Role of ADCs in Ovarian Cancer

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VERBAL DISCLOSURE – 3 years

- Dr. OMalley reports personal fees (consulting and/or advisory boards)and funding for clinical research from AstraZeneca, personal fees (consulting and/or advisory boards) and funding for clinical research from Tesaro/GSK, personal fees (consulting and/or advisory boards) and funding for clinical research from Immunogen, personal fees (consulting and/or advisory boards) from Ambry, personal fees (consulting and/or advisory boards) and funding for clinical research from Janssen/J&J, personal fees (consulting and/or advisory boards) and funding for clinical research from Abbvie, personal fees (consulting and/or advisory boards) and funding for clinical research from Regeneron, personal fees (consulting and/or advisory boards) and funding for clinical research from Amgen, personal fees (consulting and/or advisory boards) and funding for clinical research from Novocure, personal fees (consulting and/or advisory boards) and funding for clinical research from Genentech/Roche, funding for clinical research from VentiRx, funding for clinical research from Array Biopharma, funding for clinical research from EMD Serono, funding for clinical research from Ergomed, funding for clinical research from Ajinomoto Inc., funding for clinical research from Ludwig Cancer Research, funding for clinical research from Stemcentrx, Inc, funding for clinical research from CERULEAN PHARMA, personal fees (consulting and/or advisory boards) and funding for clinical research from GOG Foundation, funding for clinical research from Bristol-Myers Squibb Co, funding for clinical research from Serono Inc, funding for clinical research from TRACON Pharmaceuticals, funding for clinical research from Yale University, funding for clinical research from New Mexico Cancer Care Alliance, funding for clinical research from INC Research, Inc, funding for clinical research from inVentiv Health Clinical, personal fees (consulting and/or advisory boards) and funding for clinical research from Iovance, funding for clinical research from PRA Intl, personal fees from Myriad Genetics, personal fees (consulting and/or advisory boards) and funding for clinical research from Eisai, personal fees and funding for clinical research from Agenus, personal fees from Tarveda, personal fees (consulting and/or advisory boards) and funding for clinical research from Merck, funding for clinical research from GenMab, personal fees (consulting and/or advisory boards) and funding for clinical research from SeaGen, personal fees (consulting and/or advisory boards) from Novartis, personal fees (consulting and/or advisory boards) and funding for clinical research from Mersana, personal fees (consulting and/or advisory boards) and funding for clinical research from Clovis, personal fees from Rubis, personal fees (consulting and/or advisory boards) from Elevar, personal fees (consulting and/or advisory boards) from Takeda, personal fees (consulting and/or advisory boards) from Toray; personal fees (consulting and/or advisory boards) from INXMED; personal fees (consulting and/or advisory boards) and funding for clinical research from SDP Oncology (BBI); personal fees (consulting and/or advisory boards) from Arquer Diagnostics; personal fees (consulting and/or advisory boards) from Roche Diagnostics MSA; personal fees (consulting and/or advisory boards) from Sorrento; personal fees (consulting and/or advisory boards) from Corcept Therapeutics; personal fees (consulting and/or advisory boards) from Celsion Corp

- I serve as Clinical Trial Advisor (Ovarian Cancer) for GOG Partners and am on the GOG Foundation BOD

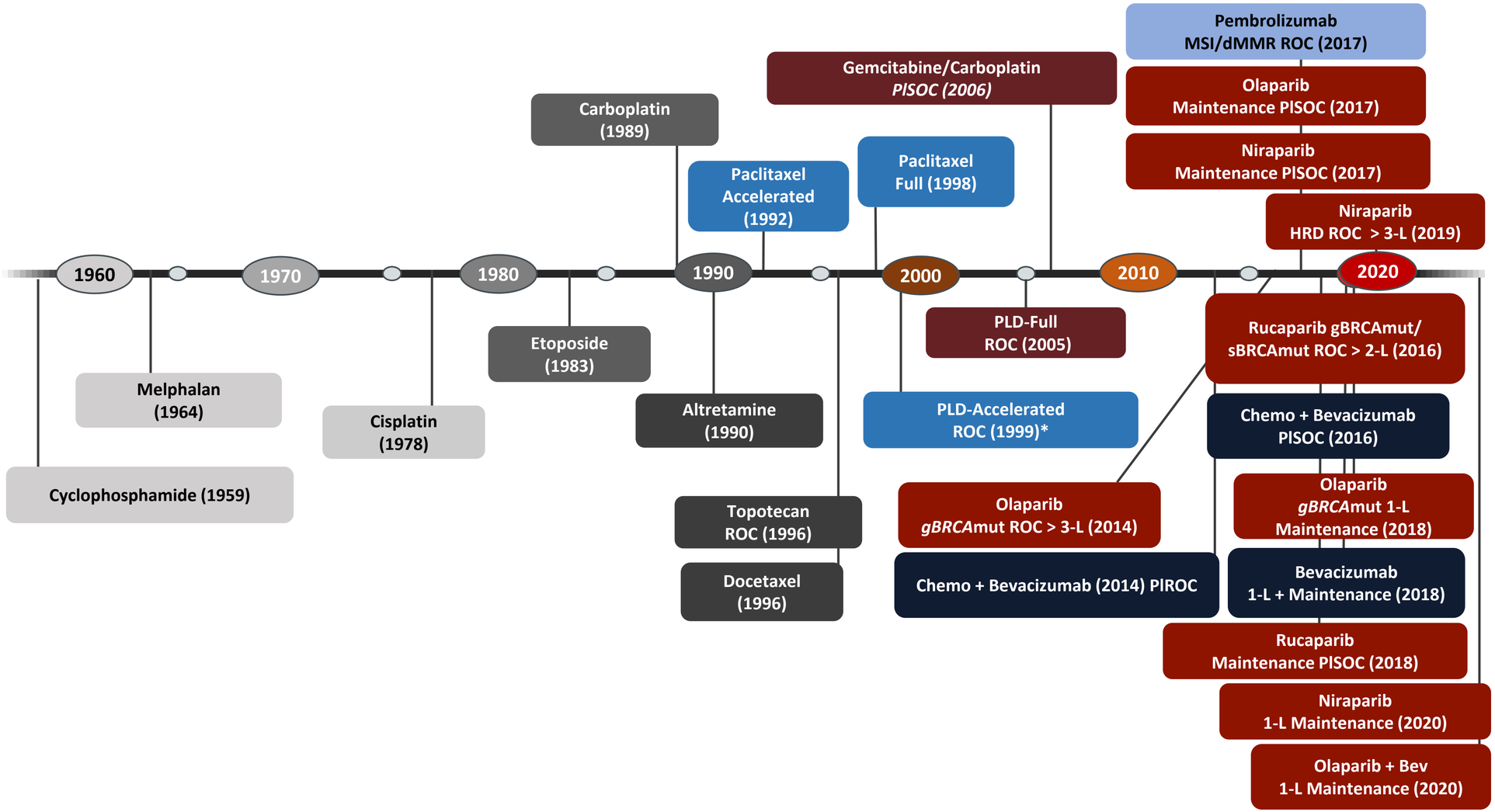
Agenda

- Background
- Targets
  - NaPi2b
    - Lifastuzumab (LIFA)
    - Upifitamab rilsodotin (UpRi):
  - Folate receptor alpha
    - STRO-002
    - MORAb-202
    - Mirvetuximab soravtansine (Mirv)

FDA-Approved Drugs for Ovarian Cancer

12+ Approvals since Nov 2014

More approvals in the last 6 years than the prior 60 years combined



Target Antigens

Target antigen	Function	Expression	ADC
Folate receptor alpha	Transmembrane protein involved in transport of folate into cells necessary for metabolism, DNA synthesis, repair, and proliferation	Ovarian: 80-96% Endometrial: 41%	Mirvetuximab soravtansine STRO-002 MORAb-202
NaPi2b	Sodium-dependent phosphate transport protein expressed in epithelial cells.	Ovarian: 80-100%	Lifastuzumab vedotin XMT-1536
Tissue Factor	Thromboplastin or factor III, involved in extrinsic coagulation pathway leading to generation of thrombin/clot formation.	Ovarian: 96% Endometrial: 15% Cervical: 34%	Tisotumab vedotin
Mesothelin	Hypothesized to be involved in cell adhesion. Expressed on mesothelial cells.	Ovarian: 60-88%	Anetumab ravtansine DMOT4039A BMS-986148
MUC16	Transmembrane protein with role in adhesion/peritoneal metastases. CA-125 represents the extracellular, cleaved portion.	Ovarian: 80%	DMUC4064A

Calo CA, **O'Malley DM.** Antibody-drug conjugates for the treatment of ovarian cancer. Expert Opin Biol Ther. 2020 Jun 8:1-13. doi: 10.1080/14712598.2020.1776253. Online ahead of print. PMID: 32463296

ADC	Target Antigen/ Antibody	Cytotoxic Payload and mechanism of action	Linker	DAR	Phase of development
Mirvetuximab soravtansine (ImmunoGen, Inc)	Folate receptor α Humanized IgG1 (M9346A)	Soravtansine (Maytansinoid DM4) Microtubule inhibitor	Sulfo-PDB	3-4	Phase III
STRO-002 (Sutro Biopharma, Inc.)	Folate receptor α Human anti-FRα IgG1 antibody (SP8166)	Proprietary 3-aminophenyl hemiasterlin agent: SC209 Proprietary tubulin-targeting payload	Proprietary cleavable linker: SC239	4	Phase I dose escalation/ expansion ongoing
MORAb-202 (Eisai Inc.) (NCT03386942)	Folate receptor α Humanized anti-human FRα farletuzumab	Eribulin mesylate Microtubule inhibitor	Cathepsin B-cleavable linker	4	Phase I ongoing
XMT-1536 (Mersana Therapeutics) (NCT03319628)	NaPi2b Humanized monoclonal antibody (SLC34A2)	Proprietary auristatin derivative (auristatin F-HPA) Microtubule inhibitor	Proprietary hydrophilic polymer scaffold	10-12	Phase I dose escalation/ expansion ongoing
Lifastuzumab vedotin (LIFA/DNIB0600A) (Genentech, Inc.)	NaPi2b Humanized monoclonal antibody (SLC34A2)	MMAE Microtubule inhibitor	Cleavable maleimidocaproyl-valyl-citrullinyl-p-aminobenzyloxycarbonyl (mc-val-cit-PABC)	3-4	Randomized phase II completed; further development discontinued

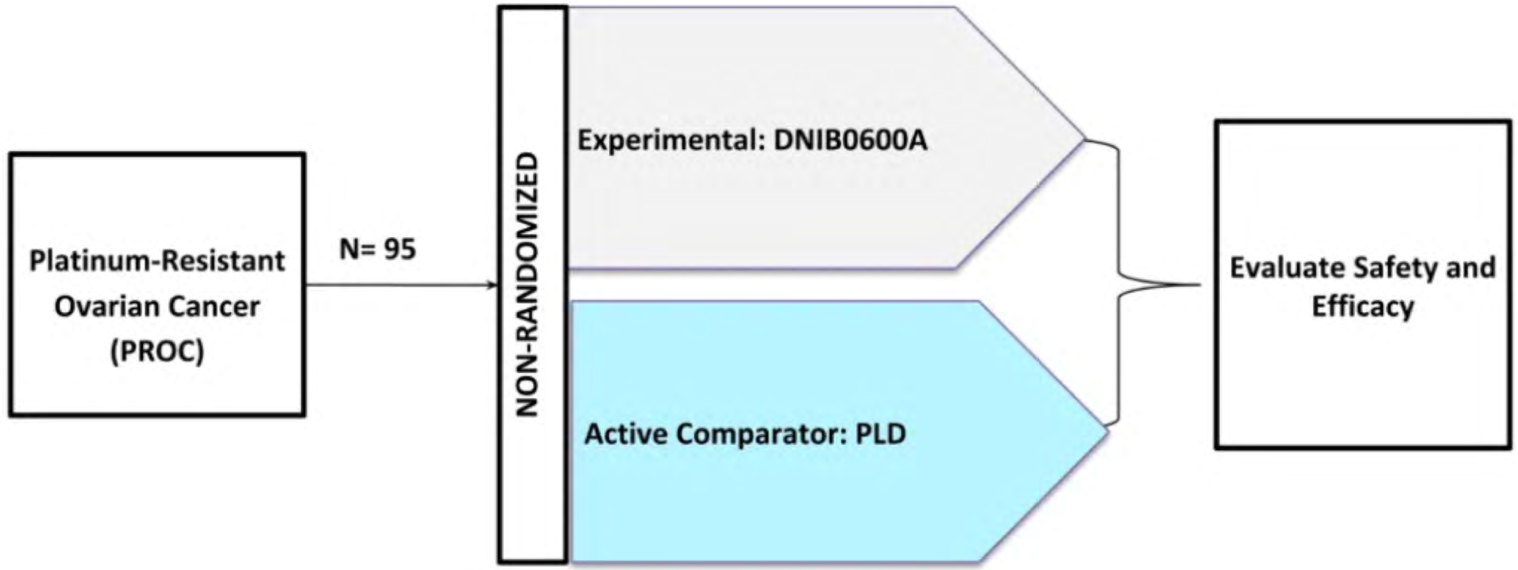
Calo CA, **O'Malley DM.** Antibody-drug conjugates for the treatment of ovarian cancer. Expert Opin Biol Ther. 2020 Jun 8:1-13. doi: 10.1080/14712598.2020.1776253. Online ahead of print. PMID: 32463296

ADC	Target Antigen/ Antibody	Cytotoxic Payload and mechanism of action	Linker	DAR	Phase of development
Tisotumab vedotin (HuMax-TF-ADC; TF011-MMAE) (Seattle Genetics, Inc.)	Tissue factor Fully human monoclonal antibody	MMAE Microtubule inhibitor	Protease cleavable valine-citrulline linker		Phase II ongoing; Phase III in cervical cancer ongoing
Anetumab ravtansine (BAY 94-9343) (Bayer)	Mesothelin Fully human IgG1 (MF-T)	Ravtansine/ DM4 Microtubule inhibitor	Sulfo-PDB	3.2	Phase II ongoing
DMOT4039A (RG7600) (Genentech, Inc.)	Mesothelin Humanized IgG1 antibody (h7D9.v3)	MMAE Microtubule inhibitor	Protease cleavable valine-citrulline linker	3.5	Phase II
BMS-986148 (Bristol-Myers Squibb)	Mesothelin Fully human IgG1 monoclonal antibody	Duocarmycin-related DNA alkylation	Protease cleavable valine-citrulline linker	1.4	Phase I/IIa ongoing
Sofituzumab vedotin (DMUC5754A) (Genentech, Inc.)	MUC16 Humanized IgG1 monoclonal antibody	MMAE Microtubule inhibitor	Protease cleavable valine-citrulline linker (maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl)	3.5	Phase I completed; further development discontinued
Anti-MUC16 TDC (DMUC4064A) (Genentech, Inc.) NCT02146313	MUC16 Humanized anti-MUC16 IgG1	MMAE Microtubule inhibitor	Cysteine-engineered THIOMAB^{TM}	2	Phase I completed

Calo CA, **O'Malley DM.** Antibody-drug conjugates for the treatment of ovarian cancer. Expert Opin Biol Ther. 2020 Jun 8:1-13. doi: 10.1080/14712598.2020.1776253. Online ahead of print. PMID: 32463296

NaPi2b

RPh2 Lifastuzumab vs. PLD



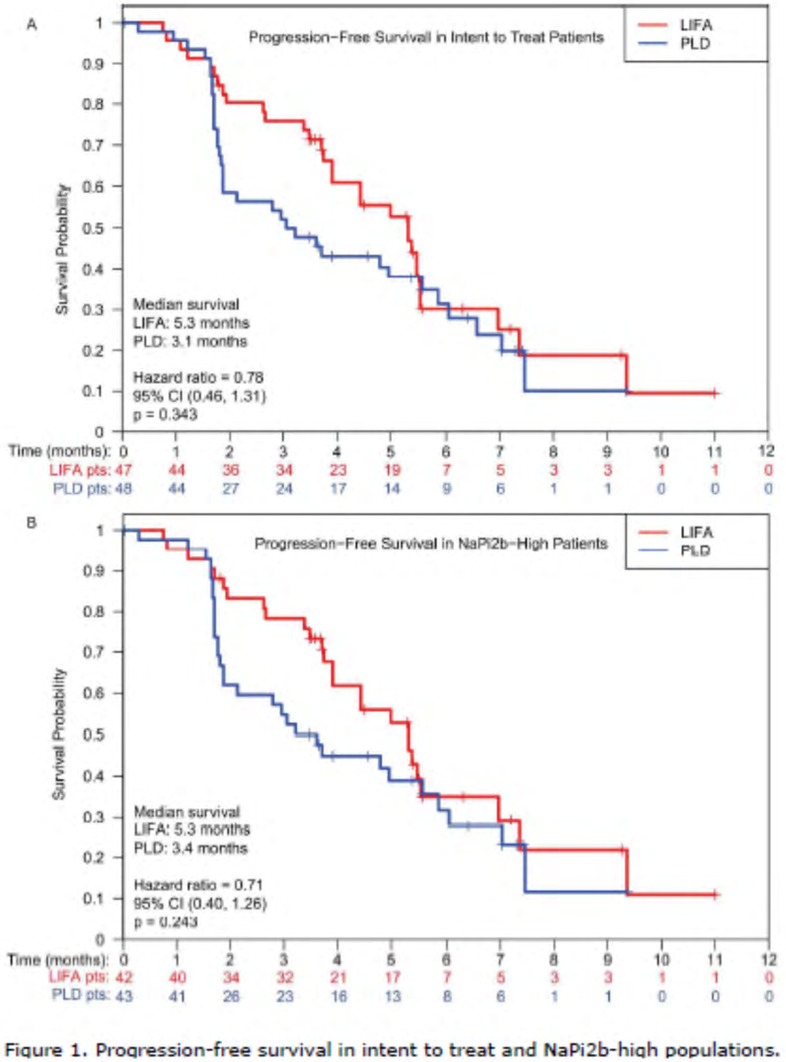


Figure 1. Progression-free survival in intent to treat and NaPi2b-high populations.

HR for stratified PFS was 0.78
(95% CI 0.46-1.31; p=0.34)

Banerjee et al. Annals of Oncology 2018

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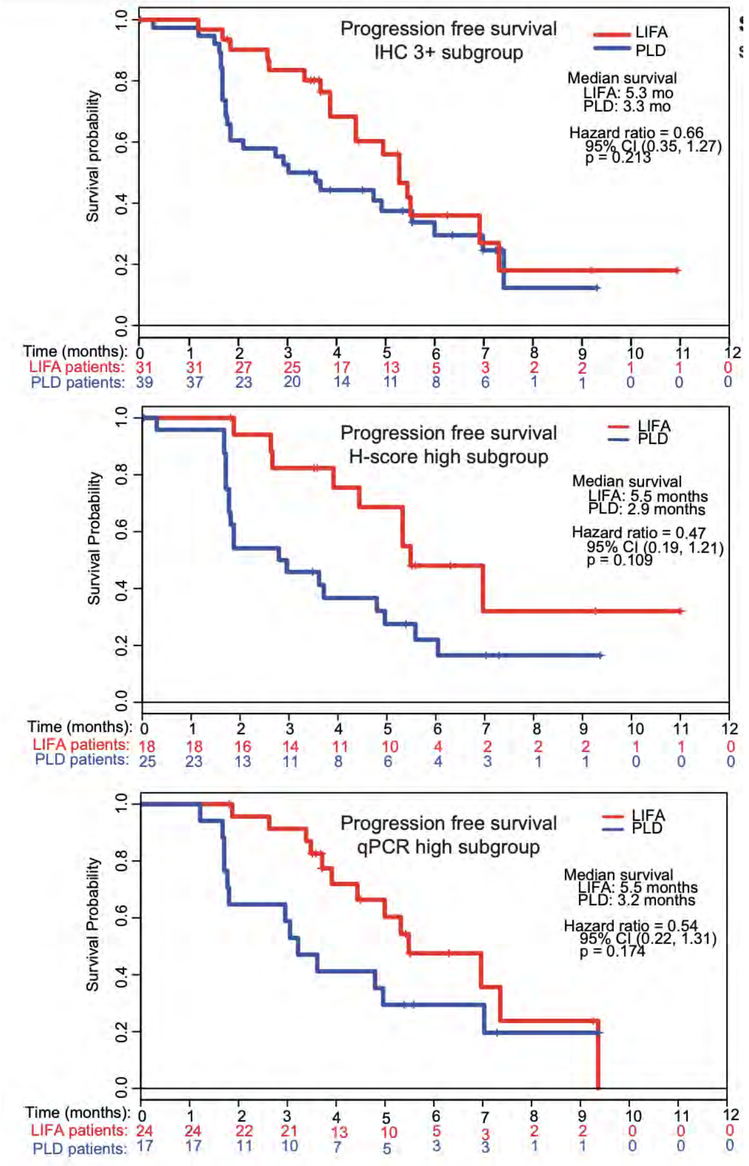
RPh2 Lifastuzumab vs. PLD Efficacy and Safety

	Lifastuzumab	PLD
ORR	34% (95% CI 22-49%)	15% (95% CI 7-28%)
Grade 3 AEs	46%	51%
SAEs	30%	30%
AEs leading to discontinuation	9%	8%
Grade ≥ 2 neuropathy	11%	4%

Banerjee et al. Annals of Oncology 2018

LIFA – Biomarker Subsets

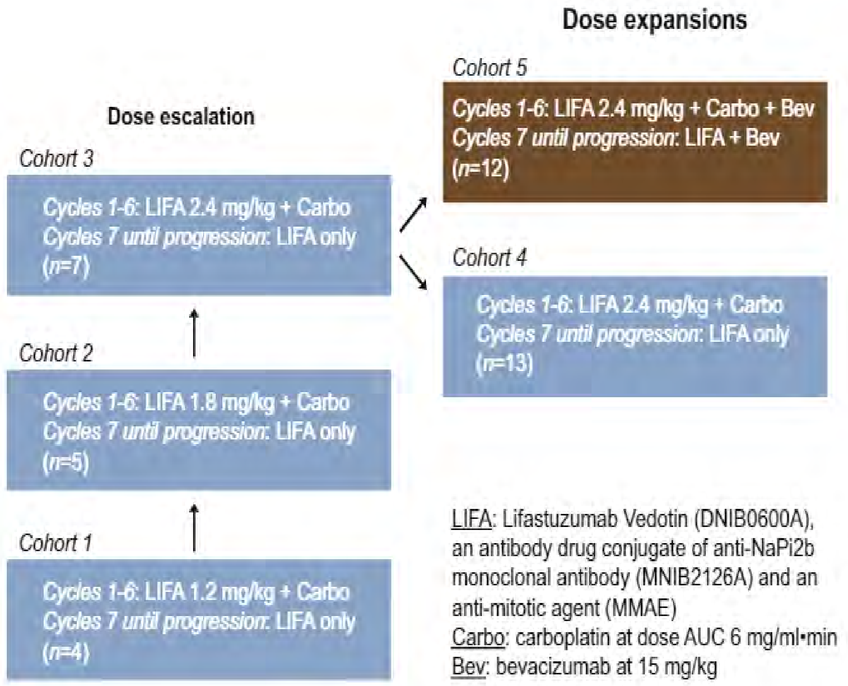


Group	ITT (n=95)		NaPi2b 2/3+ (n=85)		NaPi2b 3+ (n=70)		NaPi2b median H-score high (n=43)		NaPi2b median qPCR high (n=41)	
Arm	LIFA *n=47*	PLD *n=48*	LIFA *n=42*	PLD *n=43*	LIFA *n=31*	PLD *n=39*	LIFA *n=18*	PLD *n=25*	LIFA *n=24*	PLD *n=17*
ORR	34%	15%	36%	14%	42%	13%	44%	8%	50%	6%
Median PFS (months)	5.3	3.1	5.3	3.4	5.3	3.3	5.5	2.9	5.5	3.2
HR	0.78 (0.34)		0.71 (0.24)		0.66 (0.21)		0.47 (0.11)		0.54 (0.0174)	

- **NaPi2b membranous staining level was scored according to the following algorithm, where at least 50% of tumor cells had to be stained in order to qualify as positive in each category**
- **NaPi2b H score: [1 × (% cells 1+) + 2 × (% cells 2+) + 3 × (% cells 3+)]**
- **NaPi2b transcript levels in the tumor tissues were also determined by qRT-PCR using a validated NaPi2b/TMEM (house-keeping gene) duplex assay (Cobas z480 Real-time PCR Platform), (Roche Molecular Systems, Pleasanton, CA)**

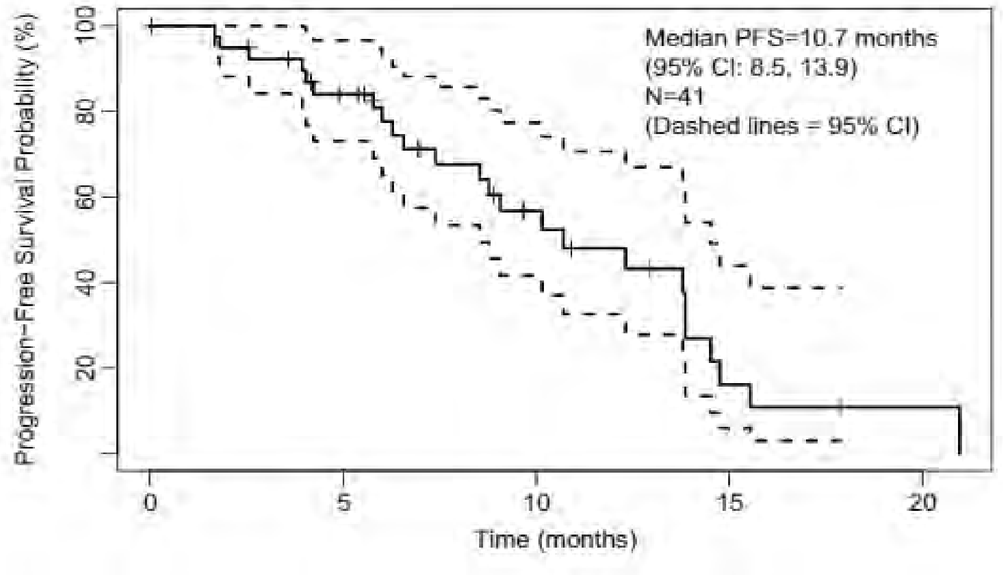
Banerjee et al. Annals of Oncology 2018

Phase Ib Lifastuzumab plus carboplatin in platinum sensitive recurrent ovarian cancer



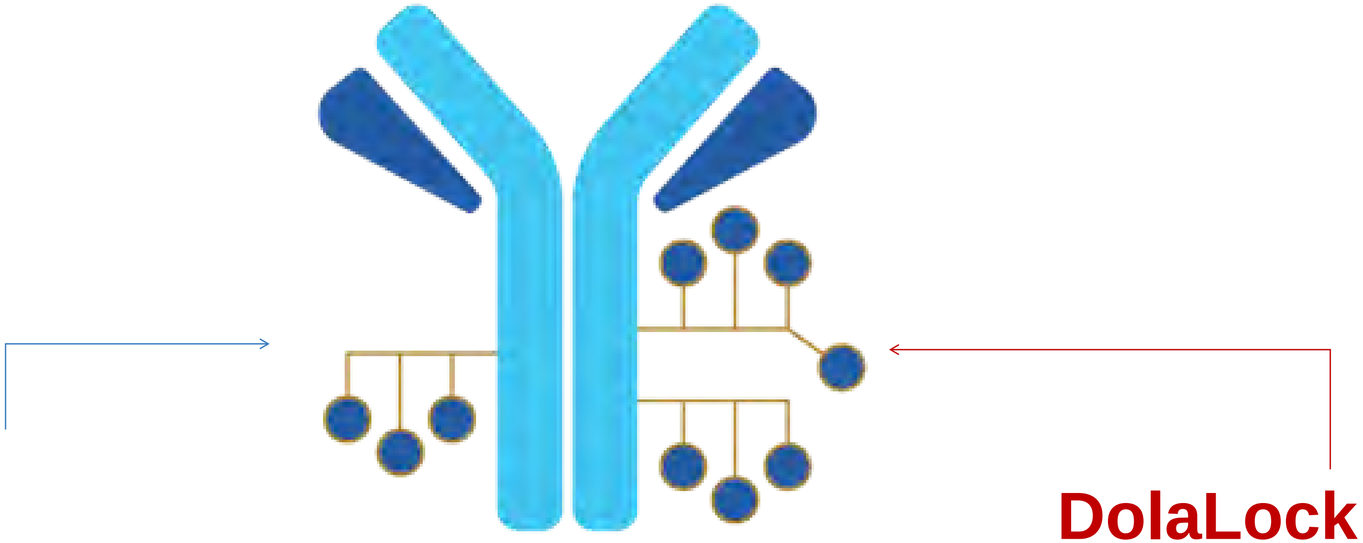
Best Response	All Patients N=41 N (%)
CR	24 (59)
PR	6 (15)
SD	13 (32)
PD	2 (5)
UE	2 (5)

ORR 74%



Moore et al. Gynecol Oncol 2020

XMT-1536 (upifitamab rilsodotin; UpRi): : NaPi2b Dolaflexin ADC



Dolaflexin

Improved therapeutic index vs other platforms

- **Polymer scaffold**
- **High Drug to Antibody Ratio (DAR) ~10-12**
- **Excellent drug like properties**

DolaLock Payload

Efficacy without severe neutropenia, neuropathy, or ocular toxicity

- **Novel auristatin**
- **Controlled bystander effect**
- **Selectively toxic to rapidly dividing cells**
- **Not a PgP substrate**
- **Induces immunogenic cell death**

Design for the Ovarian Cancer Cohort of the XMT-1536 (UpRi) Phase 1 Expansion Study

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-resistant defined as lack of response or disease progression within 3 mos after completing front-line platinum containing**

Patient population: High grade serous ovarian cancer (including fallopian tube and primary peritoneal cancer) progressing after standard treatments

- **Measurable disease per RECIST v1.1**
- **ECOG Performance Status 0 or 1**

Dosing: IV every 4 weeks until disease progression or unacceptable toxicity

- **36 mg/m2 cohort initiated in August 2019 and enrollment closed**
- **43 mg/m2 cohort initiated in December 2019 and ongoing; current dose evaluated in EXP**

Primary Objectives:

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

Secondary Objectives:

- **Association of tumor NaPi2b expression and objective tumor response using an immunohistochemistry (IHC) assay with a broad dynamic range to distinguish tumors with higher and lower NaPi2b expression (as previously reported[1,2,3])**
- **Further assessment of preliminary anti-neoplastic activity (DOR)**

Assessments:

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

Abbreviations: mos = months; EXP = expansion; RECIST = Response Evaluation Criteria in Solid Tumors; ECOG = Eastern Cooperative Oncology Group; MTD = maximum tolerated dose; **ORR = objective response rate; DCR = disease control rate; DOR = duration of response**

[1]Tolcher TW et al. J Clin Oncol 37, 2019 (suppl; abstr 3010)
[2]Richardson DL et al. Presented at SGO Annual Meeting 2020; LBA8
[3] Hamilton E et al. Presented during the 2020 European Society of Medical Oncology (ESMO) Virtual Congress

Efficacy

Best Response in Evaluable Patients with Ovarian Cancer (n = 47)				
	All (n = 47)	**Higher NaPi2b^{O} (n = 31)**	**Lower NaPi2b^{OO} (n = 13)**	**NaPi2b Not Yet Determined (n = 3)**
CR; n(%)	2 (4)	2 (6)	0	0
PR; n(%)	11 (23)	8 (26)	2 (15)	1 (33)
SD; n(%)	19 (40)	13 (42)	5 (38)	1 (33)
PD; n(%)	15 (32)	8 (26)	6 (46)	1 (33)
ORR; n (%)	**13 (28)**	**10 (32)**	**2 (15)**	**1 (33)**
DCR; n (%)	**32 (68)**	**23 (74)**	**7 (54)**	**2 (67)**

All Responses are Confirmed

***25 patients were not evaluable for RECIST response: 10 patients discontinued prior to first scans: 1 clinical progression; 1 related SAE (G5 pneumonitis); 3 unrelated SAEs; 5 withdrew consent; 15 patients did not yet have RECIST assessment as of the data cut**

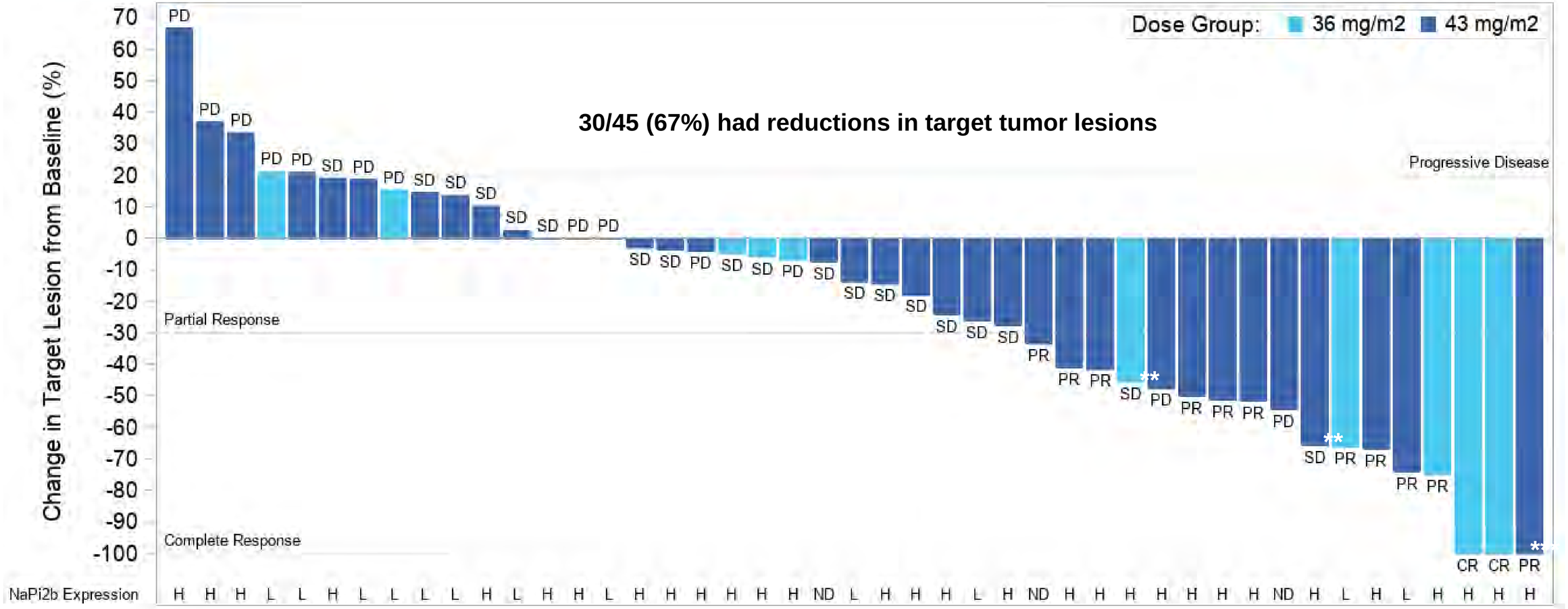
^{O} Higher NaPi2b Expression: defined in dose escalation as at / above lowest H-score at which response observed (≥110)

^{OO} Lower NaPi2b Expression: defined in dose escalation as below the lowest H-score at which response observed (<110)

[2]Richardson DL et al. Presented at SGO Annual Meeting 2020;

Efficacy

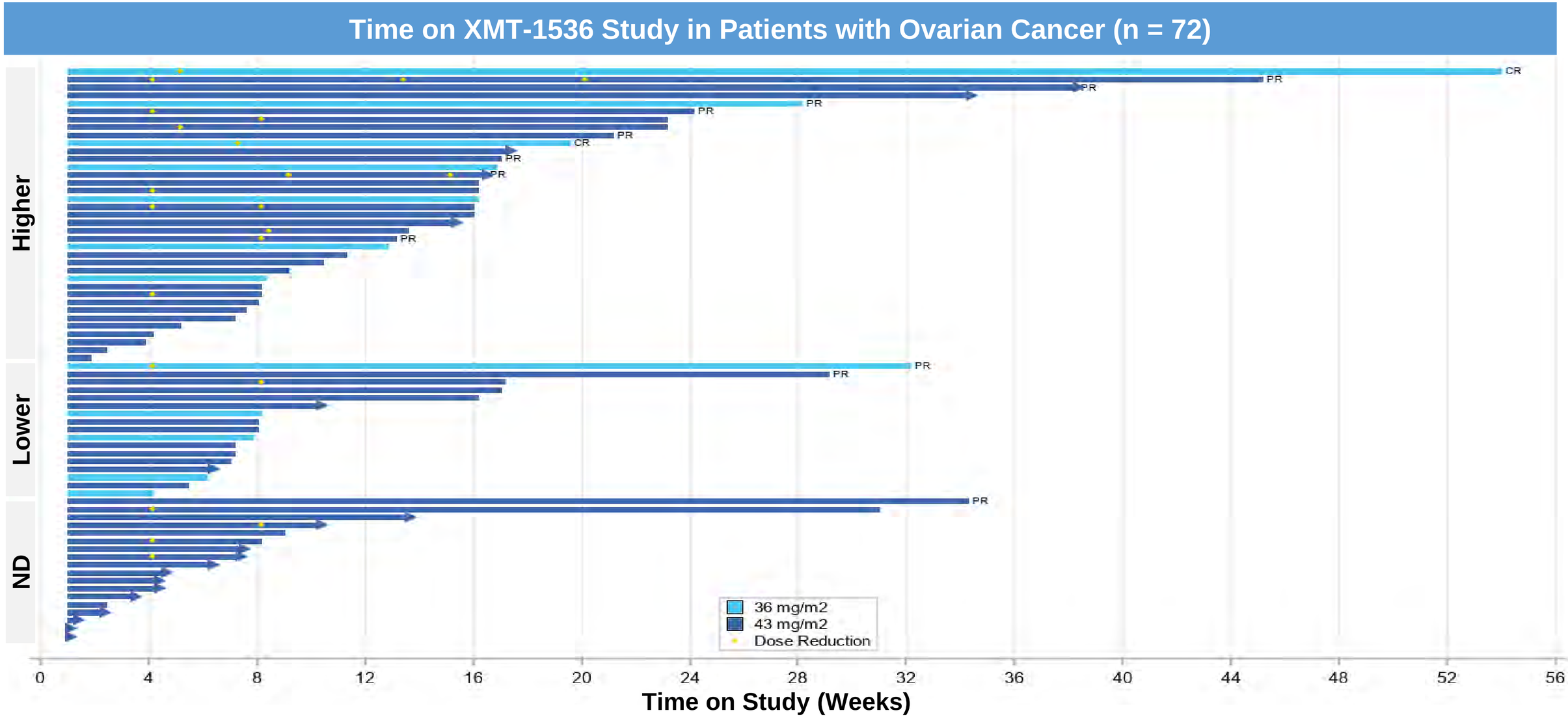
Maximum % Change from Baseline in Target Lesions in Patients with Ovarian Cancer (n = 45*)



*** 2 patients not included in waterfall plot as tumor measurement data missing in the database as of data cut; both patients had BOR of PD due to new lesions**
**** Unconfirmed response, BOR per RECIST v1.1 is SD**
***** CR of target lesions and non-CR/non-PD of non-target lesions, BOR per RECIST v1.1 is PR**
H = Higher NaPi2b Expression; L = Lower NaPi2b Expression; ND = NaPi2b Expression not yet determined or tissue not available

[2]Richardson DL et al. Presented at SGO Annual Meeting 2020;

Clear Trend to Longer Time on Study with Higher NaPi2b Expression



Abbreviations: CR = complete response; PR = partial response; H = Higher NaPi2b Expression; L = Lower NaPi2b Expression; ND = NaPi2b Expression not yet determined or tissue not available

[2]Richardson DL et al. Presented at SGO Annual Meeting 2020;

Updated

Best Response in Evaluable Patients with Ovarian Cancer (n = 75)				
	NaPi2b High (TPS≥75)	NaPi2b Low (TPS<75)	Not Yet Determined NaPi2b	All Patients
N	**38**	**23**	**14**	**75**
CR	2 (5)	0	0	2 (3)
PR	11 (29)	2 (9)	2 (14)	15 (20)
uPR	1 (3)	0	2 (14)	3 (4)
SD	19 (50)	8 (35)	7 (50)	34 (45)
PD	5 (13)	13 (57)	3 (21)	21 (28)
Confirmed ORR	**13 (34)**	**2 (9)**	**2 (14)**	**17 (23)**
DCR	**33 (87)**	**10 (43)**	**11 (79)**	**54 (72)**

Data Cut: June 10, 2021

https://ir.mersana.com/static-files/f50f16b7-c8bf-4268-903c-8f9860ccc3f5

GOG 3048 UPLIFT: Single-Arm US Registration Strategy in Platinum Resistant Ovarian Cancer

UPLIFT Design

Platinum-Resistant High-Grade Serous Ovarian Cancer

- **N=~100 Higher NaPi2b, up to ~180 Overall**
- **1-4 prior lines**
- **Prior bevacizumab not required for patients with 3 – 4 prior lines**
- **No exclusion for baseline peripheral neuropathy**
- **Enrolling regardless of NaPi2b expression**

Primary Endpoint: Confirmed ORR in higher NaPi2b

Key Secondary Endpoint: Confirmed ORR in overall population

Other Secondary Endpoints: Duration of Response; Safety

Dose: 43 mg/**m^2 IV q28d**
Global: US, Europe, Australia, Canada

PI: Deb Richardson, presented at ASCO

GOG 3048 UPLIFT: Single-Arm US Registration Strategy in Platinum Resistant Ovarian Cancer

UPLIFT Design

Platinum-Resistant High-Grade Serous Ovarian Cancer

- **N=~100 Higher NaPi2b, up to ~180 Overall**
- **1-4 prior lines**
- **Prior bev**
- **No exclusion for baseline peripheral neuropathy**
- **Enrolling regardless of NaPi2b expression**

New UPLIFT Dose: 36 mg/m2 up to a maximum of 80 mg

Primary Endpoint: Confirmed ORR in higher NaPi2b

Key Secondary Endpoint: Confirmed ORR in overall

Duration of Response; Safety

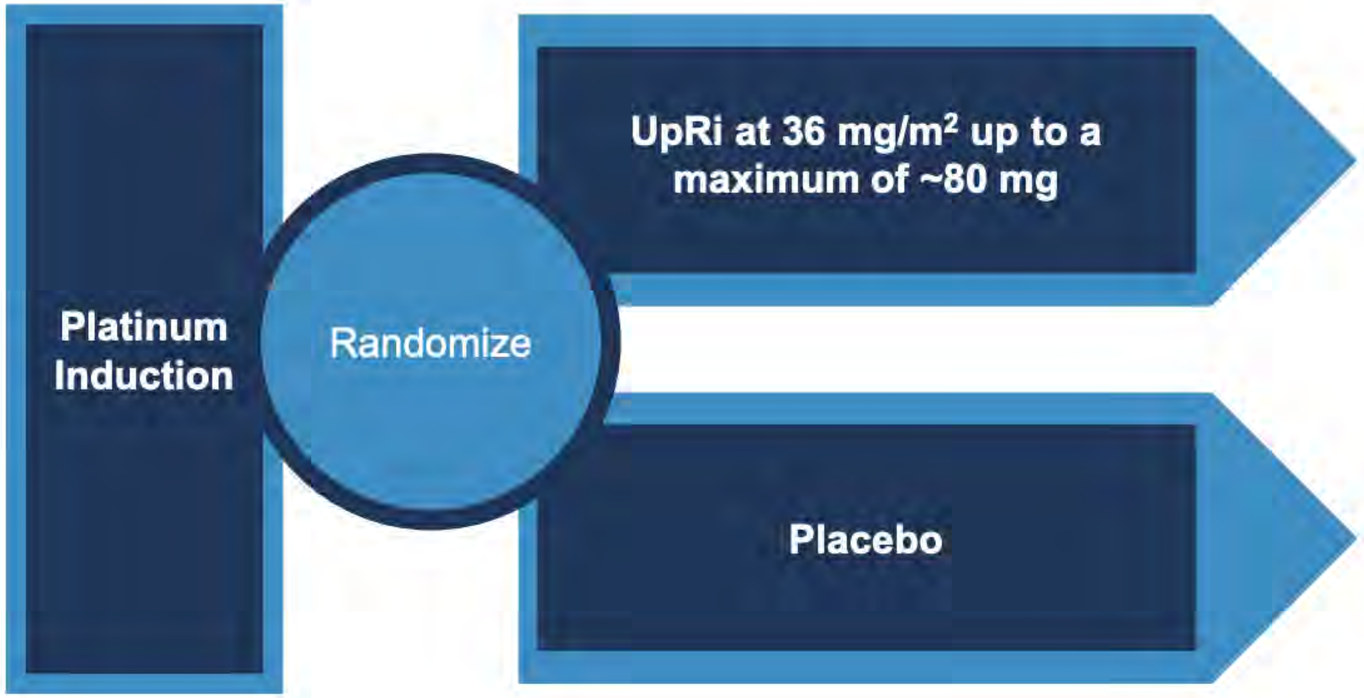
Dose: 43 mg/**m² IV q28d**

Global: US, Europe, Australia, Canada

https://ir.mersana.com/static-files/f50f16b7-c8bf-4268-903c-8f9860ccc3f5

PI: Deb Richardson, presented at ASCO

UP-NEXT GOG-3049



Key Enrollment Criteria:

- Platinum-sensitive recurrence, following platinum induction
- NaPi2b High biomarker selection by TPS≥75
- 1 – 3 prior platinum-based regimes
- Prior PARPi therapy allowed, but only required for BRCAmut
- SD in addition to CR/PR as best response following platinum induction

Primary Endpoint:

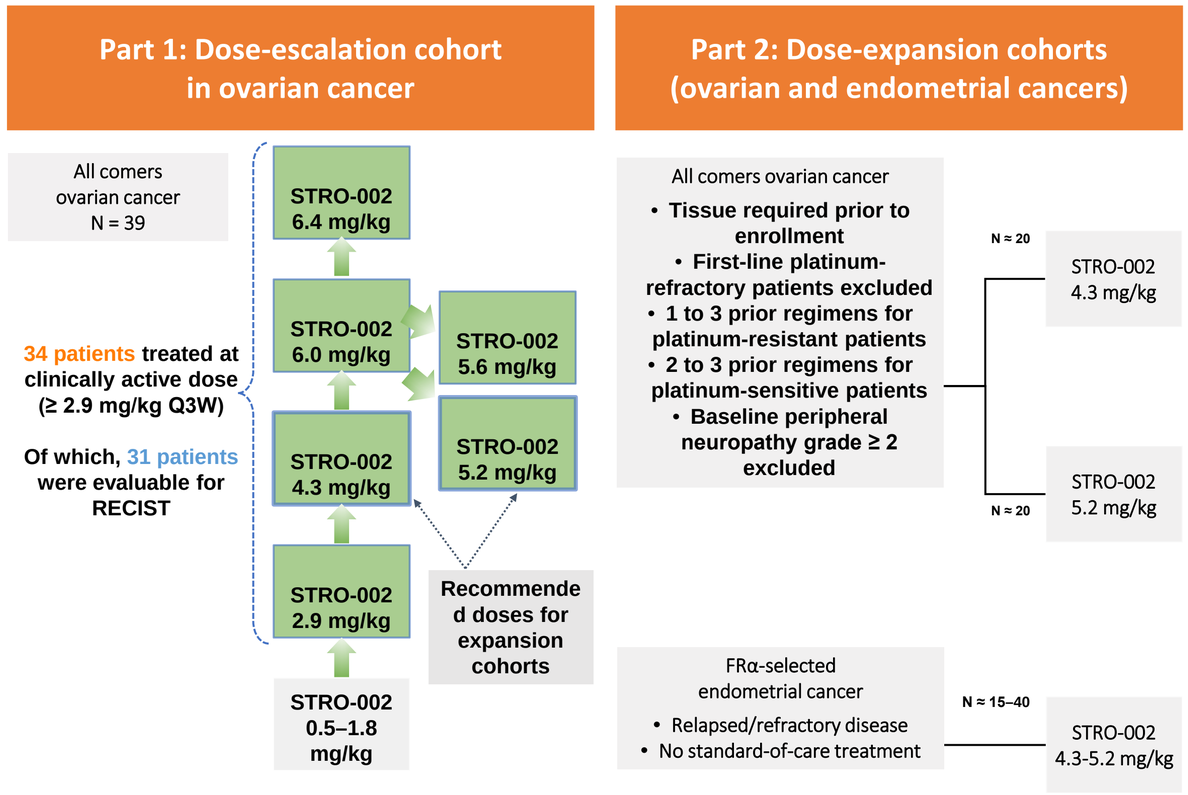
- PFS

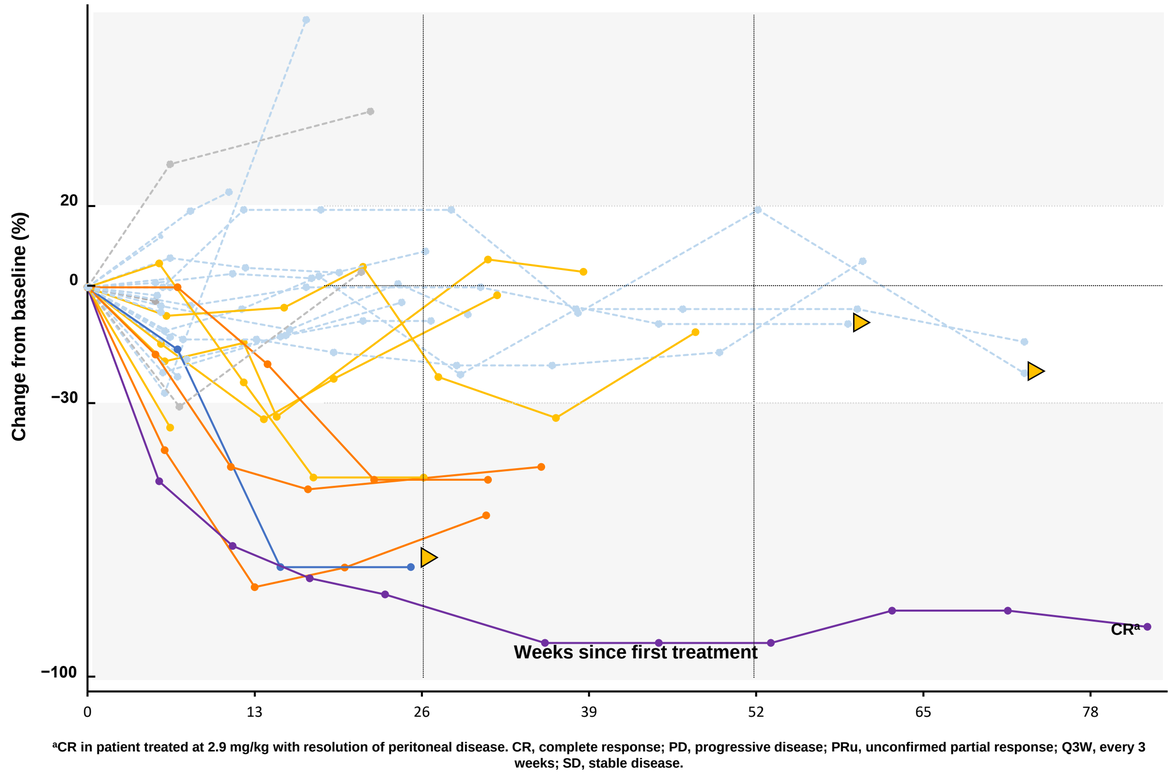
Final Design Pending CHMP Scientific Advice Plans to Initiate in 2022

PI: Deb Richardson, M.D. **https://ir.mersana.com/static-files/f50f16b7-c8bf-4268-903c-8f9860ccc3f5**

Folate Receptor Alpha

Sutro





[a]CR in patient treated at 2.9 mg/kg with resolution of peritoneal disease. CR, complete response; PD, progressive disease; PRu, unconfirmed partial response; Q3W, every 3 weeks; SD, stable disease.

Key endpoints: Safety (DLTs and TEAEs), ORR, PK profile, DOR, PFS[1], OS[1], Biomarkers

FOLR1 PS2+ score:	Weak/absent expression	Moderate expression	High expression
PR	1	1	0
PRu	2	0	1
SD	5	2	3
PD	2	0	0

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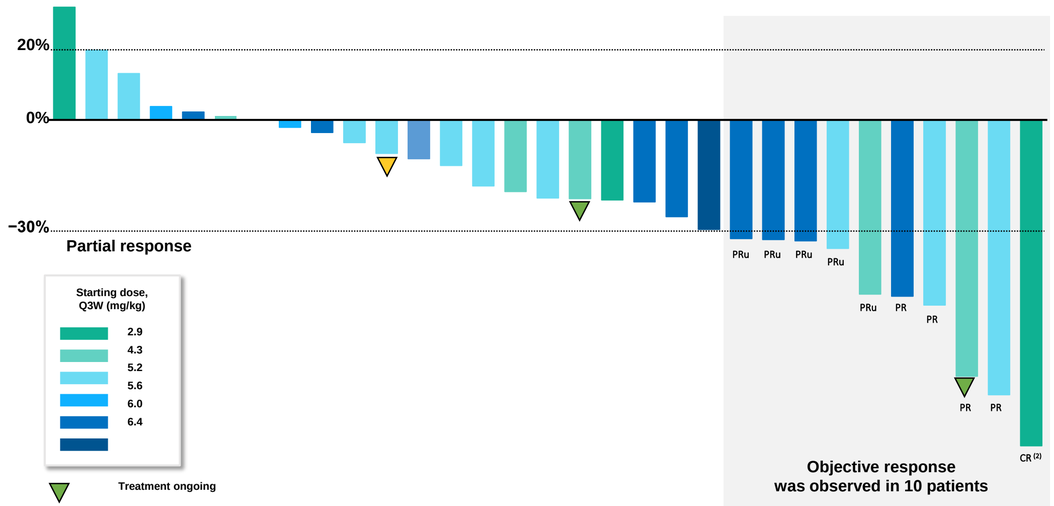
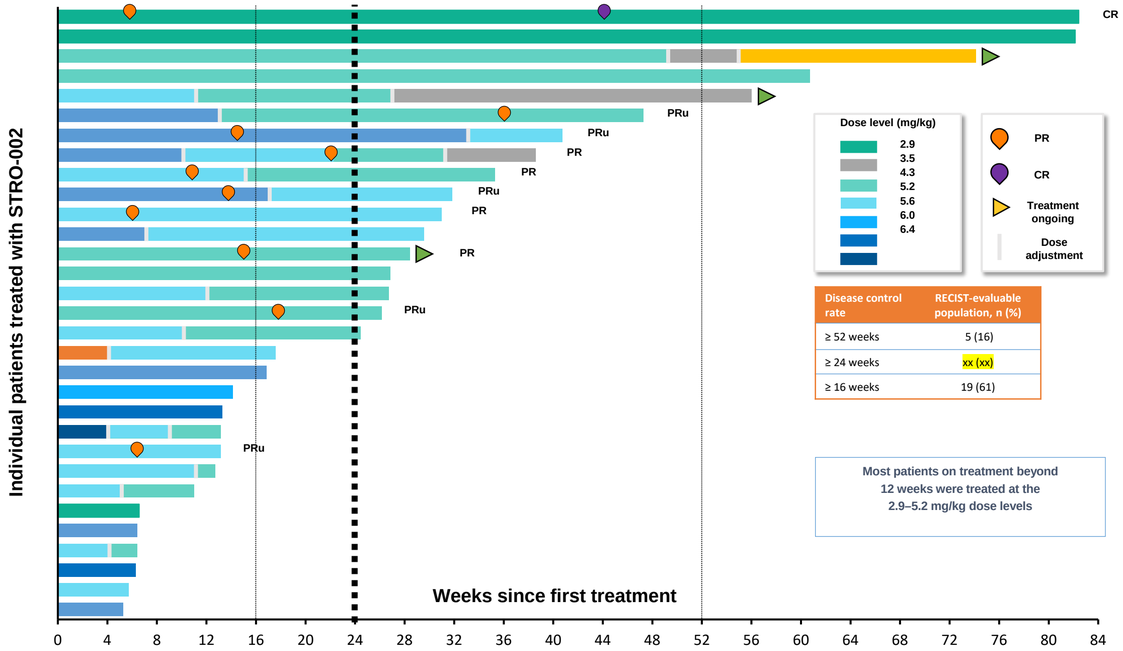
Sutro

Figure 2. Maximum change[a] in tumor target lesions in RECIST-evaluable patients treated with STRO-002 ≥ 2.9 mg/kg Q3W (N = 31)



[a]Maximum percentage change from baseline in sum of longest diameter in evaluable patients treated with STRO-002 at ≥ 2.9 mg/kg Q3W (N = 31); [b]CR in patient treated at 2.9 mg/kg with resolution of peritoneal disease. CR, complete response; PD, progressive disease; PRu, unconfirmed partial response; Q3W, every 3 weeks; SD, stable disease.

Figure 3. Treatment duration[a] and response in RECIST-evaluable patients treated with STRO-002 ≥ 2.9 mg/kg Q3W (N = 31)



[a]Duration calculated as date of PD or time from first dose to last dose given (including 4 patients deriving clinical benefit post progression per investigator assessment). CR, complete response; PD, progressive disease; PRu, unconfirmed partial response; Q3W, every 3 weeks; SD, stable disease.

Objective response per RECIST v1.1	RECIST-evaluable population (N = 31)
Responders	10
CR[b]	1
PR	9
Confirmed	4
Unconfirmed	5
SD	18
PD	3

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ORR by TPS Expression Levels (Total Samples N=33)

TPS	Overall	TPS ≤ 25%	TPS > 25%	TPS > 50%	TPS > 75%
ORR	33.3%	12.5%	40.0%	42.1%	43.8%
Number of patient samples	N=33	N=8	N=25	N=19	N=16
PR[1]	11	1	10	8	7
Potential Market Size (%)	*100%*	*~ 30%*	*~ 70%*		

Patients at the **5.2 mg/kg starting dose** and **TPS > 25%** demonstrated **53.8% ORR (n=13)**

https://www.sutrobio.com/wp-content/uploads/2022/01/Sutro-Corporate-Presentation-Jan-9-2022-FINAL.pdf

ORR by TPS Expression Levels (Total Samples N=33)

TPS	Overall	TPS ≤ 25%	TPS > 25%	TPS > 50%	TPS > 75%
ORR	33.3%	12.5%	40.0%	42.1%	43.8%
Number of patient	N=33	N=8	N=25	N=19	N=16
Size (%)					

August 18, 2021

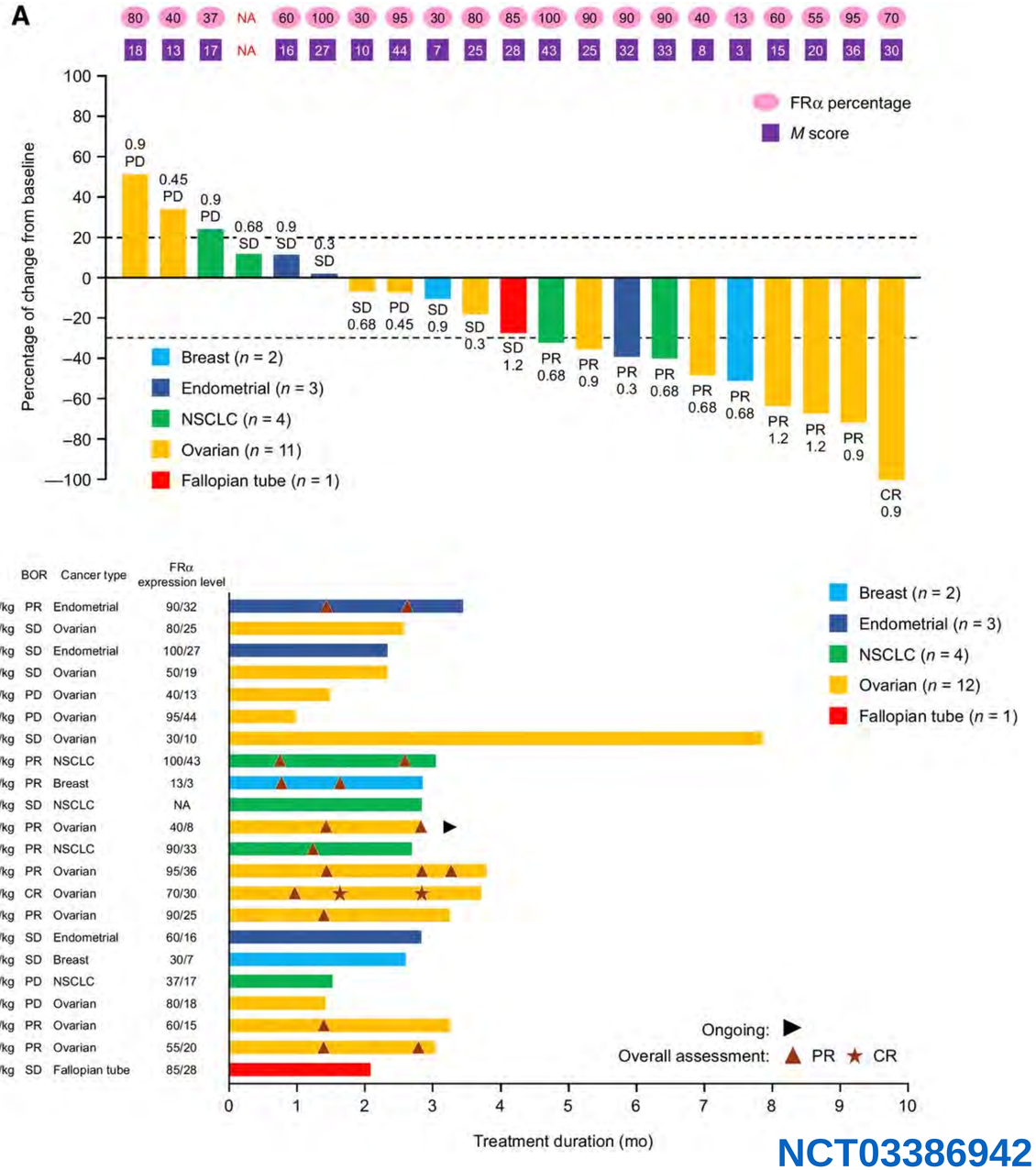
Sutro Biopharma Announces STRO-002 FDA Fast Track Designation for Patients with Advanced Ovarian Cancer

Patients at the **5.2 mg/kg starting dose**
and **TPS > 25%**
demonstrated **53.8% ORR (n=13)**

https://www.sutrobio.com/wp-content/uploads/2022/01/Sutro-Corporate-Presentation-Jan-9-2022-FINAL.pdf

MORAb-202

- MORAb-202 is an antibody–drug conjugate consisting of farletuzumab joined to eribulin by a cathepsin-B cleavable linker
- Farletuzumab is thought to induce immune-dependent cell death, although the exact underlying mechanism is unknown
- Farletuzumab negative phase III*



First-in-Human Phase 1 Study of MORAb-202, an Antibody–Drug Conjugate Comprising Farletuzumab Linked to Eribulin Mesylate, in Patients with Folate Receptor-α–Positive Advanced Solid Tumors
Toshio Shimizu, et al. Clin Cancer Res July 15 2021 (27) (14) 3905-3915

*Vergote Iet al. A randomized, double-blind, placebo-controlled, phase III study to assess efficacy and safety of weekly farletuzumab in combination with carboplatin and taxane in patients with ovarian cancer in first platinum-sensitive relapse. J Clin Oncol 2016;**34**:2271–8

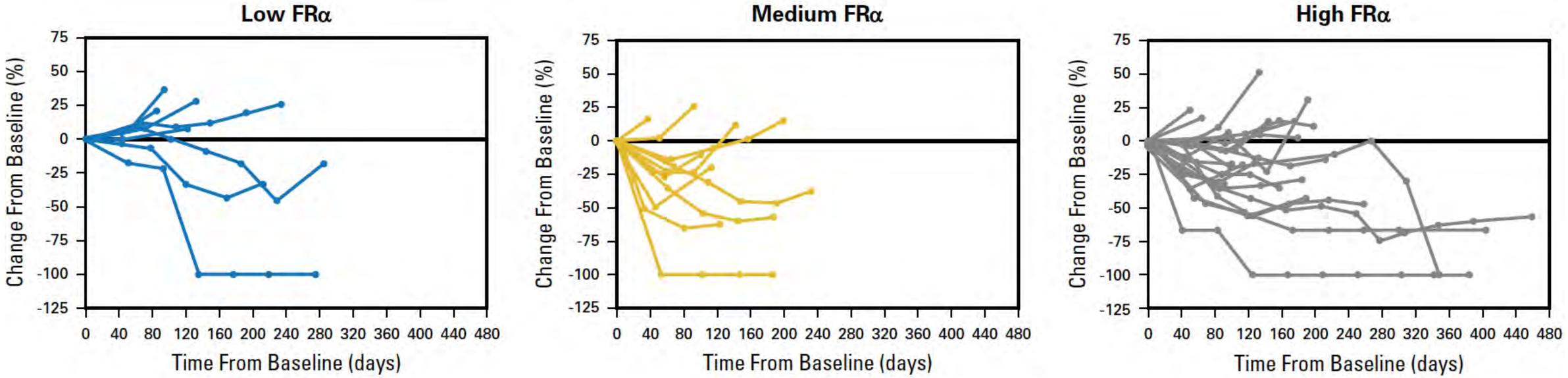
NCT03386942

Mirvetuximab soravtansine (Mirv) – FIH/Expansion

Table 3. Summary of Efficacy Measures Grouped by FRα Expression

FRα Expression	No. of Patients	CR	PR	SD	PD	ND	ORR (%)	95% CI
Low	9	0	2	6	0	1	22.2	2.8 to 60.0
Medium	14	0	4	8	2	0	28.6	8.4 to 58.1
High	23	1	5	14	2	1	26.1	10.2 to 48.4
Total	46	1	11	28	4	2	26.1	14.3 to 41.1

Abbreviations: CR, complete response; FRα, folate receptor alpha; ND, not determined; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.



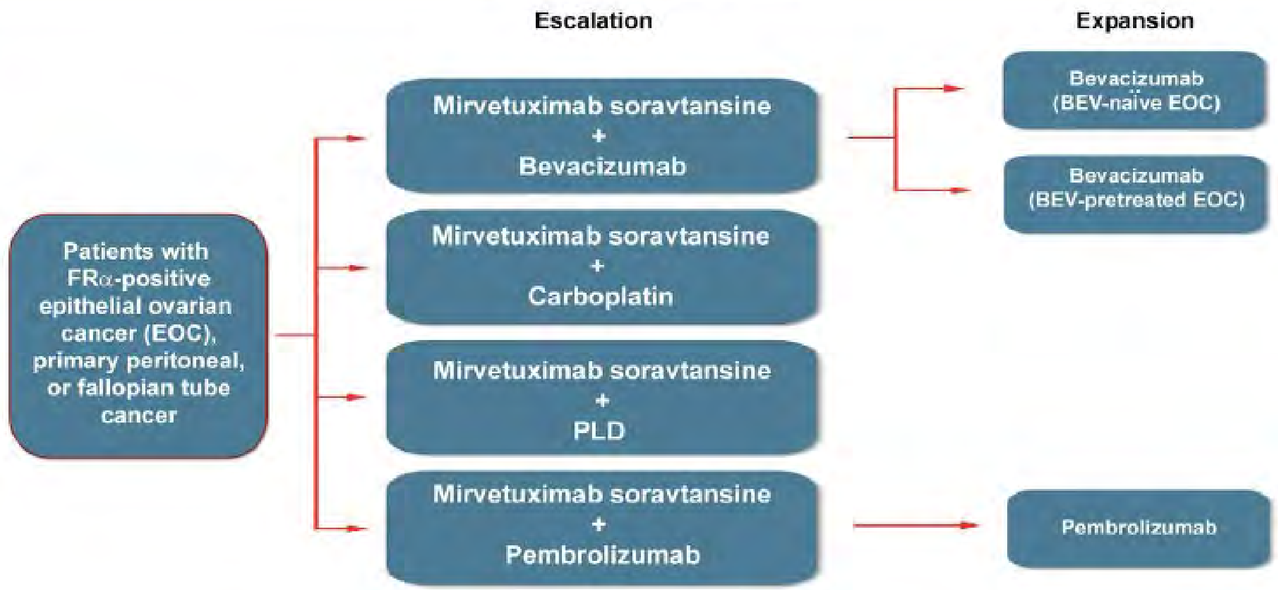
Moore KN, Martin LP, O'Malley DM, Matulonis UA, Konner JA, Perez RP, Bauer TM, Ruiz-Soto R, Birrer MJ. Safety and Activity of Mirvetuximab Soravtansine (IMGN853), a Folate Receptor Alpha-Targeting Antibody-Drug Conjugate, in Platinum-Resistant Ovarian, Fallopian Tube, or Primary Peritoneal Cancer: A Phase I Expansion Study. *J Clin Oncol.* 2017 Apr 1;35(10):1112-1118.

Moore K, Borghaei H, O'Malley D, Jeong W, Seward S, Bauer T, Perez R, Matulonis U, Running K, Zhang X, Ponte J, Ruiz-Soto R, Birrer M. Phase I dose-escalation study of mirvetuximab soravtansine (IMGN853), a folate receptor alpha-targeting antibody-drug conjugate, in patients with solid tumors. *Cancer*, 2017 Aug;123(16):3080-3087. PMID: 28440955

FORWARD-2

ASCO 2017

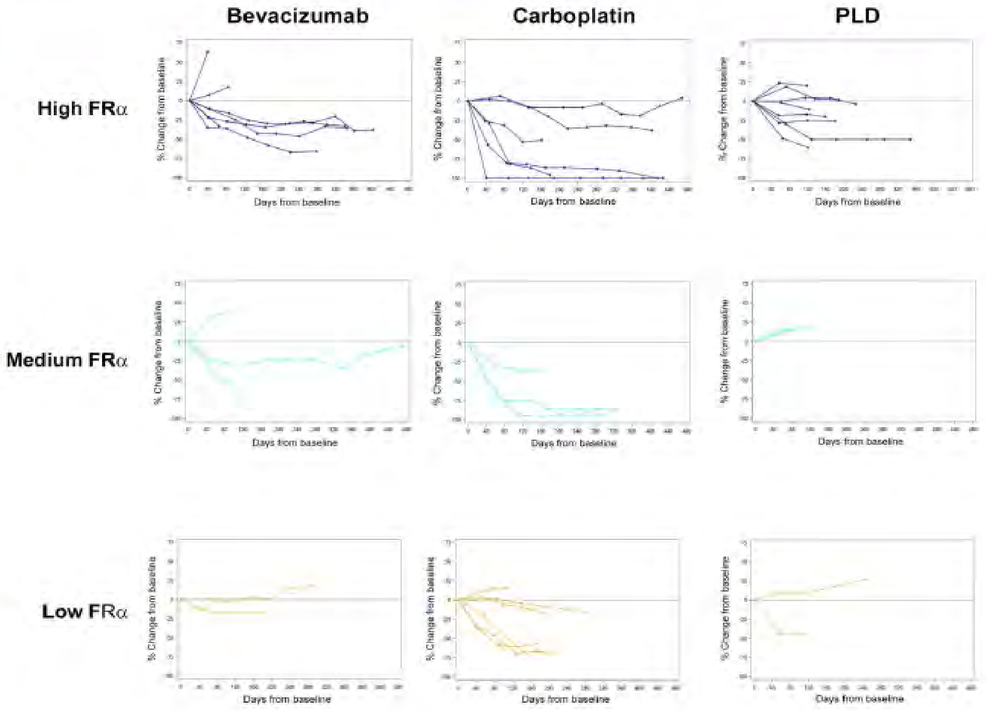
Study Schema



Confirmed ORR and Progression-Free Survival

Endpoint	Bevacizumab	Carboplatin	PLD
ORR (confirmed) 95% CI	29% (8, 58)	65% (38, 86)	13% (2, 38)
PFS (months) Median 95% CI	9.5 (3.5, 15.2)	12.1 (9.0, 15.0)	7.0 (1.7, -)

Percent Tumor Change in Target Lesions by FRα Expression



Safety findings from FORWARD II: a phase 1b study evaluating the folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC) mirvetuximab soravtansine (IMGN853) in combination with bevacizumab, carboplatin, pegylated liposomal doxorubicin (PLD), or pembrolizumab in patients with ovarian cancer

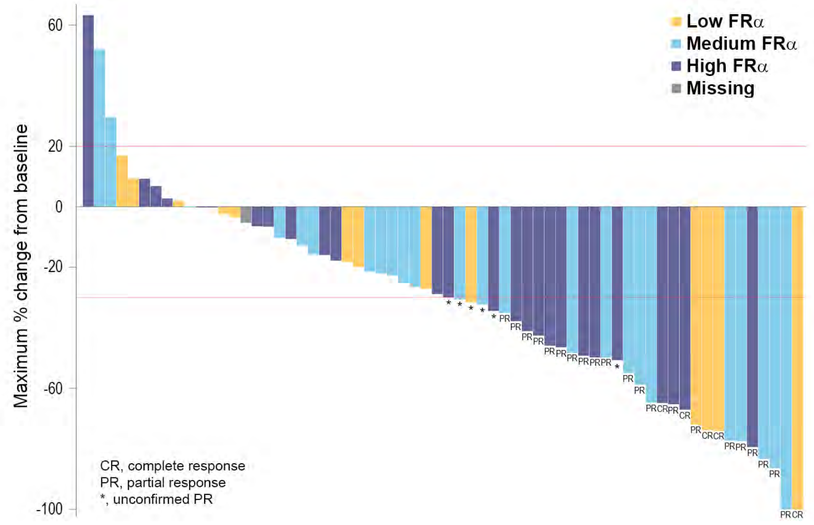
David M. O'Malley[1], Kathleen N. Moore[2], Ignace Vergote[3], Lainie P. Martin[4], Lucy Gilbert[5], Antonio Gonzalez Martin[6], Karim Malek[7], Michael J. Birrer[8], Ursula A. Matulonis[9]

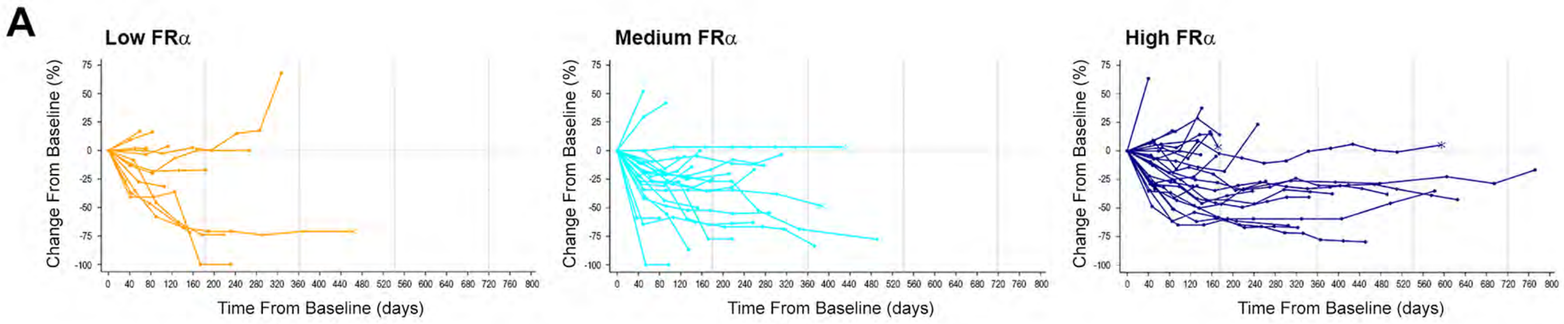
[1]The Ohio State University- James CCC, Columbus, OH; [2]University of Oklahoma Health Sciences Center, Oklahoma City, OK; [3]Leuven Cancer Institute, Leuven, Belgium; [4]Fox Chase Cancer Center, Philadelphia, PA; [5]McGill University Health Center, Montreal, Canada; [6]MD Anderson Cancer Center, Madrid, Spain; [7]ImmunoGen, Inc., Waltham, MA; [8]Massachusetts General Hospital, Boston, MA; [9]Dana Farber Cancer Institute, Boston, MA

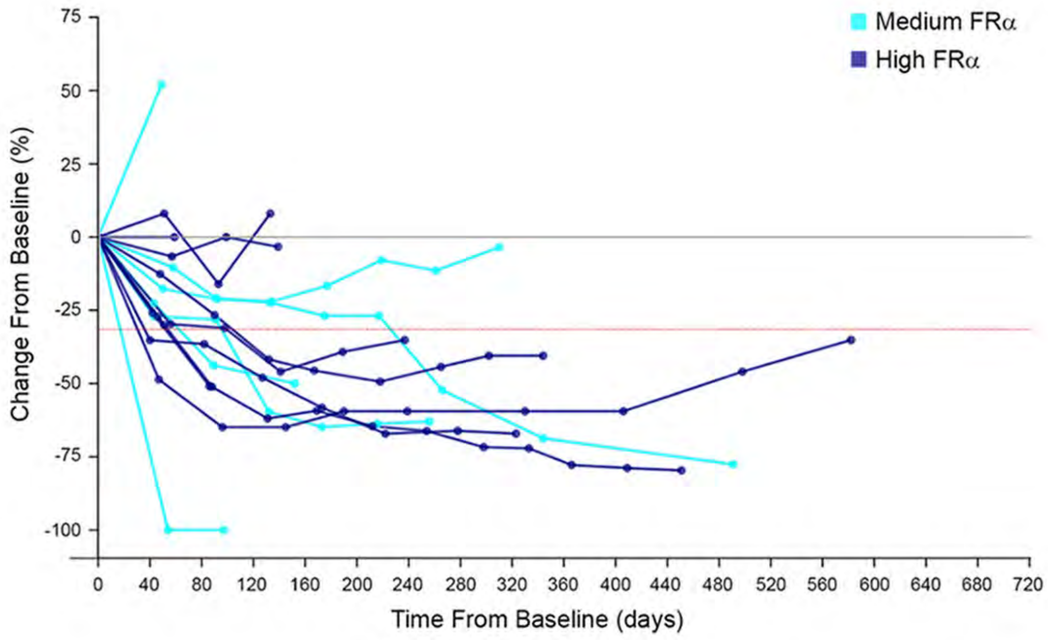
Mirv + Bev

ASCO 2019

Endpoint	Total (n = 66)	FRα Expression* Low (n = 13)	Medium (n = 24)	High (n = 28)	AURELIA-type** (n = 16)
ORR (confirmed) 95% CI	39% (28, 52)	31% (9, 61)	46% (26, 67)	39% (22, 59)	56% (30, 80)
PFS (months) Median 95% CI	6.9 (4.9, 8.6)	6.0 (2.1, 8.8)	6.9 (4.4, 9.9)	7.1 (4.4, 14.5)	9.9 (4.1, 15.9)
DOR (months) Median 95% CI	8.6 (4.9, 14.9)	ND (3.7, -)	7.4 (2.6, -)	12.0 (4.9, -)	12 (6.0, 14.9)







O'Malley DM, Matulonis UA, Birrer MJ, Castro CM, Gilbert L, Vergote I, Martin LP, Mantia-Smaldone GM, Gonzalez Martin A, Bratos R, Penson RT, Malek K, Moore KN. Phase IB Study of Mirvetuximab Soravtansine, a Folate Receptor Alpha-Targeting Antibody-Drug Conjugate, in Combination with Bevacizumab in Platinum-Resistant Ovarian Cancer. *Gyn Onc*, 2020 May;157(2):379-385. PMID 32081463

Mirv + Carbo + Bev

ESMO 2020

Dosing Schema and Summary of Drug Exposure

A

Carboplatin (AUC 5) Q3W - may be discontinued after 6 cycles at discretion of investigator

Mirvetuximab (6 mg/kg AIBW) Q3W to progression

Bevacizumab (15 mg/kg) Q3W to progression

B

No of Cycles Received	Carboplatin	Mirvetuximab soravtansine	Bevacizumab
Median (range)	6 (3-11)	12 (4-30)	13 (1-38)

Characteristic	All Patients (n = 41)
No. of prior systemic therapies, *n (%)*	
1	31 (76)
2	10 (24)
Platinum-free treatment interval, *n (%)*	
≤ 12 months	24 (59)
> 12 months	17 (41)
FRα expression* *n (%)*	
High	20 (49)
Medium	21 (51)

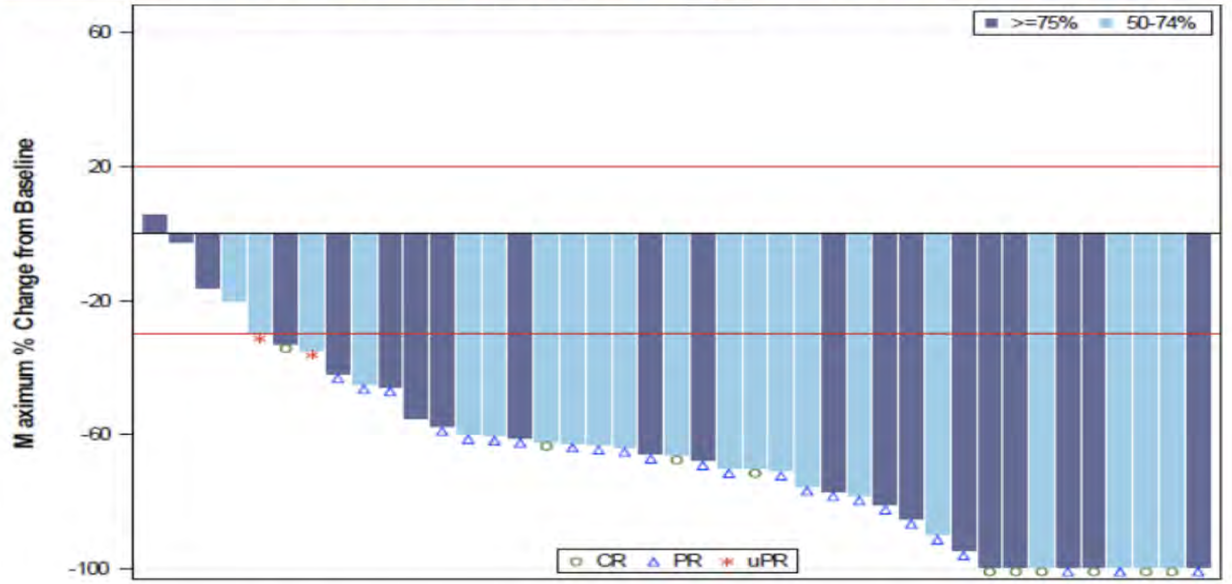
Confirmed ORR and Time-to-Event Endpoints

Endpoint	Total (n=41)	FRα Expression Medium (n=21)	FRα Expression High (n=20)
ORR (confirmed; 95% CI)	83% (68, 93)	86% (64, 97)	80% (56, 94)
DOR mo. (median; 95% CI)	10.9 (7.7, 13.6)	13.3 (6.7, 15.2)	9.9 (7.5, 12.3)
PFS mo. (median; 95% CI)	12.8 (9.1, 14.6)	12.9 (8.1, 16.2)	12.4 (9.0, 14.6)

DOR, duration of response; ND, not determined

- Pts (n=30) with 1 prior had an ORR of 90%, DOR of 9.7 mo. (7.6, 12.3) and PFS of 11.9 (9.0, 14.8)

Maximum Tumor Change (%) in Target Lesions from Baseline



CRs with <100% decrease: Lymph node target lesions that met CR definition per RECIST 1.1 (i.e. all pathological lymph nodes have reduction in short axis to <10 mm)
†Despite target lesion PR, overall response of patient at cycle 4 was PD due to appearance of new lesions

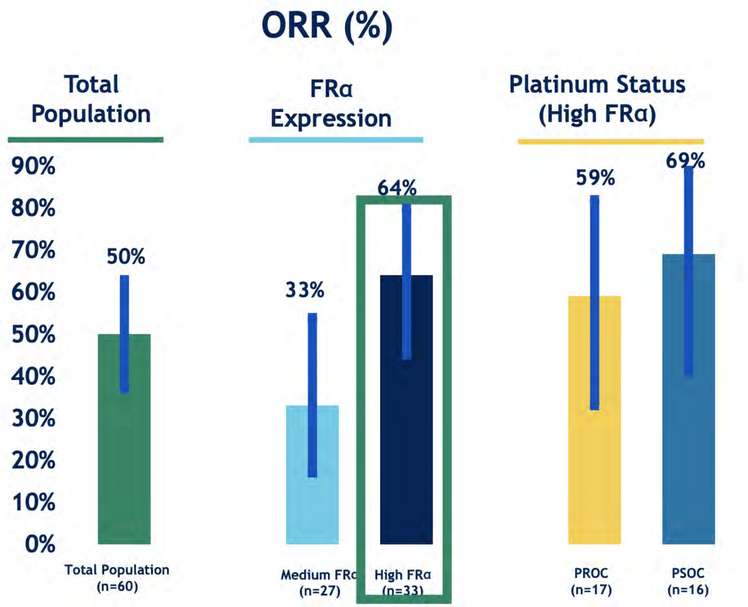
- Confirmed tumor responses were observed in 34 patients, consisting of 10 complete responses (CR) and 24 partial responses (PR); two additional patients had unconfirmed PRs as best response

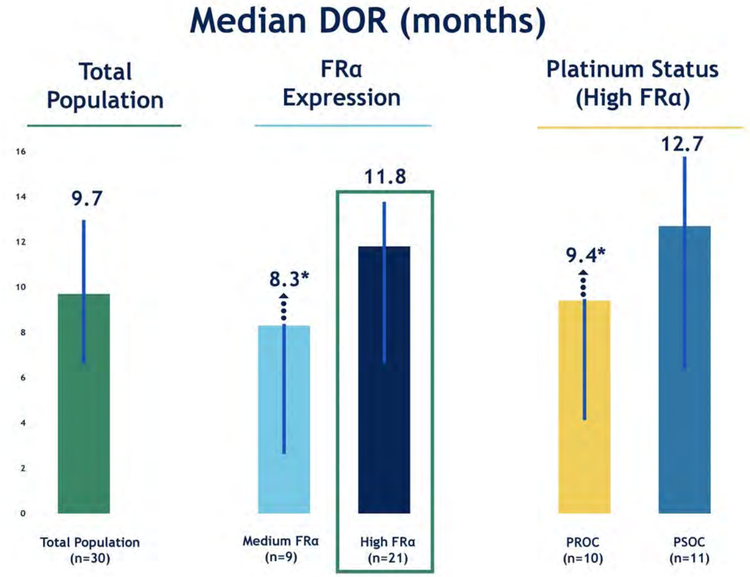
Mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in combination with carboplatin and bevacizumab: final results from a Phase 1b study in patients (pts) with ovarian cancer

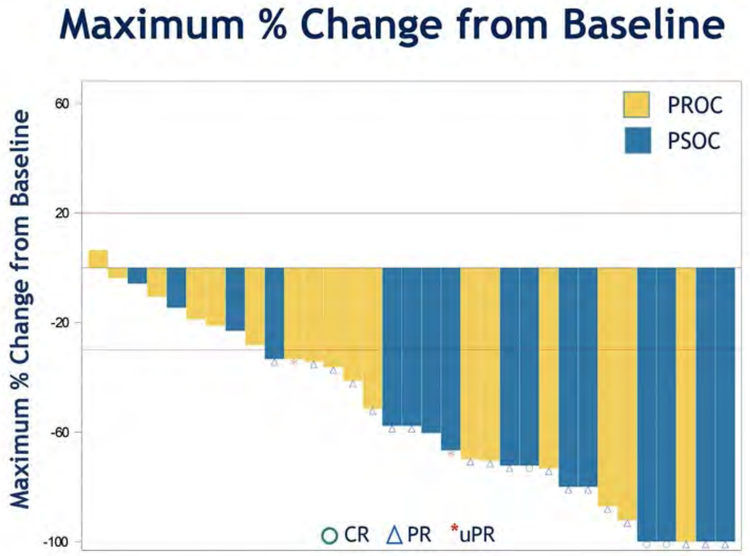
David M. O'Malley[1], Debra L. Richardson[2], Ignace Vergote[3], Lucy Gilbert[4], Lainie P. Martin[5], Gina M. Mantia-Smaldone[6], Cesar M. Castro[7], Diane Provencher[8], Ursula A. Matulonis[9], Patrick Zweidler-McKay[10], Kathleen N. Moore[2]

Mirv + Bev – Platinum Agnostic

ASCO 2021







- **50% ORR (30/60) for overall cohort**
- **64% ORR (21/33) in high FRα tumors**
  - ➢ **59% ORR (10/17) in PROC subset**
  - ➢ **69% ORR (11/16) in PSOC subset**

- **9.7 mo mDOR for overall cohort**
- **11.8 mo mDOR in high FRα tumors**
  - ➢ **9.4 mo mDOR in PROC subset**
  - ➢ **12.7 mo mDOR in PSOC subset**

- **97% (32/33)** of patients demonstrated tumor burden reduction

O'Malley DM, et al ASCO 2021

STUDY DESIGN

FORWARD I

- Platinum-resistant ovarian cancer
- FRα-positive tumor expression
  - Medium (50-74% cells positive)
  - High (≥75% cells positive)
- ECOG performance status 0 or 1
- 1-3 prior therapies

Statistical Assumptions

- Hochberg procedure
- α=0.05 (two-sided), power = 90%
  HR=0.58; control arm mPFS 3.5 mos

Mirvetuximab Soravtansine (n=248)

6 mg/kg (adjusted ideal body weight) once every 3 weeks

2:1 Randomization

Stratification Factors:
FRα expression (medium or high)
Prior therapies (1 and 2, or 3)
Choice of chemotherapy

Investigator's Choice Chemotherapy
Paclitaxel, PLD†, or Topotecan (n=118)

***Paclitaxel**: 80 mg/m² weekly*
***PLD**: 40 mg/m² once every 4 weeks*
***Topotecan**: 4 mg/m² on Days 1, 8, and 15 every 4 weeks; or 1.25 mg/m² on Days 1-5 every 3 weeks*

Primary Endpoint

Progression-free survival (PFS; by BIRC*) for ITT and high FRα populations

*BIRC = Blinded Independent Review Committee; analyzed by Hochberg procedure

Secondary Endpoints

Overall response rate (ORR)
Overall survival (OS)
Patient reported outcomes (PRO)

BARCELONA 2019 ESMO congress

†Pegylated liposomal doxorubicin
ClinicalTrials.gov Identifier: NCT02631876

Moore, K, ESMO 2019

Efficacy Results at a Glance

Intent to treat (ITT) population

Endpoint	Treatment effect size	p-value
PFS by BIRC*	HR: 0.981 mPFS: 4.1 vs 4.4	0.897
ORR by BIRC	22% vs 12%	0.015
DOR (mos)	HR = 0.982 5.7 vs 7.3	0.974
OS	HR: 0.815 mOS: 16.4 vs 14.0	0.248
PFS by INV	HR: 0.809 mPFS: 4.3 vs 4.2	0.116
ORR by INV	29% vs 16%	0.008
CA125 ORR	51% vs 27%	0.0002

FRα high subgroup

Endpoint	Treatment effect size	p-value**
PFS by BIRC	HR: 0.693 mPFS: 4.8 vs 3.3	0.049
ORR by BIRC	24% vs 10%	0.014
DOR (mos)	HR= 0.598 5.7 vs 4.2	0.374
OS	HR: 0.618 mOS: NR* vs 11.8	0.033
PFS by INV	HR: 0.667 mPFS: 5.0 vs 4.2	0.018
ORR by INV	29% vs 13%	0.007

**Nominal P value

*BIRC = Blinded Independent Review Committee NS based on Hochberg Procedure

Efficacy Results ORR and DOR

Intent to treat (ITT) population

Endpoint	Treatment effect size	p-value**
ORR by BIRC*	22% vs 12%	0.015
DOR (mos)	HR = 0.982 5.7 vs 7.3	0.974
ORR by INV	29% vs 16%	0.008

FRα high subgroup

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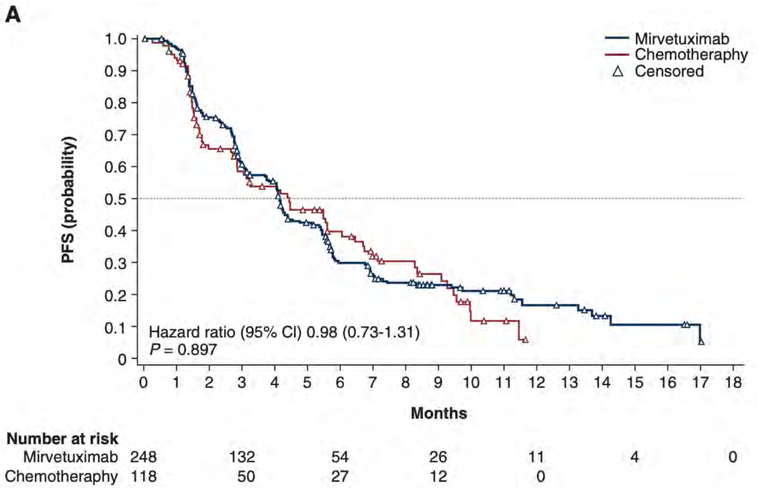
Moore, K, ESMO 2019

*BIRC = Blinded Independent Review Committee

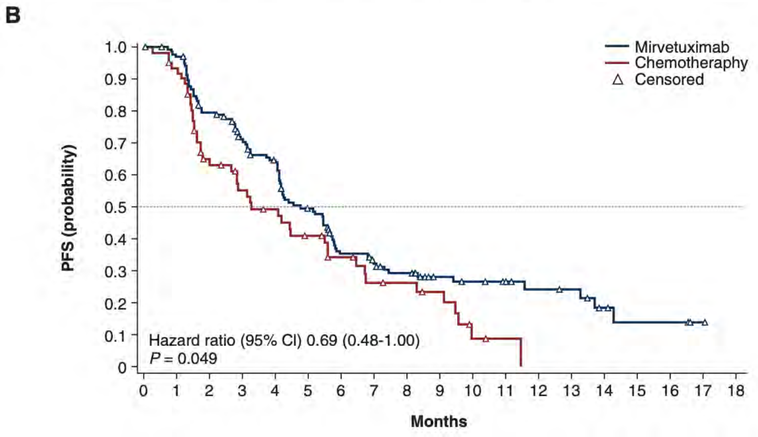
**NS per Hochberg procedure

Moore KM et al; Annals of Oncology; 32 (6) 2021

- FORWARD-1
  - Negative for primary objectives
    - ITT
    - HIGH FORa
  - FORa predictive marker for Mirv
  - FORa prognostic markers



ITT

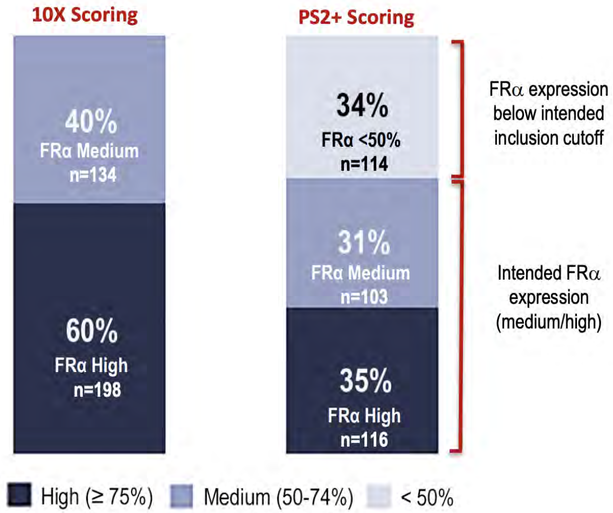


HIGH FORa

FORWARD I 10X SCORING COMPARED WITH EXPLORATORY PS2+ SCORING

Rescoring of the FORWARD I samples using PS2+ indicates:

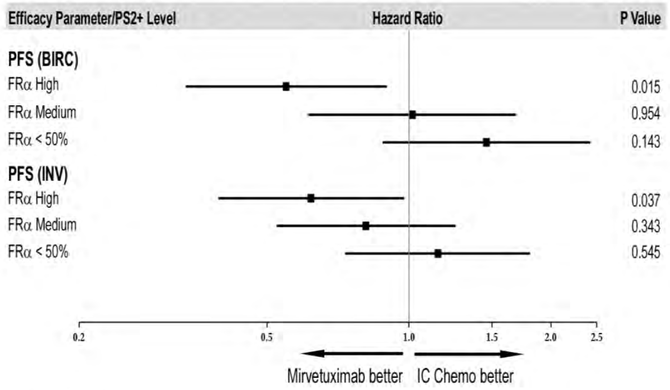
- 34% of patients enrolled in FORWARD I had low FRα levels that should have precluded enrollment; and
- the protocol-defined FRα high subset contained patients with a mixture of FRα expression levels



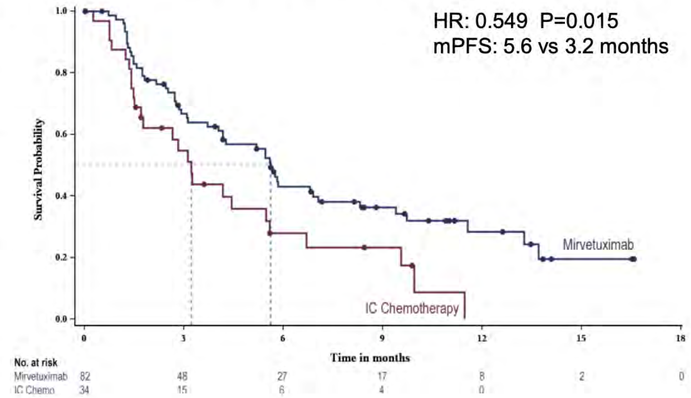
FORWARD-1

PS2+ RE-SCORING: PFS TRENDS ACROSS SUBGROUPS

PFS Hazard Ratio Plot



PFS (by BIRC) - FRα High (n=116)



P values from unstratified log-rank test

PS2+ RE-SCORING: TRENDS ACROSS SUBGROUPS

Endpoint	FRα < 50% (n=114) (Mirv vs IC Chemo)	FRα Medium (n=103) (Mirv vs IC Chemo)	FRα High (n=116) (Mirv vs IC Chemo)
PFS by BIRC (mo.)	HR: 1.458 (0.878, 2.420) mPFS: 3.8 vs 5.5	HR: 1.015 (0.611, 1.687) mPFS: 4.3 vs 5.6	HR: 0.549 (0.336, 0.897) mPFS: 5.6 vs 3.2
ORR by BIRC 95% CIs	16% vs 16% (8%, 26%) vs (6%, 31%)	28% vs 18% (18%, 40%) vs (7%, 35%)	29% vs 6% (20%, 40%) vs (1%, 20%)
OS (*August 2019*) (mo.)	HR: 0.923 (0.548, 1.554) mOS: 14.0 vs 13.4	HR: 0.936 (0.542, 1.616) mOS: 15.9 vs 20.7	HR: 0.678 (0.410, 1.119) mOS: 16.4 vs 11.4
PFS by INV (mo.)	HR: 1.149 (0.732, 1.803) mPFS: 4.0 vs 4.5	HR: 0.810 (0.523, 1.254) mPFS: 5.1 vs 2.8	HR: 0.619 (0.394, 0.975) mPFS: 5.6 vs 3.7
ORR by INV 95% CIs	18% vs 21% (11%, 29%) vs (10%, 37%)	36% vs 24% (25%, 49%) vs (11%, 41%)	38% vs 9% (27%, 49%) vs (2%, 24%)

Moore, K, ESMO 2019

SORAYA

SINGLE-ARM PIVOTAL TRIAL OF MIRVETUXIMAB IN FRα-HIGH PATIENTS WITH PLATINUM-RESISTANT OVARIAN CANCER

INCLUSION CRITERIA

106 PATIENTS

- Platinum-resistant disease (PFI < 6 months)
- FRα-high only
- Prior bevacizumab required
- Prior PARPi allowed
- 1 to 3 prior lines allowed
- Patients with BRCA mutations allowed

PRIOR TREATMENT

51% 3 prior lines of therapy

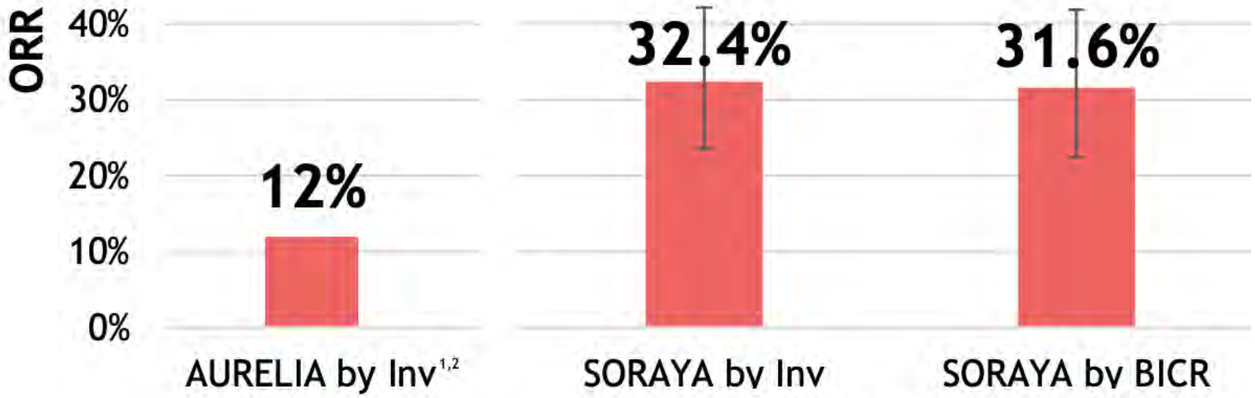
100% Received prior bevacizumab

48% Received prior PARPi

SAFETY AND TOLERABILITY

- Favorable tolerability data with >700 patients treated to date
- In SORAYA, the most common AEs were low-grade gastrointestinal and ocular events, including blurred vision, keratopathy, and nausea; 7% of patients discontinued due to treatment-related AEs, including one patient due to ocular AE

MET PRIMARY ENDPOINT



Responses were irrespective of number of prior lines or prior PARPi use

KEY SECONDARY ENDPOINT

5.9 months mDOR

By Investigator at Data Cutoff *(95% CI: 5.6, 7.7)*

Nearly half of responders still receiving mirvetuximab at data cutoff; with longer follow-up, ***mDOR could range from 5.7 to above 7 months***

1ORR for single-agent chemotherapy published in the AURELIA Study, JCO 2014, Pujade-Lauraine, E., et al.
2Disclaimer: These comparisons are not based on head-to-head clinical studies. The results from these two studies are not directly comparable.

https://investor.immunogen.com/news-releases/news-release-details/immunogen-announces-positive-top-line-results-pivotal-soraya

GOG 3045

MIRASOL

PHASE 3 RANDOMIZED TRIAL FOR MIRVETUXIMAB IN FRα-HIGH PATIENTS WITH PLATINUM-RESISTANT OVARIAN CANCER

TARGET TIMELINES

- ENROLLING GLOBALLY
- TOP-LINE DATA Q3 2022
- EXPECTED APPROVAL 2023

1:1 RANDOMIZATION

Mirvetuximab

STRATIFICATION FACTORS
IC Chemotherapy (Paclitaxel, PLD, Topotecan)
Prior Therapies (1 vs 2 vs 3)

Investigator's Choice Chemotherapy
Paclitaxel, PLD, or Topotecan

PRIMARY ENDPOINT
PFS by Investigator
BICR for Sensitivity Analysis

SECONDARY ENDPOINTS
ORR by Investigator, OS, and PRO

ENROLLMENT AND KEY ELIGIBILITY
430 patients/330 events for PFS by Investigator
Platinum-resistant disease (primary PFI >3 months)
1 to 3 prior lines of therapy
Prior bevacizumab* and prior PARPi allowed
Patients with BRCA mutations allowed

PICCOLO

SINGLE-ARM TRIAL FOR MIRVETUXIMAB IN FRα-HIGH PATIENTS WITH PLATINUM-SENSITIVE OVARIAN CANCER

NOW ENROLLING

PRIMARY ENDPOINT
ORR by Investigator

SECONDARY ENDPOINT
DOR by Investigator

ENROLLMENT AND KEY ELIGIBILITY
~75 patients
Platinum-sensitive ovarian cancer
2 or more prior systemic treatments
At least 2 prior platinum-containing regimens
Prior PARPi required if BRCA+
Appropriate for single-agent therapy

GLORIOSA

RANDOMIZED PHASE 3 TRIAL FOR MIRVETUXIMAB + BEVACIZUMAB MAINTENANCE IN FRα-HIGH PLATINUM-SENSITIVE OVARIAN CANCER

INITIATING IN Q2 2022

PRIMARY ENDPOINT
PFS

SECONDARY ENDPOINTS
OS, DOR

ENROLLMENT AND KEY ELIGIBILITY
438 patients
Platinum-sensitive ovarian cancer
1 prior platinum treatment
Prior PARPi required if BRCA+
CR, PR, or SD after treatment with platinum-based doublet + bevacizumab required

420 STUDY

SINGLE-ARM PHASE 2 TRIAL OF MIRVETUXIMAB + CARBOPLATIN FOLLOWED BY MIRVETUXIMAB CONTINUATION IN FRα-LOW, MEDIUM, AND HIGH PATIENTS WITH PLATINUM-SENSITIVE OVARIAN CANCER

INITIATING IN Q2 2022

PRIMARY ENDPOINT
ORR by Investigator

SECONDARY ENDPOINTS
DOR, PFS

ENROLLMENT AND KEY ELIGIBILITY
~110 patients
Platinum-sensitive ovarian cancer
1 prior platinum treatment
Prior PARPi required if BRCA+

https://www.immunogen.com/what-we-do/our-pipeline/

Conclusions

- ADCs are going to likely impact our treatment paradigm in ovarian cancer
  - Likely approval in PROC
  - Earlier Lines of Therapy?
- Diagnostic Testing
  - NaPi2b
  - FORa
  - Others
- Impact of approval on other agents and development?

Questions?