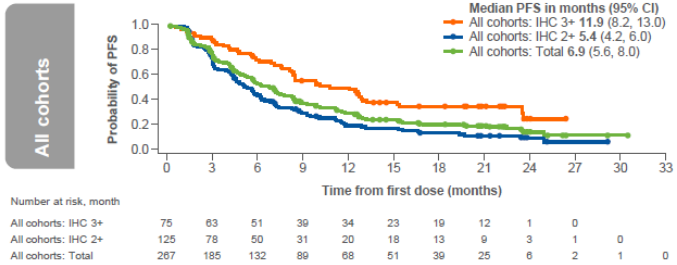
Analysis of ORR by investigator was performed in patients who received ≥1 dose of T-DXd; all patients (n=267; including 67 patients with IHC 1+ [n=25], IHC 0 [n=30], or unknown IHC status [n=12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=75) or IHC 2+ (n=125) status. Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd; all patients (n=99; including 19 patients with IHC 1+ [n=6], IHC 0 [n=9], or unknown IHC status [n=4] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=46) or IHC 2+ (n=34) status. [a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer; [b]includes patients with a confirmed objective response only

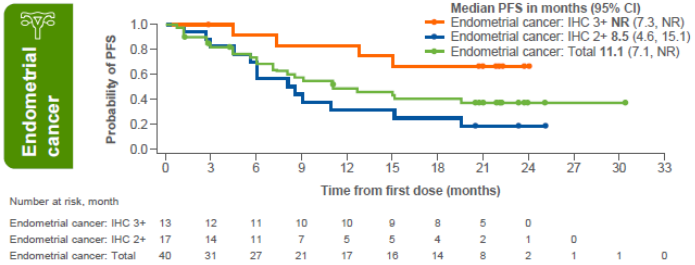
BTC, biliary tract cancer; CI, confidence interval; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NR, not reached; ORR, objective response rate; T-DXd, trastuzumab deruxtecan

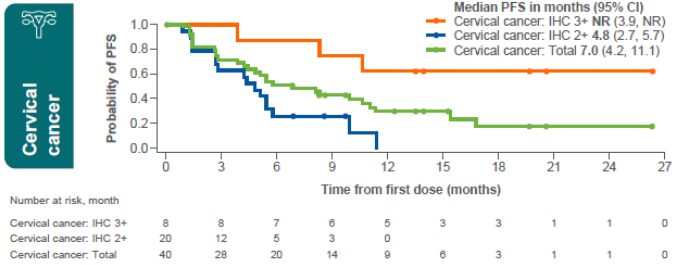
MADRID 2023 ESMO congress

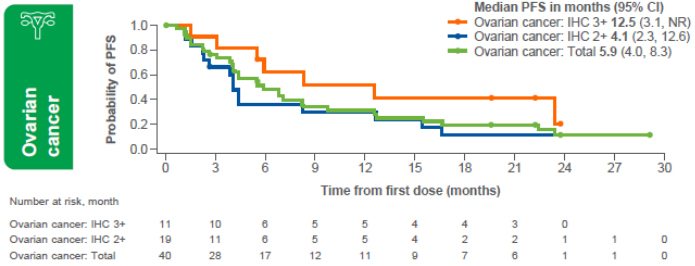
Funda Meric-Bernstam

Efficacy endpoint: PFS by HER2 status per cohort









Circle indicates a censored observation
CI, confidence interval; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NR, not reached; PFS, progression-free survival

MADRID 2023 ESMO congress

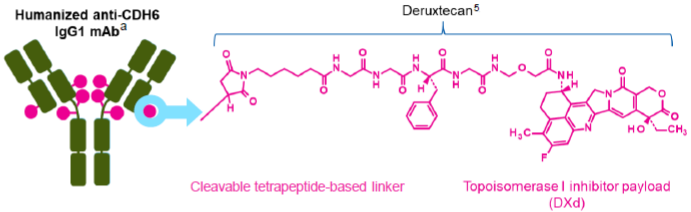
Funda Meric-Bernstam

CDH6 and Raludotatug deruxtecan (R-DXd; DS6000)

Background

- The emergence of platinum resistance in recurrent OVC is inevitable; these patients have a clear need for novel treatments[1]
- Mirvetuximab soravtansine-gynx received accelerated approval from the FDA for the treatment of patients with platinum-resistant, FRα-positive OVC (ORR: 31.7%, median DOR: 6.9 months)[2]
- Expression of CDH6 is observed in ~65–85% of patients with OVC[3,4]
- Raludotatug deruxtecan (R-DXd; DS-6000) is a CDH6-directed ADC composed of three parts: a humanized anti-CDH6 IgG1 mAb, covalently linked to a topoisomerase I inhibitor payload via a tetrapeptide-based cleavable linker[5]

R-DXd was designed with 7 key attributes



Payload mechanism of action: topoisomerase I inhibitor[5,b]
High potency of payload[5,b]
High drug-to-antibody ratio ≈8[5,b]
Payload with short systemic half-life[6,b,c]
Stable linker-payload[5,b]
Tumor-selective cleavable linker[5,b]
Bystander antitumor effect[5,b]

[a]Image is for illustrative purposes only; actual drug positions may vary. [b]The clinical relevance of these features is under investigation. [c]Based on animal data.
ADC, antibody–drug conjugate; CDH6, cadherin 6; DOR, duration of response; DXd, deruxtecan; FDA, United States Food and Drug Administration; FRα, folate receptor alpha; IgG1, immunoglobulin G1; mAb, monoclonal antibody; ORR, objective response rate; OVC, ovarian cancer.

1. Richardson DL, et al. *JAMA Oncol*. 2023;9:851–859; 2. ELAHERE™ (mirvetuximab soravtansine-gynx) prescribing information. Accessed September 1, 2023; 3. Bartolomé RA, et al. *Mol Oncol*. 2021;15:1849–1865;
4. Shintani D, et al. *Gynecol Oncol*. 2022;166(Suppl. 1):S116; 5. Suzuki H, et al. *Ann Oncol*. 2021;32(Suppl. 5):S361–S375; 6. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173–185.

MADRID 2023 ESMO congress

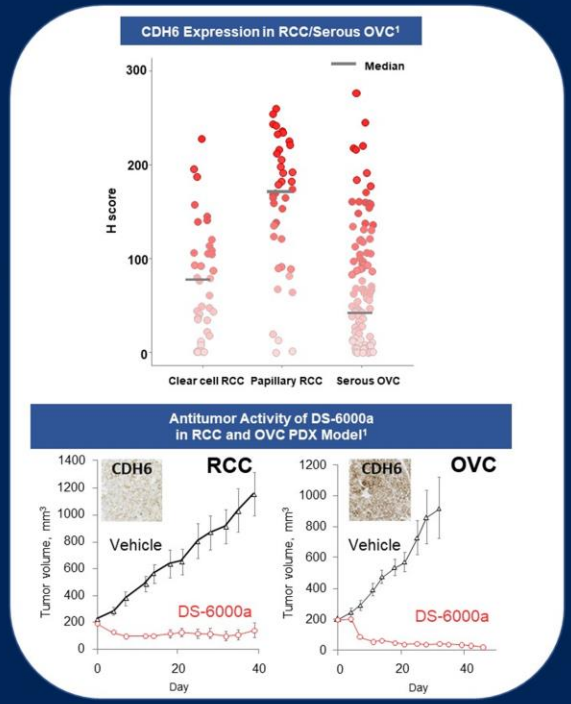
Kathleen Moore

Institut de Cancérologie de l'Ouest
unicancer PAYS DE LA LOIRE

CDH6 and Raludotatug deruxtecan (R-DXd; DS6000)

Background

- Cadherin 6 (CDH6) is part of the cadherin family, which is involved with cell-cell adhesion, organ development, and epithelial-mesenchymal transition
- CDH6 is found to be overexpressed in various cancers, particularly ovarian cancer (OVC) and renal cell carcinoma (RCC)[1]
- In preclinical studies, DS-6000a inhibited tumor growth and induced tumor regression in CDH6-expressing OVC and RCC[1]
- Here, we report initial results from the dose-escalation portion of a first-in-human trial in patients with advanced OVC and RCC (NCT04707248)



PDX, patient-derived xenograft.

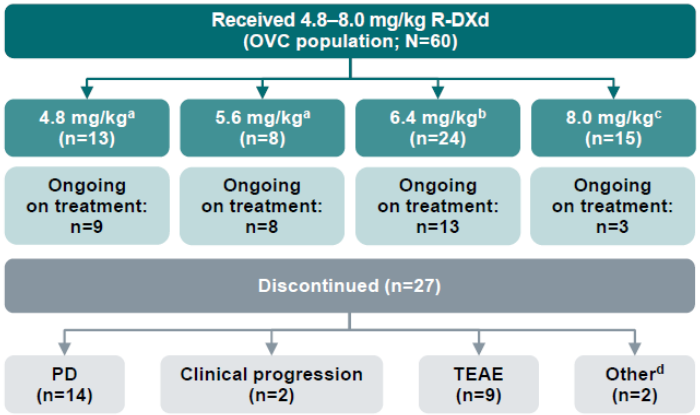
1. Hirokazu S, et al. ESMO 2021. Abstract 10P.

PRESENTED BY: Erika P. Hamilton, MD

CDH6 and Raludotatug deruxtecan (R-DXd; DS6000)

Baseline demographics and disease characteristics

Data cutoff: July 14, 2023



- Median treatment duration: 18 weeks (range: 3–115)
- 12 (20%) patients received treatment for ≥6 months
- 3 (5%) patients received treatment for ≥18 months

	OVC (4.8–8.0 mg/kg) N=60
Age, median years (range)	66 (42–82)
ECOG PS, n (%)	
0	22 (36.7)
1	38 (63.3)
Platinum-resistant disease[e], n (%)	55 (91.7)
Number of prior systemic regimens, median (range)	4 (1–13)
Received prior systemic therapy, n (%)	
Bevacizumab	41 (68.3)
PARP inhibitor	39 (65.0)
Baseline tumor CDH6 expression H-score, median (range)	125 (0–250)

[a]Enrollment ongoing. [b]Enrollment completed. [c]As of October 2022, the patients who were still receiving R-DXd at 8.0 mg/kg were dose-reduced to receive R-DXd 6.4 mg/kg. [d]Death (n=1) and informed consent withdrawn (n=1). [e]Defined as tumor progression during or within 6 months after completion of prior platinum therapy. Five patients had tumor progression 6 months after platinum therapy.

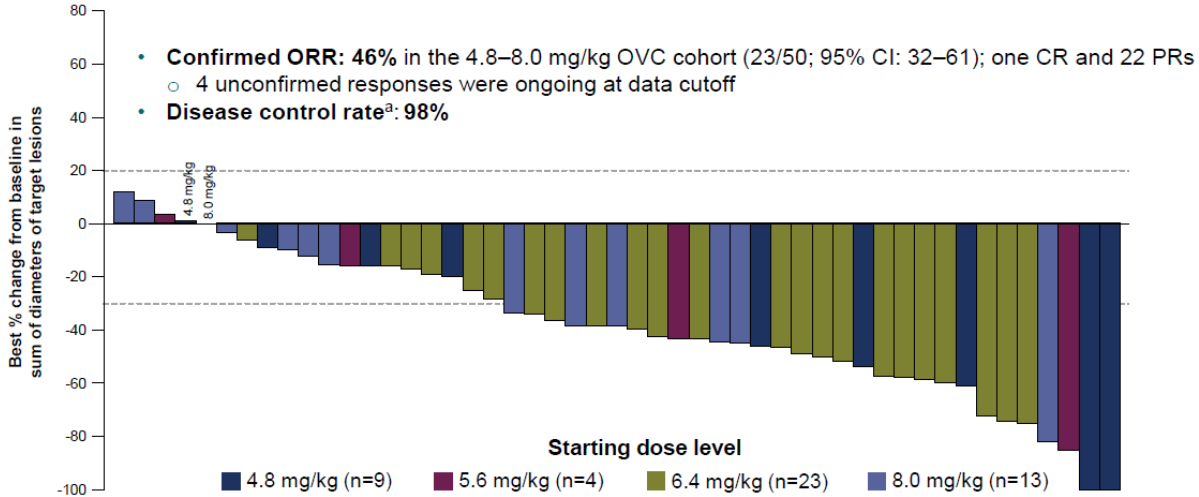
CDH6, cadherin 6; ECOG PS, Eastern Cooperative Oncology Group performance status; OVC, ovarian cancer; PARP, poly adenosine diphosphate-ribose polymerase; PD, progressive disease; TEAE, treatment-emergent adverse event.

MADRID 2023 ESMO congress

Kathleen Moore

CDH6 and Raludotatug deruxtecan (R-DXd; DS6000)

Preliminary efficacy data for R-DXd are promising in pretreated OVC patients



- **Confirmed ORR: 46%** in the 4.8–8.0 mg/kg OVC cohort (23/50; 95% CI: 32–61); one CR and 22 PRs
  - 4 unconfirmed responses were ongoing at data cutoff
- **Disease control rate**[a]**: 98%**

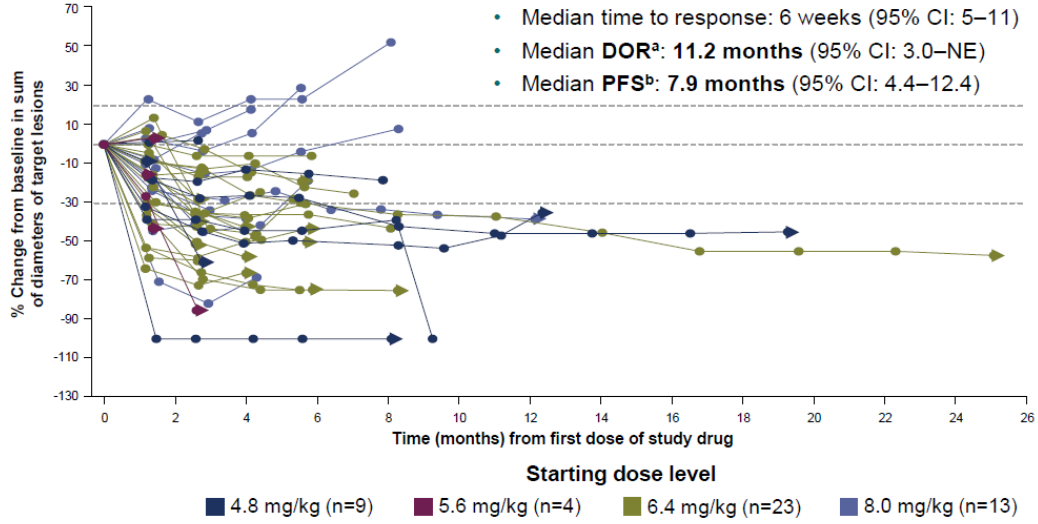
Data cutoff: July 14, 2023.
[a]CR + PR + stable disease.
The efficacy evaluable population included patients who received ≥1 dose of study treatment and completed ≥1 post-baseline tumor assessment or discontinued treatment for any reason. Change from baseline in target tumor size was assessed per RECIST v1.1. Two patients with no measurable lesions at baseline and one patient who discontinued and did not have a post-baseline tumor assessment were not included in the waterfall plot.
CI, confidence interval; CR, complete response; ORR, objective response rate; OVC, ovarian cancer; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

MADRID 2023 ESMO congress

Kathleen Moore

CDH6 and Raludotatug deruxtecan (R-DXd; DS6000)

Preliminary efficacy data for R-DXd are promising in pretreated OVC patients



Data cutoff: July 14, 2023.

[a]Median follow-up for DOR: 5.8 months (range: 1.4–16.8). [b]Median follow-up for PFS: 5.6 months (range: 0.03–25.1).

The efficacy evaluable population included patients who received ≥1 dose of study treatment and completed ≥1 post-baseline tumor assessment or discontinued treatment for any reason. Change from baseline in target tumor size was assessed per RECIST v1.1. Two patients with no measurable lesions at baseline and one patient who discontinued and did not have a post-baseline tumor assessment were not included in the spider plot.

CI, confidence interval; DOR, duration of response; NE, not estimable; OVC, ovarian cancer; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

MADRID 2023 ESMO congress

Kathleen Moore

CDH6 and Raludotatug deruxtecan (R-DXd; DS6000)

Safety profile of R-DXd is manageable

Patients with OVC who received R-DXd at 4.8–8.0 mg/kg

Overview of TEAEs

	n (%) N=60
Any TEAEs	57 (95.0)
TEAE with CTCAE Grade ≥3	31 (51.7)
TEAE associated with drug discontinuation	9 (15.0)
TEAE associated with dose interruption	22 (36.7)
TEAE associated with dose reduction	15 (25.0)
Any treatment-related CTCAE Grade ≥3 TEAE	22 (36.7)
Treatment-related TEAE associated with death	2 (3.3)[a]

- 3.3% (2/60) of patients in the 4.8–8.0 mg/kg cohort experienced Grade 5 ILD; both occurred in the 8.0 mg/kg cohort and were adjudicated as treatment-related
- 8.9% (4/45) of patients in the 4.8–6.4 mg/kg cohort experienced ILD (all Grade 2), of which 2 were adjudicated as treatment-related
- As of October 2022, the 8.0 mg/kg cohort was closed due to a higher incidence of serious and Grade ≥3 TEAEs and lack of a favorable benefit/risk ratio[b]
- Further dose assessment is ongoing at three doses: 4.8, 5.6 and 6.4 mg/kg

Data cutoff: July 14, 2023.

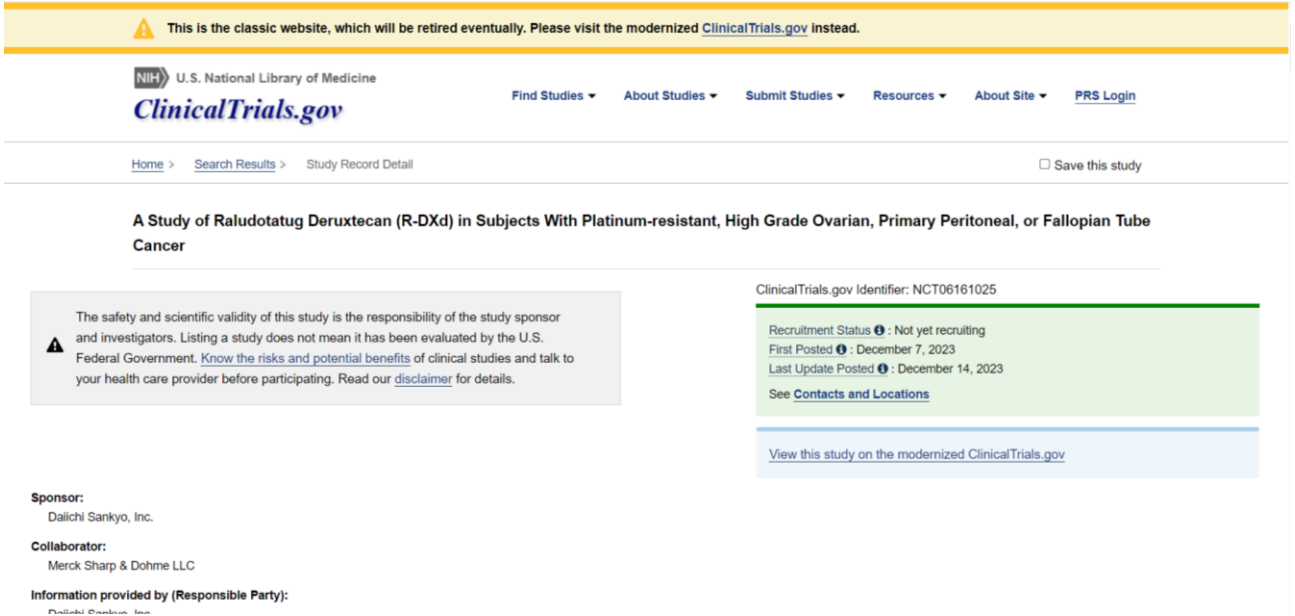
[a]Grade 5 ILD. [b]6/15 (40.0%) patients in the 8.0-mg/kg OVC cohort experienced serious and Grade ≥3 TEAEs.

CTCAE, Common Terminology Criteria for Adverse Events; ILD, interstitial lung disease; OVC, ovarian cancer; TEAE, treatment-emergent adverse event.

Most common (≥10%) treatment-related TEAEs

Preferred term	n (%) N=60	
	All grades	Grade ≥3
Nausea	35 (58.3)	1 (1.7)
Fatigue	27 (45.0)	2 (3.3)
Vomiting	20 (33.3)	1 (1.7)
Anemia	17 (28.3)	11 (18.3)
Decreased neutrophil count	15 (25.0)	7 (11.7)
Diarrhea	16 (26.7)	1 (1.7)
Decreased appetite	15 (25.0)	1 (1.7)
Decreased platelet count	10 (16.7)	3 (5.0)
Alopecia	7 (11.7)	0
Malaise	6 (10.0)	0

CDH6 and Raludotatug deruxtecan (R-DXd; DS6000)



This is the classic website, which will be retired eventually. Please visit the modernized ClinicalTrials.gov instead.

U.S. National Library of Medicine
ClinicalTrials.gov

Find Studies | About Studies | Submit Studies | Resources | About Site | PRS Login

Home > Search Results > Study Record Detail

Save this study

A Study of Raludotatug Deruxtecan (R-DXd) in Subjects With Platinum-resistant, High Grade Ovarian, Primary Peritoneal, or Fallopian Tube Cancer

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT06161025

Recruitment Status : Not yet recruiting
First Posted : December 7, 2023
Last Update Posted : December 14, 2023

See Contacts and Locations

View this study on the modernized ClinicalTrials.gov

Sponsor:
Daiichi Sankyo, Inc.

Collaborator:
Merck Sharp & Dohme LLC

Information provided by (Responsible Party):

CONCLUSIONS

MIRVETUXIMAB SORAVTANSINE est le premier ADC approuvé dans le cancer de l'ovaire (aux USA)

Premier traitement augmentant la SG dans le cancer de l'ovaire platine résistant depuis le bevacizumab

La vague continue…

Enjeu de toxicité: place pour les ADC sans payload neurotoxique?

Place des combinaisons+++