Where Science Becomes Hope

TRASTUZUMAB: NOT JUST FOR BREAST CANCER ANYMORE

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National Cancer Institute-Designated Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

DISCLOSURES

- I receive a stipend as EIC of *Gynecologic Oncology Reports*
- I have done one consulting board for Eisai and have received stipends for nonbranded talks for OncLive and Curio sponsored conferences
- Our division has received clinical trial funding support from multiple companies (Ergomed, Gilead, Corcept, Karyopharm, and Mersana)

U.S. FEMALE CANCER STATISTICS 2024

Site	Number	Deaths
Breast	310,720	42,250
Uterus	67,880	13,250
Ovary	19,680	12,740
Cervix	13,820	4,360
Vulva	6,900	1,630

American Cancer Society. Cancer Facts and Figures 2024

HER-2 NEU EXPRESSION IN GYNECOLOGIC CANCERS

- Ovarian Cancer
  - Range from 8-66%: estimated at under 25% with HER2 overexpression.
- Endometrial Cancer
  - HER2 overexpression ranges from 14-80% and HER2 gene amplification from 21-47%
  - Uterine papillary serous cancer has 25-30% overexpression
- Cervical Cancer (range from 0-87% depending on study)
  - HER2 overexpression 5.7% in ASCO/CAP compliant studies and 27% in ASCO/CAP non-compliant

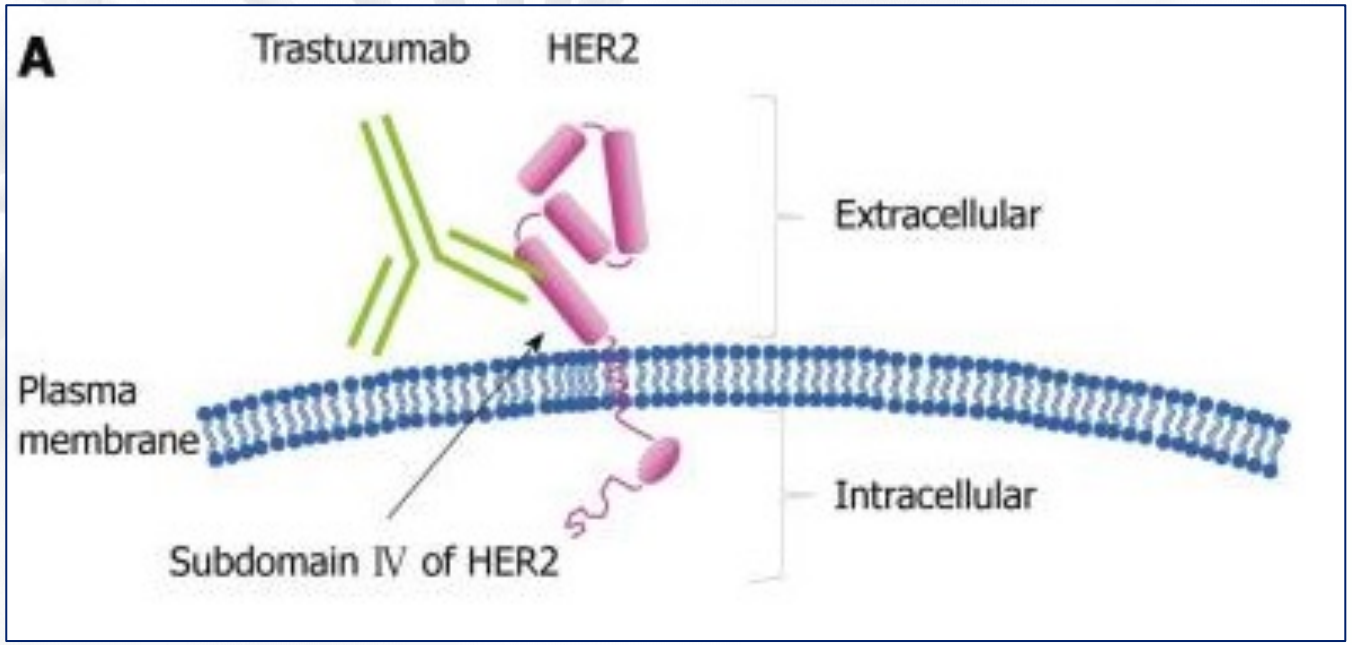
Tuefferd M et al. Her2 status in ovarian carcinomas. PLoS One. 2007; 2(11): e1138.

Buza, N. HER2 testing in endometrial serous carcinoma: Time for standardized pathology practice to meet the clinical demand. Arch Pathol Lab Med 145(6):687-91, 2021

Itkin B et al. Prevalence of HER2 overexpression and amplification in cervical cancer: A systematic review and meta-analysis. PLoS ONE 16(9): e0257976), 2021

TRASTUZUMAB

- Monoclonal antibody
- Binds to domain IV of the extracellular segment of the HER2 receptor
- Mediates antibody-dependent cellular cytotoxicity (ADCC) by inhibiting proliferation of cells that overexpress HER2



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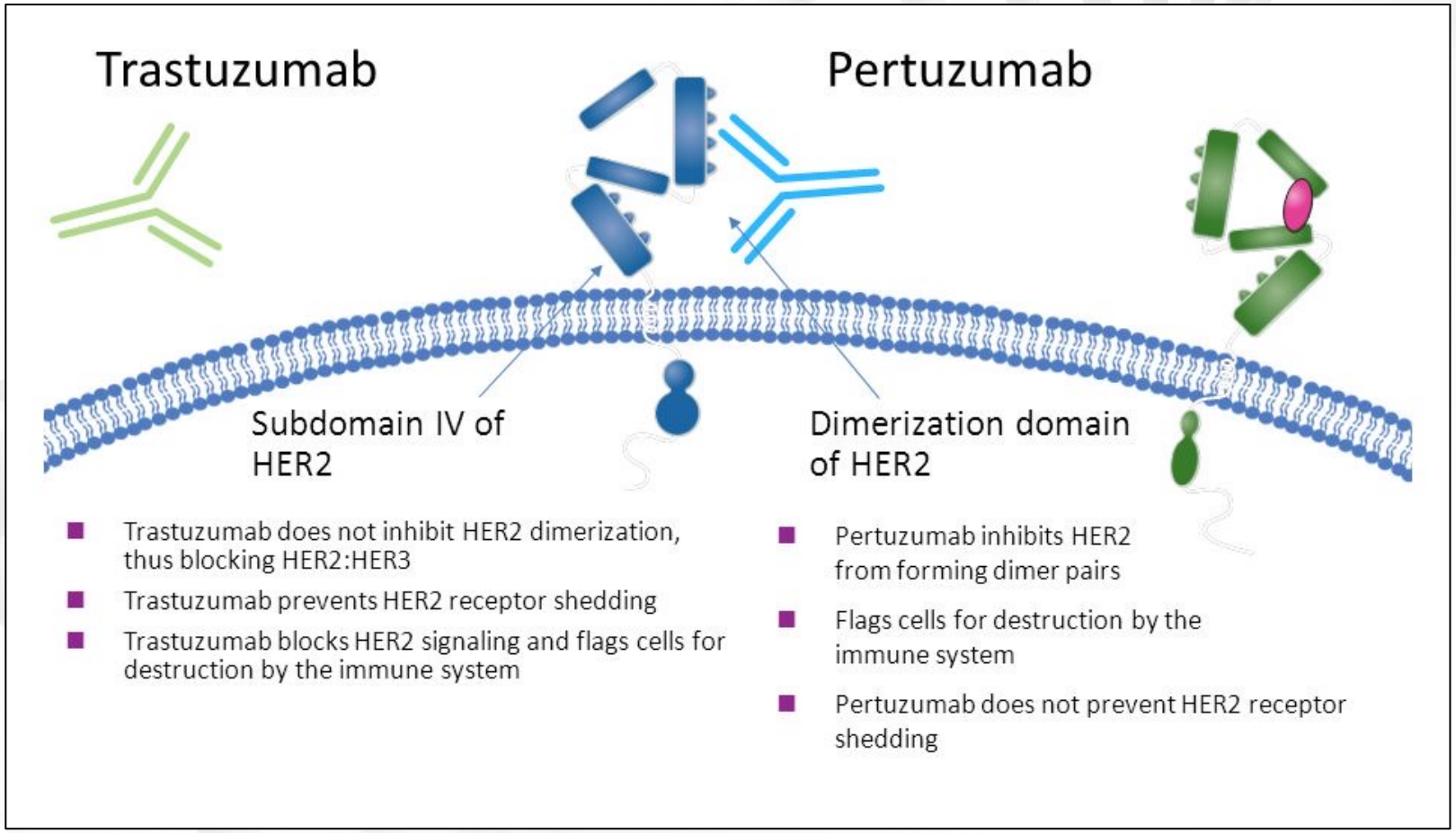
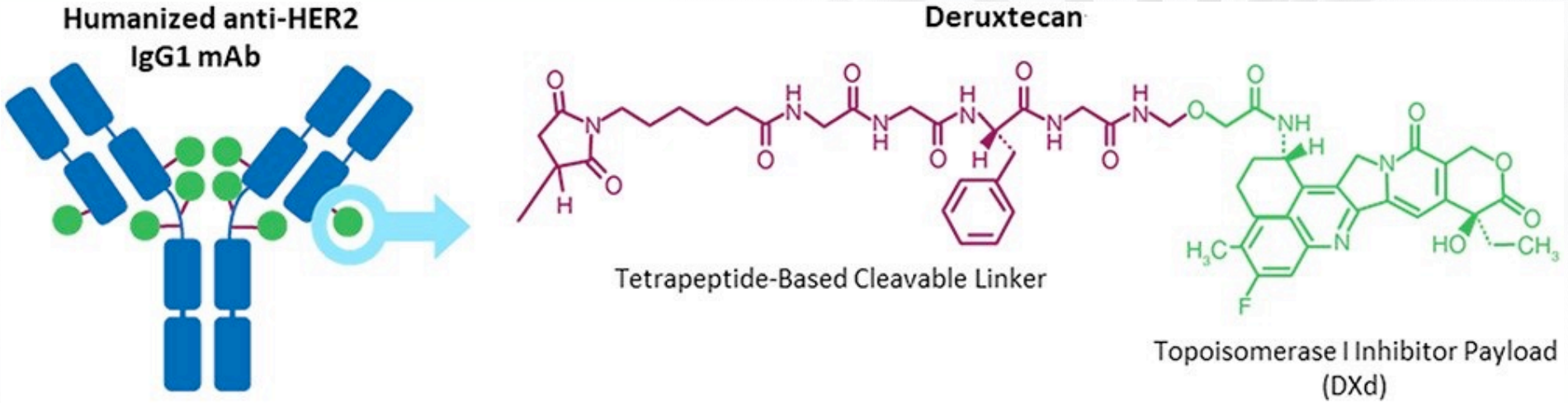
WHAT ABOUT DUAL ANTI-HER2 THERAPY?



- Trastuzumab does not inhibit HER2 dimerization, thus blocking HER2:HER3
- Trastuzumab prevents HER2 receptor shedding
- Trastuzumab blocks HER2 signaling and flags cells for destruction by the immune system

- Pertuzumab inhibits HER2 from forming dimer pairs
- Flags cells for destruction by the immune system
- Pertuzumab does not prevent HER2 receptor shedding

TRASTUZUMAB DERUXTECAN



Unique features

- High potency payload
- High drug to antibody ratio (8ish)
- Payload with short systemic half-life
- Tumor selective (cleavable linker)
- Membrane permeable payload

Slide adapted with permission from Dr. Jane Meisel

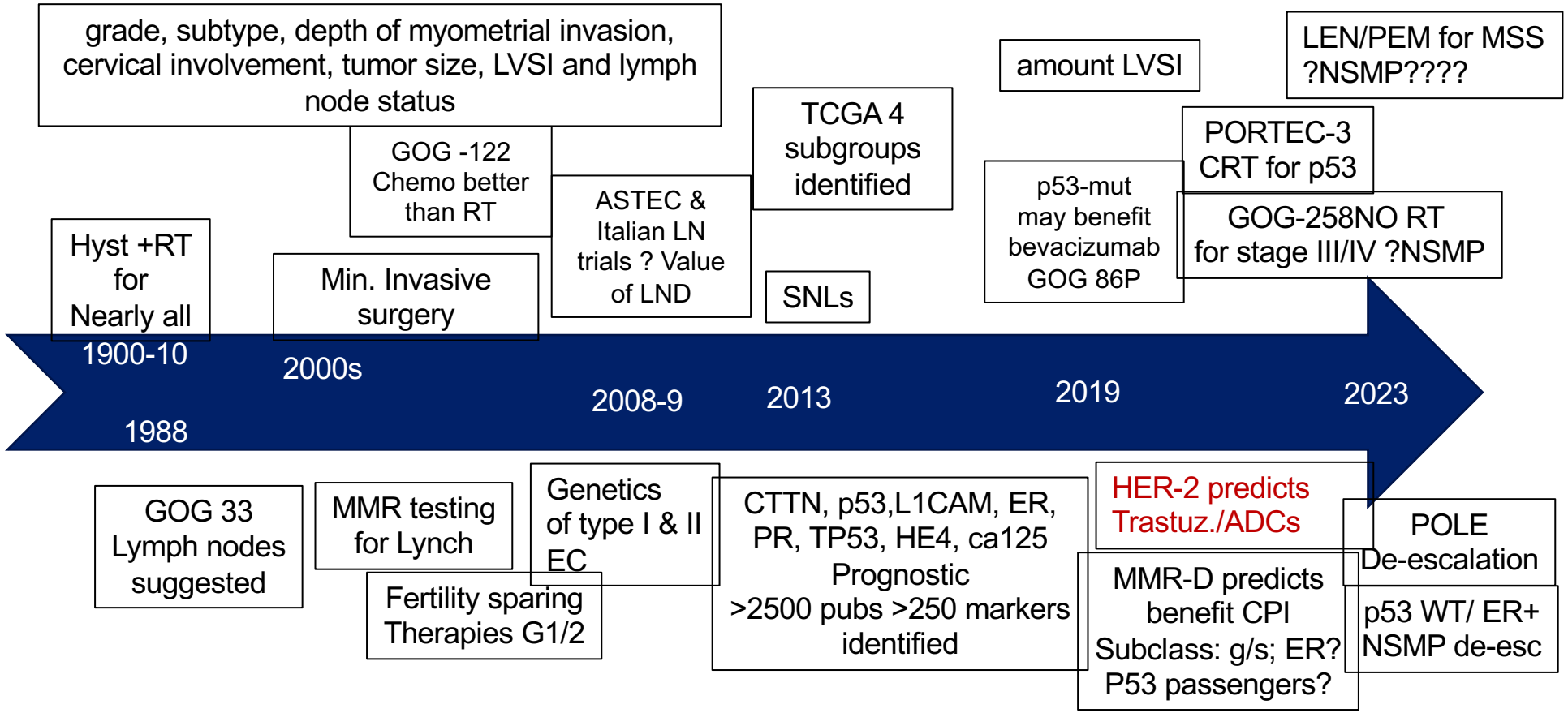
Chem Pharm Bull (Tokyo). 2019; 67 (3): 173-185. Clin Cancer Res 2016; 22 (20): 5097-5108. Pharmacol Ther. 2018; 181:126-142. Cancer Sci 2016; 107 (7): 1039-1046.

TRASTUZUMAB IN GYNECOLOGIC CANCERS

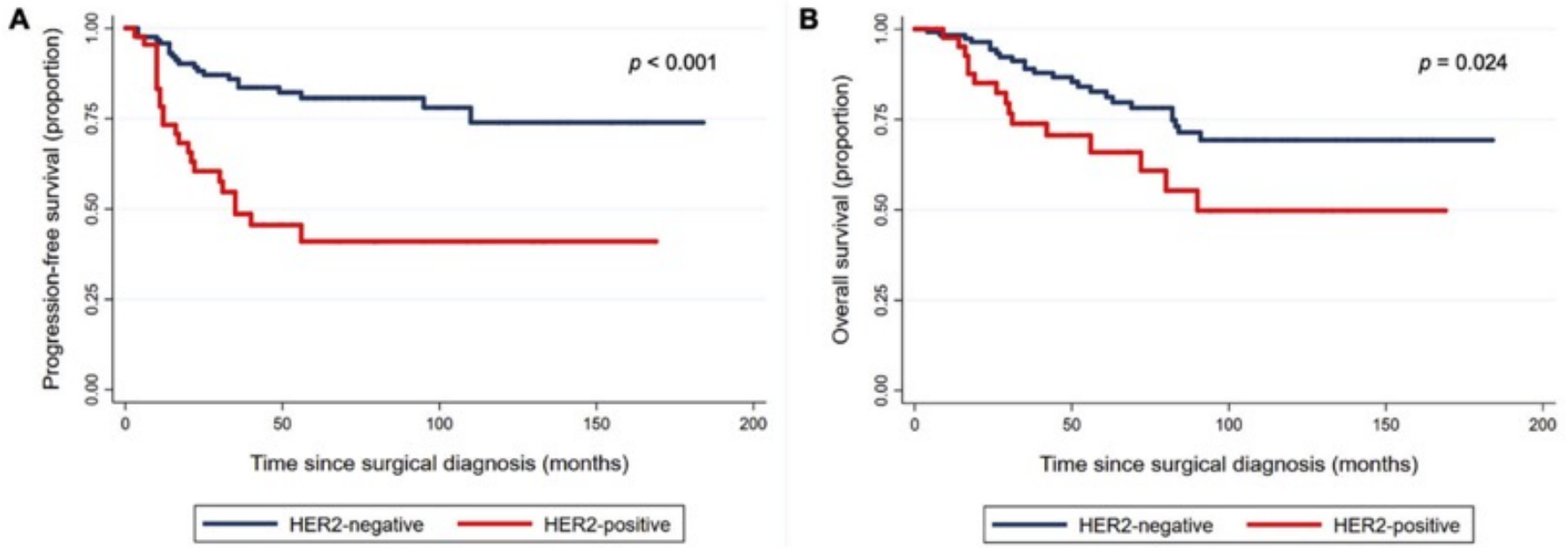
- Endometrial Cancer
  - Trastuzumab for advanced stage uterine papillary serous cancers
  - NRG-18: Current Phase 3 evaluating trastuzumab in all stages of UPSC
  - Fam-trastuzumab deruxtecan-nxki in recurrent disease (HER2 positive)
- Ovarian Cancer
  - Fam-trastuzumab deruxtecan-nxki in recurrent disease (HER2 positive)
- Cervical Cancer
  - Fam-trastuzumab deruxtecan-nxki in recurrent disease (HER2 positive)

HISTORY OF MANAGEMENT OF ENDOMETRIAL CANCER:

JOURNEY FROM PROGNOSTIC TO PREDICTIVE MARKERS



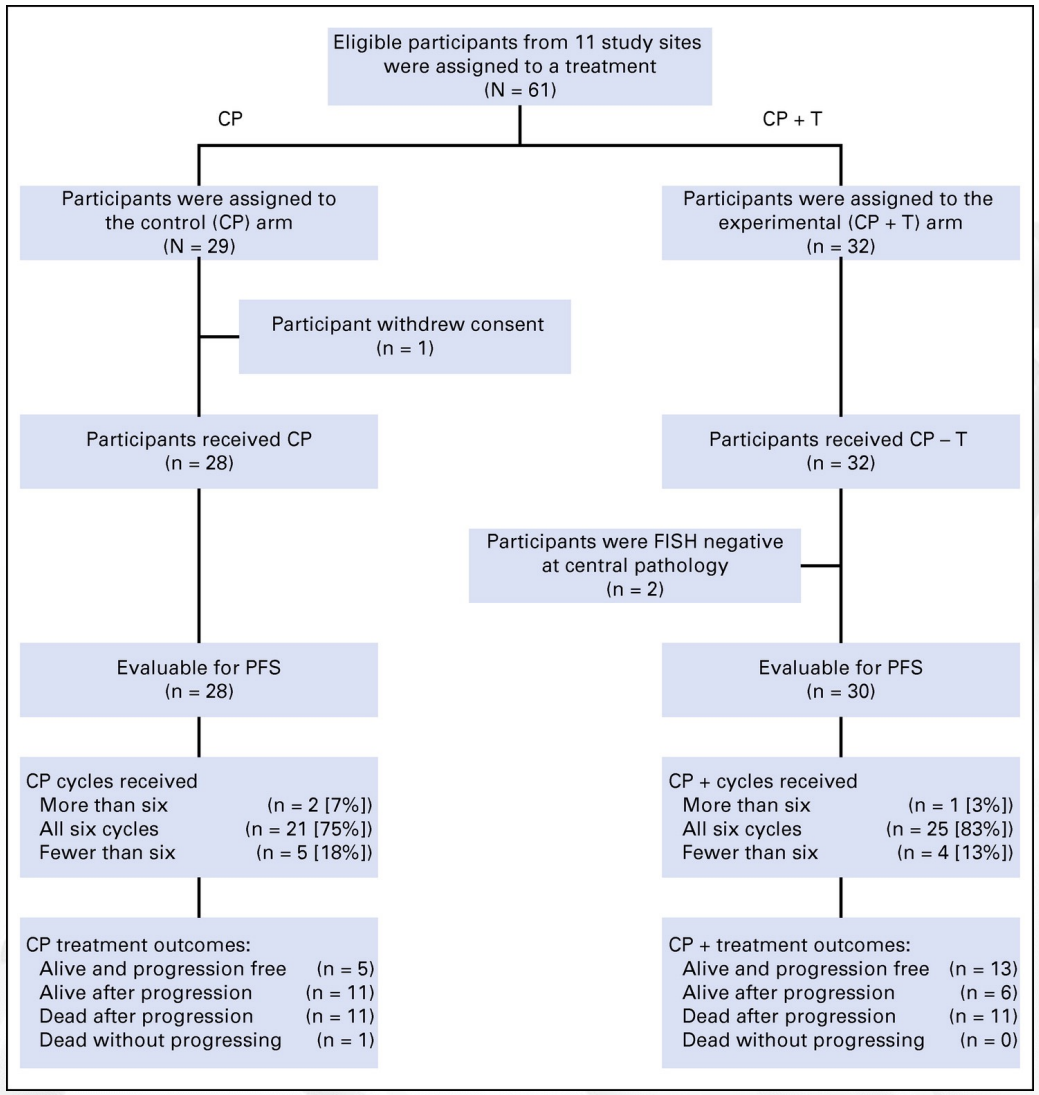
WORSE SURVIVAL OUTCOMES IN HER 2 POSITIVE STAGE 1 UTERINE PAPILLARY SEROUS CARCINOMA

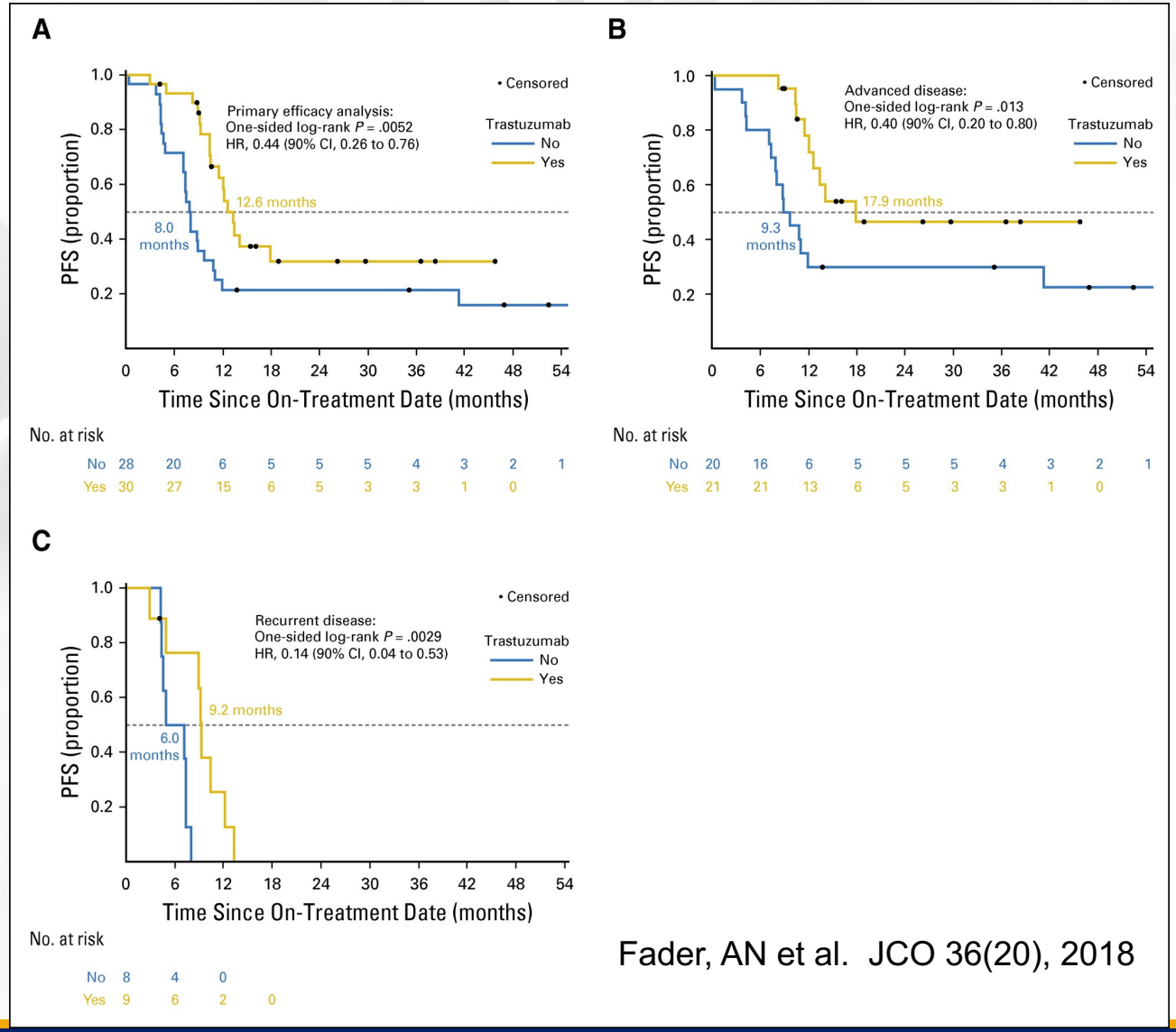


HER2 positive tumors were associated with inferior PFS (aHR 3.50, 95%CI 1.84-6.67; p < .001) and OS (aHR 2.00, 95%CI 1.04-3.88; p = .039) compared to HER2-negative tumors even when given Carbo/paclitaxel

Erickson et al *Gynecol Oncol* 2020.

RANDOMIZED PHASE II TRIAL OF TRASTUZUMAB IN UPSC

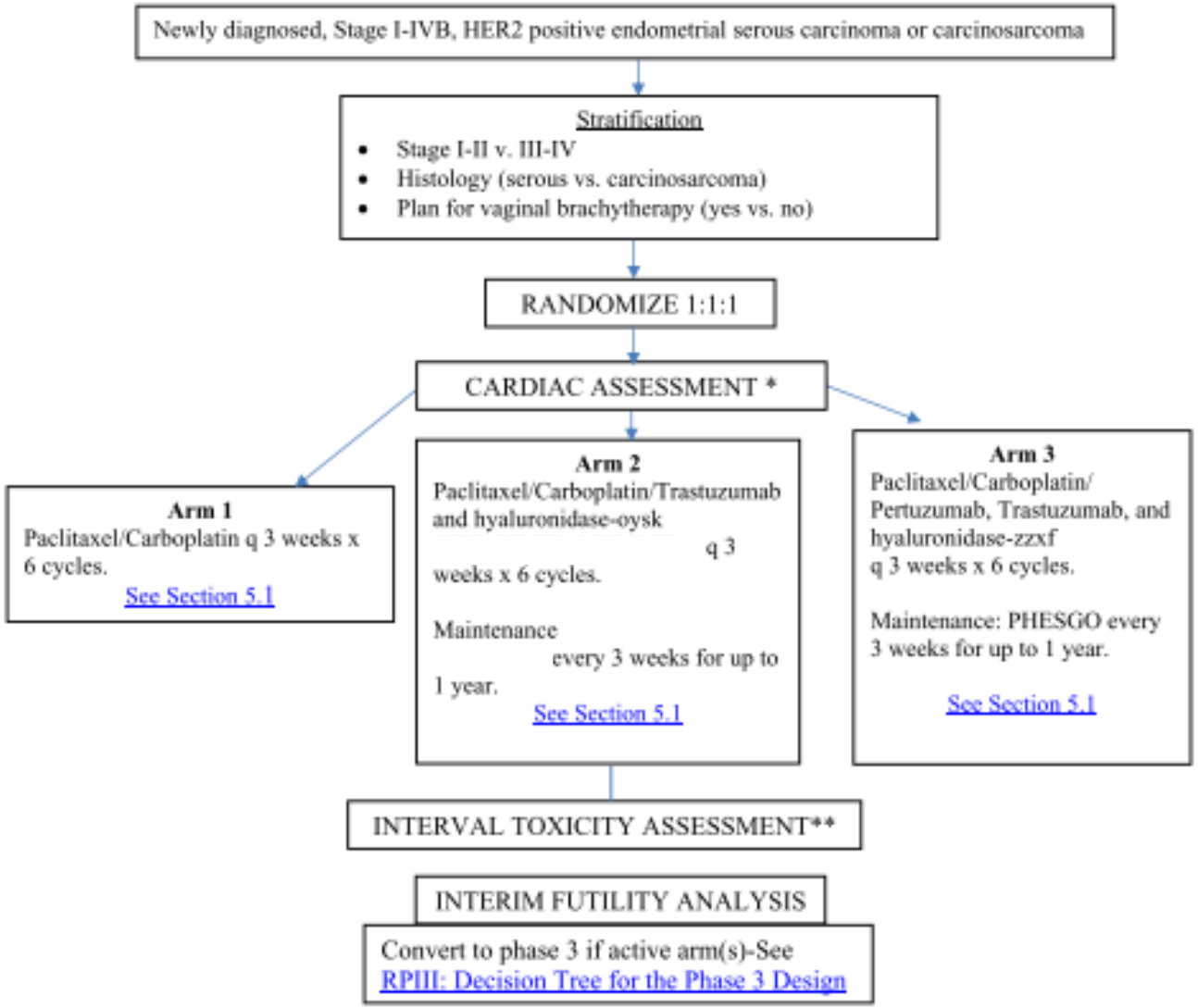




Fader, AN et al. JCO 36(20), 2018

NRG-GY026 SCHEMA

RPII: Paclitaxel/Carboplatin vs. Paclitaxel/Carboplatin/Trastuzumab and hyaluronidase-oysk
vs. Paclitaxel/Carboplatin/ Pertuzumab, trastuzumab, and hyaluronidase-zzxf → drop inactive arm(s) to Phase III



ANTIBODY DRUG CONJUGATES APPROVED/USED IN GYN

- Ovarian Cancer
  - Mirvetuximab
  - Trastuzumab deruxtecan
- Endometrial Cancer
  - Trastuzumab deruxtecan
- Cervical Cancer
  - Tisotumab vedotin
  - Trastuzumab deruxtecan

Two classes of antitumor drugs are commonly used as payloads in ADCs[1]

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

FDA approved ADC as of January 2024

Solid tumours		
Trastuzumab emtansine	Anti-HER2 antibody with a DM1 (maytansine derivative) payload and a non-cleavable linker conjugated using lysine–amide coupling with an average DAR of 3.5	HER2$^+$ breast cancer (2013)
Enfortumab vedotin	Anti-nectin-4 antibody with an MMAE payload and a cleavable valine–alanine linker conjugated using partial cysteine alkylation with an average DAR of 3.8	Urothelial carcinoma (2019), in combination with pembrolizumab (2023)
Trastuzumab deruxtecan	Anti-HER2 antibody with a DXd (exatecan derivative) payload and a cleavable glycine–glycine–phenylalanine–glycine linker conjugated using full homogeneous cysteine alkylation with an average DAR of 7.7	HER2$^+$ breast cancer (2019), HER2$^+$ gastric cancer (2021), HER2^{low} breast cancer (2022)
Sacituzumab govitecan	Anti-TROP2 antibody with an SN-38 payload and a cleavable lysine–PAB and carbonate linker conjugated using full homogeneous cysteine alkylation with an average DAR of 7.6	TNBC (2020), urothelial carcinoma (2021), HR$^+$, HER2$^-$ breast cancer (2023)
Tisotumab vedotin	Anti-TF antibody with an MMAE payload and a cleavable valine–citrulline linker conjugated using cysteine alkylation (partial) with an average DAR of 4	Cervical cancer (2021)
Mirvetuximab soravtansine	Anti-FRα antibody with a DM4 (maytansine derivative) payload and a cleavable disulfide linker conjugated using lysine–amide coupling with an average DAR of 3.5	FRα$^+$ ovarian, fallopian tube and peritoneal cancers (2022)

nature reviews clinical oncology
https://doi.org/10.1038/s41571-023-00850-2

NCCN UTERINE/OVARIAN/CERVICAL CANCER GUIDELINES 2024

SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

Primary or Adjuvant Therapy (Stage I–IV)	
Chemoradiation Therapy	**Systemic Therapy**
<u>Preferred Regimens</u> • Cisplatin plus RT followed by carboplatin/paclitaxel[1,2] <u>Other Recommended Regimens</u>[a] <u>(if cisplatin and carboplatin are unavailable)</u> • Capecitabine/mitomycin[3] • Gemcitabine[4] • Paclitaxel[5,6]	<u>Preferred Regimens</u> • Carboplatin/paclitaxel[7] • Carboplatin/paclitaxel/pembrolizumab (for stage III–IV tumors, except for carcinosarcoma) (category 1)[b,c,d,8] • Carboplatin/paclitaxel/dostarlimab-gxly (for stage III–IV tumors) (category 1)[c,d,e,9] • Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive uterine serous carcinoma)[d,f,g,10] • Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive carcinosarcoma)[d,f,g,10]

<u>Useful in Certain Circumstances</u>

- PD-L1–positive tumors
  - Nivolumab[f,g,18]
- HER2-positive tumors (IHC 3+ or 2+)
  - Fam-trastuzumab deruxtecan-nxki[19]

Original Reports | Gynecologic Cancer

Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial

Funda Meric-Bernstam, MD[1]; Vicky Makker, MD[2,3]; Ana Oaknin, MD[4]; Do-Youn Oh, MD[5]; Susana Banerjee, PhD[6]; Antonio González-Martín, MD[7]; Kyung Hae Jung, MD[8]; Iwona Ługowska, MD[9]; Luis Manso, MD[10]; Aránzazu Manzano, MD[11]; Bohuslav Melichar, MD[12]; Salvatore Siena, MD[13]; Daniil Stroyakovskiy, MD[14]; Anitra Fielding, MBChB[15]; Yan Ma, MSc[16]; Soham Puvvada, MD[15]; Norah Shire, PhD[15]; and Jung-Yun Lee, MD[17]

DOI https://doi.org/10.1200/JCO.23.02005

Meric-Bernstam, F et al. J Clin Oncol. 2024 Jan 1; 42(1): 47–58.

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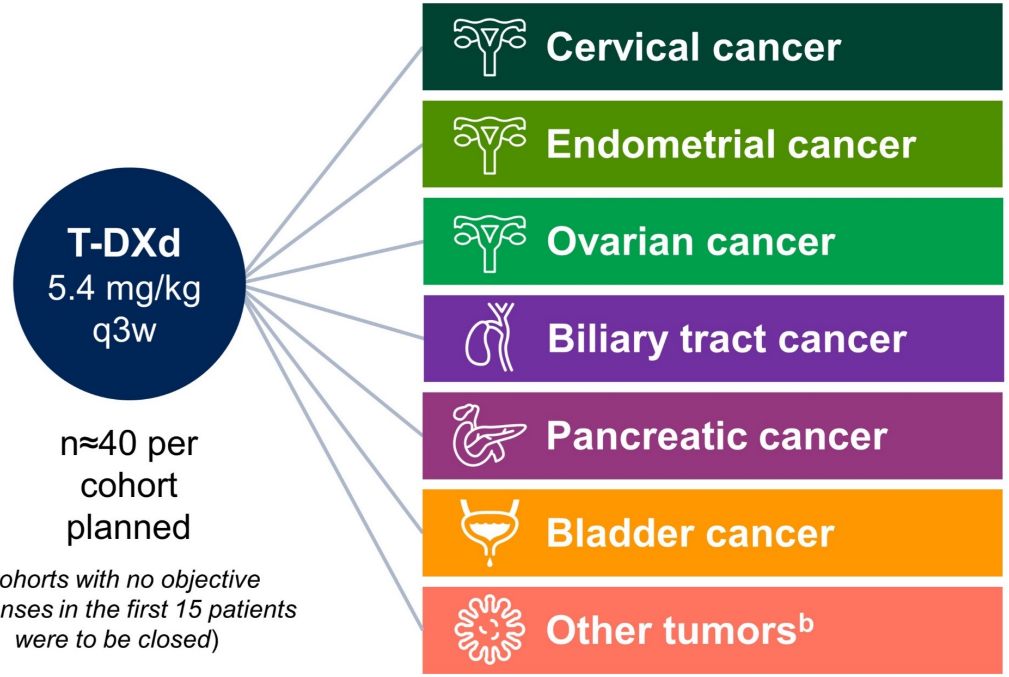
- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer guidelines[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1



Primary endpoint

- Confirmed ORR (investigator)[c]

Secondary endpoints

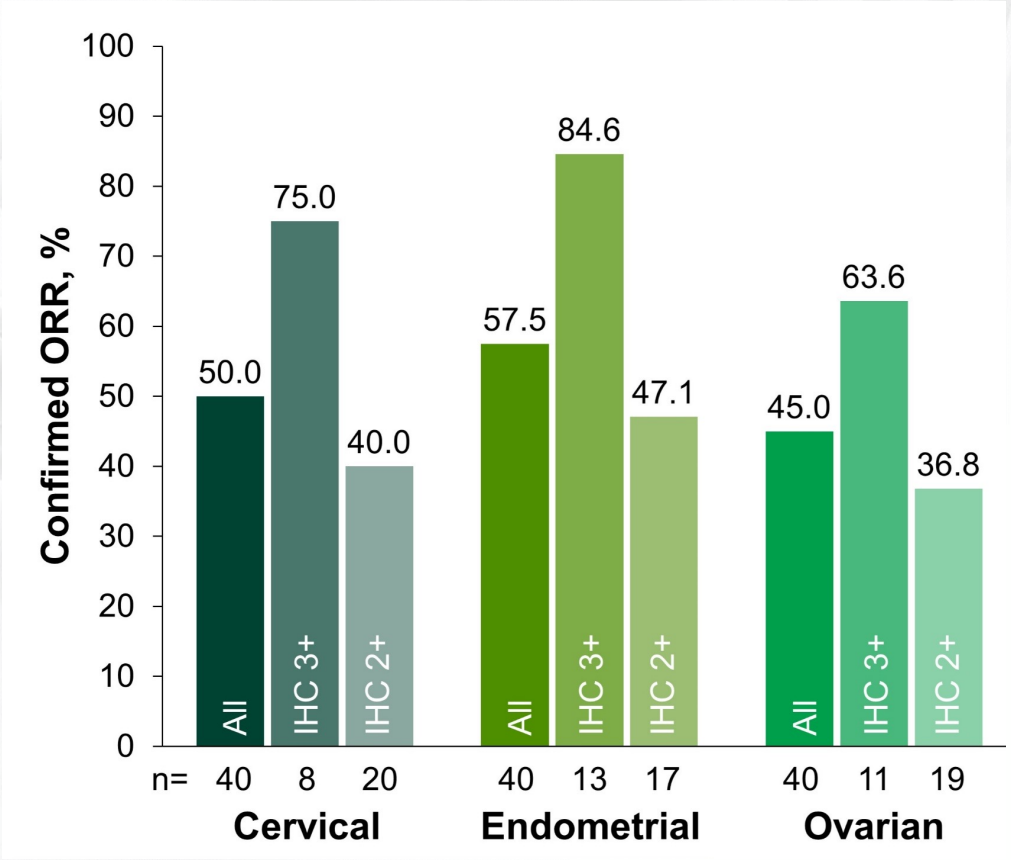
- DOR[c]
- DCR[c]
- PFS[c]
- OS
- Safety

Data cut-off for analysis:

- Nov 16, 2022

Efficacy

		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)

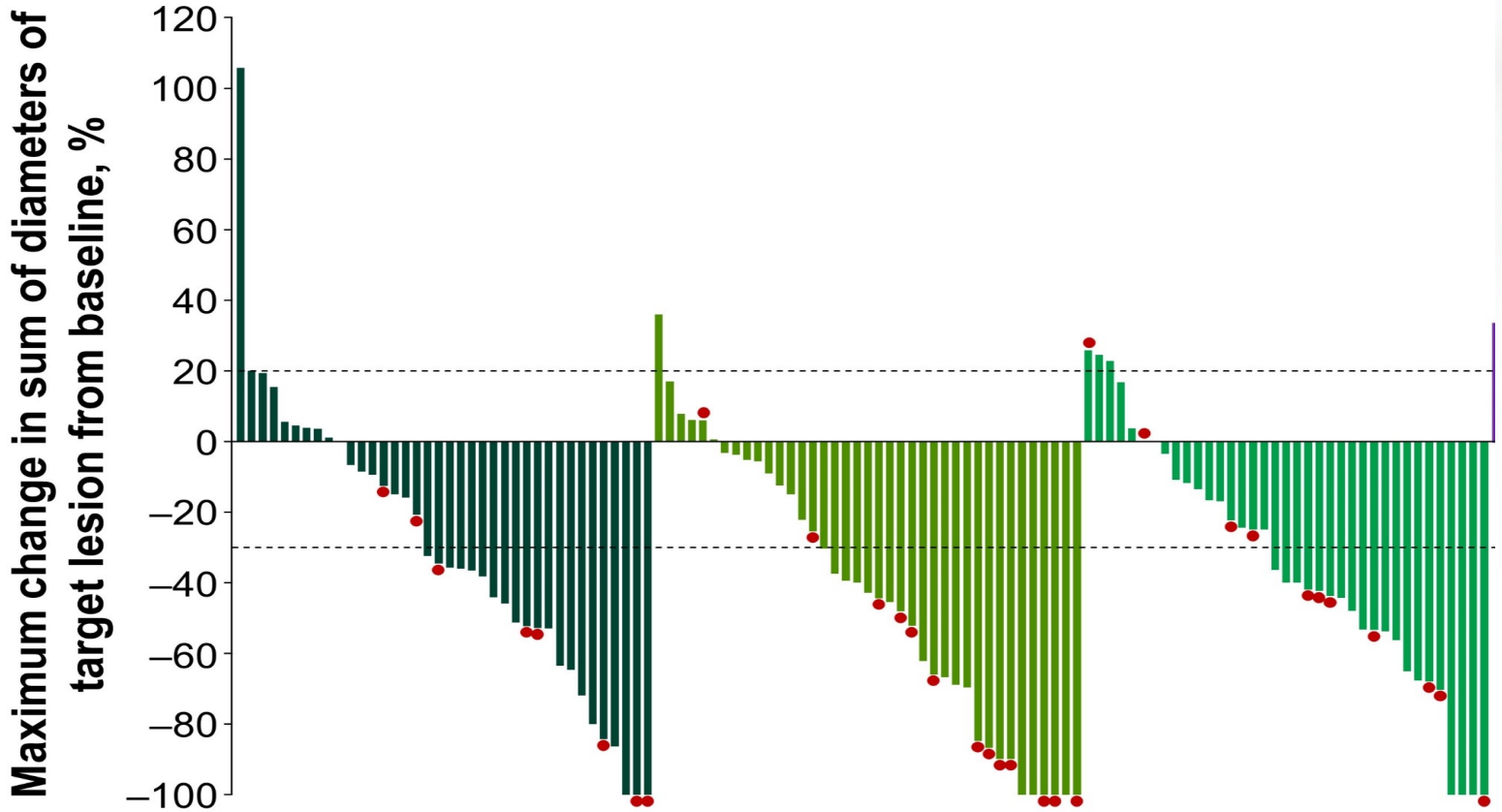


	All patients (N=99)	IHC 3+ (n=46)	IHC 2+ (n=34)
Median DOR, months (95% CI)	11.8 (9.8–NE)	22.1 (9.3–NE)	9.8 (4.2–12.6)

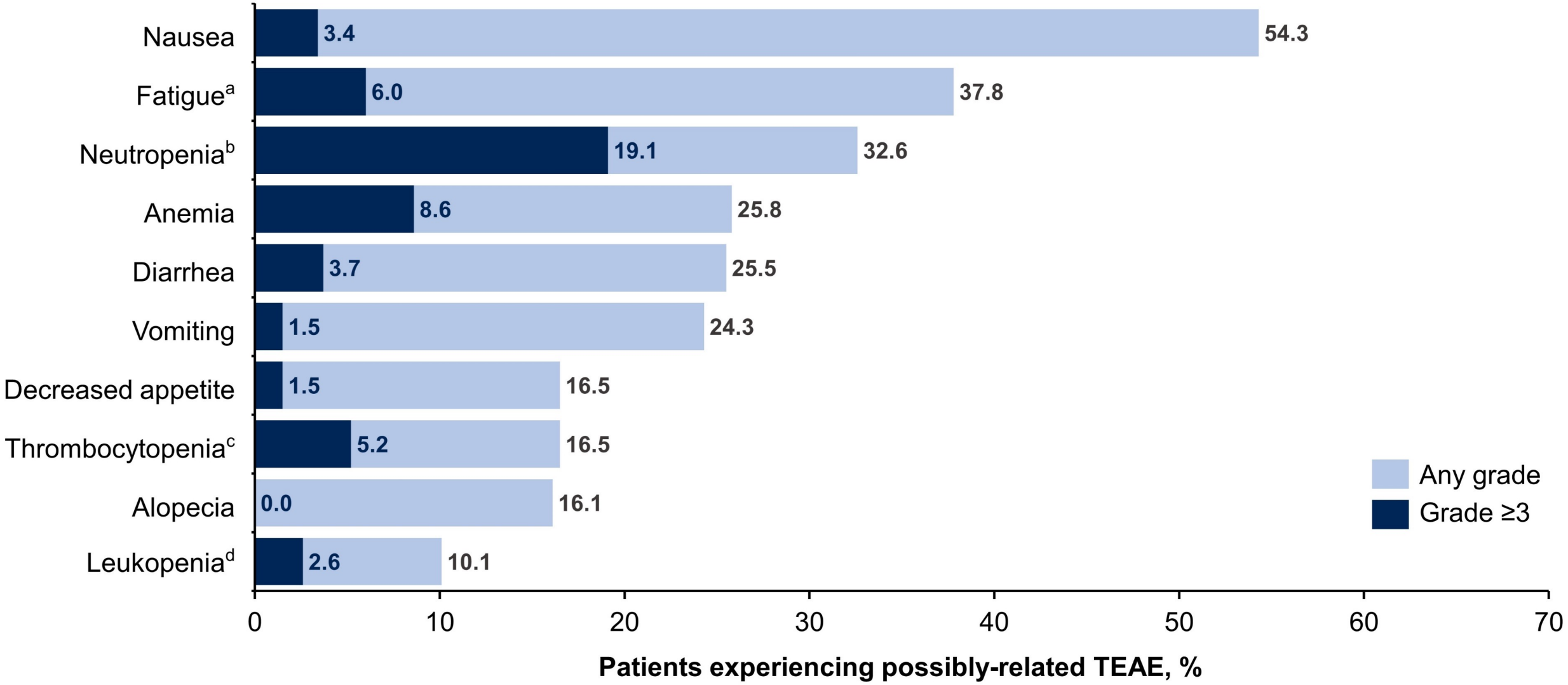
Analysis of ORR was performed in patients who received ≥1 dose of T-DXd; all patients (n=267; including 67 patients with IHC 1+ [n=25], IHC 0 [n=30], or unknown IHC status [n=12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=75) or IHC 2+ (n=125) status. Analysis of DOR was 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.

PRESENTED BY: Funda Meric-Bernstam, MD

TRASTUZUMAB-DERUXTECAN: GYN TUMORS



TOXICITY


Nausea
3.4
54.3
Fatigue[a]
6.0
37.8
Neutropenia[b]
19.1
32.6
Anemia
8.6
25.8
Diarrhea
3.7
25.5
Vomiting
1.5
24.3
Decreased appetite
1.5
16.5
Thrombocytopenia[c]
5.2
16.5
Alopecia
0.0
16.1
Leukopenia[d]
2.6
10.1
Any grade
Grade ≥3
0
10
20
30
40
50
60
70
Patients experiencing possibly-related TEAE, %

TRASTUZUMAB DERUXTECAN FOR HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2-EXPRESSING ADVANCED OR RECURRENT UTERINE CARCINOSARCOMA (NCCH1615): THE STATICE TRIAL

- Phase II trial, patients were classified as HER2-high (IHC 3 or 2+) or HER2-low (IHC 1+) regardless of FISH status.
- The overall response rates in the HER2-high and HER2-low groups were 54.5% and 70.0% respectively
- No difference in duration of response, PFS (6.2 vs. 6.7 months) or OS in the two groups
- Grades 1-2 and 3 pneumonitis/interstitial lung disease occurred in eight (24%) and one (3%) patient, respectively

Nishikawa T et al. . JCO 2023 May 20;41(15):2789-2799.

DESTINY-02 TOXICITY IN GYN CANCER PATIENTS

TABLE 2. Incidence of Drug-Related Adverse Events

Adverse Event	Endometrial Cancer (n = 40)	Cervical Cancer (n = 40)	Ovarian Cancer (n = 40)
Drug-related adverse events, No. (%)	36 (90.0)	36 (90.0)	34 (85.0)
Grade ≥3	14 (35.0)	19 (47.5)	21 (52.5)
Serious adverse events	4 (10.0)	3 (7.5)	11 (27.5)
Leading to discontinuation	3 (7.5)	3 (7.5)	1 (2.5)
Leading to dose modification[a]	13 (32.5)	13 (32.5)	18 (45.0)
Associated with death	2 (5.0)	0	0
Most common drug-related adverse events (>10% of total patients), No. (%)			

*** Interstitial lung disease-10.5%, majority grade 1-2 but three were fatal (one endometrial, one biliary, one other)

Meric-Bernstam, F et al. J Clin Oncol. 2024 Jan 1; 42(1): 47–58.

NEW DIRECTIONS TO IMPROVE ADC'S

nature reviews clinical oncology
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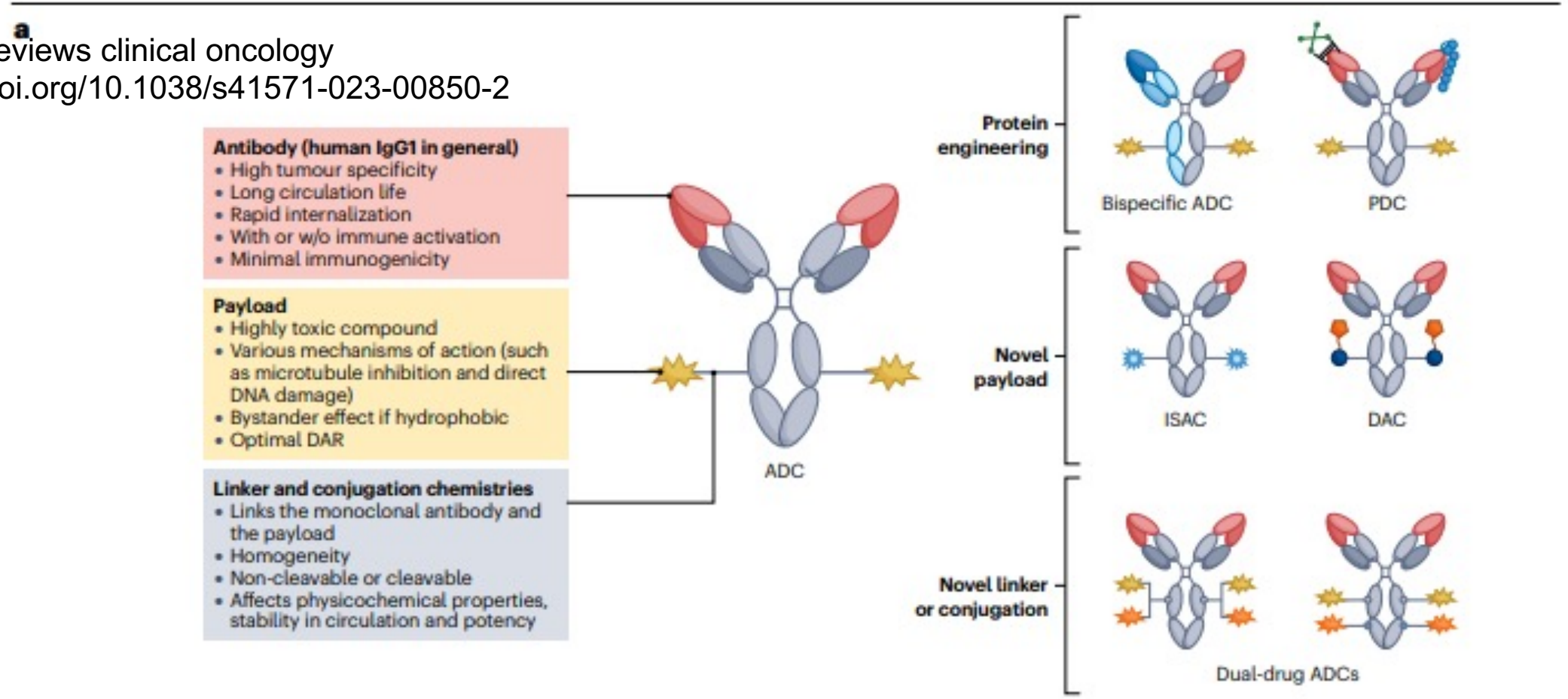

DAC, protein degrader–antibody conjugate; FcγR; Fcγ receptor; ISAC, immune-stimulating antibody conjugate; NK, natural killer; PDC, probody–drug conjugate; w/o, without

QUESTIONS?