An Industry Supported Symposium at the IGCS 2025 Annual Global Meeting

From Data to Decisions: Evolving Opportunities in Platinum Resistant Ovarian Cancer

This session is not included in the main event CME/CPD credit.

Cape Town, South Africa

Friday, November 7, 2025

12:40-14:10 (GMT +2)

This educational activity is supported by an independent medical education grant from Corcept Therapeutics, Inc.

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Welcome and Introductions

Debra Richardson, MD

University of Oklahoma, Stephenson Cancer Center,
Oklahoma City, Oklahoma, USA

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MODERATOR

Debra Richardson, MD

University of Oklahoma
Stephenson Cancer Center
Oklahoma City, Oklahoma, USA

FACULTY

Nicoletta Colombo, MD, PhD

European Institute of Oncology
University of Milan-Bicocca
Milan, Italy

David O'Malley, MD

The Ohio State University
Comprehensive Cancer Center
Columbus, Ohio, USA

Domenica Lorusso, MD, PhD

Humanitas University,
Pieve Emanuele,
Humanitas San Pio X Hospital
Milan, Italy

Faculty Disclosures

Name	Role in Activity	Disclosures
Debra Richardson, MD	Moderator	**Consultant:** Mersana **Advisor:** Araris; AstraZeneca; Genmab;Incyclix GlaxoSmithKline; Immunogen; Daiichi Sankyo, Repare Tx **Speaker:** GlaxoSmithKline, Zentalis **Research Grant:** GlaxoSmithKline
Nicoletta Colombo, MD	Speaker	**Financial Interests:** Invited Speaker/Lectures: AstraZeneca, Eisai, GSK, MSD/Merck Advisory Boards: Roche; AstraZeneca; MSD; GlaxoSmithKline; Immunogen; Eisai; Oncxerna, Nuvation Bio, Gilead, Regeneron, Novocure, Seagen, Abbvie, Lilly, BeOne Research Grants: AstraZeneca, GSK, Roche **Non-financial Interests:** Leadership Role, Chair, Scientific Committee: ACTO (Alleanza contro il tumore ovarico) **Member:** Nomination Committee ESMO
David O'Malley, MD	Speaker	**Personal Fees for Advisory Boards/Consultant Eligible Companies (24 months):** AbbVie; AstraZeneca; Corcept Therapeutics; Duality Bio; Eli Lilly; GlaxoSmithKline; GOG Foundation; Merck & Co; Merck Sharp & Dohme Corp.; Regeneron Pharmaceuticals; Verastem, Inc; Zentalis **Institution Receives Funds for clinical research.**
Domenica Lorusso, MD	Speaker	**Consulting/Advisory Board:** AstraZeneca, Clovis Oncology, GSK, MSD, Immunogen, Genmab, Seagen, Oncoinvest, Corcept, Sutro, Daiichi Sankyo, Novocure **Speakers bureau:** AstraZeneca, Clovis Oncology, GSK, MSD, Genmab, Immunogen, Seagen **Honoraria/Expenses:** Astra Zeneca, Corcept, Clovis Oncology, Daiichi Snakyo, Genmab, Gsk, Immunogen, MSD, Novartis, Oncoinvest, Novocure, Seagen, Sutro, Pharma&, Roche, Incyte. **Founded Research:** Astra Zeneca, Clovis Oncology, Pharma&, Genmab, PharmaMar, GSK, Immunogen, Incyte, MSD, Novartis Roche, Seagen, Alkermes, Corcept

Learning Objectives

Upon completion of the activities in this series, learners will demonstrate increased knowledge regarding:

- Evaluate Breakthrough Data: Review and contextualize pivotal 2025 congress data on novel therapies in platinum-resistant ovarian cancer.
- Interpret Clinical Impact of New Trials: Analyze updated PFS/OS findings, trial design nuances, and their practical implications for personalized treatment planning.
- Map the Evolving Therapeutic Landscape: Position emerging treatments within the current ovarian cancer algorithm, identifying opportunities for sequencing or combination.
- Enhance Multidisciplinary Application: Foster real-world clinical dialogue among oncology professionals to translate data into meaningful care strategies.

Agenda

Welcome and Framing the Discussion
All Faculty

What's New in Platinum-Resistant Ovarian Cancer: Highlights from ASCO, ESMO GYN, and ESMO 2025,
Nicoletta Colombo, MD, PhD – European Institute of Oncology and University of Milan-Bicocca, Milan, Italy

Innovative Mechanisms and Combinations: Beyond ADCs in 2025
Domenica Lorusso, MD, PhD – Humanitas University, Pieve Emanuele, Humanitas San Pio X Hospital, Milan, Italy

Making Sense of the Curves: How to Interpret New PFS/OS Data
The Ohio State University Comprehensive Cancer Center – James Cancer Hospital, Columbus, OH

Faculty Panel: Treatment Integration and What's Next
All Faculty

Audience Q&A

Closing Remarks
Debra Richardson, MD, University of Oklahoma, Stephenson Cancer Center, Oklahoma City, Oklahoma, USA

What's New in Platinum-Resistant Ovarian Cancer: Highlights from ASCO, ESMO GYN, and ESMO 2025

Nicoletta Colombo, MD, PhD

European Institute of Oncology and
University of Milan-Bicocca
Milan, Italy

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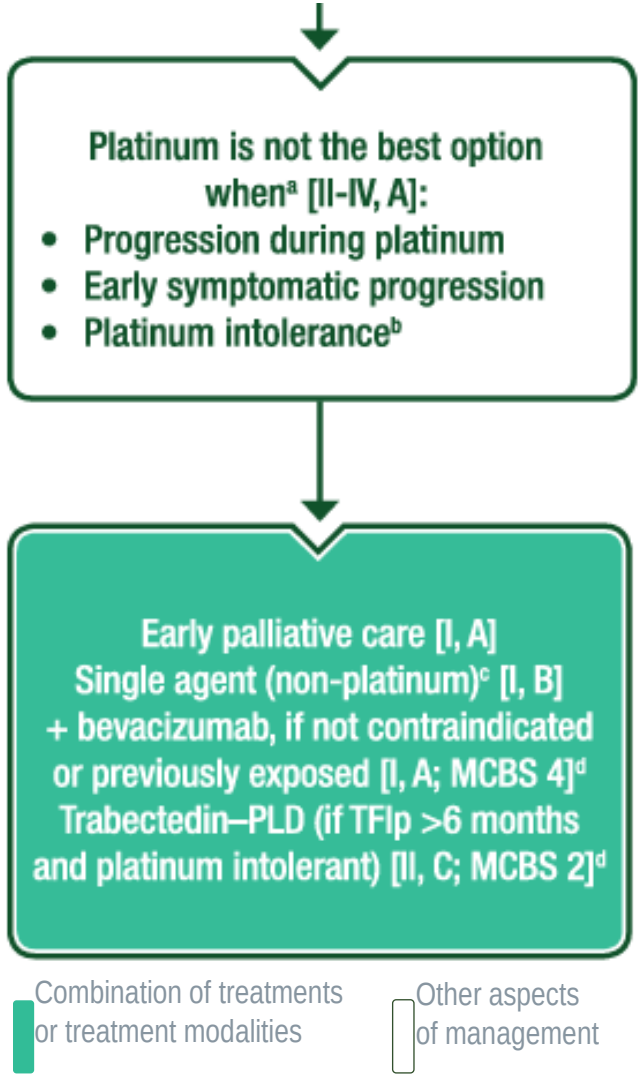
Management of recurrent disease

Systemic therapy when platinum is **NOT** an option

- **Patients with good performance status should be prioritised for novel therapies within clinical trials**
- **For patients not candidates to receive platinum, integrating palliative care early in the treatment pathway is strongly recommended [I, A]**
- **Single-agent non-platinum options that can be recommended include weekly paclitaxel, PLD, topotecan and gemcitabine [I, B]**



PLD, pegylated liposomal doxorubicin; TFIp, treatment-free interval from last platinum.
González-Martín A, et al. Ann Oncol 2023;34:833-48.

What’s next ?

Platinum Ineligible Ovarian Cancer

ANTIBODY DRUG CONJUGATED (ADCS)

Mirvetuximab-soravtansine [1]

Trastuzumab-deruxtecan [2]

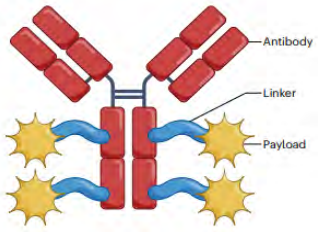
Raludotatug- Deruxtecan [3]

Rinatabart Sesutecan (Rina-S)[4]

AZD5335 [5]

Ly4170156 [6]

NAPISTAR 1-01 [7]

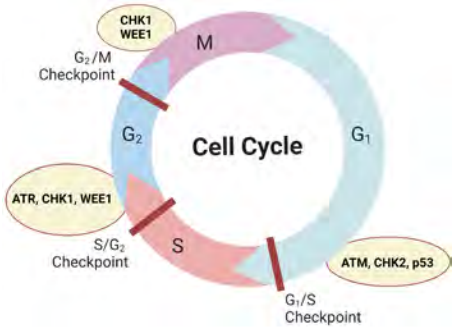


CELL CYCLE REGULATION AND DNA REPAIR

ADAVOSERTIB [8]

azenosertib[9]

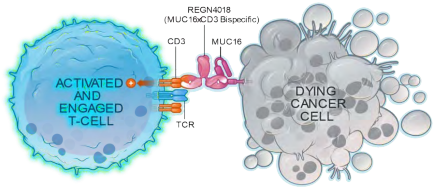
CDK2i [10]



IMMUNOTHERAPY

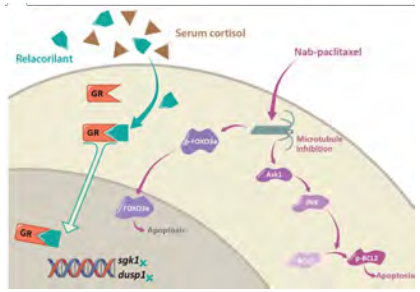
Paclitaxel/pembro [11]

UBAMATAMAB [12]



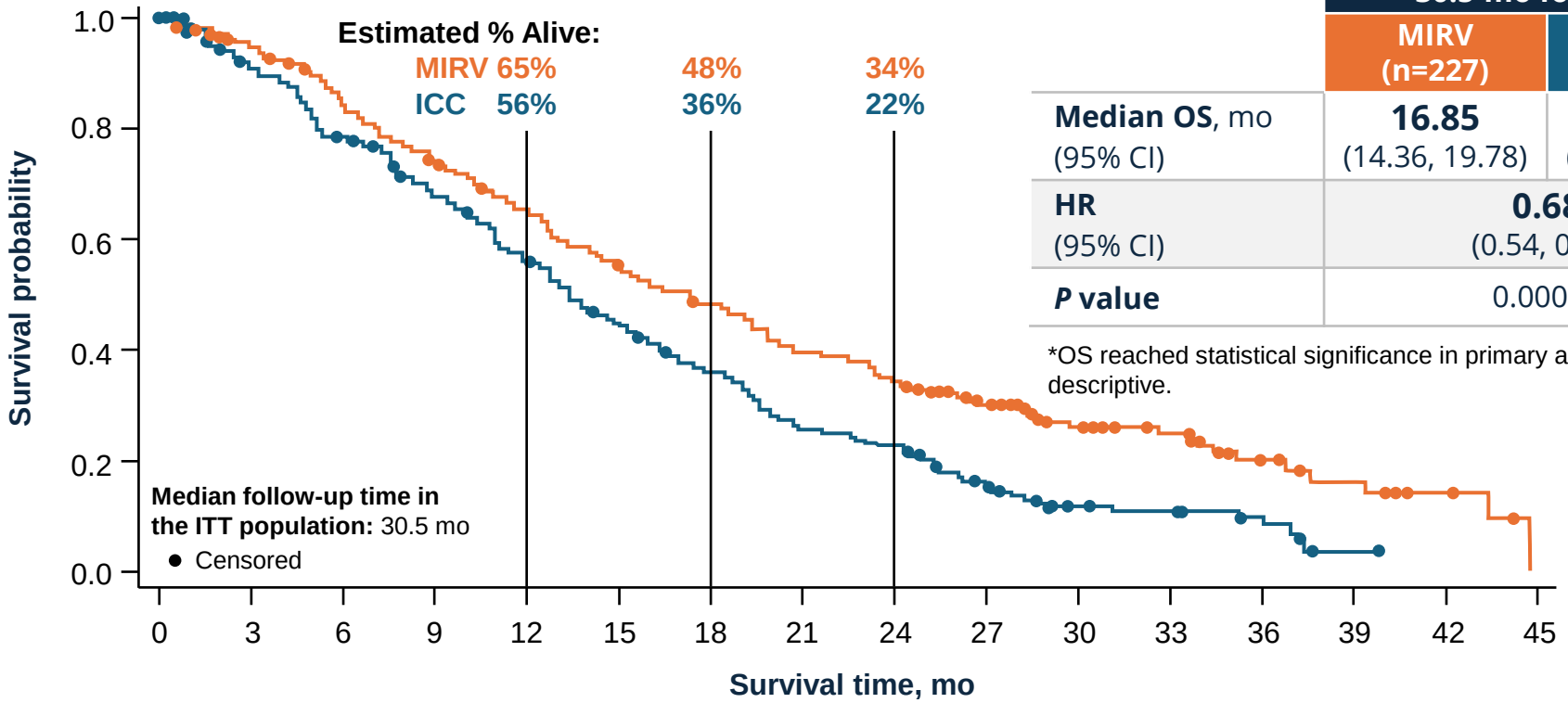
GLUCOCORTICOID RECEPTOR

RELACORILANT [13]



[1] [NCT04296890 – Soraya] [NCT04209855 – Mirasol]; [2] [NCT04482309]; [3] [NCT04707248]; [4] [NCT06619236]; [5] [NCT05797168] ; [6] [NCT06400472]; [7] [NCT06303505]; [8] [NCT03579316]; [9] [NCT02595892]; [10] [INCB123667]; [11] [NCT05116189]; [12] [NCT03564340] [13] [NCT05257408 – Rosella]; [NCT03776812 – phase II];

Mirvetuximab Soravtansine
Mirasol : Final Overall Survival (median follow up 30.5 months)



	Final analysis[a] 30.5-mo follow-up		Primary analysis[b] 13.1-mo follow-up	
	MIRV (n=227)	ICC (n=226)	MIRV (n=227)	ICC (n=226)
Median OS, mo (95% CI)	**16.85** (14.36, 19.78)	**13.34** (11.37, 15.15)	16.46 (14.46, 24.57)	12.75 (10.91, 14.36)
HR (95% CI)	**0.68** (0.54, 0.84)		0.67 (0.50, 0.89)	
***P* value**	0.0004*		0.0046	

*OS reached statistical significance in primary analysis. The *P* value at the final analysis is descriptive.

Number of patients at risk:

MIRV	227	204	178	156	135	114	98	80	70	50	33	25	12	8	4	0
ICC	226	186	159	134	110	85	67	48	42	25	13	11	7	1	0	

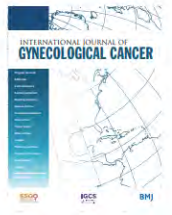
At the final analysis, the HR for OS (0.68) **continued to favor MIRV** over ICC, with patients treated with MIRV exhibiting a **32% reduction in risk of death**

HR, hazard ratio; ICC, investigator's choice chemotherapy; ITT, intent-to-treat; MIRV, mirvetuximab soravtansine-gynx; OS, overall survival; PFS, progression-free survival.

[a]Data cutoff: September 26, 2024. [b]Data cutoff: March 6, 2023.

Moore KN, et al. *N Engl J Med.* 2023;389(23):2162-2174.

Antibody Drug Conjugates in ovarian cancer

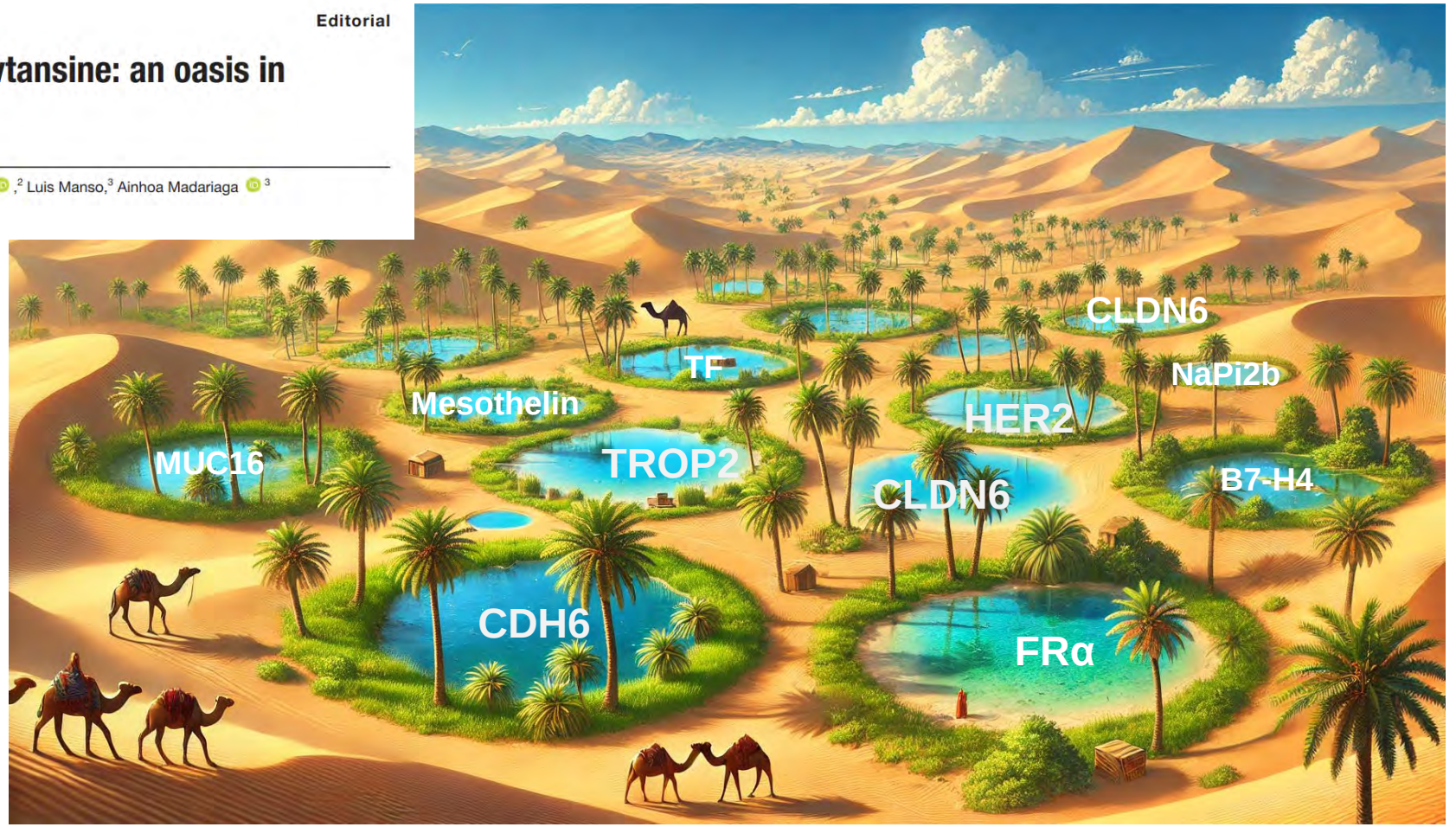


Editorial

Mirvetuximab soravtansine: an oasis in the desert?

Luisa Bonilla [1], Lawrence Kasherman [2], Luis Manso,[3] Ainhoa Madariaga [3]

Future?



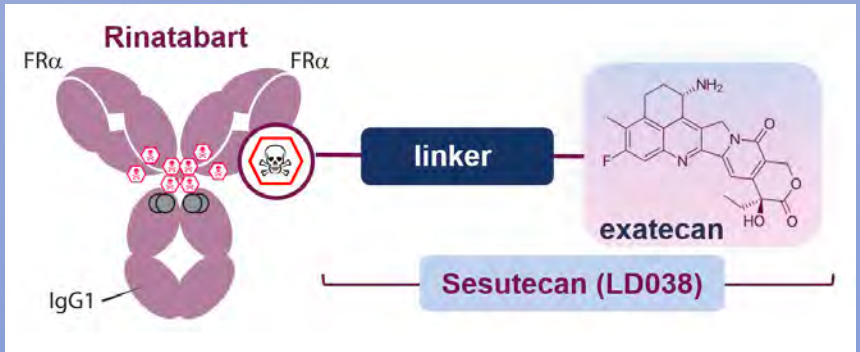
With permission of Ainhoa Madariaga

Targeting FRα

Rinatabart sesutecan (Rina-S)

Novel FRα-directed ADC

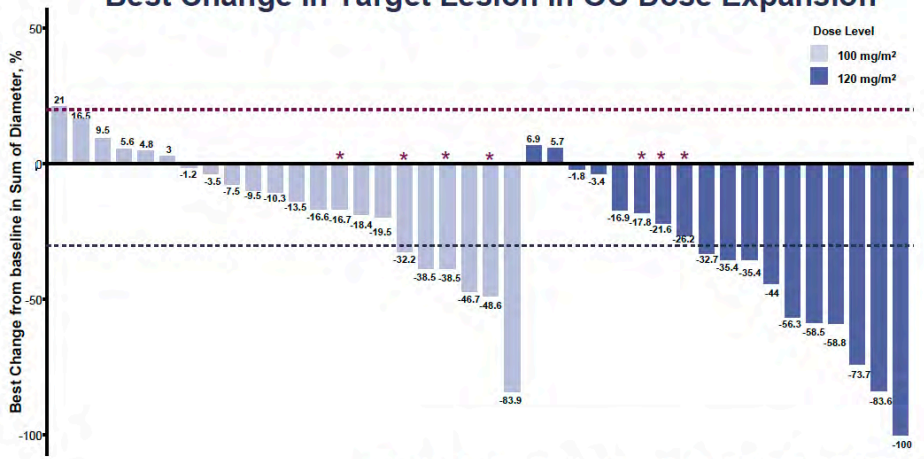
- Highly hydrophilic linker, sesutecan
- Topoisomerase 1 inhibitor payload



OC Dose Expansion	Rina-S 100 mg/m² n = 22[b]	Rina-S 120 mg/m² n = 18[b]
Confirmed ORR,[a,b] % (95% CI)	18.2 (5.2-40.3)	50.0 (26.0-74.0)
Best overall response,[b] n (%)		
CR	0	1 (5.6)
PR	4 (18.2)	8 (44.4)
SD	15 (68.2)	7 (38.9)
PD	3 (13.6)	1 (5.6)
Not evaluable	0	1 (5.6)
DCR, % (95% CI)	86.4 (65.1-97.1)	88.9 (65.3-98.6)
Median DOR (95% CI)	NR (NR-NR)	

Treatment duration, range: 3.0-42.0+ weeks
Median on-study follow-up: 24 weeks

Best Change in Target Lesion in OC Dose Expansion



*Prior mirvetuximab soravtansine treatment[c]

Median no. of cycles: 6.5 (100 mg/m²) and 7.0+ (120 mg/m²)

Phase 3 RainFol/GCT1184-02/ENGOT-OV86/GOG3107

https://clinicaltrials.gov/study/NCT06619236

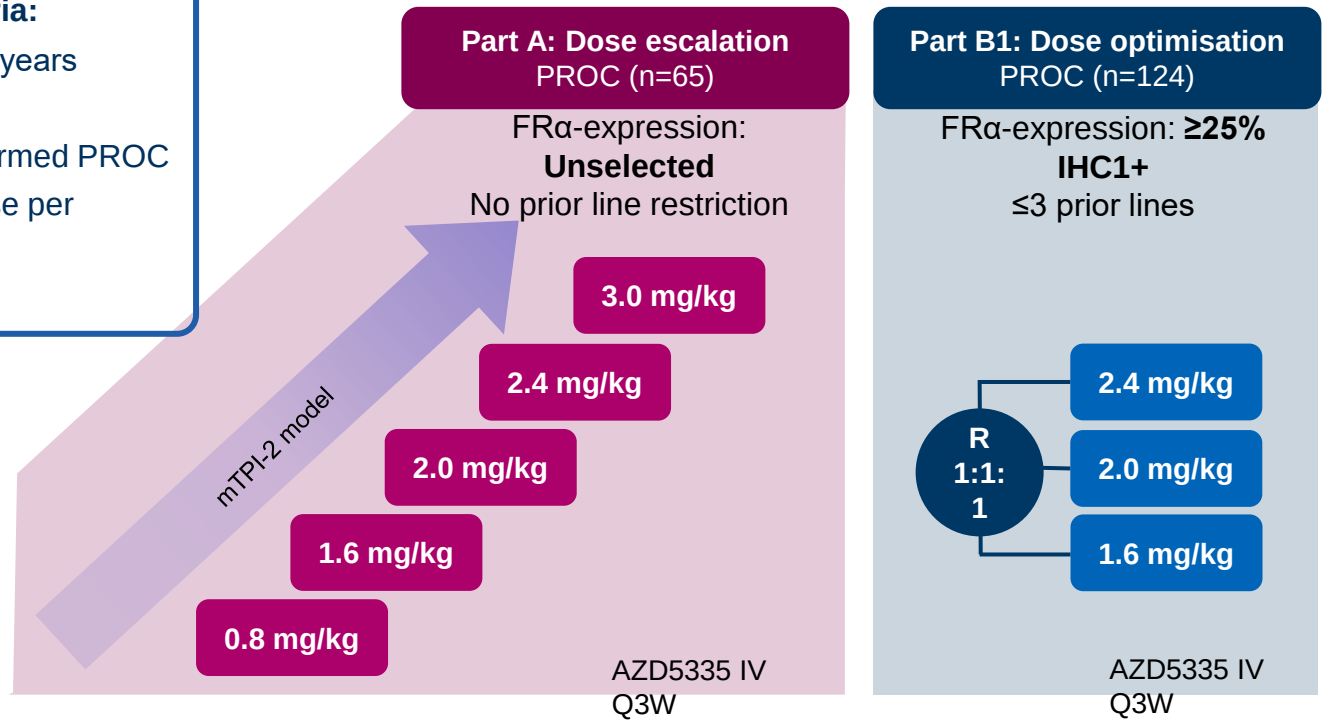
1. https://clinicaltrials.gov/study/NCT05579366. 2. Lee, EK et al. ESMO 2024 Abstract 719MO

AZD5335: An FRα-targeting TOP1i ADC

FONTANA Module 1: A Phase 1/2a, first-in-human, open-label study (NCT05797168)

Key inclusion criteria:

- Patients aged ≥18 years
- ECOG PS 0 or 1
- Histologically confirmed PROC
- Measurable disease per RECIST v1.1

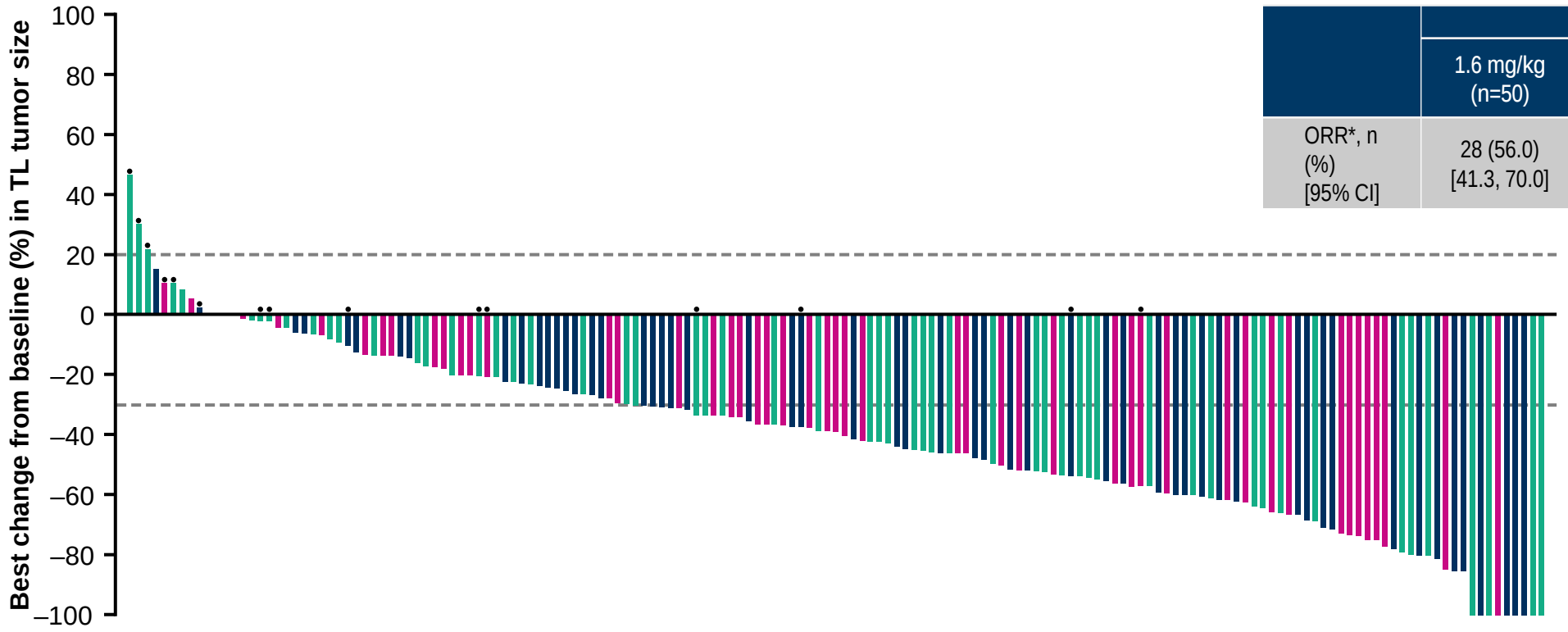


Baseline characteristic	Parts A + B1 N=189
Age, median (range) years	63.0 (40–82)
ECOG PS, n (%)	
0	87 (46.0)
1	102 (54.0)
Median number of prior lines of therapy (range)	3.0 (1–9)
Prior therapy received, n (%)	
PARP inhibitor	119 (63.0)
Bevacizumab	130 (68.8)
FRα-targeted therapy	8 (4.2)
TOP1 inhibitor	8 (4.2)

Primary endpoints: Safety and tolerability including AEs, SAEs, and DLTs **Secondary endpoints:** ORR, DoR, PFS

Full analysis set, defined as all patients who received study intervention in Part A and Part B1. Data cutoff: 11 July 2025.
AE, adverse event; DLT, dose-limiting toxicity; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FRα, folate receptor α; IHC1+, immunohistochemistry 1+ intensity; IV, intravenous; mTPI-2, modified toxicity probability interval-2; ORR, objective response rate; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival; PROC, platinum-resistant ovarian cancer; Q3W, every 3 weeks; R, randomisation; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SAE, serious adverse event; TOP1, topoisomerase 1

AZD5335 demonstrates efficacy across 1.6–2.4 mg/kg dose range



	Parts A + B1		
	1.6 mg/kg (n=50)	2.0 mg/kg (n=57)	2.4 mg/kg (n=61)
ORR*, n (%) [95% CI]	28 (56.0) [41.3, 70.0]	32 (56.1) [42.4, 69.3]	30 (49.2) [36.1, 62.3]

Among patients who received 1.6, 2.0, or 2.4 mg/kg AZD5335 in Parts A + B1, the overall ORR* was 53.6% (95% CI: 45.7, 61.3).

The most common TEAEs across the 1.6–2.4 mg/kg dose range were nausea, fatigue, and neutropenia.

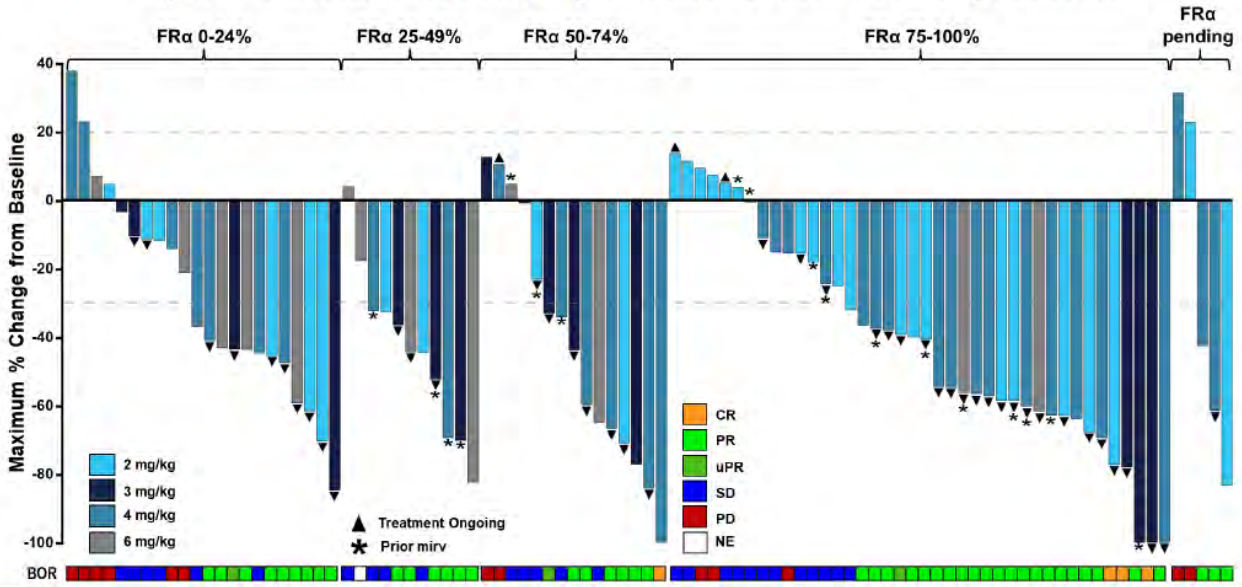
Interim response evaluable set, defined as all dosed patients with measurable disease at baseline who have ≥15 weeks follow-up or 2 post-baseline scans ≥4 weeks apart, according to RECIST v1.1 criteria. Data cutoff: 11 July 2025. *Confirmed ORR.

CI, confidence interval; ORR, objective response rate; PD, progressive disease; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; TL, target lesion

Oaknin, ESMO 2025

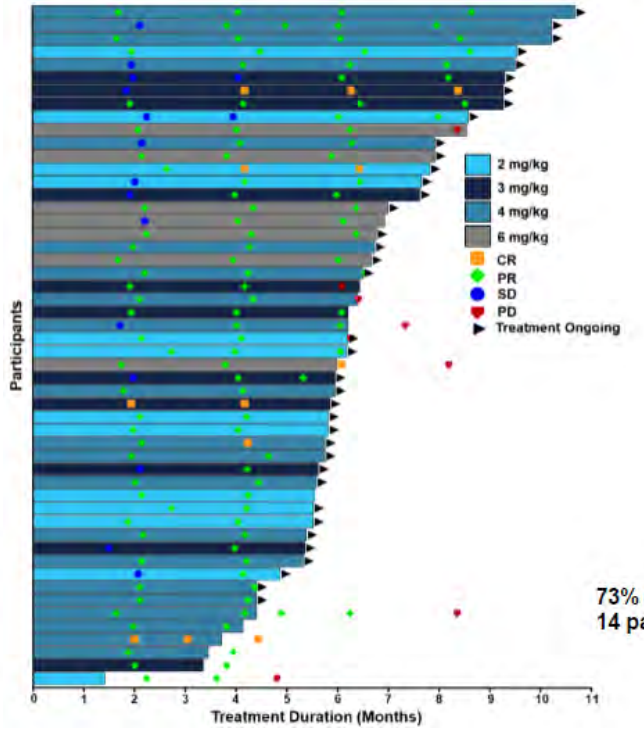
Initial results from a first-in-human phase 1 study of LY4170156, an ADC targeting folate receptor alpha (FRα), in advanced ovarian cancer and other solid tumors.

Fig 1. Antitumor activity by dose level and FRα expression



Efficacy Evaluable Patients	FRα 0-24% (n=25)	FRα 25-49% (n=12)	FRα 50-74% (n=16)	FRα ≥75% (n=46)	FRα pending (n=5)	Total (N=104)
ORR[a], % (n/N)	40 (10/25)	50 (6/12)	50 (8/16)	54 (25/46)	60 (3/5)	50 (52/104)
CR, n	-	-	1	3	-	4
PR, n	10[b]	6	7[b]	22[b]	3	48[c]
DCR[d], % (n/N)	68 (17/25)	83 (10/12)	81 (13/16)	83 (38/46)	60 (3/5)	78 (81/104)

Fig 2. Treatment Duration in Responders



73% (38/52) of responding patients are ongoing.
14 patients discontinued (6 due to PD)

Most common adverse events: Nausea, fatigue, myelotoxicity

NCT06400472

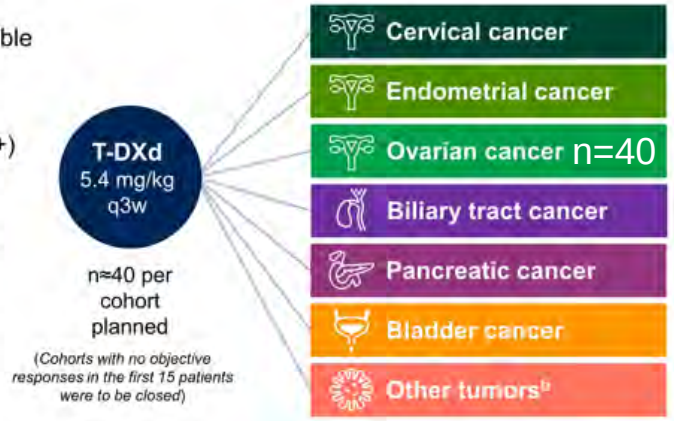
Antibody Drug Conjugates in Ovarian Cancer

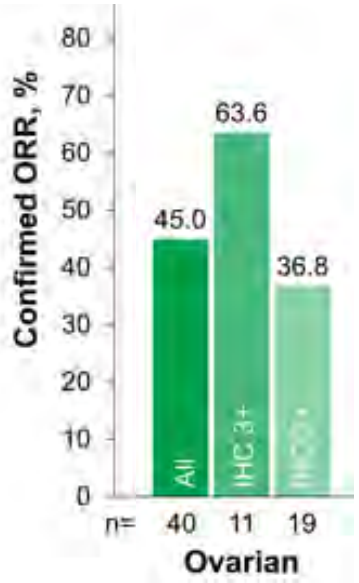
Targeting HER2

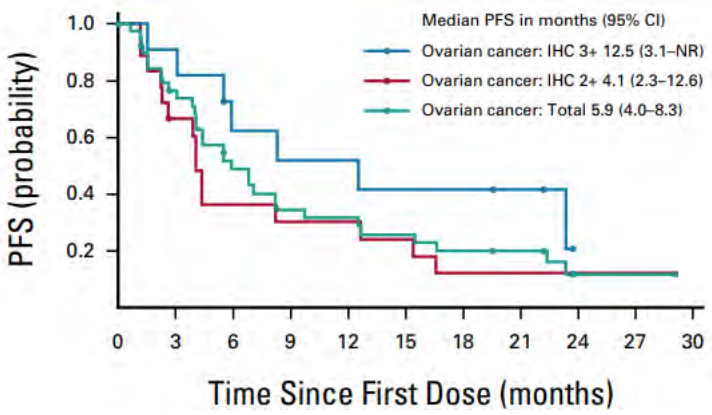
T-DXd: anti-HER2 IgG1, tetrapeptide cleavable linker, topoisomerase I inhibitor payload

Destiny Pantumor-02: Phase II T-DXd multi-tumour

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer guidelines[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1







ORR 45% (4 CR, 14 PR), response duration 11.3m (4.1–NR)
FDA accelerated approval for HER2 IHC 3+

Meric-Bernstam et al. JCO 2024

Targeting Cadherin 6 (CDH6)

REJOICE-Ovarian01 study design

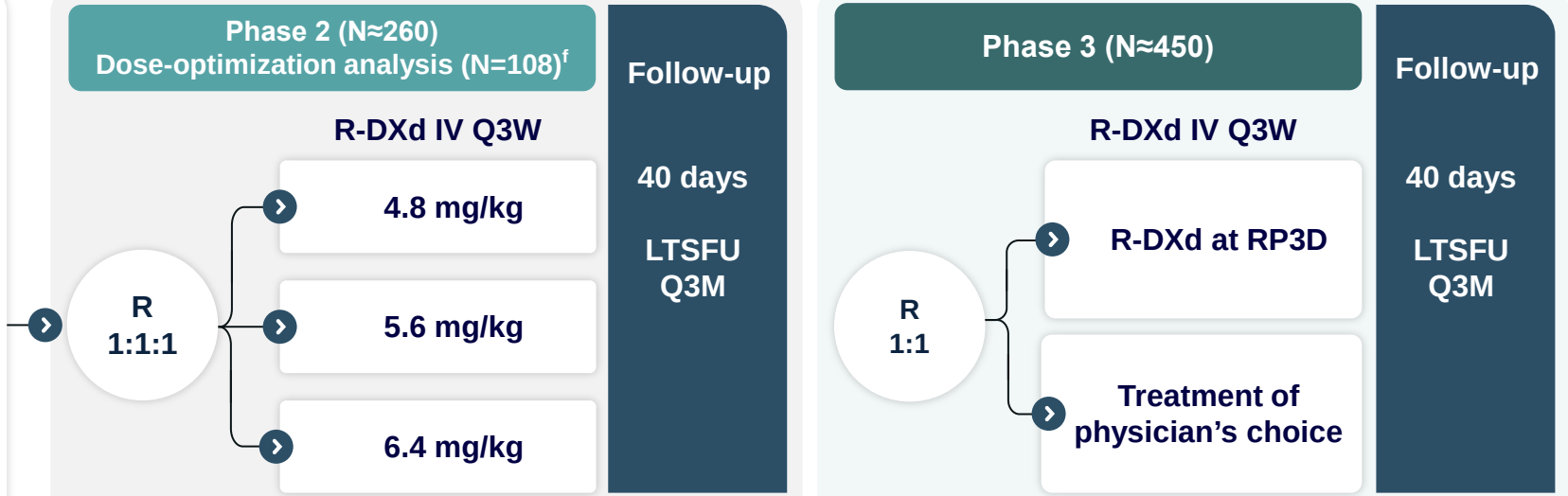
A Phase 2/3 multicenter, randomized study of R-DXd in patients with platinum-resistant, high-grade serous or endometroid ovarian, primary peritoneal, or fallopian tube cancer[1,2]

Key eligibility criteria

- High-grade serous or high-grade endometrioid ovarian, primary peritoneal, or fallopian tube cancer[a]
- 1−3 prior LOT, including bevacizumab[b]
- Platinum-resistant disease[c] (primary platinum-refractory disease is exclusionary)
- Prior mirvetuximab soravtansine[d] (for tumors with high FRα expression)
- ECOG PS 0−1
- No prior CDH6-targeting agents or ADCs with a linked exatecan derivative
- No selection by tumor CDH6 expression

Stratification factors

- Number of prior LOT (1 vs 2–3)
- CDH6 expression (≥75% vs <75%)[e]
- TPC (paclitaxel vs other; Phase 3 only)



Primary endpoint
ORR per BICR[g]

Key secondary endpoints
ORR per inv[g]
DOR per BICR and inv[g]

Primary endpoints
ORR per BICR[g]
PFS per BICR[g]

Key secondary endpoints
OS
QOL

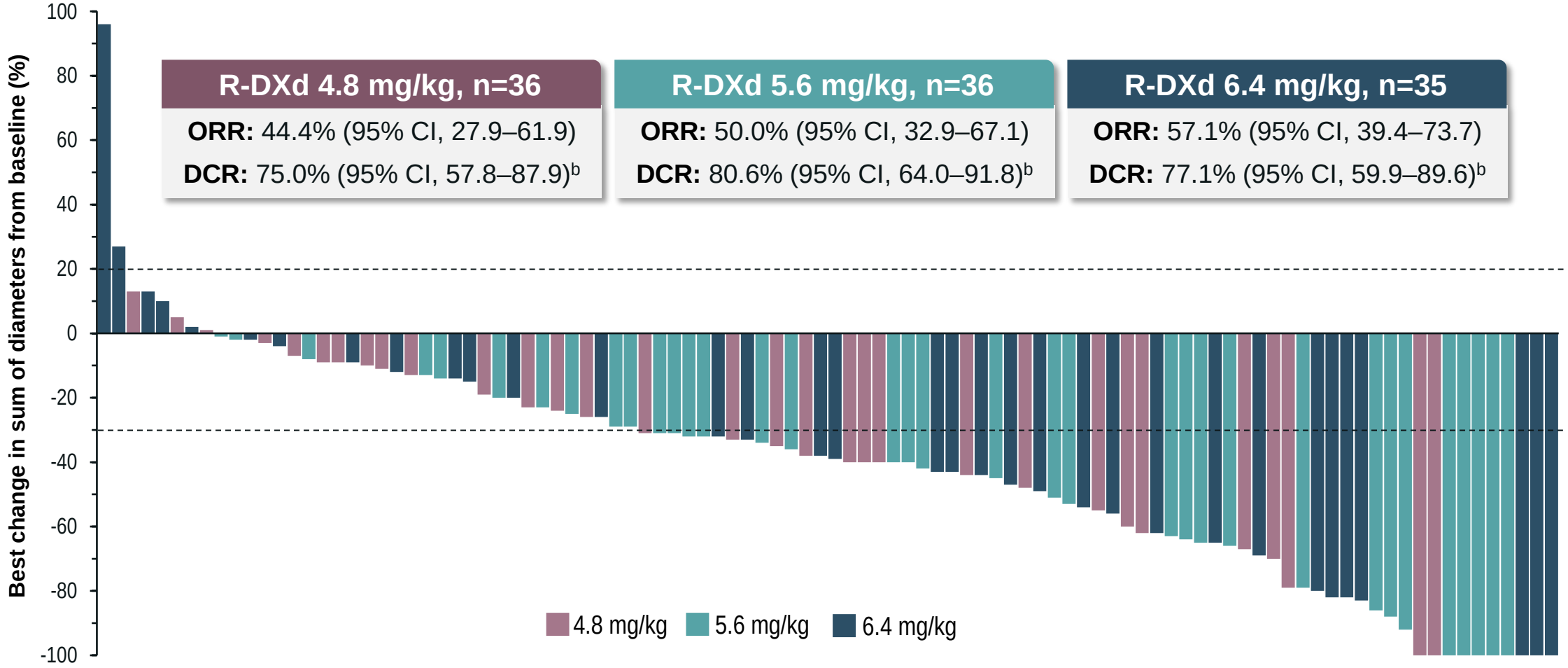
[a]Patients must have ≥1 lesion not previously irradiated and amenable to biopsy; must consent to provide a pretreatment biopsy and, in Phase 2 only, an on-treatment biopsy tissue sample and have ≥1 measurable lesion per RECIST 1.1. [b]Unless ineligible. [c]Defined as 1 line of prior platinum therapy (≥4 cycles with best response of not PD) with radiologically documented progression >90 and ≤180 days following last dose of platinum therapy, or 2–3 lines of prior platinum therapy (≥2 cycles) with radiologically documented progression ≤180 days following the last dose of platinum. [d]Unless ineligible, not approved or not available locally. [e]A stratification cutoff of 75% tumor cell membrane staining at any intensity was selected based on the median observed percentage tumor cell membrane staining (at any intensity) in the Phase 1 study population.[3] [f]Overall, 108 patients were randomized to receive R-DXd. One patient did not receive treatment, so 107 patients were treated and were included in the safety analysis set. [g]Per RECIST 1.1.

ADC, antibody–drug conjugate; BICR, blinded independent central review; CDH6, cadherin 6; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FRα, folate receptor alpha; FU, follow-up; IV, intravenous; inv, investigator; LOT, lines of therapy; LTSFU, long-term survival follow up; ORR, objective response rate; OS, overall survival; RP3D, recommended phase 3 dose; PD, progressive disease; Q3M, every 3 months; QOL, quality of life; Q3W, every 3 weeks; R, randomization; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; TPC, treatment of physician's choice.

1. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT06161025. Accessed 26 June 2025. 2. Ray-Coquard I, et al. Poster presentation at American Society Clinical Oncology 2024; May 31–June 4; Chicago, IL, USA. Poster TPS5625. 3. Moore KN, et al. Oral presentation at the Society of Gynecologic Oncology 2024 Annual Meeting on Women's Cancer. March 16–18, 2024; San Diego, CA, USA.

Ray-Coquard, ESMO 2025

Clinically meaningful tumor responses were seen irrespective of dose[a]



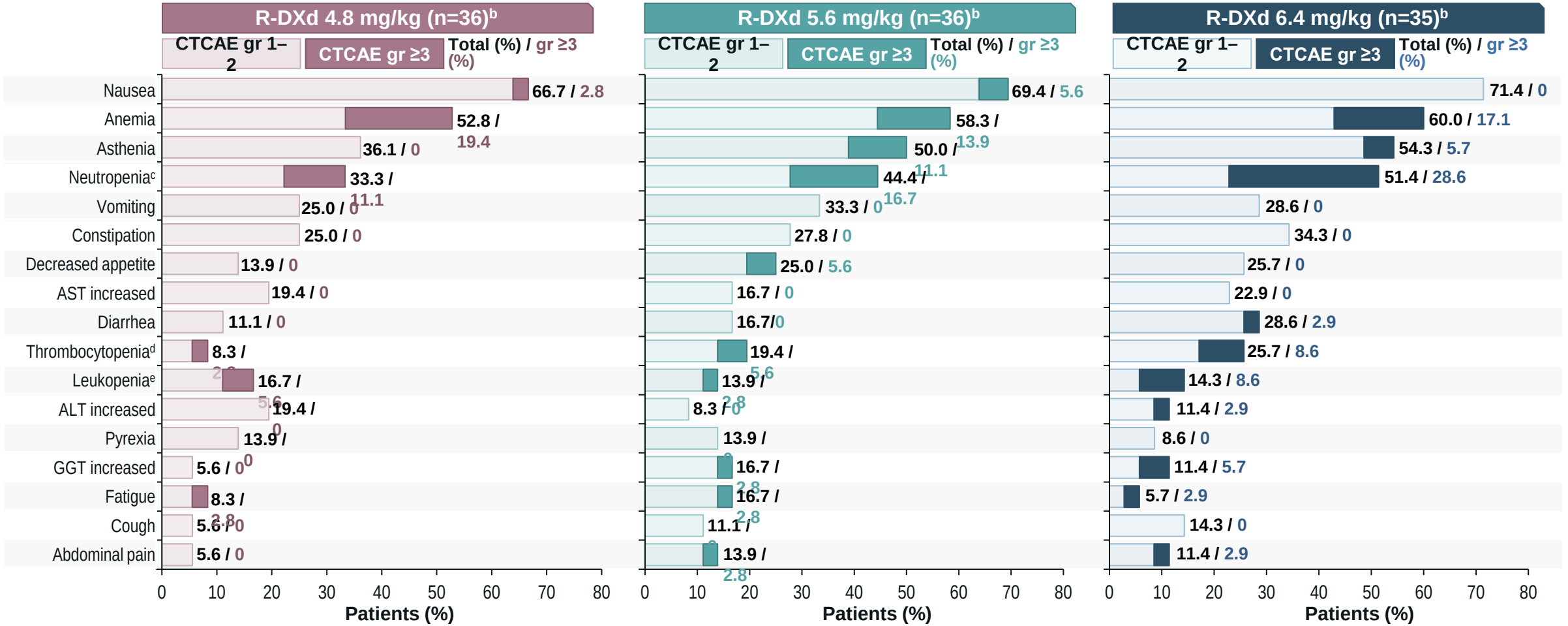
Data cutoff: February 26, 2025. The median follow-up for 4.8-mg/kg, 5.6-mg/kg, and 6.4-mg/kg cohorts was 5.6 months (95% CI, 4.7–6.3), 5.6 months (95% CI, 4.6–5.8), and 5.2 months (95% CI, 4.9–5.8), respectively.

[a]Antitumor response assessed by BICR per RECIST 1.1. Only patients with measurable disease at baseline and ≥1 post-baseline tumor scan, both by BICR, were included in the waterfall plot (n=100). Six patients (R-DXd 4.8 mg/kg [n=5]; 6.4 mg/kg [n=1]) did not have measurable disease at baseline and one patient (R-DXd 5.6 mg/kg) had no adequate post-baseline tumor assessment. [b]DCR is defined as percentage of patients with BOR of CR, PR, or SD (per RECIST 1.1).

BICR, blinded independent central review; CI, confidence interval; DCR, disease control rate; ORR, objective response rate; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

Ray-Coquard, ESMO 2025

The 5.6-mg/kg dose provided the optimal benefit–risk profile
Most common TEAEs (≥10% of overall population)[a]



Nausea, anemia, asthenia and neutropenia were the most common TEAEs across all doses

Data cutoff: February 26, 2025.

[a]TEAEs reported in ≥10% of all patients who received R-DXd 4.8–6.4 mg/kg. Reported safety events are defined by MedDRA preferred terminology. [b]Grade 4 hematologic TEAEs reported at 4.8 mg/kg: neutropenia[c] (n=2), thrombocytopenia[d] (n=1); at 5.6 mg/kg: neutropenia[c] (n=2), thrombocytopenia[d] (n=1), leukopenia[e] (n=1); at 6.4 mg/kg: neutropenia[c] (n=3), thrombocytopenia[d] (n=1), lymphopenia (n=1). No grade 5 hematologic TEAEs were reported at any dose. Grade 3 febrile neutropenia was reported in 2 patients, one each in the R-DXd 5.6 and 6.4 mg/kg cohorts. [c]Neutropenia is defined as the grouped incidence of events reported under the preferred terms '*neutropenia*' and '*neutrophil count decreased*', with a maximum of one event per patient per grouped preferred term. [d]Thrombocytopenia is defined as the grouped incidence of events reported under the preferred terms '*thrombocytopenia*' and '*platelet count decreased*', with a maximum of one event per patient per grouped preferred term. [e]Leukopenia is defined as the preferred term '*white blood cell count decreased.*'

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; GGT, gamma-glutamyltransferase; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

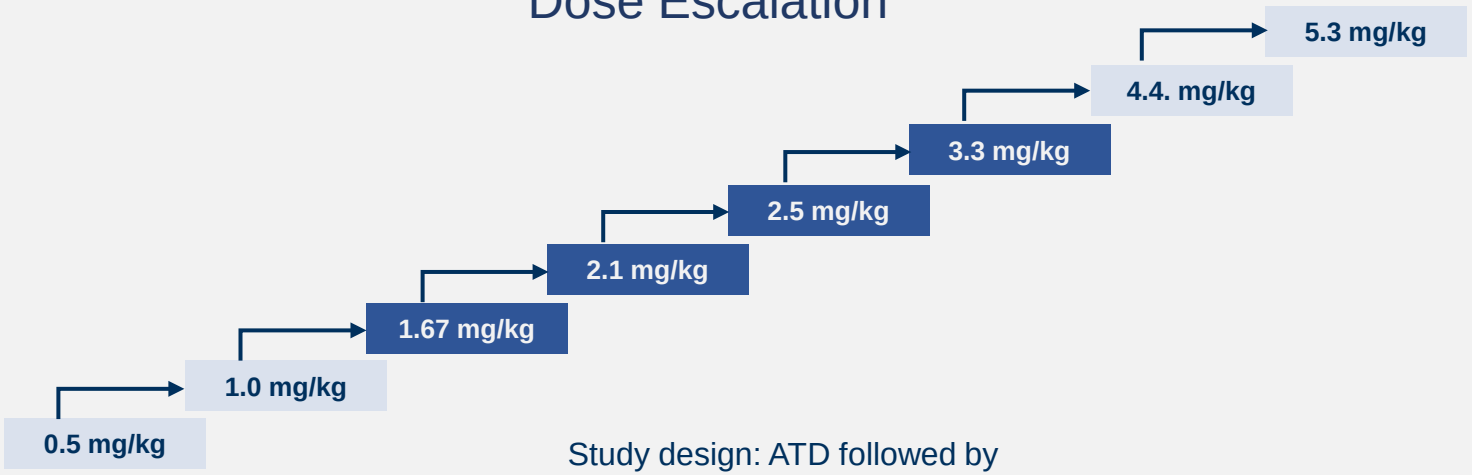
Ray-Coquard, ESMO 2025

NAPISTAR 1-01: Study Design

Antonio Gonzalez-Martin, ESMO 2025

A multicenter, FIH dose escalation and optimization Phase I/IIa Study (NCT06303505), investigating the NaPi2b ADC TUB-040 in PROC*

Phase I
Dose Escalation



Study design: ATD followed by BOIN

Phase IIa
Dose Optimization

- Dose 1
- Dose 2

Key Eligibility Criteria

- Histologically confirmed, platinum resistant, high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer
- A maximum of 5 platinum-based and 2 non-platinum prior lines of therapy
- ECOG 0-1
- No prior treatment with an ADC containing a TOPO-I inhibitor payload
- No biomarker selection based on NaPi2b expression

Objectives and Endpoints

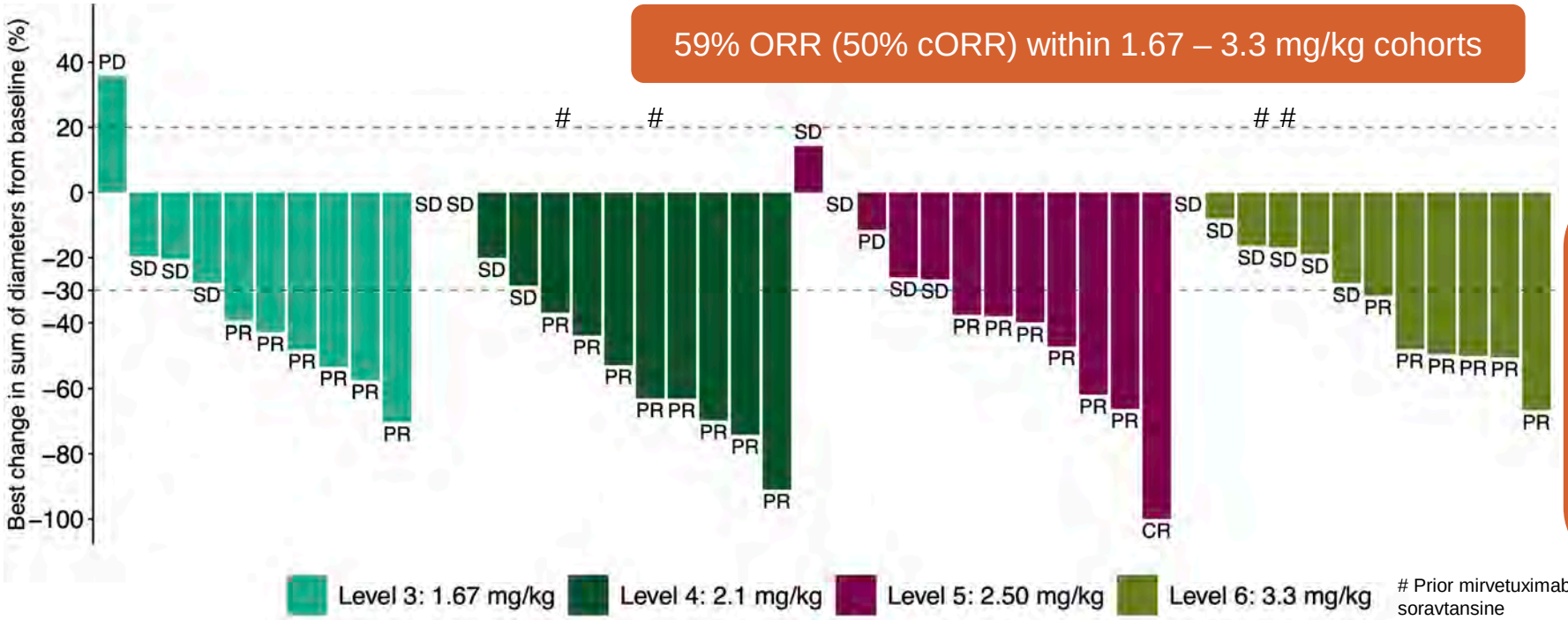
- Safety and tolerability
- Determination of MTD
- ORR per RECIST 1.1, DCR, DoR, PFS and OS
- PK parameters of TUB-040
- Immunogenicity
- Quality of life

* NAPISTAR 01-1 also includes an NSCLC arm, which is currently being explored independently from the PROC arm. Cut off: 01 September 2025. ADAs, anti-drug antibodies; ADC=antibody-drug conjugate; ATD, accelerated titration dosing; BOIN, Bayesian optimal interval; DCR, disease control rate; DoR, duration of response; FIH, first-in-human; MTD, maximum tolerated dose; NaPi2b, sodium-dependent phosphate transporter protein 2B; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PBC, platinum-based chemotherapy; PFS, progression-free survival; PK, pharmacokinetics; PROC, platinum-resistant ovarian cancer.

Efficacy across a wide therapeutic range with complete responses

Antonio Gonzalez-Martin, ESMO 2025

59% ORR (50% cORR) within 1.67 – 3.3 mg/kg cohorts



Prior mirvetuximab soravtansine

Across 1.67 – 3.3 mg/kg:

- Onset of activity at low doses
- Complete response observed
- CA125 response rate[4] 81%
- 93% (25/27) of responding patients are ongoing
- 80% (37/46) of patients remain on treatment, indicating durable benefit

Efficacy	1.67 mg/kg (n=10)	2.1 mg/kg (n=12)	2.5 mg/kg (n=12)	3.3 mg/kg (n=12)	Dose Levels 1.67-3.3 mg/kg (n=46)	All evaluable patients 0.5 – 5.3 mg/kg (n=66)[1]
ORR[2] n (%)	6 (60)	8 (67)	7 (58)	6 (50)[3]	27 (59)	36 (55)
Confirmed ORR, n (%)	4 (40)	7 (58)	7 (58)	5 (42)	23 (50)	26 (39)
DCR n (%)	9 (90)	12 (100)	11 (92)	12 (100)	44 (96)	64 (97)
Confirmed DCR, n (%)	9 (90)	12 (100)	11 (92)	12 (100)	44 (96)	60 (91)
Confirmed CR, n (%)	0	0	1 (8)	0	1 (2)	1 (2)

1. N=66 evaluable patients who had at least 1 RECIST response assessment across doses from 0.5 – 5.3 mg/kg. There were no responses observed at doses below 1.67 mg/kg. 2. Responses of PR/CR per RECIST at a minimum of 1 post-baseline assessment. 3. Efficacy data in patients treated at 3.3 mg/kg continue to mature. 4. CA125 responses determined per GCIG; 34 responders in 42 CA125 evaluable subjects. CR, complete response; DCR, disease control rate; PR, partial response; SD, stable disease. Data Cut off: 01 September 2025.

Platinum Ineligible Ovarian Cancer

ANTIBODY DRUG CONJUGATED (ADCS)

Mirvetuximab-soravtansine [1]

Trastuzumab-deruxtecan [2]

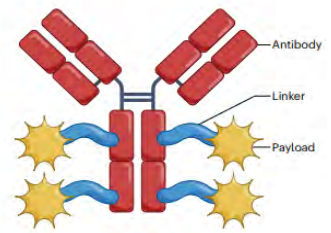
Raludotatug- Deruxtecan [3]

Rinatabart Sesutecan (Rina-S)[4]

AZD5335 [5]

Ly4170156 [6]

NAPISTAR 1-01 [7]

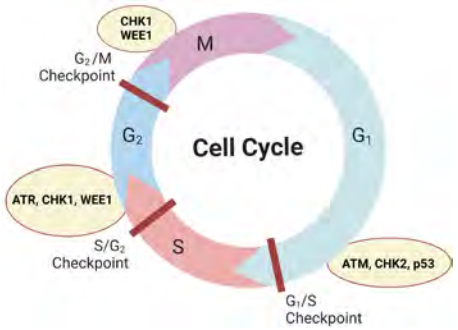


CELL CYCLE REGULATION AND DNA REPAIR

ADAVOSERTIB [8]

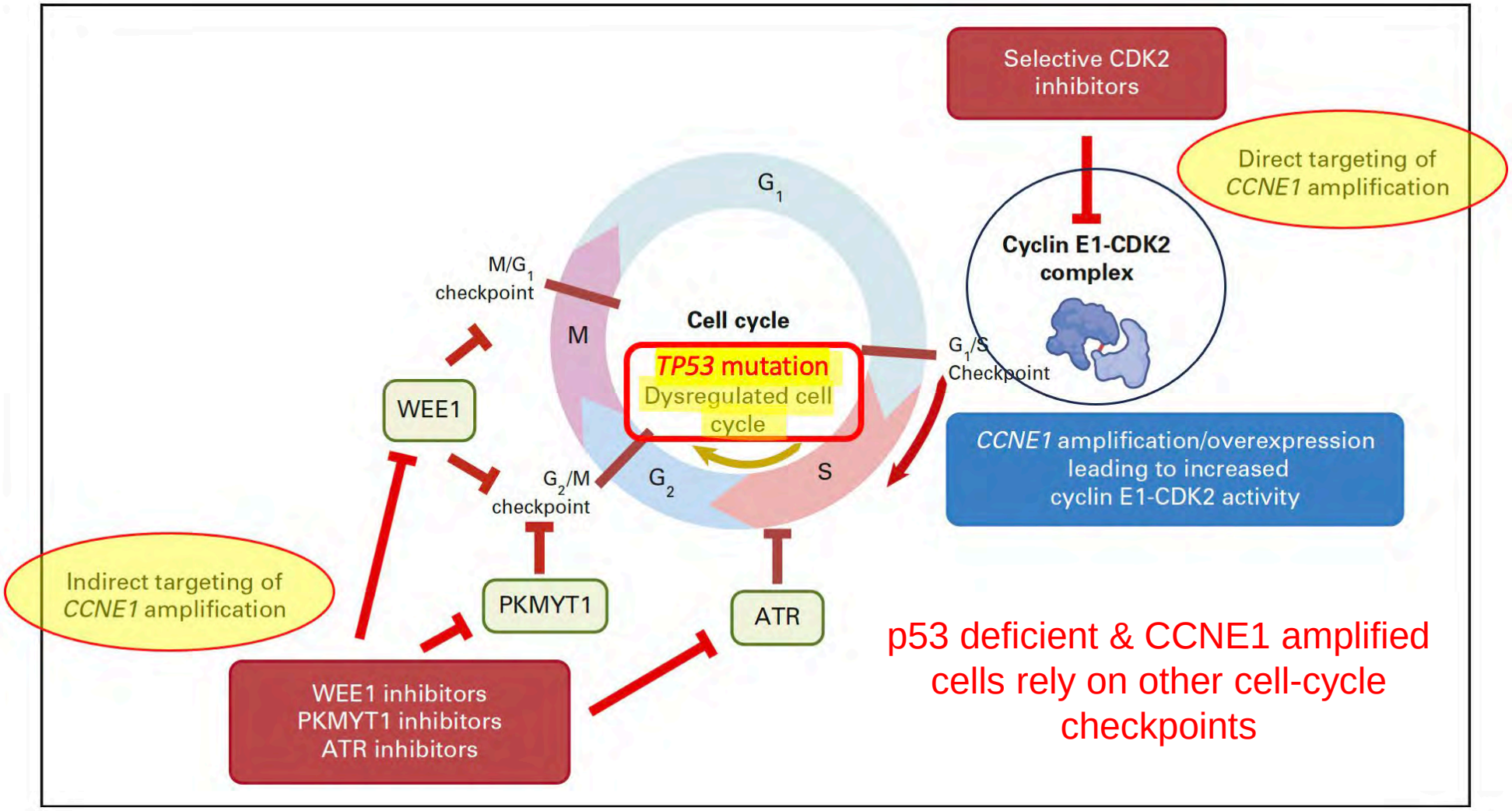
azenosertib[9]

CDK2i [10]



[1] [NCT04296890 – Soraya] [NCT04209855 – Mirasol]; [2] [NCT04482309]; [3] [NCT04707248]; [4] [NCT06619236]; [5] [NCT05797168] ; [6] [NCT06400472]; [7] [NCT06303505]; [8] [NCT03579316]; [9] [NCT02595892]; [10] [INCB123667]; [11] [NCT05116189]; [12] [NCT03564340] [13] [NCT05257408 – Rosella]; [NCT03776812 – phase II];

Exploiting Replication stress in *CNNE1* amplified tumours

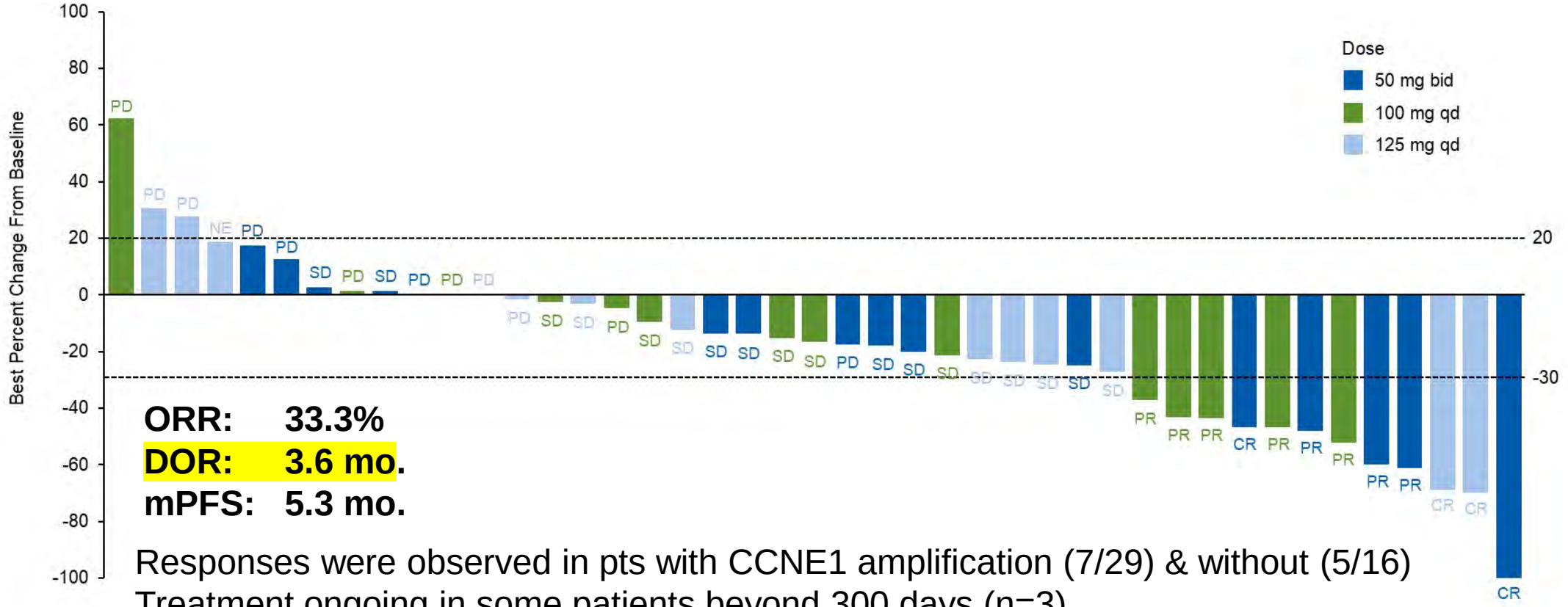


Au-Yeung G etal., JCO 2023

Direct Targeting of CCNE1

CDK2-inhibitors in Platinum Resistant/Refractory Ovarian cancer

INCB123667: Phase 1B, CCNE1 amplified or overexpressed EOC (n=45)



ORR: 33.3%

DOR: 3.6 mo.

mPFS: 5.3 mo.

Responses were observed in pts with CCNE1 amplification (7/29) & without (5/16)

Treatment ongoing in some patients beyond 300 days (n=3)

Good tolerability

Damian S et al., ASCO 2025 abstract #5514

Damian S et al., Journal of Clinical Oncology 2025 Vol. 43 Issue 16_suppl Pages 5514-5514

Platinum Ineligible Ovarian Cancer

ANTIBODY DRUG CONJUGATED (ADCS)

Mirvetuximab-soravtansine [1]

Trastuzumab-deruxtecan [2]

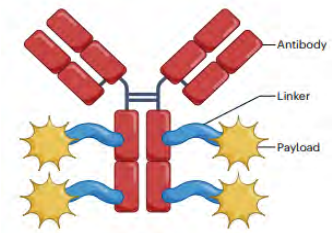
Raludotatug- Deruxtecan [3]

Rinatabart Sesutecan (Rina-S)[4]

AZD5335 [5]

Ly4170156 [6]

NAPISTAR 1-01[7]



CELL CYCLE REGULATION AND DNA REPAIR

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azenosertib[9]

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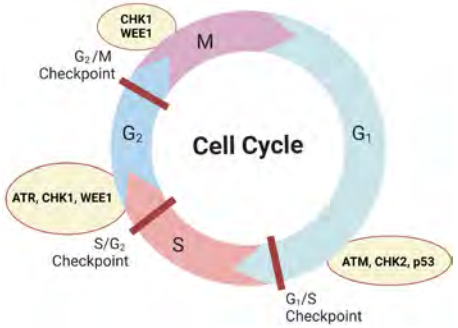
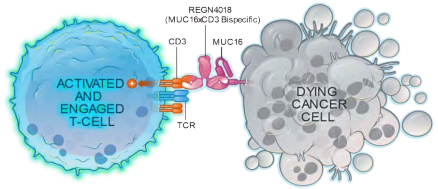


IMMUNOTHERAPY

Paclitaxel/pembro [11]

UBAMATAMAB [12]



[1] [NCT04296890 – Soraya] [NCT04209855 – Mirasol]; [2] [NCT04482309]; [3] [NCT04707248]; [4] [NCT06619236]; [5] [NCT05797168] ; [6] [NCT06400472]; [7] [NCT06303505]; [8] [NCT03579316]; [9] [NCT02595892]; [10] [INCB123667]; [11] [NCT05116189]; [12] [NCT03564340] [13] [NCT05257408 – Rosella]; [NCT03776812 – phase II];

Immune Checkpoint Inhibitors In Ovarian Cancer: Phase 3 Evidence

1st-Line				
• JAVELIN-10				X
• IMAgyn050				X
• DUO-O			ARPi	X
• ATHENA Co			ARPi	X
• FIRST			ARPi	?
• KEYLINK 001			ARPi	X
„Platin-sensitiv				
• ATALANTE				X
• ANITA			ARPi	X
„Platin-resistan				
• JAVELIN-200				X
• NRG GY 009				X
• AGO OVAR 2				X
• KEYNOTE-B96	(Pembro)	CHT + IO ± Bev		?

No clinically meaningful activity of Immune Checkpoint Inhibitors

Irrespective of:

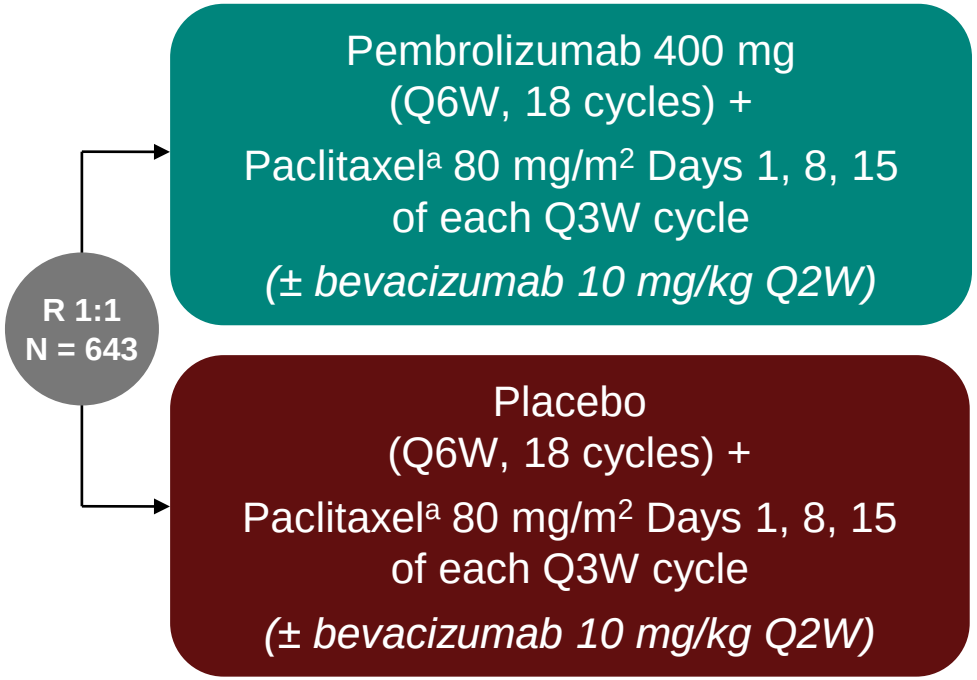
- line of treatment
- Combination (Bev & PARPi)

Data of 3 phase 3 trials still awaited

ENGOT-ov65/KEYNOTE-B96 Study Design (NCT05116189)

Key Eligibility Criteria

- Histologically confirmed epithelial ovarian, fallopian tube, or primary peritoneal carcinoma
- 1 or 2 prior lines of therapy; at least 1 platinum-based chemotherapy
  - Prior anti-PD-1 or anti-PD-L1, PARPi and bevacizumab permitted
- Radiographic progression within 6 months after the last dose of platinum-based chemotherapy
- ECOG PS 0 or 1



Stratification Factors

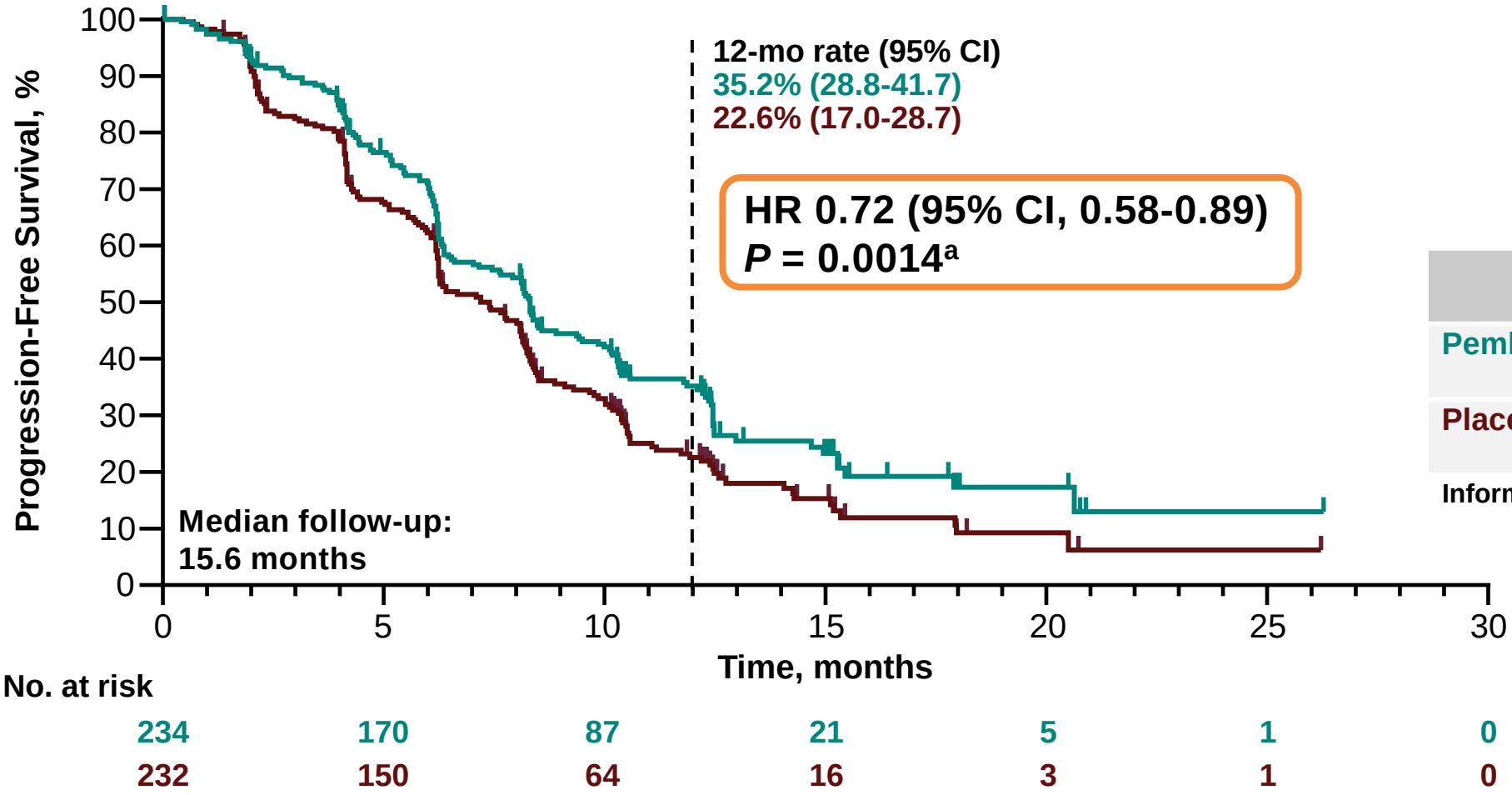
- Planned bevacizumab use (yes vs no)
- Region (US vs EU vs ROW)
- PD-L1 CPS (<1 vs 1 to <10 vs ≥10)[b]

Primary Endpoint: PFS per RECIST v1.1 by investigator

Key Secondary: OS

[a]Docetaxel (75 mg/m^2 Q3W) may be considered in participants with severe hypersensitivity reaction to paclitaxel or an adverse event requiring discontinuation of paclitaxel after consultation with the Sponsor. [b]The combined positive score (CPS) was assessed at a central laboratory using PD-L1 IHC 22C3 pharmDx and defined as the number of PD-L1 CPS ≥1 cells (tumor cells, lymphocytes, macrophages) divided by the total number of tumor cells × 100.

Progression-Free Survival in the CPS ≥1 Population at IA1



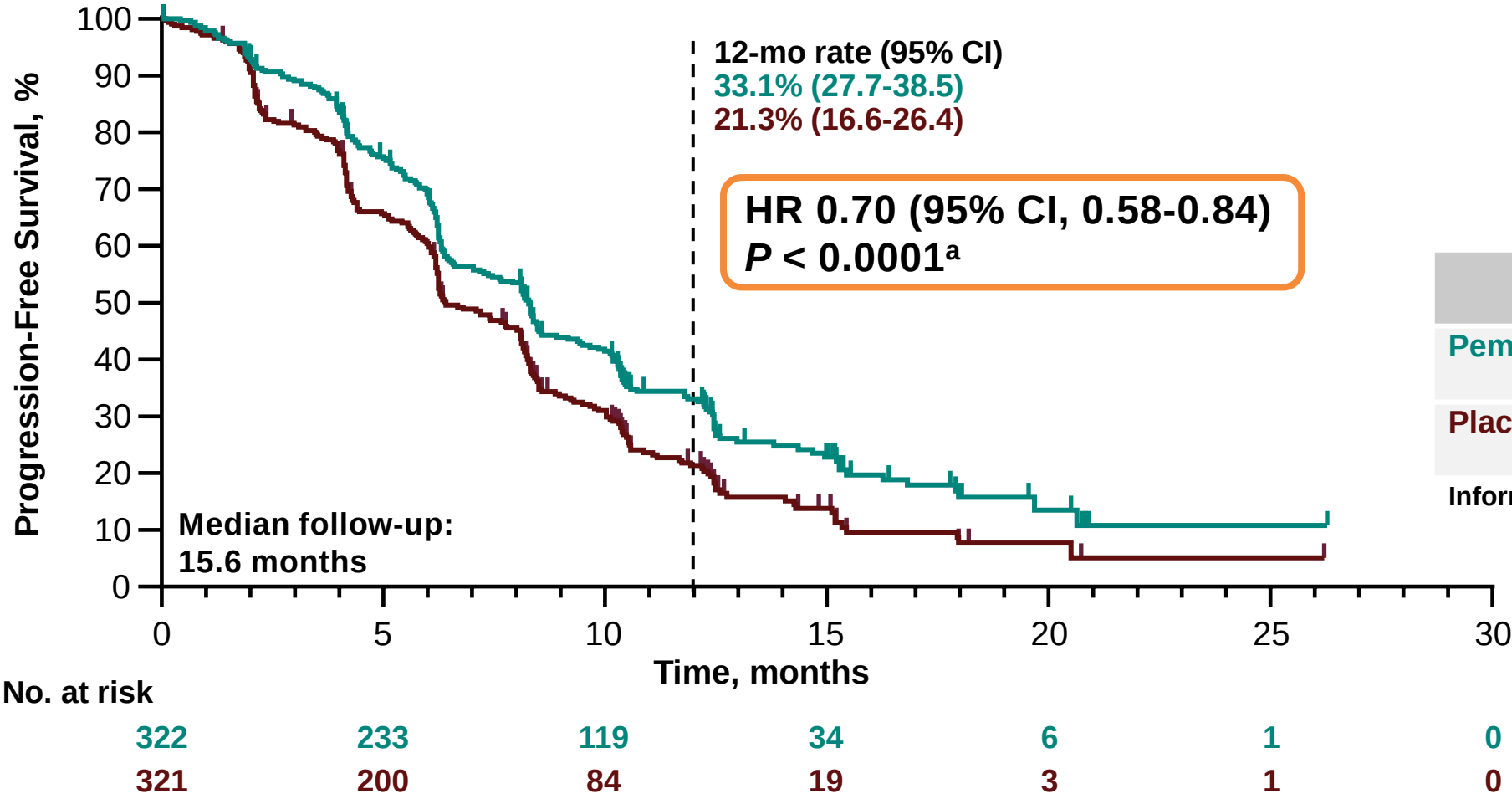
	Pts w/ Event	Median, mo (95% CI)
Pembro Arm	69.2%	8.3 (7.0-9.4)
Placebo Arm	77.6%	7.2 (6.2-8.1)

Information fraction: 87.9%

Response assessed per RECIST v1.1 by investigator review. [a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. The observed p-value crossed the prespecified nominal boundary of 0.0116 at this planned first interim analysis; because the success criterion of the PFS hypothesis was met, no formal testing of PFS will be performed at later analyses. Data cutoff date: April 3, 2024.

Colombo N, ESMO 2025

Progression-Free Survival in the ITT Population at IA1

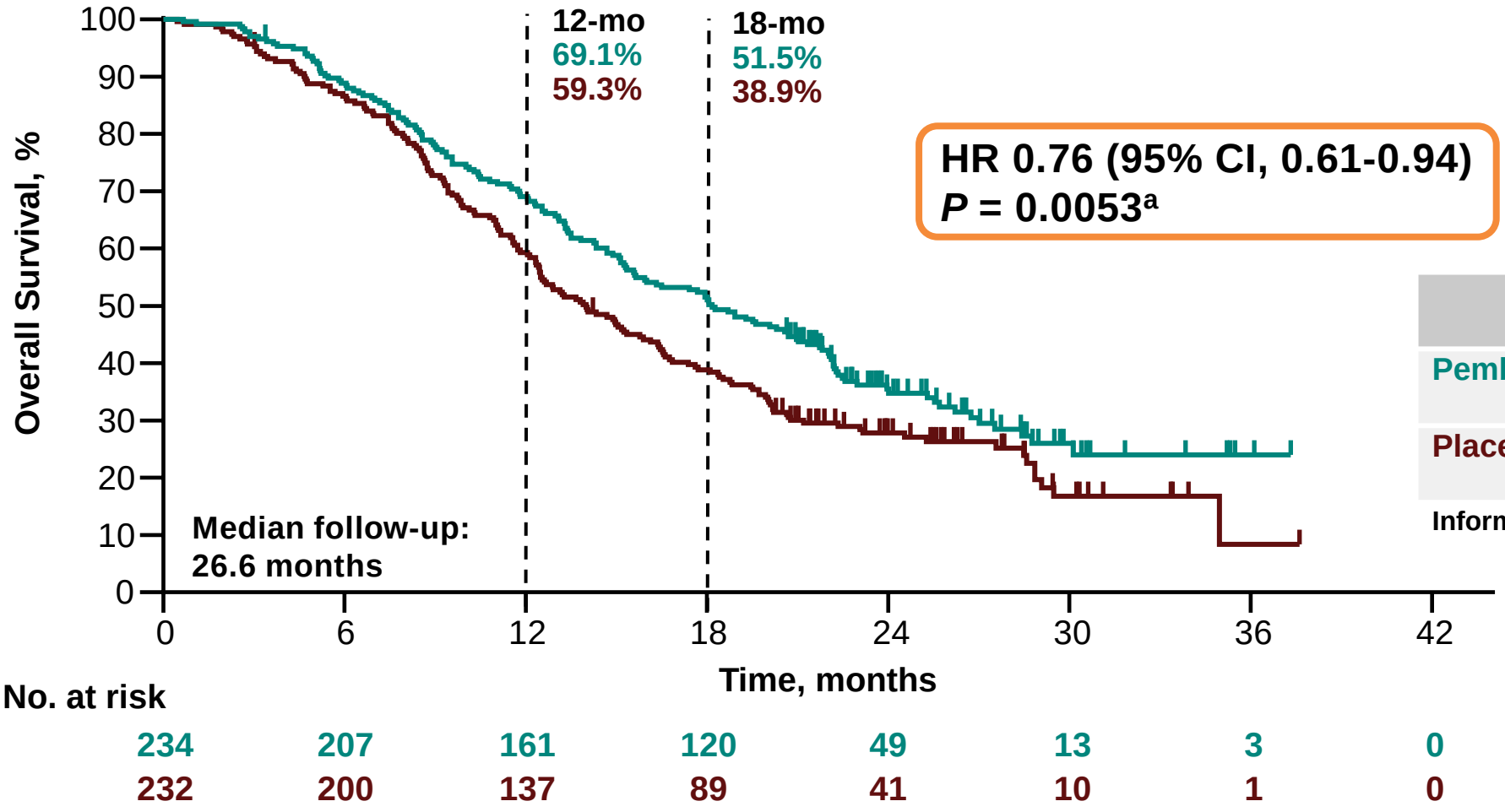


	Pts w/ Event	Median, mo (95% CI)
Pembro Arm	71.7%	8.3 (7.2-8.6)
Placebo Arm	78.8%	6.4 (6.2-8.1)

Information fraction: 89.5%

Response assessed per RECIST v1.1 by investigator review. [a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. The observed p-value crossed the prespecified nominal boundary of 0.0023 at this planned first interim analysis; because the success criterion of the PFS hypothesis was met, no formal testing of PFS will be performed at later analyses. Data cutoff date: April 3, 2024.

Key Secondary Endpoint: Overall Survival in the CPS ≥1 Population at IA2



HR 0.76 (95% CI, 0.61-0.94)
***P* = 0.0053[a]**

	Pts w/ Event	Median, mo (95% CI)
Pembro Arm	67.1%	18.2 (15.3-21.0)
Placebo Arm	75.4%	14.0 (12.5-16.1)

Information fraction: 90.0%

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. The observed p-value crossed the prespecified nominal boundary of 0.0083 at this planned second interim analysis. Data cutoff date: March 5, 2025.

Colombo N, ESMO 2025

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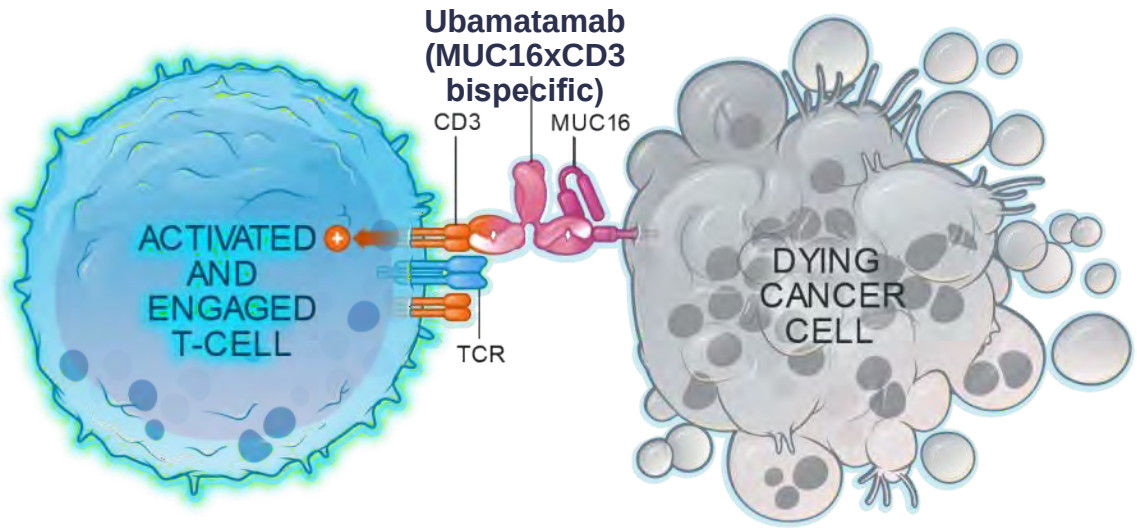
Ubamatamab (REGN4018) in Advanced Ovarian Cancer



- Ubamatamab is a human bispecific antibody, developed using VelocImmune technology
- Ubamatamab is designed to bridge MUC16 on cancer cells with CD3-expressing T cells to facilitate T-cell activation and cytotoxicity[4]
- In immune-deficient mice, ubamatamab combined with human immune cells led to dose-dependent antitumor activity against intraperitoneal MUC16- expressing ovarian tumour cells and malignant ascites[5,6]

1. National Cancer Institute. Available at: https://seer.cancer.gov/statfacts/html/ovary.html. Accessed January 20, 2022; 2. Siddiqui MK et al. Gynecol Oncol. 2017;146:44–51; 3. Pujade-Lauraine et al. J Clin Oncol. 2014; 13:1302-8; 4. Crawford A et al. Sci Transl Med. 2019;11:1–13; 5. Crawford A et al. Abstract presented at AACR 2018, Chicago, USA; 6. Crawford A et al. Oral presentation at PEGS Boston Summit 2020, Virtual.

Randomised phase 2 study of ubamatamab ± cemiplimab in patients (pts) with platinum-resistant ovarian cancer (OC)

Figure 2. Comparison of best overall tumour response across treatment Arms A, B and C*

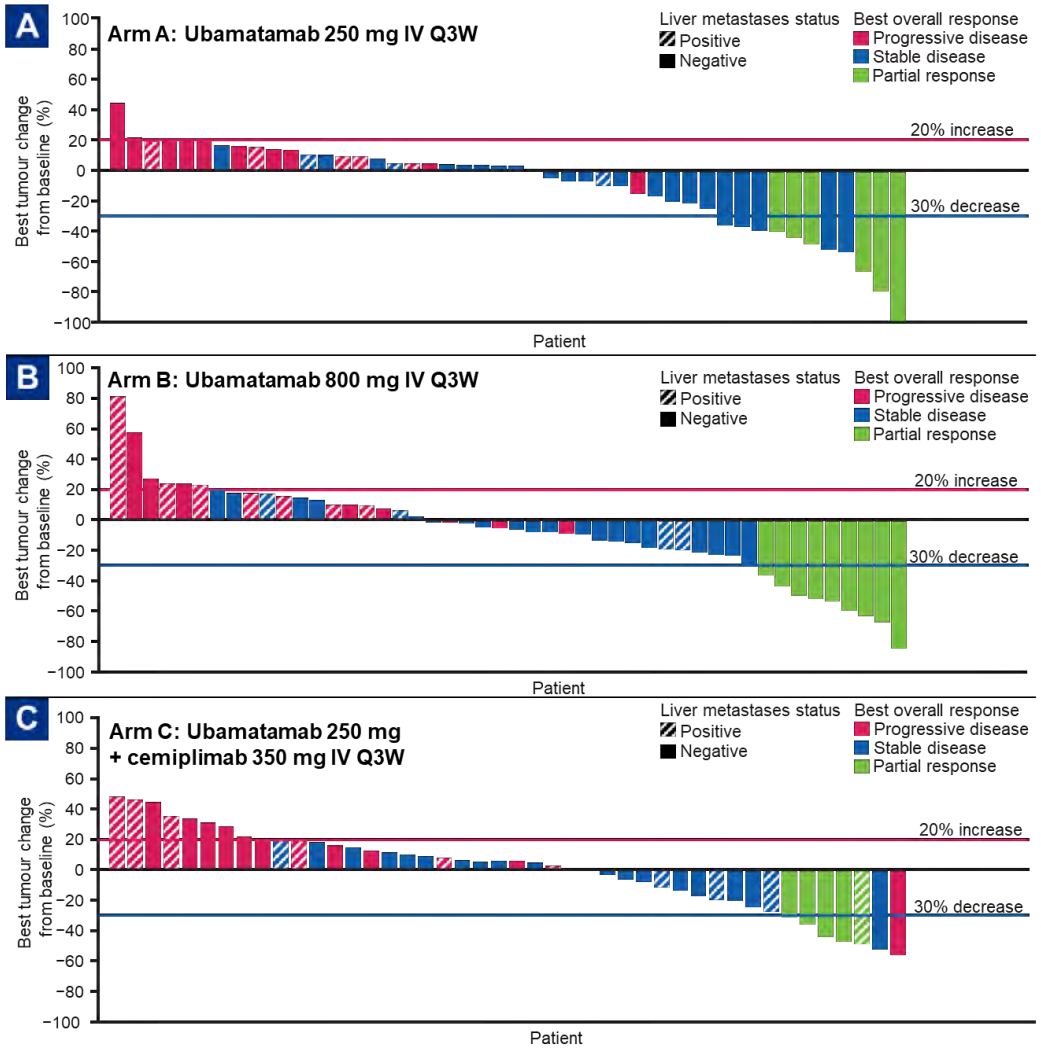
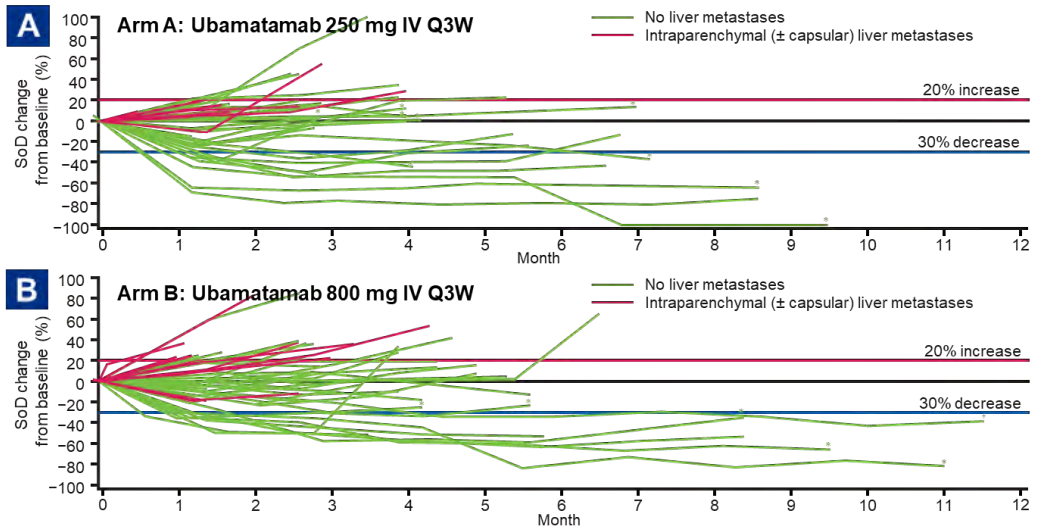


Figure 3. Comparison of DOR spider plots for treatment Arms A and B



	Arm A: Ubamatamab 250 mg IV Q3W n=50	Arm B: Ubamatamab 800 mg IV Q3W n=50
Median DOR (range), months	5.7 (2.8–NE)	10.5 (2.5–NE)

Data cut-off: 15 Jan 2025. *Patient remains on treatment as of data lock; †Patient continued treatment beyond 12 months.
DOR, duration of response; IV, intravenous; NE, not evaluable; Q3W, once every 3 weeks; SoD, sum of diameters.

Jung-Yun Lee, ESMO 2025

Platinum ineligible ovarian cancer

ANTIBODY DRUG CONJUGATED (ADCS)

Mirvetuximab-soravtansine [1]

Trastuzumab-deruxtecan [2]

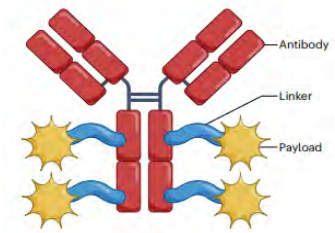
Raludotatug- Deruxtecan [3]

Rinatabart Sesutecan (Rina-S)[4]

AZD5335 [5]

Ly4170156 [6]

NAPISTAR 1-01[7]

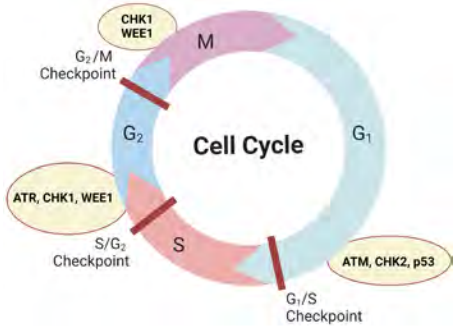


CELL CYCLE REGULATION AND DNA REPAIR

ADAVOSERTIB [8]

azenosertib[9]

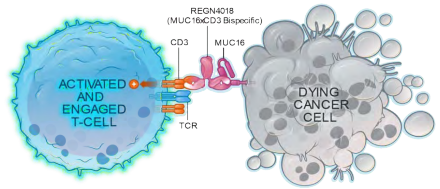
CDK2i [10]



IMMUNOTHERAPY

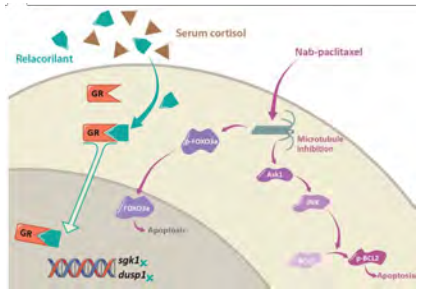
Paclitaxel/pembro [11]

UBAMATAMAB [12]



GLUCOCORTICOID RECEPTOR

RELACORILANT [13]



[1] [NCT04296890 – Soraya] [NCT04209855 – Mirasol]; [2] [NCT04482309]; [3] [NCT04707248]; [4] [NCT06619236]; [5] [NCT05797168] ; [6] [NCT06400472]; [7] [NCT06303505]; [8] [NCT03579316]; [9] [NCT02595892]; [10] [INCB123667]; [11] [NCT05116189]; [12] [NCT03564340] [13] [NCT05257408 – Rosella]; [NCT03776812 – phase II];

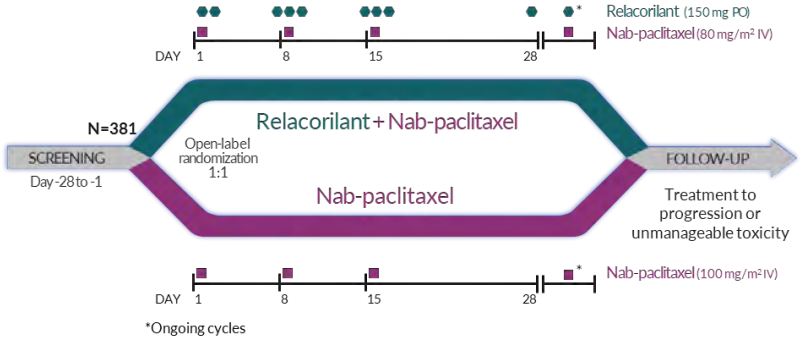
ROSELLA

- Relacorilant is a novel, selective GR antagonist (SGRA) that restores the sensitivity of cancers to cytotoxic chemotherapy[3,5,6]

Population

- Epithelial ovarian, primary peritoneal or fallopian tube cancer
- ECOG performance status 0 or 1
- Progression <6 months after the last dose of platinum therapy (excluding no response to, or progression in <1 month of primary platinum)
- 1–3 prior lines of therapy
- Must have received prior bevacizumab

NCT05257408



Stratification Factors
- Prior lines of therapy (1 vs >1)
- Region (North America vs Europe vs Korea, Australia, & Latin America)

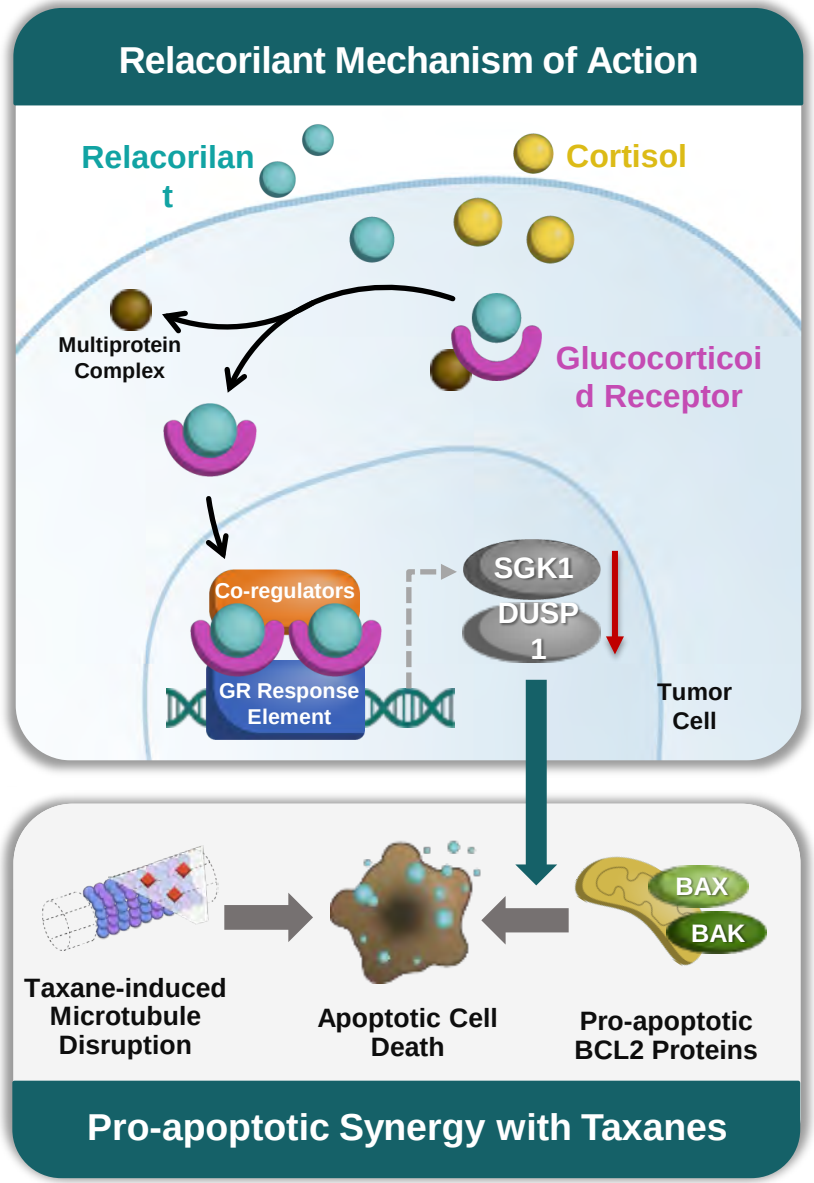
Dual Primary Endpoints

- Progression-free survival (PFS) by RECIST v1.1 per blinded independent central review
- Overall survival

Secondary Endpoints

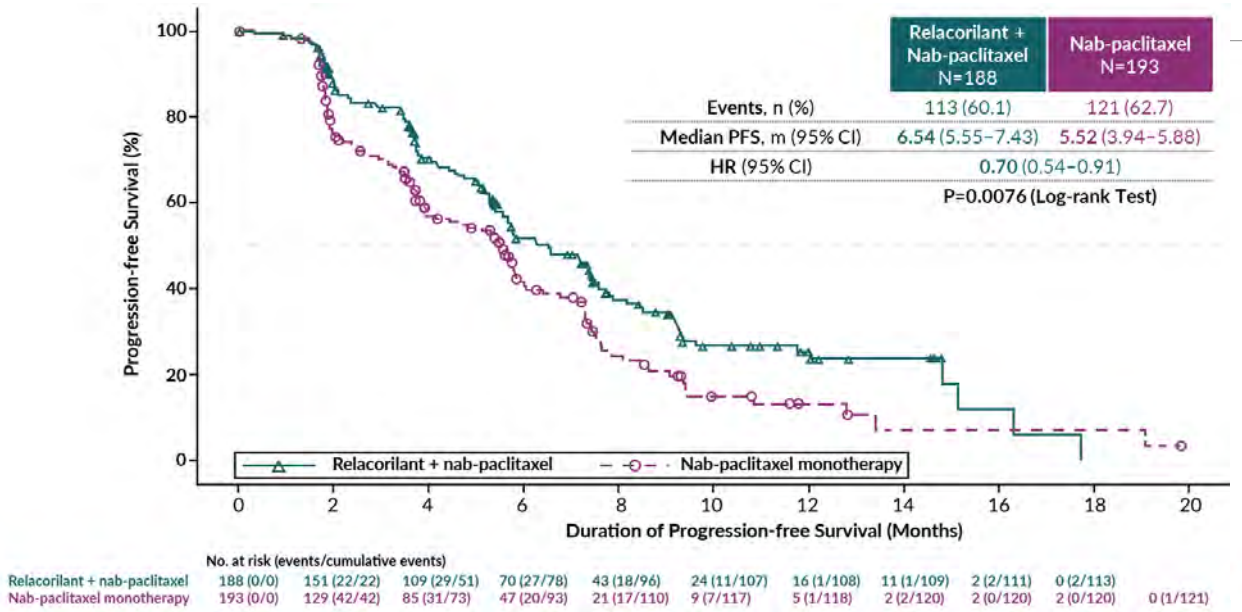
- PFS by RECIST v1.1 per Investigator
- ORR, DoR, CBR (RECIST v1.1)
- Response by CA-125 GCIG criteria
- Combined response (RECIST v1.1 and CA-125 GCIG criteria)
- Safety

First patient enrolled: 5th January 2023
Last patient enrolled: 8th April 2024
Data cutoff: 24th February 2025
Conducted at 117 sites in 14 countries.

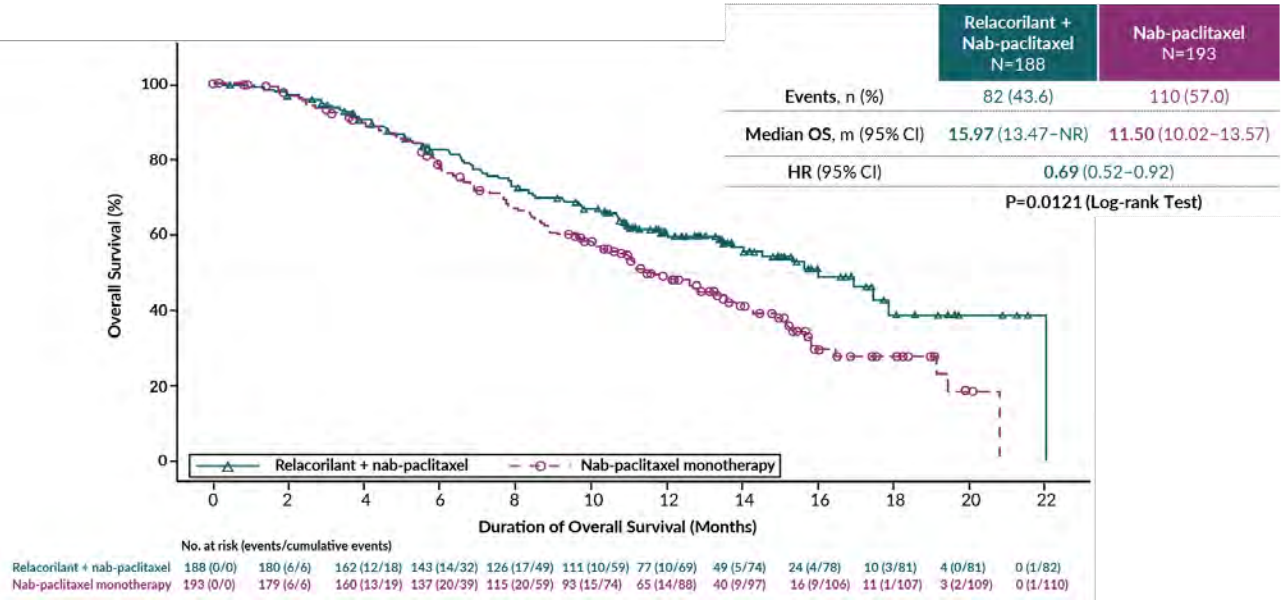


1. Martorana, et al. *Int J Gynecol Cancer*. 2025;35(1):100009. 2. Veneris, et al. *Gynecol Oncol*. 2017;146(1):153-60. 3. Greenstein, et al. *Oncotarget*. 2021;12(13):1243-55. 4. Melhelm, et al. *Clin Cancer Res*. 2009;15(9):3196-3204. 5. Stringer-Reasor, et al. *Gynecol Oncol*. 2015;138(3):656-62. 6. Munster, et al. *Clin Cancer Res*. 2022;28(15):3214-24. 7. Colombo, et al. *J Clin Oncol*. 2023;41(30):4779-89.

ROSELLA | Relacorilant Significantly Improved Progression-Free Survival Assessed by Blinded Review



ROSELLA | Relacorilant Improved Overall Survival at this Interim Analysis (not yet significant)



statistical significance threshold at the interim analysis: P≤0.0001

Alexander Olawaiye, ASCO 2025, Lancet 2025

ADCs and much more for PROC patients !!

Innovative Mechanisms and Combinations: Beyond ADCs in 2025

Domenica Lorusso, MD, PhD

Humanitas University, Pieve Emanuele
Humanitas San Pio X Hospital
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The Chrysalis: Going back to biology to elevate outcomes

What's going on in there?

1. **Enhanced understanding of mechanisms of resistance, additivity and development of novel agents (ex: relacorilant, batiraxcept)**
2. Elucidation of cell surface and intracellular targets and better delivery of potent anti-cancer agents: ADCs/Bispecifics/Novel conjugates
3. Increased understanding of cell cycle machinery in cancer and next-generation target development, Ex: CDK2, ATRi/PARPi
4. Re-evaluation of the biology behind and the definitions of recurrence. PSOC and PROC no longer serve us

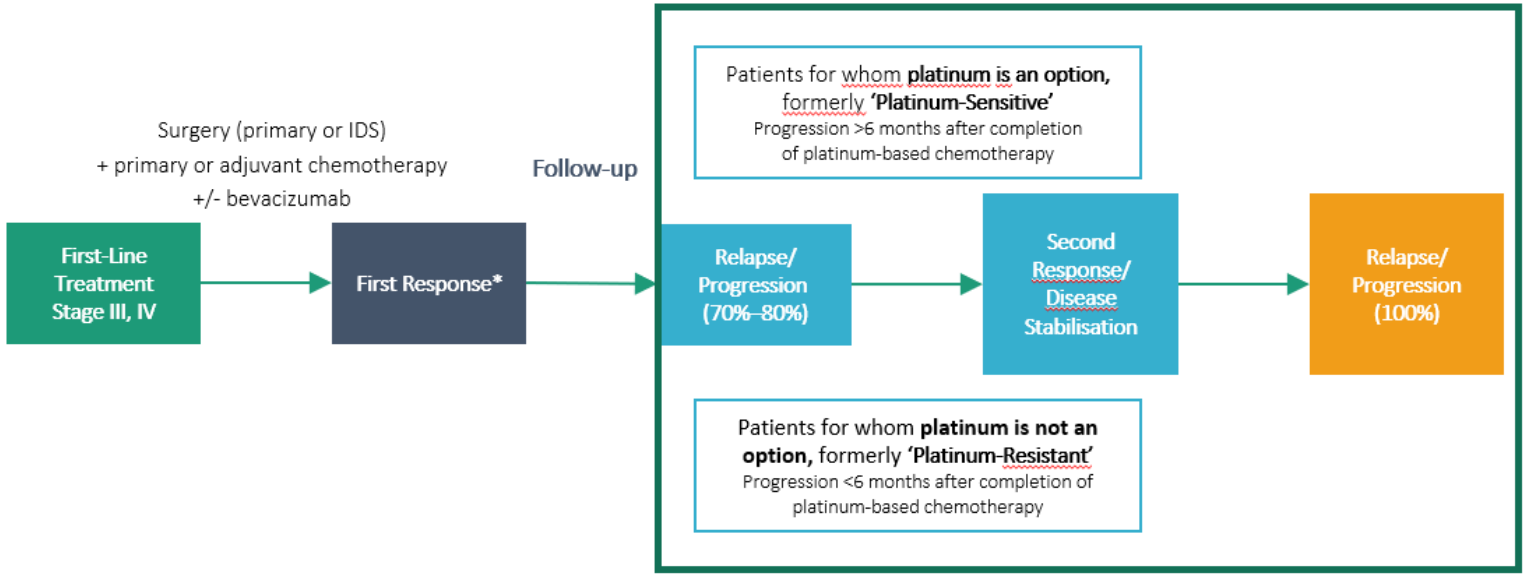


Figure from Suski JM et al. Cancer Cell 2021

Cortisol and the Glucocorticoid Receptor Pathway in Cancer

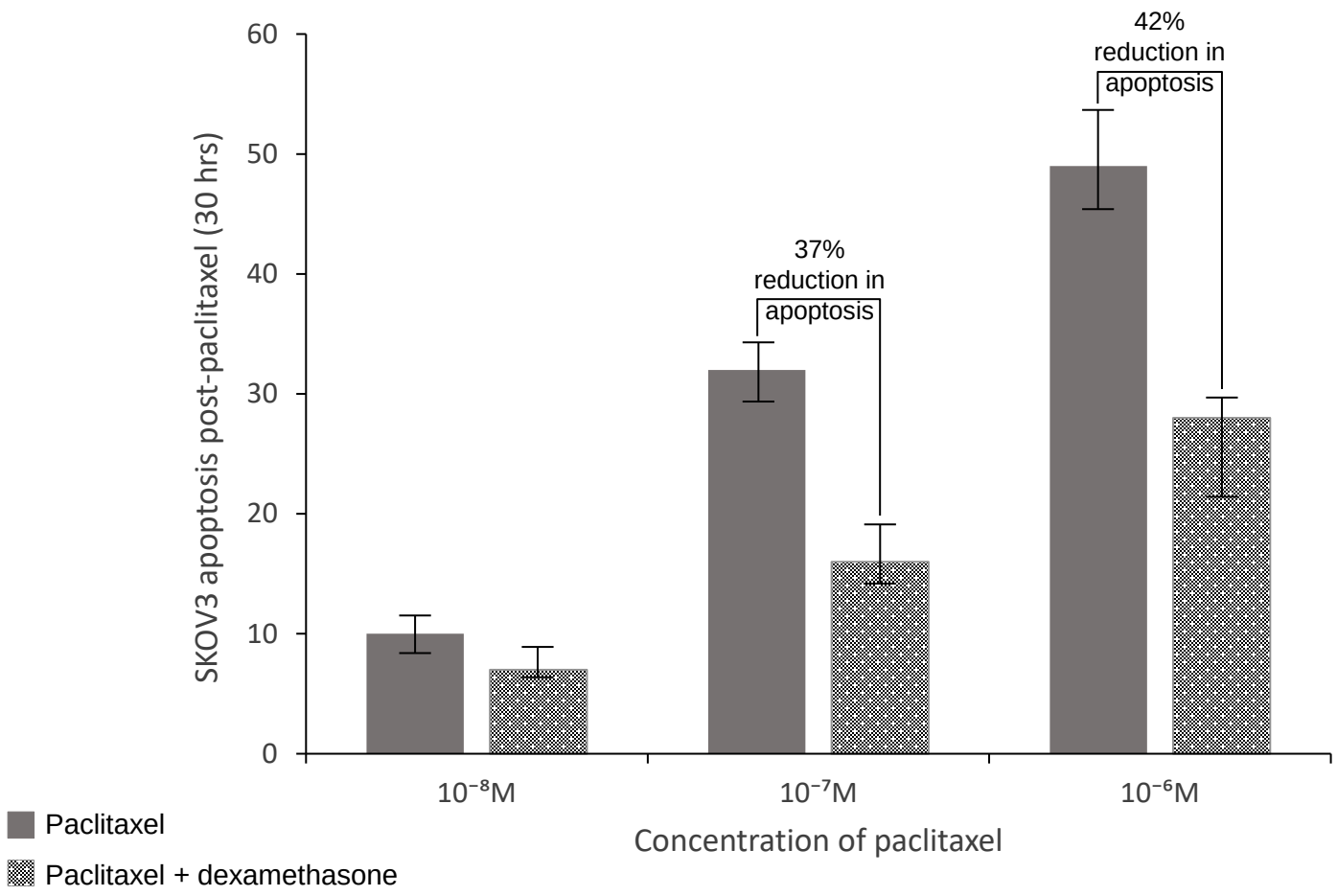
- The glucocorticoid receptor (GR) is commonly expressed in ovarian carcinoma.[1]
- The normal range for morning serum cortisol, 276–552 nM, is higher than the concentration at which half-maximal glucocorticoid receptor activation occurs (9.5 nM); furthermore, endogenous cortisol levels are disrupted in states of physical and psychosocial stress.[2,3]
- Pre-clinical studies suggest that activation of the glucocorticoid receptor by physiological cortisol levels may reduce the effectiveness of chemotherapy.[4]

1.Colombo N et al. *J Clin Oncol.* 2023;41(30):4779-4789. 2. Veneris JT et al. *Gynecol Oncol.* 2017;146(1): 153–16. 3. Greenstein AE et al. *Int Immunopharmacol.* 2023:120:110312. 4. Greenstein AE et al. *Oncotarget*. 2021;12(13):1243-1255

Pre-Clinical Study: Activation of the GR Pathway Reduced Chemotherapy Activity

In Vitro – Ovarian Cancer Cell Line SKOV3

- The effect of GR pathway activation on paclitaxel activity was evaluated in the ovarian cancer cell line SKOV3
- Cells were cultured in the absence of growth factors for 24 hours and then treated with either dexamethasone (10^{-6} mol/L) or ethanol for 1-hour before treatment with varying concentrations of paclitaxel
- A reduction in apoptosis relative to control was observed with dexamethasone pretreatment in the 10^{-7} and 10^{-6} mol/L paclitaxel concentrations



Melhem A et al. *Clin Cancer Res.* 2009;15(9):3196-204.

Targeting Glucocorticoid Receptor

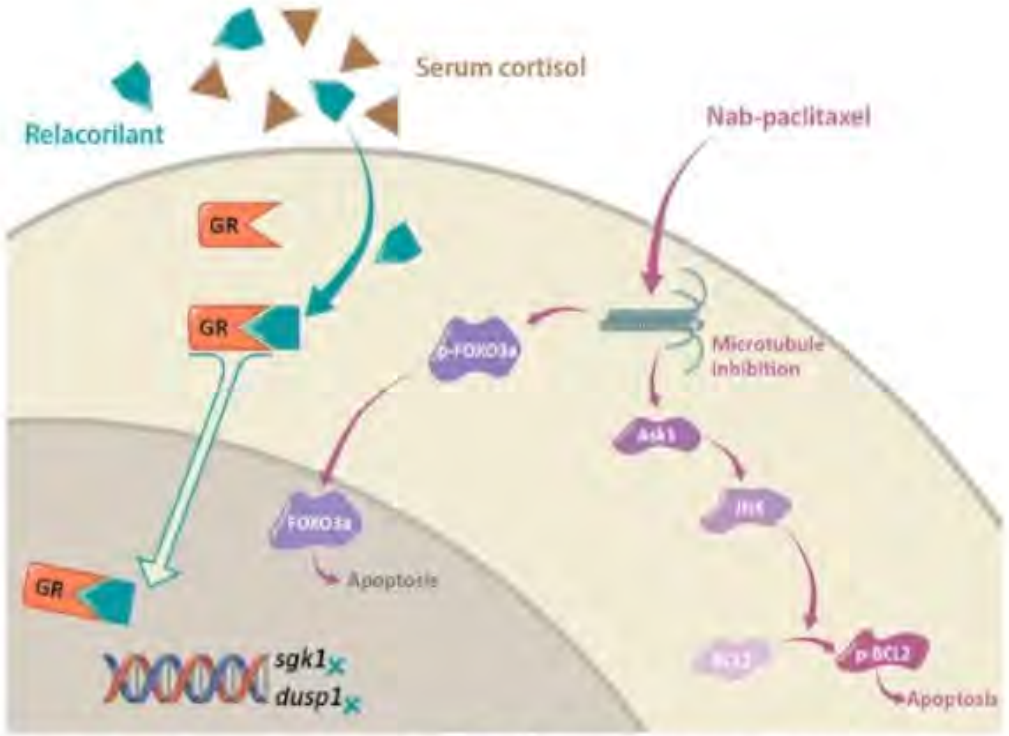
Cortisol levels can suppress immune activation and tumor cell apoptosis by activating GR

GR activation up-regulates pro-survival pathways (SGK1, DUSP1) [1]

GR is abundantly expressed in ovarian tumors, and high GR expression is associated with poor outcomes [2]

GR inhibition/modulation may delay or overcome resistance to ChT and relieve immune suppression

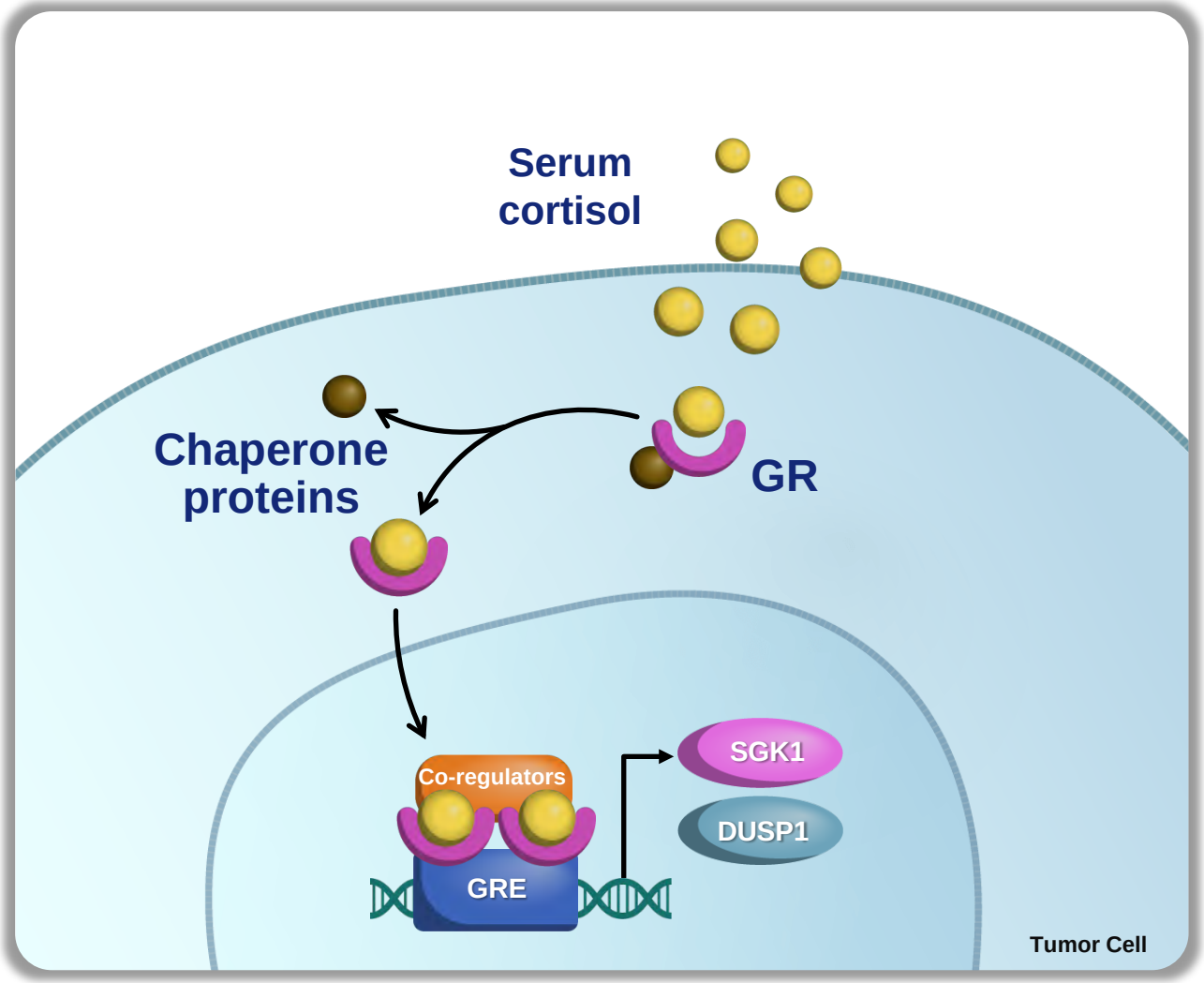
Relacorilant is a high-affinity modulator of the GR.



NCT03776812 phase II study [3] demonstrates improvement in PFS, DOR and OS in RELA+NP group vs NP alone

1. Melhem A et al. *Clin Cancer Res.* 2009;15(9):3196-204. 2. Veneris J et al. *Int J Gynecol Cancer.* 2019;29(2):357-364. Colombo N et al. *J Clin Oncol.* 2022;40(Suppl_17):LBA5503.

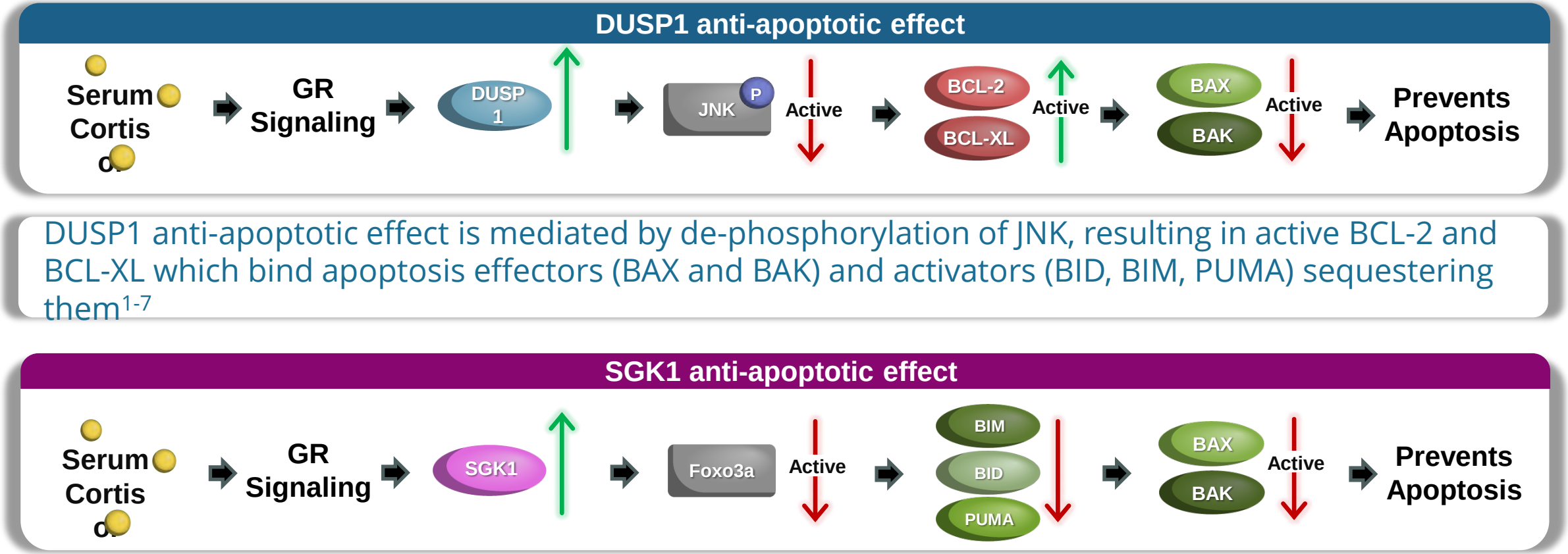
Activation of GR Pathway in Tumor Cell



- The GR is a ligand-activated transcription factor that belongs to the nuclear receptor family[1]
- Endogenous cortisol modulates the GR and affects transcription of target genes[1,2]
- Cortisol binding to the GR leads to the release of chaperone proteins, and translocation of the ligand-receptor complex to the nucleus[1,2]
- In the nucleus, cortisol-bound GR homodimerizes and binds the glucocorticoid response element (GRE) on the DNA[1,2]
- Binding to the GRE on the promoter region of target genes recruits co-regulators that mediate transcriptional activation[1,2]
- Together, these steps promote transcription of several genes including serum/glucocorticoid-inducible kinase 1 (SGK1) and dual-specificity phosphatase 1 (DUSP1)[1,2]

1.Buonaiuto R et al. *Biomolecules.* 2023;13(4):653. 2. Kadmiel M et al. *Trends Pharmacol Sci*..2013;34(9):518-530.

GR Pathway Activation: Mediating Anti-Apoptotic Protein Expression and Apoptosis Inhibition (II)

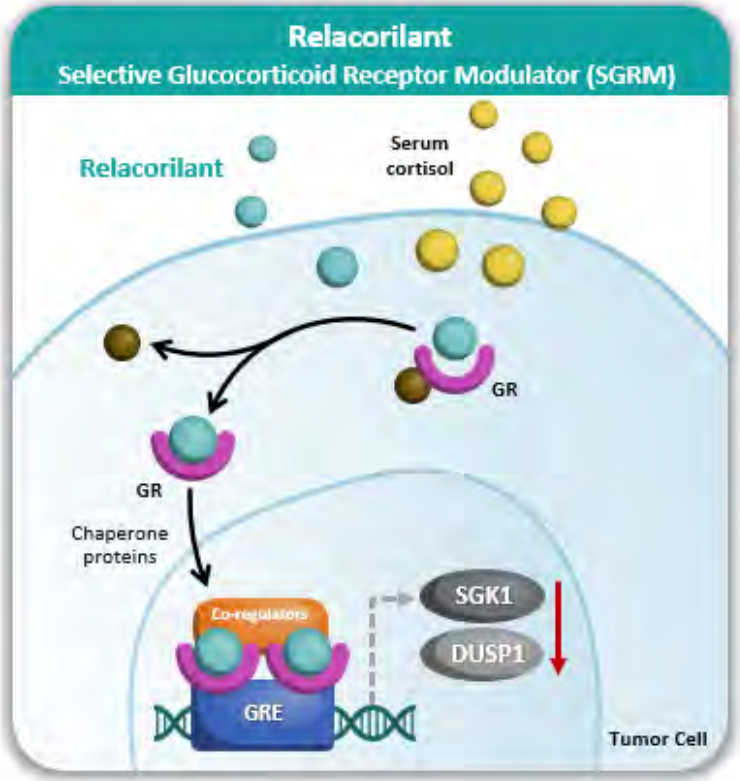


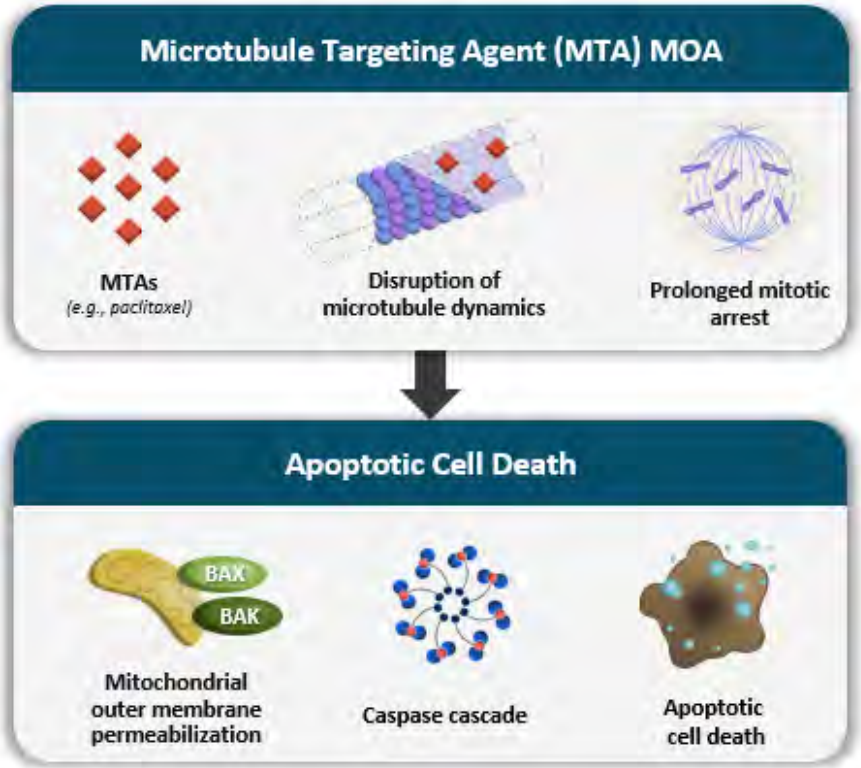
DUSP1 anti-apoptotic effect is mediated by de-phosphorylation of JNK, resulting in active BCL-2 and BCL-XL which bind apoptosis effectors (BAX and BAK) and activators (BID, BIM, PUMA) sequestering them[1-7]

SGK1 anti-apoptotic effect is mediated by phosphorylation of the BID, BIM, and PUMA transcription factor FOXO3a which results in its degradation[1-7]

1. Melhem A et al. *Clin Cancer Res.* 2009;15(9):3196-204
2. Stringer-Reasor EM et al. *Gynecol Oncol.* 2015;138(3):656-62.
3. Buonaiuto R et al. *Biomolecules.* 2023;13(4):653.
4. Liu Y et al. *Mol Cancer.* 2018;17(1):104.
5. Whitaker RH et al. *Cells.* 2019; 8(4): 346.
6. Pedley R et al. *Biol Chem.* 2016;397(7):595-605.
7. Dhanasekaran DN et al. *Oncogene.* 2008;27(48):6245-51.

Relacorilant:
A Selective GR Modulator Suppressing Anti-Apoptotic Proteins





Results from *in vitro* studies and xenograft models suggest that relacorilant may improve tumor sensitivity to chemotherapy[1]

- Relacorilant is a selective glucocorticoid receptor modulator (SGRM) that competitively binds to the glucocorticoid receptor at nanomolar concentrations (Ki=0.15 nM)[2]
- In pre-clinical studies relacorilant suppressed the expression of genes that encode for antiapoptotic proteins[4]

Relacorilant is an investigational product that has not been approved for any use in any country; its safety and efficacy have not been

1. Greenstein AE and Hunt HJ. *Oncotarget.* 2021;12(13):1243-1255.
2. Greenstein AE and Hunt HJ. *Int Immunopharmacol.* 2023:120:110312.
3. Melhem A et al. *Clin Cancer Res.* 2009;15(9):3196-204.
4. Stringer-Reasor EM et al. *Gynecol Oncol.* 2015;138(3):656-62.
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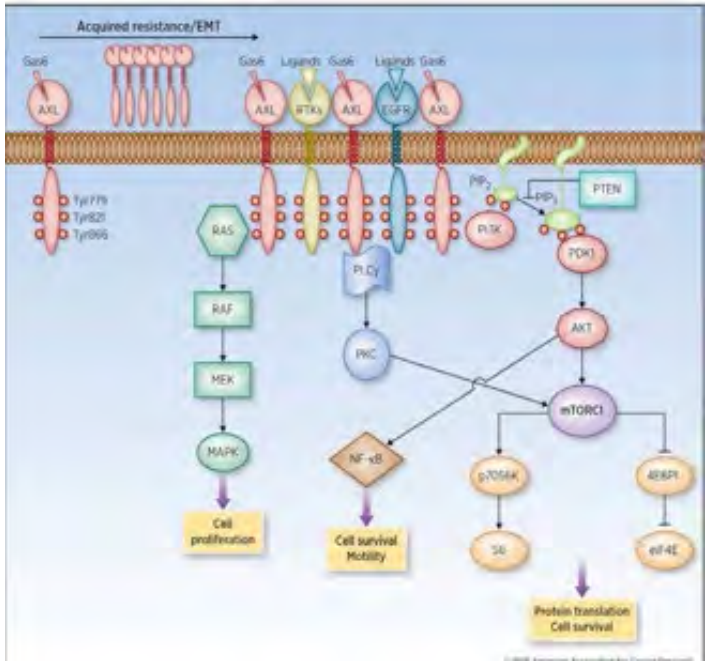
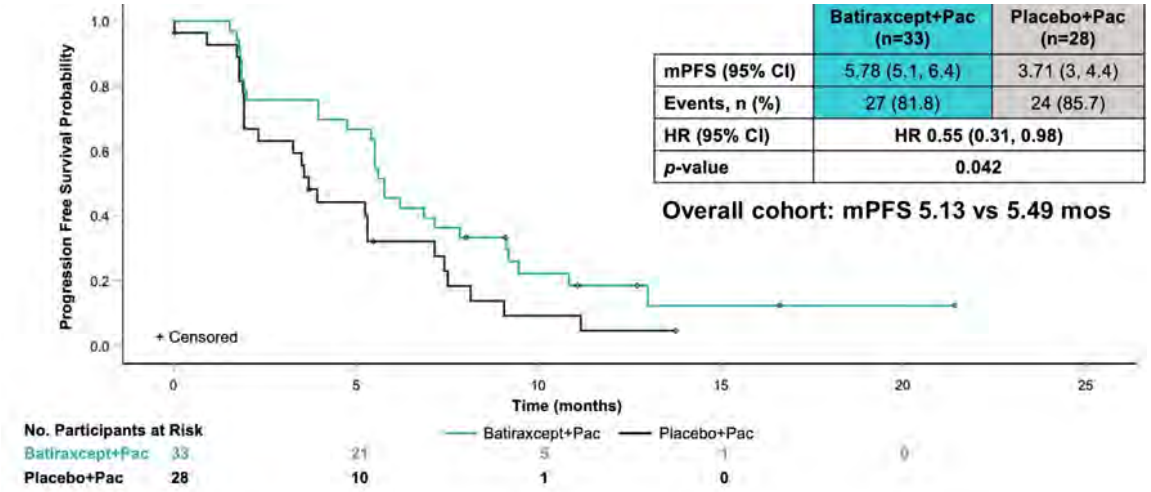
The Butterfly: Helping our patients stay aloft

Batiraxcept AXL high exp subgp

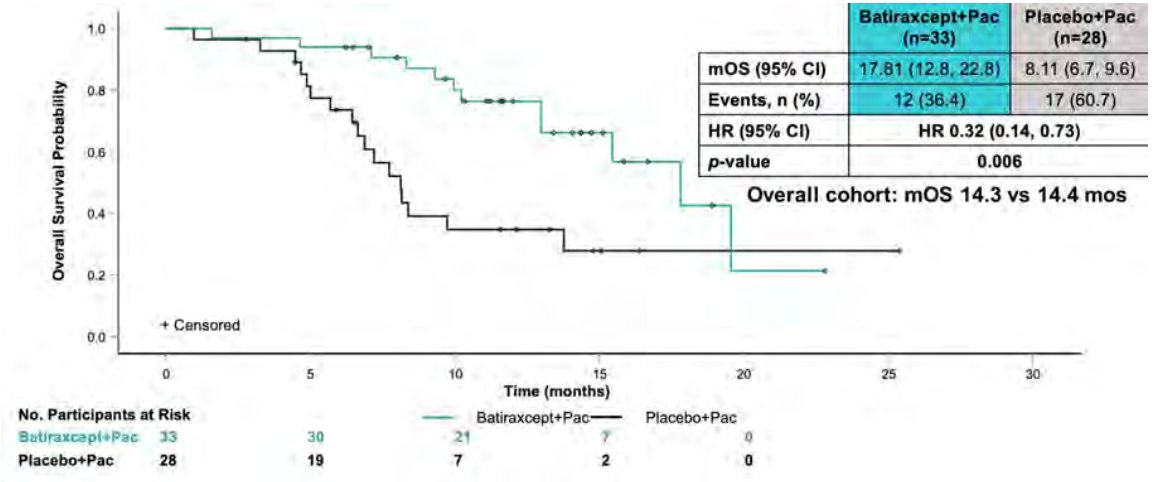


AXL is highly expressed in EOC, especially those that are treatment resistant. The ligand is GAS6 and activation leads to EMT, stemness and poor outcomes



	Batiraxcept+Pac (n=33)	Placebo+Pac (n=28)
mPFS (95% CI)	5.78 (5.1, 6.4)	3.71 (3, 4.4)
Events, n (%)	27 (81.8)	24 (85.7)
HR (95% CI)	HR 0.55 (0.31, 0.98)	
p-value	0.042	

Overall cohort: mPFS 5.13 vs 5.49 mos



	Batiraxcept+Pac (n=33)	Placebo+Pac (n=28)
mOS (95% CI)	17.81 (12.8, 22.8)	8.11 (6.7, 9.6)
Events, n (%)	12 (36.4)	17 (60.7)
HR (95% CI)	HR 0.32 (0.14, 0.73)	
p-value	0.006	

Overall cohort: mOS 14.3 vs 14.4 mos

Fuh et al. ASCO 2024

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- Not all the HRD are platinum and parp sensitive

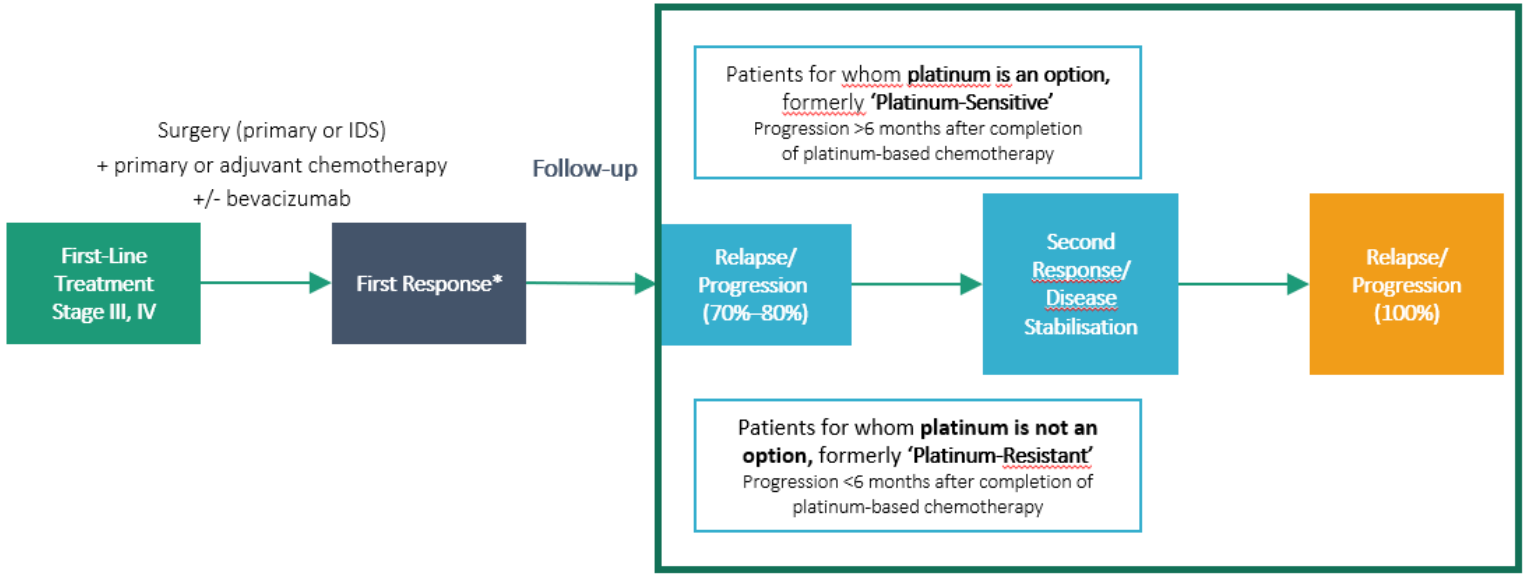


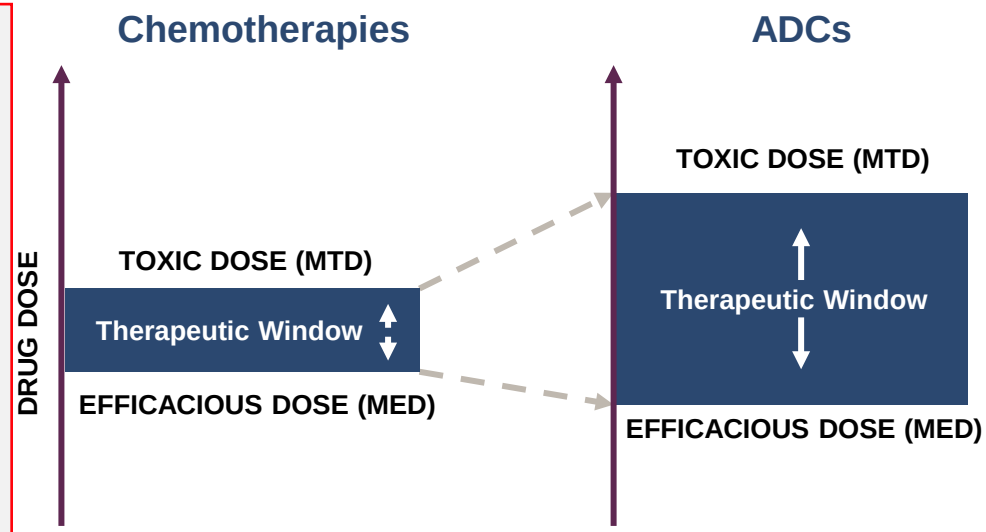
Figure from Suski JM et al. Cancer Cell 2021

ADCs are engineered to limit systemic toxicity and improve the therapeutic index of cytotoxic agents

ADCs are a class of targeted therapies that are designed to selectively deliver cytotoxic drugs to cancer cells

Systemic chemotherapies

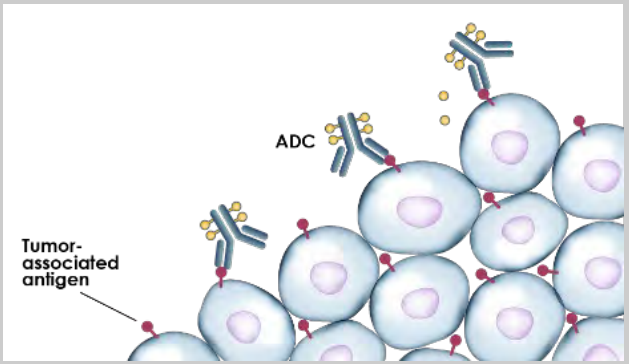
- Cytotoxic agents that target rapidly dividing cancerous and healthy cells
- Severe side effects limit administrable dose
- **Narrow therapeutic window** resulting from a small therapeutic index



$$\text{THERAPEUTIC INDEX} = \frac{\text{MTD}}{\text{MED}}$$

ADC, antibody-drug conjugate; MED, minimum effective dose; MTD, maximum tolerated dose.

ADCs

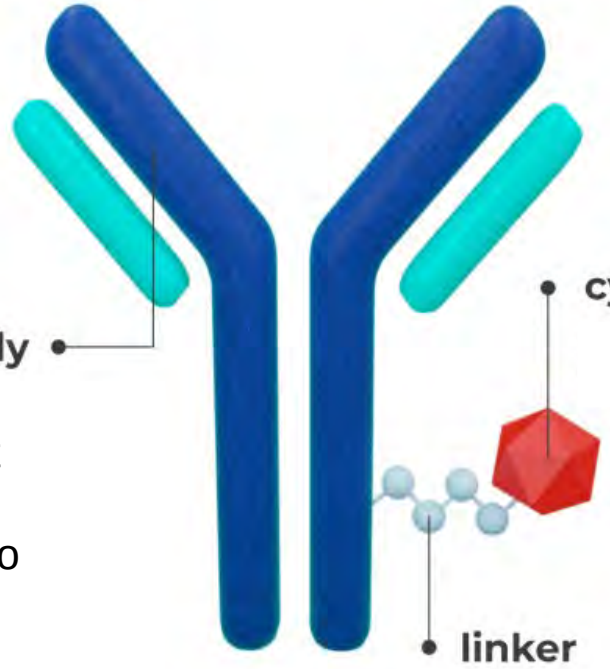


- Designed to reduce off-target toxicities of potent cytotoxic payloads
- Broader therapeutic window by limiting exposure of healthy tissue to cytotoxic drugs

Criscitiello C et al. *J Hematol Oncol*. 2021;14(1):20.
Panowski S et al. *MAbs*. 2014;6(1):34–45.

Structure of ADCs

ADCs contains 3 main components:



monoclonal antibody

Binds specifically to a target antigen (eg. a cell receptor) that is uniquely expressed on the surface of cancer cells relative to normal tissue

cytotoxic payload

A cytotoxic agent; approved ADC payloads target microtubules or DNA in tumor cells to inhibit cell division

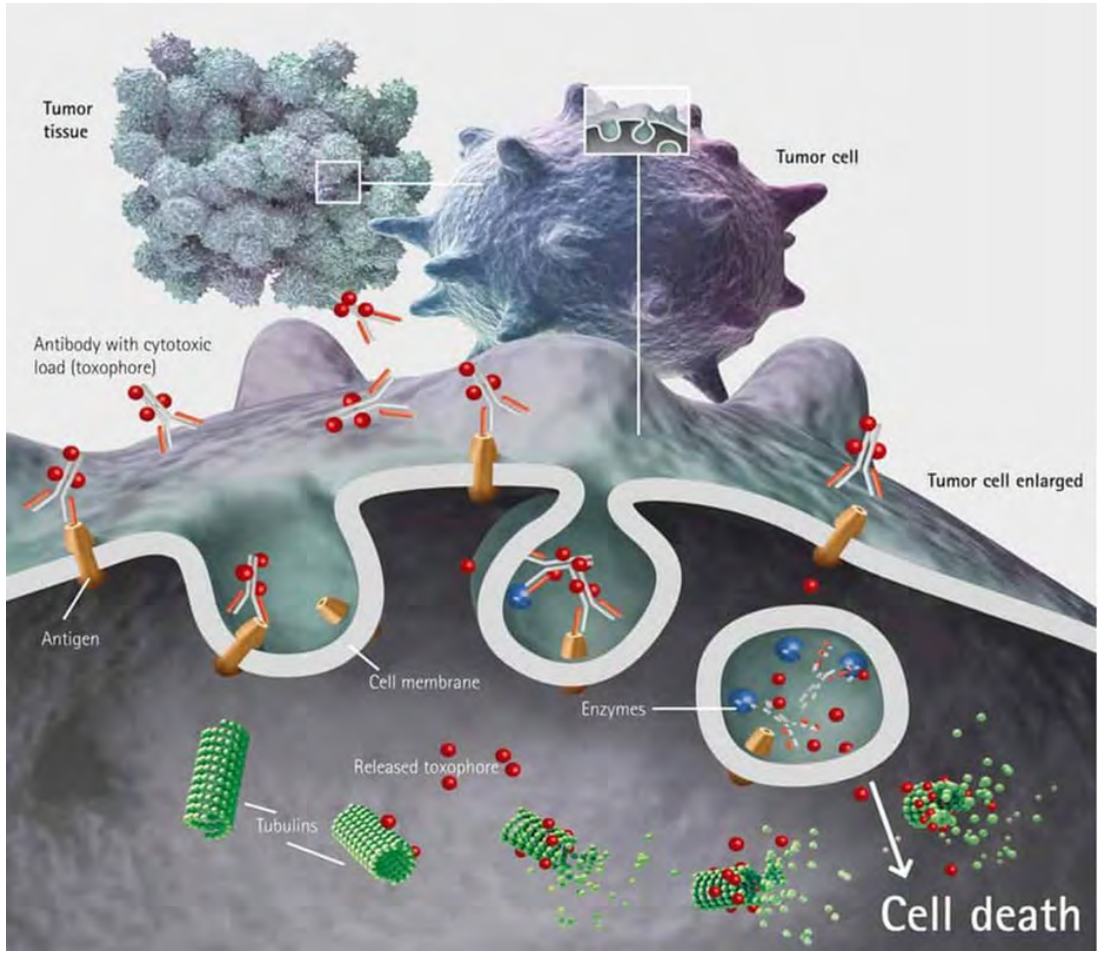
linker

Connects the monoclonal antibody to the cytotoxic payload
Some linkers allow payload permeation through the target cell's membrane, thereby allowing «bystander killing» of neighboring cancer cells (including those without expression of the target antigen)

Calo CA et al. *Expert Opin Biol Ther.* 2021;21(7):875-887
Peters C et al. *Biosci Rep*. 2015;35(4):e00225.
Fu Z et al. *Signal Transduct Target Ther.* 2022;7(1):93.
Moore KN et al. *Future Oncol.* 2018;14(17):1669-1678

Mechanism of Action

- The ADC localizes to tumor and binds to target antigen
- The ADC is internalized
- The internalized vesicles fuse with other vesicles and enter the endosome-lysosome pathway
- Proteases digest the antibody to release the toxins which induce apoptosis



https://www.adcreview.com/the-review/antibody-drug-conjugate-development/ last access Feb2024

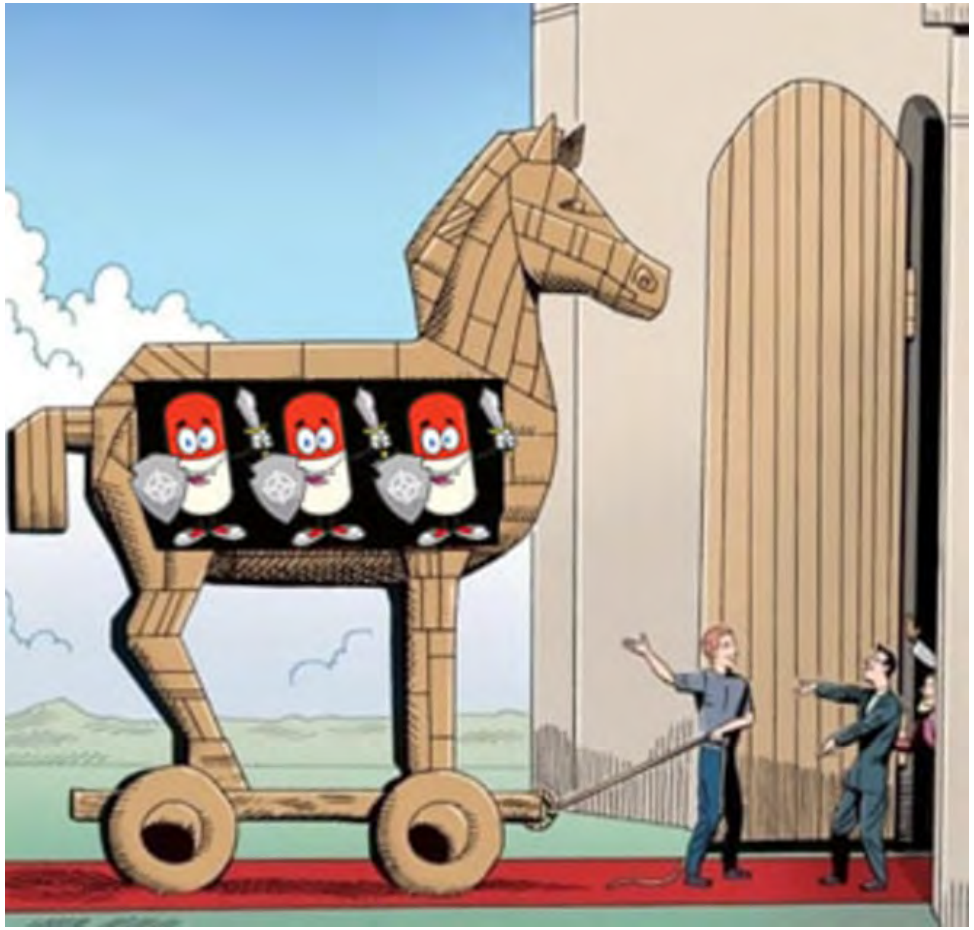
Targets

Antibody targets should have high expression levels on tumor and not on normal tissue

Antibody targets should be present on the cell surface so the ADC can find them

Antibody targets should be internalizing so that the ADC is transported into the cell

Like a Trojan Horse



The linker is designed to ensure that the ADC is highly stable in circulation, yet efficiently releases the payload in the tumor

Cleavable linker

- Uses the inherent properties of tumor cells to selectively release cytotoxic payload (protease- sensitive, pH-sensitive, glutathione-sensitive)
- Potential for premature payload release (pH-sensitive linkers)
- Examples: gemtuzumab ozogamicin, brentuximab vedotin

Noncleavable linker

- No obvious drug release mechanism, relies on the complete lysosomal proteolytic degradation of the antibody
- More stable in circulation
- Limited diffusion to neighboring cancer (or healthy) cells
- Example: trastuzumab emtansine

Linker must be stable in serum and extracellular environment, and cleavable once in the tumor cells.

Stable linkers in ADCs maintain antibody concentration in circulation, preventing premature cytotoxic drug release and reducing off-target effects

Drago JZ et al. *Nat Rev Clin Oncol*. 2021;18(6):327–344.
Lu J et al. *Int J Mol Sci*. 2016;17(4):561.
Sau S et al. *Drug Discov Today*. 2017; 22(10):1547–1556.

Payload is the effector component of the ADC

Two classes of antitumor drugs are commonly used as payloads in ADCs:

Considerations	Targets rapidly proliferating cells	Potent agents that may target DNA independent of cell cycle
Classes	• Auristatins (eg, MMAE, MMAF) • Eribulin • Hemiasterlin • Maytansinoids (eg, DM1, DM4) • Tubulysin	• Calicheamicin • Duocarmycin • Pyrrolobenzodiazepine • Topoisomerase inhibitor
Examples	• Mirvetuximab soravtansine • Tisotumab vedotin	• Sacituzumab govitecan • Trastuzumab deruxtecan

ADC, antibody-drug conjugate; DM1, maytansine 1; DM4, maytansine 4; DNA, deoxyribonucleic acid; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F

Fu Z et al. *Signal Transduct Target Ther*. 2022;7(1):93.
Tang H et al. *Front Pharmacol*. 2019;10:373.
Chen H et al. *Molecules*. 2017;22(8):1281.
Yurkovetskiy AV et al. *Mol Cancer Ther*. 2021;20(5):885–895.
Donaghy H et al. *MAbs*. 2016;8(4):659–671.
Cheng X et al. *Mol Cancer Ther*. 2018;17(2):2665–2675.
Staudacher AH et al. *Br J Cancer*. 2017;117(12):1736–1742.

The Bystander Killing Effect With ADCs

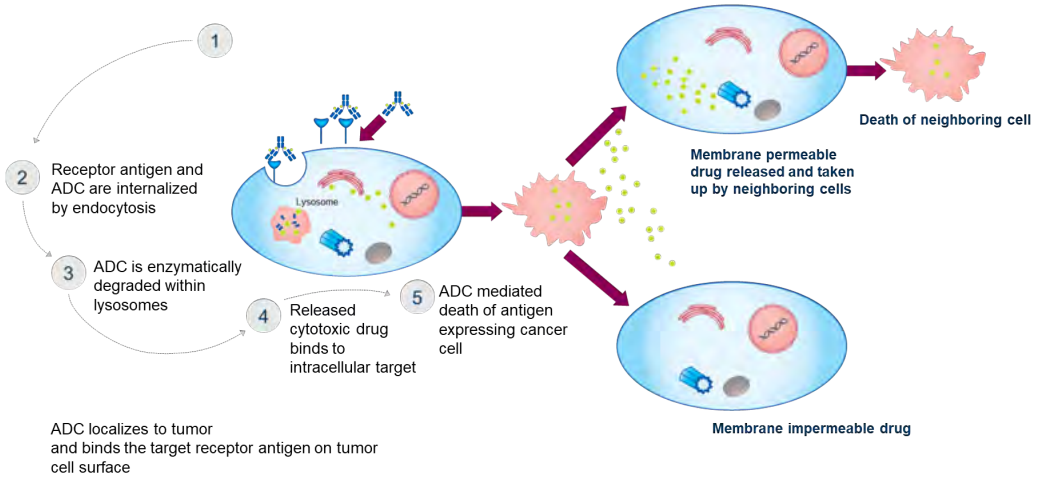
Target antigen expression of an ADC may not be uniform in all tumor cells, which can prevent full penetration of ADCs into solid tumors

Bystander effect is an important characteristic, especially in tumors with heterogeneous antigen expression

1. Membrane-permeable payloads diffuse from target cell into neighboring cells, leading to cell death
2. Under amenable extracellular conditions, payload may be released into the extracellular space

ADCs with disulfide linkers and maytansinoid (a microtubule-targeting cytotoxic agent) payloads have been associated with bystander killing

Bystander effect can be an advantage in heterogeneous tumors if the neighbor cell is a tumor cell; however, if payloads diffuse into healthy tissue or bloodstream, this can lead to off-target toxicity



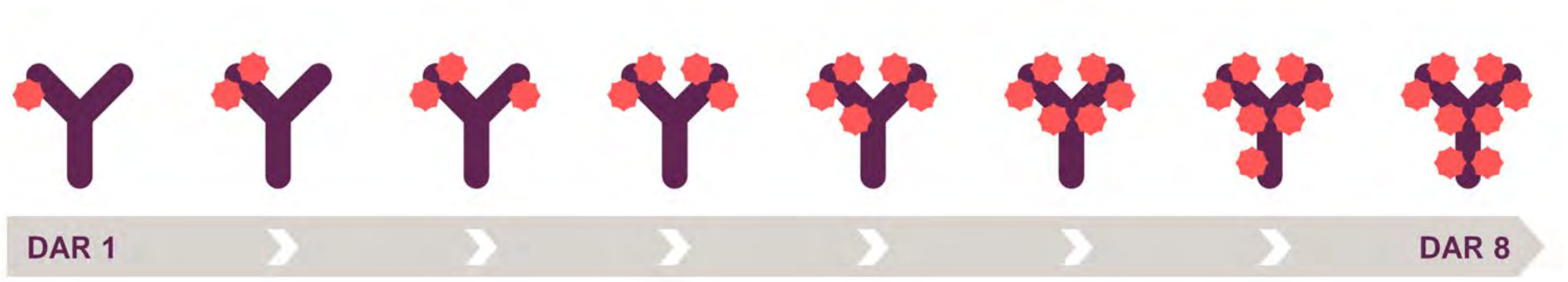
Ab O et al. *Mol Cancer Ther.* 2015;14(7):1605-1613
Kovtun YV et al. *Cancer Res.* 2006;66(6):3214-3221
Trail et al., Pharmacology & Therapeutics 2018

Drug-to-Antibody Ratio: an important property of ADCs

The drug-to-antibody ratio (DAR) is the average number of drug molecules conjugated to a single ADC

DAR is important in determining ADC efficacy and safety

- Low drug loading can decrease potency
- High drug loaduing can influence toxicity and pharmacokinetics



Drug-to-Antibody Ratio

Pettinato MC et al. *Antibodies (Basel).* 2021;10(4):42.3

Lu D et al. *Pharm Res.*2015;32(6):1907-1919

Reis A et al.Robust methods for the detailed analysis of drug-to-antibody ratio (DAR) and drug load distribution. ProteoBlog by ProteoGenix. January 10,22 www.proteogenix.science/scientific-corner/adc/dar-drug-load-distribution/ Accessed February 2024

Antigens exploited for ADC development in OC1

Reported expression in OC	60–100%	70%	5–60%	55–100%	80–90%	95%	25–100%	70–90%

Some ADCs may only demonstrate efficacy in higher expression levels of the target antigen.[2,3]

Domenica Lorusso, MD, PhD

1. Chelariu-Raicu A, et al. Int J Gynecol Cancer. 2023 2. Moore KN, et al. European Society for Medical Oncology (ESMO) Annual Meeting. 2019; Presentation 992O. 3. Meric-Bernstam F, et al. J Clin Oncol. 2024.

More than 40 ADCs in clinical development for OC

Target	Drug	Payload	Mechanism of Action	Linker	DAR
FRα	Mirvetuximab Soravtansine (IMGN853)	DM4	Inhibition of tubulin polymerization	Cleavable	3.5
	Luveltamab Tazevibulin (STRO-002)	SC239 (Hemiasterlin)	Inhibition of tubulin polymerization	Valine-citruline (cleavable)	4
	Farletuzumab Ecteribulin (MORAb-202)	Eribulin mesylate	Inhibition of microtubules	Valine-citruline (cleavable)	4
	Rinatabart sesutecan (PRO1184)	Exatecan	Inhibition of topoisomerase I	cleavable hydrophilic	8
HER2	Trastuzumab Deruxtecan (DS-8201a)	Deruxtecan	Inhibition of topoisomerase I	Peptide-based (enzime cleavable)	8
	Trastuzumab Duocarmazine (SYD985)	Duocarmycin	DNA alkylation	Mb-Val-Cit-PABC	2.7
	DB-1303/BNT323	P1003	Inhibition of topoisomerase I	cleavable maleimide tetrapeptide-based	8
TROP2	Sacituzumab Tirumotecn (MK-2870)	Proprietary belotecan derivative	Inhibition of topoisomerase I	sulfonyl pyrimidine-CL2A-carbonate	7.4
	Sacituzumab Govitecan (IMMU-132)	SN-38 (irinotecan metabolite)	Inhibition of topoisomerase I	Acid cleavable	7.5
	Datopotomab Deruxtecan (Dato-Dxd)	Deruxtecan	Inhibition of topoisomerase I	Cleavable tetrapeptide-based linker	~4
CDH6	Raludotatug Deruxtecan (R-DXd; DS-6000)	Deruxtecan	Inhibition of topoisomerase I	tetrapeptide-based cleavable	8
B7H4	AZD8205	MMAE (monomethyl auristatin E)	Inhibition of topoisomerase I	Val-ala peptide linker with a PEG8 spacer	8
	SGN-B7H4V	MMAE	Multimodal	Protease-cleavable mc-vc linker	4
	XMT-1660	AF-HPA/AF	Inhibition of tubulin polymerization	Polymer scaffold (cleavable)	6
CLDN6	TORL-1-23	MMAE	Inhibition of tubulin polymerization	cathepsin hydrolysable dipeptide VC	4
NaPi2b	Upifitamab Rilsodotin (XMT-1536)	Auristatin derivative	Inhibition of tubulin polymerization	Polymer scaffold conjugated (cleavable ester)	~10
Mesothelin	Anetumab ravtansine (BAY94-9343)	DM4	Inhibition of microtubule polymerization	reducible SPDB linker	3
	RC-88	MMAE	Inhibition of tubulin polymerization	thiol bridging PY-MAA-VC-PAB	4
Tissue Factor	XB002	Auristatin	Inhibition of tubulin polymerization	Protease cleavable valine-citrulline (vc) linker	3
MUC16	DMUC4064A	Monomethyl auristatin E	Inhibition of tubulin polymerization	protease-cleavable linker	2

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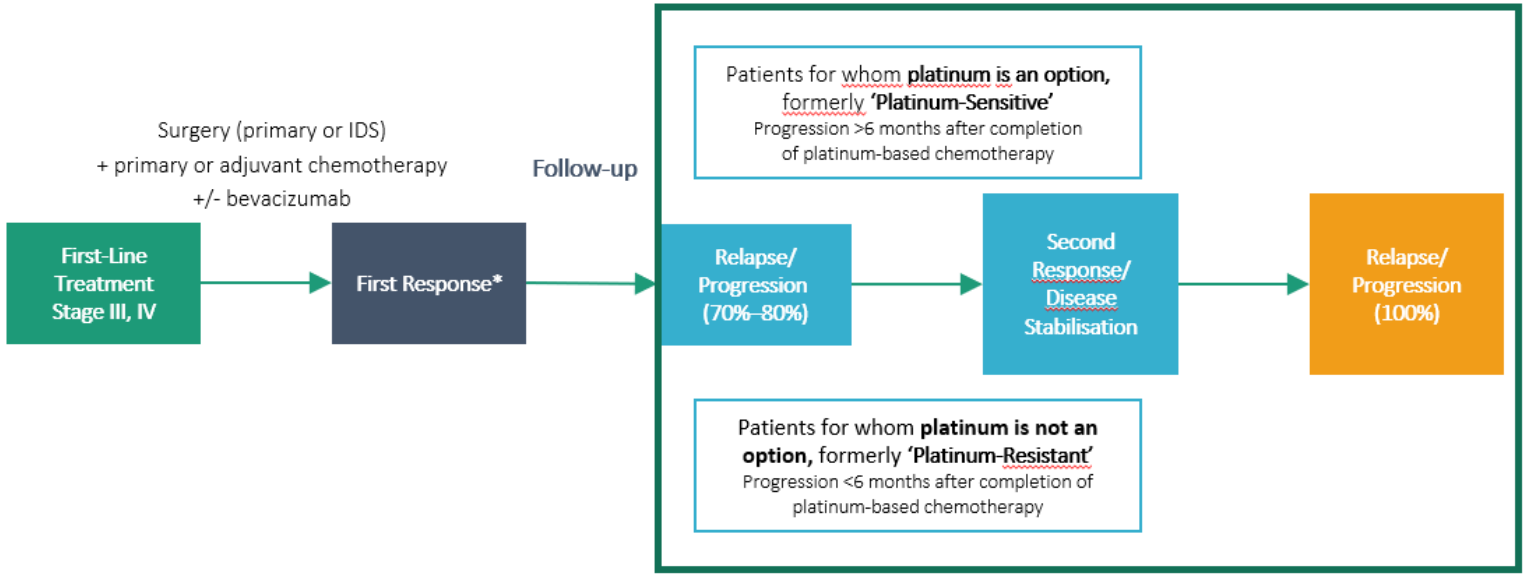


Figure from Suski JM et al. Cancer Cell 2021

EPIK-O

PI3K Alpelisib Plus Olaparib in Platinum-Resistant, High-grade Serous OC

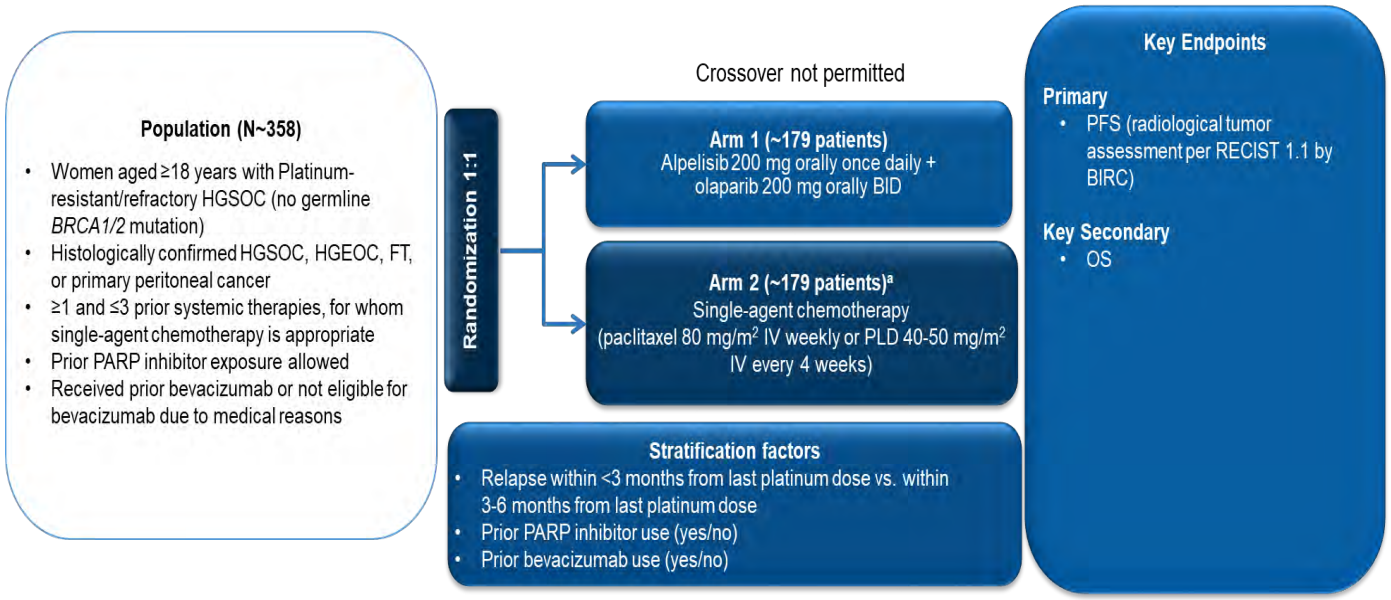


Table. Primary and Key Secondary End Points

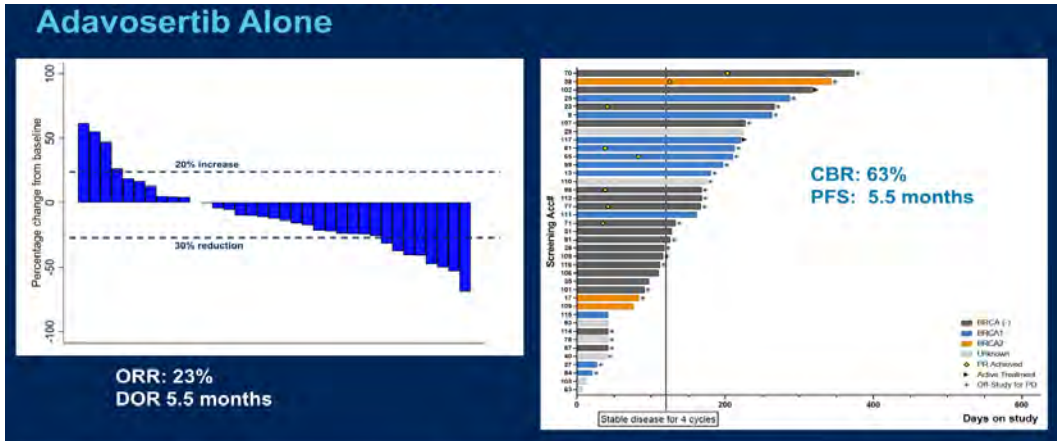
	ALP + OLA N=180	**TPC** N=178
PFS, BICR		
Events, n (%)	134 (74.4)	110 (61.8)
Median (95% CI), months	3.6 (3.4-4.3)	3.9 (3.7-5.4)
HR (95% CI)	1.14 (0.88-1.48)	
ORR, BICR		
Response rate (95% CI), %	15.6 (10.6-21.7)	13.5 (8.8-19.4)
DOR, BICR		
Median (95% CI), months	7.4 (5.0-12.9)	5.6 (3.8-NE)
OS		
Events, n (%)	75 (41.7)	63 (35.4)
Median (95% CI), months	10.0 (7.5-NE)	10.6 (9.9-14.4)
HR (95% CI)	1.22 (0.87-1.71)	

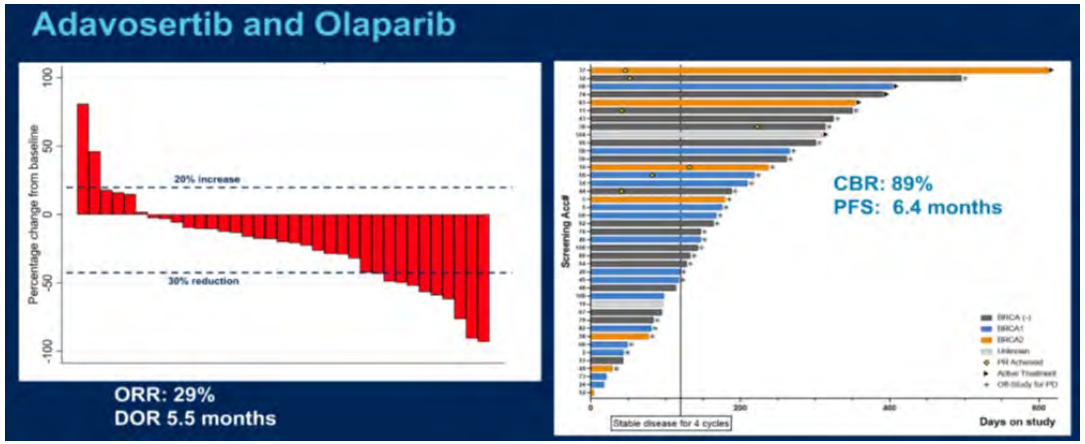
EPIK-O did not meet its primary efficacy objective of improvement in PFS with alpelisib + olaparib versus TPC among patients with platinum-resistant/refractory HGSOC with no BRCA mutation

Kostantinopoulos PA et al. Presented at SGO 2024

EFFORT

Randomized 2-arm non-comparative phase II study of WEE1 inhibitor adavosertib with or without olaparib in women with PARP-resistant OC





Endpoint	A arm n=35	A/O arm n=35
ORR (90% CI)	23% (12–38)	29% (16–44)
Duration of response, months (95% CI)	5.5 (2.8–NE)	6.4 (2.8–14.6)
CBR (90% CI)	63% (48–76)	89% (76–96)
Median PFS, months (90%CI)	5.5 (3.9–6.9)	6.8 (4.3–8.3)

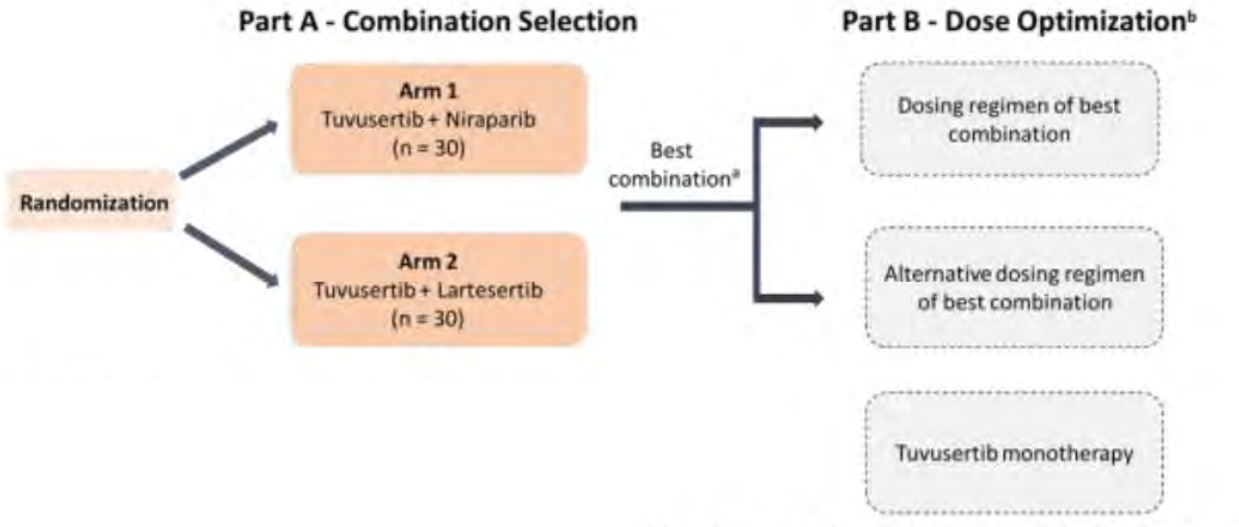
Westin S et al. presented at ASCO 2021

DDriver

DNA DAMAGE RESPONSE SIGNALLING PATHWAY ORCHESTARTED BY ATM AND ATR KINASES MAY PLAY A ROLE IN PARPIS RESISTANCE **PREMATURELY CLOSED FOR FUTILITY**

Phase 2 study of the ATR inhibitor tuvusertib in combination with the PARP inhibitor niraparib or the ATM inhibitor lartesertib in HRD-positive epithelial ovarian cancer that progressed on prior PARP inhibitor therapy

Study population:
Patients with epithelial ovarian cancer that has progressed on prior PARPi therapy*
- Stratified by BRCA1/2 status vs BRCA wildtype



Endpoints:
- Primary: OR
- Secondary: AEs, DoR, PFS

*Clinically benefited from PARPi maintenance prior to documented progression, as defined by at least 6 months of treatment duration with no progressive disease observed

NCT06433219

Targeting *CCNE1*

CCNE1 amplification is associated with PARPis and platinum resistance

INCB123667, a potent and selective CDK2 inhibitor

- Approximately 50% of ovarian cancers overexpress cyclin E1

Variable	50 mg bid (n=16)	100 mg qd (n=14)	125 mg qd (n=15)
Overall response rate, n (%) [95% CI]	5 (31.3) [11.0, 58.7]	5 (35.7) [12.8, 64.9]	2 (13.3) [1.7, 40.5]
Complete response	2 (12.5)	0 (0)	2 (13.3)
Partial response	3 (18.8)	5 (35.7)	0 (0)
Stable disease	7 (43.8)	5 (35.7)	6 (40.0)
Progressive disease	4 (25.0)	4 (28.6)	4 (26.7)
Not evaluable/missing, n (%)	0 (0)	0 (0)	3 (20.0)
Disease control rate, n (%) [95% CI]	12 (75.0) [47.6, 92.7]	10 (71.4) [41.9, 91.6]	8 (53.3) [26.6, 78.7]
Duration of response, median (95% CI), months	4.5 (1.7, NE)	3.6 (1.9, NE)	-
Progression-free survival, median (95% CI), months	5.5 (2.0, 7.3)	4.5 (2.0, 6.2)	5.4 (1.8, 9.0)

Baseline Characteristic	Total (N=90)
Age, median (range), years	62.0 (37.0-80.0)
≥65 years, n (%)	31 (34.4)
Race, n (%)	
White	64 (71.1)
Asian	8 (8.9)
Not reported/unknown/missing	18 (20.0)
ECOG PS, n (%)	
0	68 (75.6)
Histology, n (%)	
Serous	72 (80.0)
Clear cell	5 (5.6)
Endometrioid	1 (1.1)
Other*	12 (13.3)
Cyclin E1 overexpression,† n (%)	83 (92.2)
CCNE1 amplification,† n (%)	51 (56.7)
Prior systemic therapies, median (range)	4 (1-12)
Prior PARPi, n (%)	62 (68.9)
Prior bevacizumab, n (%)	69 (76.7)

Lorusso D et al. ASCO 2025

The Chrysalis: Going back to biology to elevate outcomes

What's going on in there?

1. Enhanced understanding of mechanisms of resistance, additivity and development of novel agents (ex: relacorilant, batiraxcept)
2. Elucidation of cell surface and intracellular targets and better delivery of potent anti-cancer agents: ADCs/Bispecifics/Novel conjugates
3. Increased understanding of cell cycle machinery in cancer and next-generation target development, Ex: CDK2, ATRi/PARPi
4. **Re-evaluation of the biology behind and the definitions of recurrence.**

- PSOC and PROC no longer serve us,

- Not all the HRD are platinum and parp sensitive

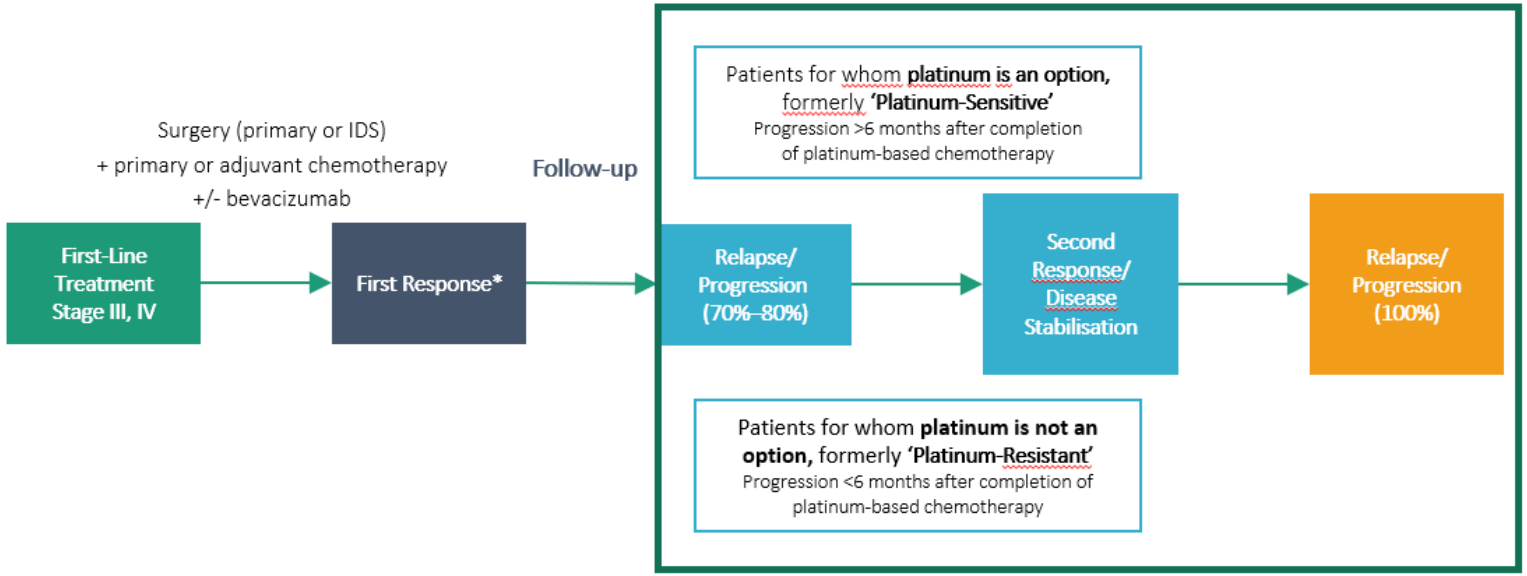


Figure from Suski JM et al. Cancer Cell 2021

Progression during 1L maintenance PARPi

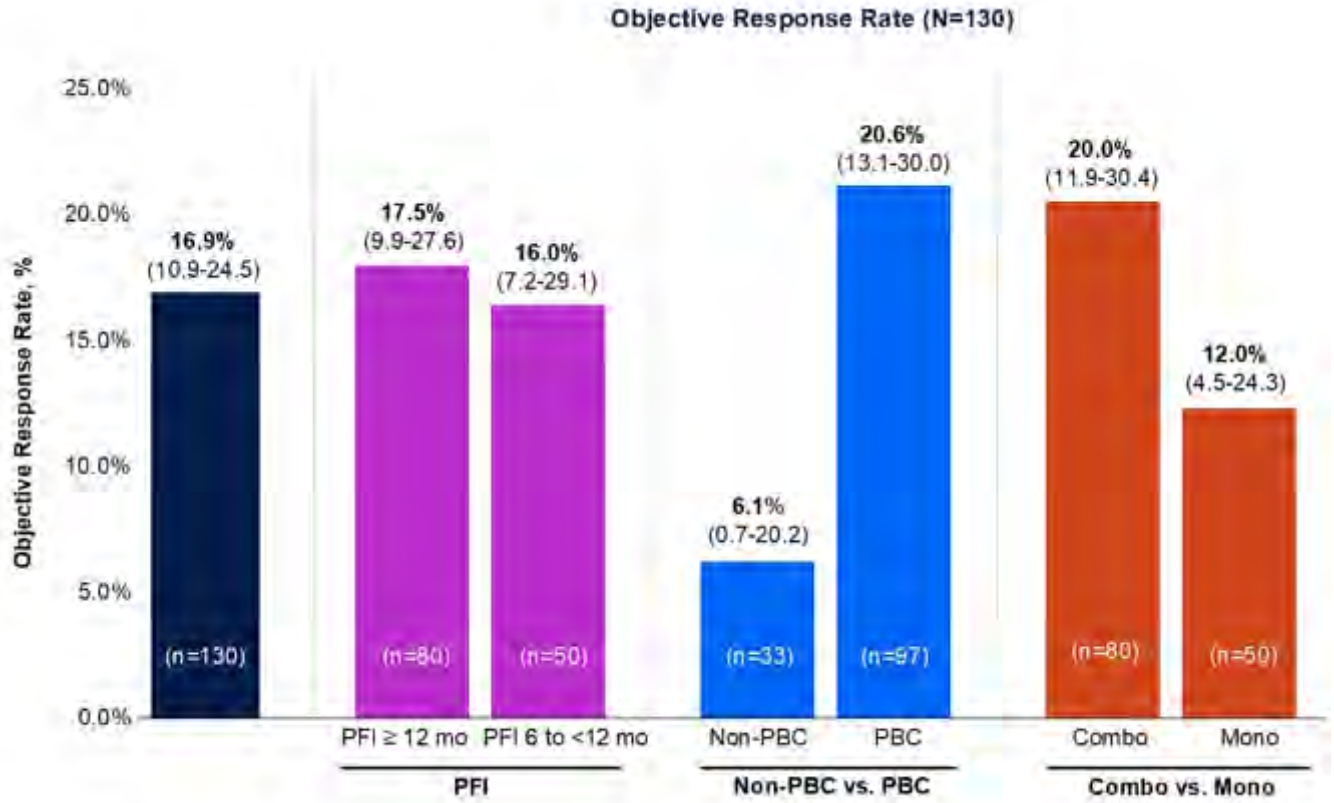
- Approvals for PARPi as 1L maintenance for high-grade ovarian cancer have transformed care
- Increasing 1L PARPi has also led to **increasing numbers of patients with platinum sensitive recurrence who have progressed on maintenance PARPi**
- Traditional definition of platinum sensitivity may be less relevant in patients with progression on 1L PARPi :
  - Shorter benefit of 2L therapy in patients who progressed on PARPi in SOLO2 and PAOLA-1
  - May be due to shared mechanisms of resistance to platinum and PARPi

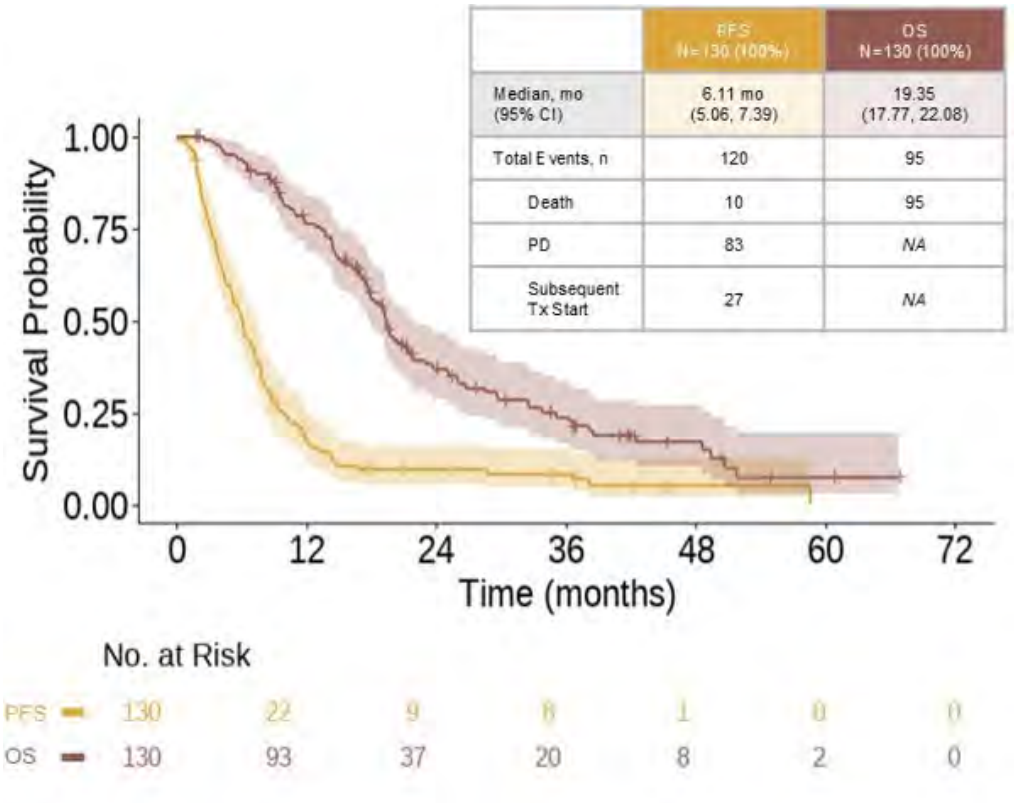
Trial	Approximate % of patients progressing on 1L PARP inhibitor maintenance*
SOLO1 (all *BRCA*m)	**27%**
PRIMA	**71%**
*BRCA*m	53%
*BRCA*wt, HRD test +	62%
HRD test -	85%
PAOLA-1	**55%**
t*BRCA*m	24%
t*BRCA*wt, HRD test +	48%
t*BRCA*wt, HRD test -	77%
ATHENA-MONO	**55%**
*BRCA*m	32%
*BRCA*wt, LOH high	55%
*BRCA*wt, LOH low	65%

*Estimated from Kaplan-Meier curves where proportions not directly reported

Slide courtesy of Drs. Rebecca Porter and Joyce Liu

If progression on PARPi is the new “high risk” marker for poor anticipated response to platinum, what do we know about expectations for platinum in this setting?





	PFS N=130 (100%)	OS N=130 (100%)
Median, mo (95% CI)	6.11 mo (5.06, 7.39)	19.35 (17.77, 22.08)
Total Events, n	120	95
Death	10	95
PD	83	*NA*
Subsequent Tx Start	27	*NA*

ORR is 20% at highest and mPFI is around 6-7 months

Coleman et al. ASCO 2025

@DrKatyMoore

Evaluating Efficacy Within PSOC

Used as treatment or maintenance?
Selection for biomarker?
We should know prior ADC (both target and payload)

ADCs context

	Sac TMT N=5 (PSOC)	Datopotomab deruxtecan N=9 PSOC	PICCOLO N=79	Raludotatug (PS) N=18
Payload	Topo I: belotecan	Topo I: deruxtecan	DM4	Topo I: deruxtecan
DAR	7.4	4	4	8
Reference	Wang ESMO 2024	Oaknin ESMO 2024	Secord ESMO Gyn	Moore ESMO Gyn
ORR (%)	60	66.7	51.9	72.2
DOR	ND	ND	8.25 (5.55-10.78)	5.7 (95% CI, 4.2–NE
mPFS	ND	ND	6.93 (5.85-9.59)	8.1 (4.1–NE)
Target	TROP2	TROP2	FR	CDH6

Courtesy of Ignacio Romero

Evaluating Efficacy Within PSOC

Factors affecting efficacy

First PSOC relapse

Heavily pretreated

PARP resistant

PSOC data

Study / Trial	Author	Population (N)	Treatment Arms	ORR, n (%)	Median DoR (months)	Median PFS (months)	Median OS (months)	Median Follow-up (months)	Prior PD on PARPi (%)
OCEANS	Aghajanian	484	Bevacizumab + Gemcitabine/Carboplatin (Bev+GC)	78.5	10.3	12.4	32.9/33.6	24	Not reported
GOG-213	Coleman	674	Carboplatin/Paclitaxel ± Bevacizumab	~60	Not reported	12.0	33.6	~36	Not reported
AGO OVAR 2.21	du Bois	682 (345 experimental / 337 standard)	Experimental: Carboplatin + PLD + Bev Standard: Carboplatin + Gemcitabine + Bev	Not reported	Not reported	Experimental: 13.3 (95% CI, 11.7–14.2) Standard: 11.6 (95% CI, 11.0–12.7)	31.9/27.8	Experimental: 12.4 (IQR 8.3–21.7) Standard: 11.3 (IQR 8.0–18.4)	Not reported
PICCOLO	Alvarez-Secord	79	Mirvetuximab ravtansie	51.9	8.25	6.93	27.17	24 mo	59/79
Raludotatug	Moore	18	Raludotatug deruxtecan	72.2	5.7	8.1	NA	Not reported	12 cases
Medidata® Pooled Analysis	Coleman	130	N/A	16.9 (95% CI, 10.9–24.5)	Not reported	6.11 (95% CI, 5.06–7.39)	19.35 (95% CI, 17.77–22.08)	Not reported	96.9%

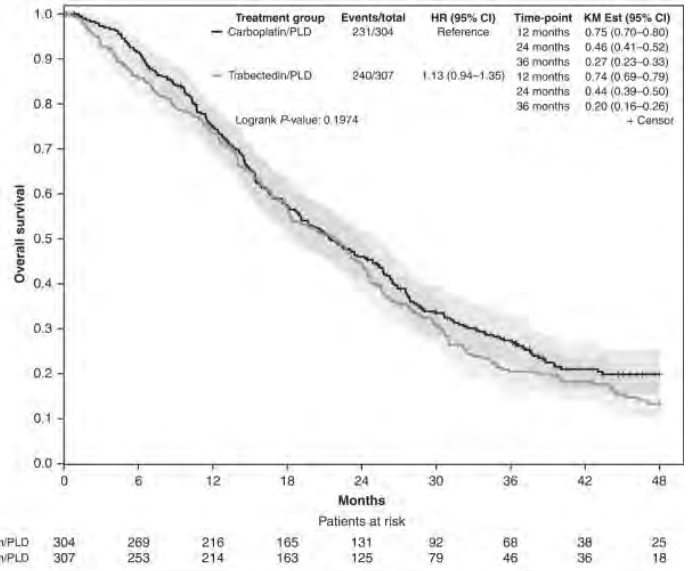
Courtesy of Ignacio Romero

Aghajanian C, et al. Bevacizumab and Paclitaxel-Carboplatin chemotherapy in platinum-sensitive recurrent ovarian cancer: the OCEANS trial. *J Clin Oncol*. 2012;30(17):2039-2045. Coleman RL, et al. Bevacizumab and Paclitaxel-Carboplatin Chemotherapy for Platinum-Sensitive Recurrent Ovarian Cancer (GOG-213): A Randomized Phase III Trial. *J Clin Oncol*. 2017;35(30):3402-3410. du Bois A, et al. Carboplatin–Pegylated Liposomal Doxorubicin Plus Bevacizumab Versus Carboplatin–Gemcitabine Plus Bevacizumab for Platinum-Sensitive Recurrent Ovarian Cancer (AGO OVAR 2.21; ENGOT-ov17): A Randomised, Phase 3 Trial. *Lancet Oncol*. 2020;21(7):1030-1039. Coleman RL, et al. Poster presented at: 2025 American Society of Clinical Oncology Annual Meeting; May 30-June 3, 2025; Chicago

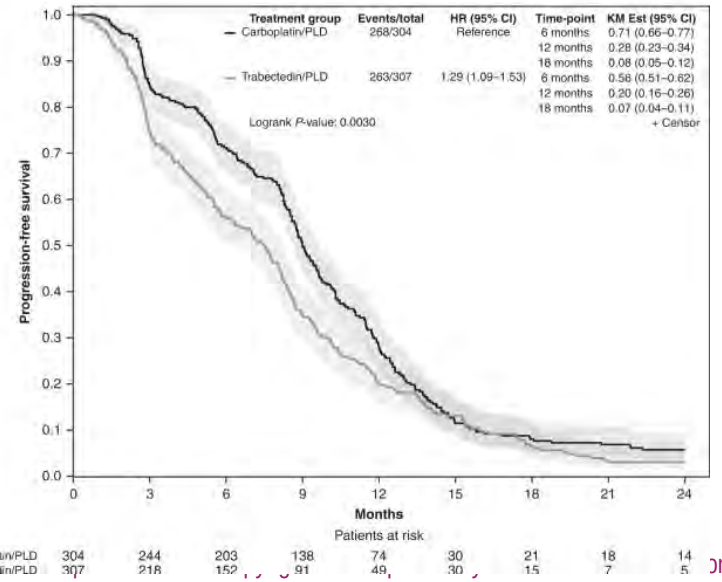
Artificial Prolongation of Platinum-Free Interval in Advanced OC

MITO 8

OS

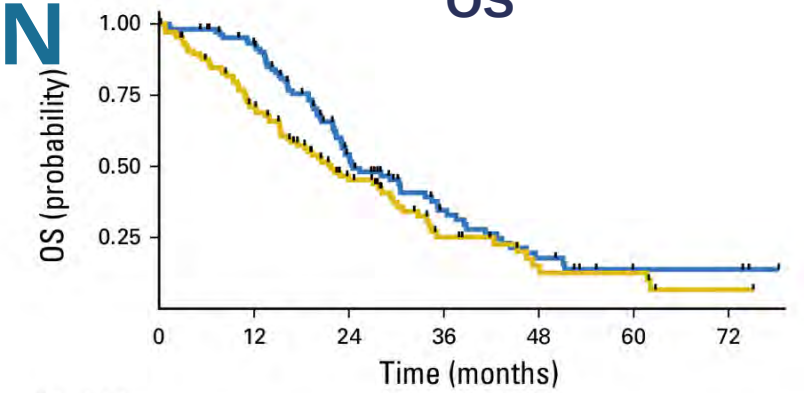


PFS



INOVATYON

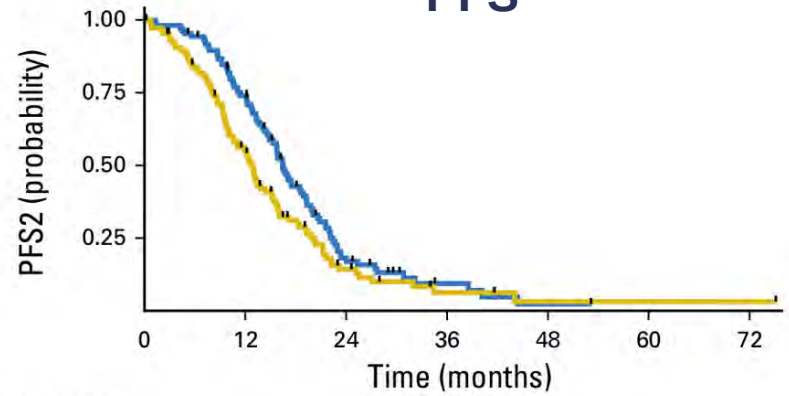
OS



No. at risk:

PBC followed by NPBC	108	92	45	21	10	3	3	PB
NPBC followed by PBC	107	71	34	13	6	5	1	NP

PFS



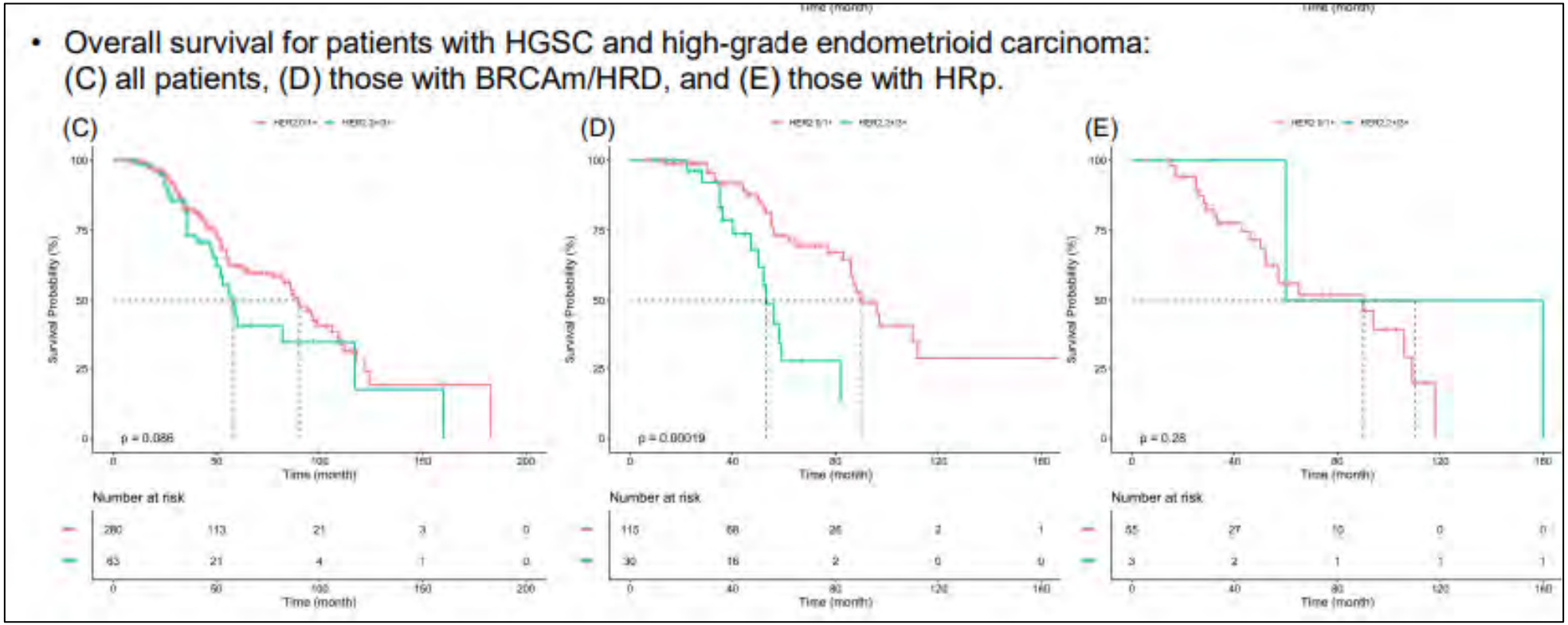
No. at risk:

PBC followed by NPBC	108	74	15	4	1	0	0
NPBC followed by PBC	107	55	11	3	1	1	1

Colombo N et al. Br J Cancer 2023 Apr;128(8):1503-1513

Pignata S et al. JCO 2017 Oct 10;35(29):3347-3353

Biomarkers in Frontline therapy will evolve to BRCA (y/n) , HRD (? GIS level) and tumor associated antigens like HER2



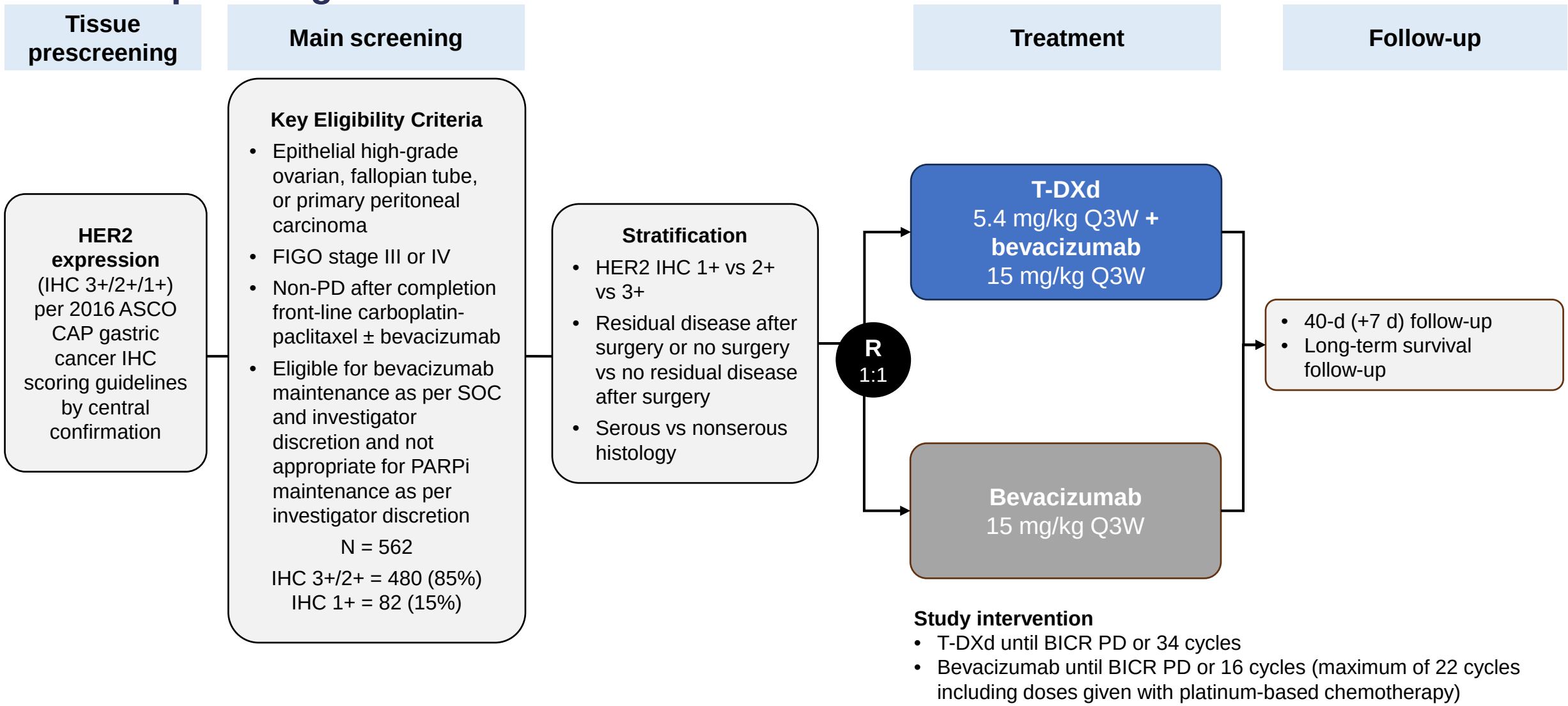
BRCAm/HRD: HER 2 2+ or 3+ appears negatively prognostic.

a) Is this “fixable” with PARPI or
b) This is a group that does poorly with PARPi and should be included in HER2 ADC studies?

@DrKatyMoore

Lee D et al. ESMO 2024 765P

This may open new opportunities for patients:
Phase 3 DESTINY-Ovarian01: T-DXd + Bevacizumab as 1L maintenance therapy in HER2-Expressing Ovarian Cancer[1]



Study intervention
- T-DXd until BICR PD or 34 cycles
- Bevacizumab until BICR PD or 16 cycles (maximum of 22 cycles including doses given with platinum-based chemotherapy)

1. https://clinicaltrials.gov/study/NCT06819007; [ENGOT-ov89/GOG 3112].

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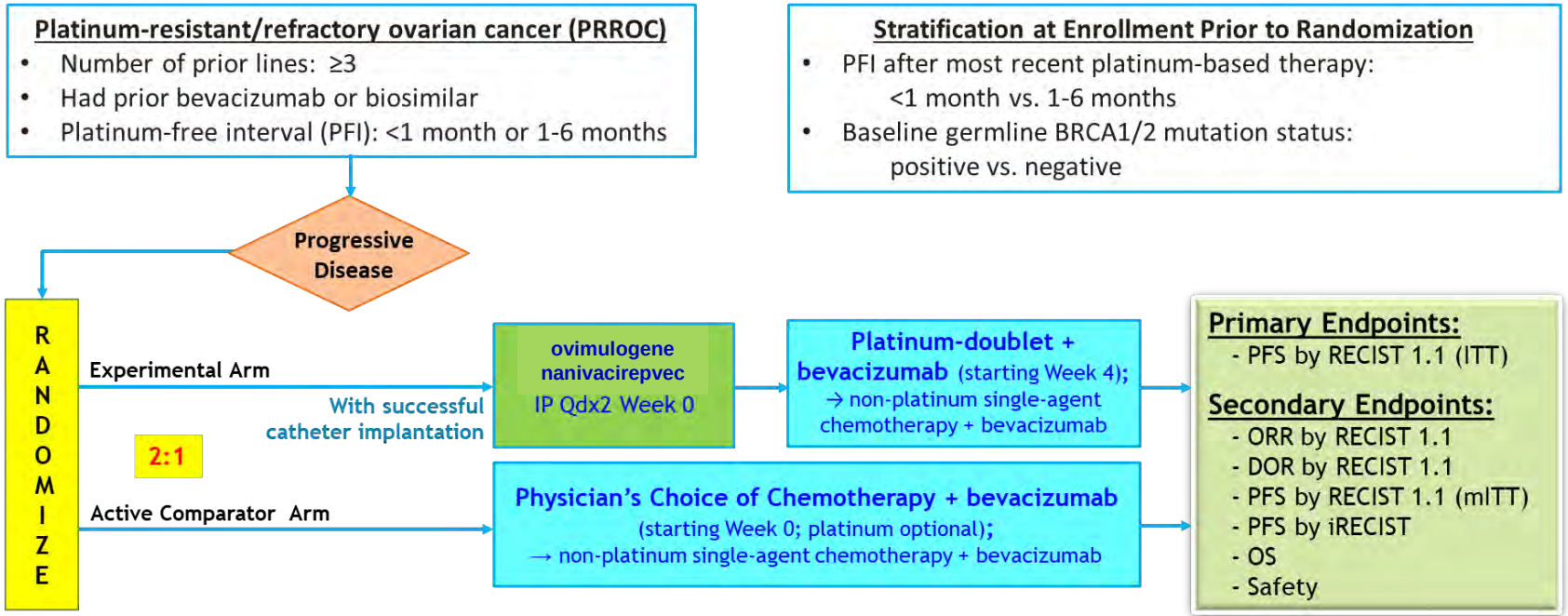
THE REVIVAL OF IMMUNOTHERAPY IN OVARIAN CANCER: GOG-3076/ovimulogene nanivacirepvec-022/OnPrime

A Randomized Phase 3 Study Assessing the Efficacy and Safety of ovimulogene nanivacirepvec followed by Platinum-doublet Chemotherapy and Bevacizumab Compared with Physician's Choice of Chemotherapy and Bevacizumab in Women with Platinum-Resistant/Refractory Ovarian Cancer (PRROC)

SCAN ME

(NPI: Robert Holloway, MD;
Co-NPIs: Premal Thaker, MD, Ramez Eskander, MD, Erin Crane, MD)



- Olvimulogene nanivacirepvec: oncolytic vaccinia virus-based immunotherapy
- virus-mediated immune activation
- re-sensitization of tumor cells to chemotherapy
- No maximal limit on the number of prior lines
- Temporary intraperitoneal dialysis catheter can be placed either through laparoscopy or interventional radiology (requires backup surgical option available if IR placement fails)
- Institutional BioSafety Committee, BSL-1 practice, -70C ± 10 freezer required

PLEASE ENROLL

NCT05281471

Olvi-Vec = ovimulogene nanivacirepvec (o-v)

TAKE HOME MESSAGES

- Platinum resistant OC patients have historically represented a group of patients with dismal prognosis
- Recently 3 randomized phase 3 trial have reported for the first time OS advantage oin this population (Mirvetuximab, Relacorilant+Nab Paclitaxel and Pembrolizumab+Weekly paclitaxel)
- New treatment strategies are under evaluation: ADC and Cell cycles check point inhibitors among the most promising
- The focus of clinical reserach in the next years should be focused on parp resistant patients, HRp population , and a better biological characterization of HRD patients that still represent un unresolved clinical problem

Making Sense of the Curves: How to Interpret New PFS/OS Data

David O'Malley, MD

The James Comprehensive Cancer Center
The Ohio State University
Columbus, OH

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Agenda

Critical review - efficacy signals in recent trials

- Clinical relevance of medians and hazard ratios
- Crossover influence
- Tail-of-the-curve effects

Contemporary Examples

- MIRASOL
- ROSELLA
- KEYNOTE-B96
- First Line Therapies

Median PFS/OS

- Quick, Simple. Easy
- 50% of patients have experienced the event
- Underestimate benefit when curves separate late or show tail durability.
- Limited when majority of events occur early (e.g. first or second disease assessment)
- Ignores whether a subset of patients derive long-term benefit.

KM Curves

- Focus on the shape and separation of the curves
- What's important is not just where the median is, but how and when the curves separate.
  - Early separation: often cytotoxic or ADC-like effect (rapid disease control).
  - Late separation: typical of immune therapies, where delayed responses occur.
  - Crossing curves: heterogeneity in treatment response (e.g., delayed IO benefit).

Oh DY, Rokutanda N, Żotkiewicz M, He P, Stocks J, Johnson ML. Delayed Separation of Kaplan-Meier Curves is Commonly Observed in Studies of Advanced/Metastatic Solid Tumors Treated with Anti-PD-(L)1 Therapy: Systematic Review and Meta-Analysis. Target Oncol. 2025 Jan;20(1):45-56. doi: 10.1007/s11523-024-01108-2. Epub 2024 Nov 10. PMID: 39522075; PMCID: PMC11762587.

Hazard Ratio (HR)

- The hazard ratio reflects the instantaneous risk of the event over the entire follow-up period.
- E.g. HR = 0.65: roughly a 35% relative risk reduction.
  - What does that even mean?
  - How does one visualize a HR?
- Interpret HR with the confidence interval and p-value.
- The HR summarizes the overall pattern, BUT the curve tells you when and how that benefit happens.
- Does the curve tell the real story?

Recurrent

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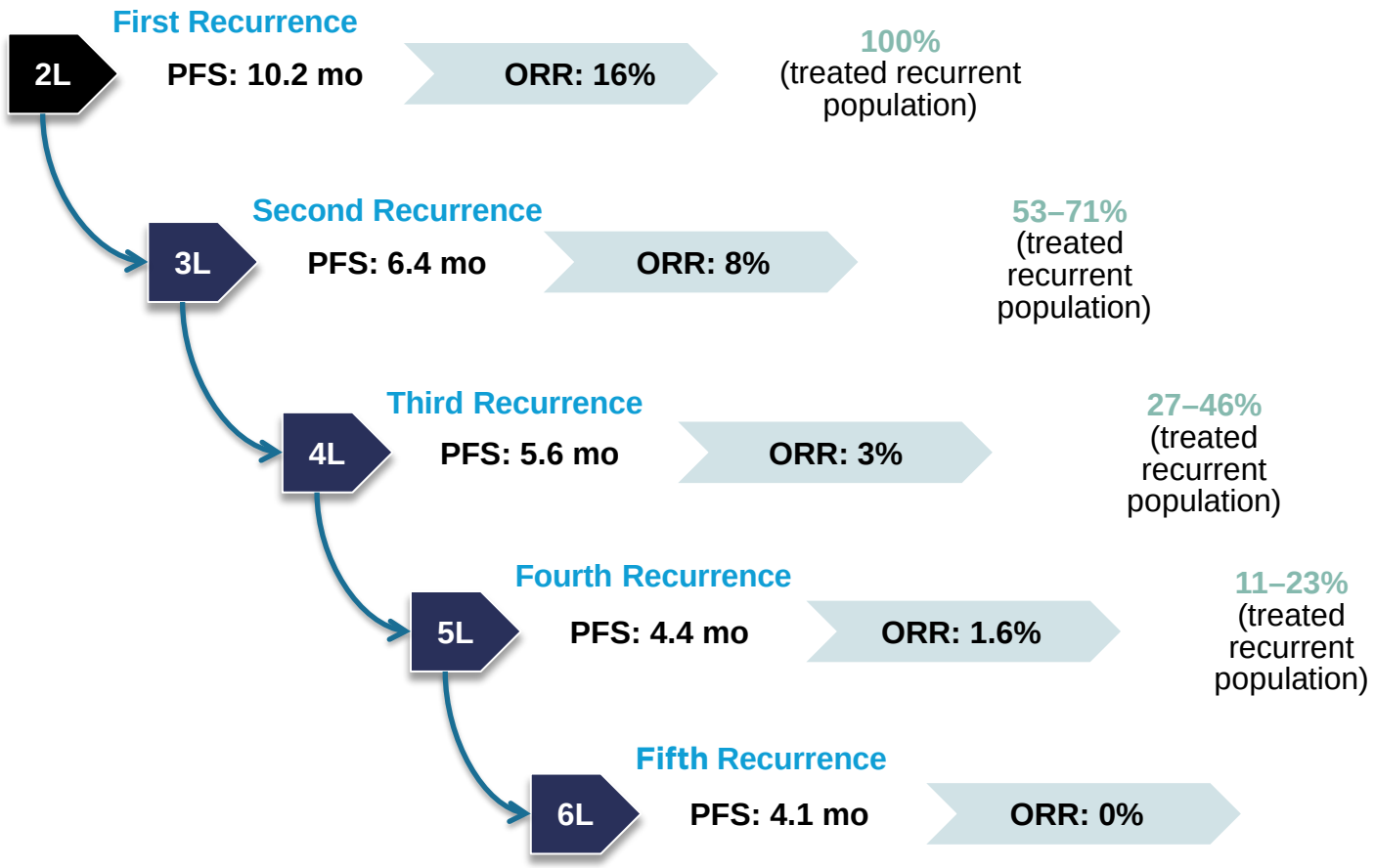
Line of Therapy “Drop Off” Between Lines & Impact on PFS/ORR

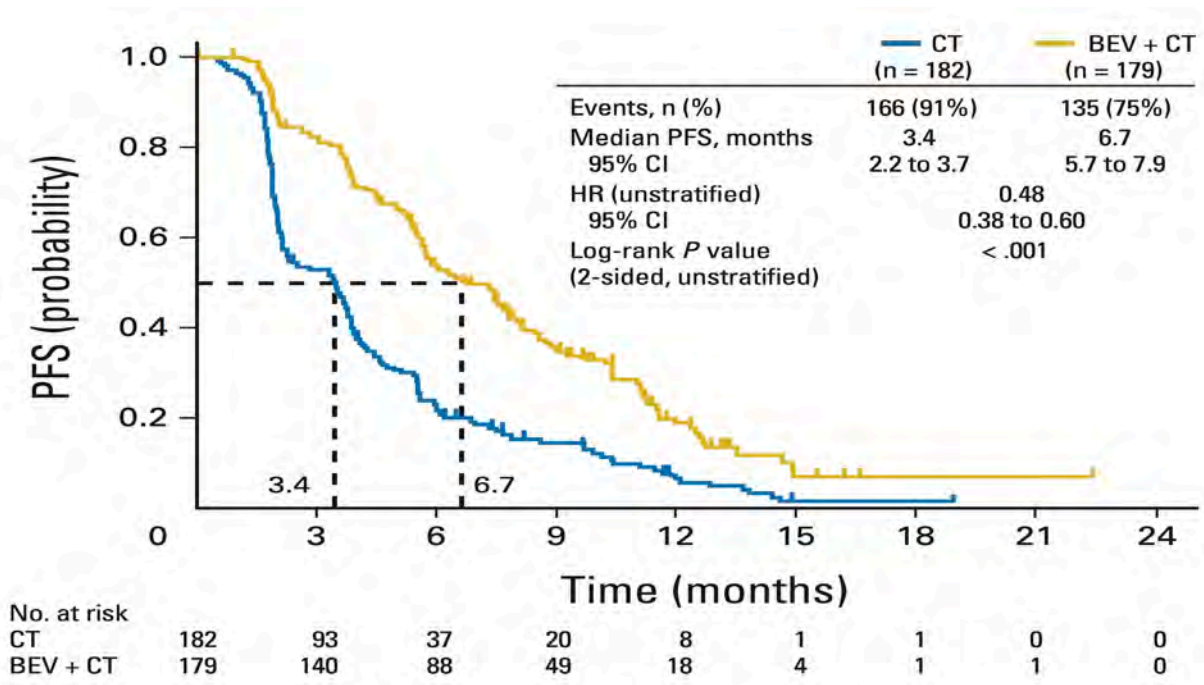


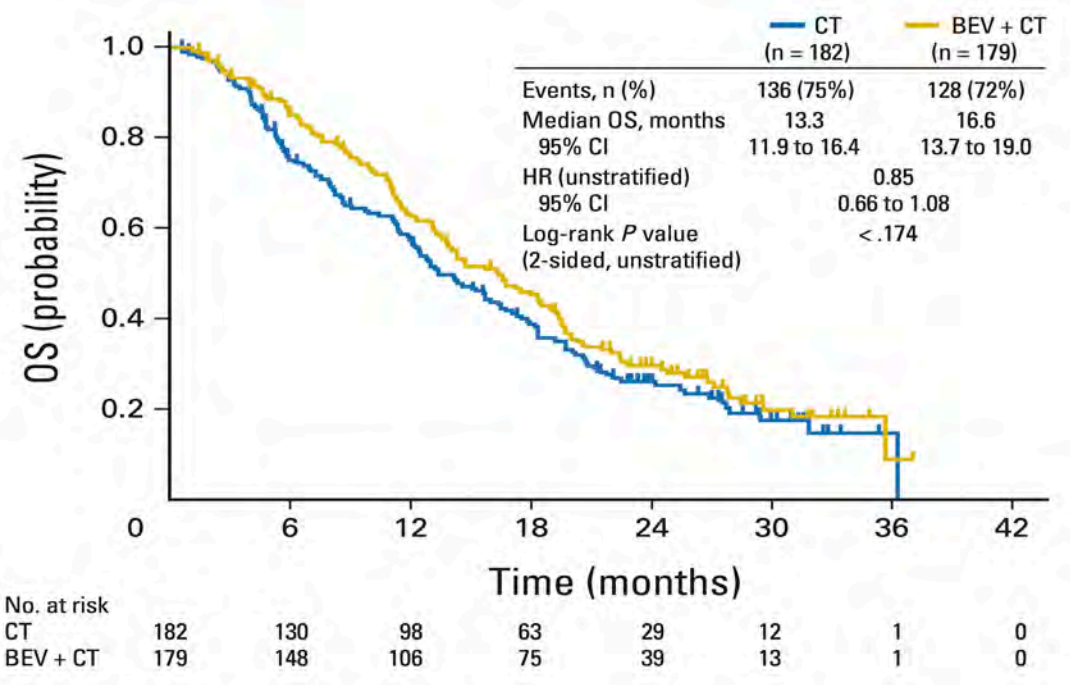
mPFS ranges after treatment with various chemotherapy regimens[1-3]

mo, month; mPFS, median progression-free survival; ORR, overall response rate; PFS, progression-free survival

Hanker LC, et al. Ann Oncol. 2012;23(10):2605–2612; 2. Pignata S, et al. Ann Oncol. 2017;28(suppl 8):viii51–viii56; 3. Griffiths RW, et al. Int J Gynecol Cancer. 2011;21(1):58–65; 4. Colombo N, et al. Ann Oncol. 2019;30(5):672–705; 5. González-Martín A. Ann Oncol. 2023;34(10):833–848.

Aurelia: PFS/OS





Pujade-Lauraine E, et al. J Clin Oncol, 2014.

Contemporary Perspective: Efficacy in PROC

Study	Study Population	Chemo Arm	ORR	Median PFS & OS
JAVELIN Ovarian 200[1] (n=190)	PROC/25% Plat-refractory 1-3 priors (28% prior BEV)	Pegylated liposomal doxorubicin (PLD)	**4%**	**PFS: 3.5 months** OS: 15.7 months
FORWARD I **Primary[2] (n=118)** **Re-read[3] (n=61)**	**PROC , all high FRα** 1-3 priors (33% prior BEV)	Paclitaxel or PLD or Topotecan	**1^0 : 12%** **Re-R: 6%**	**1^0 PFS: 4.4** **Re-R PFS: 3.2 months** 1^0 OS: 12 months
CORAIL[4] (n=442)	PROC 1- 3 priors (46% prior BEV)	PLD or Topotecan	**12.2%**	**PFS: 3.6 months** OS: 11 months
NINJA[5] (n=316)	PROC 77% Progression on prior plt permitted > 2 priors	Gemcitabine or PLD	**13.2%**	**PFS: 3.8 months** OS: 12.1 months
VBL-OVAL/GOG 3018[6] (n=409)	PROC **Up to 5 prior lines of txt** **ECOG 0-1**	Weekly Paclitaxel	**29.6%**	**PFS: 5.4 months** OS: 13.1 months
AXLerate/GOG 3059[7] (n=366)	PROC 1-4 priors (51% prior BEV)	Weekly Paclitaxel	**Not yet reported**	**PFS: 5.4 months** OS: 13.1 months
MIRASOL[8] (n=453)	**PROC, all high FRα** 1-3 priors (62% prior BEV)	Paclitaxel or PLD or Topotecan	**Mirv: 42%** **PCC: 16%**	PFS: 5.6 vs. **3.98 months** OS: 16.5 vs. 12.8 months

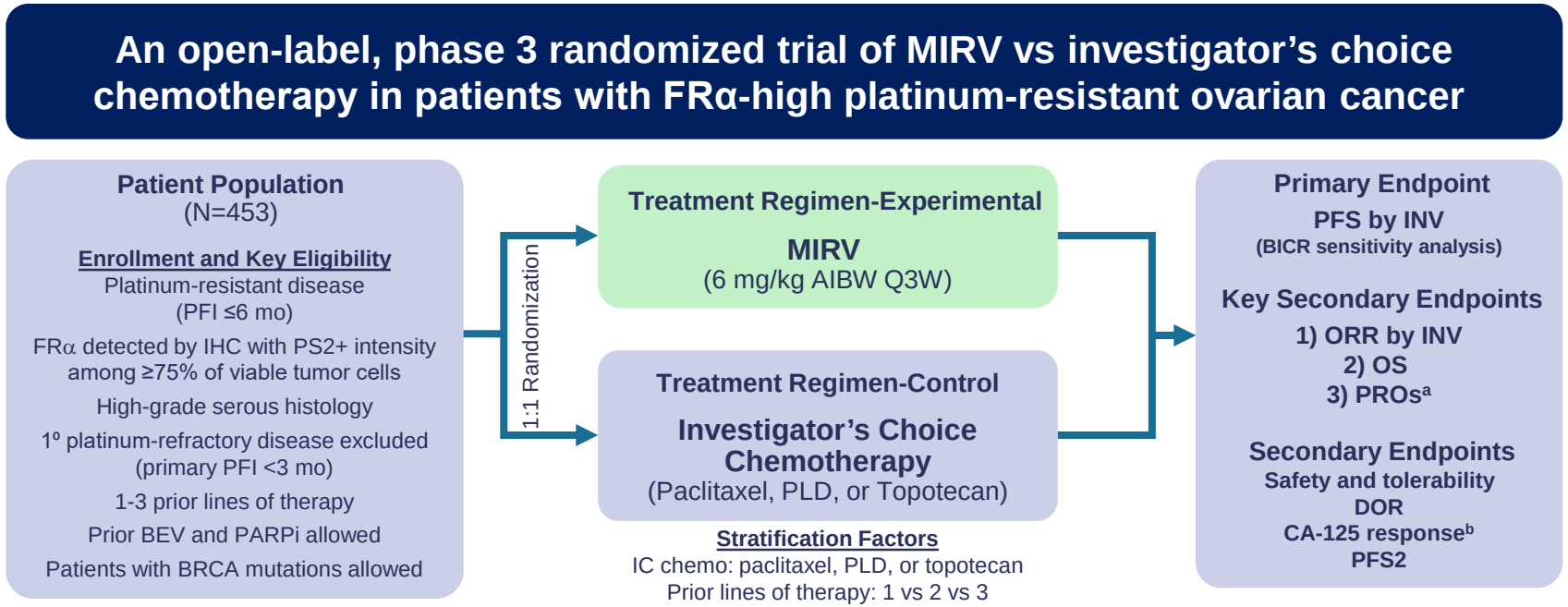
Pujade Lauraine E et al. *Lancet Oncol.* 2021;22(7):1034-1046 2. Moore KN et al. ESMO 2019. Abstract 4093. 3. Moore KN et al. *Ann Oncol.* 2021;32(6):757-765. 4. Gaillard SL et al. *Gynecol Oncol*. 2021;163(2):237-245. 5. Hamanishi J et al. *J Clin Oncol*. 2021;39(33):3671-3681. 6. Phase 3 OVAL trial. Press release. VBL Therapeutics; July 19, 2022. https://www.globenewswire.com/news-release/2022/07/19/2482252/0/en/VBL-Therapeutics-Announces-Top-Line-Data-from-Phase-3-OVAL-Trial-of-Ofra-Vec-in-Patients-with-Platinum-Resistant-Ovarian-Cancer.html. [7]https://ir.aravive.com/news-releases/news-release-details/aravive-announces-top-line-results-phase-3-axlerate-oc-study; [8]https://meetings.asco.org/abstracts-presentations/226803

The Impact of Weekly Paclitaxel in Regulatory Process (Ovary)

Study	Study population	Chemotherapy arm	ORR, %	mPFS, mo mOS, mo
OVAL (n=409)	≤5 priors, PROC, excluded refractory (70% prior bev)	Weekly paclitaxel +/- ofranergene obadenovec	**28.9%/ 29.6%**	5.29/5.36 13.37/13.14
AXLerate (n=360)	PROC 1–4 priors, PROC (51% prior bev)	Weekly paclitaxel +/- batiraxcept	**25.2%/ 26.2%**	5.13/5.49 14.29/14.39
INNOVATE-3 (n=558)	PROC ≤5 priors (65.9% prior bev)	Weekly paclitaxel +/- TTF	**30.3/ 31.6%**	4.1/ 4.7 12.2/11.9
PROFECTA-II (n=150)	PROC ≤ 5 priors (81% prior bev)	Weekly paclitaxel +/- afuresertib	**25%/ 18%**	4.3/4.1 11.2/13.1
AURELIA (n=115)	PROC ≤2 priors; 25% platinum refractory (8% prior bev)	Weekly paclitaxel +/- bev	**30.2%/53.3%**	10.4/3.9 22.4/13.2
ROSELLA (n=381)	PROC ≤3 priors, 7% platinum refractory (100% prior bev)	Weekly Abraxane +/- relacorilant	**36.9%/ 30.1%**	6.54/5.52 15.97/11.5 (int)
AXLerate (n=61)	PROC 1–4 priors, PROC (51% prior bev) just AXL high	Weekly paclitaxel +/- batiraxcept	**NR**	5.78/3.71 17.8/8.11

Arend RC et al. J Clin Oncol. 2024 42(2):170; Fuh KC et al. J Clin Oncol 42, 2024(suppl 17; abstr LBA 5515); Vergote I et al. European Journal of Cancer, 2025; Herzog T et al. SGO 2025; Poveda et al. Annals of Oncology 2012, Olawaiye A et al. Lancet 2025

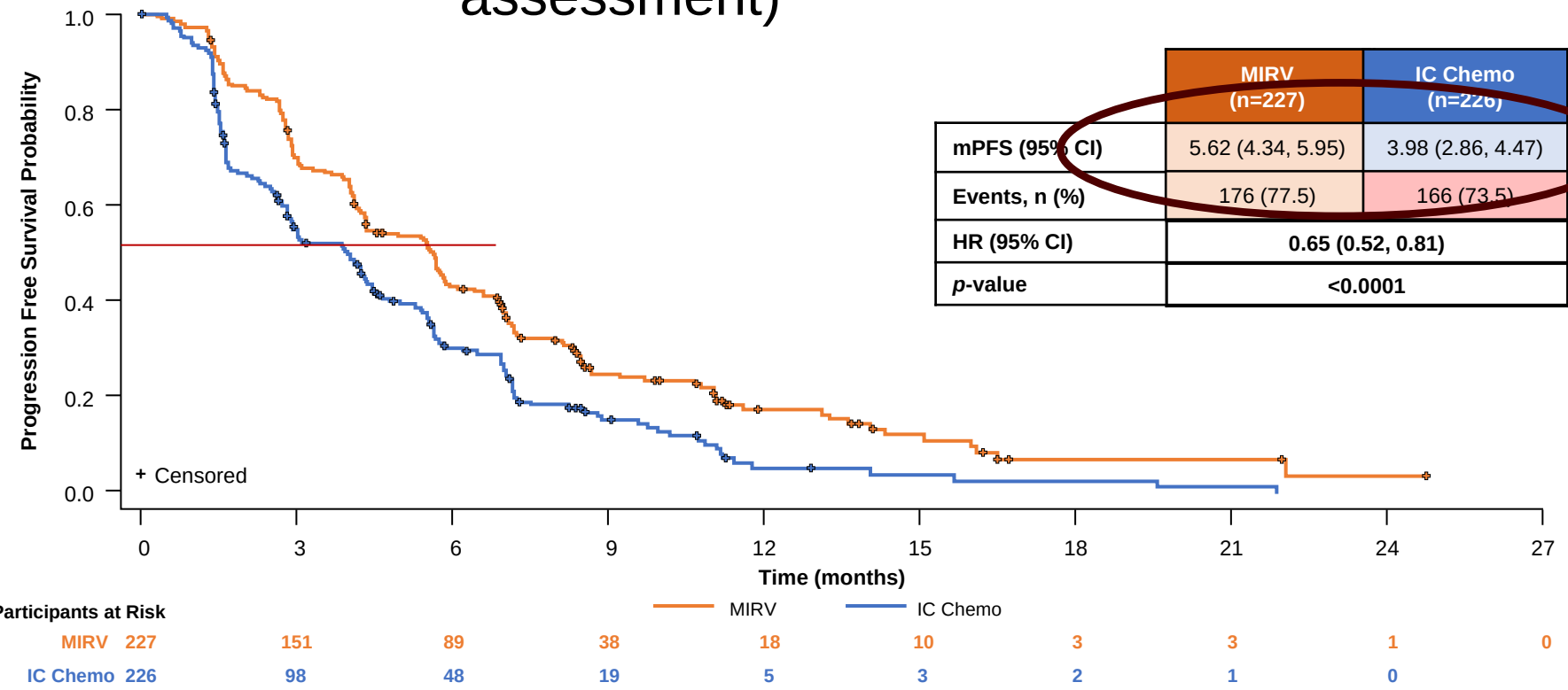
MIRASOL: Study Design[1,2]



NCT04209855

MIRASOL: Progression-Free Survival by Investigator

- Medians: Limited when majority of events occur early (e.g. first or second disease assessment)

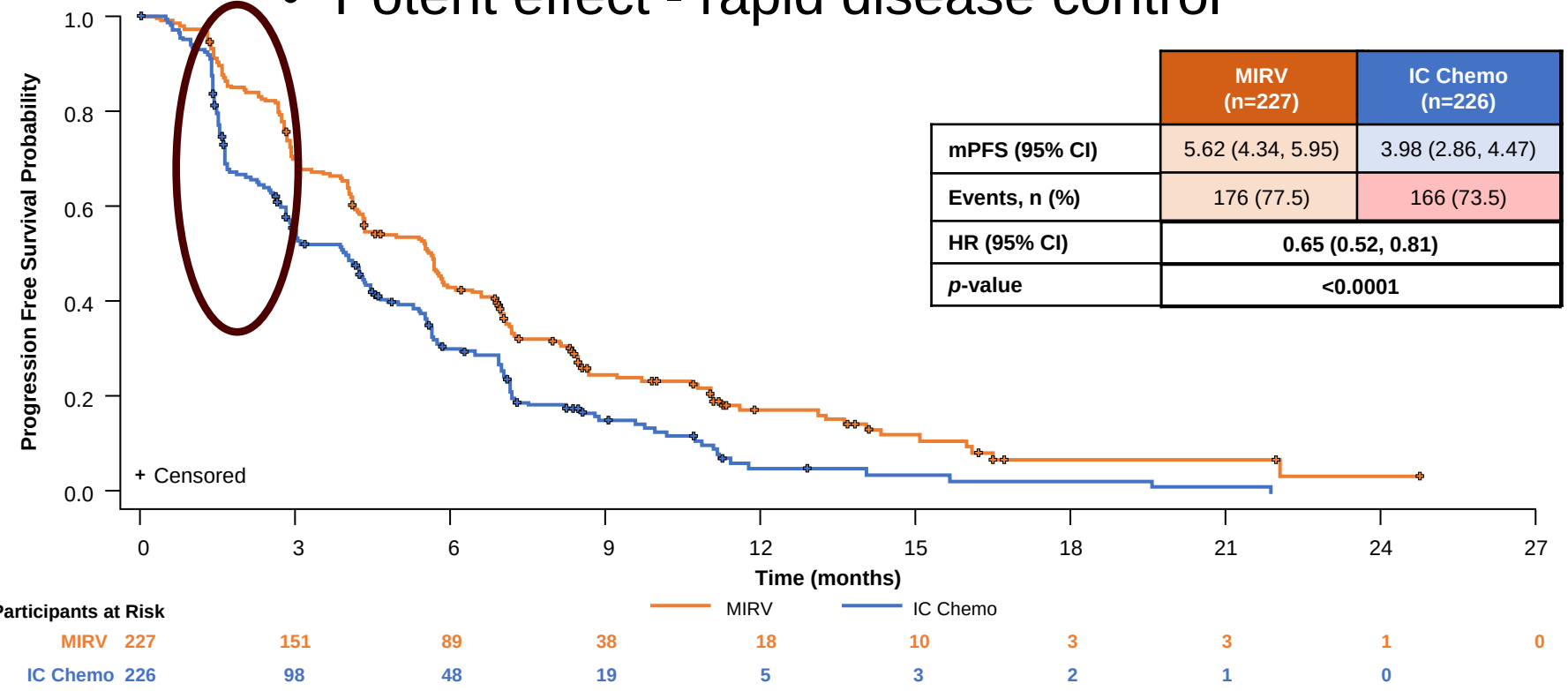


	MIRV (n=227)	IC Chemo (n=226)
mPFS (95% CI)	5.62 (4.34, 5.95)	3.98 (2.86, 4.47)
Events, n (%)	176 (77.5)	166 (73.5)
HR (95% CI)	0.65 (0.52, 0.81)	
p-value	<0.0001	

Moore, NEJM (2023) 389:2162-74

MIRASOL: Progression-Free Survival by Investigator

- Early and sustained separation of the curves
- Potent effect - rapid disease control

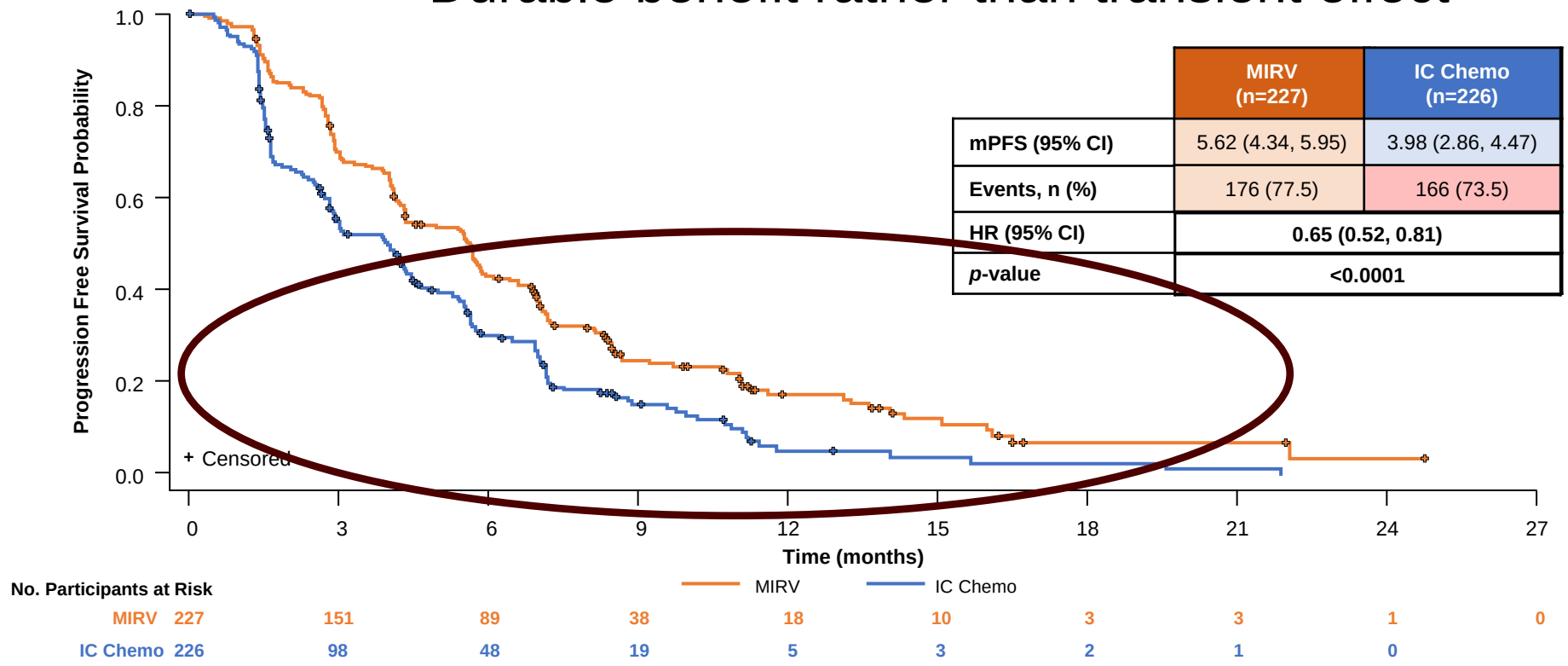


	MIRV (n=227)	IC Chemo (n=226)
mPFS (95% CI)	5.62 (4.34, 5.95)	3.98 (2.86, 4.47)
Events, n (%)	176 (77.5)	166 (73.5)
HR (95% CI)	0.65 (0.52, 0.81)	
p-value	<0.0001	

Moore, NEJM (2023) 389:2162-74

Primary Endpoint: Progression-Free Survival by Investigator

- Separation continues
- Durable benefit rather than transient effect



	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**	

Moore, NEJM (2023) 389:2162-74

Overall Response Rate by Investigator (N=453)

	MIRV (n=227)	IC Chemo (n=226)
ORR **n, 95% CI**	**42%** 96, (35.8, 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**

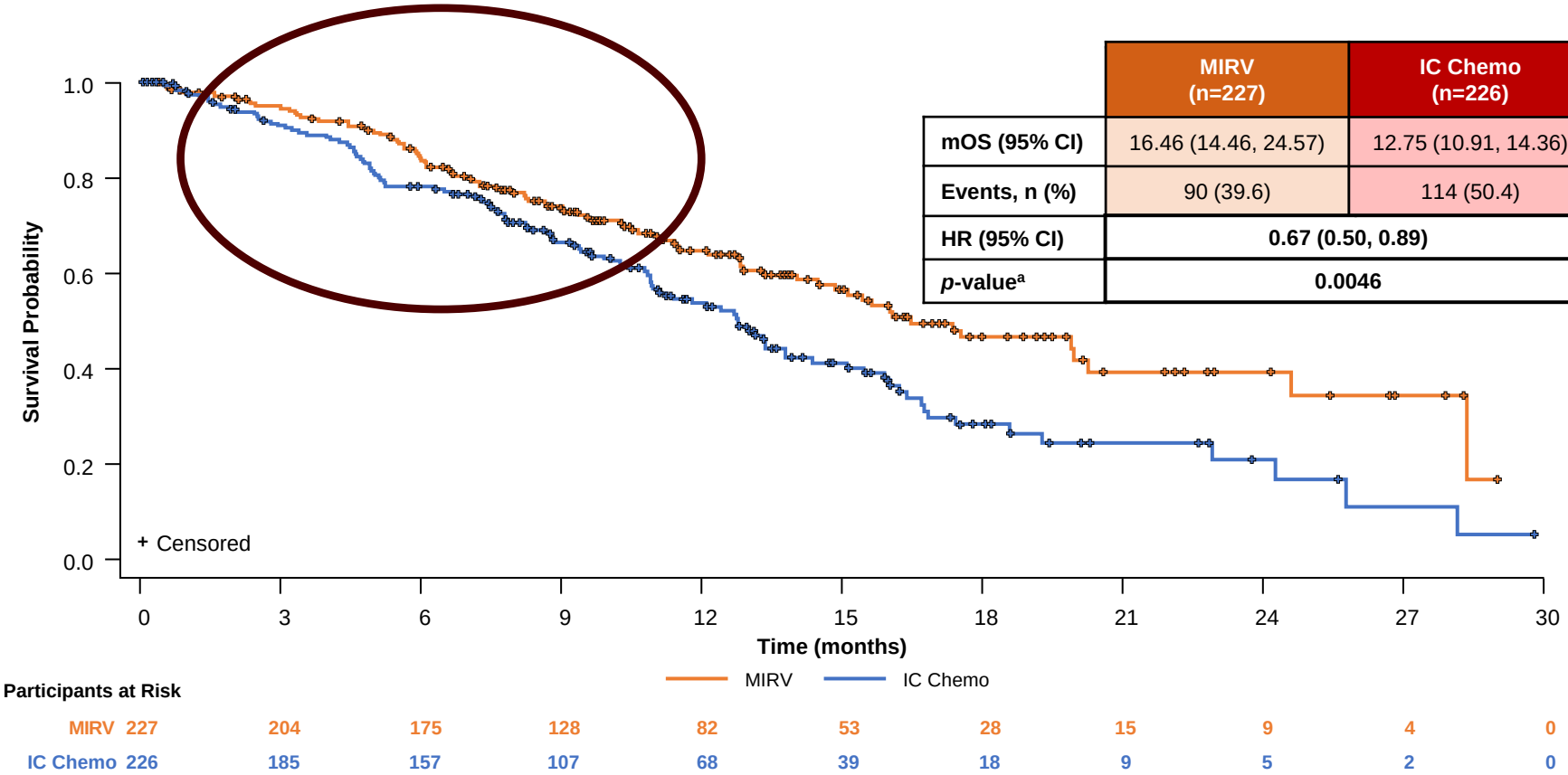
Moore, NEJM (2023) 389:2162-74

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.

MIRASOL: Overall Survival

Curves separate early and stay apart



	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

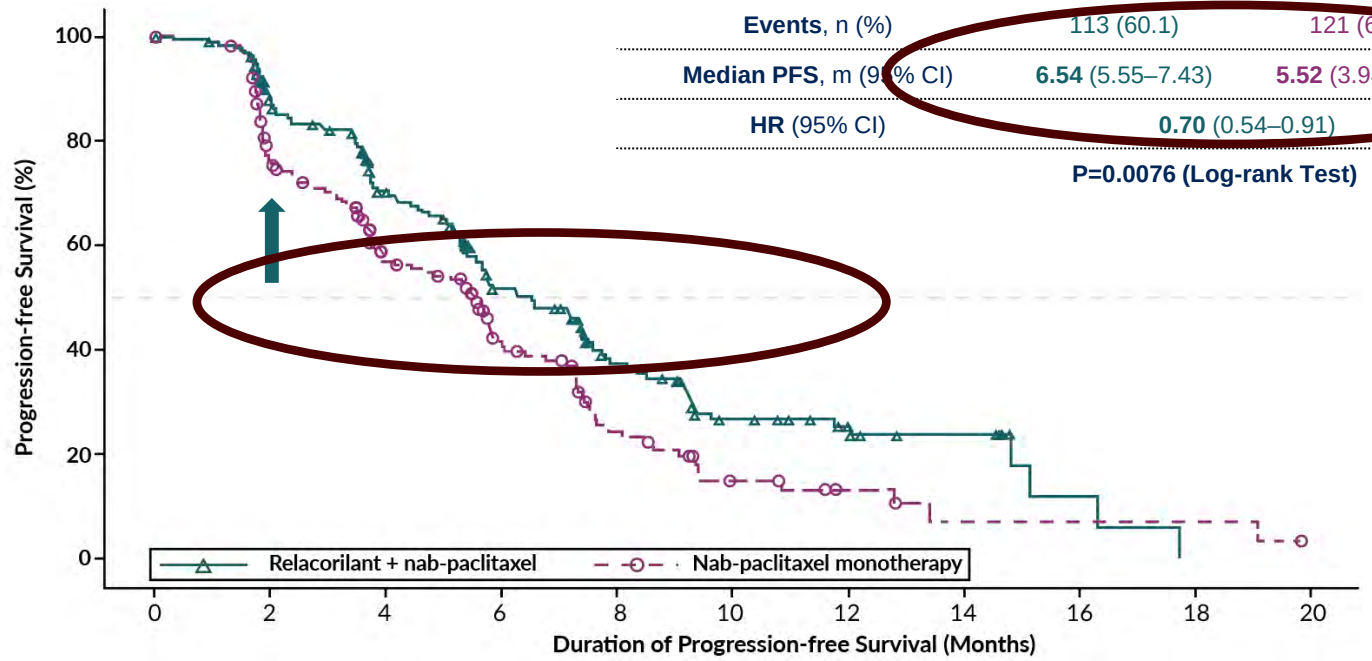
Moore, NEJM (2023) 389:2162-74

ROSELLA | PFS Assessed by BICR

Medians: Limited when majority of events occur early

	Relacorilant + Nab-paclitaxel N=188	Nab-paclitaxel N=193
Events, n (%)	113 (60.1)	121 (62.7)
Median PFS, m (95% CI)	**6.54** (5.55–7.43)	**5.52** (3.94–5.88)
HR (95% CI)	**0.70** (0.54–0.91)	

P=0.0076 (Log-rank Test)



No. at risk (events/cumulative events)

Relacorilant + nab-paclitaxel	188 (0/0)	151 (22/22)	109 (29/51)	70 (27/78)	43 (18/96)	24 (11/107)	16 (1/108)	11 (1/109)	2 (2/111)	0 (2/113)	
Nab-paclitaxel monotherapy	193 (0/0)	129 (42/42)	85 (31/73)	47 (20/93)	21 (17/110)	9 (7/117)	5 (1/118)	2 (2/120)	2 (0/120)	2 (0/120)	0 (1/121)

Median follow-up time: 9.0 months; statistical significance threshold: P≤0.04. The Kaplan–Meier method was used to estimate the curves, median estimates and the 95% confidence intervals (CI) for progression-free survival in each treatment arm. The HR and the associated 95% CI were estimated using a Cox regression model with treatment group as the main effect and stratification factors at randomization as covariates. BICR, blinded-independent central review; CI, confidence interval; HR, hazard ratio; m, months; PFS, progression-free survival.

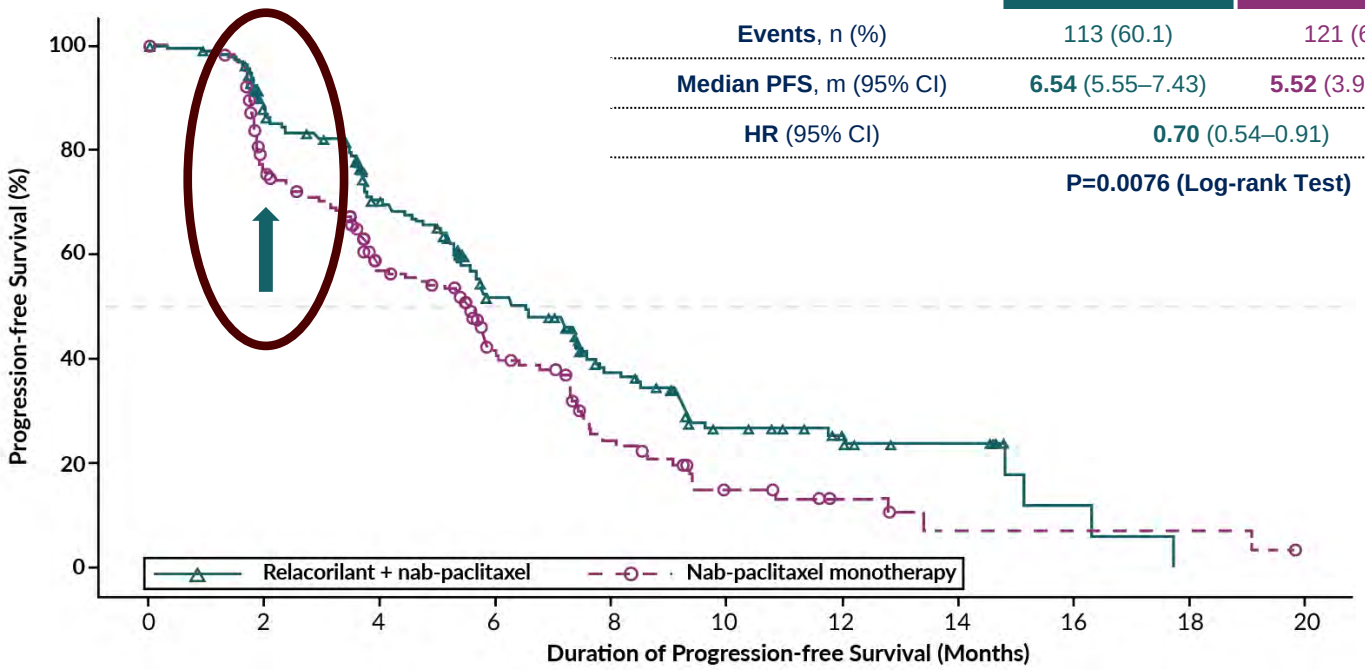
ROSELLA | PFS Assessed by BICR

Not just where the median is, but how and when the curves separate.

Early separation: often cytotoxic or ADC-like effect

	Relacorilant + Nab-paclitaxel N=188	Nab-paclitaxel N=193
Events, n (%)	113 (60.1)	121 (62.7)
Median PFS, m (95% CI)	**6.54** (5.55–7.43)	**5.52** (3.94–5.88)
HR (95% CI)	**0.70** (0.54–0.91)	

P=0.0076 (Log-rank Test)



No. at risk (events/cumulative events)

Relacorilant + nab-paclitaxel	188 (0/0)	151 (22/22)	109 (29/51)	70 (27/78)	43 (18/96)	24 (11/107)	16 (1/108)	11 (1/109)	2 (2/111)	0 (2/113)
Nab-paclitaxel monotherapy	193 (0/0)	129 (42/42)	85 (31/73)	47 (20/93)	21 (17/110)	9 (7/117)	5 (1/118)	2 (2/120)	2 (0/120)	2 (0/120)	0 (1/121)

Median follow-up time: 9.0 months; statistical significance threshold: P≤0.04. The Kaplan–Meier method was used to estimate the curves, median estimates and the 95% confidence intervals (CI) for progression-free survival in each treatment arm. The HR and the associated 95% CI were estimated using a Cox regression model with treatment group as the main effect and stratification factors at randomization as covariates. BICR, blinded-independent central review; CI, confidence interval; HR, hazard ratio; m, months; PFS, progression-free survival.

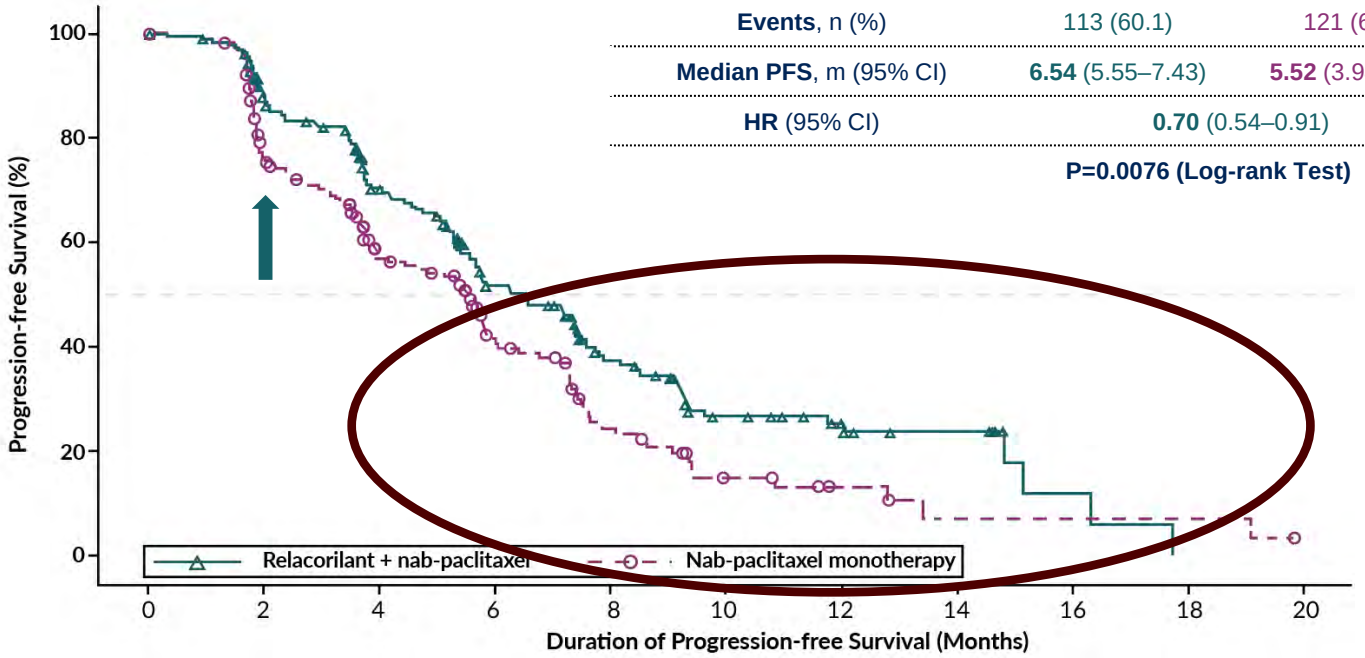
ROSELLA | PFS Assessed by BICR

Not just where the median is, but how and when the curves separate.

Late separation: typical of immune therapies, where delayed responses occur

	Relacorilant + Nab-paclitaxel N=188	Nab-paclitaxel N=193
Events, n (%)	113 (60.1)	121 (62.7)
Median PFS, m (95% CI)	**6.54** (5.55–7.43)	**5.52** (3.94–5.88)
HR (95% CI)	**0.70** (0.54–0.91)	

P=0.0076 (Log-rank Test)



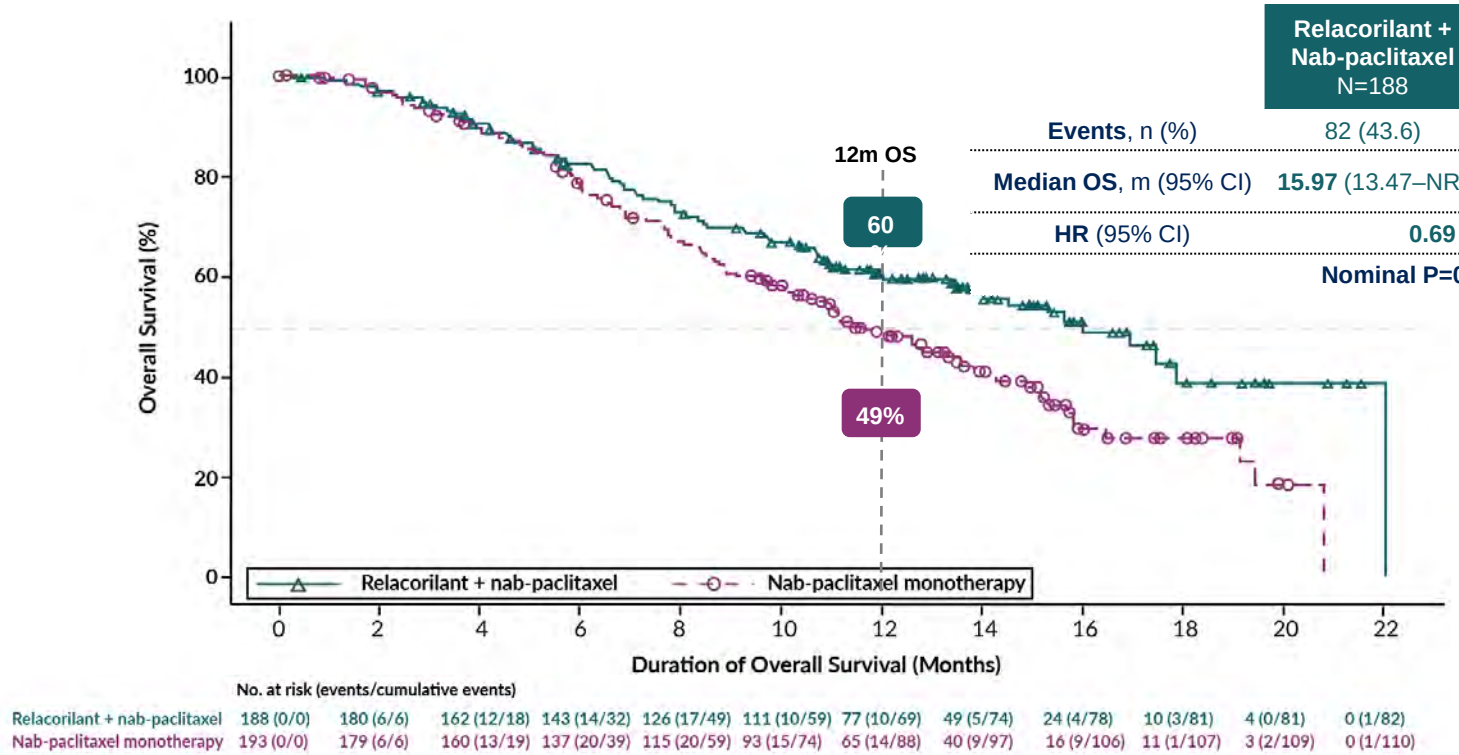
No. at risk (events/cumulative events)

Relacorilant + nab-paclitaxel	188 (0/0)	151 (22/22)	109 (29/51)	70 (27/78)	43 (18/96)	24 (11/107)	16 (1/108)	11 (1/109)	2 (2/111)	0 (2/113)	
Nab-paclitaxel monotherapy	193 (0/0)	129 (42/42)	85 (31/73)	47 (20/93)	21 (17/110)	9 (7/117)	5 (1/118)	2 (2/120)	2 (0/120)	2 (0/120)	0 (1/121)

Median follow-up time: 9.0 months; statistical significance threshold: P≤0.04. The Kaplan–Meier method was used to estimate the curves, median estimates and the 95% confidence intervals (CI) for progression-free survival in each treatment arm. The HR and the associated 95% CI were estimated using a Cox regression model with treatment group as the main effect and stratification factors at randomization as covariates. BICR, blinded-independent central review; CI, confidence interval; HR, hazard ratio; m, months; PFS, progression-free survival.

ROSELLA | Overall Survival - Interim Analysis

Median follow-up of 13·9 months



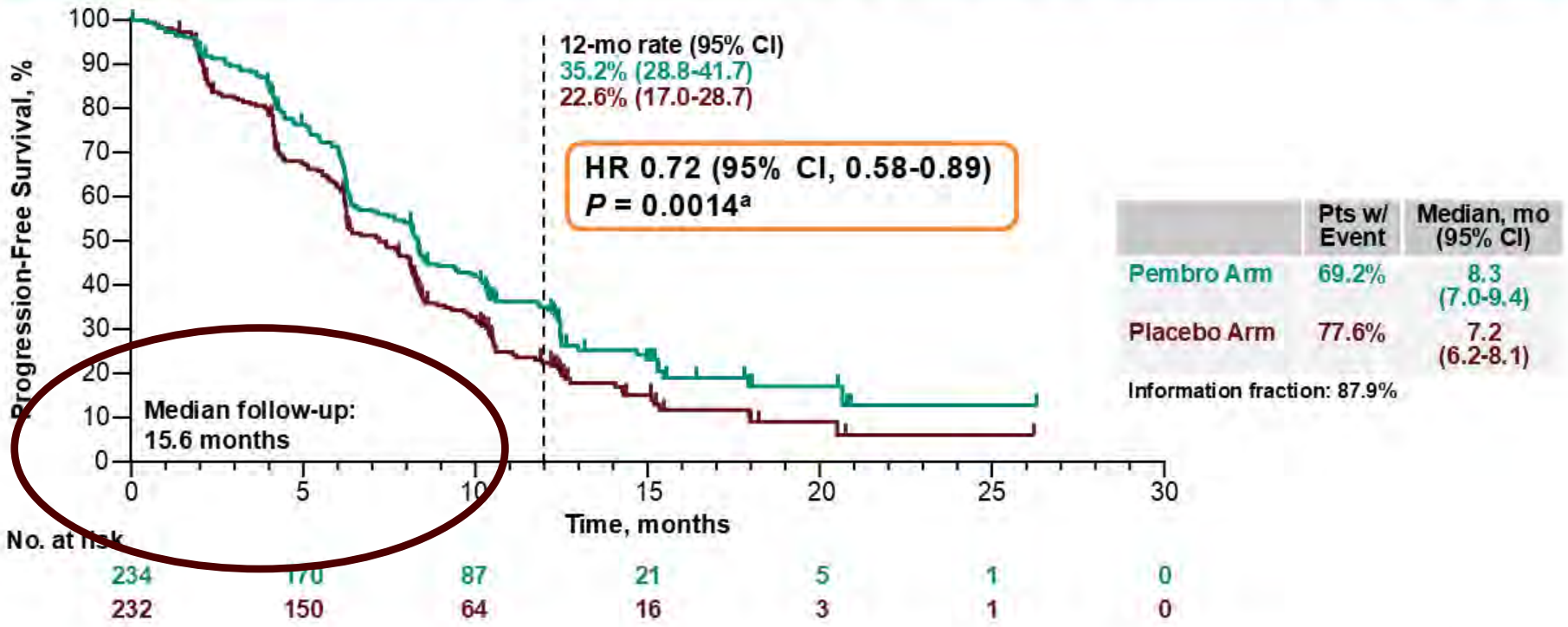
	Relacorilant + Nab-paclitaxel N=188	Nab-paclitaxel N=193
Events, n (%)	82 (43.6)	110 (57.0)
Median OS, m (95% CI)	**15.97** (13.47–NR)	**11.50** (10.02–13.57)
HR (95% CI)	**0.69** (0.52–0.92)	
Nominal P=0.0121 (Log-rank Test)		

Median follow-up time: 13.9 months; statistical significance threshold at the interim analysis: P≤0.0001; statistical significance threshold at the final analysis: P≤0.0499. The Kaplan–Meier method was used to estimate the curves, median estimates and the 95% confidence intervals (CI) for overall survival in each treatment arm. The HR and the associated 95% CI were estimated using a Cox regression model with treatment group as the main effect and stratification factors at randomization as covariates. CI, confidence interval; HR, hazard ratio; m, months; NR, not reached; OS, overall survival.

KEYNOTE-B96

N Colombo KNB96 ESMO 2025

Progression-Free Survival in the CPS ≥1 Population at IA1



	Pts w/ Event	Median, mo (95% CI)
Pembro Arm	69.2%	8.3 (7.0-9.4)
Placebo Arm	77.6%	7.2 (6.2-8.1)

Information fraction: 87.9%

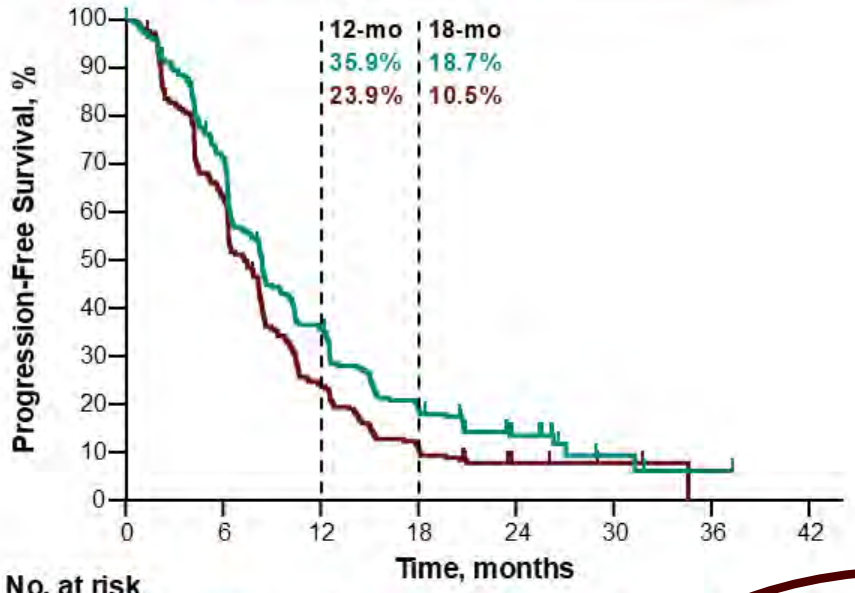
Response assessed per RECIST v1.1 by investigator review. [a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. The observed p-value crossed the prespecified nominal boundary of 0.0116 at this planned first interim analysis; because the success criterion of the PFS hypothesis was met, no formal testing of PFS will be performed at later analyses. Data cutoff date: April 3, 2024.

KEYNOTE-B96

N Colombo KNB96 ESMO 2025

Progression-Free Survival in the CPS ≥1 and ITT Populations at IA2

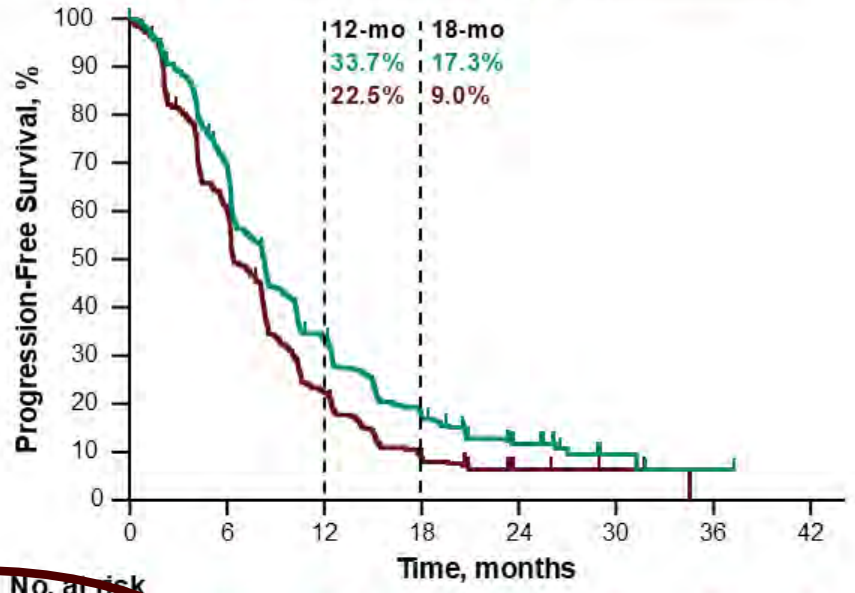
CPS ≥1 Population	Median, months	Events	HR (95% CI)
Pembro Arm	8.3	81.6%	0.75[a] (0.61-0.91)
Placebo Arm	7.2	86.6%	



No. at risk

234	158	77	39	12	3	1	0
232	138	50	22	5	2	0	0

ITT Population	Median, months	Events	HR (95% CI)
Pembro Arm	8.3	83.2%	0.73[a] (0.62-0.86)
Placebo Arm	6.4	87.2%	



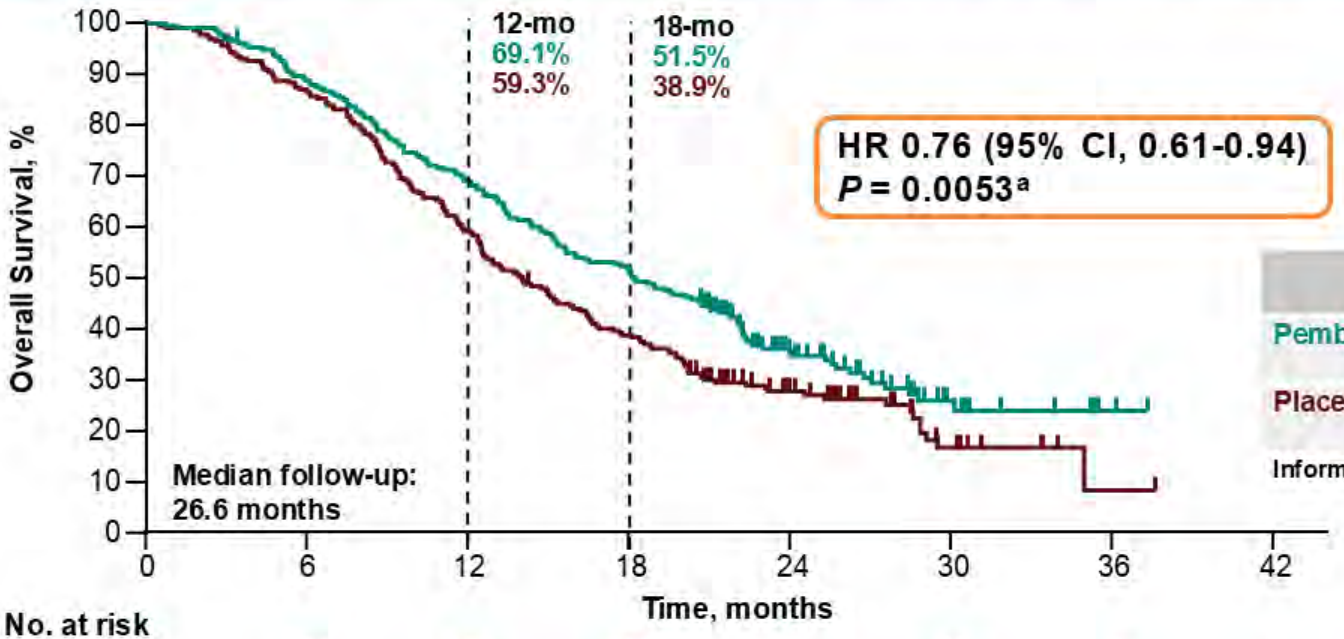
No. at risk

322	213	99	49	16	3	1	0
321	184	64	25	6	2	0	0

Median follow-up: 26.6 months

Response assessed per RECIST v1.1 by investigator review. [a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. No statistical testing for PFS was done at this analysis because significance was achieved at IA1. Data cutoff date: March 5, 2025.

Key Secondary Endpoint: Overall Survival in the CPS ≥1 Population at IA2



	Pts w/ Event	Median, mo (95% CI)
Pembro Arm	67.1%	18.2 (15.3-21.0)
Placebo Arm	75.4%	14.0 (12.5-16.1)

Information fraction: 90.0%

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. The observed p-value crossed the prespecified nominal boundary of 0.0083 at this planned second interim analysis. Data cutoff date: March 5, 2025.

Impact of Cross Over-ARIEL4/Subsequent Therapy

Crossover and Subsequent Treatments

	Platinum Resistant		Partially Platinum Sensitive		Fully Platinum Sensitive	
	Rucaparib (n=120)	Chemotherapy (n=59)	Rucaparib (n=65)	Chemotherapy (n=31)	Rucaparib (n=48)	Chemotherapy (n=26)
Median duration of randomised treatment, mo (range)[a]	5.6 (0–44)	4.4 (0–25)	7.6 (0–60)	4.5 (0–11)	13.7 (0–53)	3.4 (1–8)
Subsequent anticancer treatment reported, n (%)						
Yes	69 (57.5)	45 (76.3)	40 (61.5)	26 (83.9)	26 (54.2)	22 (84.6)
No	51 (42.5)	14 (23.7)	25 (38.5)	5 (16.1)	22 (45.8)	4 (15.4)
Type of first subsequent treatment, n (%)						
Crossover rucaparib	NA	41 (91.1)	NA	25 (96.2)	NA	14 (63.6)
Other PARPi	1 (1.4)	0	0	0	1 (3.8)	4 (18.2)
Platinum-based chemotherapy	29 (42.0)	1 (2.2)	27 (67.5)	1 (3.8)	20 (76.9)	2 (9.1)
Nonplatinum-based chemotherapy	36 (52.2)	2 (4.4)	11 (27.5)	0	5 (19.2)	1 (4.5)
Other[b]	3 (4.3)	1 (2.2)	2 (5.0)	0	0	1 (4.5)
Median duration of crossover rucaparib, mo (range)	NA	9.4 (2–39)	NA	9.7 (0–36)	NA	9.9 (1–37)
<6 months, n (%)	NA	14 (34.1)	NA	7 (28.0)	NA	2 (14.3)
≥6 months, n (%)		27 (65.9)		18 (72.0)		12 (85.7)

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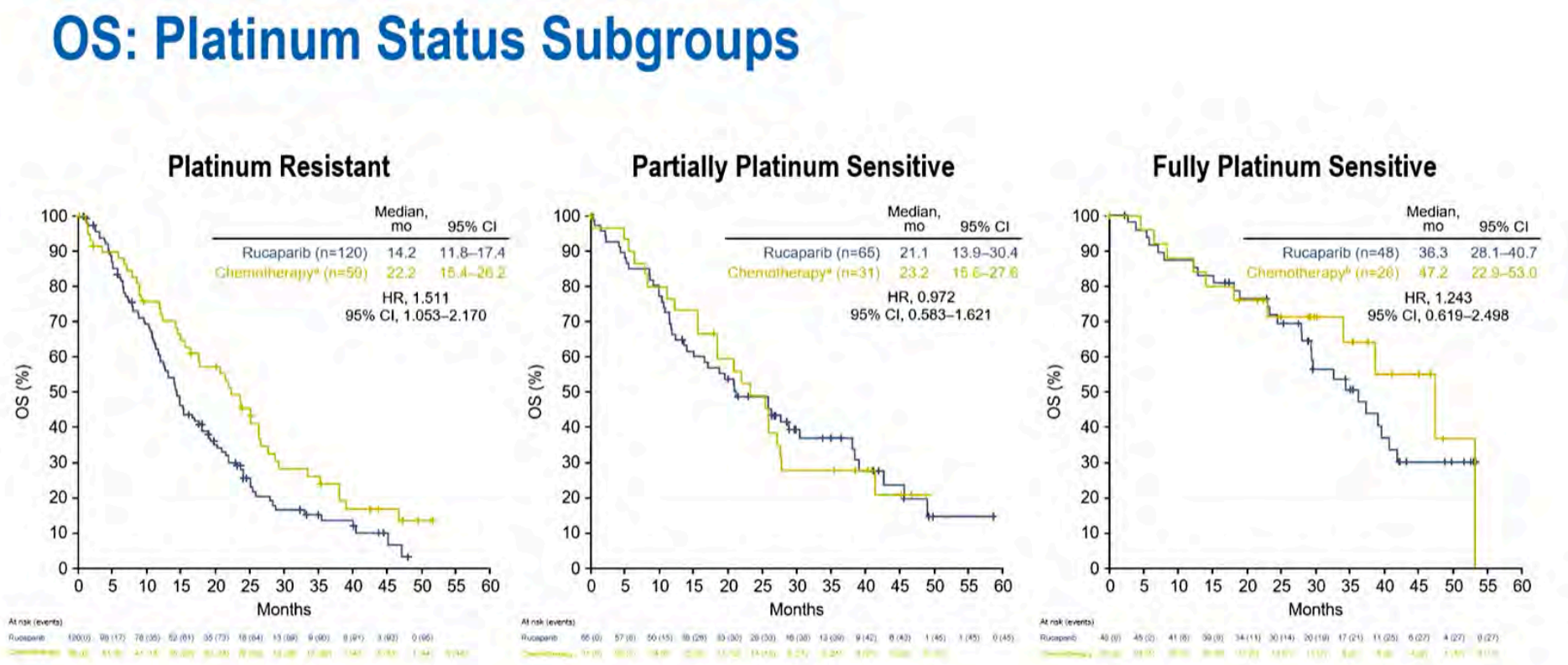
Impact on OS?



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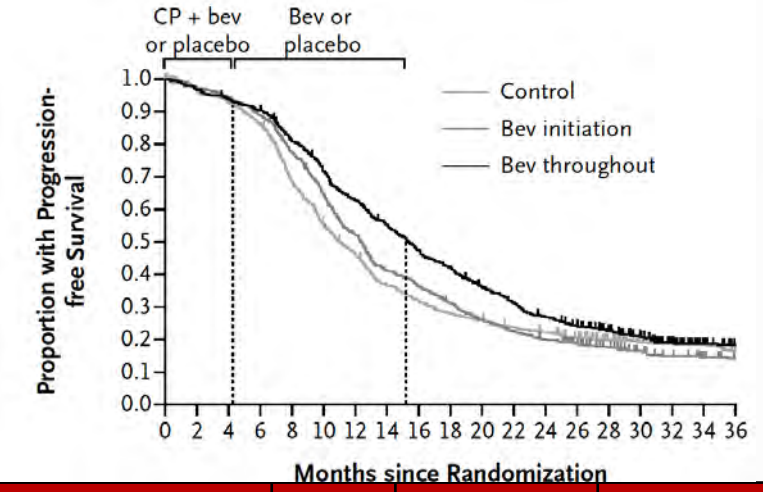
First Line

GOG FOUNDATION® Transforming the standard of care

GOG PARTNERS

Bev as maintenance therapy in 1st line therapy
showing a statistically significant improvement in PFS

GOG-0218[1] | Combination and maintenance bevacizumab with chemotherapy

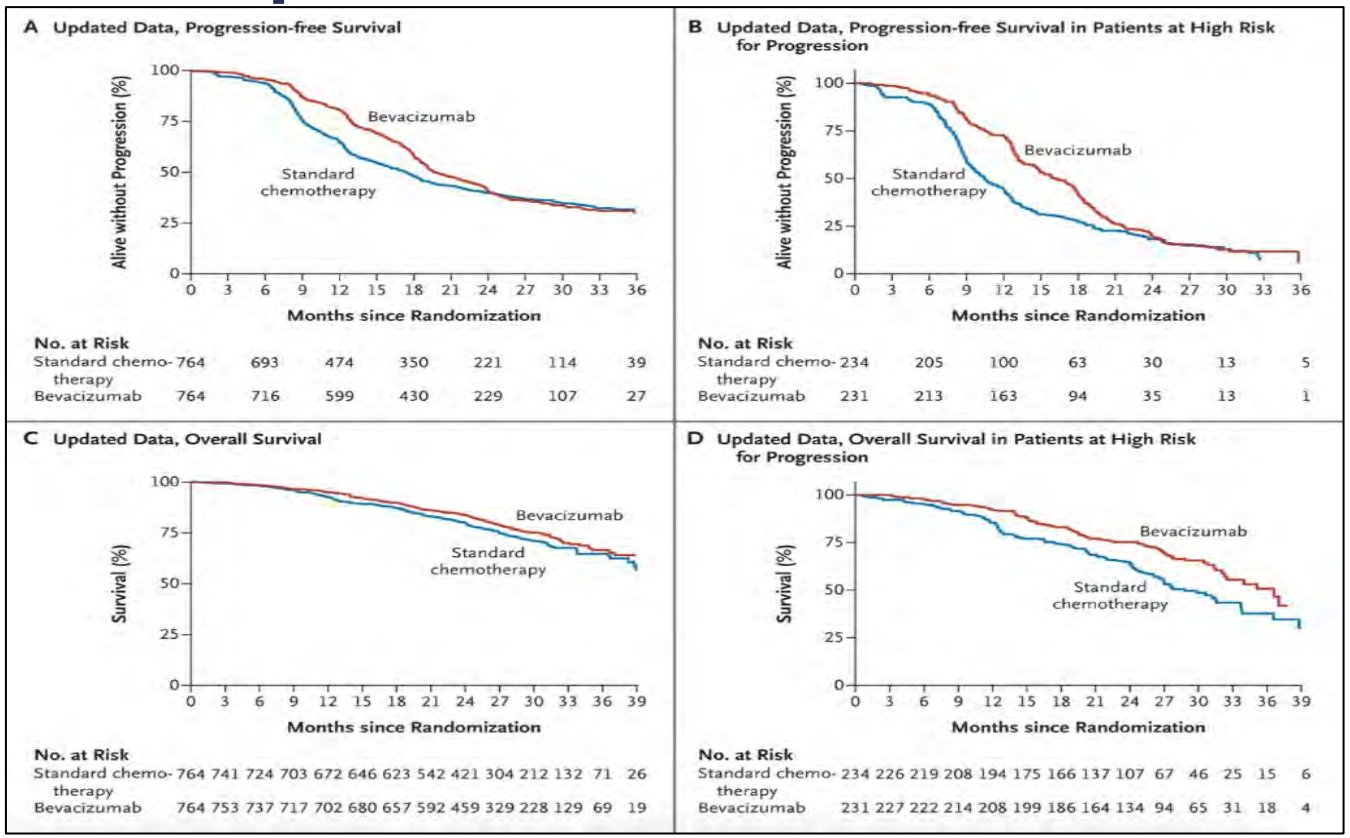


	CPP (n = 625)	CP + Bev (n = 625)	CP + Bev → Bev (n = 623)
Patients with event, n (%)	423 (68)	418 (69)	360 (58)
Median PFS, mo	10.3	11.2	14.1
Stratified analysis HR (95% CI)		0.908 (0.795-1.040)	0.717 (0.625-0.824)
One-sided P (log rank)		.16	<.001
Updated median PFS, mo	**12.0**	**12.8**	**18.2**
Stratified HR (95% CI)		**0.83 (0.70, 0.98)**	**0.62 (0.52, 0.75)**
Two-sided *p*-value		**Not significant**	**<0.0001**

- Focus on the shape and separation of the curves
- What's important is not just where the median is, but how and when the curves separate.
  - HR: 0.62
  - Shape of the Curve
    - Banana Curve

1. Burger RA, et al. *N Engl J Med* 2011;365:2473–2483;

ICON7: Updated PFS and OS



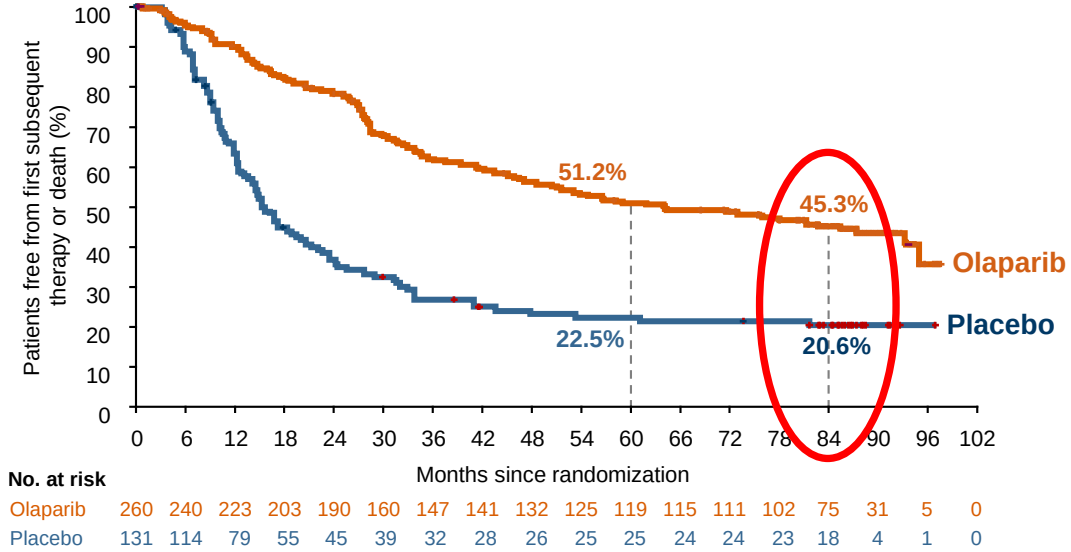
Final OS Results	Standard chemotherapy	Bevacizumab	log-rank
Restricted mean survival time	44.6 months	45.5 months	*P* = .85
Poor prognosis patients restricted mean survival time	34.5 months	39.3 months	*P* = .03
Non-high-risk patients restricted mean survival time	49.7 months	48.4 months	*P* = .20

OS, overall survival; PFS, progression-free survival.

Perren et al. *N Engl J Med.* 2011;365:2484-2496; Oza et al. *Lancet Oncol.* 2015;16:928-936.

The Tails of the Curves

SOLO1/GOG-3004:
Maintenance Olaparib Time to First Subsequent Therapy



	Olaparib (n = 260)	Placebo (n = 131)
Events, n (%)	135 (51.9)	98 (74.8)
Median TFST, months	**64.0**	**15.1**
	HR 0.37 (95% CI 0.28–0.48)	

- The median PFS is informative, but the **large proportion of long-term progression-free patients** (the tail) that the median alone understates.

- Median summarizes the 50% event time but **misses the clinical importance of the tail** (patients who remain progression-free long after the median), so using median alone underestimates long-term benefit.

CI, confidence interval; HR, hazard ratio

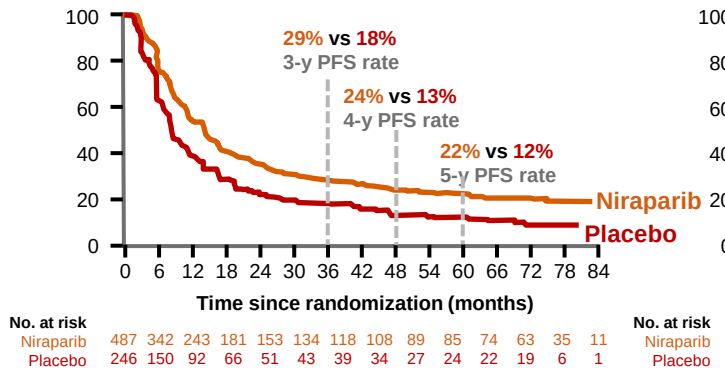
DiSilvestro P. Presented at ESMO 2022. September 9-13. Paris, France. Presentation 5170.

PRIMA/GOG-3012:

PFS in Overall, HRd, HRp Patient Populations

Overall Population

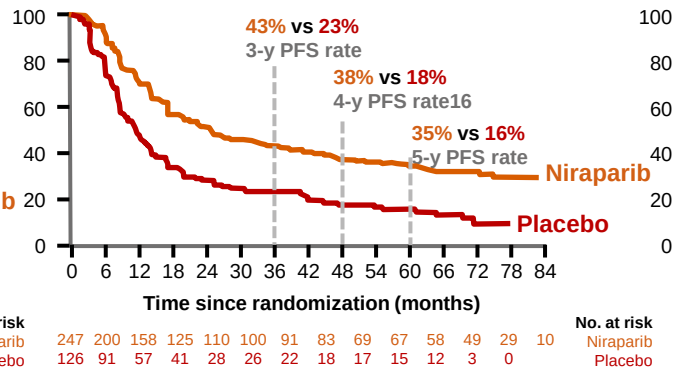
HR (95% CI)**: 0.66** (0.55–0.78)



No. at risk														
Niraparib	487	342	243	181	153	134	118	108	89	85	74	63	35	11
Placebo	246	150	92	66	51	43	39	34	27	24	22	19	6	1

HRd Population

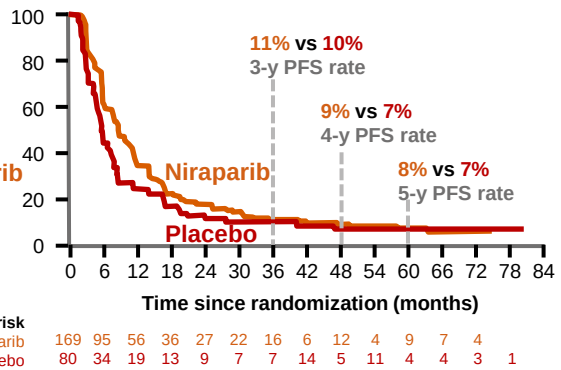
HR (95% CI)**: 0.51** (0.40–0.66)



No. at risk														
Niraparib	247	200	158	125	110	100	91	83	69	67	58	49	29	10
Placebo	126	91	57	41	28	26	22	18	17	15	12	3	0	

HRp Population

HR (95% CI)**: 0.67** (0.50–0.89)

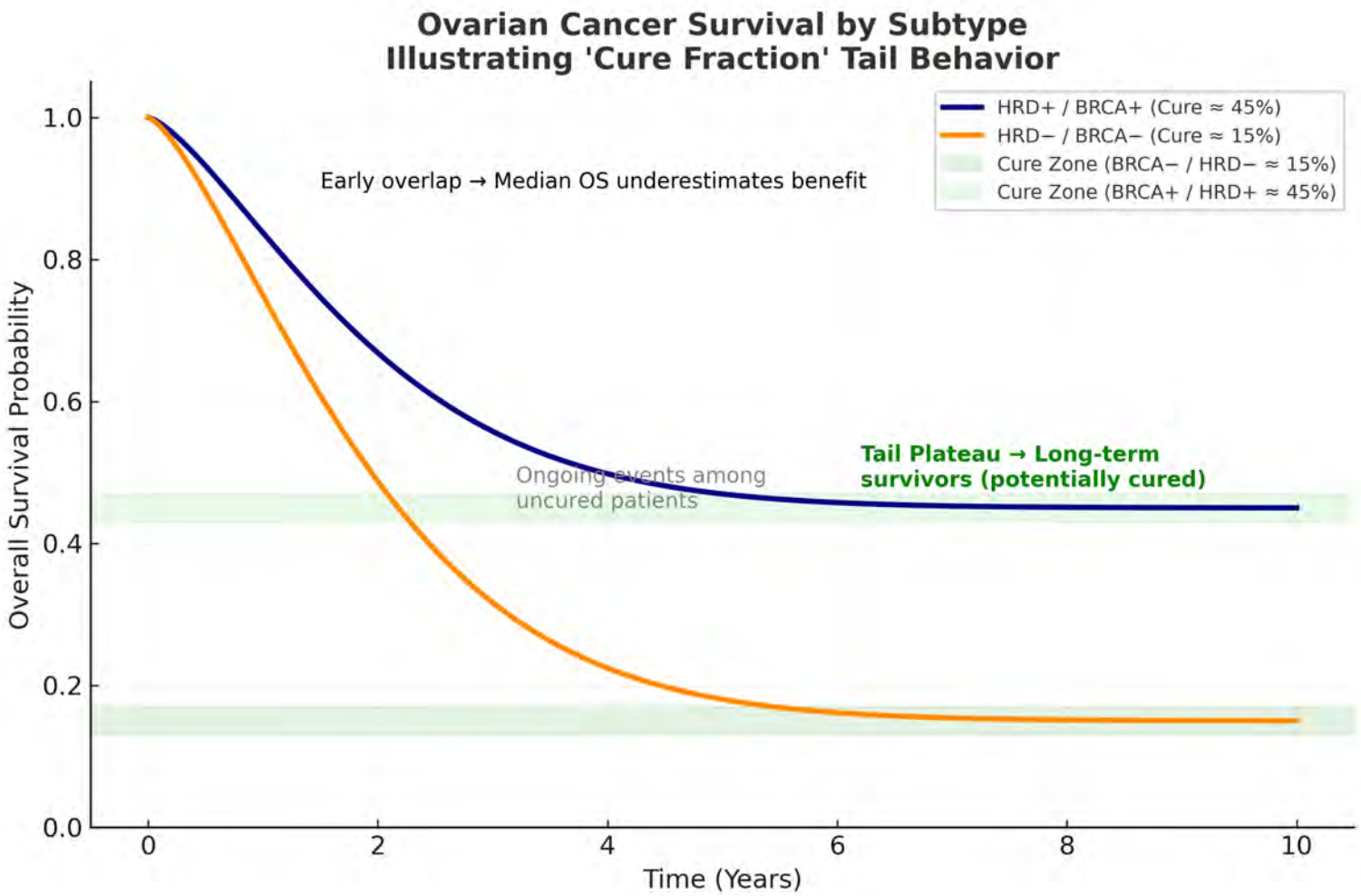


No. at risk														
Niraparib	169	95	56	36	27	22	16	6	12	4	9	7	4	
Placebo	80	34	19	13	9	7	7	14	5	11	4	4	3	1

- Data cutoff date: April 8, 2024, median follow-up of 6.2 years
- Among patients alive at 5 years in the HRd population, patients who received niraparib were twice as likely to be progression free (35%) than patients who received placebo (16%)
- Delaying progression is critical to maintain health-related quality of life[1]

CI, confidence interval; HRd, homologous recombination deficient; HRp, homologous recombination proficient; No., number; PFS, progression-free survival.

1. Chase DM, et al. *Gynecol Oncol*. 2022;166(3):494-502. 2. González-Martin A, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting; 13-17 September 2024; Barcelona, Spain.


Ovarian Cancer Survival by Subtype
Illustrating 'Cure Fraction' Tail Behavior
HRD+ / BRCA+ (Cure ≈ 45%)
HRD− / BRCA− (Cure ≈ 15%)
Cure Zone (BRCA− / HRD− ≈ 15%)
Cure Zone (BRCA+ / HRD+ ≈ 45%)
Early overlap → Median OS underestimates benefit
Ongoing events among uncured patients
Tail Plateau → Long-term survivors (potentially cured)
Overall Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
Time (Years)

Challenges of Overall Survival in First Line Therapy

1) Unmeasured variables
2) Prolonged post-progression survival
3) High rates of treatment crossover
4) Imbalances in subsequent lines of therapy

Monk BJ, Coleman RL, O'Malley DM, Moore KN, González-Martín A, Herzog TJ. Decoding the End Points of Poly (ADP-ribose) Polymerase Inhibitor Trials in Ovarian Cancer. J Clin Oncol. 2025 Oct 31:JCO2501721. doi: 10.1200/JCO-25-01721. Epub ahead of print. PMID: 41172232.

Are There Alternatives to Consider?

- **Landmark survival rates** at clinically meaningful times (e.g., 2-yr, 3-yr, 5-yr PFS/OS) — direct, intuitive.
- **Restricted Mean Survival Time (RMST)** difference over a pre-specified follow-up window — captures average time gained.
- **Proportion progression-free / alive at fixed timepoints** (with 95% CIs).
- **Visual inspection** of curve shape (timing of separation, plateau, censoring density).

Pazdur R et al. Endpoints for assessing drug activity in clinical trials. J Natl Cancer Inst. 1999;91(17):1281-1287.
Broglio KR, Berry DA. Detecting an overall survival benefit that is derived from progression-free survival. J Natl Cancer Inst. 2009;101(23):1642-1649
Royston P, Parmar MKB. The use of restricted mean survival time to estimate treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt. Stat Med. 2013;32(28):4698-4715.
FDA Guidance for Industry. Clinical trial endpoints for the approval of cancer drugs and biologics. U.S. FDA, 2018.
Pazdur R, Blumenthal GM. Assessing benefit in cancer trials with non-proportional hazards. Clin Cancer Res. 2019;25(9):2677-2682.
Anderson KM et al. Visualizing survival curves: beyond the median. Clin Trials. 2021;18(3):269-277.

Are There Models Which Predicts the Probability of Curative Intent?

Approach	Predicts	Statistical Form	Typical Use
Cure Model (Mixture/Non-mixture)	Biological cure probability	Parametric survival with logistic component	Long-term survival studies
Logistic Regression	Curative vs palliative treatment decision	Binary logistic	Health services / registry data
Cox or Parametric Survival Models	Long-term survival (proxy for cure)	Survival regression	Clinical nomograms
Bayesian Cure Rate Models	Posterior cure probability	Hierarchical Bayesian	Research modeling

Andersson TM et al., *J Clin Oncol* 2018;36(10):951–959.

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Royston P, Parmar MKB. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modeling. Stat Med. 2002;21(15):2175–97.

Demicheli R, et al. Bayesian modeling of cure probability in recurrent ovarian cancer. Biostatistics. 2019;20(3):512–526.

Summary

- When describing these curves, remember: medians are just snapshots.
- HR tells you the overall direction, but the curve shape — its timing, tail, and censoring pattern — reveals the real clinical behavior.
- In platinum-resistant ovarian cancer, these curves stay apart — something we've haven't seen before.
- First Line Therapies - curative intent needs to be the goal
  - Need alternatives metrics to define curative intent
  - OS impact continues to be a challenge

Faculty Panel:
Treatment Integration and What's Next

All Faculty

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Audience Q&A

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Closing Remarks

Debra Richardson, MD,

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Thank You

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