Role of Antibody-Drug Conjugates in Gynecologic Malignancies

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Overview

- ADCs: What are they
- ADCs in Gynecologic Cancers:
  - Ovary:
    - Mirvetuximab Soravtansine
  - Cervix:
    - Tisotumab vedotin-tftv
  - Investigational:
    - Endometrial: Upifitamab rilsodotin (UpRi)

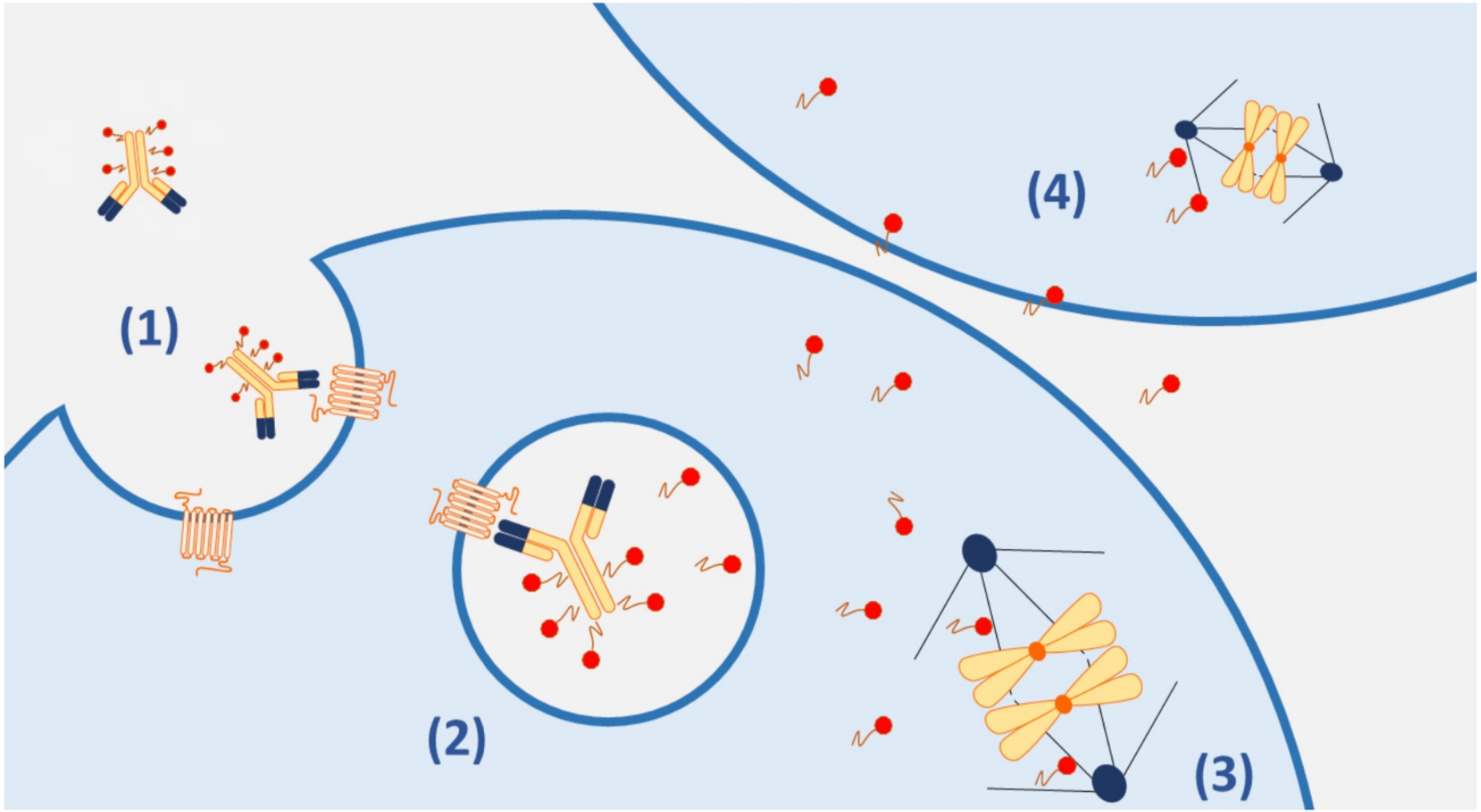
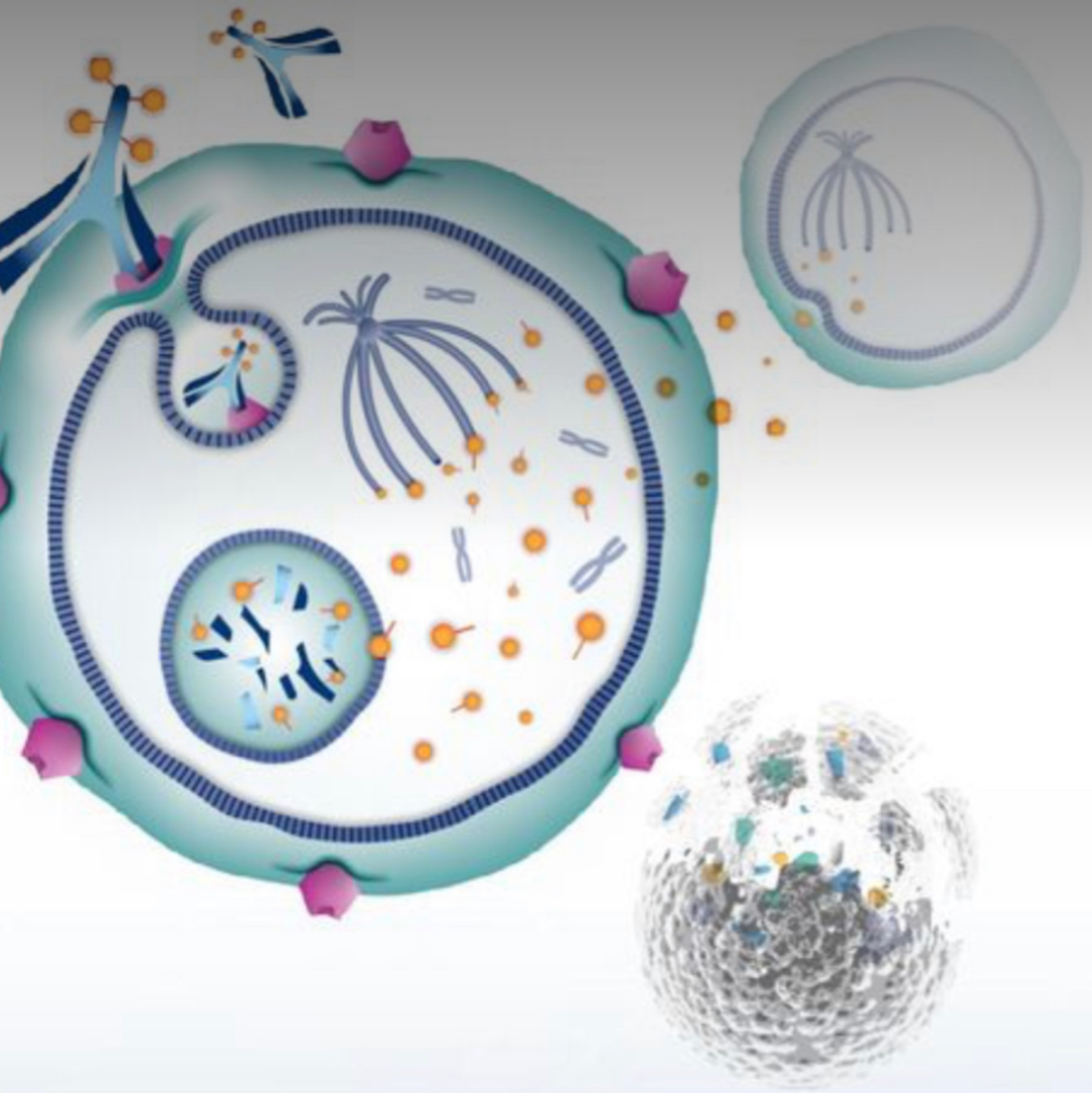


Figure 1. Main mechanisms of action of ADCs. (1). The ADC complex binds to the target antigen on the cancer cell membrane and is internalized; (2). in the lysosome, the payloads are released through linkers cleavage or antibody degradation (in case of non-cleavable linkers); (3). the cytotoxic payloads cause drug-specific microtubule inhibition; (4). the diffusion of cytotoxic payloads across the cell membranes can result in the death of neighboring antigen negative cells (bystander effect)

Nerone M, et al. Explor Target Antitumor Ther 2022; 3:149-71.

Mirvetuximab soravtansine



AN INTEGRATED SYSTEM

Linker

- Cleavable linker stable in the blood stream
- Bystander killing of neighboring cancer cells

Ultra-potent anticancer agent

- DM4 — a potent tubulin-targeting agent

Antibody (Ab)

- A folate receptor α (FRα)-binding antibody

Target

- Highly expressed in ovarian and other cancers

Efficacy and Safety of Mirvetuximab Soravtansine in Patients With Platinum-Resistant Ovarian Cancer With High Folate Receptor Alpha Expression: Results From the SORAYA Study

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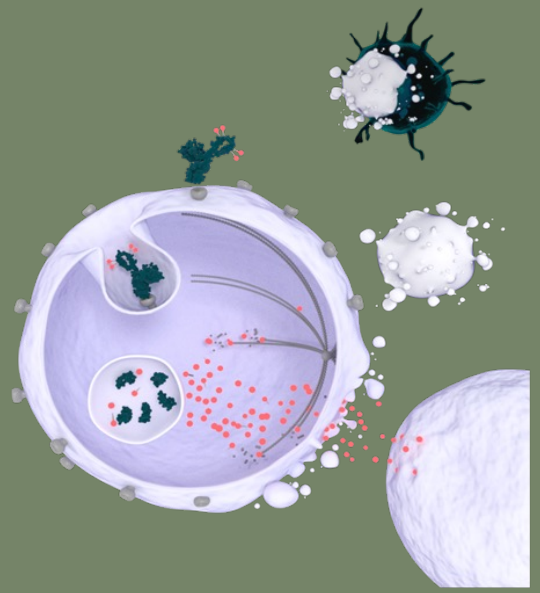


SORAYA

SORAYA: Study Design and Patient Population

Objective: Evaluate efficacy and safety of MIRV in patients with FRα-high platinum-resistant ovarian cancer

Primary endpoint: Confirmed ORR by investigator

- ORR by blinded independent central review for sensitivity analysis

Key secondary endpoint: Duration of response

Patient population

- Platinum-resistant ovarian cancer (recurrence within 6 months after last platinum dose) treated with 1 to 3 prior regimens
  - Primary platinum-refractory disease* was excluded
- High-grade serous histology
- All enrolled received prior bevacizumab; prior PARP inhibitor was allowed
- Tumor demonstrated FRα-high membrane staining with IHC PS2+ scoring
  - **≥75%** of cells staining positive with **≥2+** staining intensity

Treatment schedule

- Patients received MIRV 6 mg/kg, adjusted ideal body weight, IV once every 3 weeks

Sample size calculation: 105 patients

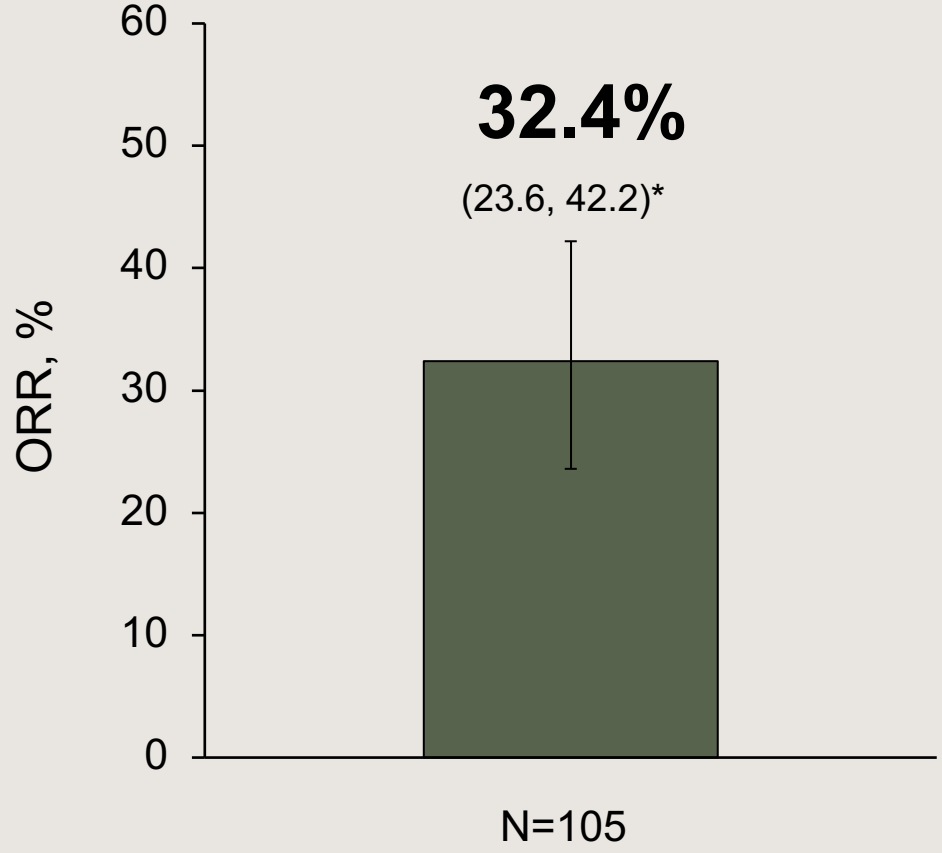
- 110 patients planned to result in approximately 105 efficacy-evaluable patients
- 90% power to detect a difference in ORR of 24% vs 12% using a 1-sided binomial test and a 1-sided α level of 0.025
- 12% was chosen as the ORR to rule out based on the ORR for single-agent chemotherapy reported in prior trials of platinum-resistant ovarian cancer, which ranges from 4% to 13%[1-4]

Baseline Demographics and Clinical Characteristics

Characteristic		All Patients (N=106)
Age, median (range)		62 (35–85 years)
Primary cancer diagnosis,* n (%)	Epithelial ovarian cancer	85 (80)
	Fallopian tube cancer	8 (8)
	Primary peritoneal cancer	12 (11)
Stage at initial diagnosis,† n (%)	I–II	2 (2)
	III	63 (59)
	IV	40 (38)
BRCA mutation, n (%)	Yes	21 (20)
	No/unknown	85 (80)
No. of prior systemic therapies, n (%)	1	10 (9)
	2	41 (39)
	3	54 (51)
Prior exposure, n (%)	Bevacizumab	106 (100)
	PARP inhibitor	51 (48)
Primary platinum-free interval, n (%)	3–12 months‡	64 (60)
	>12 months	42 (40)
Platinum-free interval, n (%)	0–3 months	39 (37)
	3–6 months	64 (60)

Data cutoff: November 16, 2021.
Patients with ECOG PS of 0, n=60 (57%); 1, n=46 (43%).
*Primary cancer diagnosis includes 1 patient with serous tubal intraepithelial carcinoma. †One patient missing information for stage at initial diagnosis. ‡Includes 1 patient with primary platinum-free interval of 2.8 months.
ECOG PS, Eastern Cooperative Oncology Group performance status; PARP, poly ADP-ribose polymerase.

Investigator-Assessed Objective Response Rate in Overall Efficacy Evaluable Population

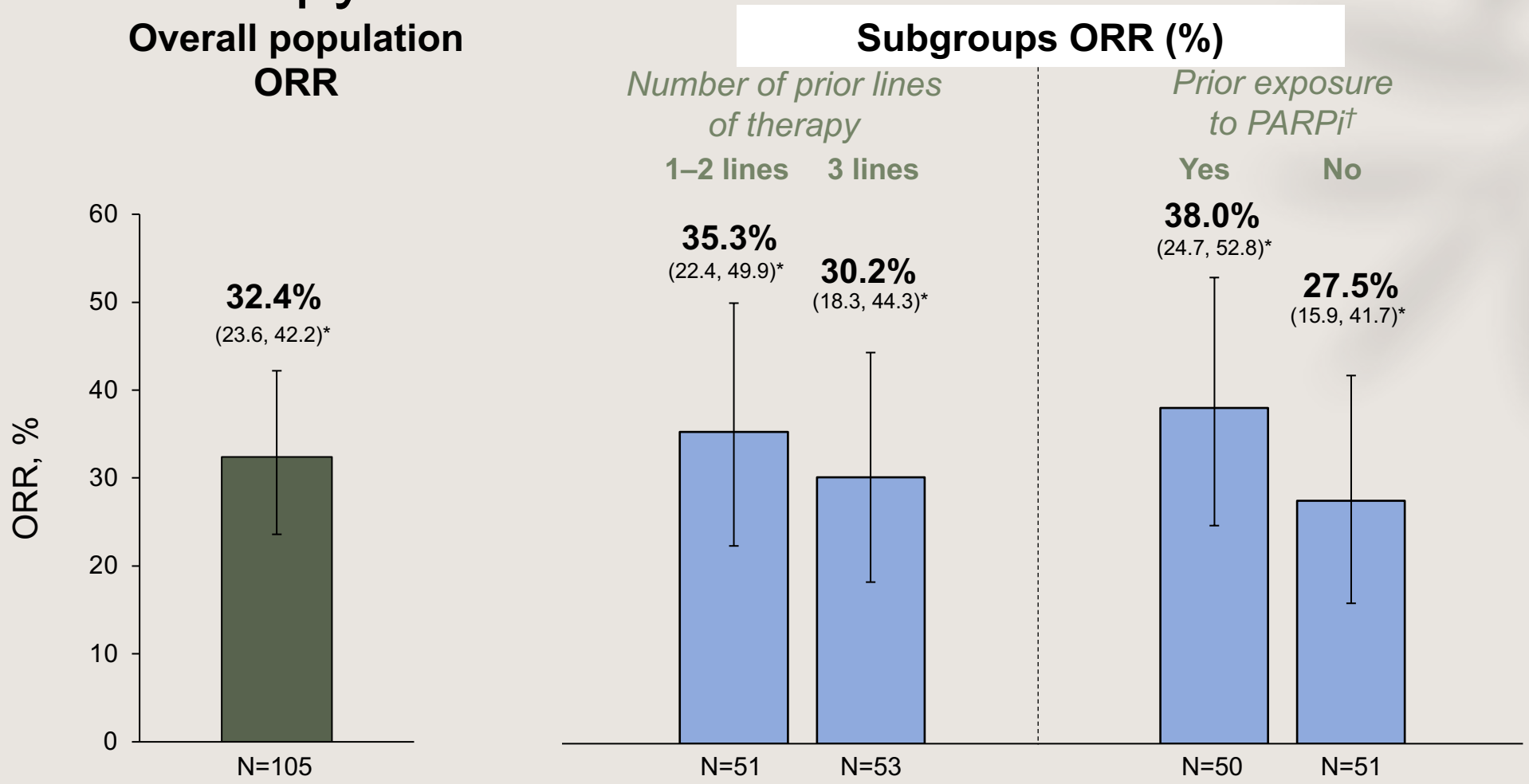


34 responders

- 5 complete responses
- 29 partial responses

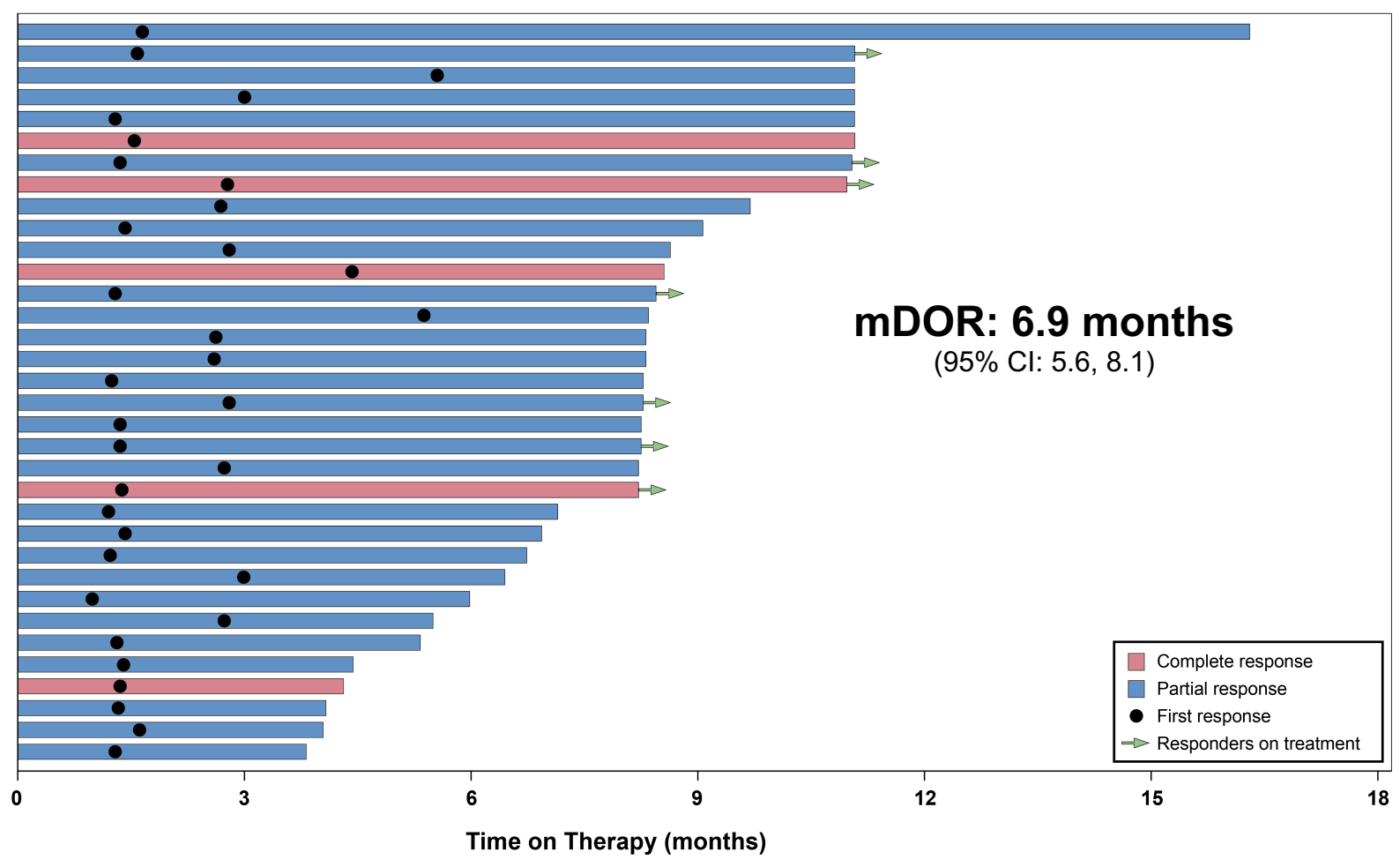
Data cutoff: November 16, 2021.
The denominator for the percentage is the number of patients in the investigator-assessed efficacy evaluable population. Patients without at least 1 postbaseline RECIST assessment were treated as not evaluable.
*95% exact confidence interval is estimated by Clopper-Pearson method (Clopper-Pearson exact CI).
ORR, confirmed objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

Investigator-Assessed Objective Response Rate by Prior Therapy



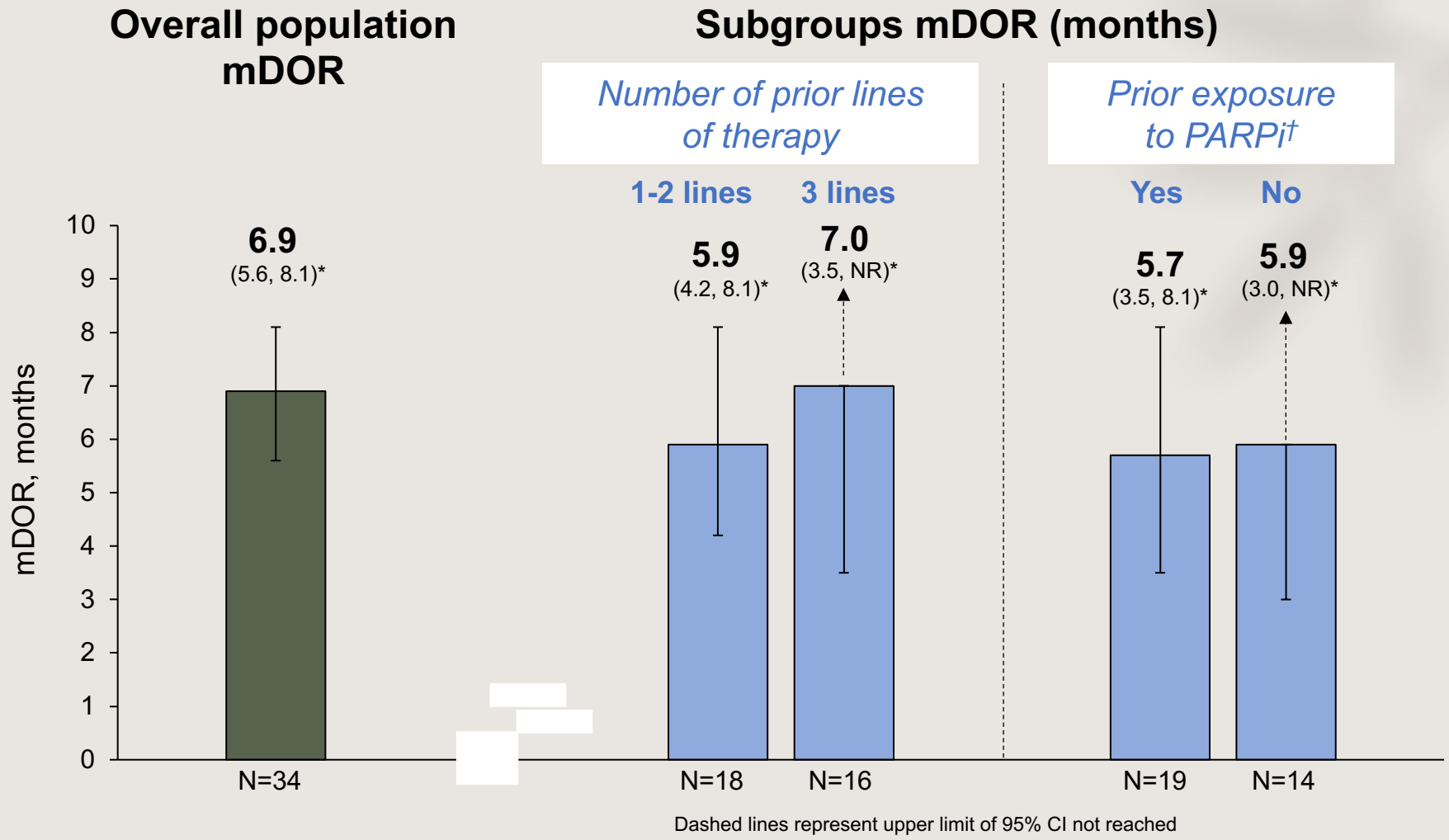
Data cutoff: November 16, 2021.
The denominator for the percentage is the number of patients in the investigator-assessed population in each analysis. Patients without at least 1 postbaseline RECIST assessment were treated as not evaluable.
*95% exact CI is estimated by Clopper-Pearson method (Clopper-Pearson exact CI). †Prior PARPi exposure was uncertain for 4 patients in the investigator-assessed population.
CI, confidence interval; ORR, confirmed objective response rate; PARPi, poly ADP-ribose polymerase inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors.

Investigator-Assessed Duration of Response for Patients With Complete and Partial Responses



Data cutoff: March 3, 2022.
CI, confidence interval; mDOR, median duration of response.

Investigator-Assessed Duration of Response by Prior Therapy



Data cutoff: March 3, 2022.
*95% confidence interval. †Prior PARPi exposure was uncertain for 1 patient in the investigator-assessed population.
CI, confidence interval; mDOR, median duration of response; NR, not reached; PARPi, poly ADP-ribose polymerase inhibitor.

Efficacy Endpoints Assessed by Investigator and BICR

Endpoints	Investigator-Assessed (N=105)	BICR-Assessed (N=95)
ORR, n (%)	**34 (32.4)**	**30 (31.6)**
95% CI	[23.6, 42.2]	[22.4, 41.9]
Best overall response, n (%)		
Complete response	**5 (4.8)**	**5 (5.3)**
Partial response	29 (27.6)	25 (26.3)
Stable disease	48 (45.7)	53 (55.8)
Progressive disease	20 (19.0)	8 (8.4)
Not evaluable	3 (2.9)	4 (4.2)
mDOR, months	**6.9**	**11.7**
95% CI	[5.6, 8.1]	[5.0, NR]
mPFS, months	**4.3**	**5.5**
95% CI	[3.7, 5.1]	[3.8, 6.9]

Data cutoff: November 16, 2021, investigator-assessed DOR: March 3, 2022.
BICR, blinded independent central review; CI, confidence interval; DOR, duration of response; mDOR, median duration of response; MIRV, mirvetuximab soravtansine; mPFS, median progression-free survival; NR, not reached; ORR, confirmed objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors.

Treatment-Related Adverse Events (≥10%)

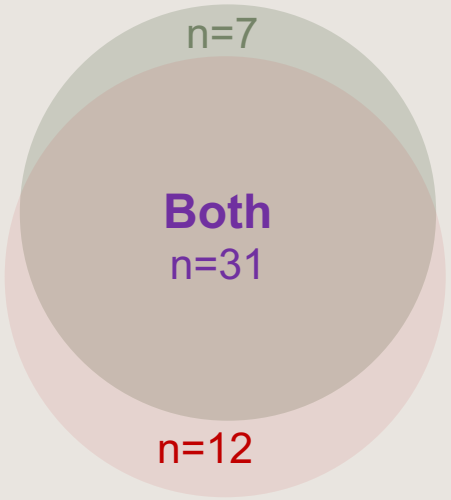
TRAEs, n (%)	All Grades	Grade 3	Grade 4
Patients with any event	91 (86)	29 (27)	1 (1)
Blurred vision	43 (41)	6 (6)	0 (0)
Keratopathy*†	38 (36)	8 (8)	1 (1)
Nausea	31 (29)	0 (0)	0 (0)
Dry eye	24 (23)	2 (2)	0 (0)
Fatigue	24 (23)	1 (1)	0 (0)
Diarrhea	23 (22)	2 (2)	0 (0)
Asthenia	16 (15)	1 (1)	0 (0)
Photophobia	15 (14)	0 (0)	0 (0)
Peripheral neuropathy	13 (12)	0 (0)	0 (0)
Decreased appetite	13 (12)	1 (1)	0 (0)
Vomiting	12 (11)	0 (0)	0 (0)
Neutropenia	11 (10)	1 (1)	0 (0)

- Most AEs were low-grade, reversible ocular and GI events
- Serious grade ≥3 TRAEs were reported in 8% of patients
- TRAEs led to dose delay in 32% and dose reduction in 19%
- 7 patients (7%) discontinued treatment due to TRAEs
- 1 death was recorded as possibly related to study drug
  - Respiratory failure
  - Autopsy: No evidence of drug reaction; lung metastases

Data cutoff: November 16, 2021.
*The grouped preferred term "Keratopathy" includes the following preferred terms: "corneal cyst," "corneal disorder," "corneal epithelial microcysts," "keratitis," "keratopathy," "limbal stem cell deficiency," "corneal opacity," "corneal erosion," "corneal pigmentation," "corneal deposits," "keratitis interstitial," "punctate keratitis," and "corneal epithelial defect." †One patient experiencing a grade 4 event recorded as keratopathy was based upon the visual acuity evaluation of one eye (20/200). This patient had confirmed grade 2 corneal changes, and both the visual acuity and these corneal changes resolved completely (grade 0) in 15 days by ophthalmic exam.
AE, adverse event; GI, gastrointestinal; TRAEs, treatment-related adverse events.

Unique Events Specific to MIRV: Keratopathy and Blurred Vision

Events developed in 50/106 (47%) patients: mostly low grade

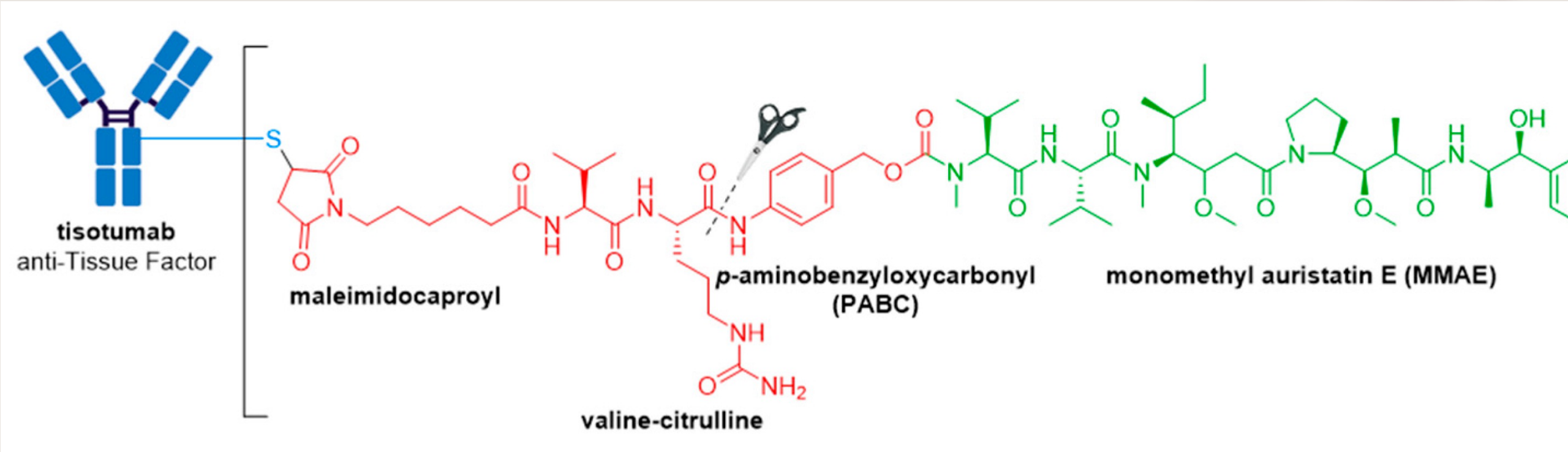


- **Proactive supportive care**
  - Lubricating artificial tears
  - Corticosteroid eye drops
- **Predictable**
  - Median time to onset: cycle 2 (~1.5 months)
- **Manageable with dose modifications, if needed**
  - 22% of patients (23/106) had dose delay and/or reduction
- **Reversible**
  - At data cutoff: >80% of patients with grade 2–3 events had resolved to grade 0–1
    - 9 patients still receiving MIRV or being followed up for resolution
- **<1% discontinuation due to ocular events**
  - 1 of 106 patients discontinued due to grade 4 keratopathy,† which resolved within 15 days

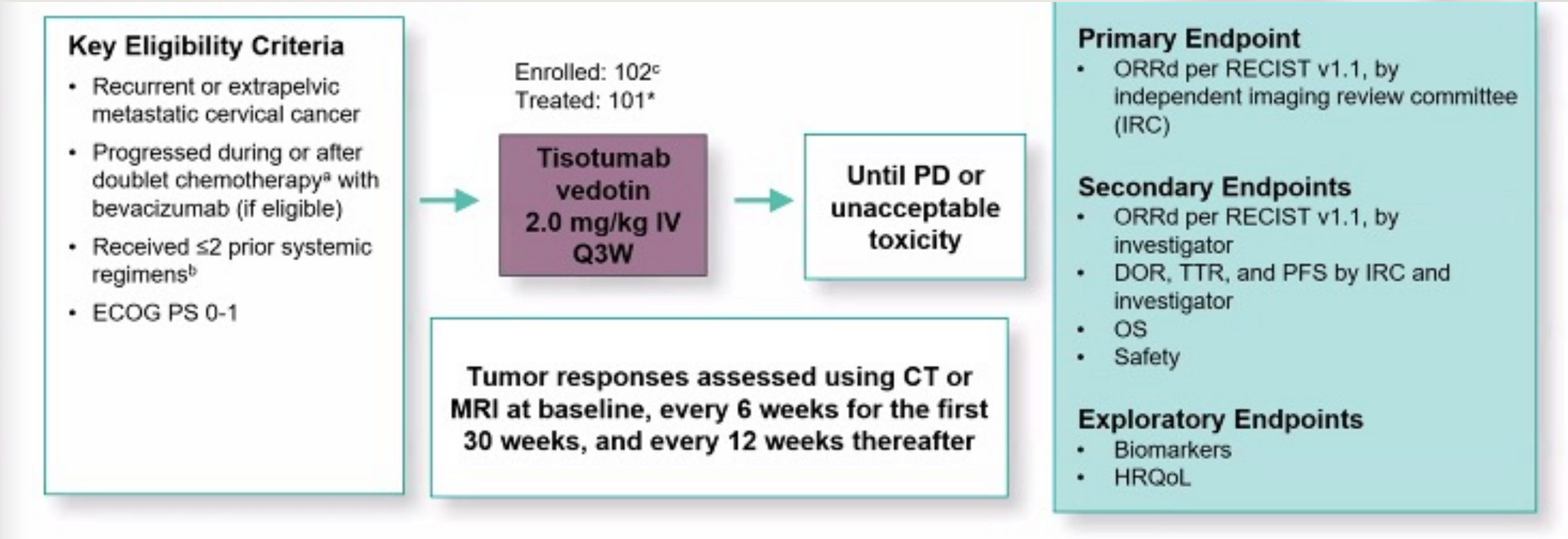
Data cutoff: November 16, 2021.
The grouped preferred term "Keratopathy" includes the following preferred terms: "corneal cyst," "corneal disorder," "corneal epithelial microcysts," "keratitis," "keratopathy," "limbal stem cell deficiency," "corneal opacity," "corneal erosion," "corneal pigmentation," "corneal deposits," "keratitis interstitial," "punctate keratitis," and "corneal epithelial defect." †One patient experiencing a grade 4 event recorded as keratopathy was based upon the visual acuity evaluation of one eye (20/200). This patient had confirmed grade 2 corneal changes, and both the visual acuity and these corneal changes resolved completely (grade 0) in 15 days by ophthalmic exam.
MIRV, mirvetuximab soravtansine.

Tisotumab Vedotin

- Target: Tissue Factor
- Payload: Monomethyl auristatin E (MMAE)

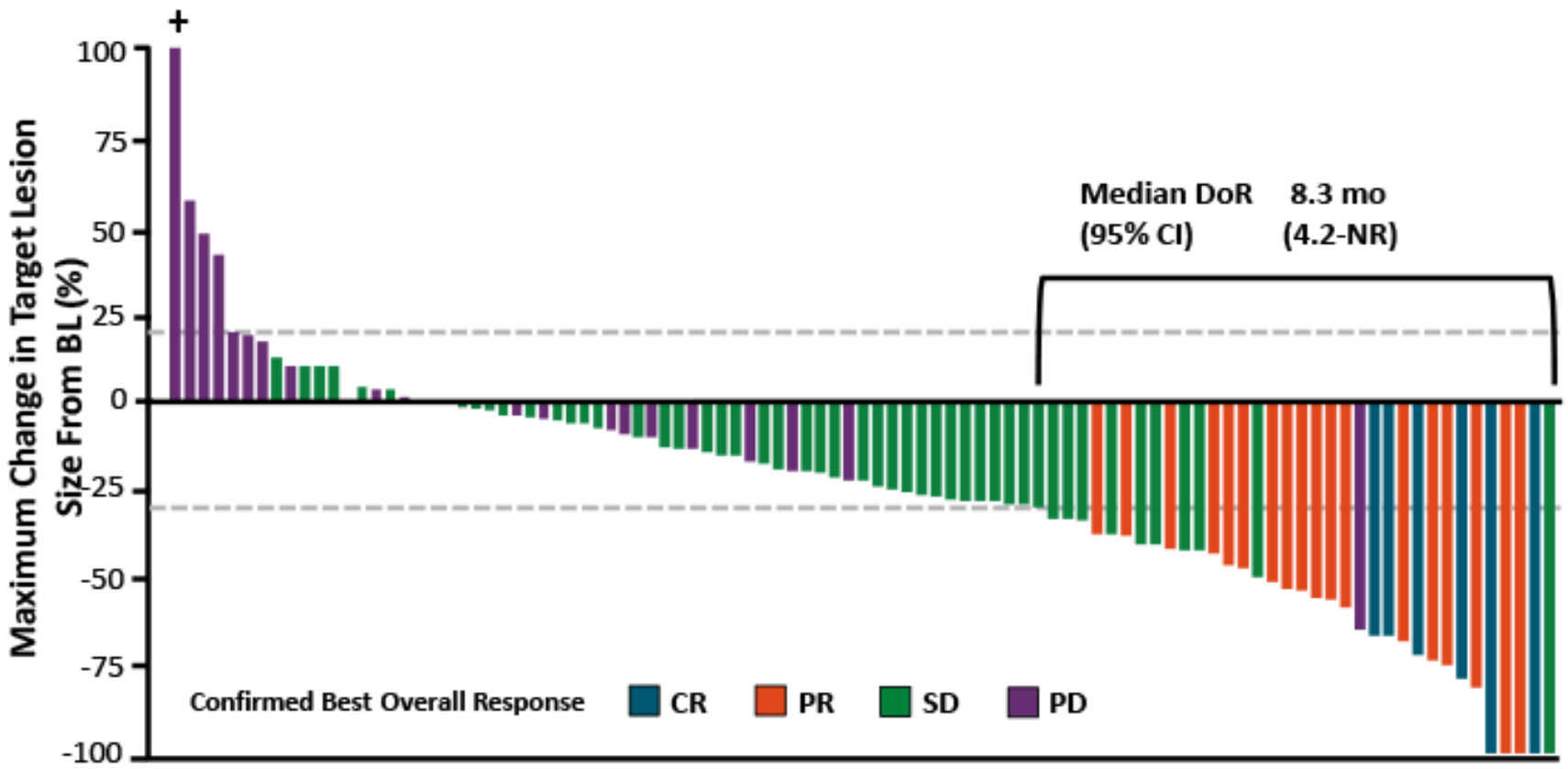


innovaTV



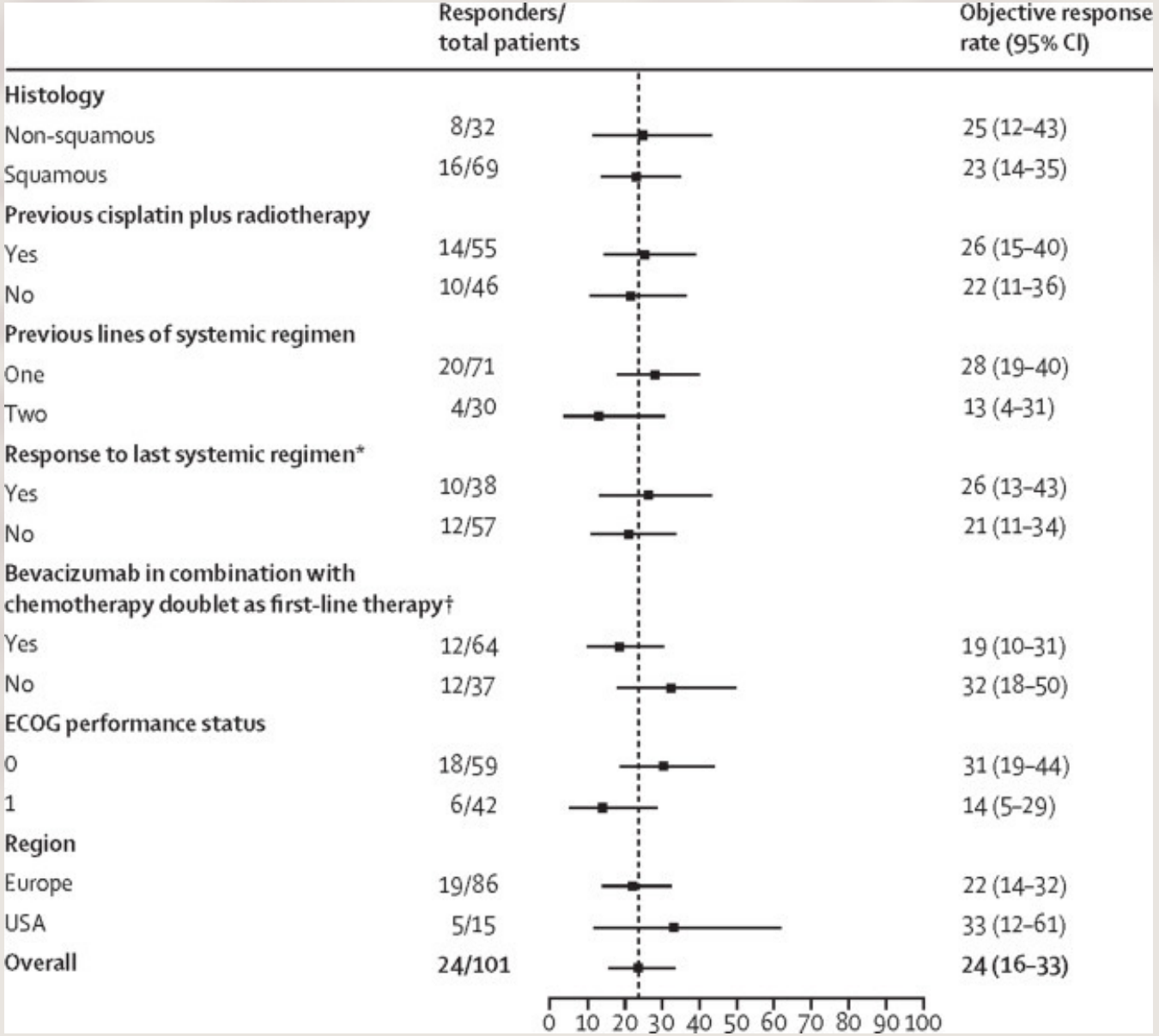
Coleman, RL, et al. Lancet Oncol 2021; 22:609-19.

innovaTV: Results



	N = 101
Confirmed ORR, % (95% CI)	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)

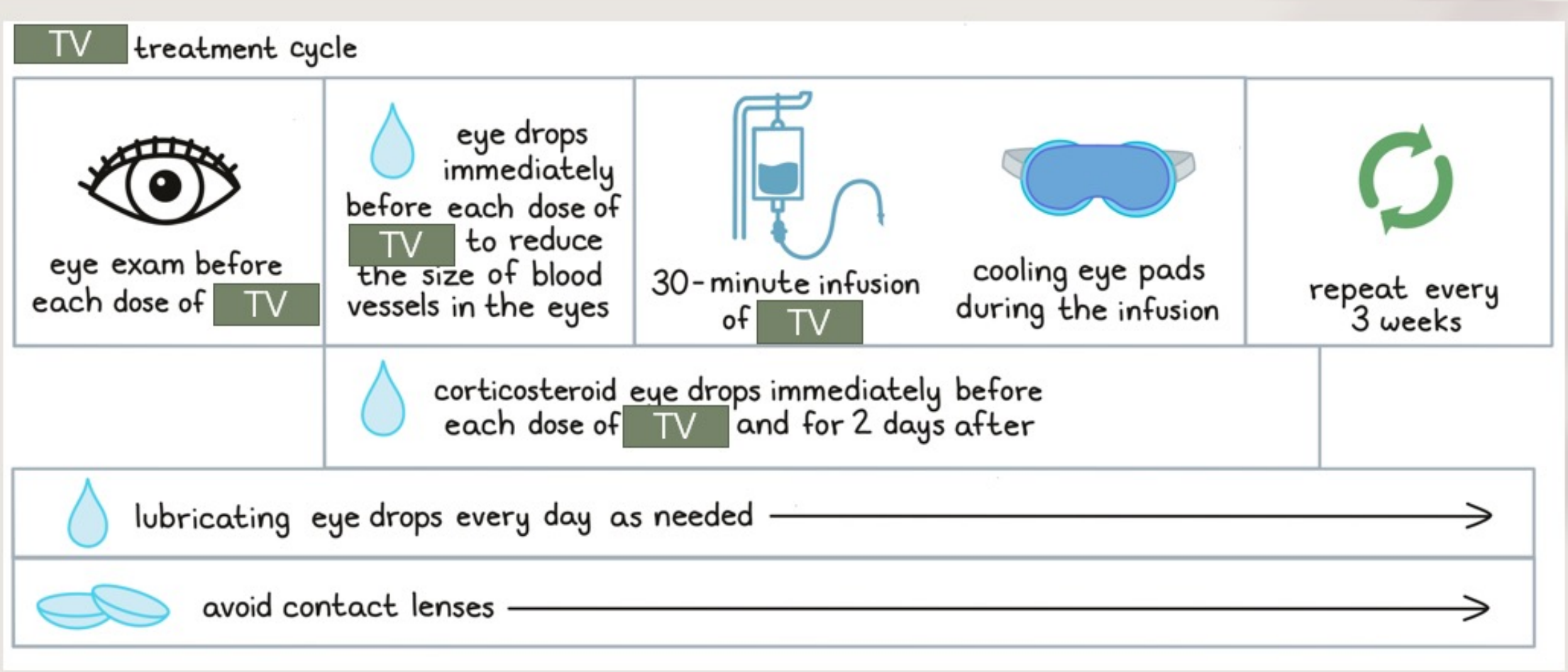
Coleman, RL, et al. Lancet Oncol 2021; 22:609-19.



innovaTV: Subgroup analysis for ORR

Coleman, RL, et al. Lancet Oncol 2021; 22:609-19.

Tisotumab vedotin: Ocular toxicity



ADCs in clinical trial

ADC (Target)	Disease indication	Clinical Trial (NCT)
Upifitamab rislodotin (Napi2B)	Ovarian cancer	NCT03319628 (Single-agent, UPLIFT) NCT05329545 (Maintenance, UP-NEXT) NCT04907968 (Combination study, UPGRADE)
Anetumab ravtansine (Mesothelin)	Ovarian cancer	NCT02751918 (Combination) NCT033587311 (Combination)
DB-1303 (HER2)	Endometrial cancer	NCT05150691 (HER2+ or HER2 low)
Trastuzumab duocarmazine (HER2)	Endometrial cancer	NCT04205630 (HER2+)
Sacituzumab govitecan (Trop2)	Endometrial cancer	NCT04251416

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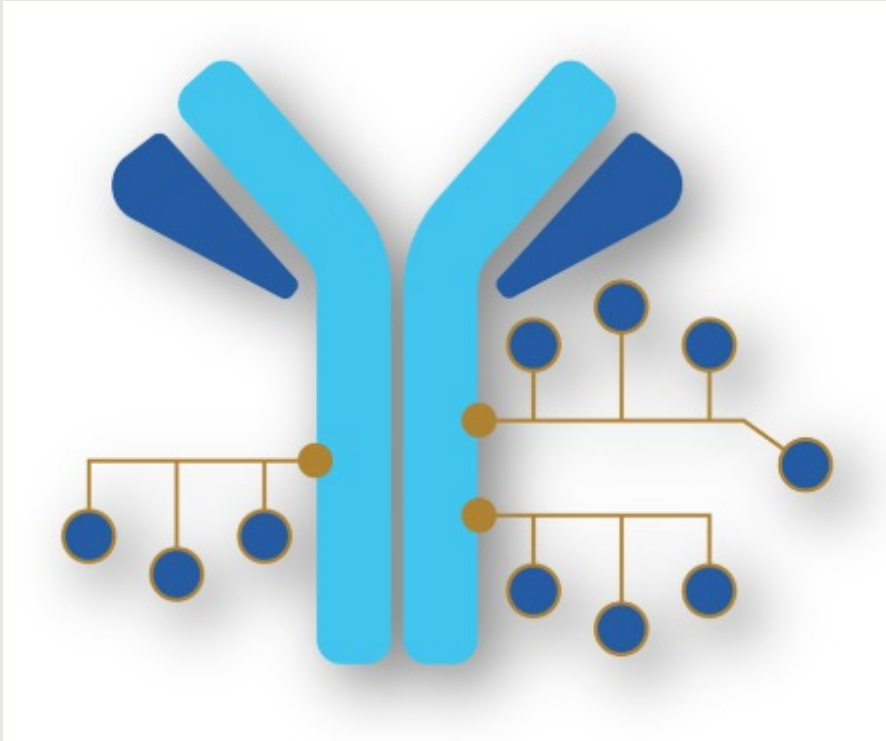
Anetumab ravtansine (Mesothelin)	Ovarian cancer	**NCT02751918 (Combination)** **NCT033587311 (Combination)**
DB-1303 (HER2)	Endometrial cancer	NCT05150691 (HER2+ or HER2 low)
Trastuzumab duocarmazine (HER2)	Endometrial cancer	NCT04205630 (HER2+)
Sacituzumab govitecan (Trop2)	Endometrial cancer	**NCT04251416**

Upifitamab Rilsodotin

- Target: Napi2B
  - Sodium-dependent phosphate transport protein 2B
  - Expressed in 75-90% of epithelial ovarian cancers
- Platform: Dolaflexin
  - Drug is not directly attached to antibody; attachment is via proprietary flexible scaffold that is cleavable.
- Payload: Auristatin
  - Drug:Antibody ratio of 12:1 to 15:1



Upifitamab Rilsodotin: UPLIFT

Phase 1b/II study in volunteers with platinum-resistant ovarian cancer

SGO 2022: Interim results (n=97)

- 64% had High expression (Tumor Proportion Score ≥75%
  - ORR 34% (13/38)
  - Median DOR: 5 months
- Entire cohort:
  - ORR 23% (17/75)
  - NO difference in response rates across dose levels
- Most frequent TRAE: fatigue, nausea, AST elevation, thrombocytopenia, decreased appetite

Richardson D, et al. Gynecol Oncol 2022; 160:S48

Anetumab ravtansine + Liposomal Doxorubicin

- Target: Mesothelin
- Payload: Maytansinoid tubulin inhibitor (DM4)
- Phase IB results presented in 2018:
  - Volunteers had platinum-resistant ovarian cancer(n=21)
  - Comparator: None (Phase 1B/II)
  - Outcomes:
    - MTD: AR 6.5 mg/kg plus PLD 30 mg/m2
    - G3-4 AES: neutropenia (24%), thrombocytopenia (9.5%)
    - ORR 52% (no CR), 29% had PR >250d

Biulat et al. J Clin Oncol 10.1200/JCO.2018.36.15_suppl.5571

Anetumab ravtansine plus Bevacizumab

- Volunteers had platinum-resistant or refractory ovarian cancer; prior treatment with bevacizumab ok (88% Mesothelin+)
- Comparator: Bevacizumab plus paclitaxel
- Outcomes:
  - RP2D: AR 2.2 mg/kg/week + Bev 10mg/kg q2w (cycle= 28d)
  - ORR: 18% vs 55% with BP
  - Median PFS: 5.3 vs 9.6m
  - Met criteria for futility and study stopped

Lheureux, et al. J Clin Oncol 2022; 10.1200/JCO.2022.40.16_suppl.5514

Sacituzumab govitecan

- Endometrial cancer included as part of basket study for people with advanced solid tumors (not enriched for Trop-2)
- Volunteers: 18, median 3.5 prior treatment lines
- Outcomes:
  - ORR 22% (95%CI, 6.4-47.6). No CRs.
  - Median PFS = 3.2m (95%CI 1.9-9.4)
  - Median OS = 11.9m (95%CI 4.7-NR)
- Ongoing studies in Trop-2 positive (TROPICS-2) and in endometrial cancer

Santin, et al. J Clin Oncol 2020; 10.1200/JCO.2020.38.15_suppl.6081

Conclusions

- ADCs are now approved for the treatments of recurrent ovarian and metastatic cervical cancer
  - Unique toxicities are seen with both approved agents (MS and TV)
- Ongoing clinical trials:
  - Aimed at exploiting proteins enriched in gynecologic cancers
  - Evaluating impact of ADCs with activity in other diseases
  - Cannot assume that the same target across diseases results in similar efficacy

Questions