Novel Agents in Ovarian Cancer in a Flash!

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Introduction

- Ovarian cancer is a lethal gynecologic cancer with an estimated 184,799 deaths worldwide annually.
- In the past decade, 14 drug approvals for treatment of epithelial ovarian cancer have occurred, all of them led by three drug classes:
    - Anti-angiogenic
    - PARP inhibitors
    - Anti-PD-1 agent with tumor agnostic biomarker-based approvals
- However, to date, No biomarker-directed therapy is indicated in the EU.
- Still novel therapies are needed: Antibody Drug Conjugates (ADC) are the next frontier in personalized therapy

International Agency for Research on Cancer. IARC Factsheet: Ovary. World Health Organization; NCCN Clinical Practice Guidelines in Oncology – Ovarian Cancer Version 1.2022.

ADC: The Next Frontier in Personalized Therapy

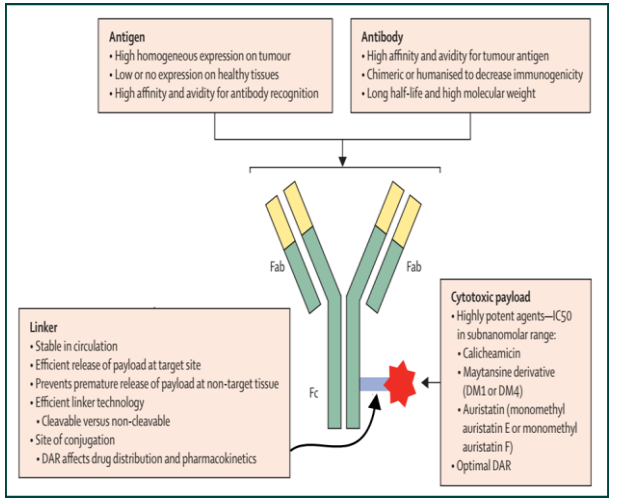
Why?

- ADC allows us to target specific tumor-associated antigens
- Deliver highly potent chemotherapy directly to the tumor
- Offer patients a differentiated safety profile
- Open the opportunities for combination therapies in the near future which may replace standard systemic chemotherapy

Chau CH, Steeg PS, Figg WD. Antibody-drug conjugates for cancer. Lancet. 2019;394(10200):793-804

Antibody Drug Conjugates in Ovarian Cancer

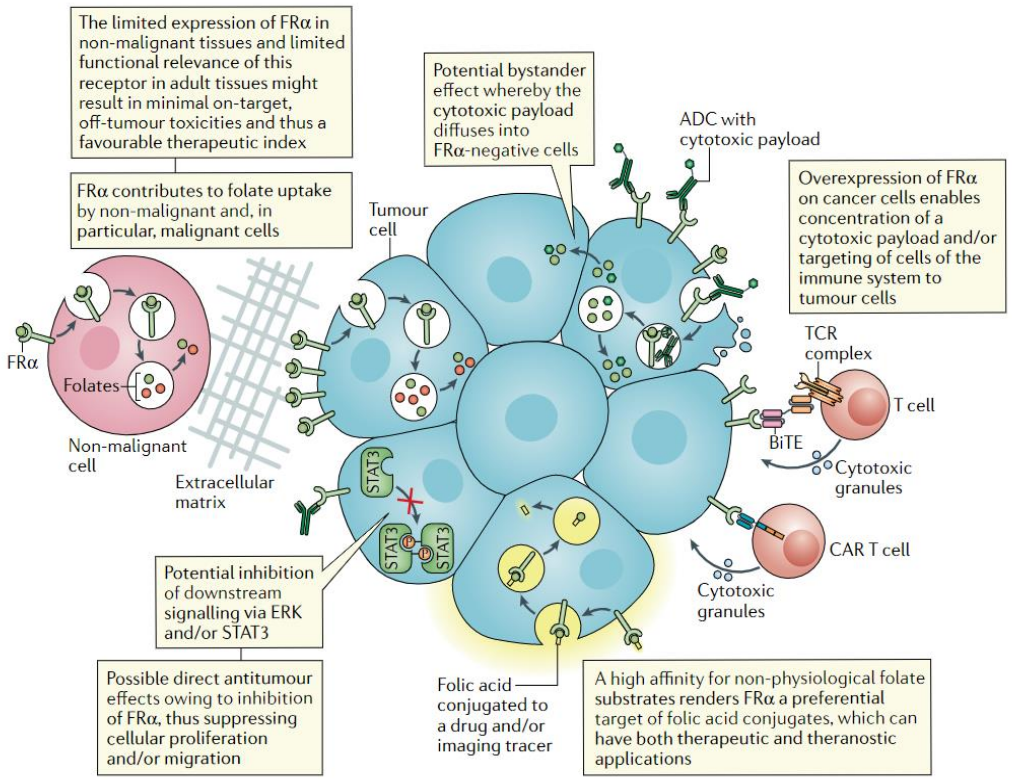
Antibody Drug Conjugate	Target	Linker	Payload	Payload Action	Drug Antibody Ratio
Mirvetuximab soravtansine	Folate Receptor α	Sulfo-SPDB, cleavable disulfide	DM4	Microtubule	3.5
STRO-002 (luveltamab tazevibulin)	Folate Receptor α	Protease-labile Val-Cit-PABA	SC209	Microtubule	4
MORAb-202	Folate Receptor α	Cathepsin-B cleavable	Eribulin	Microtubule	4
Upifitamab rilsodotin	NaPi2b	Protease-labile	AF-HPA	Microtubule	10
Fam-trastuzumab deruxtecan	HER2	Dxd	TOP1		7-8



Adapted from Molecules 2021 Sep 27;26 (19)5847; Clinical Trials.gov; Oaknin A. et al, ASCO annual meeting 2023; Moore KN et al, ASCO annual meeting 2023; Richardson DL et al, SGO Annual Meeting on Women's Cancers, 2022

Targeting Folate Receptor Alpha (FRα)

An Ideal Target for Ovarian Cancer



- **Folate receptor alpha** is a membrane protein that binds to and transports folate into cells.

- **FR alpha** is restricted on normal cells and **highly over-expressed** on the surfaces of a number of cancer cells:
  - ✓ HGSOC approx. 80% of cells positive for some expression of FR alpha.
  - ✓ **FR alpha expression is retained** in recurrent and metastatic tumors **and is not significantly altered in response to chemotherapy.**

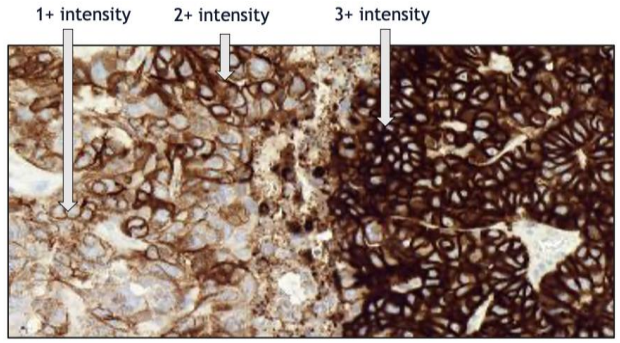
- FR alpha overexpression allows(ADC) for delivery of:
  - ✓ a highly potent molecule of chemotherapy to FR alpha cells
  - ✓ diffusion of the payload(chemotherapy) into FR alpha negative cells that are adjacent via the bystander effect.

Scaranti M, Cojocaru E, Banerjee S, Banerji U. *Nature Reviews*. 2020.

Targeting Folate Receptor Alpha (FRα)

Level of Target Expression required may depend on the ADC

1. **FRα is most highly expressed on the surface of serous epithelial ovarian cancers (EOC) – as assessed by immunohistochemistry (IHC)**



- **PS2+ of FRα Distribution :** Scoring of Folate Receptor Alpha with **≥ 2+ staining intensity**:% of FRα positive cells

Negative	0%
Very Low	
Low	
Medium	%
High	**≥ 75%**

Mirvetuximab

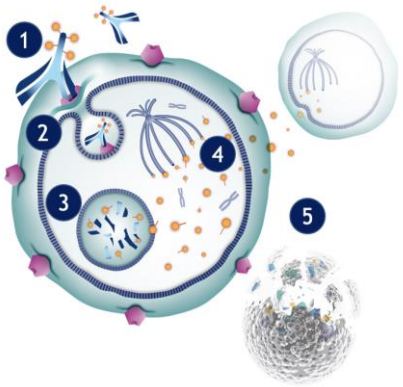
TPS(Tumor Proportion Score) is the percentage of cells stained positive at any intensity for FRα

- Establish[illegible] or indications
- Does not [illegible] staining intensity
- Simple and straightforward for pathology read

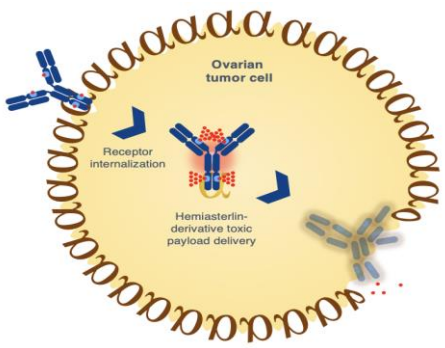
Luveltamab

- **Enriched population defined as TPS >25%**

Ventana Medical Systems, Inc, Tucson, AZ; ImmunoGen. 2021. Data on File



Targeting the Folate Receptor



Mirvetuximab

- The antibody portion of MIRV binds to FRα found on the surface of epithelial ovarian cancer cells
- MIRV is internalized via endocytosis
- MIRV is degraded within the lysosome to release its **cytotoxic payload (DM4)**
- DM4 disrupts tubulin resulting in mitotic arrest and apoptosis
- DM4 also diffuses through the lipophilic cell membrane allowing bystander killing on adjacent tumor cells

Luveltamab tazevibulin or STRO-002

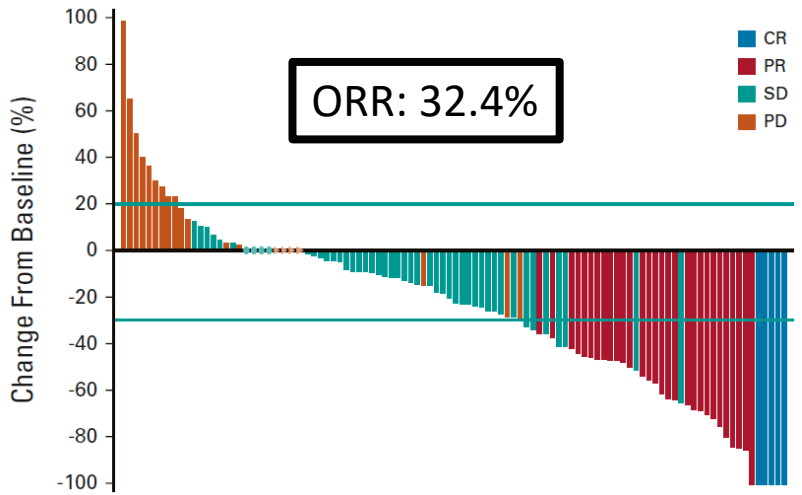
- SUTRO Cell-Free Platform: allows an specific linker and cytotoxic payload position which optimizes target binding and anti-tumor activity
- Consistent product design: Every molecule is the same, delivering consistent DAR4 payload across FolRα expression levels
- Citotoxic Tumor Activity: Release of **payload(microtubule inhibitor, hemiasterlin)** in circulation is minimized, while intratumor cell cytotoxin delivery is efficient
- Payload-induced tumor cell stress stimulates innate immune cells, helping generate anti-tumor immunity

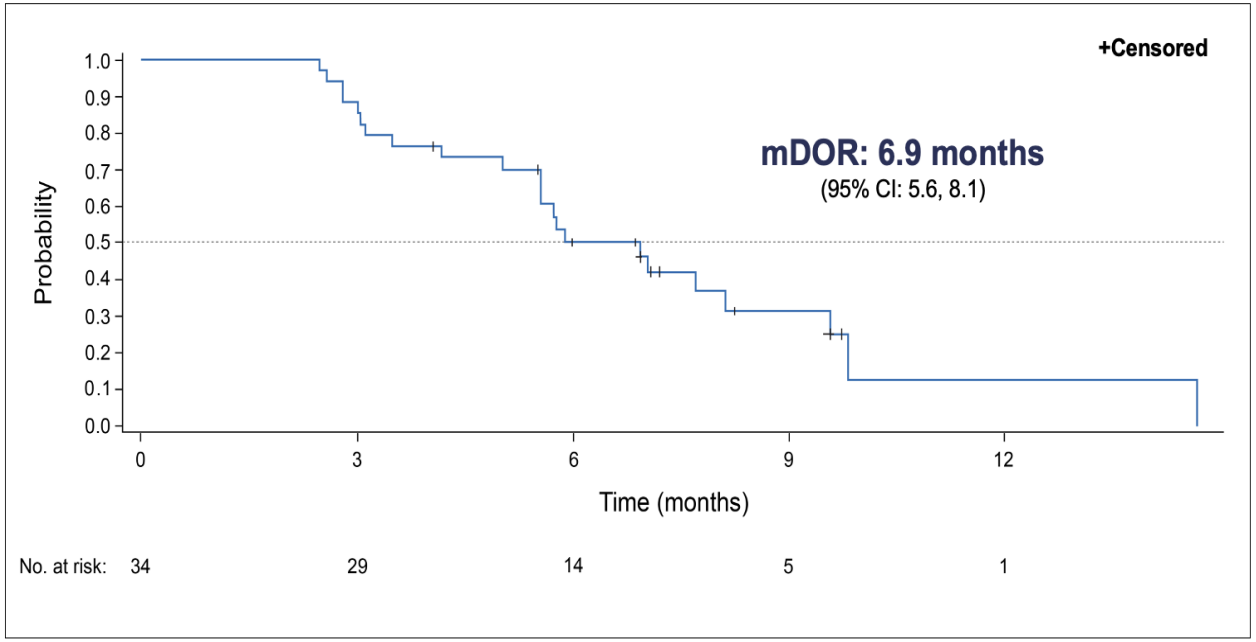
original reports

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

Ursula A. Matulonis, MD[1]; Domenica Lorusso, MD, PhD[2]; Ana Oaknin, MD, PhD[3]; Sandro Pignata, MD, PhD[4]; Andrew Dean, MBChB, MRCP, FRACP[5]; Hannelore Denys, MD, PhD[6]; Nicoletta Colombo, MD, PhD[7,8]; Toon Van Gorp, MD, PhD[9]; Jason A. Konner, MD[10]; Margarita Romeo Marin, MD, PhD[11]; Philipp Harter, MD, PhD[12]; Conleth G. Murphy, MD[13]; Jiuzhou Wang, PhD[14]; Elizabeth Noble, BS[14]; Brooke Esteves, BSN[14]; Michael Method, MD, MPH, MBA[14]; and Robert L. Coleman, MD[15]

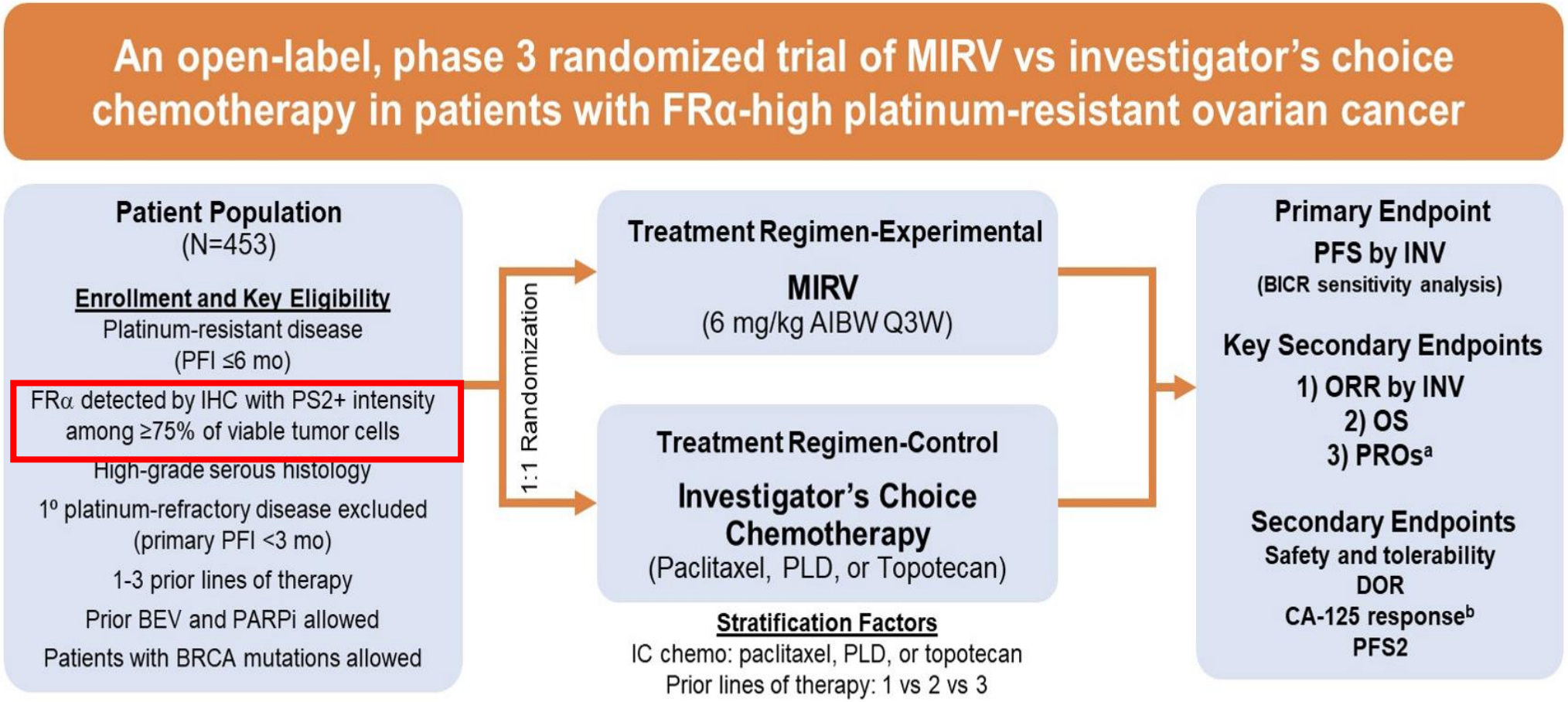
FDA approval of Elahere (mirvetuximab soravtansine-gynx) for FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or peritoneal cancer





Published at JCO on Jan 30 2023.

MIRASOL (GOG3045/ENGOT-ov55)



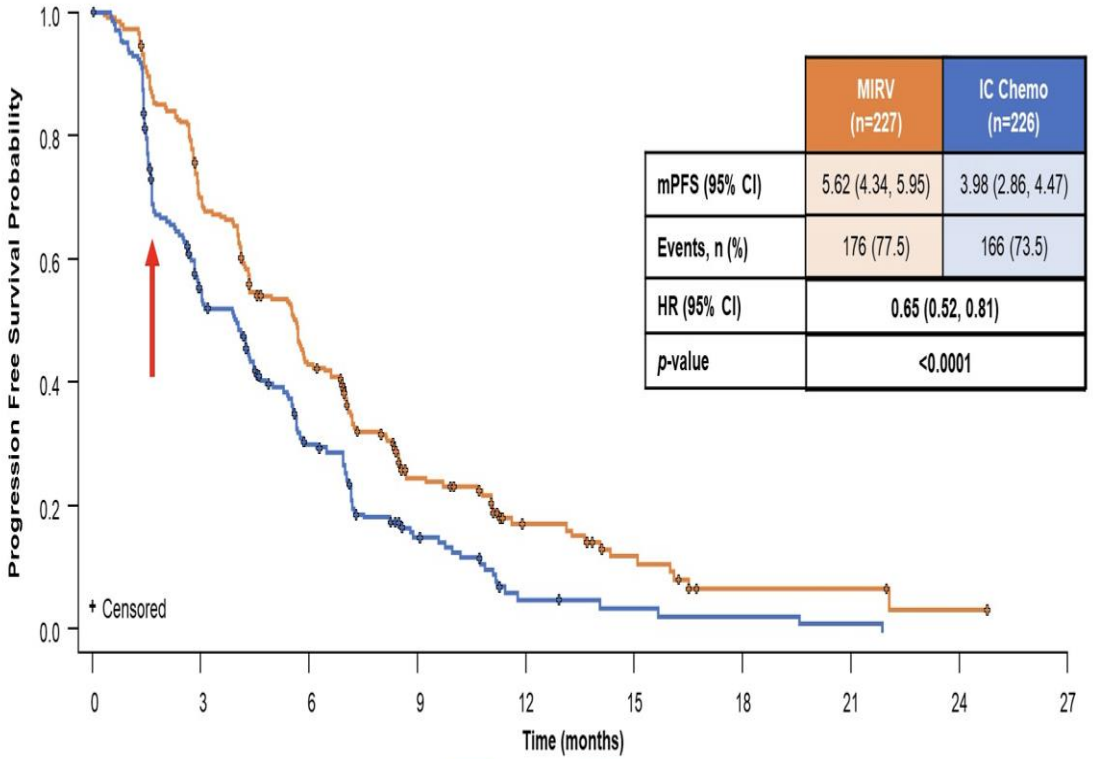
AIBW, adjusted ideal body weight; BEV; bevacizumab; BICR, blinded independent central review; BRCA, BReast CAncer gene; CA-125, cancer antigen 125; chemo, chemotherapy; DOR, duration of response; FRα, folate receptor alpha; IC, investigator's choice; IHC, immunohistochemistry; INV, investigator; MIRV, 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.

Presented by K. Moore et al at ASCO 2023

MIRASOL: Primary and Key Secondary End-Points

Primary Endpoint: Progression-Free Survival by Investigator



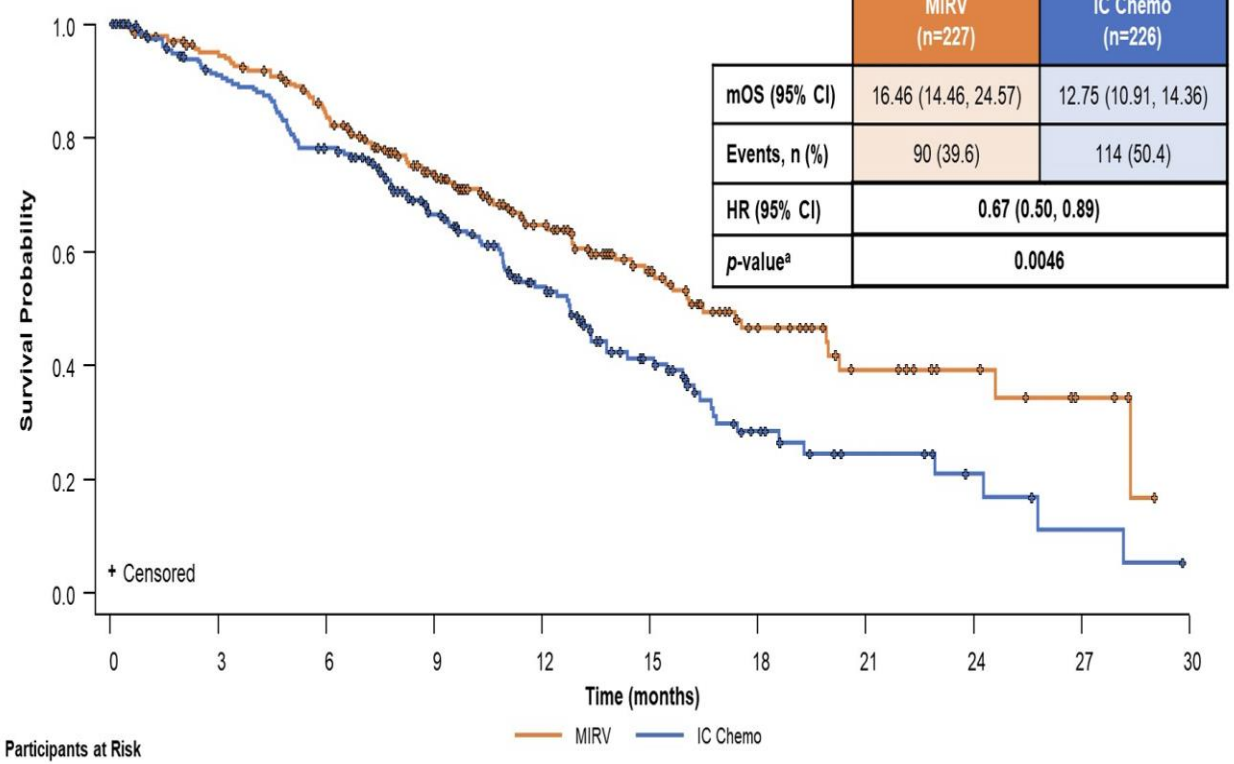
	MIRV (n=227)	IC Chemo (n=226)
mPFS (95% CI)	5.62 (4.34, 5.95)	3.98 (2.86, 4.47)
Events, n (%)	176 (77.5)	166 (73.5)
HR (95% CI)	0.65 (0.52, 0.81)	
p-value	<0.0001	

No. Participants at Risk

MIRV 227	151	89	38	18	10	3	3	1	0
IC Chemo 226	98	48	19	5	3	2	1	0	

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 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	

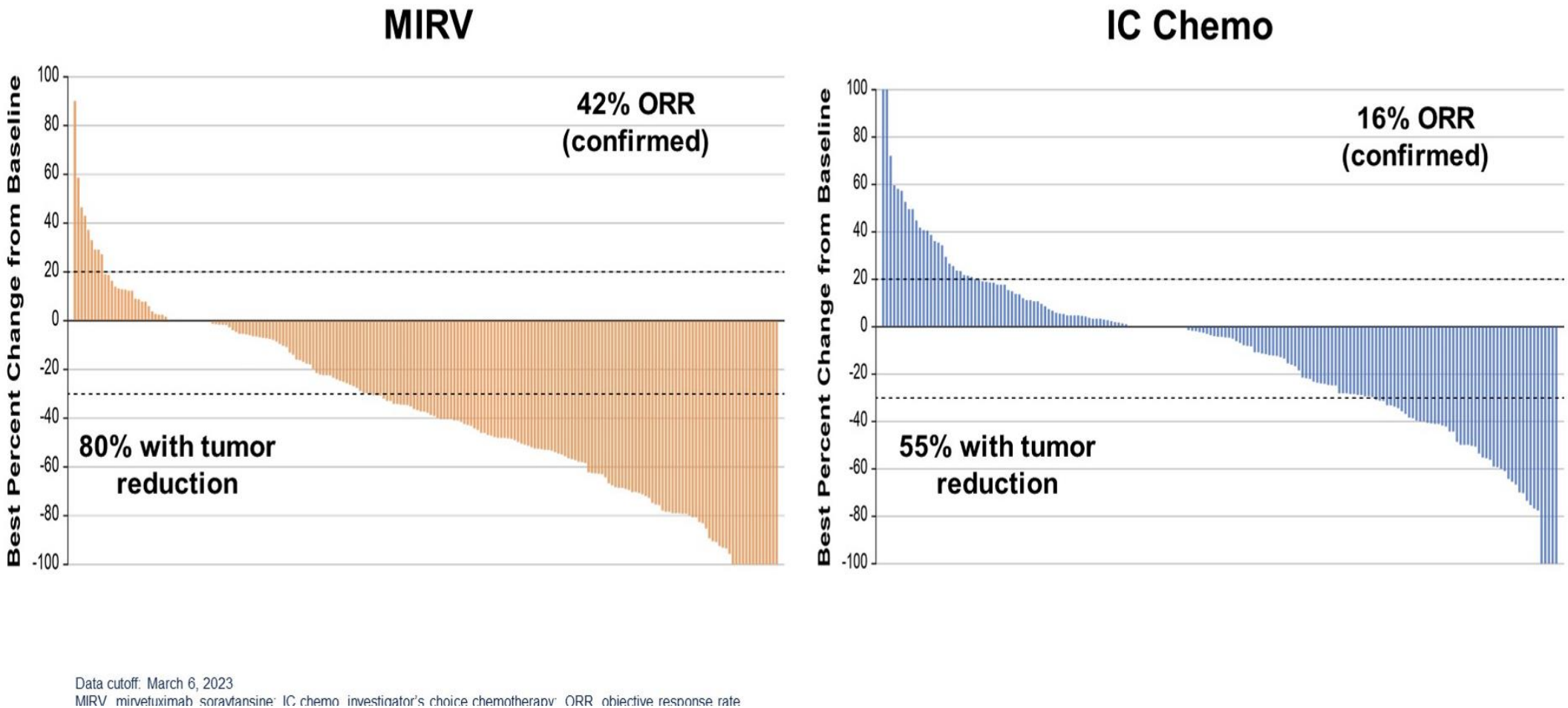
No. Participants at Risk

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

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 K. Moore et al at ASCO 2023

Maximum Percentage Change in Target Lesion Size from Baseline by Investigator (N=453)



Data cutoff: March 6, 2023

MIRV, mirvetuximab soravtansine; IC chemo, investigator's choice chemotherapy; ORR, objective response rate

Presented by K. Moore et al at ASCO 2023

STRO-002-GM1: phase 1 dose expansion cohort of luveltamab tazevibulin in recurrent epithelial ovarian cancer designed to optimize dose

NCT03748186

- Recurrent disease
  - Platinum resistant
    1–3 prior regimens or
    platinum-sensitive
    2–3 prior regimens
- Fresh or archival tissue required
- No mandate for FolRα expression
- At least 1 target lesion

N=44

R
1:1

Luveltamab
4.3 mg/kg Q3W
n=23

Luveltamab
5.2 mg/kg Q3W
n=21

- Primary endpoint: ORR by RECIST v1.1
- Secondary endpoints: Safety, PK, PFS, DOR

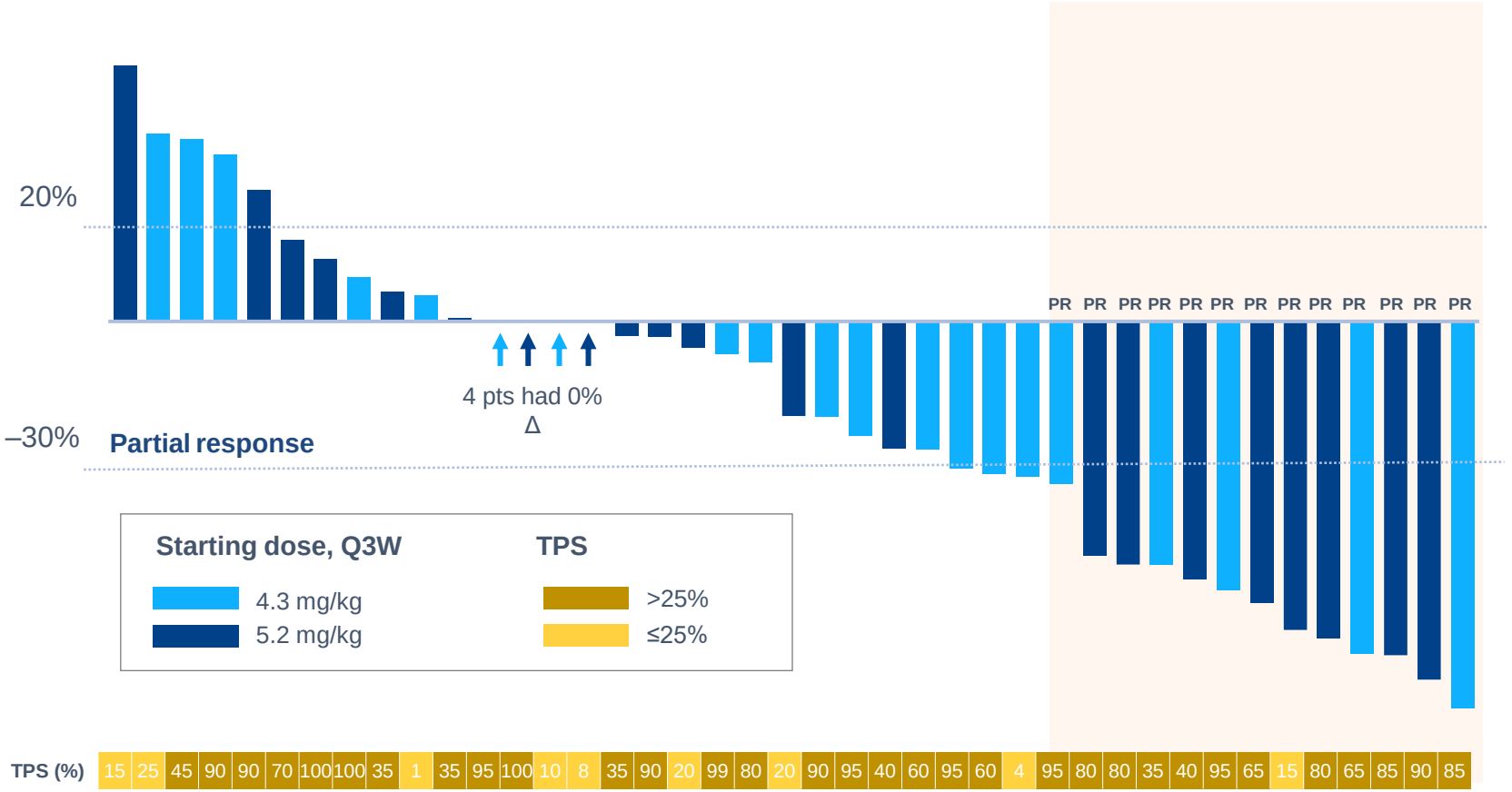
- FolRα expression was determined retrospectively after enrollment
- FolR1 IHC assay (Ventana Medical Systems) using tumor proportion score (TPS)
- Dose reductions required for grade 4 neutropenia regardless of whether it was reported as an AE
- Growth factors allowed per institutional standard of care
- Ophthalmologist assessment for potential ocular AEs at baseline and every 2 cycles
  - No requirement for prophylactic ocular corticosteroids or antibiotics

AE, adverse event; DOR, duration of response; IHC, immunohistochemistry; PK, pharmacokinetic; Q3W, every 3 weeks; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors.

1. ClinicalTrials.gov. www.clinicaltrials.gov/ct2/show/NCT03748186. Accessed May 1, 2023.

All-comers patient population (FolRα-unselected) demonstrated an ORR of 32% per RECIST v1.1

Maximum Reduction in Tumor Target Lesions in RECIST-Evaluable Patients (N=41)



ORR: 31.7% in unselected pts

- 37.5% for FoLRα >25% by TPS

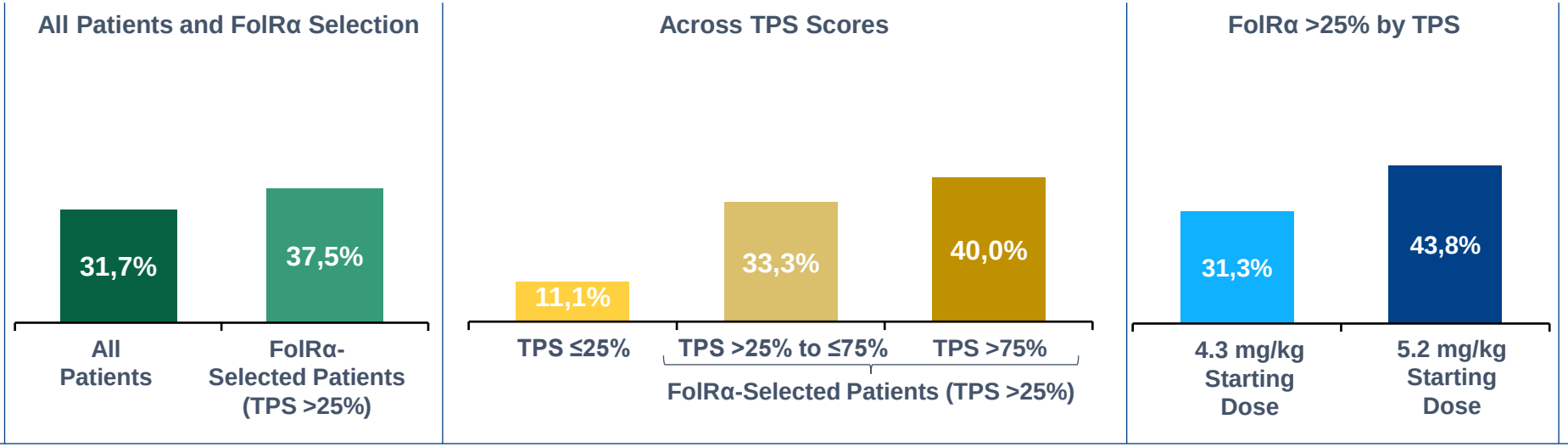
Disease control rate: 78% in unselected pts

- 81% for FolRα >25% by TPS

Data as of April 18, 2023.
PR, partial response. ORR, objective response rate.

Clinical activity seen at both doses across a broad range of FolRα expression levels

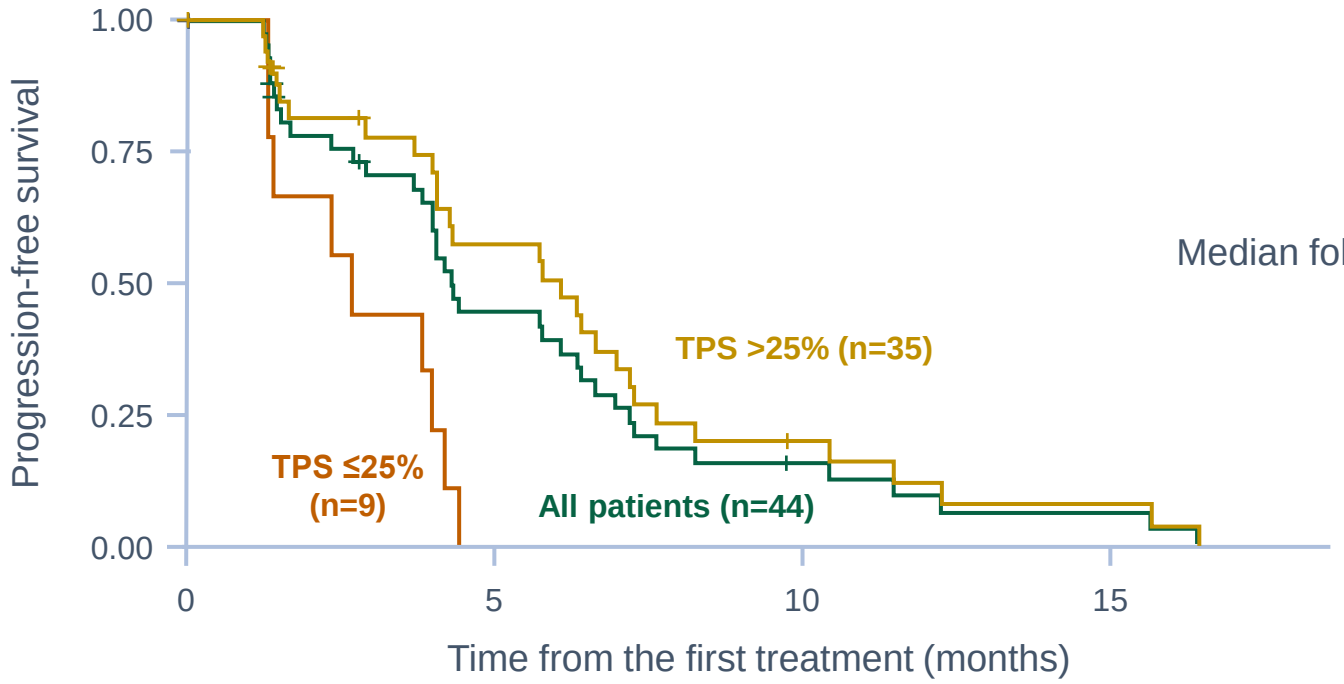
Treatment Response in RECIST-Evaluable Patients (N=41)



RECIST-evaluable patients	N=41	n=32	n=9	n=12	n=20	n=16	n=16
PR	13	12	1	4	8	5	7
ORR (95% CI), %	**31.7 (18.1, 48.1)**	**37.5 (21.1, 56.3)**	**11.1 (0.3, 48.3)**	**33.3 (9.9, 65.1)**	**40.0 (19.1, 63.9)**	**31.3 (11.0, 58.7)**	**43.8 (19.8, 70.1)**

Data are as of April 18, 2023.
FolRα-selected defined as TPS >25%.
CI, confidence interval; ORR, objective response rate.

Luveltamab resulted in PFS of 6.1 months and median DOR of 5.5 months in the FolRα selected population (TPS >25%)

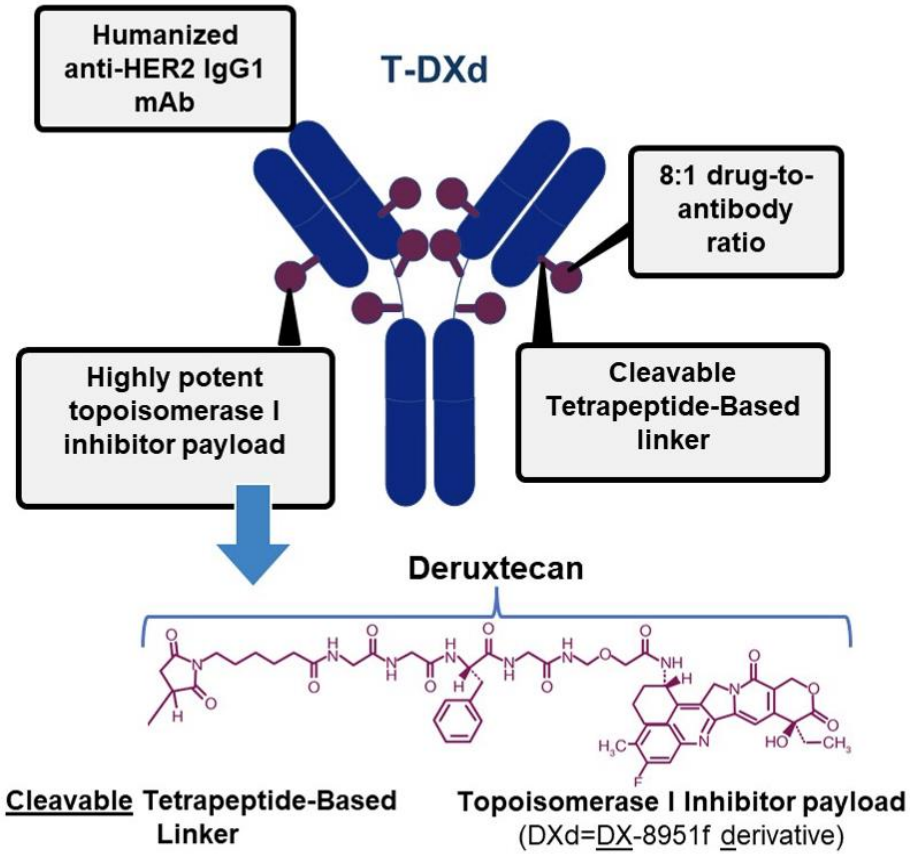


Median follow-up: 12.9 months

	All Patients (N=44)	FolRα ≤25% by TPS (n=9)	FolRα >25% by TPS (n=35)
Median DOR (range), months	5.4 (2.9, 11.0)	2.9 (NA)*	5.5 (2.5, 11.0)
Median PFS (95% CI), months	4.3 (3.8, 6.3)	2.7 (1.3, 4.2)	6.1 (4.1, 7.2)

*One response. DOR calculated for pts with responses only (all, n=13 pts; FolRα, ≤ 25% 1 pt; FolRα >25%, 12 pts). NA, not applicable.

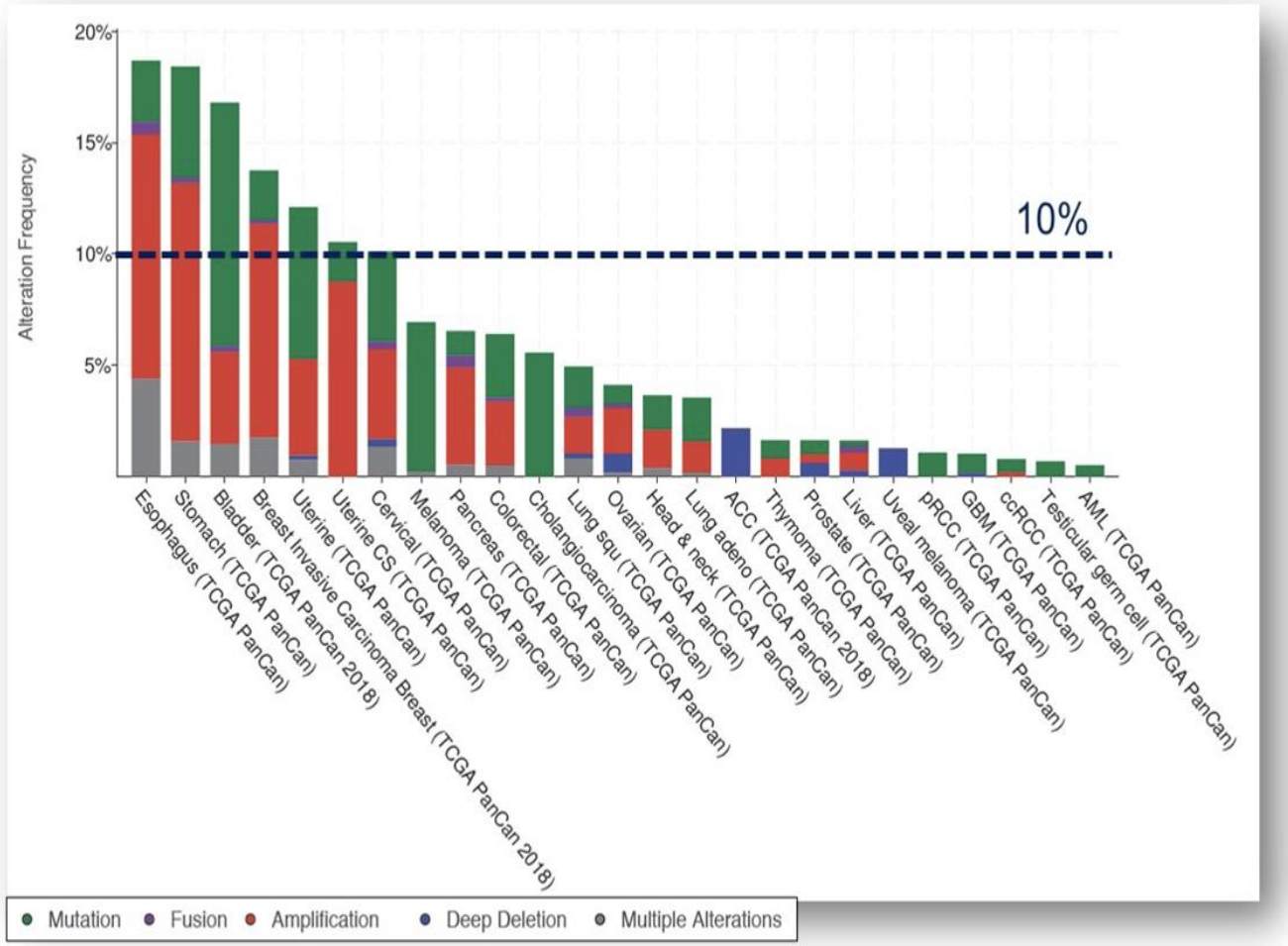
Trastuzumab Deruxtecan (T-DXd):an anti-Her2 ADC

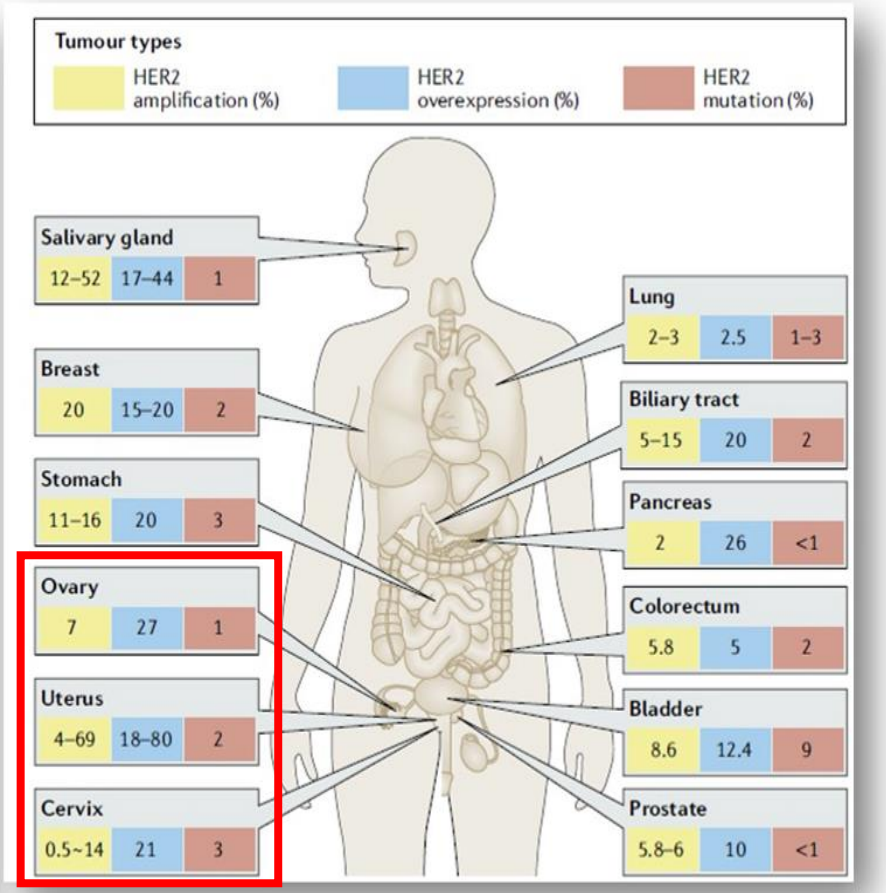


Seven Key Attributes[a,1–5]
Payload mechanism of action: topoisomerase I inhibitor
High potency of payload
High drug-to-antibody ratio ≈8
Payload with short systemic half-life
Stable linker payload
Tumor-selective cleavable linker
Bystander antitumor effect

Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173–185. 2. Ogitani Y, et al. *Clin Cancer Res.* 2016;22(20):5097–5108. 3. Trail PA, et al. *Pharmacol Ther*. 2018;181:126–142. 4. Okamoto H, et al. *Xenobiotica*. 2020;50(10):1242–1250. 5. Nagai Y, et al. *Xenobiotica*. 2019;49(9):1086–1096.

HER2 Dysregulation in Cancer





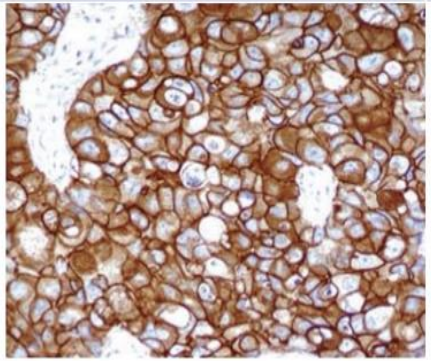
- HER2 overexpression, amplification, and mutations across tumor types

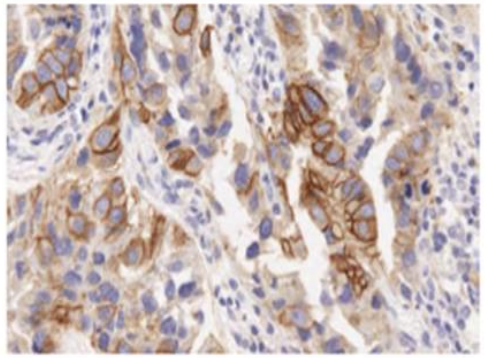
The Cancer Genome Atlas (TCGA), Nature 2012
AACR Project Genomics Evidence Neoplasia Information Exchange (GENIE)
Oh, DY et al. Nature Reviews Clinical Oncology 2020

HER2 IHQ Testing

The CAP/ASCP/ASCO Guidelines for HER2 testing

	Breast	Gastric (Surgical specimen)	Gastric (Biopsy specimen)
IHC 3+ positive	· Circumferential membrane staining that is complete, intense · **> 10% of tumor cells**	· Strong complete, basolateral or lateral membranous reactivity · ≥ **10% of tumor cells**	· Strong complete, basolateral or lateral membranous reactivity · **Tumor cell cluster (≥ 5 cells)** · irrespective of percentage of tumor cells stained





- Heterogeneous HER2 in gastric (vs breast)
- Most of previous studies of T-DXd assessed HER2 by gastric criteria
  - DESTINY-Lung01, DESTINY-CRC01, and HERB study for BTC

https://www.leicabiosystems.com/sites/default/files/2020-10/Oracle%20HER2%20Interpretation%20Guide%20%28Gastric%29.pdf

DESTINY-PanTumor02: A Phase 2 Study of T-DXd for HER2-Expressing Solid Tumors: *An open-label, multicenter study (NCT04482309)*

- 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

T-DXd 5.4 mg/kg q3w

n≈40 per cohort planned

(Cohorts with no objective responses in the first 15 patients were to be closed)

- Cervical cancer
- Endometrial cancer
- Ovarian cancer
- Biliary tract cancer
- Pancreatic cancer
- Bladder cancer
- Other tumors[b]

Primary endpoint

- Confirmed ORR (investigator)[c]

Secondary endpoints

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

Data cut-off for analysis:

- Nov 16, 2022

		All patients (N=267)
HER2 testing for eligibility, n (%)[a]	Local	205 (76.8)
	Central	61 (22.8)
	Unknown[b]	1 (0.4)
HER2-expression for eligibility, n (%)[a]	IHC 3+	108 (40.4)
	IHC 2+	153 (57.3)
	IHC 1+[c]	5 (1.9)
	Unknown[b]	1 (0.4)
Centrally confirmed HER2 status for efficacy evaluation, n (%)	IHC 3+	75 (28.1)
	IHC 2+	125 (46.8)
	IHC 1+	25 (9.4)
	IHC 0	30 (11.2)
	Unknown[d]	12 (4.5)

- 77% enrollment by local assessment
- Central confirmation: IHC 1+ or 0: 20%(N=50)

[a]Patients were eligible for either test. All patients were centrally confirmed. [b]Patients with tumors that express HER2, excluding tumors in the tumor-specific cohorts, and breast cancer, non-small cell lung cancer, gastric cancer, and colorectal cancer.
[c]Investigator-assessed per Response Evaluation Criteria In Solid Tumors version 1.1.

1. Hofmann M, et al. *Histopathology 2008*;52(7):797–805.

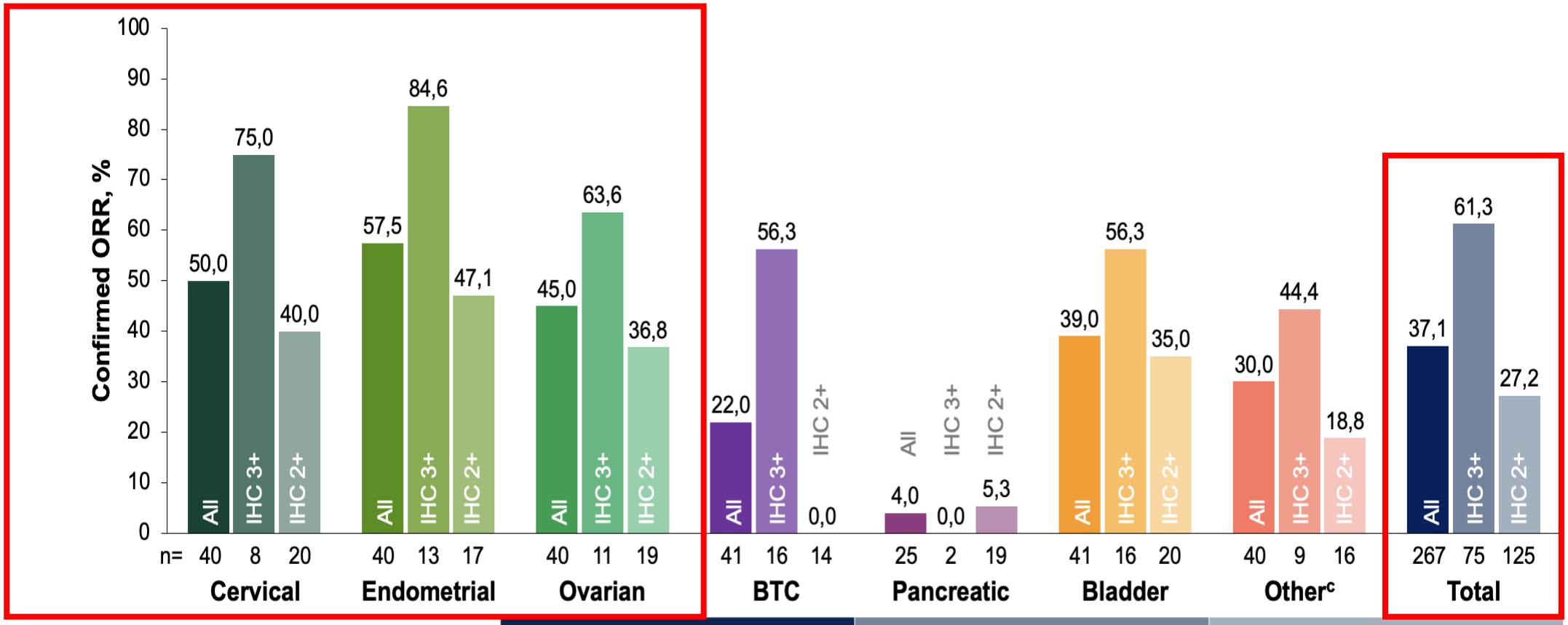
Efficacy endpoints: ORR, DCR and DOR

		Cervical (n=40)	Endometrial (n=40)	Ovarian (n=40)
Investigator assessment				
ORR, n (%)		**20 (50.0)**	**23 (57.5)**	**18 (45.0)**
Best overall response, n (%)	Complete response	2 (5.0)	7 (17.5)	4 (10.0)
	Partial response	18 (45.0)	16 (40.0)	14 (35.0)
	Stable disease	12 (30.0)	13 (32.5)	14 (35.0)
	PD	7 (17.5)	4 (10.0)	7 (17.5)
	Not evaluable	1 (2.5)	0	1 (2.5)
DCR[a] at 12 weeks, n (%)		27 (67.5)	32 (80.0)	28 (70.0)
Median DOR, months (95% CI)		9.8 (4.2–NE)	NR (9.9–NE)	11.3 (4.1–NE)
Independent central review: ORR, n (%)		16 (40.0)	21 (52.5)	17 (42.5)

Analysis of response and DCR was performed in patients who received ≥1 dose of T-DXd (n=267). Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd (n=99).

[a]Confirmed complete response, confirmed partial response or stable disease.

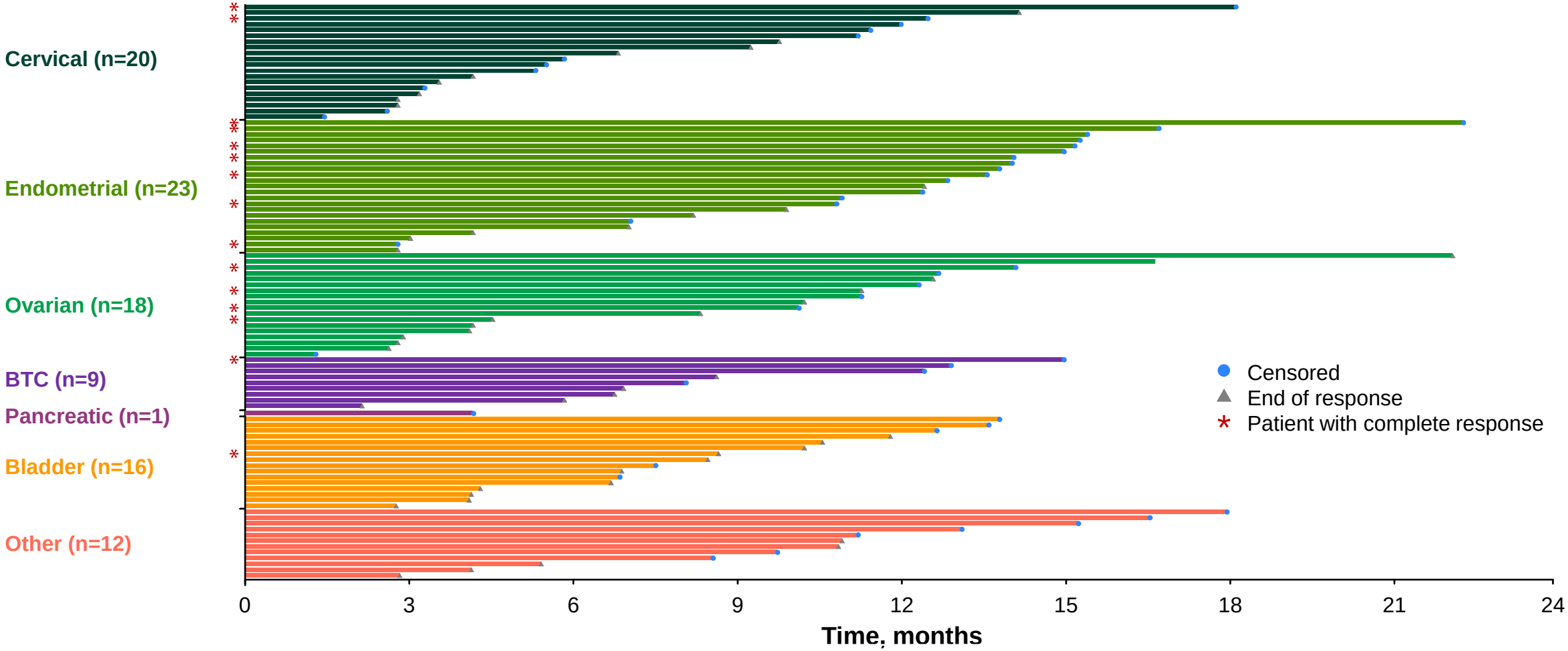
Objective Response Rate by HER2 status



	All patients (N=99)	IHC 3+ (n=46)	IHC 2+ (n=34)
Median DOR, months (95% CI)	11.8 (9.8–NE)	22.1 (9.3–NE)	9.8 (4.2–12.6)

Analysis of ORR was performed in patients who received ≥1 dose of T-DXd; all patients (n=267; including 67 patients with IHC 1+ [n=25], IHC 0 [n=30], or unknown IHC status [n=12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=75) or IHC 2+ (n=125) status. Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd; all patients (n=99; including 19 patients with IHC 1+ [n=6], IHC 0 [n=9], or unknown IHC status [n=4] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=46) or IHC 2+ (n=34) status. [a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer.
BTC, biliary tract cancer; CI, confidence interval; DOR, duration of response; IHC, immunohistochemistry; NE, non-estimable; ORR, objective response rate.

Duration of Objective Response



Kaplan-Meier estimate of response at 12 months (%)	Cervical	Endometrial	Ovarian	BTC	Pancreatic	Bladder	Other	All
	47.6	72.3	45.8	41.7	0	23.2	53.6	49.6

Analyses were performed in patients with objective response who received ≥1 dose of T-DXd (n=99). At data cut-off, 44 patients (16.5%) are still ongoing treatment, and 128 patients (47.9%) remain in the study. BTC, biliary tract cancer.

Tumor agnostic approvals

	Pembrolizumab	Dostarlimab	Pembrolizumab	Larotrectinib	Entrectinib	Selpercatinib	Dabrafenib +Trametinib
Biomarker	MSI-H, dMMR	MSI-H, dMMR	TMB-H	NTRK fusion	NTRK fusion	RET fusion	BRAF V600E
FDA Approvals	2017 2022 (full approval)	2021	2020	2018	2019	2022	2022
N	149 (updated 504)	209	102	55 (updated 140)	54	41	131 36 in paediatric pts
ORR	**39.6%** (CR 7.4%) **33.3%** (CR 10.3%)	**41.6%** (CR 9.1%)	**29%** (CR 4%)	**75%** (CR 22%)	**57%**	**44%** (CR 4.9%)	**41%** 25% in paediatric pts
Efficacy (data for approved indications in label)	• mDOR: Not reached/ 63ms with update	• mDOR: 34.7ms	• DOR: >12ms in 57% of pts	• DOR>12ms: 39% • Updated ORR: 67% with mDoR of 49.3 ms	• DOR ranged from 2.8 to 26.0+ ms	• mDOR: 24.5 ms	• mDOR: 7.7-31.2 ms across tumor types

- T-DXd in DPT-02:
  - ORR 37.1% and mDOR 11.8ms in all pts
  - ORR 61.3% and mDOR 22.1ms in IHC 3+

Conclusions

- ADCs as new targeted agents are paving a new ovarian cancer landscape

- **Mirvetuximab is the first ADC** that demonstrated statically significant and clinically meaningful improvement in PFS, ORR and OS compared to IC chemotherapy for platinum-resistant **OvCa patients with high-folate receptor expressing by PS2.**

- **Luveltamab tazevibulin (STRO-002) has shown** robust clinical activity in patients with recurrent ovarian cancer in both, **all comers population and those with TPS>25%:** has the potential to bring ADC to a wider OvCa population.

- **T-DXd** to be a potential new treatment option for patients with HER2-expressing Gyn malignancies: Results deserve discussion with Regulatory Agencies.