ANTICORPI CONIUGATI NEI TUMORI GINECOLOGICI

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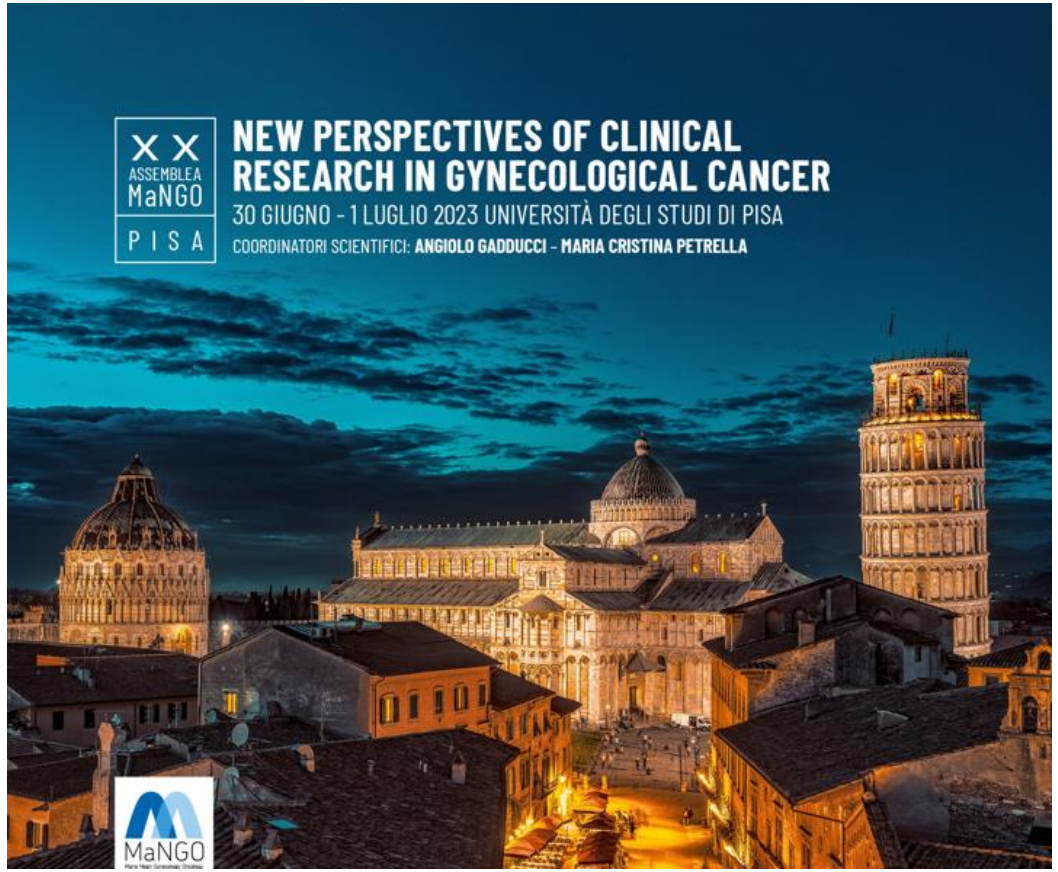
Outline

- ADC platform: components and mechanisms of action
- The beginning in gynecological oncology
- ADC related adverse events



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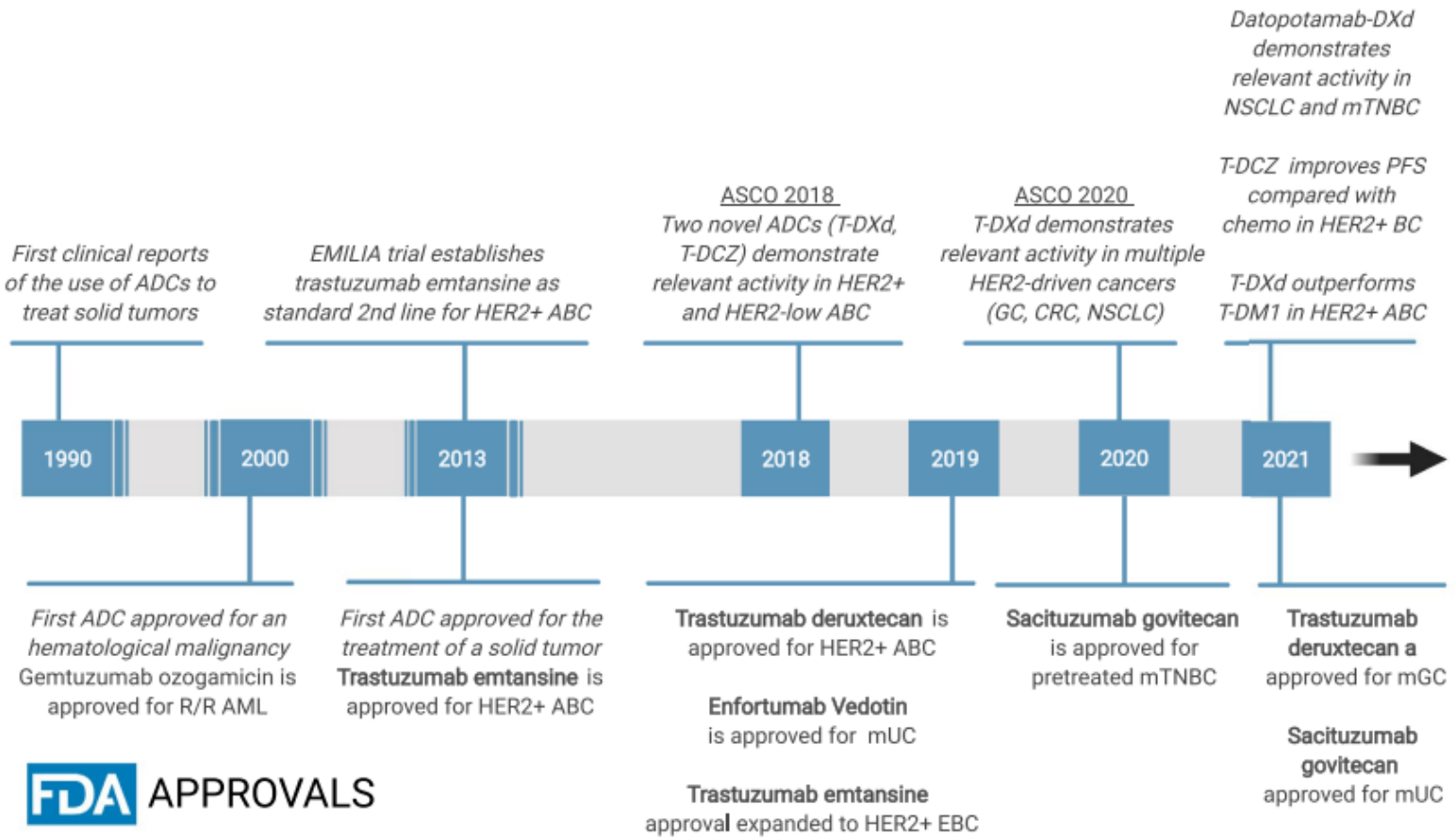
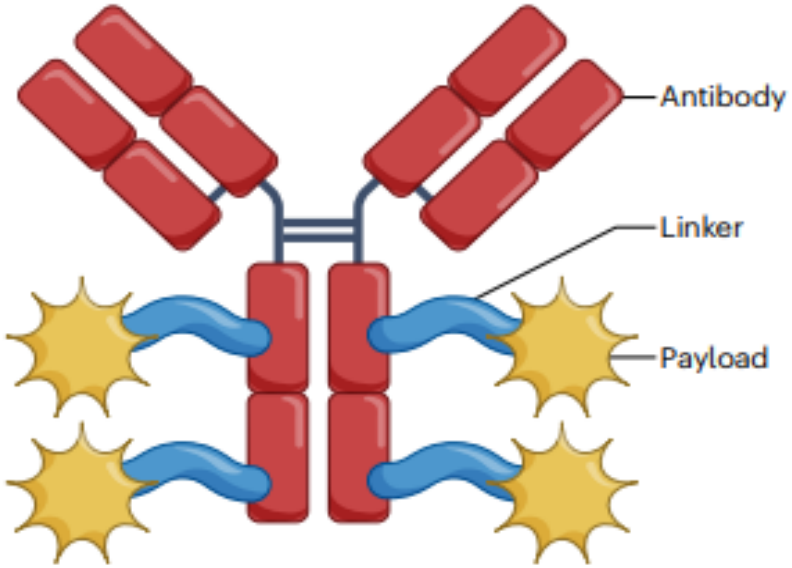
ADC: the beginning of a never ending story?

Ehrlich's magic bullet concept: delivering a toxic drug to tumour cells while sparing the others



Tarantino P, et al; CA CANCER J CLIN 2022

Structure and target of action of conventional ADCs



Three key elements:

- a monoclonal **antibody** (humanized or fully human) that binds to an antigen preferentially expressed on the tumour cell surface (ensuring specific binding to tumour cells);
- a covalent **linker** that ensures that the payload is not prematurely released in the blood but is released within the tumour cell;
- a cytotoxic **payload** that will induce tumour cell apoptosis.

Target:

cell-surface proteins that are higly exspressed on tumour cells but non on non-malignant cells

- Homogeneous target expression on tumour cells
- Rate of target turnover, internalization and lysosomal processing

Dumontet C, et al; Nature Reviews Drug Discovery 2023

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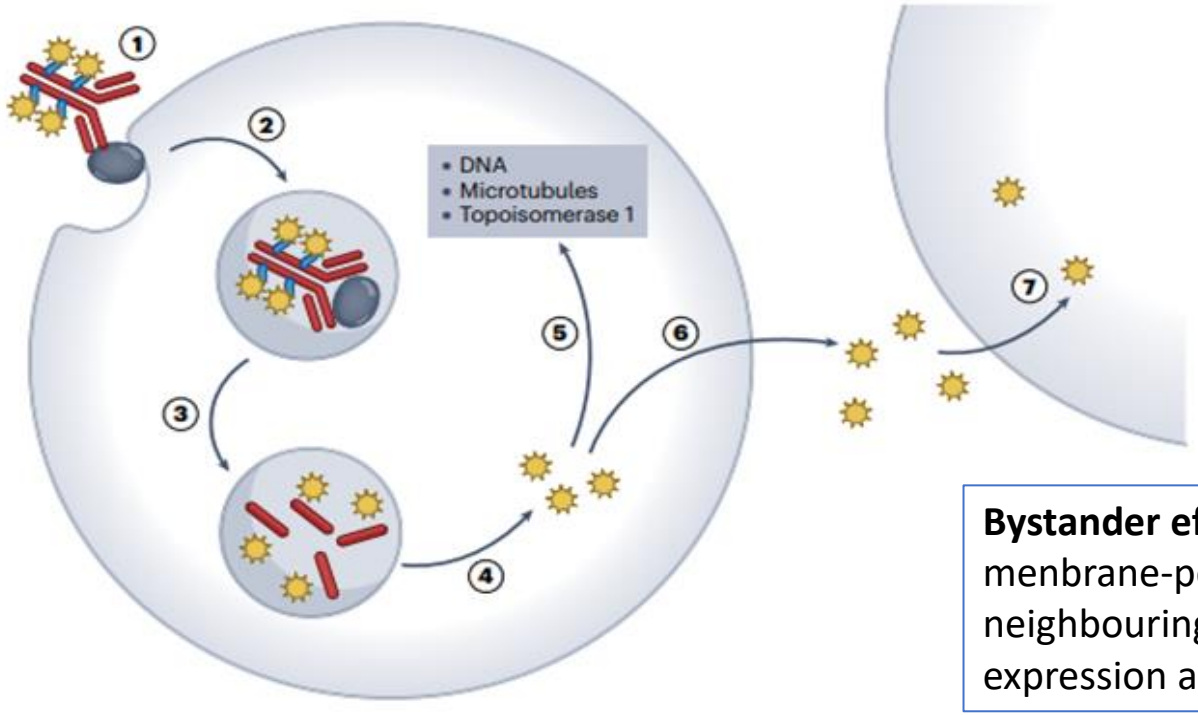
Mechanism of action of conventional ADCs

Cytotoxic activity

- Binding to specific antigen; Antibody engagement leads to ADC complex internalization
- Most ADCs are processed and antibody proportion degradated by lysosomal.
- The payload is released in the cytoplasm and takes its effect on the cell, leading to cell death.



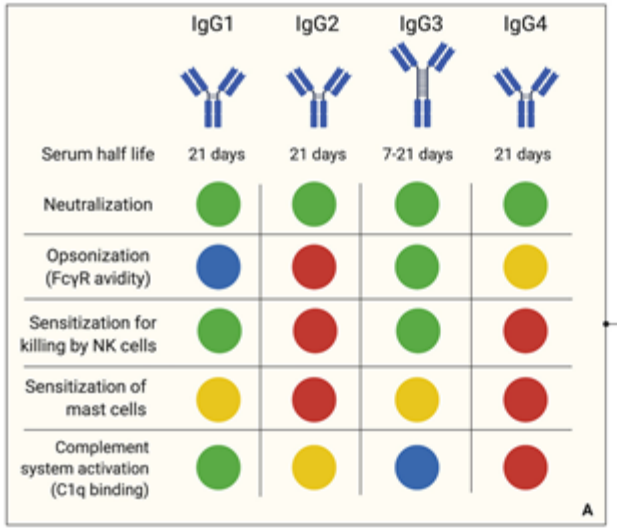
Bystander effect:
menbrane-permeable payloads enter neighbouring cells regardless of target expression and can also kill these cells

Antitumour effects of Ab:

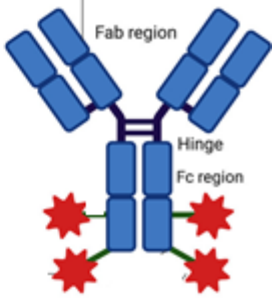
- enhancement of antitumour immunity though the induction of Ab-dependent cytotoxicity.
- Inhibition of oncogenic signaling pathways.

Dumontet C, et al; Nature Reviews Drug Discovery 2023

Antibody: cell selectivity, serum half life

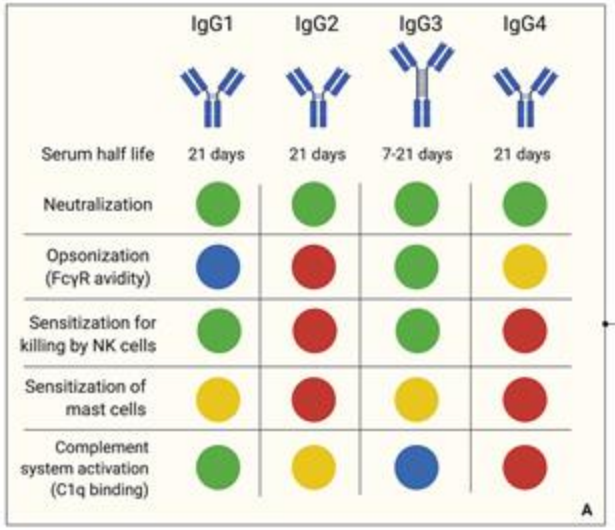


Most approved ADCs rely on an IgG1: long serum half-life, higher complement fixation (C1q binding) and high region γ receptor (FcγR) binding avidity.



Tarantino P, et al; CA CANCER J CLIN 2022; Drago JZ, et al; Nat Rev Clin Oncol 2021

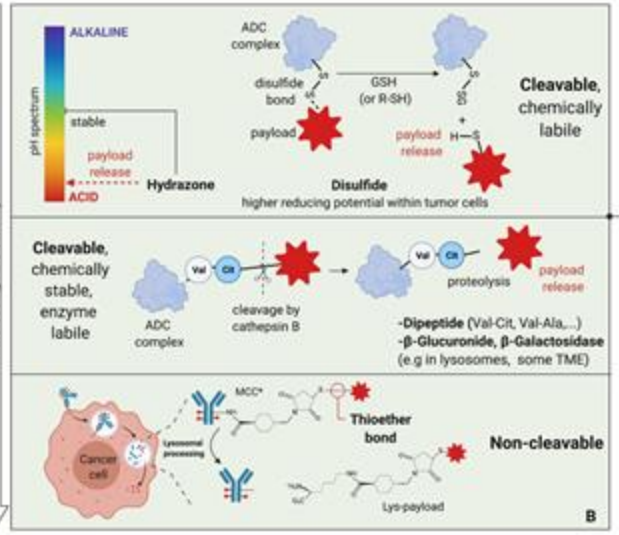
Antibody: cell selectivity, serum half life

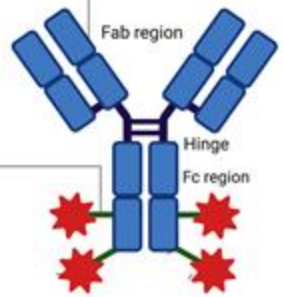


- Antibody: most approved ADCs rely on an IgG1: long serum half-life, higher complement fixation (C1q binding) and high region γ receptor (FcγR) binding avidity.
- Reduced antigenicity (humanized or fully human).

Linker: PK properties

increasing ADC stability





Linker: the choice of a linker determines most of the ADC pharmacokinetic properties as well as safety and efficacy profiles.

- cleavable: higher plasma instability but higher potential for payload release in the TME and transmembrane diffusion (bystander effect);
- non-cleavable: plasma stability, requires intracellular lysosomal degradation.

Tarantino P, et al; CA CANCER J CLIN 2022; Drago JZ, et al; Nat Rev Clin Oncol 2021

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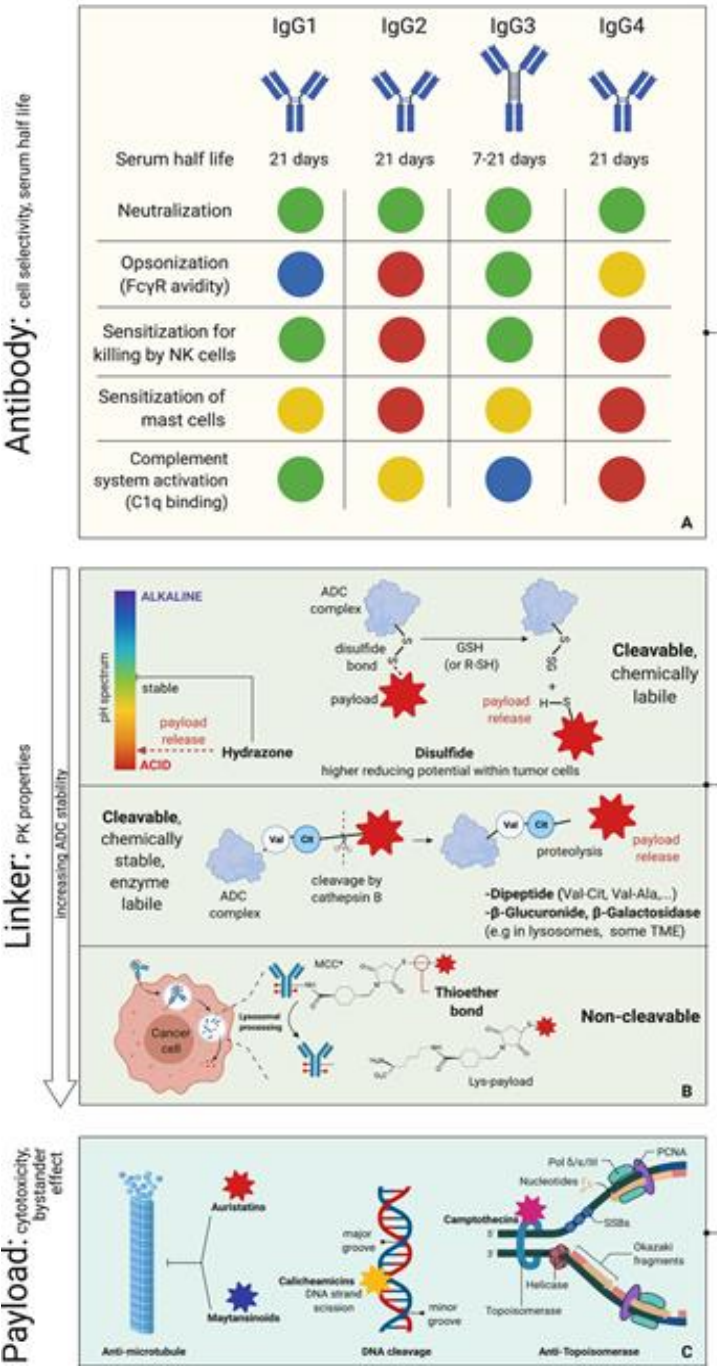

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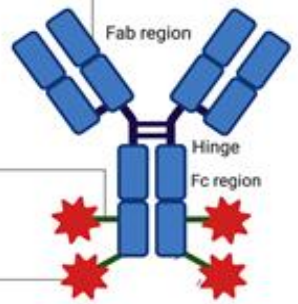


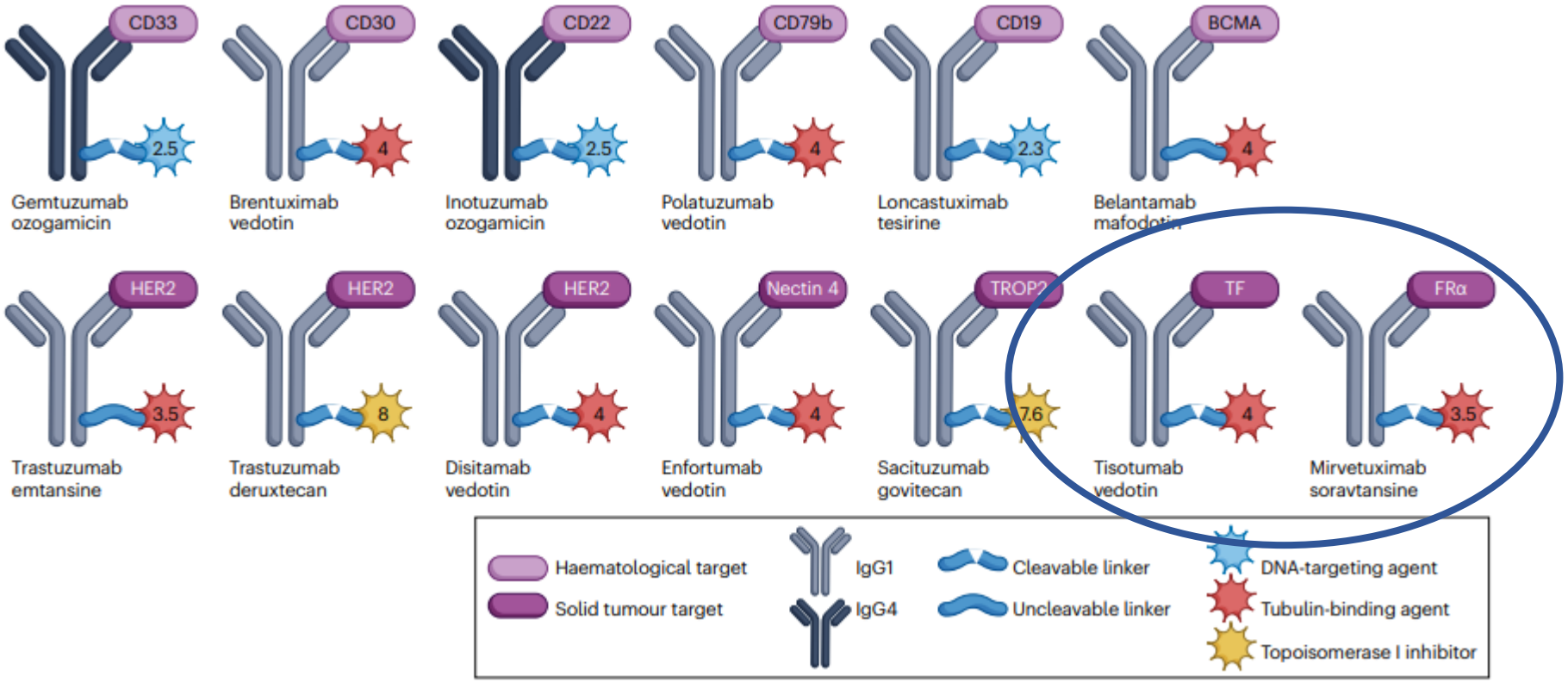
Linker: the choice of a linker determines most of the ADC pharmacokinetic properties as well as safety and efficacy profiles.

- cleavable: higher plasma instability but higher potential for payload release in the TME and transmembrane diffusion (bystander effect);
- non-cleavable: plasma stability but requires lysosomal degradation, retention of charged payload and impact on cell permeability.

Payload: due to large dimension of mAb, their tissue penetration is limited (only 0.1% of ADCs reaches cancer cells): potent cytotoxic agents (Auristatins, Maytansinoids, Calicheamicins, Camptothecins).
ADCs activity depends on the drug-antibody ratio: the average number of payload attached to each mAb.

Tarantino P, et al; CA CANCER J CLIN 2022; Drago JZ, et al; Nat Rev Clin Oncol 2021

Approved ADCs in Oncology



Tarantino P, et al; CA CANCER J CLIN 2022

2023 ASCO ANNUAL MEETING

Phase III MIRASOL (GOG 3045/ENGOT-ov55) Study: Mirvetuximab Soravtansine vs. Investigator's Choice of Chemotherapy in Platinum-Resistant, Advanced High-Grade Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancers with High Folate Receptor-Alpha (FRα) Expression

Kathleen N. Moore[1], Antoine Angelergues[2], Gottfried E. Konecny[3], Susana Banerjee[4], Sandro Pignata[5], Nicoletta Colombo[6], John Moroney[7], Casey Cosgrove[8], Jung-Yun Lee[9], Andrzej Roszak[10], Shani Breuer[11], Jacqueline Tromp[12], Diana Bello Roufai[13], Lucy Gilbert[14], Rowan Miller[15], Tashanna Myers[16], Yuemei Wang[17], Anna Berkenblit[17], Domenica Lorusso[18], Toon Van Gorp[19]

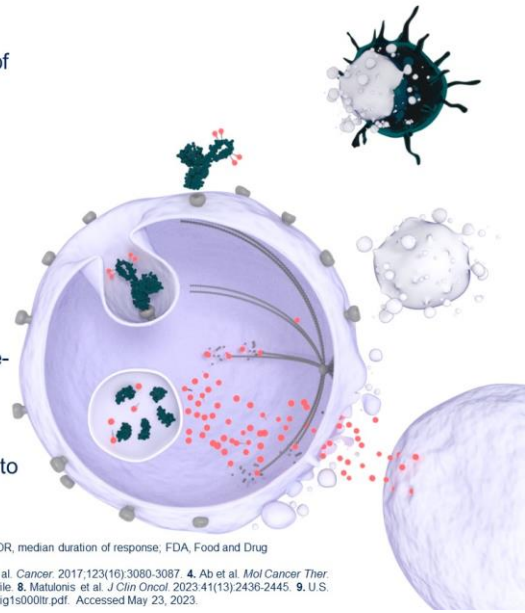
[1]Stephenson Cancer Center University of Oklahoma College of Medicine, Oklahoma City, OK, USA; [2]Groupe Hospitalier Diaconesses Croix Saint Simon, Paris, France; [3]UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA; [4]The Royal Marsden NHS Foundation Trust - Royal Marsden Hospital, London, UK; [5]Istituto Nazionale Tumori- G. Pascale, Naples, Italy; [6]European Institute of Oncology IRCCS, Milan, Italy and University of Milan-Bicocca, Milan, Italy; [7]The University of Chicago, Chicago, IL, USA; [8]The Ohio State University, Columbus, OH, USA; [9]Severance Hospital, Seoul, South Korea; [10]Wielkopolskie Centrum Onkologii, Poznan, Poland; [11]Hadassah Ein Kerem – Sharett, Jerusalem, Israel; [12]Amsterdam UMC, Amsterdam, The Netherlands; [13]Hopital Rene Huguenin, Institut Curie, Saint-Cloud, France; [14]McGill University Health Centre, Montreal, Canada; [15]University College London Hospital, London, UK; [16]Baystate Medical Center, Springfield, MA, USA; [17] ImmunoGen, Inc., Waltham, MA, USA; [18]Fondazione Policlinico Universitario A. Gemelli, IRCCS and Catholic University of Sacred Heart, Rome, Italy; [19]University Hospital Leuven Leuven Cancer Institute, Leuven, Belgium

ENGOT European Network of Gynaecological Oncological Trial groups

GOG FOUNDATION Transforming the standard of ca

Background

- No randomized phase 3 trial has shown an overall survival (OS) benefit of a novel therapy in platinum-resistant ovarian cancer (PROC)[1, 2]
- Mirvetuximab soravtansine (MIRV) is an ADC comprising a FRα-binding antibody, cleavable linker, and maytansinoid DM4, a potent tubulin-targeting agent[3,4]
- FRα is expressed in ~90% of ovarian carcinomas,[5, 6] with 35-40%[7] of PROC tumors exhibiting high FRα expression (≥75% of tumor cells positive with ≥2+ intensity)[8]
- MIRV demonstrated an ORR of 32% and mDOR 6.9 months in the single-arm study SORAYA[8] of BEV pre-treated PROC to support accelerated approval by the FDA[9]
- MIRASOL is the confirmatory, randomized, global phase 3 trial designed to support approval worldwide



PFS, progression-free survival; OS, overall survival; FRα, folate receptor alpha; ORR, objective response rate; ADC, antibody-drug conjugate; mDOR, median duration of response; FDA, Food and Drug Administration; BEV, bevacizumab; US, United States; EU, Europe.

1. Pujade-Lauraine et al. *J Clin Oncol.* 2014;32(13):1302-1308. **2.** Richardson et al. *JAMA Oncol.* 2023;10.1001/jamaoncol.2023.0197. **3.** Moore et al. *Cancer.* 2017;123(16):3080-3087. **4.** Ab et al. *Mol Cancer Ther.* 2015;14(7):1605-1613. **5.** Markert et al. *Anticancer Res.* 2008;28(6A):3567-3572. **6.** Martin et al. *Gynecol Oncol.* 2017;147(2):402-407. 7. Data on file. **8.** Matulonis et al. *J Clin Oncol.* 2023;41(13):2436-2445. **9.** U.S. FOOD & DRUG ADMINISTRATION. BLA ACCELERATED APPROVAL. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/761310Orig1s000ltr.pdf. Accessed May 23, 2023.

MIRASOL (NCT04209855) – Study Design[1,2]

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

Patient Population
(N=453)

Enrollment and Key Eligibility
Platinum-resistant disease
(PFI ≤6 mo)
FRα detected by IHC with PS2+ intensity among ≥75% of viable tumor cells
High-grade serous histology
1º platinum-refractory disease excluded (primary PFI <3 mo)
1-3 prior lines of therapy
Prior BEV and PARPi allowed
Patients with BRCA mutations allowed

1:1 Randomization

Treatment Regimen-Experimental
MIRV
(6 mg/kg AIBW Q3W)

Treatment Regimen-Control
Investigator's Choice Chemotherapy
(Paclitaxel, PLD, or Topotecan)

Stratification Factors
IC chemo: paclitaxel, PLD, or topotecan
Prior lines of therapy: 1 vs 2 vs 3

Primary Endpoint
PFS by INV
(BICR sensitivity analysis)

Key Secondary Endpoints
1) ORR by INV
2) OS
3) PROs[a]

Secondary Endpoints
Safety and tolerability
DOR
CA-125 response[b]
PFS2

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

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

[b]Gynecological Cancer InterGroup (GCIG) criteria.

1. ClinicalTrials.gov identifier: NCT04209855. Updated June 16, 2022. Accessed October 5, 2022. https://clinicaltrials.gov/ct2/show/NCT04209855
2. Moore K, et al. Presented at: 2020 American Society of Clinical Oncology Annual Meeting; May 29-31, 2020; Virtual. Abstract TPS6103.

Baseline Demographics and Stratification Factors (N=453)

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

Data cutoff: March 6, 2023. **14% of patients remain on MIRV; 3% remain on IC Chemo**

BRCA, BReast CAncer gene; PARPi, poly (ADP-ribose) polymerase inhibitors; MIRV, mirvetuximab soravtansine; IC Chemo, investigator's choice chemotherapy; PLD, pegylated liposomal doxorubicin.

[a]Five patients (2%) in the MIRV arm and five patients in the IC chemo arm (2%) were missing information for stage at initial diagnosis. [b]One patient (<1%) in the MIRV arm was missing information on primary platinum-free interval. [c]One patient (<1%) in the MIRV arm and 3 patients (1%) in the IC chemo arm enrolled with platinum-free interval of >6 months

2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY: Kathleen Moore, Associate Director of Clinical Research, Stephenson Cancer Center University of Oklahoma College of Medicine
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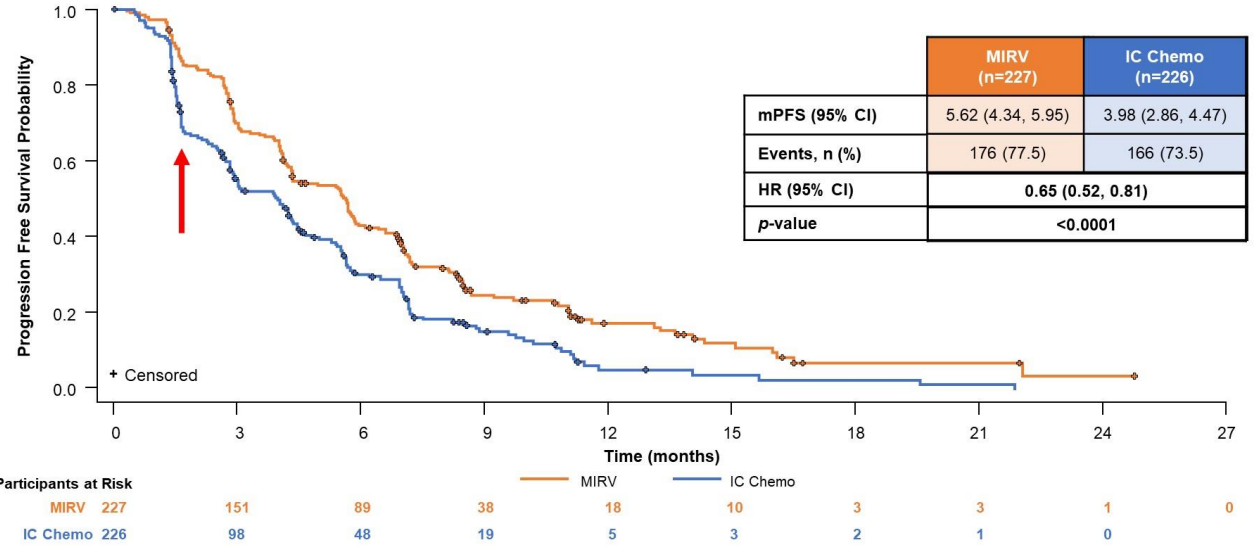
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

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	

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

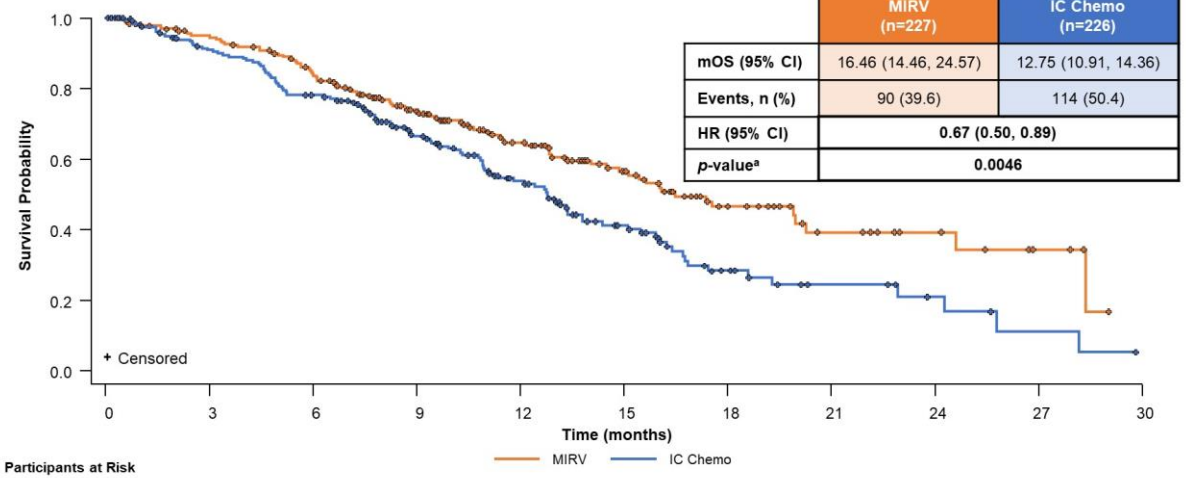
Overall Response Rate by Investigator (N=453)

	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**

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.

Overall Survival



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

Data cutoff: March 6, 2023; median follow-up time: 13.11 months
MIRV, mirvetuximab soravtansine; IC Chemo, investigator's choice chemotherapy; mOS, median overall survival; CI, confidence interval; HR, hazard ratio.
[a]Overall survival is statistically significant based on pre-specified boundary p-value at interim analysis = 0.01313

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

Mirvetuximab Soravtansine: ongoing trial

PICCOLO

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

PRIMARY ENDPOINT
ORR by Investigator

SECONDARY ENDPOINT
DOR by Investigator

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

GLORIOSA

RANDOMIZED PHASE 3 TRIAL
FOR MIRVETUXIMAB +
BEVACIZUMAB MAINTENANCE
IN FRα-HIGH PSOC PATIENTS

PRIMARY ENDPOINT
PFS

SECONDARY ENDPOINT
OS

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

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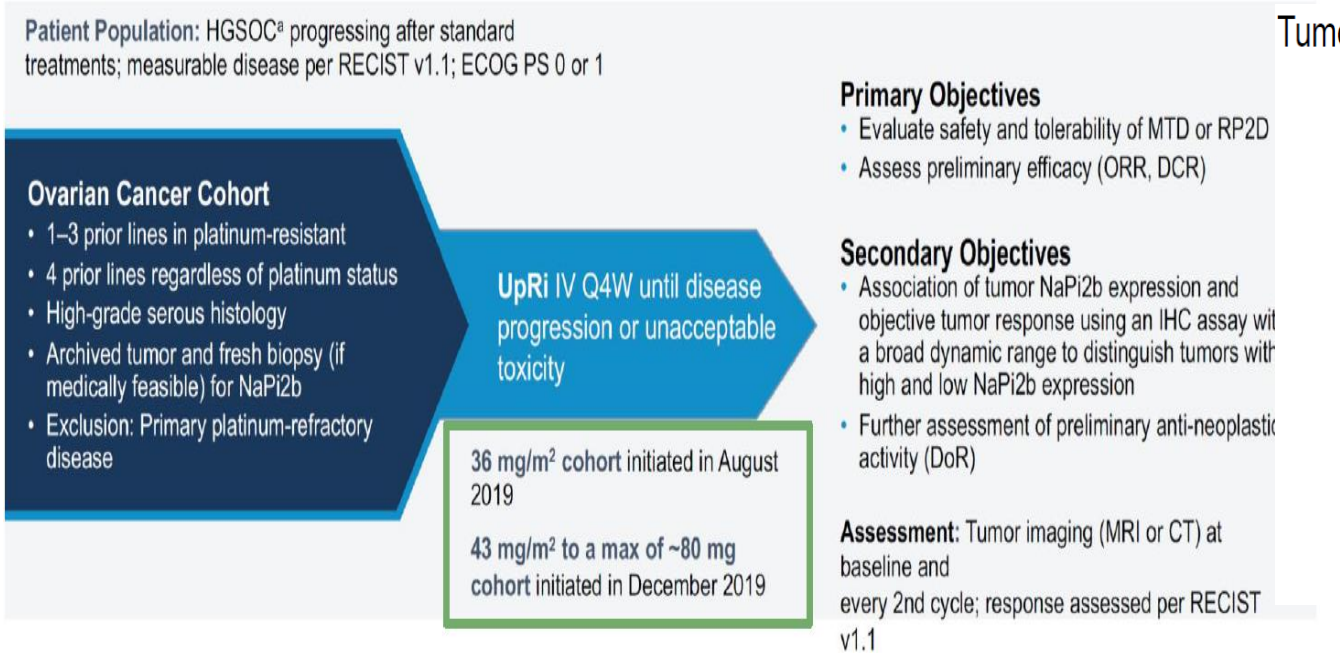
NaPi2b sodium dependent phosphate transporter

- Anti **NaPi2b ADC** sodium dependent phosphate transporter;
- Broad expression in ovarian cancer and limited expression in healthy tissue (up to 80-90% epithelial OC);
- Upifitamab Rilsodotin is a first in class Dolaflexin ADC targeting NaPi2b with auristatineas cytotoxic payload.

UpRi PHASE 1 STUDY EXPANSION COHORT OVARIAN CANCER



Tumor shrinkage in 67%

		All Dose Levels	Dose Group 36	Dose Group 43
NaPi2b-High (TPS ≥75)	N	38	16	22
	ORR, n (%)	**13 (34)**	**7 (44)**	**6 (27)**
	CR, n (%)	2 (5)	2 (13)	0
	PR, n (%)	11 (29)	5 (31)	6 (27)
	DCR, n (%)	33 (87)	12 (75)	21 (95)
All NaPi2b Levels	N	75	25	48
	ORR, n (%)	**17 (23)**	**9 (36)**	**8 (17)**
	CR, n (%)	2 (3)	2 (8)	0
	PR, n (%)	15 (20)	7 (28)	8 (17)
	DCR, n (%)	54 (72)	18 (72)	35 (73)

- **Median DoR in patients (all dose levels) with NaPi2b-high ovarian cancer (n=13): 5 months**
- No obvious difference in median DoR observed between Dose Groups 36 and 43

Richardson et al, SGO 2022

Upifitamab Rilsodotin: ongoing trial

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

Mersana THERAPEUTICS

Patient Population:

No Pre-Selection for NaPi2b

Inclusion Criteria:
Platinum Resistant Ovarian Cancer
1 – 4 Prior Lines

Exclusion Criteria:
1 – 2 Prior Lines Bev-naïve
Primary Platinum Refractory Disease

Global:	Dose:	N:
US, Europe, Australia, Canada	43 mg/m² q4w	~180 Patients

Primary Endpoint:
Confirmed ORR in higher NaPi2b

Key Secondary Endpoint:
Confirmed ORR in overall population

Other Secondary Endpoints:
- Duration of Response
- Safety

11

UP-NEXT

- **UP-NEXT** is a global Phase 3, double-blind, randomized, placebo-controlled study of UpRi monotherapy maintenance in patients with NaPi2b-positive platinum-sensitive recurrent ovarian cancer

Key Enrollment Criteria
- Patients with platinum-sensitive recurrent HGSOC[a]
- 4–8 cycles of platinum-based therapy in second to fourth line setting[b]
- Best response to last line of treatment: NED, CR, PR, or SD[c]
- ECOG PS 0–1
- NaPi2b-positive (TPS ≥75) tumor based on archival or fresh tumor biopsy
- Prior PARPi required for patients with known deleterious *BRCA* mutations
- Patients who received bevacizumab in combination with their last platinum-containing regimen are excluded

N≈350 Randomized 2:1

UpRi 30 mg/m² (Capped at BSA 2.2 m²) IV q4w

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

Placebo q4w

Primary Endpoint
- PFS by BICR

Secondary and Exploratory Endpoints
- PFS by investigator
- ORR by investigator
- OS
- Safety
- PROs

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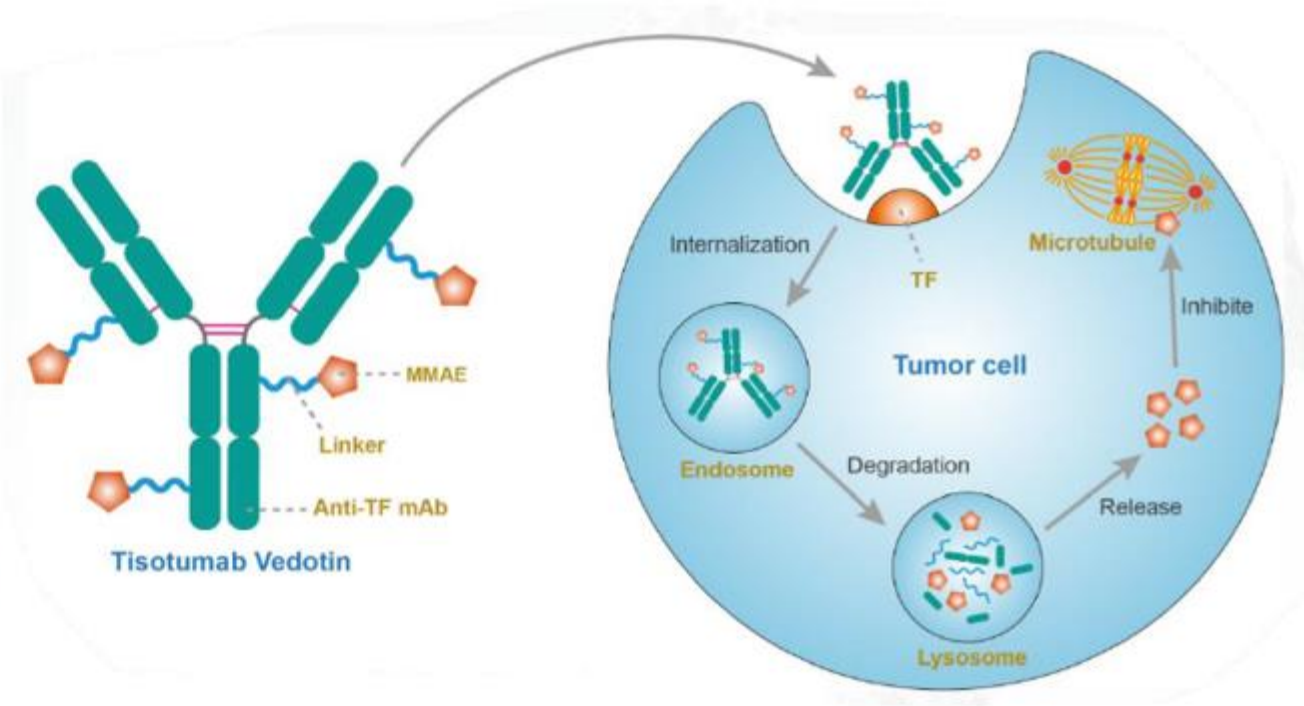
ADC in Cervical Cancer: Tisotumab Vedotin

Tisotumab vedotin is an investigational antibody-drug conjugate directed to tissue factor (TF) and covalently linked to the microtubule-disrupting agent MMAE via a protease-cleavable linker[1,2]

TF is highly prevalent in cervical cancer and other solid tumours and is associated with cancer pathophysiology and poor prognosis[3-5]

- TF is co-opted by tumour cells to promote tumour growth, angiogenesis, and metastasis[6]
- In normal physiology, TF's primary role is to initiate the coagulation cascade after vascular injury[6]

Tisotumab vedotin has multiple anti-tumour effects[1,2,7]



Breij EC, *et al.* Cancer Res 2014;74(4):1214–26; 2. De Goeij BE, *et al.* Mol Cancer Ther 2015;14(5):1130–40; 3. Pan L, *et al.* Mol Med Rep 2019;19:2077–86; 4. Cocco E, *et al.* BMC Cancer 2011;11:263; 5. Zhao X, et al. Exp Ther Med 2018;16:4075-4081; 6. Forster Y, et al. Clin Chim Acta 2006;364:12-21; 7. Alley SC, et al. American Association for Cancer Research Annual Meeting: March 29-April 3, 2019; Atlanta, GA, USA; Abstract #221.
Coleman R. *et al.* Presented at ESMO Virtual Congress 2020. By permission of Prof R. Coleman.

GOG 3023/ENGOT CX6/INNOVATV 204

Key eligibility criteria:

- Recurrent or extrapelvic metastatic cervical cancer
- Progressed during or after doublet chemotherapy[a] with bevacizumab (if eligible)
- Received ≤2 prior systemic regimens[b]
- ECOG PS 0-1

Enrolled: 102[c]
Treated: 101*

Tisotumab vedotin 2.0 mg/kg IV Q3W

Until PD or unacceptable toxicity

Tumour responses assessed using CT or MRI at baseline, every 6 weeks for the first 30 weeks, and every 12 weeks thereafter

Primary endpoint:

- ORR[d] per RECIST v1.1, by independent imaging review committee (IRC)

Secondary endpoints:

- ORR[d] per RECIST v1.1, by investigator
- DOR, TTR, and PFS by IRC and investigator
- OS
- Safety

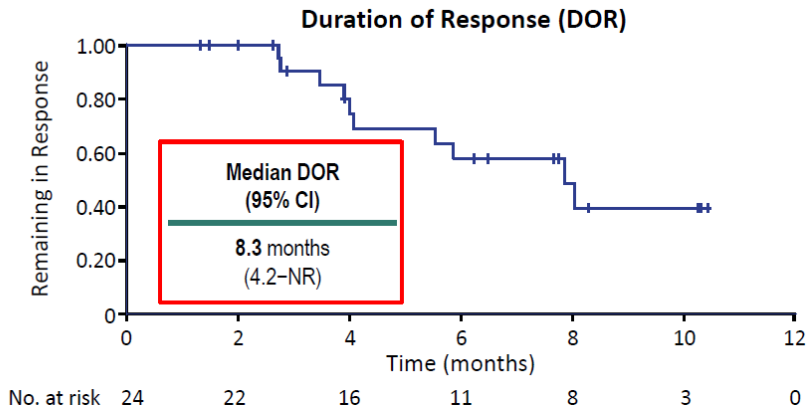
Exploratory endpoints:

- Biomarkers
- HRQoL

*Study sample size calculated assuming a confirmed ORR of 21% to 25% with tisotumab vedotin and to provide ≥80% power to exclude an ORR of ≤11%[e]

[a]Paclitaxel plus platinum (cisplatin or carboplatin) or paclitaxel plus topotecan. [b]Adjuvant or neoadjuvant chemotherapy or if administered with radiation therapy, was not counted as a prior systemic regimen. [c]June 2018 to April 2019. [d]Responses were confirmed by subsequent repeat imaging performed ≥4 weeks after initial response assessment. [e]Using one-sided exact binomial test at 0.025 significance level.

	N=101
Confirmed ORR (95% CI),[a] %	**24 (15.9–33.3)**
CR, n (%)	7 (7)
PR, n (%)	17 (17)
SD, n (%)	49 (49)
PD, n (%)	24 (24)
Not evaluable, n (%)	4 (4)



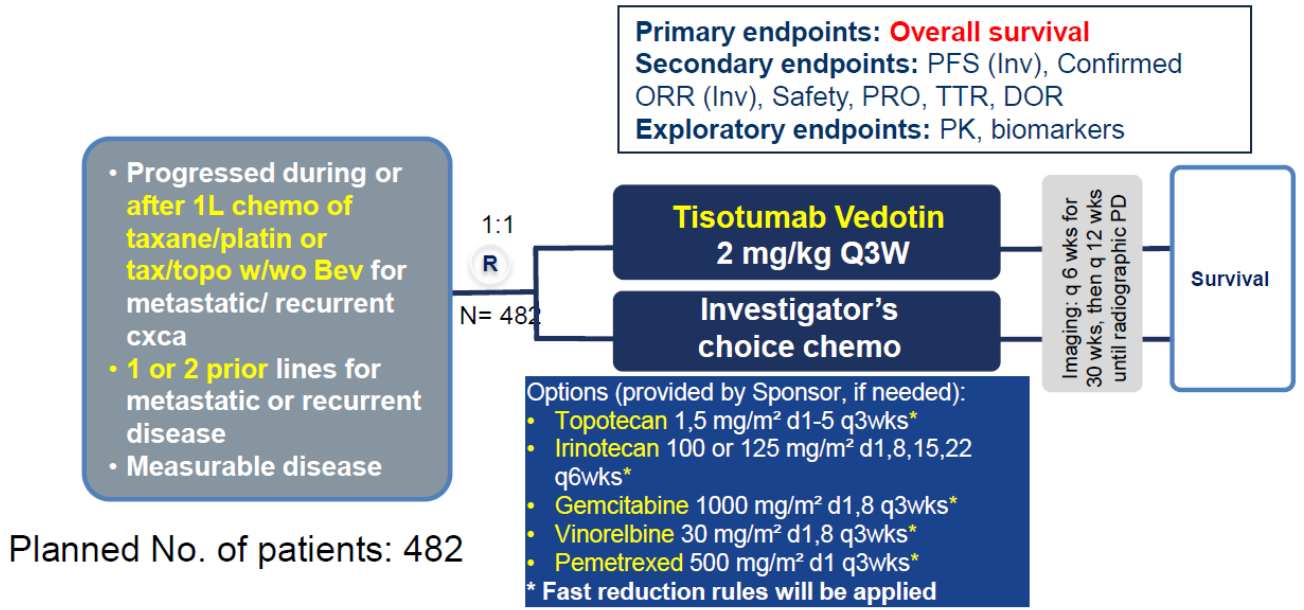
Clinically meaningful and durable responses were observed

Data cutoff: February 06, 2020. Median duration of follow-up: 10.0 months.
[a]Based on the Clopper-Pearson method.

Coleman RL et al. ESMO 2020. Abstract LBA32. Coleman RL. Lancet Oncol. 2021

Tisotumab Vedotin: ongoing trial

ENGOT CX12/GOG3057/ INNOVATV 301



Planned No. of patients: 482

Tisotumab Vedotin + Bevacizumab or Pembrolizumab or Carboplatin in Recurrent/Metastatic Cervical Cancer: Phase 1b/2 ENGOT-Cx8/GOG-3024/innovaTV 205 Study Dose-Escalation Results

Bradley J. Monk,[1] Toon Van Gorp,[2] Domenica Lorusso,[3] Roisin Eilish O'Cearbhaill,[4] Anneke Westermann,[5] Susana Banerjee,[6] Dearbhaile Catherine Collins,[7] Jaroslav Klat,[8] Kristine Madsen,[9] Jean-Francois Baurain,[10] Amanda Jackson,[11] Ingrid Boere,[12] Sandro Pignata,[13] Eelke Gort,[14] John Moroney,[15] Ibrahima Soumaoro,[16] Camilla Mondrup Andreassen,[17] Leonardo Viana Nicacio,[18] Christine Gennigens,[19] Ignace Vergote [20]

[1]Arizona Oncology (US Oncology Network), University of Arizona College of Medicine, Creighton University School of Medicine, Phoenix, AZ, USA; [2]Gynecological Oncology, KU Leuven University Hospitals Leuven, Leuven, Flanders, Belgium; [3]Fondazione IRCCS, Foundation Policlinico Universitario Agostino Gemelli IRCCS; [4]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [5]Academisch Medisch Centrum, Amsterdam, The Netherlands; [6]The Royal Marsden NHS Foundation Trust, London, UK; [7]Cork University Hospital/Oncology Trials Unit, Cork, Ireland; [8] University Hospital Ostrava, Ostrava, Czech Republic; [9]Righospitalet, University Hospital of Copenhagen, Copenhagen, Denmark; [10]Université Catholique de Louvain (UCLouvain), Brussels, Belgium; [11]University of Cincinnati Cancer Center, Cinnacinnati, OH, USA; [12]Department of Medical Oncology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands; [13]Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, Napoli, Italy; [14]University Medical Center Utrecht, The Netherlands; [15]Department of Obstetrics and Gynecology, University of Chicago, IL, USA; [16]Genmab US, Inc., Princeton, NJ, USA; [17]Genmab, Copenhagen, Denmark; [18] Seagen Inc., Bothell, WA, USA; [19]Department of Medical Oncology, Centre Hospitalier Universitaire de Liege, Liege, Belgium; [20]Belgium and Luxembourg Gynaecological Oncology Group, University of Leuven, Leuven Cancer Institute, Leuven, Belgium

Tisotumab Vedotin + Carboplatin in First-Line or + Pembrolizumab in Previously Treated Recurrent/Metastatic Cervical Cancer: Interim Results of ENGOT-Cx8/GOG-3024/innovaTV 205

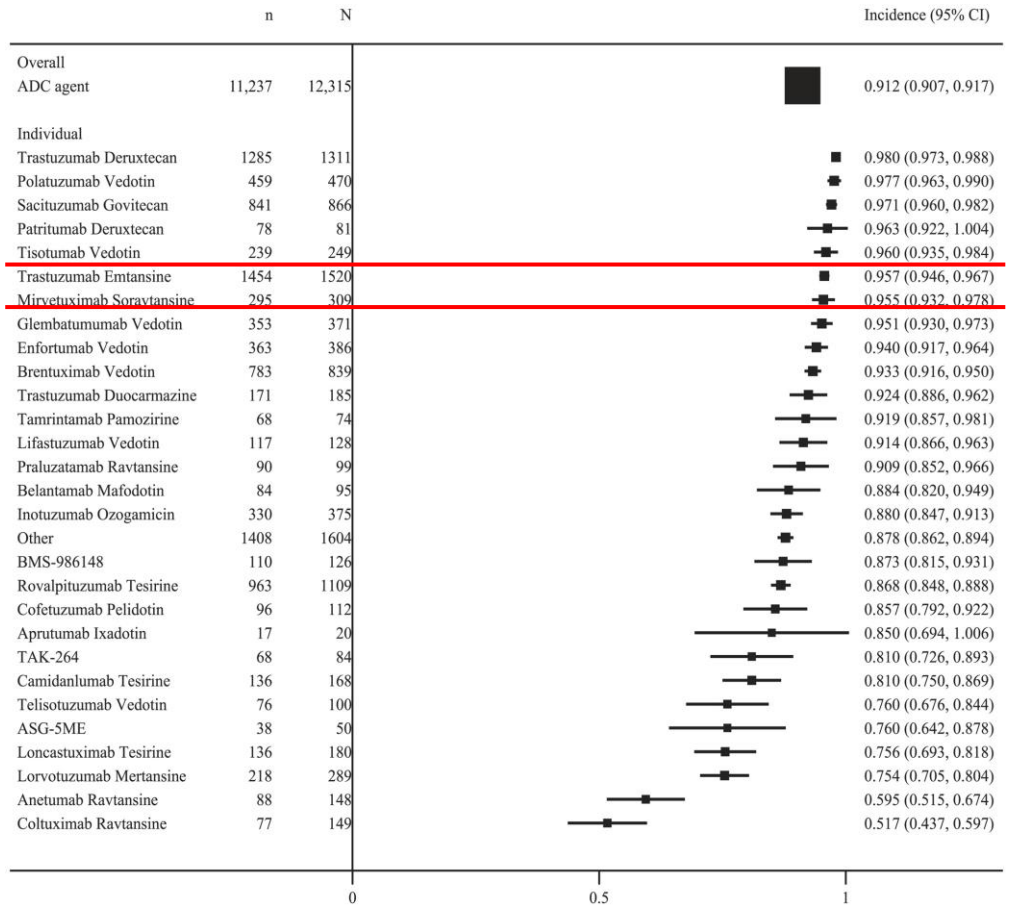
Ignace Vergote,[1] Bradley J. Monk,[2] Roisin E. O'Cearbhaill,[3] Anneke Westermann,[4] Susana Banerjee,[5] Dearbhaile Catherine Collins,[6] Mansoor Raza Mirza,[7] David O'Malley,[8] Christine Gennigens,[9] Sandro Pignata,[10] Bohuslav Melichar,[11] Azmat Sadozye,[12] Frederic Forget,[13] Krishnansu S. Tewari,[14] Eelke Gort,[15] Ibrahima Soumaoro,[16] Camilla Mondrup Andreassen,[17] Leonardo Viana Nicacio,[18] Els Van Nieuwenhuysen,[1] Domenica Lorusso[19]

[1]Belgium and Luxembourg Gynaecological Oncology Group, University of Leuven, Leuven Cancer Institute, Leuven, Belgium; [2]Arizona Oncology (US Oncology Network), University of Arizona College of Medicine, Creighton University School of Medicine, Phoenix, AZ, USA; [3]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA; [4]Amsterdam University Medical Centers, Amsterdam, Netherlands; [5]The Royal Marsden NHS Foundation Trust, London, UK; [6]Cork University Hospital/Oncology Trials Unit, Cork, Ireland; [7]Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark; [8]Division of Gynecology Oncology, Department of Gynecology and Obstetrics, The Ohio State University College of Medicine, Columbus, Ohio, USA; [9]Department of Medical Oncology, Liège University Hospital, Liège, Belgium; [10]Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, Naples, Italy; [11]Palacký University Medical School and Teaching Hospital, Olomouc, Czech Republic ; [12]NHS Greater Glasgow and Clyde, Glasgow, United Kingdom; [13]Centre Hospitalier de l'Ardenne, Libramont, Belgium; [14]University of California, Irvine Medical Center, Orange, CA, USA; [15]University Medical Center Utrecht, Utrecht, Netherlands; [16]Genmab US, Inc., Princeton, NJ, USA; [17]Genmab A/S, Copenhagen, Denmark; [18]Seagen Inc., Bothell, WA, USA; [19]Fondazione IRCCS, Foundation Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

Ignace Vergote

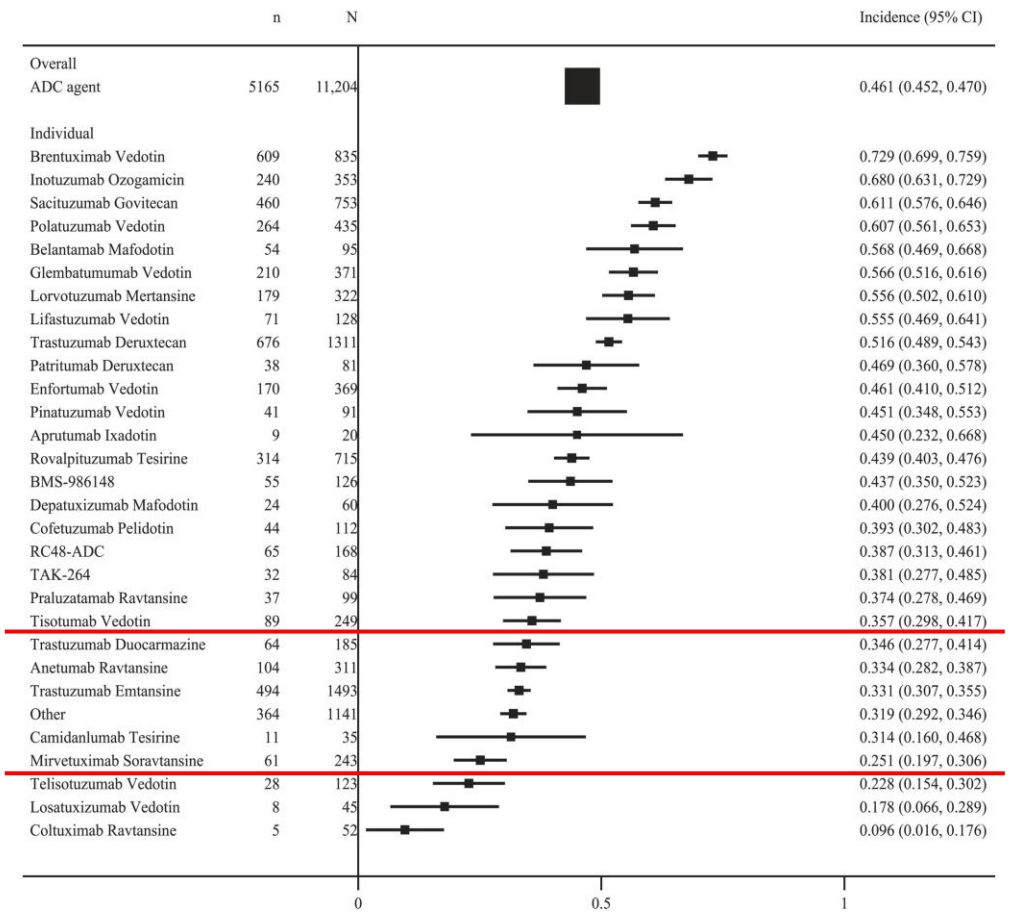
ADC RELATED AE'S

The overall incidence of all-grade TRAEs



Tisotumab Vedotin: 96%
Mirvetuximab Soravtansine: 95.5%

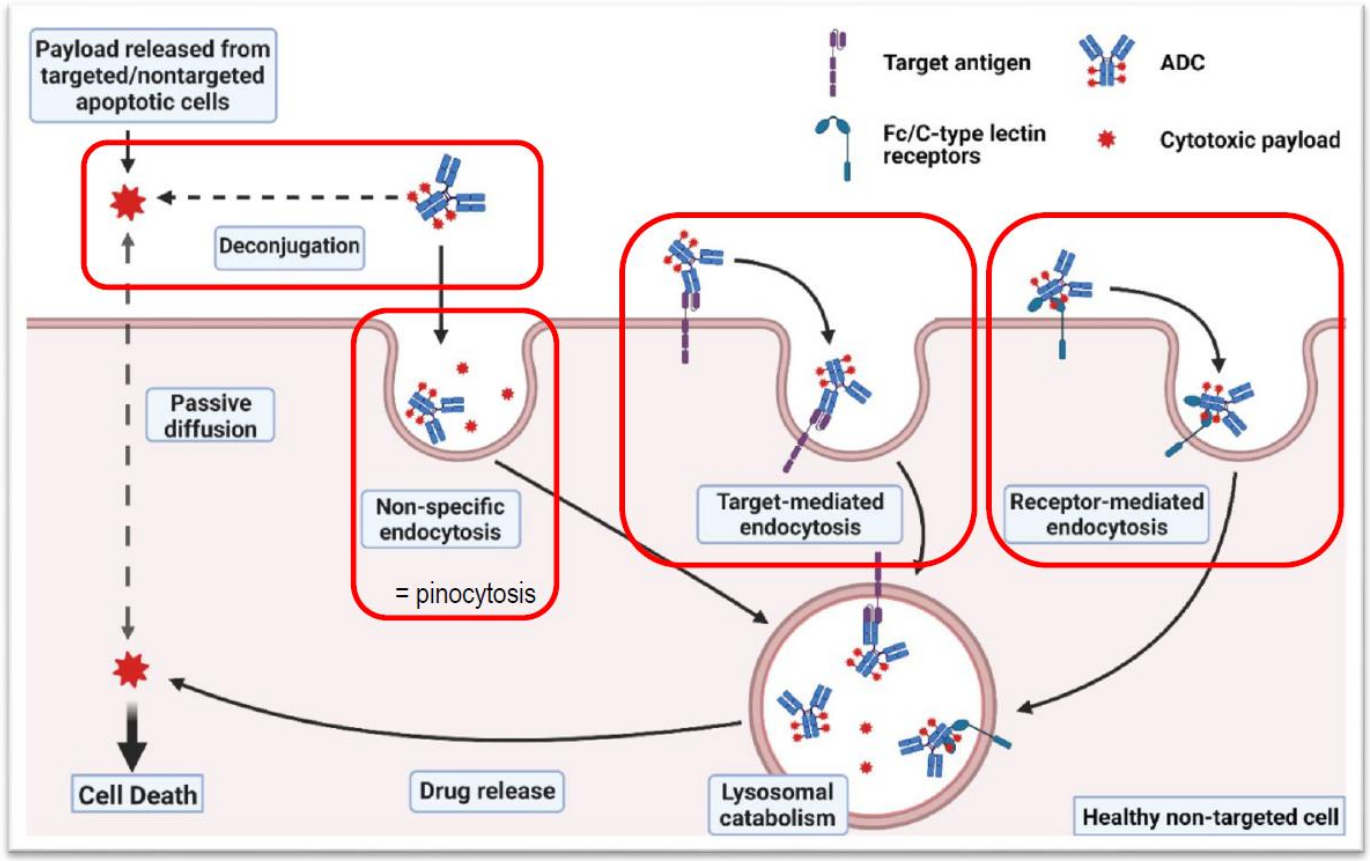
The overall incidence of grade ≥3 TRAEs



Tisotumab Vedotin: 35.7%
Mirvetuximab Soravtansine: 25.1%

Zhu Y, et al; Cancer 2023

ADC RELATED AEs



On target, off tumour AEs:

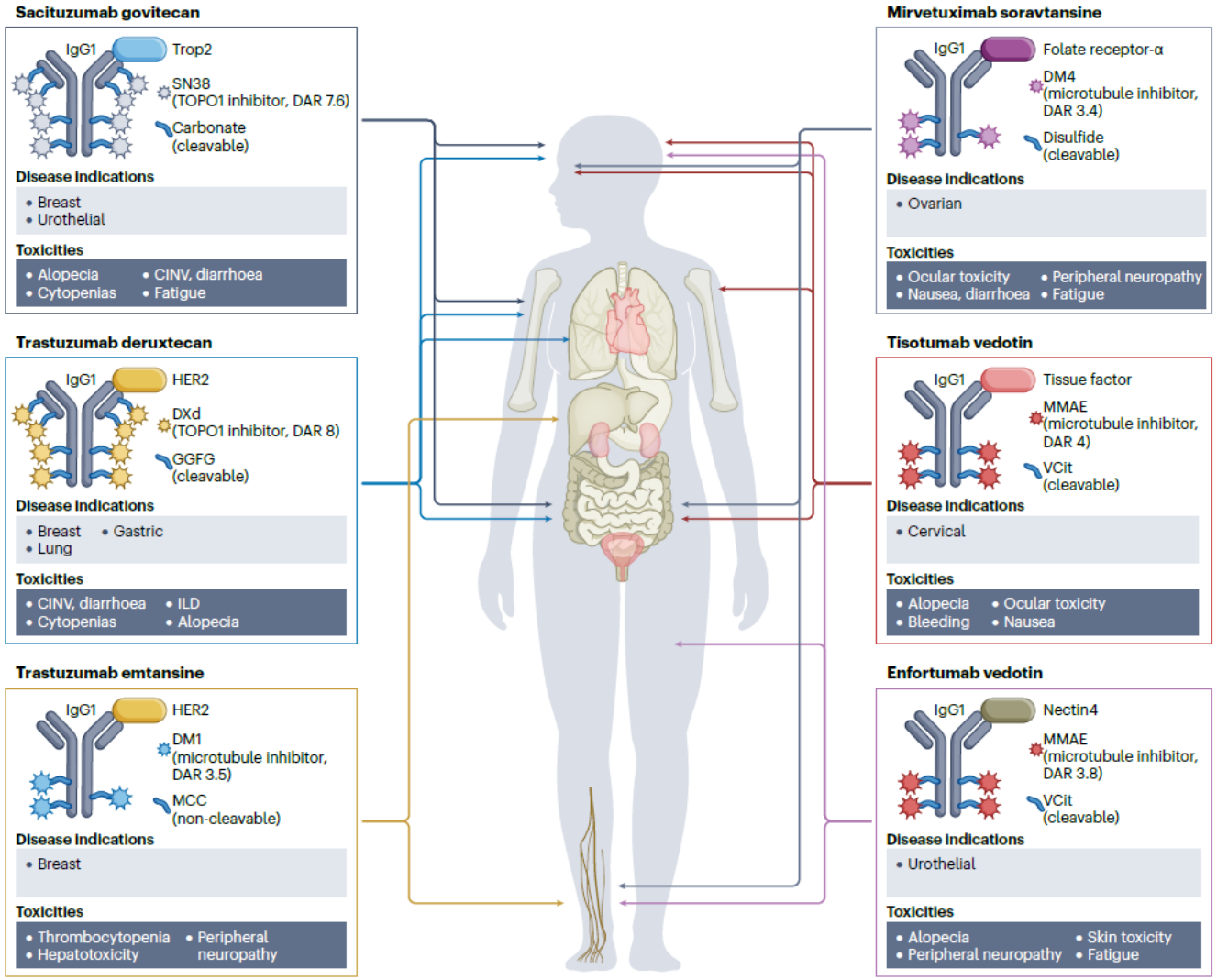
- Expression of the ADC target on non-malignat cells;
- Interaction between Fc domain with Fc receptor expressed by immune cells.

Off target, off tumour AEs (unrelated to the antigen targeted, toxicity profile of the drug):

- Premature release of payload in the systemic circulation;
- Bystander effect;
- Non-specific enodocytosis (pinocytosis by macrophages in a variety o tissue);
- Payload-linker complex can react with serum albumin.

Tarantino P, et al; Nat Rev Clin Oncol 2023

ADC RELATED AEs

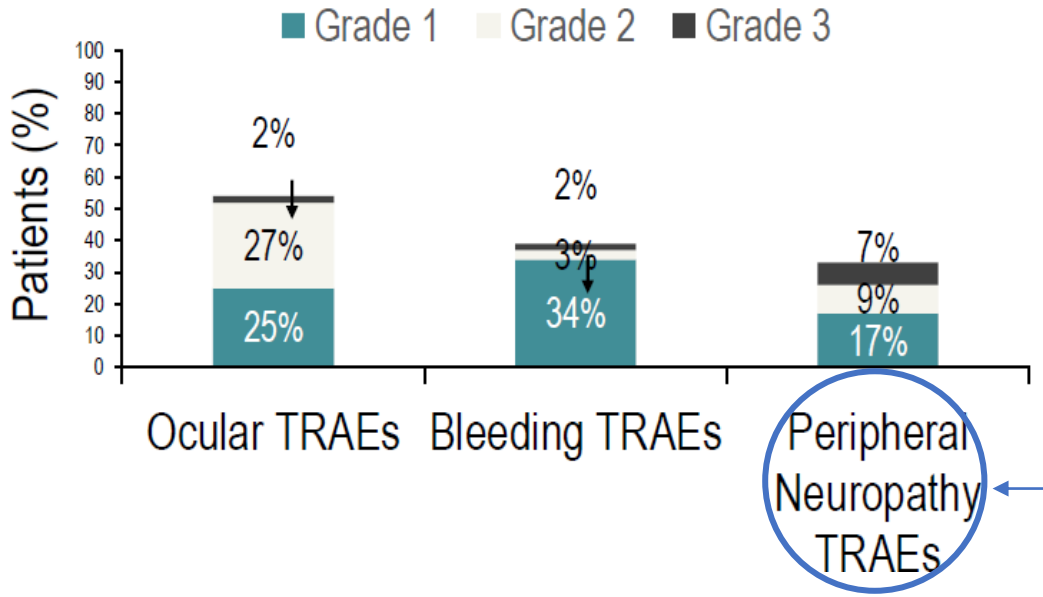


HEMATOLOGICAL AEs: Off target cytotoxic damage into hematopoietic stem cells of the bone marrow

Incidences of G≥3 AEs (%)	MMAE	DM4
Neutropenia (%)	37.0	23.9
Thromcytopenia (%)	28.8	22.6
Lymphopenia (%)	22.6	36.5
Febrile neutropenia (%)	17.1	-
Anemia (%)	15.3	-
WBC decrease (%)	11.2	-

Tarantino P, et al; Nat Rev Clin Oncol 2023; Zhu Y, et al; Cancer 2023

Most common TRAEs with Tisotumab Vedotin: GOG3023/ENGOT CX6/INNOVAT 204



Non-specific uptake (off-target)

Most common all grade ocular adverse reactions

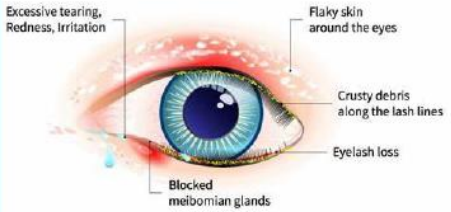
40% conjunctival adverse reactions

29% dry eye

21% corneal adverse reactions

8% blepharitis

BLEPHARITIS



GRADE 2 CONJUNCTIVITIS: WITHHOLD, RECOVER AND DOSE REDUCE

Most common all grade hemorrhage adverse reactions

44% epistaxis

10% hematuria

10% vaginal hemorrhage

Most common all grade peripheral neuropathy adverse reactions

20% peripheral neuropathy

11% peripheral sensory neuropathy

5% peripheral sensorimotor neuropathy

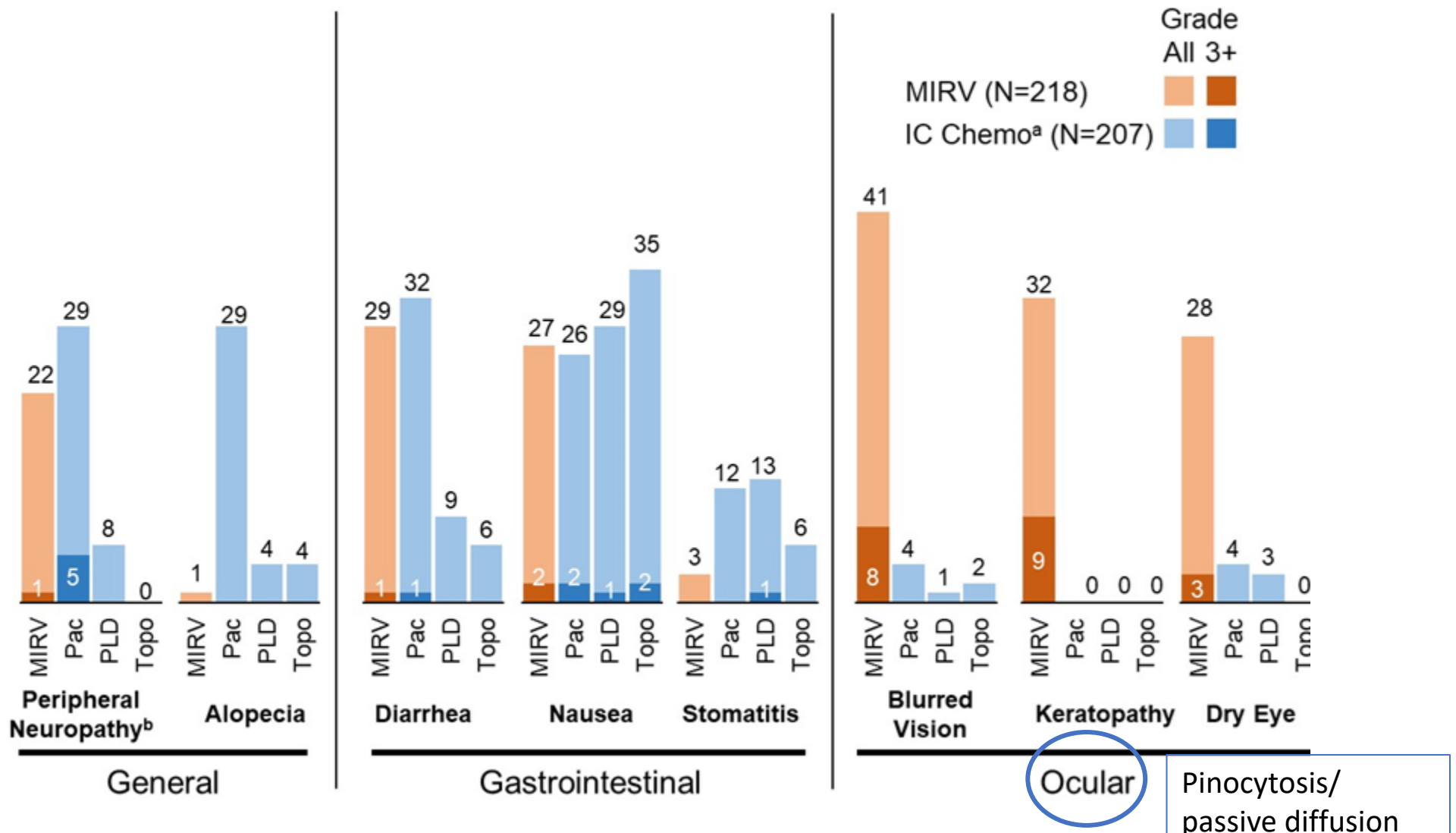
3% motor neuropathy

3% muscular weakness

1% demyelinating peripheral polyneuropathy

Coleman RL et al. ESMO 2020. Abstract LBA32. Coleman RL. Lancet Oncol. 2021

Most common TRAEs with Mirvetuximab Soravtansine: MIRASOL trial



Pinocytosis/ passive diffusion (off-target)

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

Conclusions: ADCs a never ending story

- ADCs are now a recognized component of the anticancer armamentary;
- Despite their ideally targeted mechanism of action, most ADCs still conferm frequent and sometimes life-threatining toxicities;
- The awareness and the management of AEs are crucial for preventing and mitigating related toxicities;
- Challenges for the future:
  - Increase tumor specificity→select the best.
  - Better investigate mechanisms of toxicity and strategies to overcome it.

Thanks for your attention!

MaNGO
Mario Negri Gynecologic Oncology