XXII ASSEMBLEA MaNGO MILANO

STANDARD TREATMENTS AND NEW DIRECTIONS IN GYNAECOLOGICAL CANCERS

MILANO June 26th-29th, 2025

Responsabili Scientifici:
NICOLETTA COLOMBO, FRANCESCO RASPAGLIESI

MaNGO

New Approaches in Platinum Resistant Ovarian Cancer: the ADC's innovation

The therapeutic algorithm of recurrent disease: how ADCs could change clinical practice?

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IT-ELAH-250076
Presentation made on behalf of AbbVie. The content of the presentation has been created independently and autonomously

Conflict of interest

Ilaria Colombo

- Consultancy/Advisory/Expert Opinion: AZ, GSK, MSD, BionTech, Abbvie, Incyte, Beigene
- Institutional grants for clinical trials (PI): MSD, Bayer, Vivesto, Incyte, AZ, Orion, Tolremo, Debio.
- Member of the Advisory Board for the European School of Oncology (ESO)
- Vice President of the Gynecological Cancer Project Group for the Swiss Group for Clinical Cancer Research (SAKK)

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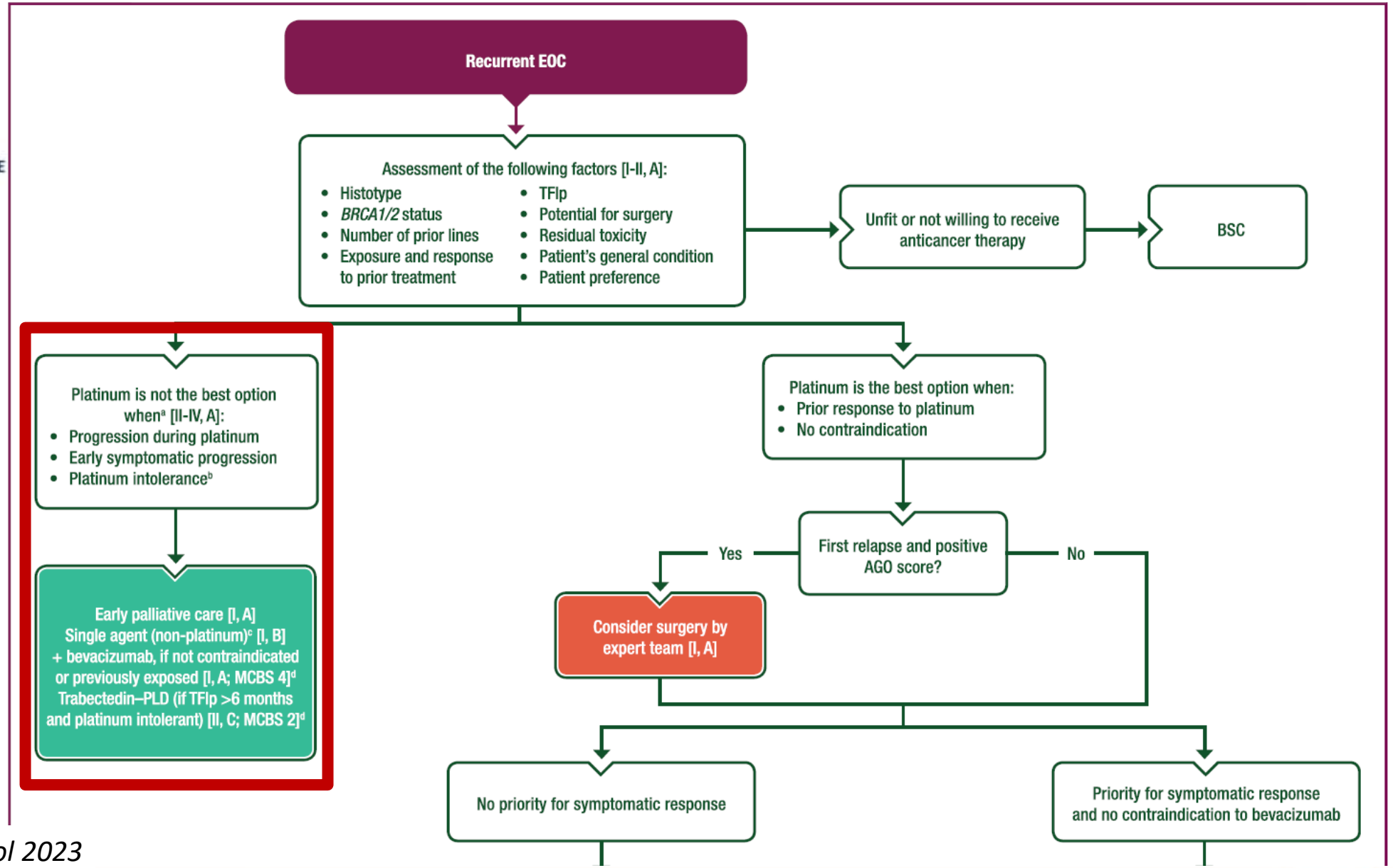
Guidelines

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE



Gonzalez-Martin, Ann Oncol 2023

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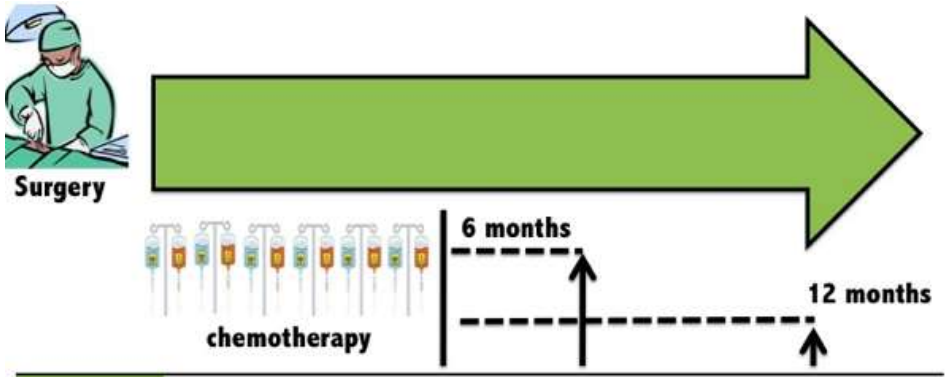
Evolution of platinum-resistance definition

Arbitrary 6 months cut-off



Platinum sensitivity classification	Refractory	Resistant	Partially sensitive	Sensitive
Probability of second platinum response	0%	< 10%	30%	> 50%

Tapia, 2013

ESMO

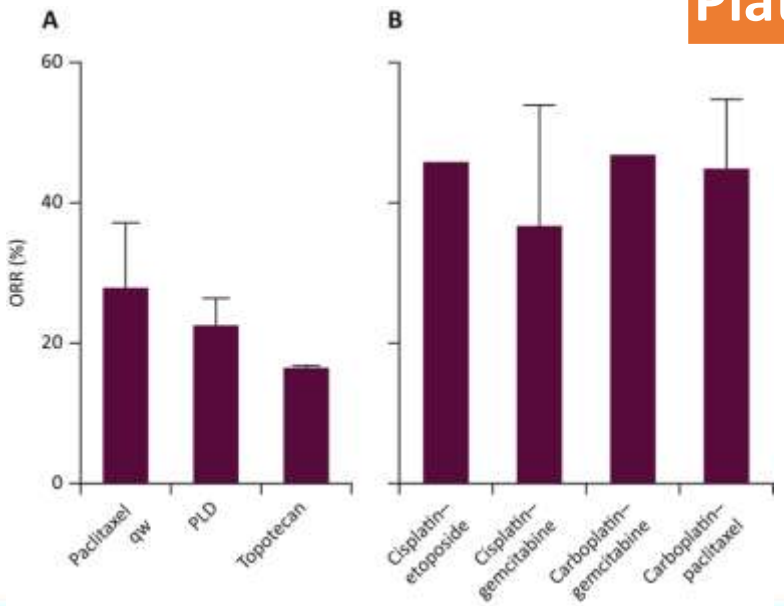
ANNALS OF ONCOLOGY

REVIEW

The systemic treatment of recurrent ovarian cancer revisited

T. Baert[1,2*], A. Ferrero[3], J. Sehouli[4], D. M. O'Donnell[5], A. González-Martín[6], F. Joly[7], J. van der Velden[8], P. Blecharz[9], D. S. P. Tan[10,11], D. Querleu[12], N. Colombo[13,14], A. du Bois[15] & J. A. Ledermann[16]

Platinum-eligibility



Baert, Ann Oncol 2021

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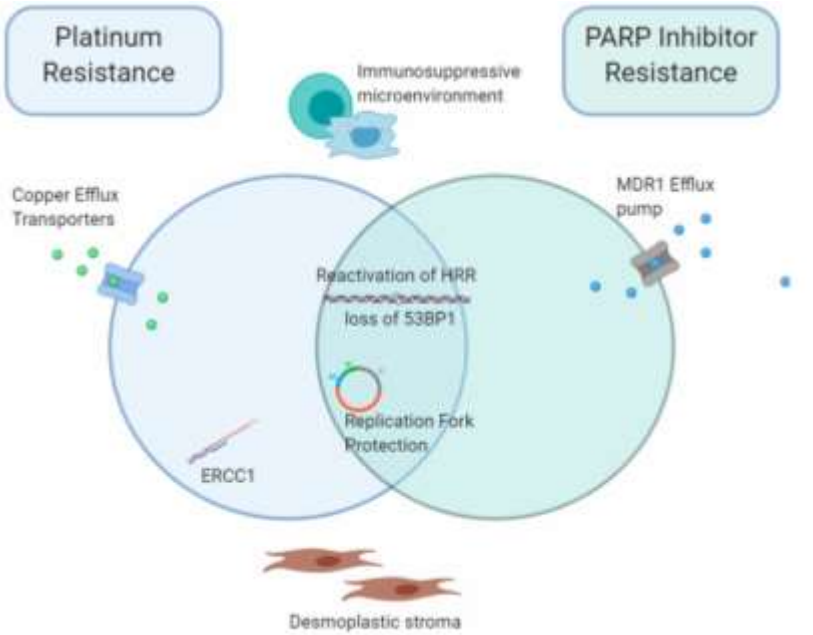
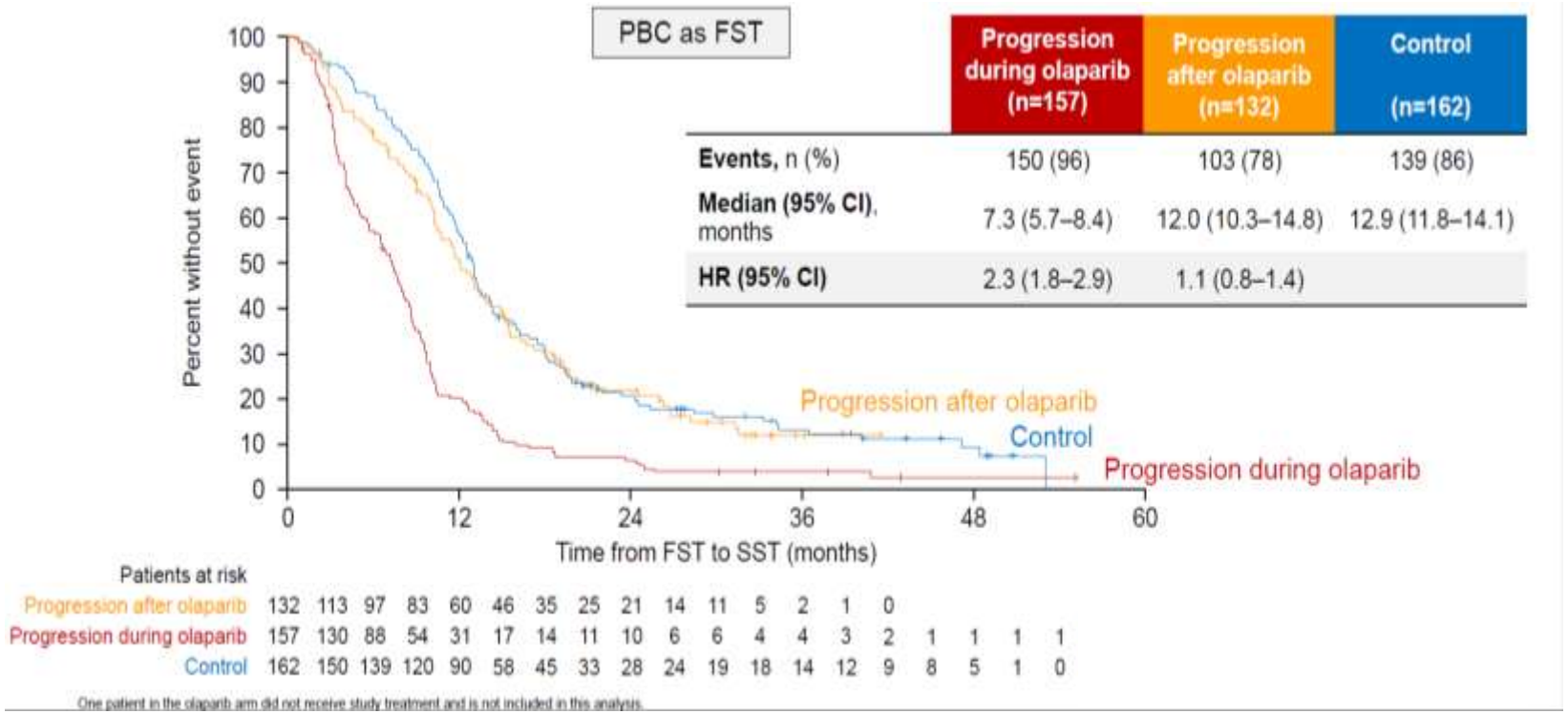
Progression to PARPi



McMullen, Cancers 2020

Effect of platinum after PD to PARPi in PAOLA1 trial

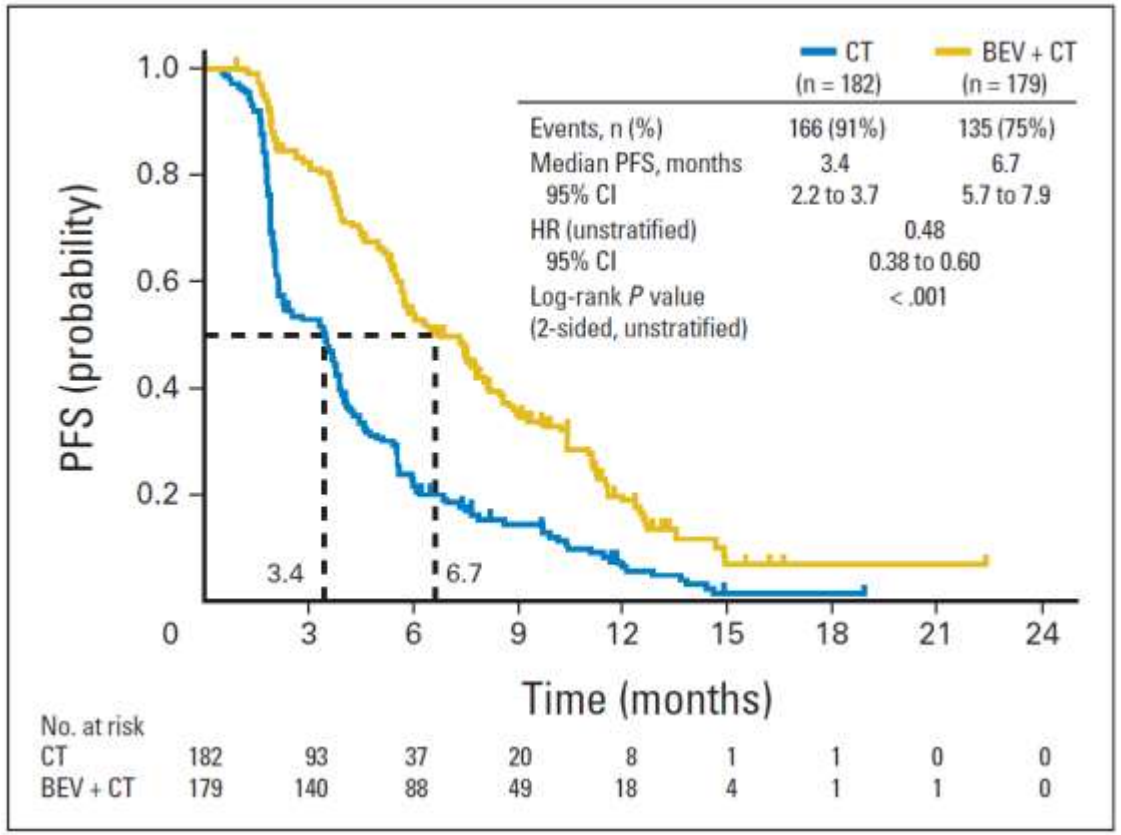


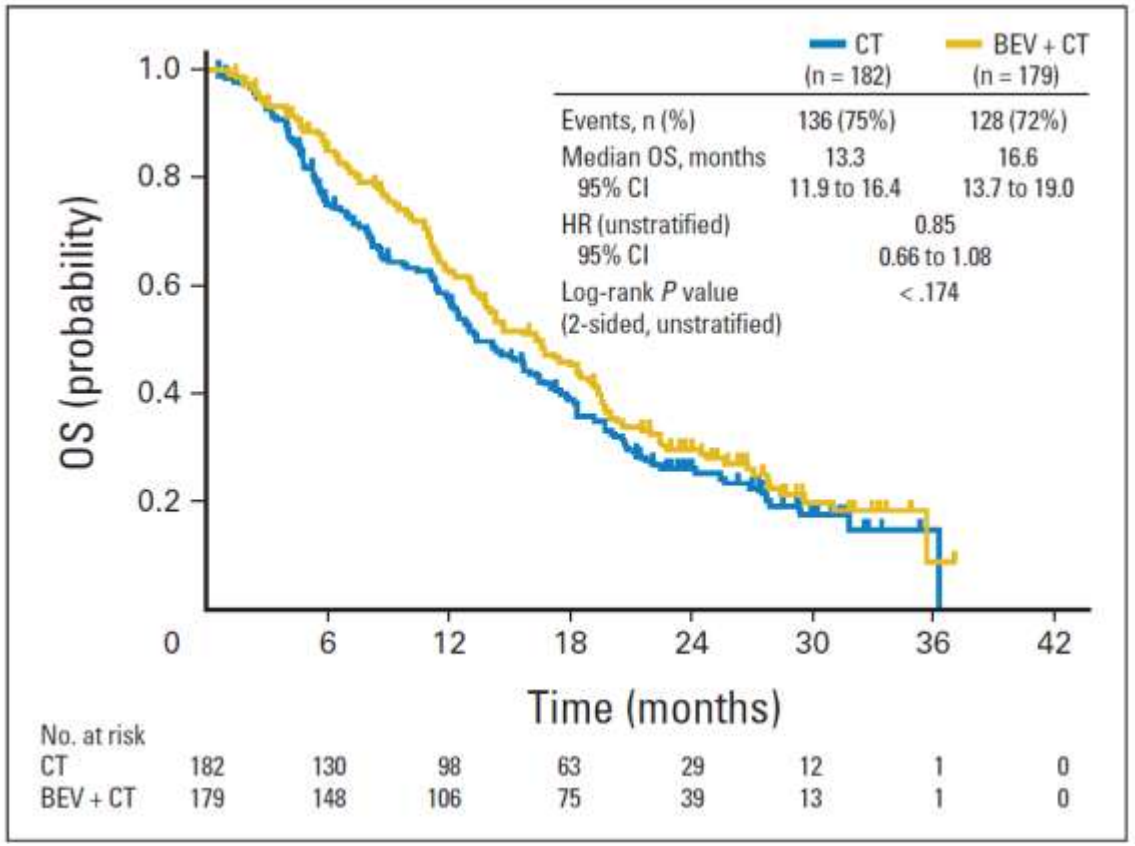
	Progression during olaparib (n=157)	Progression after olaparib (n=132)	Control (n=162)
Events, n (%)	150 (96)	103 (78)	139 (86)
Median (95% CI), months	7.3 (5.7–8.4)	12.0 (10.3–14.8)	12.9 (11.8–14.1)
HR (95% CI)	2.3 (1.8–2.9)	1.1 (0.8–1.4)	

Harter, Ann Oncol 2025

Target therapies in platinum resistant ovarian cancer

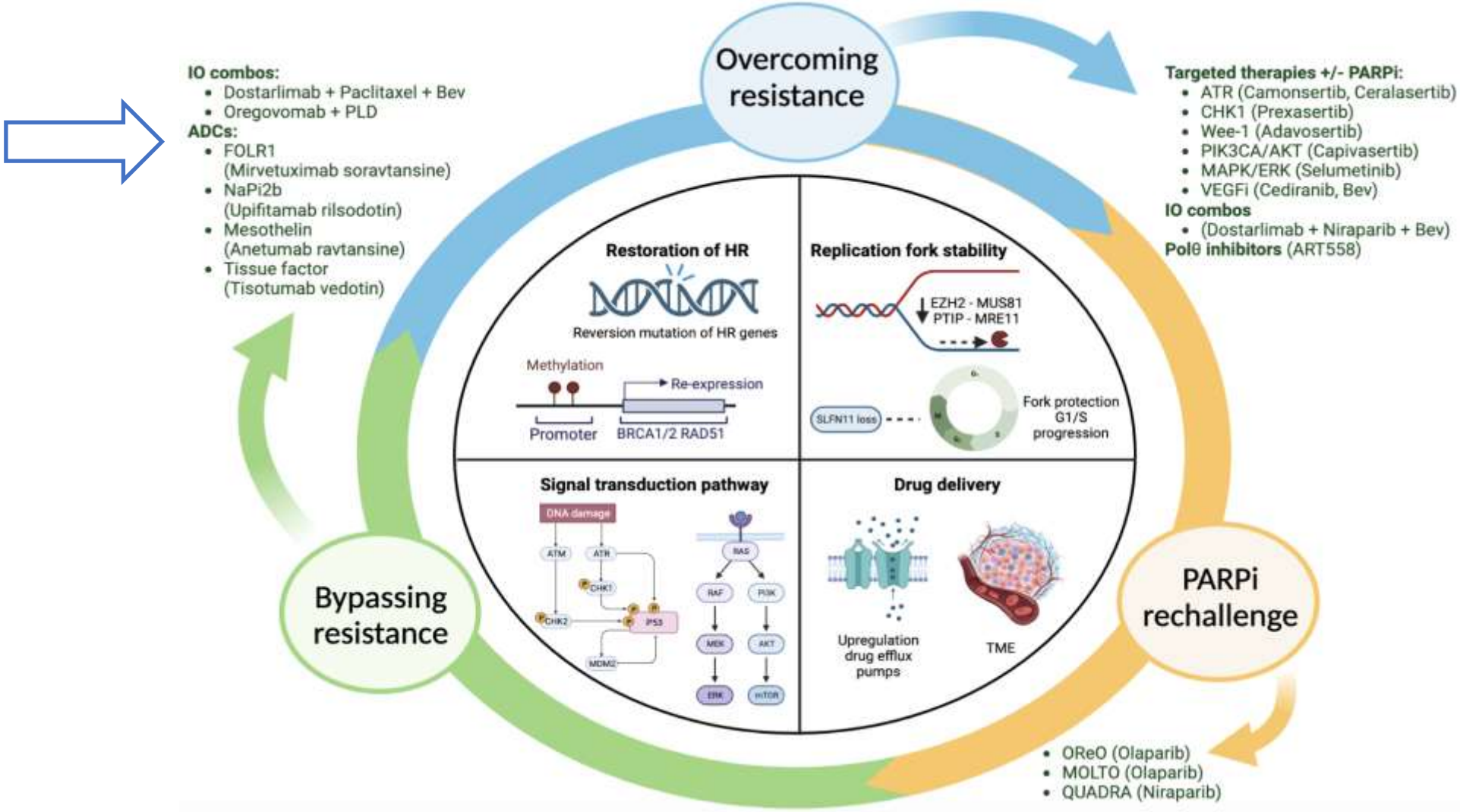
AURELIA Trial: Bevacizumab plus single agent chemotherapy





Pujade-Lauraine, JCO 2014

Treatment options to overcome resistance



Gonzalez-Ochoa E, Oza AM CCR 2023

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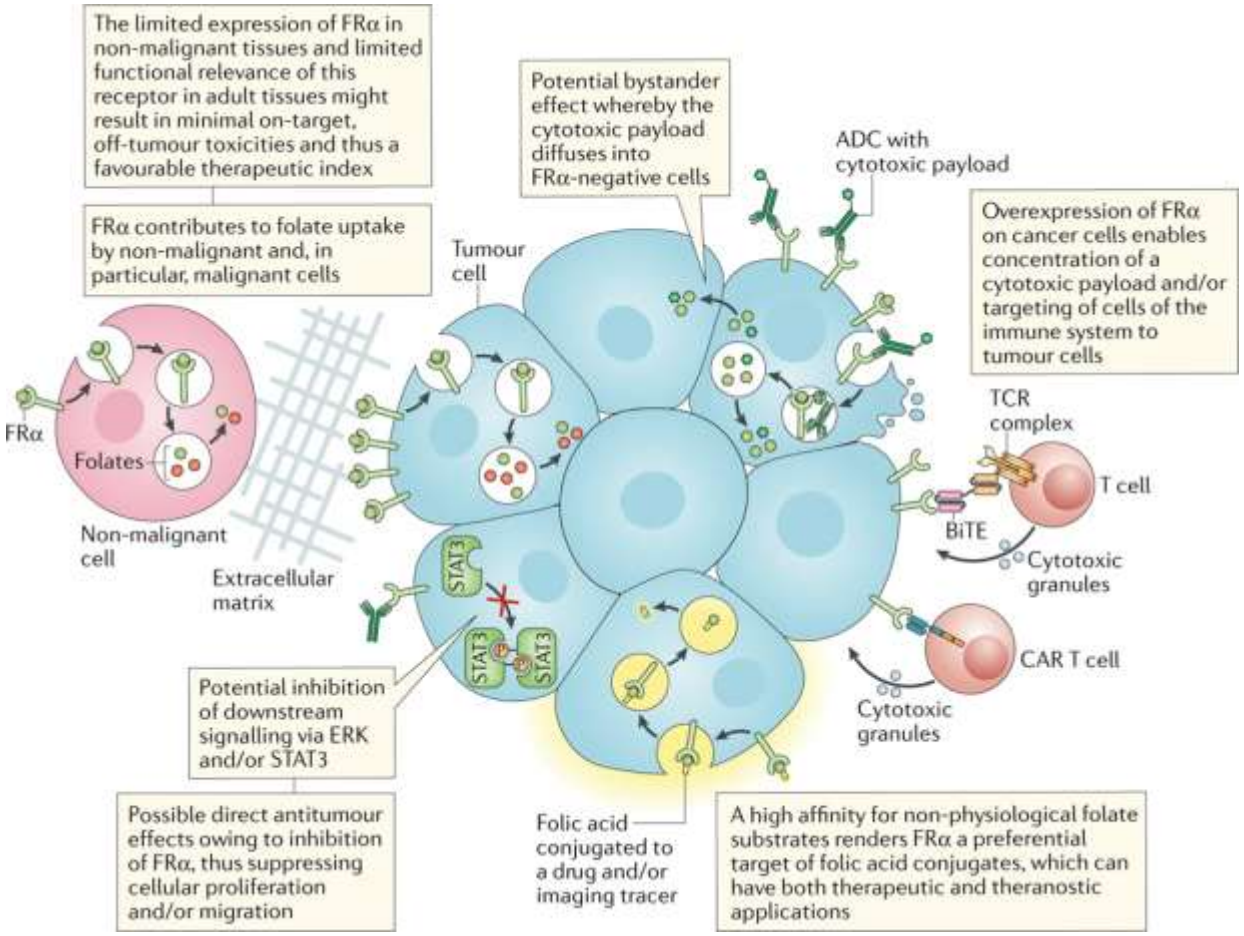
Mirvetuximab Soravtansine in Ovarian Cancer



- **Folate Receptor alfa (FRα) is a cell surface folate receptor** that mediates folate transport into epithelial cells
- Involved in **pro-survival signals** in ovarian cancer
- **Expression is limited in normal cells**
- **High expression on the surface of epithelial ovarian cancer** cells as determined by immunohistochemistry

Scaranti, Nat Rev Clin Oncol 2020

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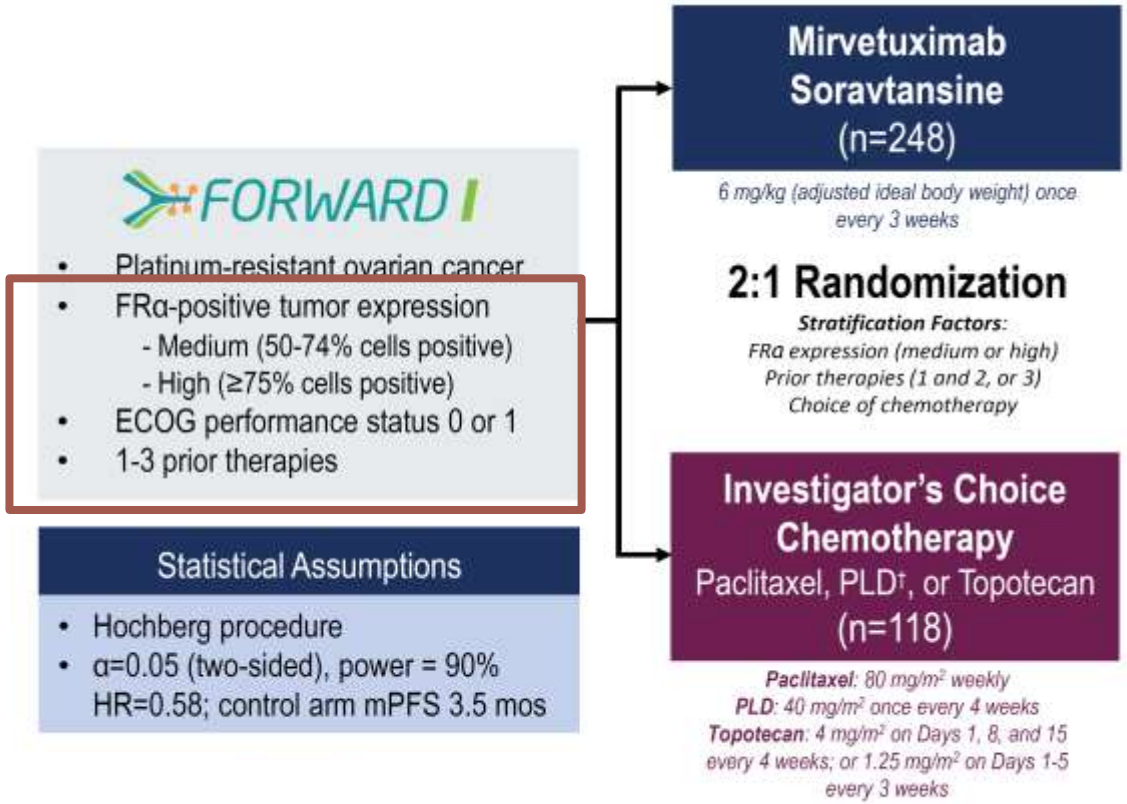
Mirvetuximab Soravtansine: FORWARD 1 trial

Phase 3 trial in medium-high FRα



Primary Endpoint

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

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

Secondary Endpoints

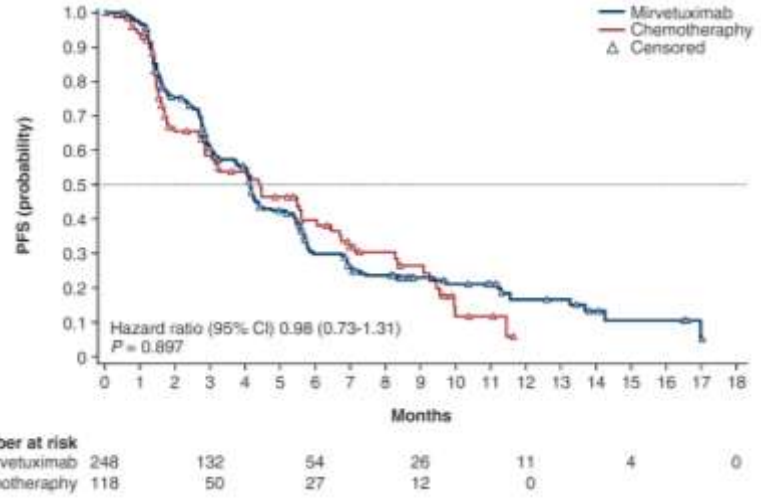
Overall response rate (ORR)
Overall survival (OS)
Patient reported outcomes (PRO)

†Pegylated liposomal doxorubicin
ClinicalTrials.gov Identifier: NCT02631876

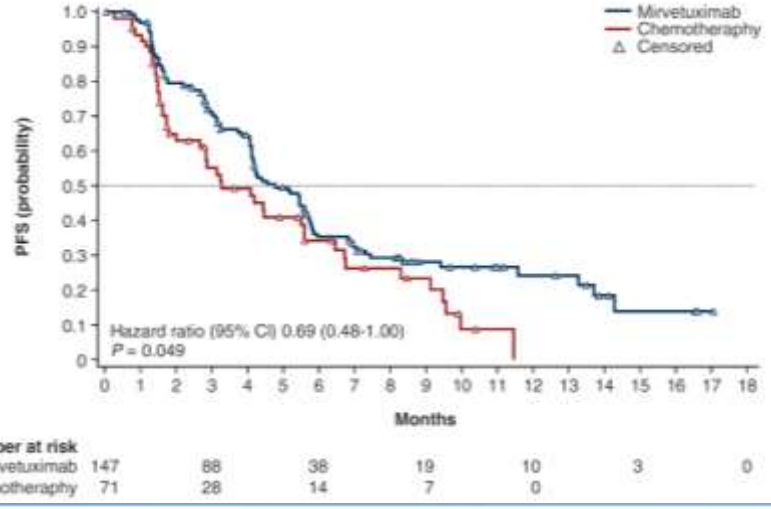
Moore, Ann Oncol 2021

Mirvetuximab Soravtansine: FORWARD 1 trial

ITT population



FRα high



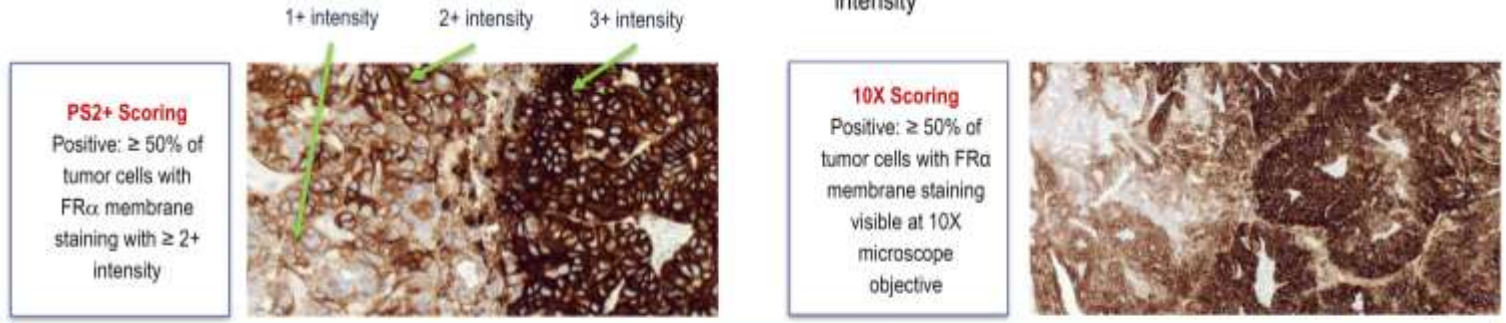
The importance of the biomarker

PS2+ Scoring

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

10X Scoring

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



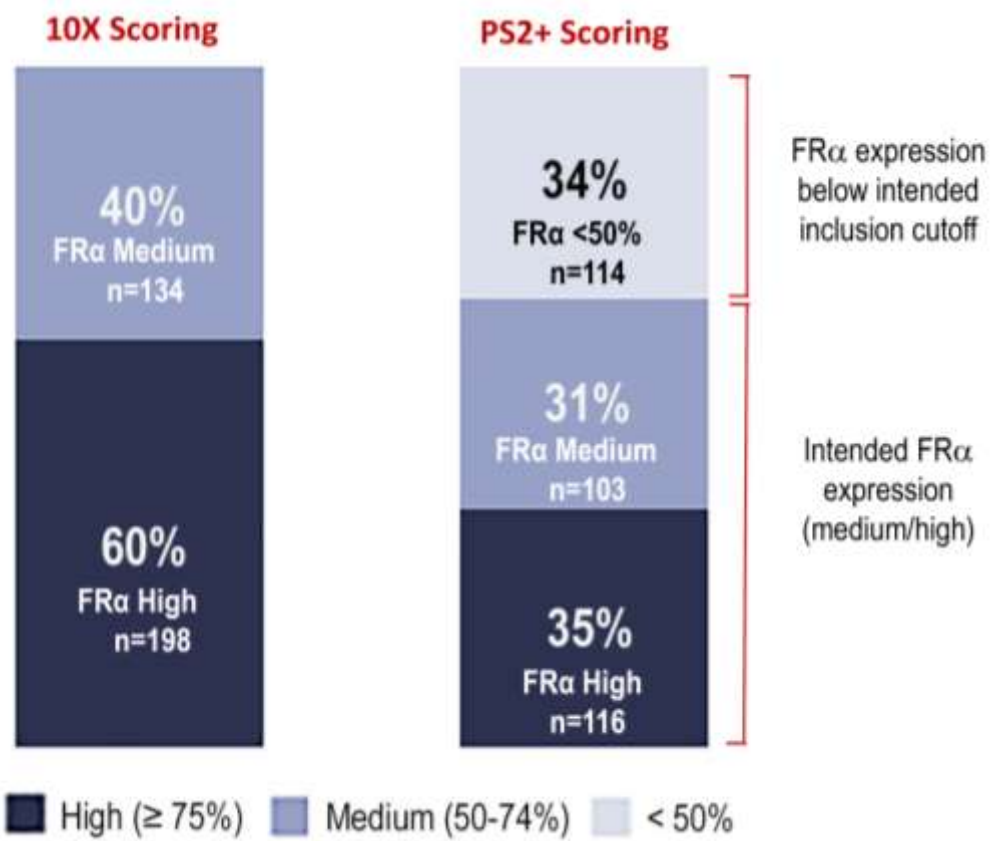
Bridging study indicated that 10X scoring was sufficient for patient selection

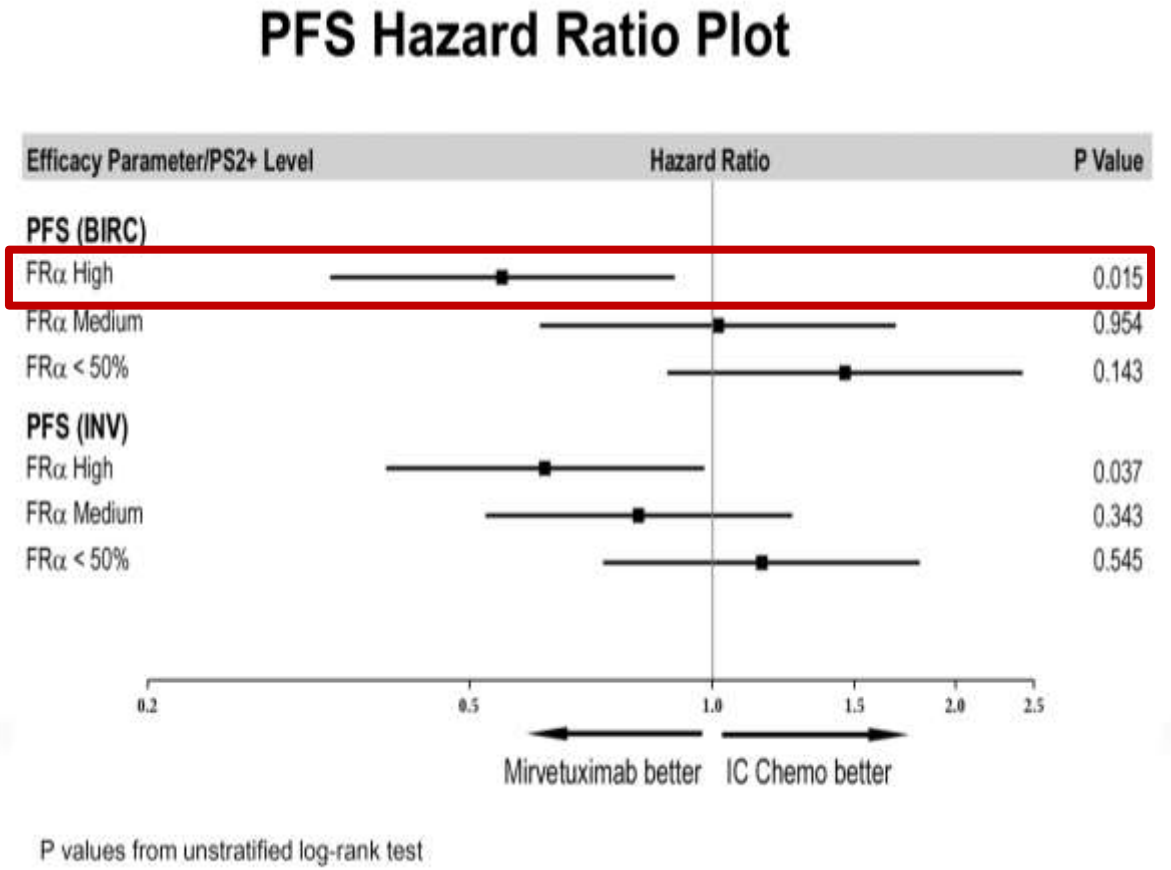
Exploratory analyses suggest that the change in scoring method from PS2+ to 10X introduced a population of patients into FORWARD I with lower levels of FRα expression than intended

Moore, Ann Oncol 2021

Mirvetuximab Soravtansine: the importance of biomarker

Efficacy according the FRα scoring

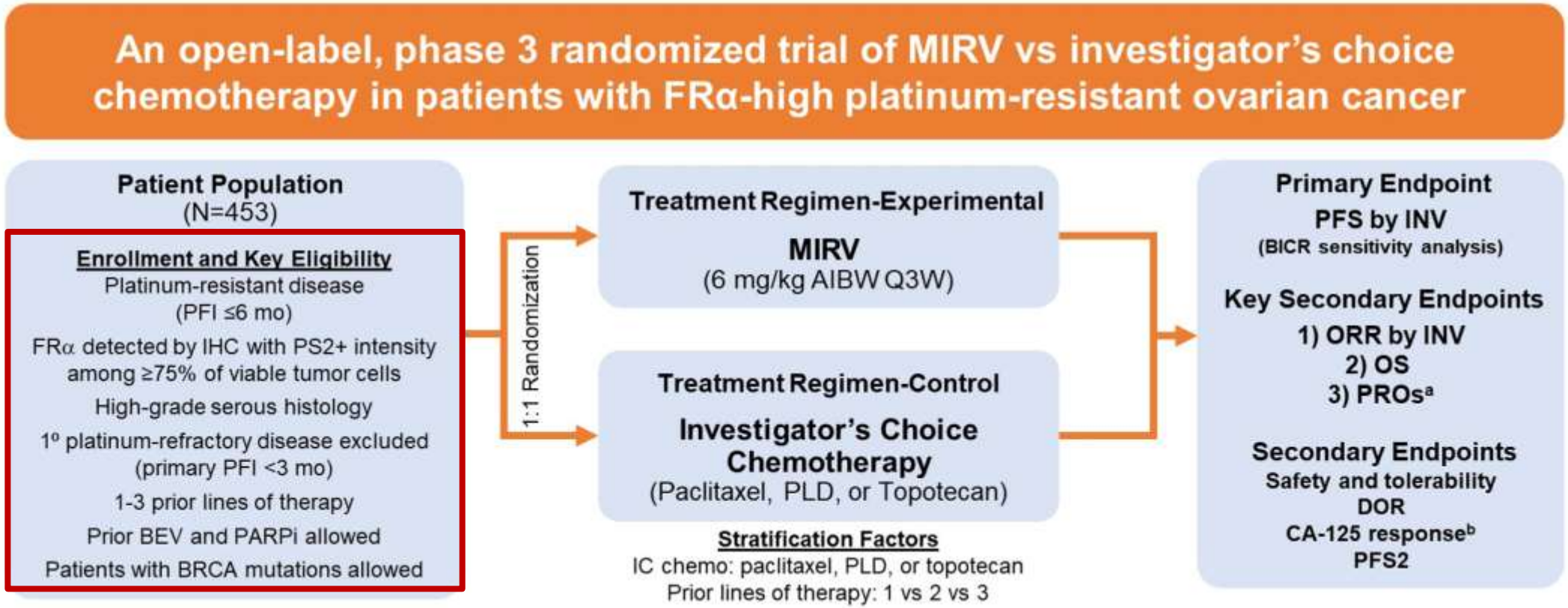




Moore, Ann Oncol 2021

Mirvetuximab Soravtansine: MIRASOL trial

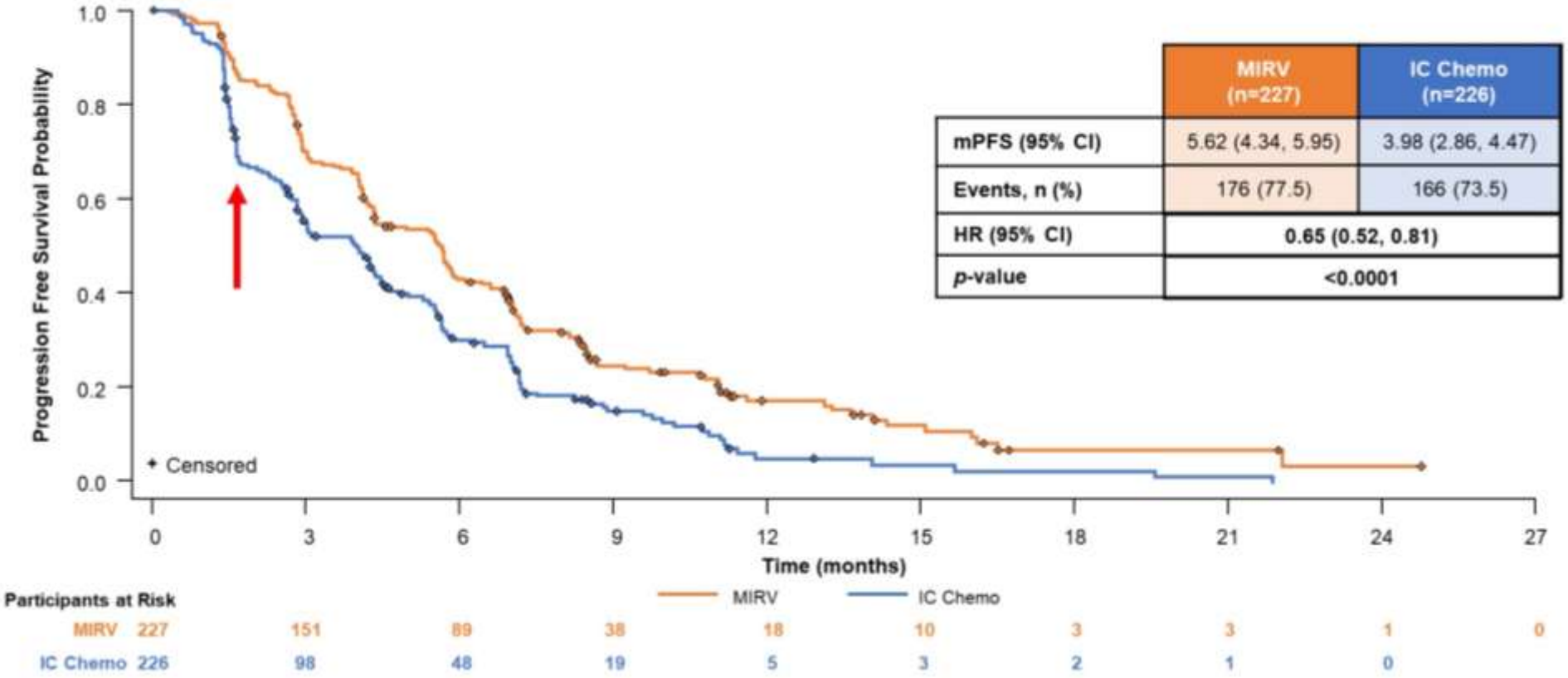
High FRα expression



Moore, NEJM 2023

MIRASOL trial: Efficacy

Primary Endpoint: Progression-Free Survival by Investigator



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

Moore, NEJM 2023

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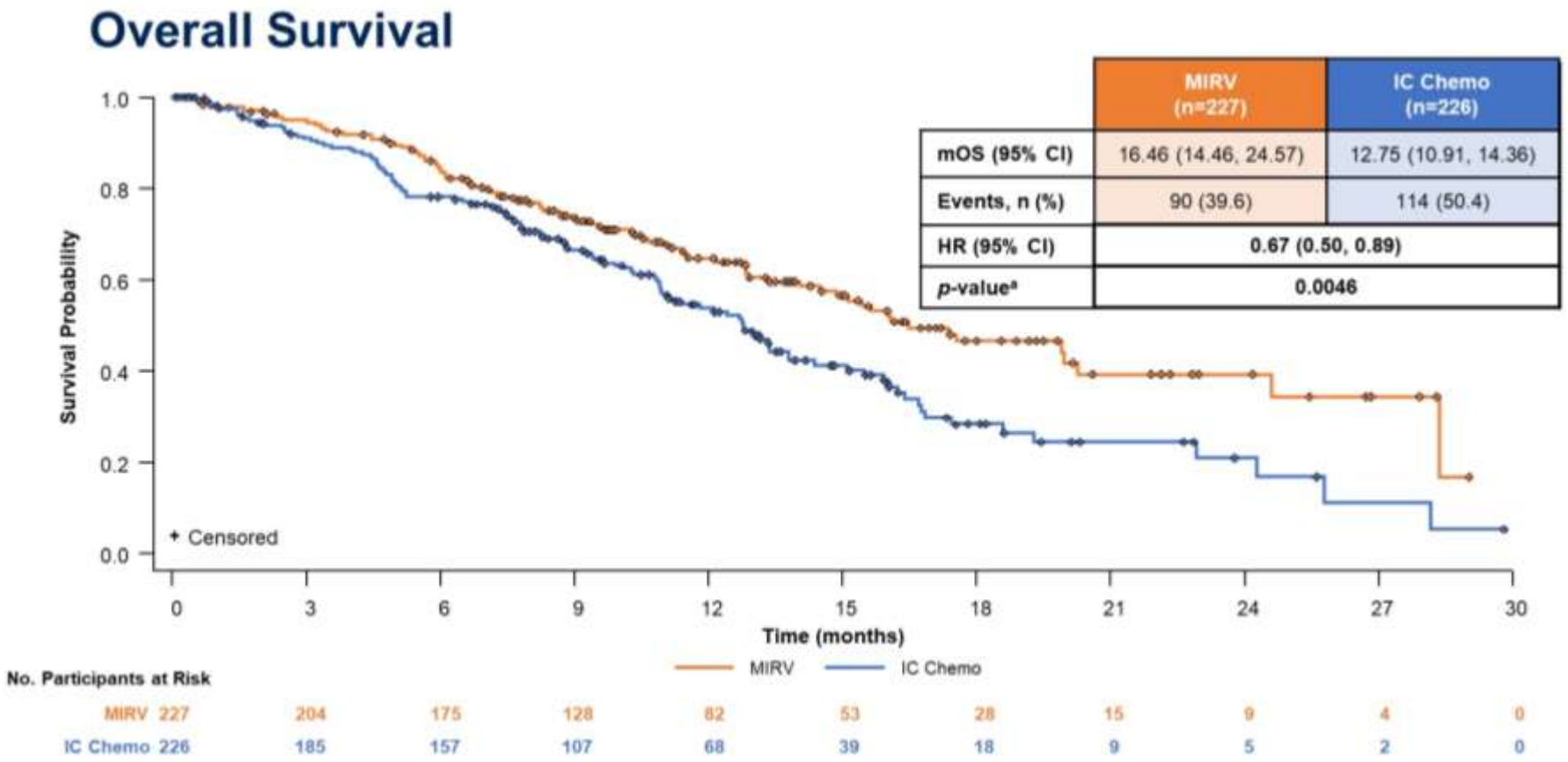
MIRASOL trial: Efficacy



	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	

Moore, NEJM 2023

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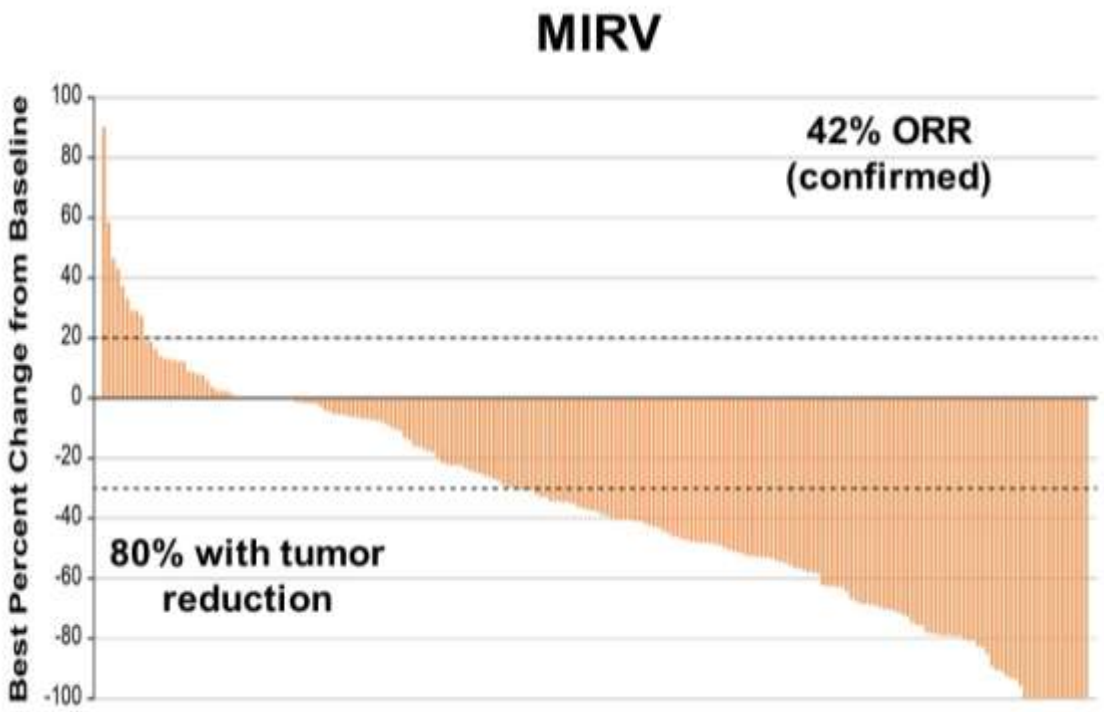
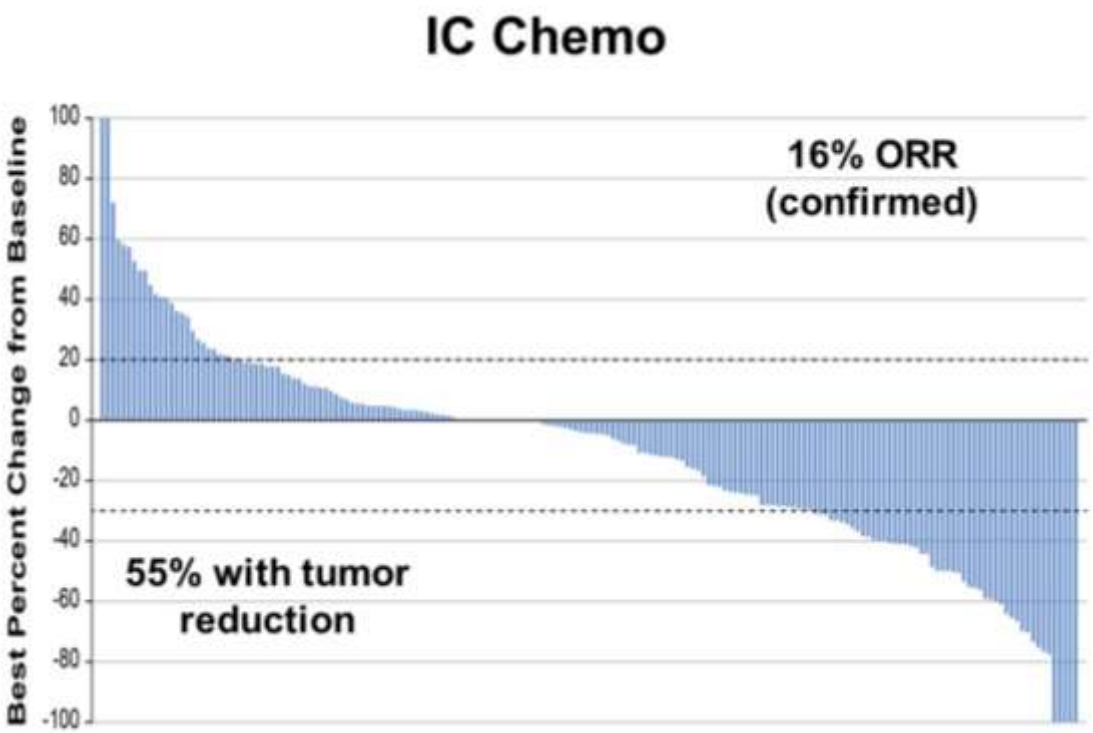
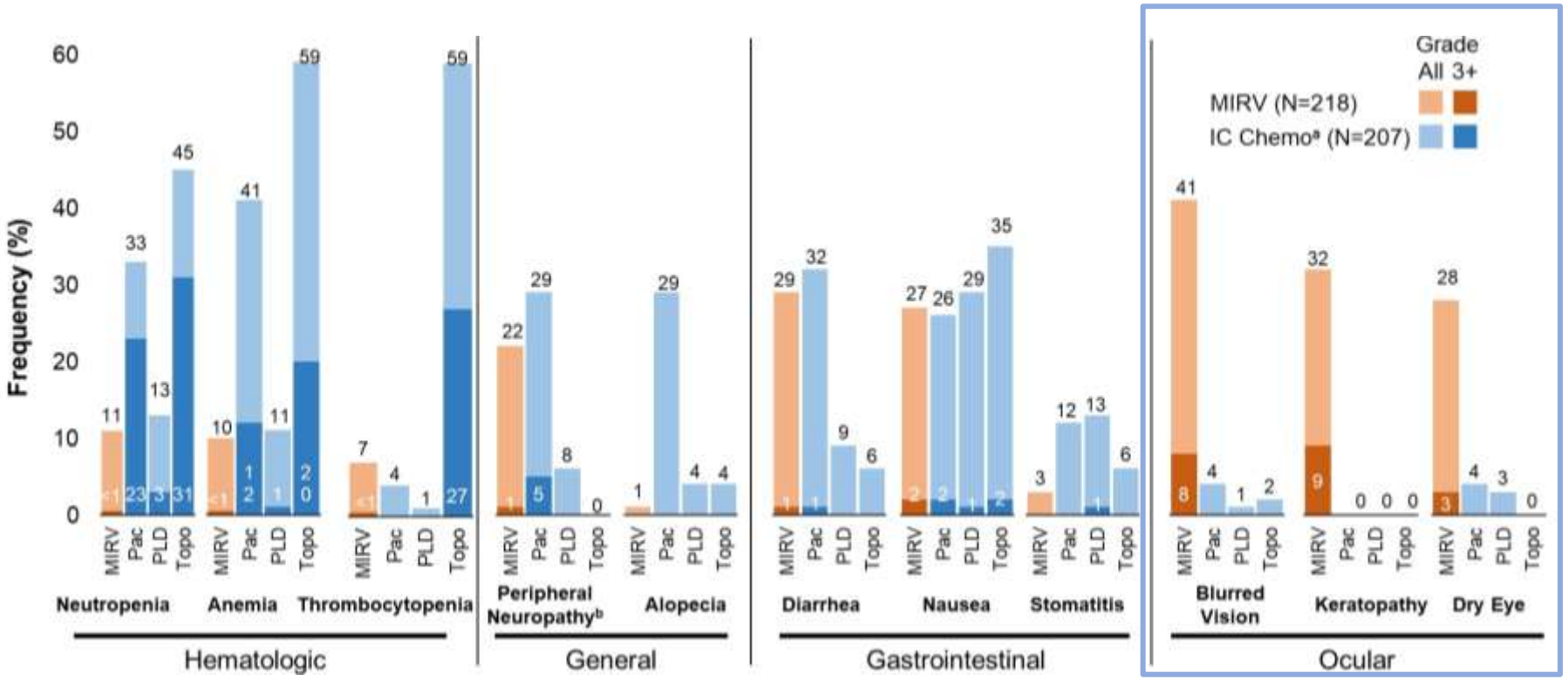
MIRASOL trial: Efficacy





Moore, NEJM 2023

MIRASOL trial: Safety

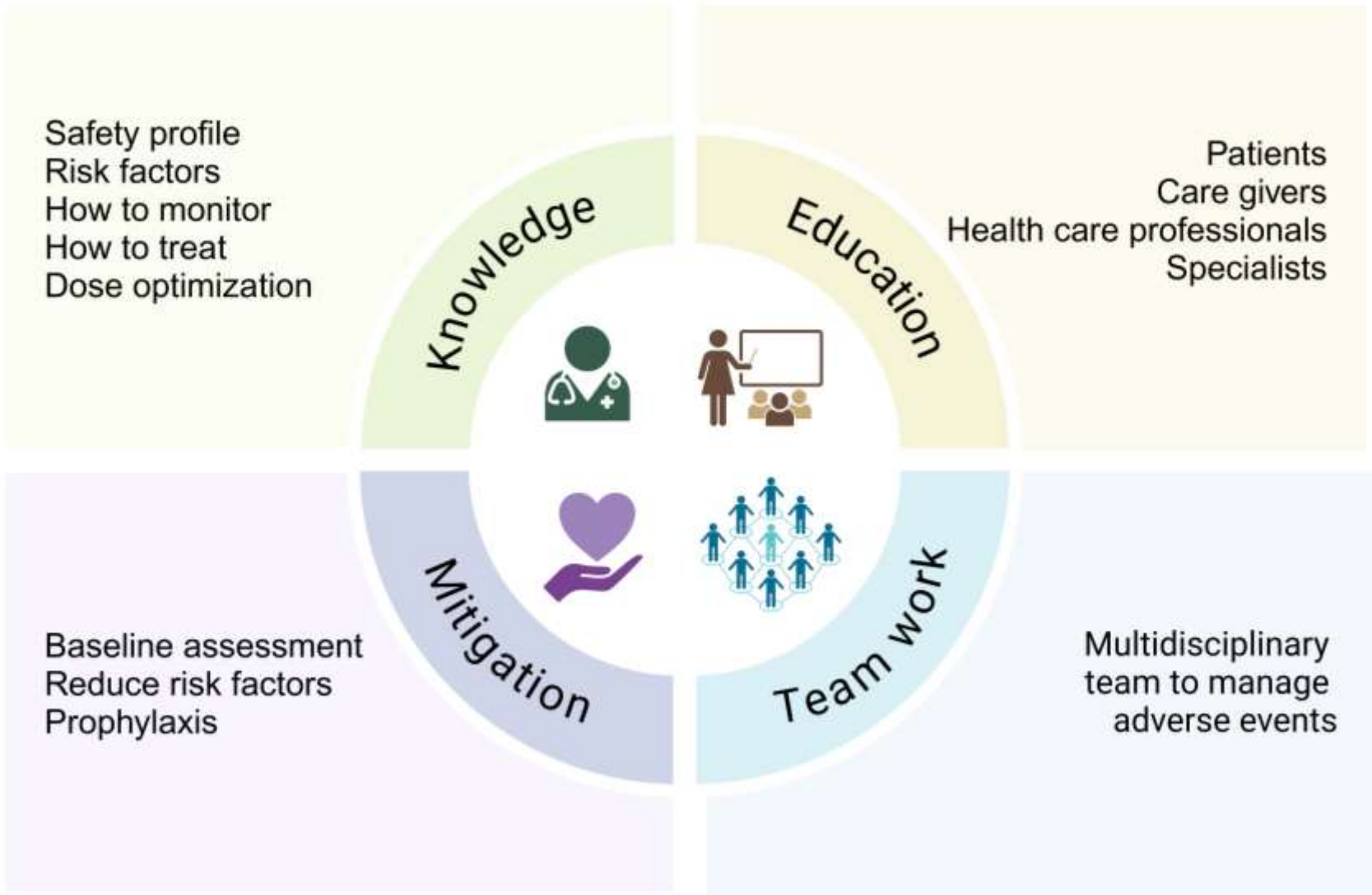


- 56% **ocular AE**
- Majority **resolved to G≤1**
- **No G4**
- **Median time onset**: 5.4 weeks
- 4 pts (1.8%) **discontinue** due to ocular AE
- No corneal ulceration or perforations and no permanent alterations

Moore, NEJM 2023

IT-ELAH-250076

How to manage safety?



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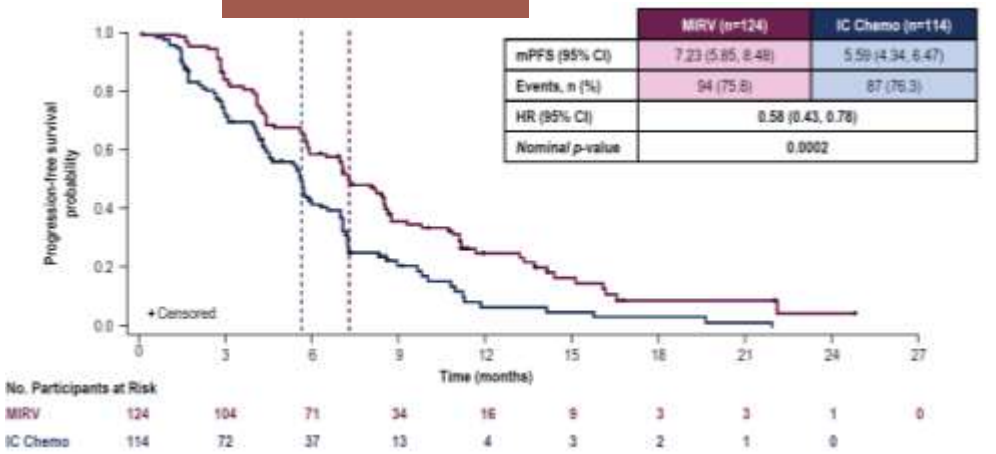
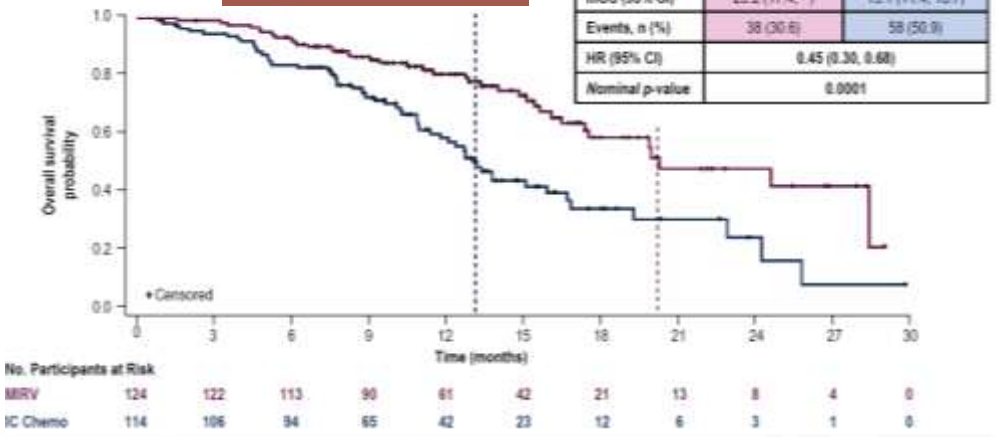
MIRASOL trial: Impact of dose reduction

55% of patients in the MIRV arm 50% of patients in the IC chemo arm had dose modifications

PFS: HR 0.58



OS: HR 0.45



ITT: PFS HR 0.65
OS HR 0.67

	MIRV (n=124)	IC Chemo (n=114)
ORR n, 95% CI	**60%** 74, (50.5, 68.4)	**26%** 30, (18.5, 35.4)
Best overall response, n (%)		
CR	10 (8.1)	0
PR	64 (51.6)	30 (26.3)
SD	44 (35.5)	61 (53.5)
PD	5 (4.0)	18 (15.8)
Not evaluable	1 (0.8)	5 (4.4)

IIT population: ORR 42%

Banerjee, ESMO Gyne 2024

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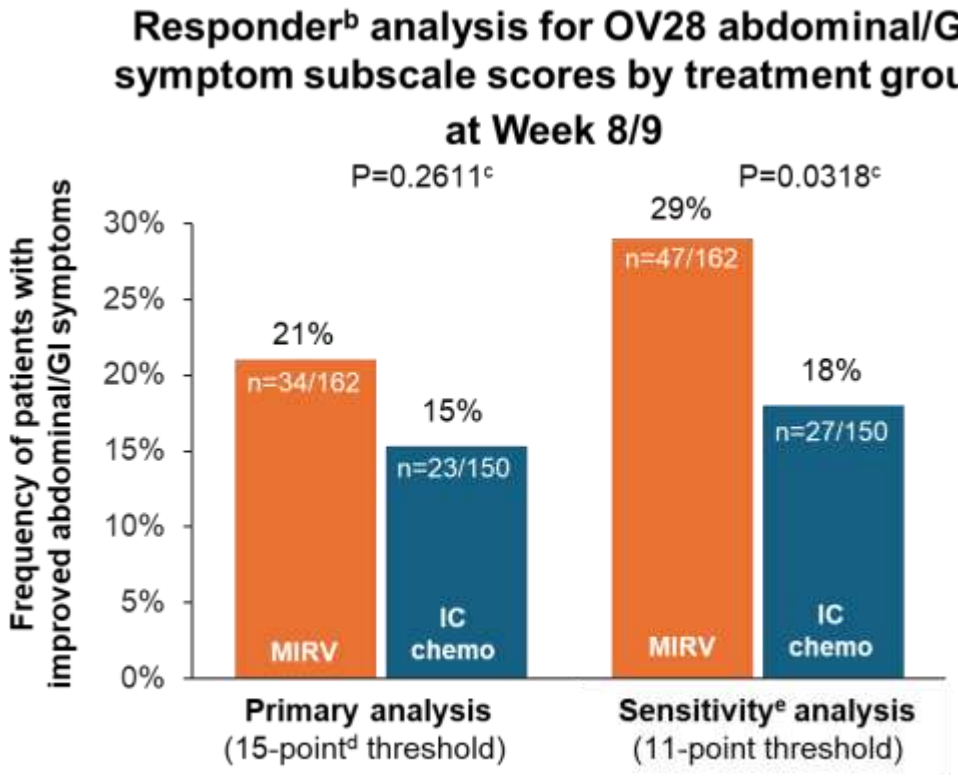
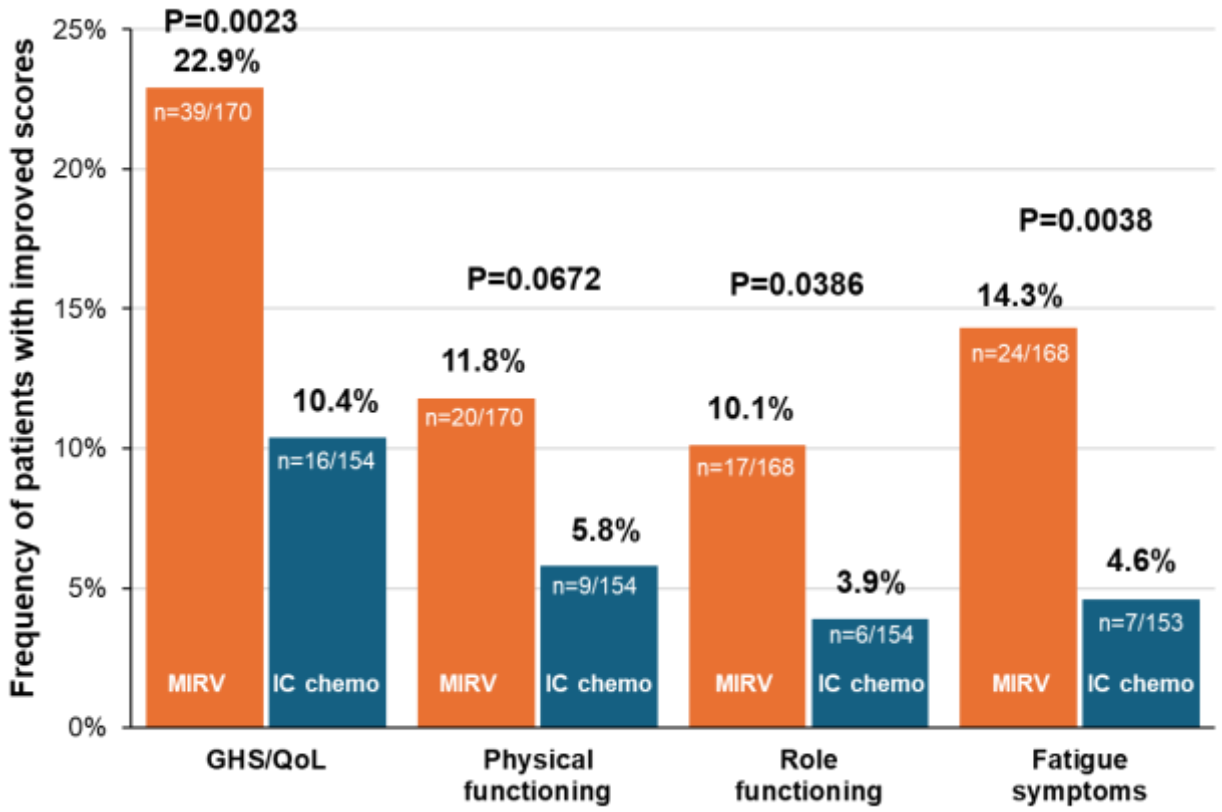
MIRASOL – QOL



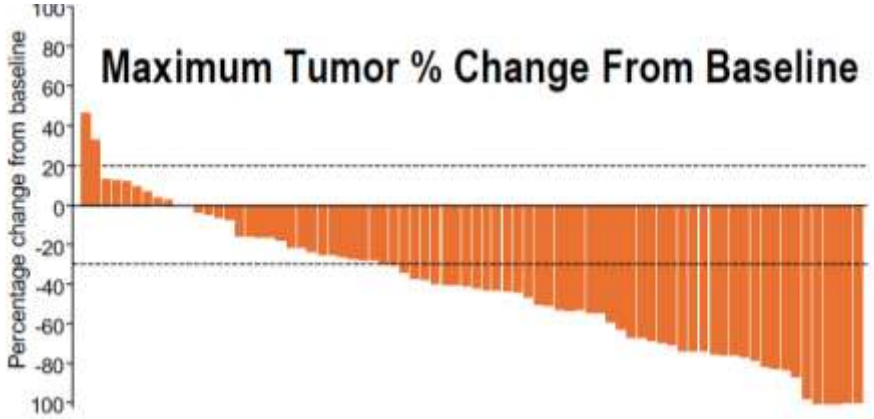


Konecny, SGO 2024; Garcia ESGO 2025

Mirvetuximab Soravtansine: The FUTURE

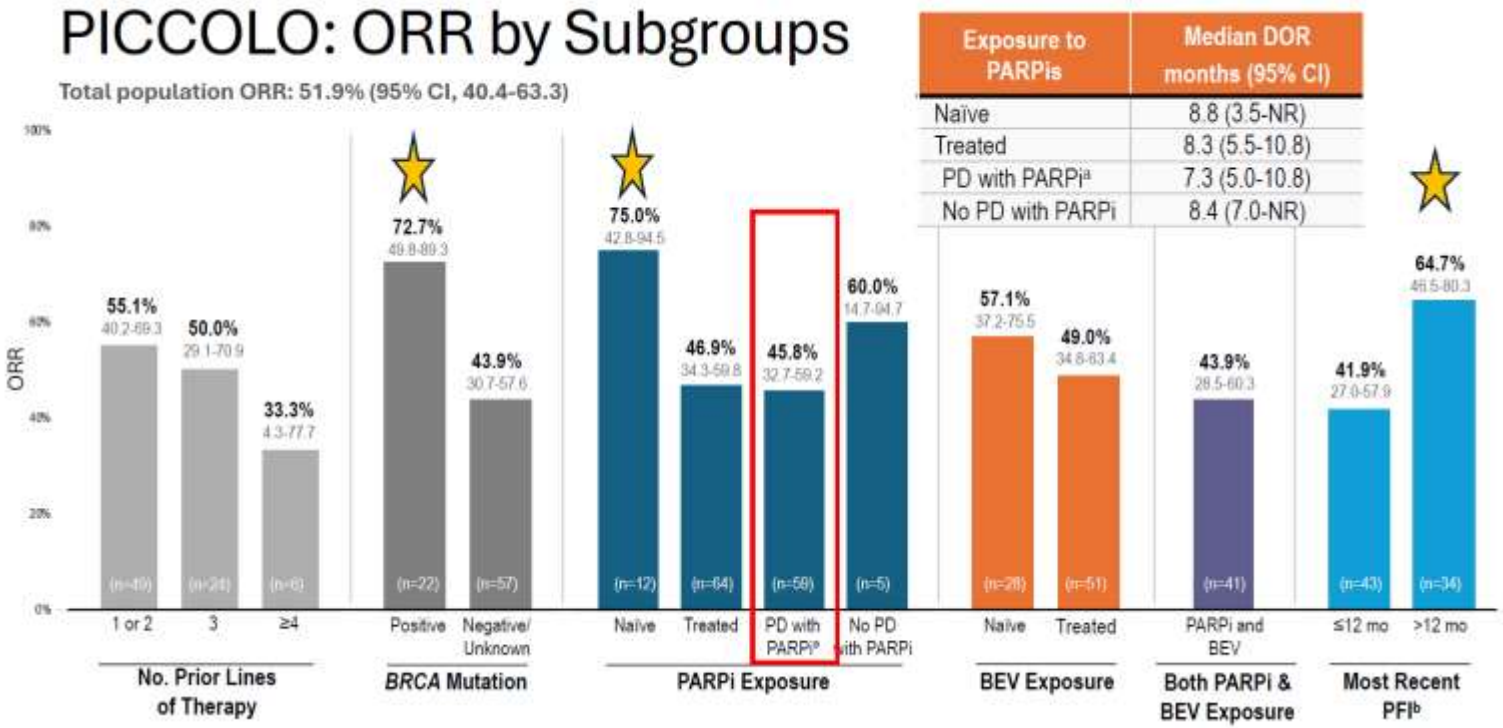
Can we move Mirve in earlier settings?

PICCOLO Trial in platinum-sensitive OC



Primary Endpoint	N=79
ORR, n (%) 95% CI	41 (51.9) 40.4-63.3
Best Response, n (%)	
CR	6 (7.6)
PR	35 (44.3)
SD	29 (36.7)
PD	7 (8.9)

Secondary Endpoints	
Median DOR[a]	n=41
Months (95% CI)	8.25 (5.6-10.8)
Median PFS	N=79
Months (95% CI)	6.93 (5.8-9.6)



Exposure to PARPis	Median DOR months (95% CI)
Naïve	8.8 (3.5-NR)
Treated	8.3 (5.5-10.8)
PD with PARPi[a]	7.3 (5.0-10.8)
No PD with PARPi	8.4 (7.0-NR)

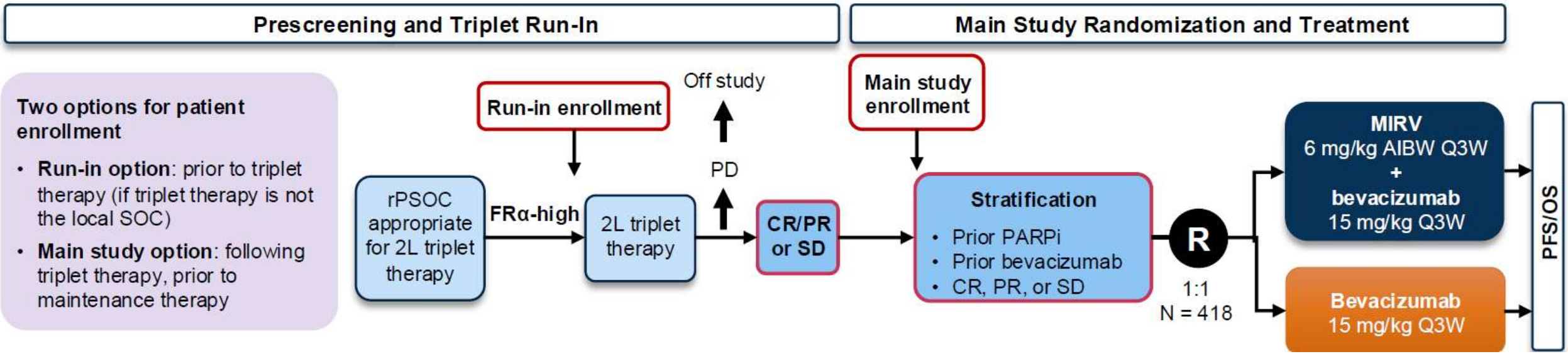
Alvarez Secord, Ann Oncol 2025

Mirvetuximab Soravtansine: The FUTURE

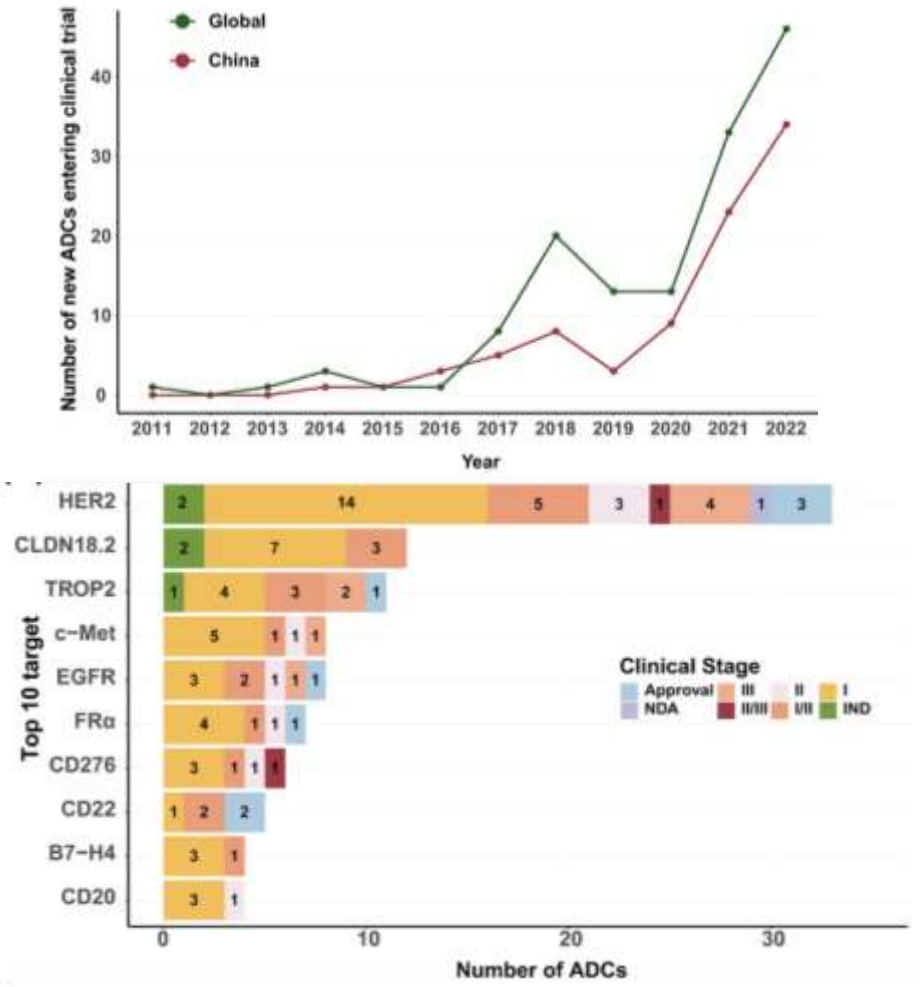
Can we use Mirve as maintenance strategy?
Can we combine Mirve with Bevacizumab?

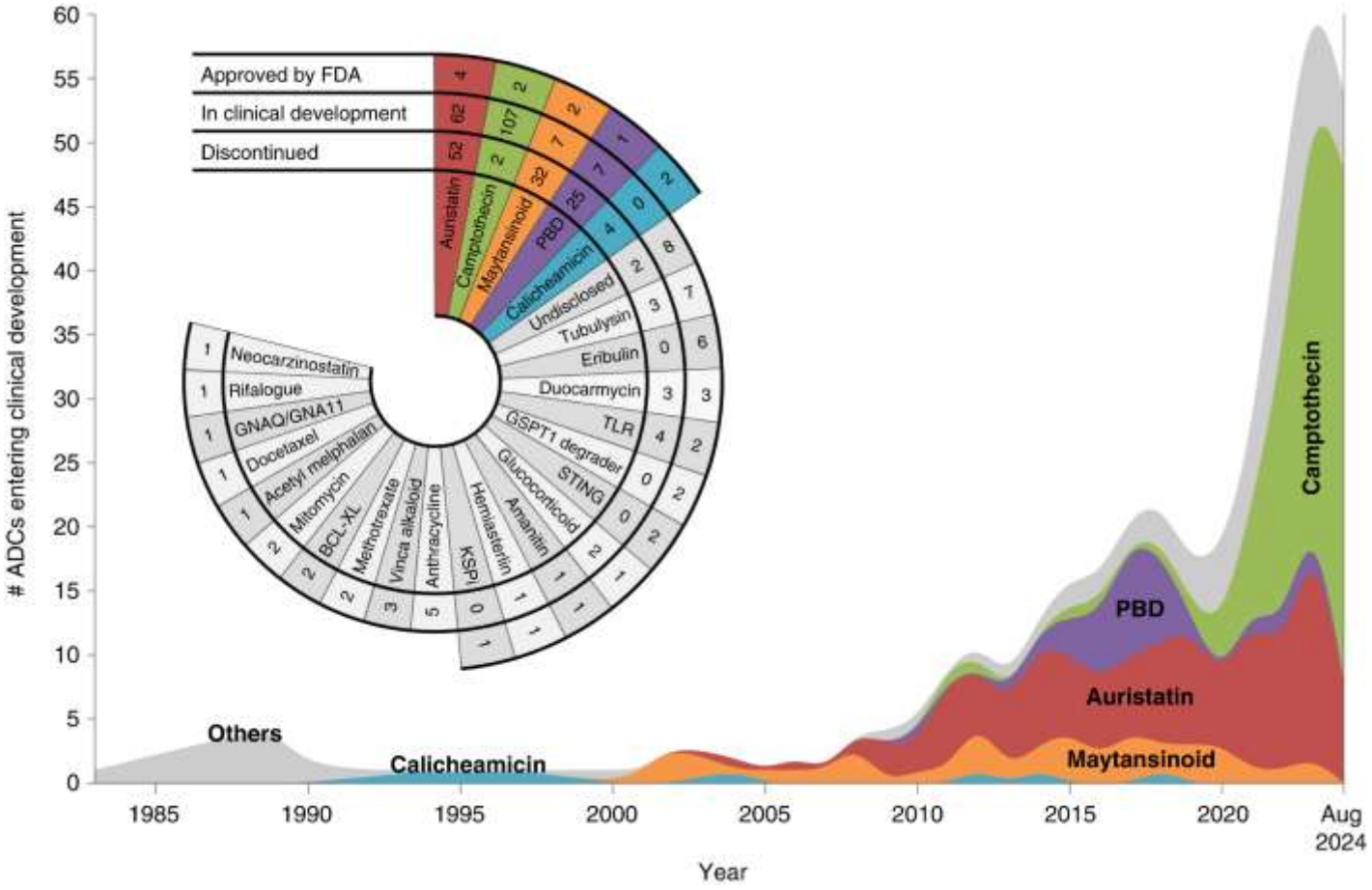
GLORIOSA Trial in platinum-sensitive OC

Phase 3 GLORIOSA Study Design



The ADC revolution in oncology





Ruan, Cancer Communications 2023; Colombo R, Cancer Discovery 2024

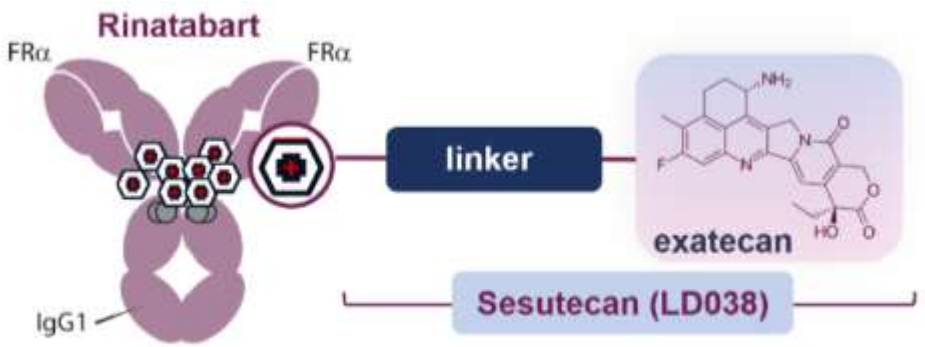
Targeting FRα: The FUTURE

Can we expand the indication for FRα targeting ADC using a different payload and regardless FRα expression?

Rinatabart sesutecan (Rina-S) is an investigational, novel ADC composed of[11]:

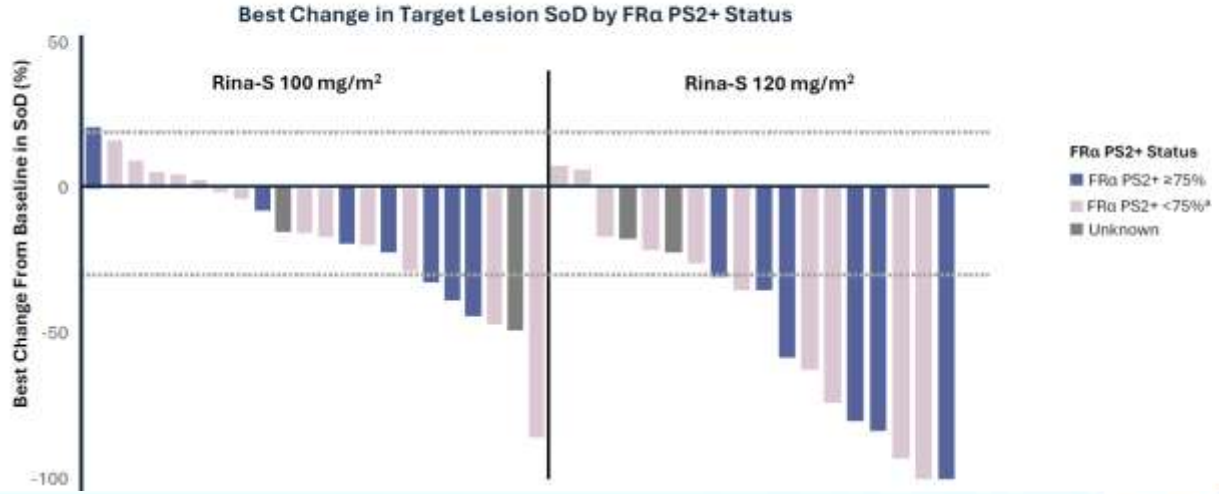
- A human monoclonal antibody directed at FRα
- A novel hydrophilic protease-cleavable linker
- Exatecan, a topoisomerase I inhibitor

Rina-S features a high, homogenous drug-to-antibody ratio of 8[10]



	Rina-S 100 mg/m² (n=22)[a]	Rina-S 120 mg/m² (n=18)[a]
Median on-study follow-up, weeks (range)	46.4 (6.6, 65.3)	48.1 (10.9-65.9)
Confirmed ORR[b], % (95% CI)	22.7 (7.8-45.4)	55.6 (30.8-78.5)
Confirmed response, n (%)		
CR	1 (4.5)	2 (11.1)
PR	4 (18.2)	8 (44.4)
SD	14 (63.6)	6 (33.3)
NE	0	1 (5.6)
Disease control rate, % (95% CI)	86.4 (65.1-97.1)	88.9 (65.3-98.6)

Response by FRα Expression

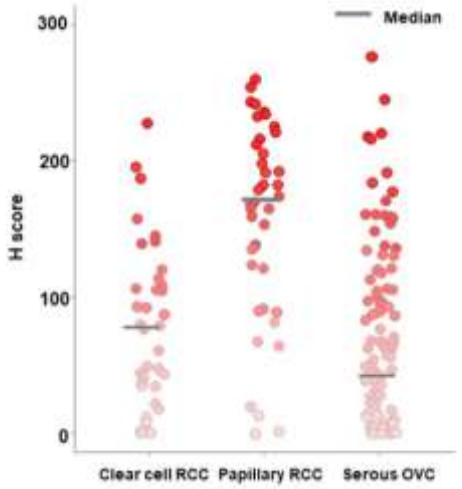


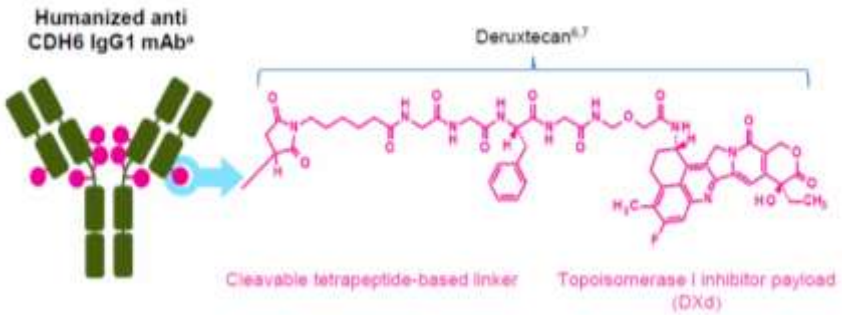
Lee, SGO 2025

The FUTURE: which are other promising new targets and ADCs?

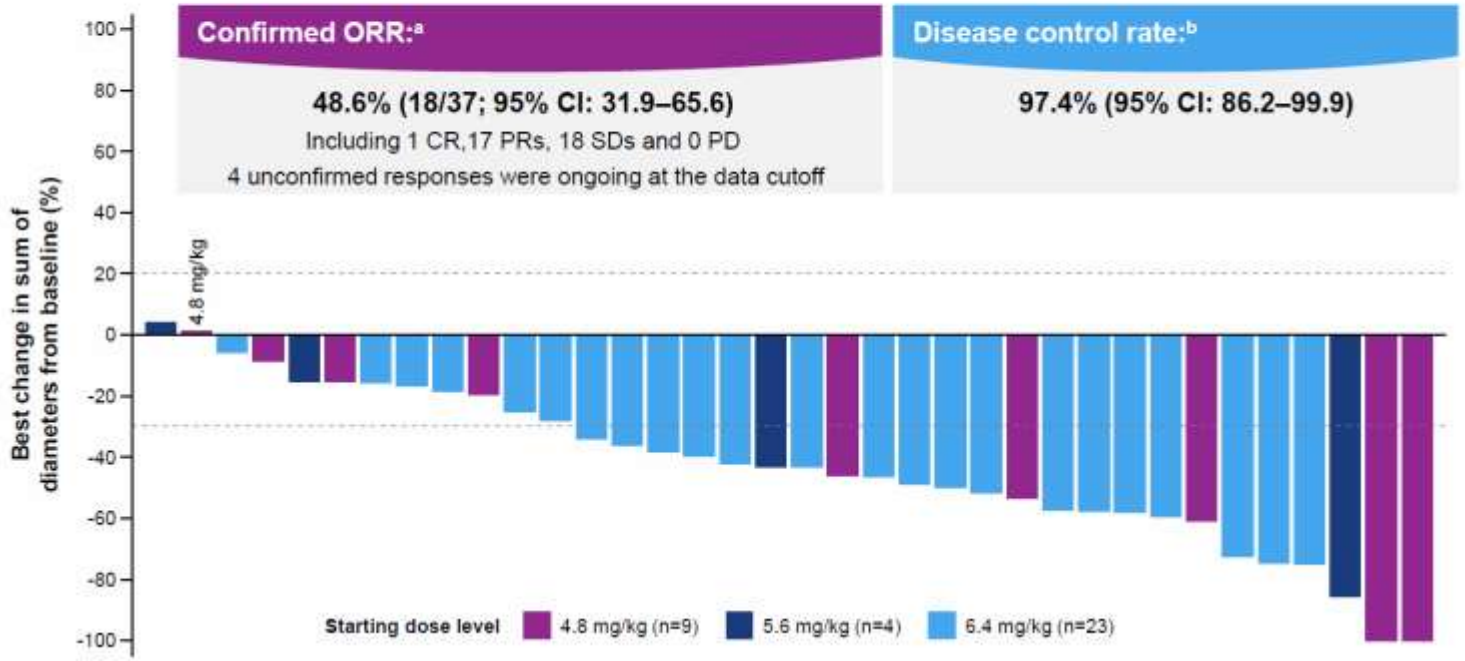
Cadherin 6

CDH6 Expression in RCC/Serous OVC





Preliminary antitumor activity of R-DXd is promising in heavily pretreated patients with OVC receiving doses of 4.8–6.4 mg/kg



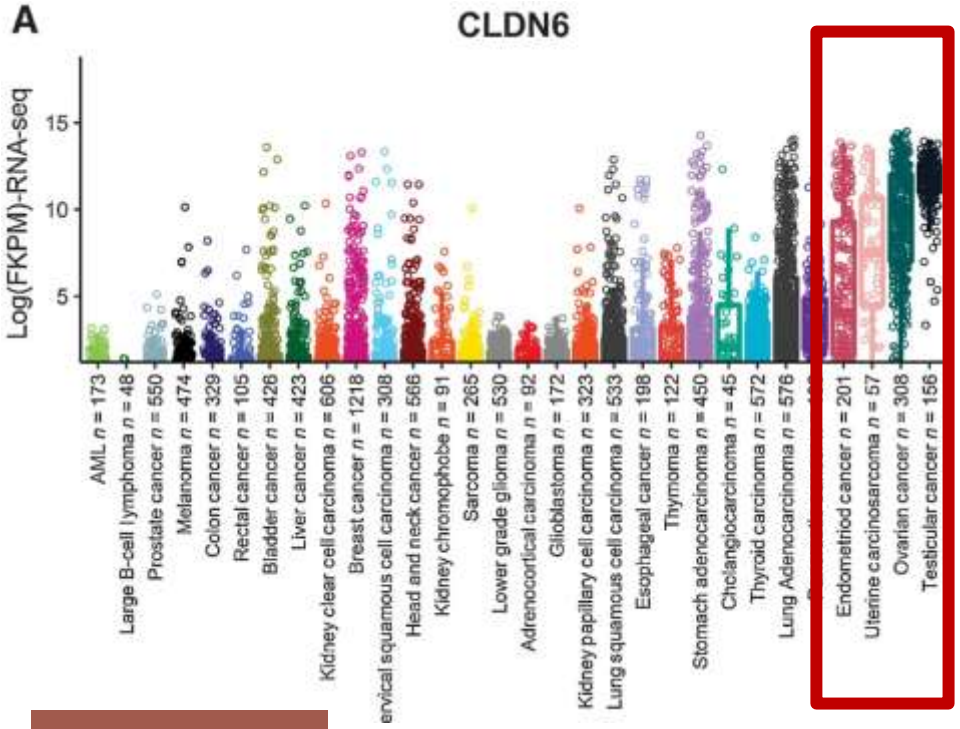
Raludotatug Deruxtecan (R-DXd)

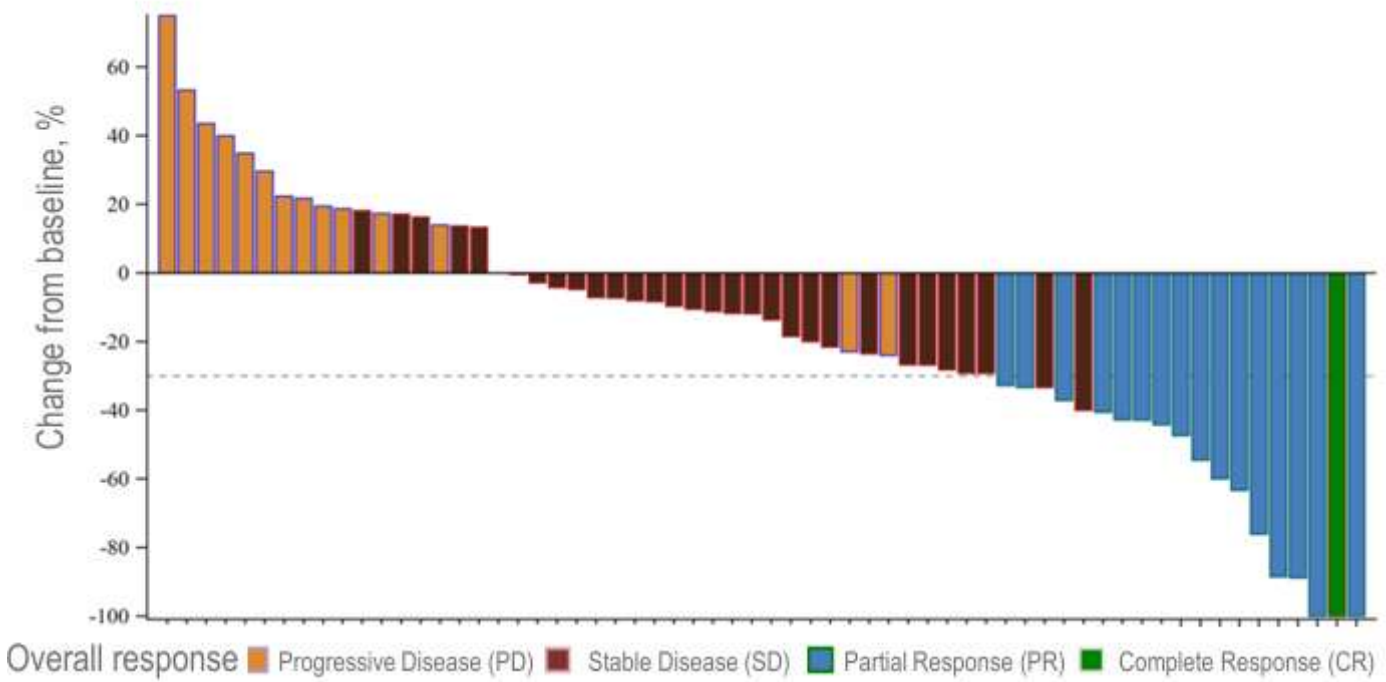
Suzuki, Mol Cancer Ther 2024; Moore SGO 2025

IT-ELAH-250076

The FUTURE: which are other promising targets in OC?

Claudine 6





TORL-1-23

CLDN6 targeting ADC with a vc-MMAE linker-payload and a DAR ~4

Activity in CLDN6+ PROC

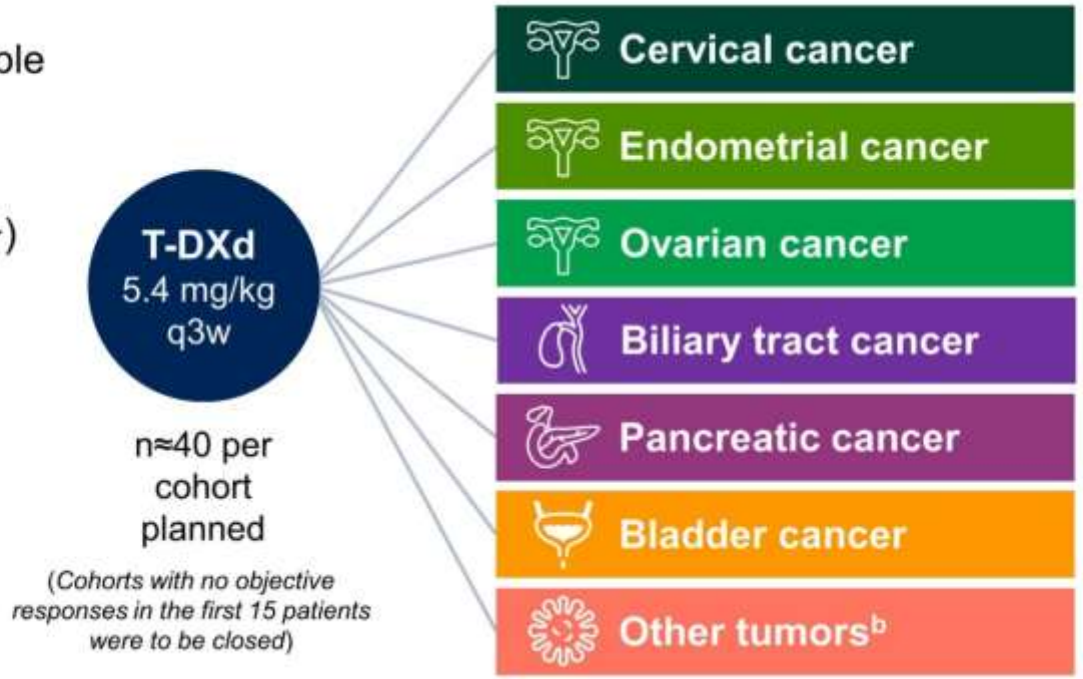
- ORR, 50% (4/8) at the 2.4 mg/kg dose
- ORR, 42% (5/12) at the 3.0 mg/kg dose

McDermott CCR 2023; Konecny, ESMO 2024

Targeting HER2

DESTINY-PanTumor02 study

- 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



Primary endpoint

- Confirmed ORR (investigator)[c]

Secondary endpoints

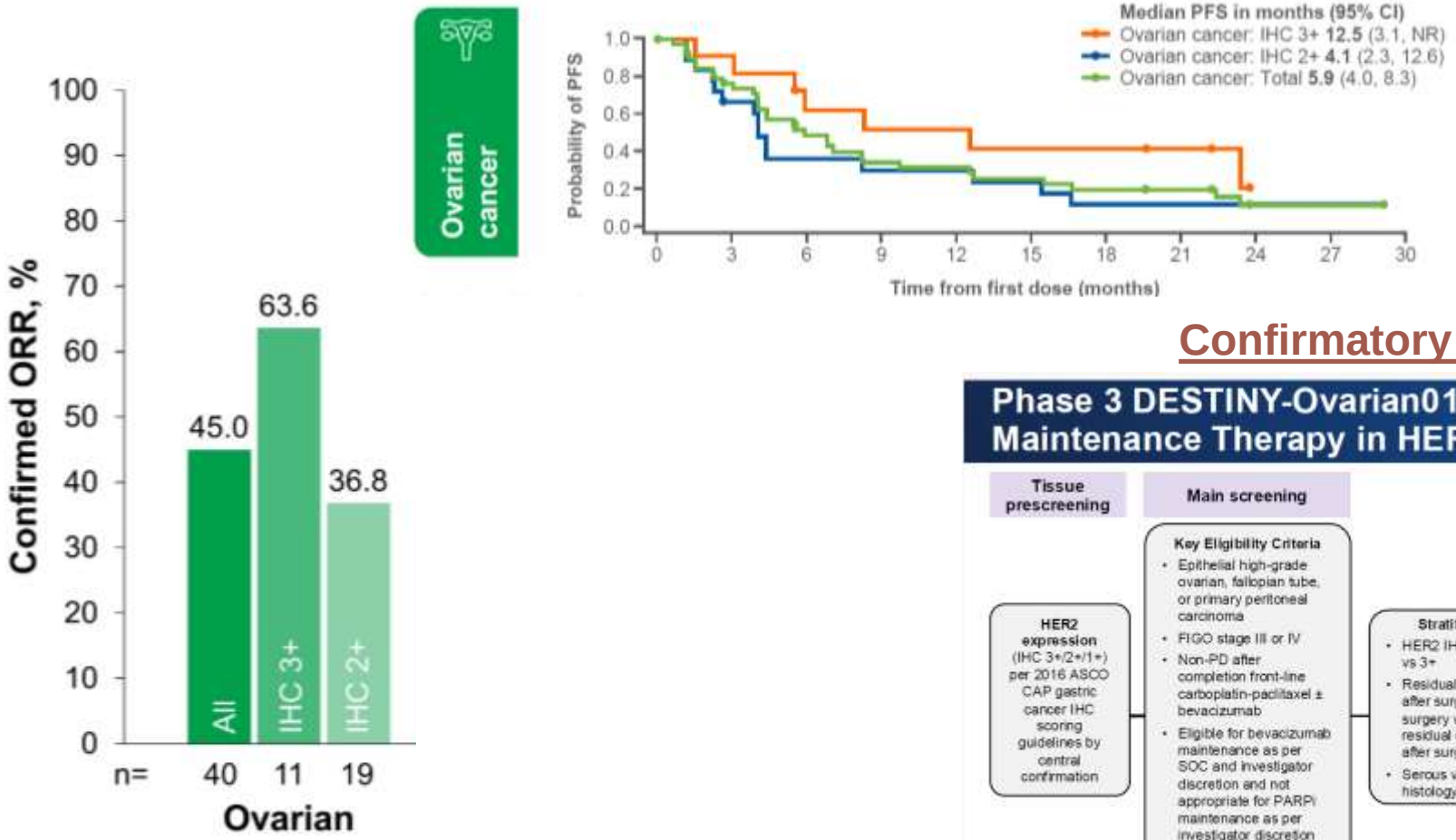
- DOR[c]
- DCR[c]
- PFS[c]
- OS
- Safety

Data cut-off for analysis:

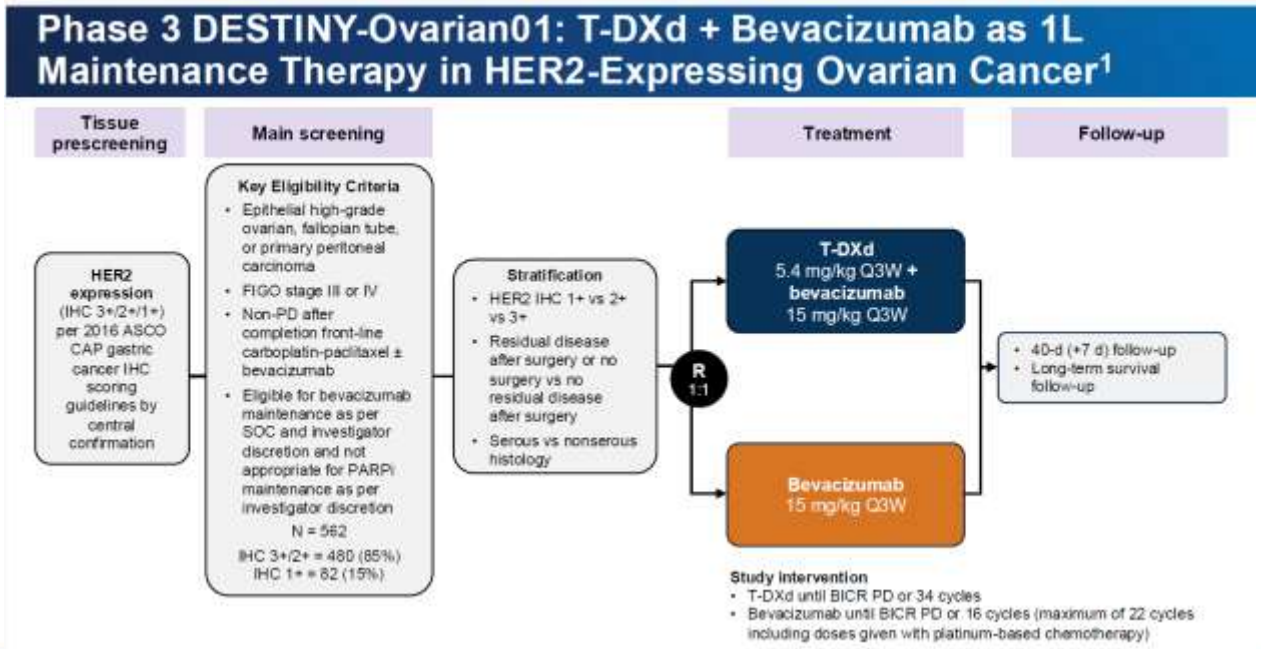
- Nov 16, 2022

Meric-Bernstam, JCO 2024

Targeting HER2: THE PRESENT



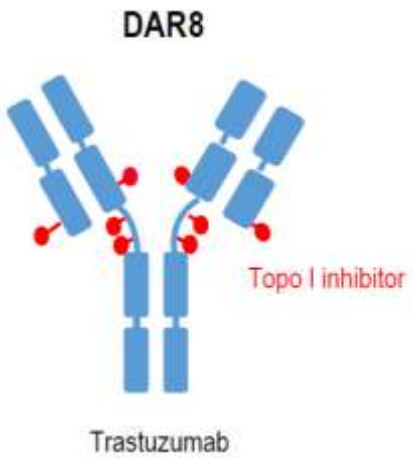
Confirmatory Phase 3 trials in OC

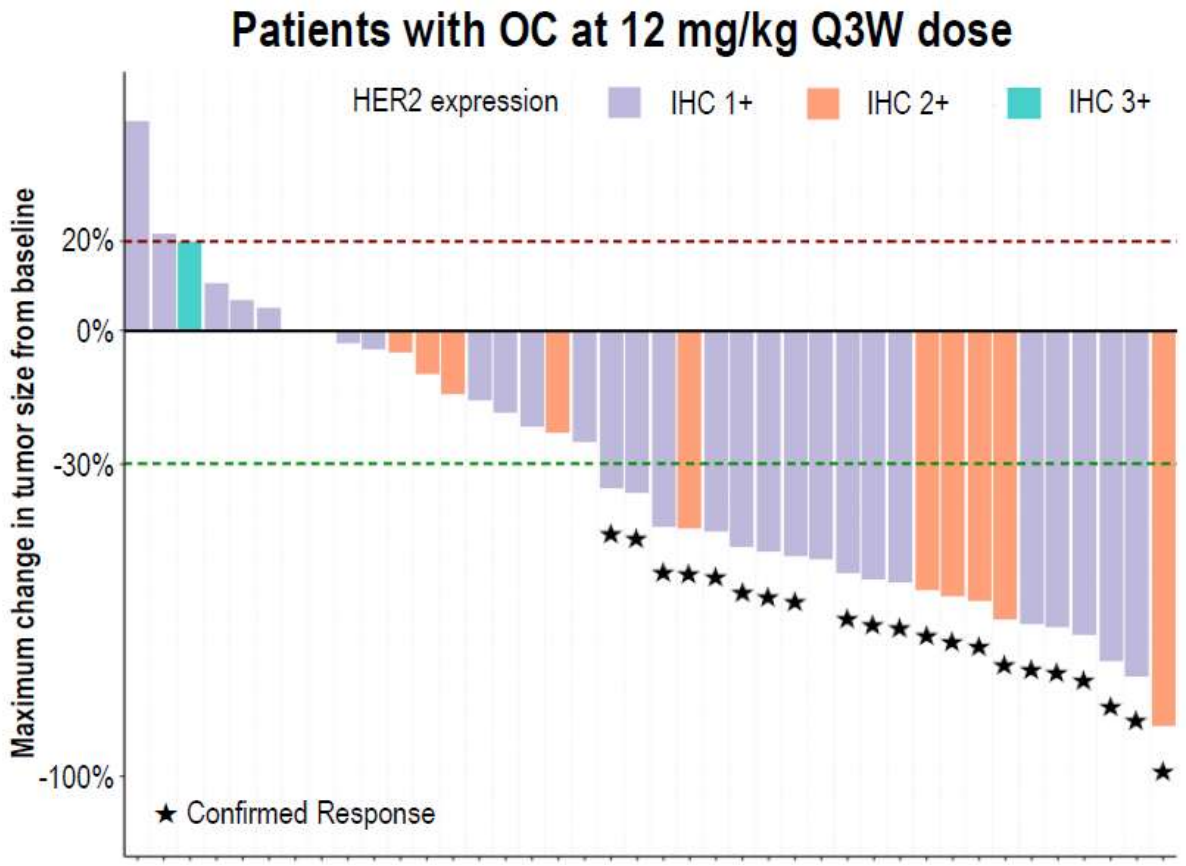


Meric-Bernstam, JCO 2024

Targeting HER2: new ADC on the horizons

IBI354





Shu, ESMO 2024

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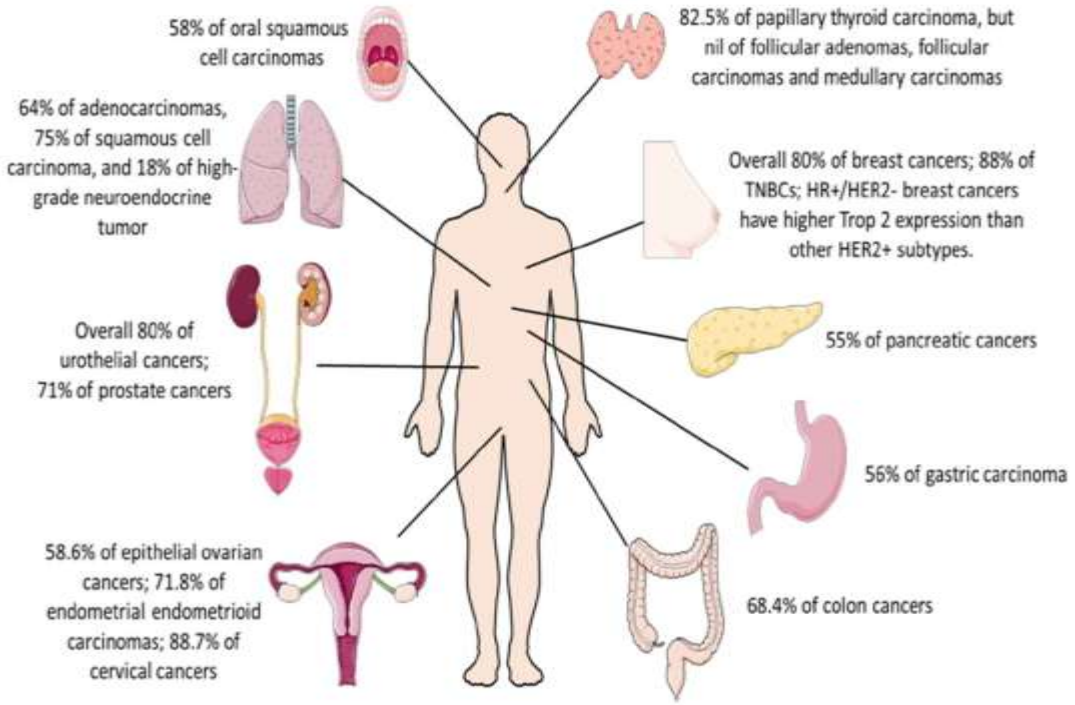
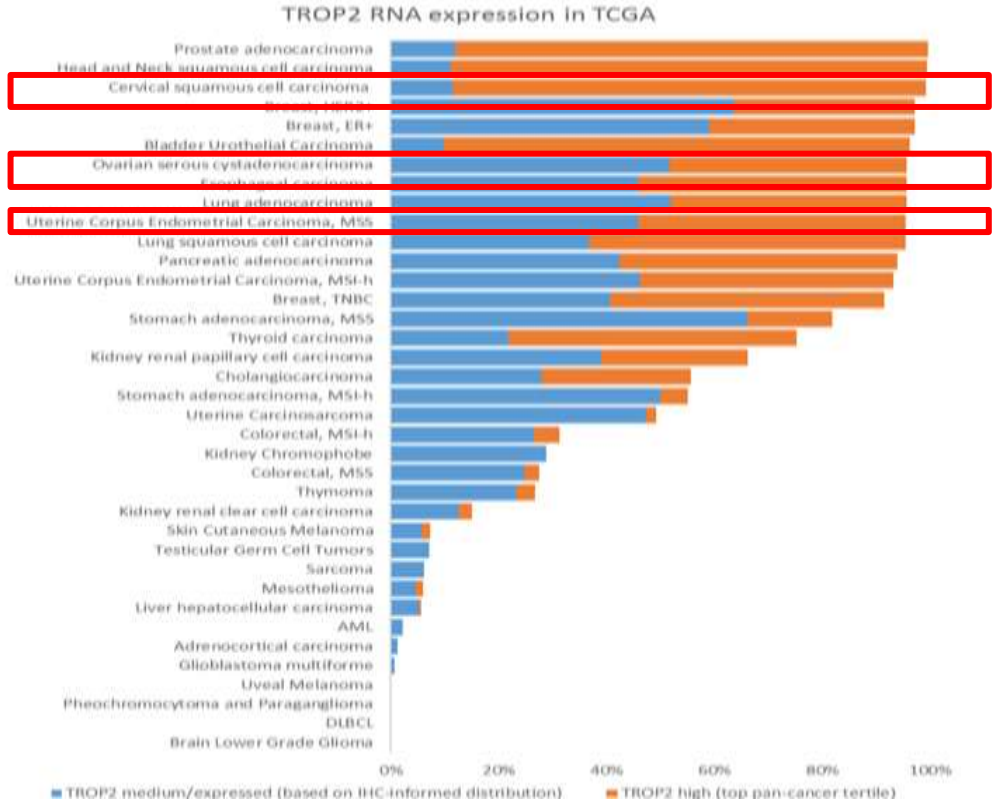
Targeting TROP2 across Gyne Cancers

Trophoblast cell surface antigen 2 (TROP2) is a transmembrane calcium signal transducer promoting tumor proliferation by regulating the calcium ion signaling pathway and cyclin expression and reducing fibronectin adhesion



TROP-2 is Highly Expressed in GYN cancers



Wen Y et al. Ann Transl Med. 2022; Cheng Y, et al. Front. Oncol. 2022; . Liao, S et al. Preprints. 2020,

IT-ELAH-250076

ADC Targeting TROP2 in Ovarian Cancer

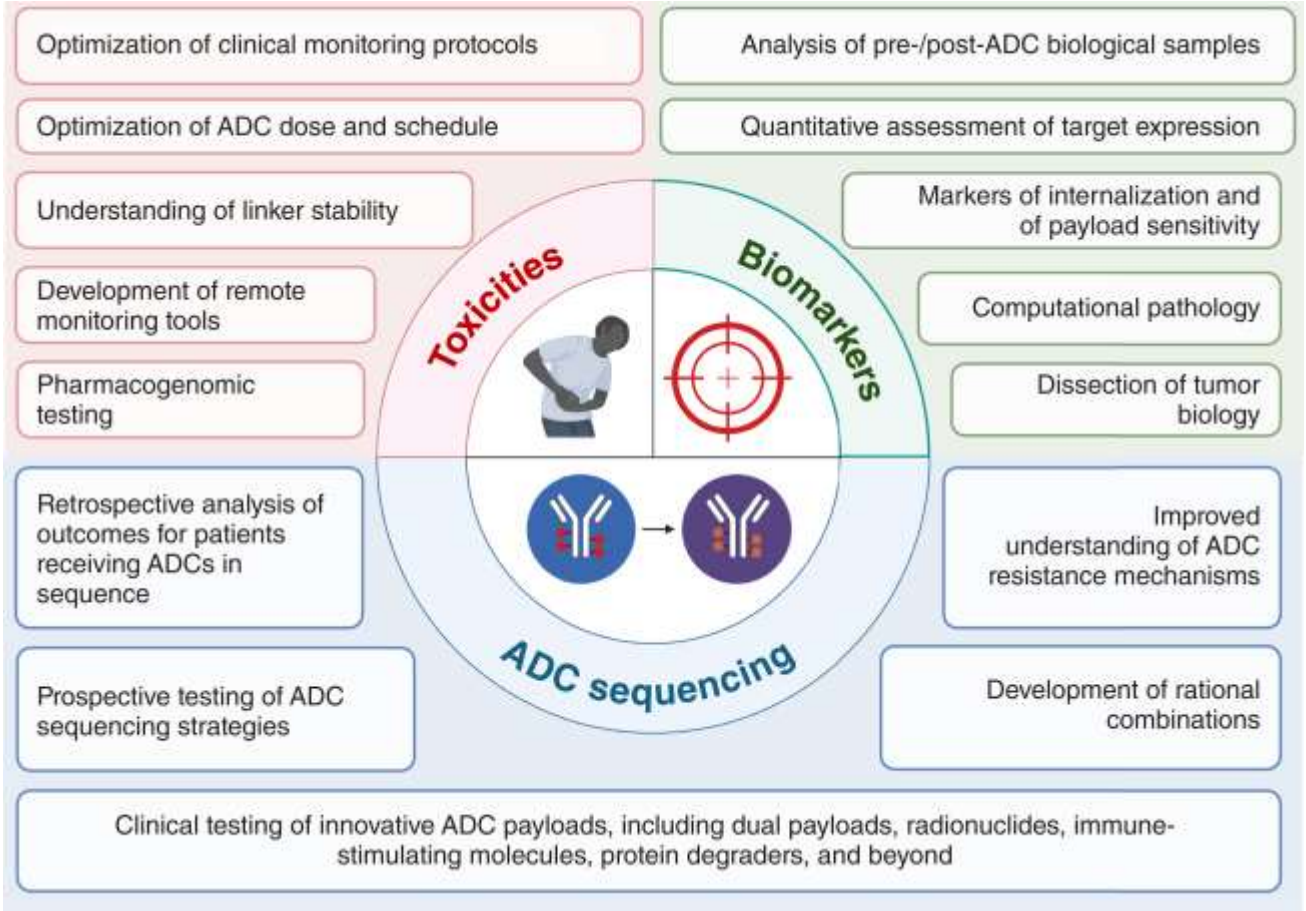
	Sacituzumab tirumotecan (MK-2870) 5mg/kg D1, D15 N=35 (PROC)	**Datopotamab deruxtecan** N=26 (PROC)	**SHR A1921** Q 21 day dosing 3.0mg/kg (N=26) Day 1, 8 2.0mg/kg (N=20)
Payload	Belotecan derivative Topoisomerase I	Topoisomerase 1- deruxtecan	Topoisomerase 1 (proprietary SHR9265)
DAR	7.4	4	4
Prior Bev	NR	71.4%	76% 60.0%
ORR (PROC)	37.1% (PROC)	34.6% (95% CI 17.2- 55.7)	42.3% (95% CI 23.4-63.1) 58.8% (95% CI 32.9-81.6)
DOR (PROC)	5.3 months (2.1, 24.4+)	5.6 months (2.9-NC)	9.9 months (4.5-NC) 6.3 months (3.0-NC)
mPFS	6.0 months (95% CI 3.9-7.3) (inclusive of PSOC)	5.6 months (inclusive of PSOC)	7.9 (4.2-NR) 6.9 (4.2- 9.6)

Which is the role of biomarker expression? Does it matter?

Open questions and challenges

Dose optimization
Treatment duration
Sequence
Safety
QoL
Biomarkers
Setting
Resistance Mechanisms

How to choose among many ADCs?
Which will be the best SoC arm in trials?

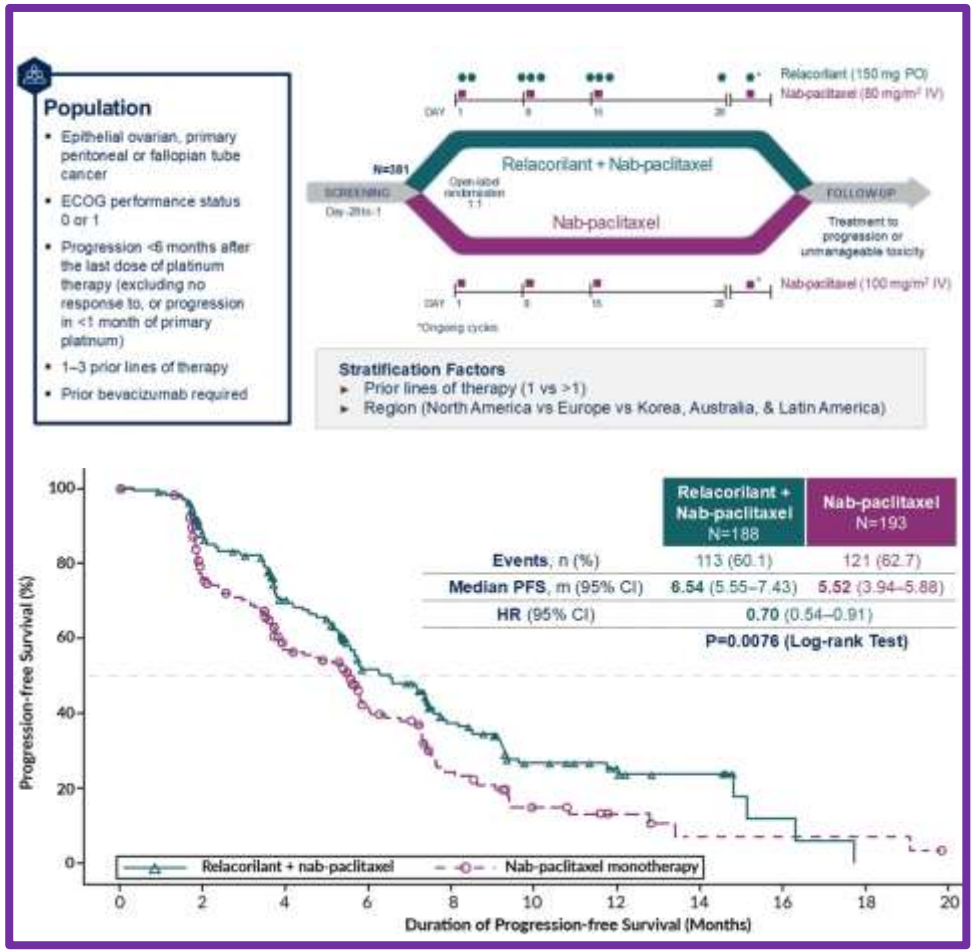


Colombo R, Cancer Discovery 2024

IT-ELAH-250076

What else is coming beyond ADC?

ROSSELLA: Relacorilant



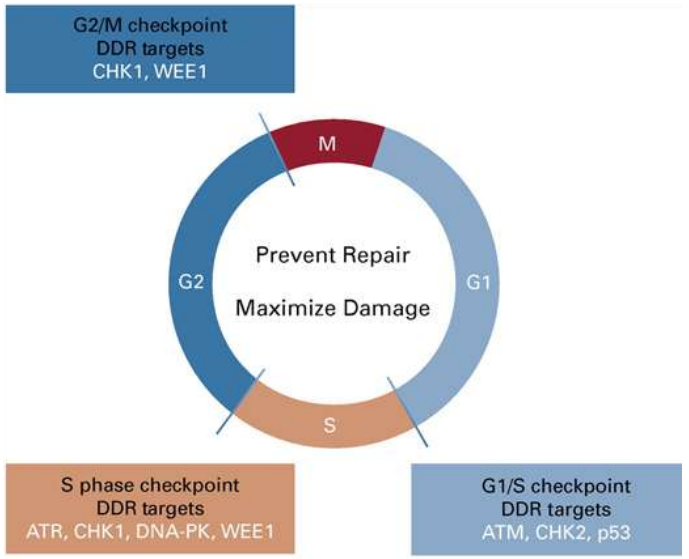
Olawaiye, ASCO 2025

KEYNOTE B96

PRESS RELEASE

Phase 3 KEYNOTE-B96 trial, also known as ENGOT-ov65, met its primary endpoint of progression-free survival (PFS) for the treatment of patients with platinum-resistant recurrent ovarian cancer whose tumors expressed PD-L1 and in all comers. The study also met a secondary endpoint of overall survival (OS) in patients whose tumors express PD-L1

Cell-cycle check points



ATRi
ATMi
WEE1i
CDK2i

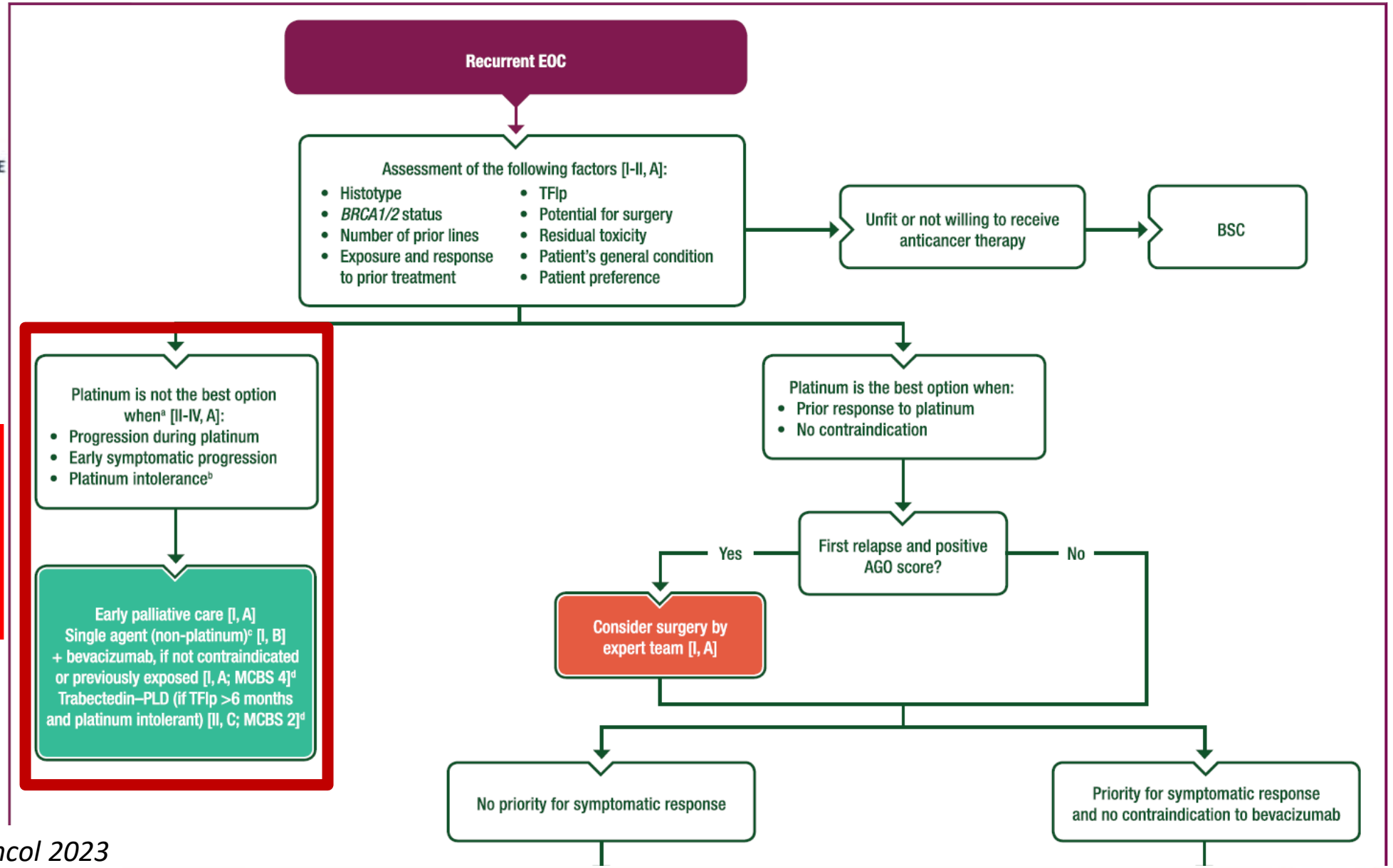
Gourley, JCO 2019

IT-ELAH-250076

Guidelines

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Mirvetuximab for FR high tumors



Gonzalez-Martin, Ann Oncol 2023

Take home message

- **Platinum resistant ovarian** cancer is still characterized by **poor prognosis** and few effective agents are available
- In patients with **high FRα expression**, **Mirvetuximab** has improved **PFS** and **OS** and represents a **standard of care treatment** in this biomarker-selected population
- Correct **mitigation and management of adverse events** is paramount to maintain patients under an effective treatment and improve QoL
- **Different ADCs** are under development and will further reshape the treatment paradigm of ovarian cancer
- Many **open questions are still present**, such as biomarkers selection, correct sequence and overcoming mechanisms of resistance

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Thanks for your attention

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