Gynecologic Malignancies

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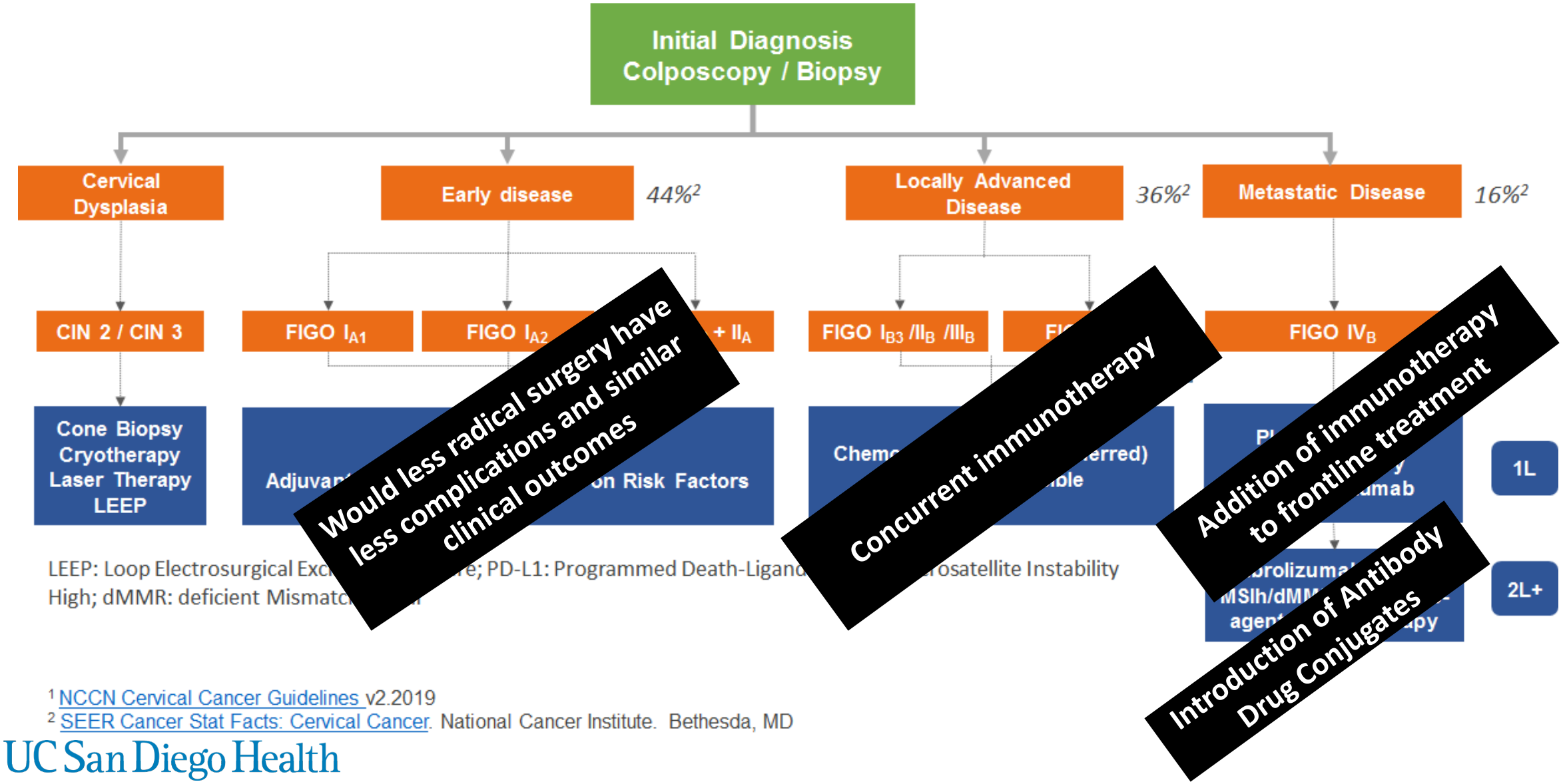
UC San Diego Health

Agenda

- Cervical Cancer
  - Is conservative surgery acceptable? SHAPE and ROCC trials
  - Immunotherapy in front line treatment of metastatic or recurrent cervical cancer
  - Introduction of Antibody Drug Conjugates to the treatment of cervical cancer
- Endometrial Cancer
  - Immunotherapy in front line treatment of metastatic and recurrent endometrial cancer
  - Introduction of Antibody Drug Conjugates to the treatment of endometrial cancer

Cervical cancer treatment paradigm



LEEP: Loop Electrosurgical Exci…re; PD-L1: Programmed Death-Ligand… …rosatellite Instability High; dMMR: deficient Mismatc…

[1] NCCN Cervical Cancer Guidelines v2.2019
[2] SEER Cancer Stat Facts: Cervical Cancer. National Cancer Institute. Bethesda, MD

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Radical Hysterectomy – complication rates

- Intra-operative (1-5%):
  - Blood transfusion 2-5%
  - Ureteral injury 1-2%
  - Bladder injury 0.8-2.5% higher in MIS
  - Nerve injury 0.4-2.2% higher in MIS
  - Vascular injury 1-2%
- Post-operative (1-5%):
  - Delayed bladder fxn 5%
  - Vaginal vault complocation 0.8-4% higher in MIS
  - GU fistula/stricture 2-3%
  - Neuropathy 0.8-2.2%
  - SSI 1-2%
  - Wound complication: 1-6% higher in Open
  - Lymphedema/lymphocele 1%

Obermair et al. AJOG 2020

Defining a low-risk group

- Covens et al 2002 (PMID 11748991)
  - –842 pts w/ radical sx for clinical stage IA1/2 and IB1 cervical cancer
  - –6% positive LN rate; 4% positive parametrial rate
  - **–Subgroup n=536 w/ neg LN, <2cm tumor, DOI < 10 mm -> 0.6% +parametria**
- Wright et al 2007 (PMID – 17654664)
  - –594 pts w/ radical sx +PND from 1989-2005
  - –11% +parametria: assoc w/ hist, adv gr, deep invasion, LVSI, large tumor, adv stage, uterine/vag involvement, +P/PALN AND assoc w/ incr recurr & decre DFS/OS
  - **–Subgroup of neg nodes, no LVSI, tumor <2cm -> 0.4% +parametria**
- Frumovitz et al 2009 (PMID – 19546764)
  - –350 pts w/ radical sx +PND from 1990-2006
  - –7.7% +parametria: assoc w/ >2cm tumor, higher gr, LVSI and +PLN
  - **–Subgroup n=125 w/ no LVSI, tumor <=2cm, any hist, all gr -> 0% +parametria**

SHAPE trial (Canadian Cancer Trials Group)

- **CCTG CX.5-SHAPE** trial enrolled 700 patients with low-risk SCC, AC, ASC of the cervix and randomly assigned them to RH or SH plus PLND
- **Population:** Low-risk disease = stage IA2 and IB1 with lesions < 2 cm of HPV-related cervical cancer histology. Limited stromal invasion was allowed (< 10 mm on LEEP/cone and < 50% depth on MRI)
- **Primary outcome:** 3-yr Pelvic recurrence rate for SH was 2.52% compared to 2.17% for RH (a difference of 0.35% with 90% CI [-1.62%, 2.32%]).
- **Secondary outcome:** SH had significantly less acute surgery-related adverse events within 4 weeks of surgery compared with RH (42.6% vs 50.6%; *P* = .04).
- Other outcomes: 3-year extra-pelvic recurrence-free survival (98.1% vs 99.7%) and overall survival (99.1% vs 99.4%) were also similar between the simple and radical hysterectomy approaches

SCC: squamous cell carcinoma; AC: adenocarcinoma; ASC: adenosquamous carcinoma.
RH: radical Hysterectomy; SH: simple hyst; PLND: Pelvic lymph node dissection

Plante M, et al. 2023 ASCO annual meeting

ROCC trial

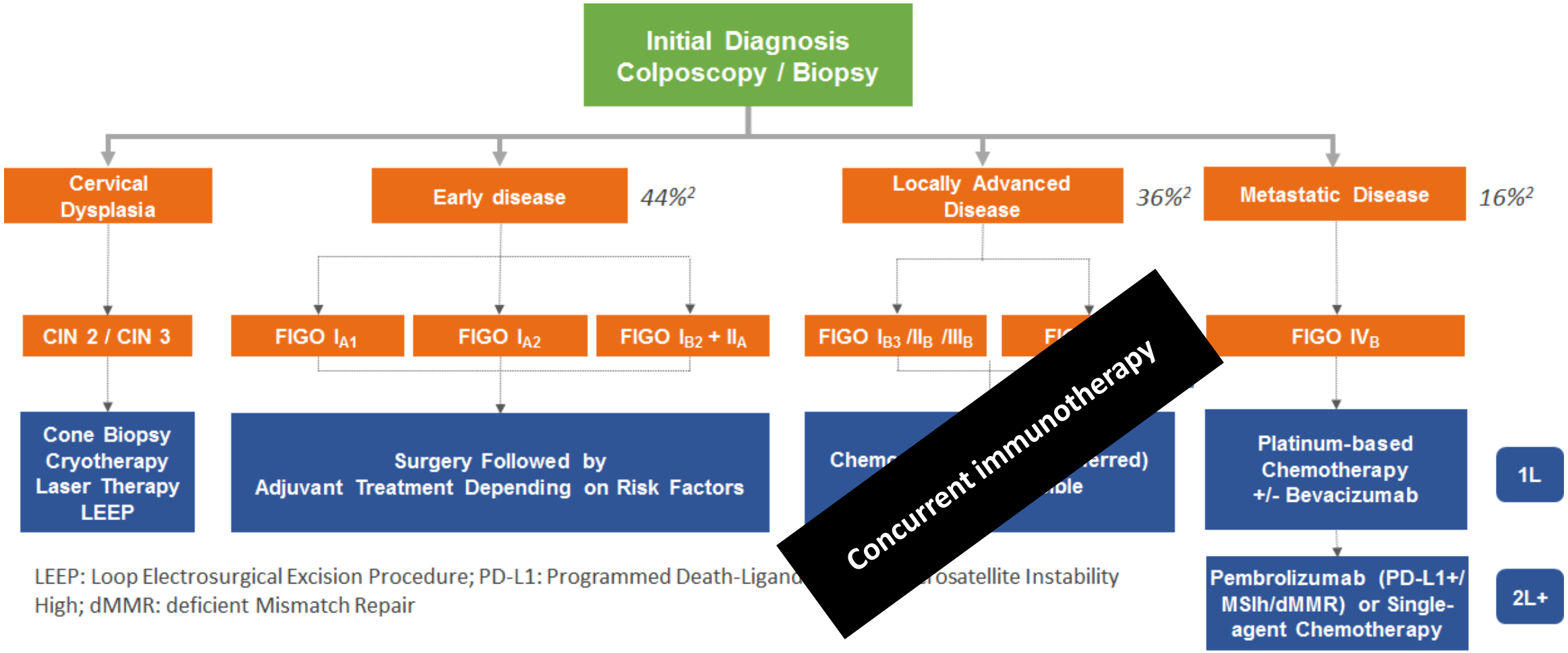
ROCC/GOG-3043: A randomized non-inferiority trial of robotic versus open radical hysterectomy for early-stage cervical cancer.

ROCC is a multi-center, prospective, randomized, non-inferiority trial. The primary objective is to determine whether robotic-assisted (RBT) radical hysterectomy is not inferior to abdominal (OPEN) approach with respect to 3-year disease-free survival (DFS). Secondary objectives include DSS, OS, patterns of recurrence, peri- and postoperative complications, long-term morbidity, impact on patient-reported outcome (PRO) measures and development of lower extremity lymphedema (LEL).

Key inclusion criteria include patients with histologically confirmed adenocarcinoma, squamous cell, and adenosquamous cell carcinoma of FIGO 2018 stage IA2-IB2

Bixel KL, et al. 2022 ASCO annual meeting

Cervical cancer treatment paradigm



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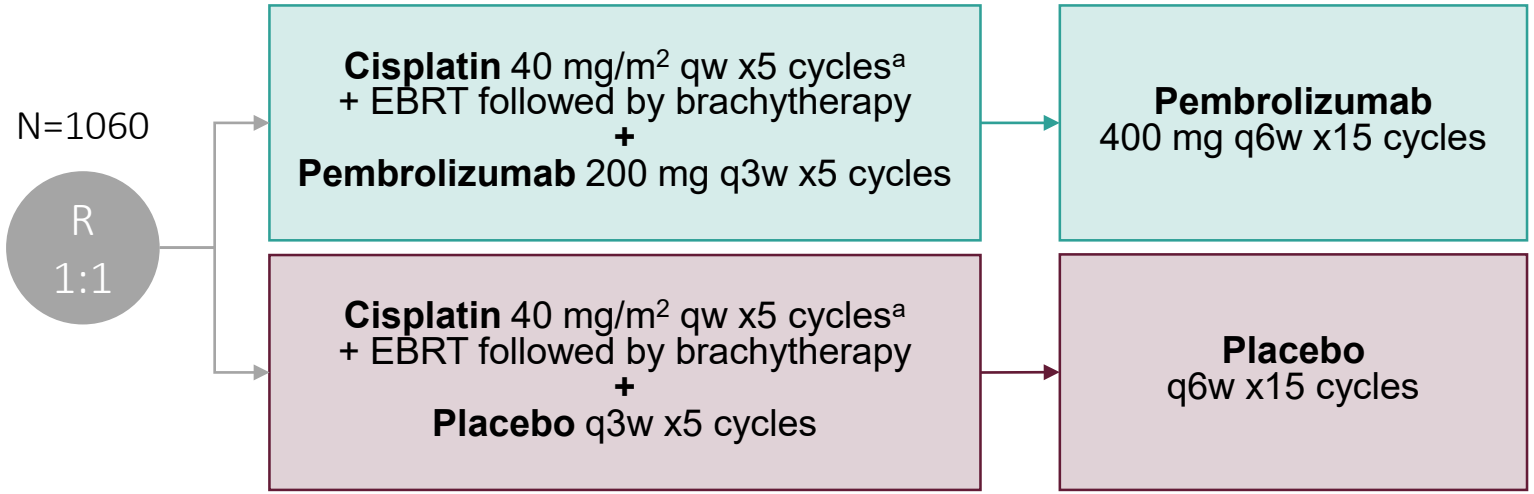
KEYNOTE-A18: Phase 3 Trial of Pembrolizumab + Chemoradiotherapy for High-Risk Locally Advanced Cervical Cancer

- FIGO 2014 stage IB2-IIB (node-positive) or stage III-IVA (node-positive or node-negative)
- RECIST 1.1 measurable or non-measurable disease
- Treatment naïve



- Stratification factors: planned EBRT type (IMRT or VMAT vs non-IMRT or non-VMAT), stage at screening (stage IB2-IIB vs III-IVA), and planned total radiotherapy dose (<70 Gy vs ≥70 Gy [EQ2D])

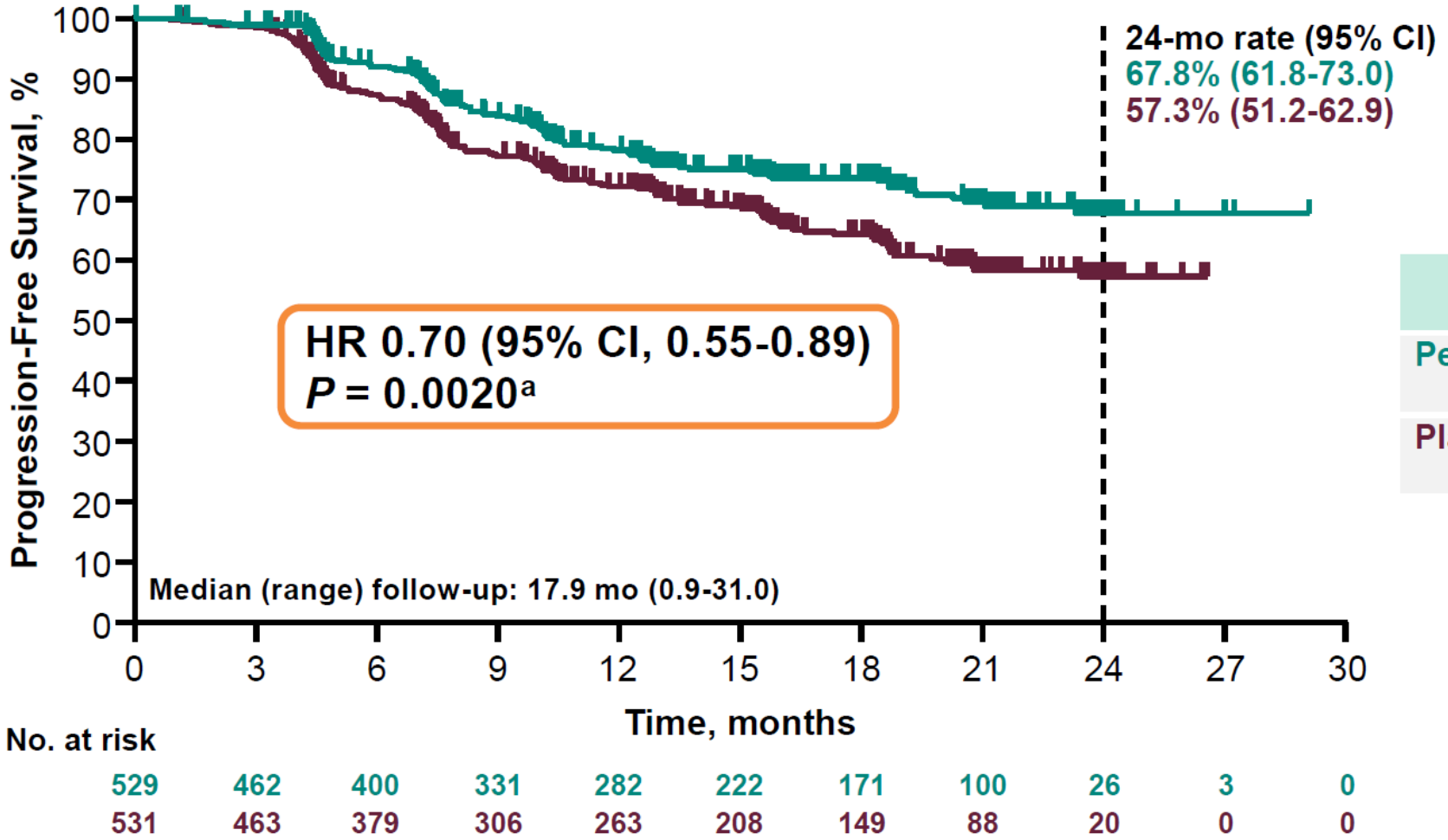
Endpoints
- Primary: PFS and OS
- Key secondary: 24-mo PFS, ORR, PROs, and safety

Pembrolizumab is not FDA approved for the treatment of locally advanced cervical cancer at this time

[a] A sixth cycle was allowed per investigator discretion.

Lorusso D, et al. 2023 Annual ESMO Meeting. Abstract LBA38.

KEYNOTE-A18: PFS

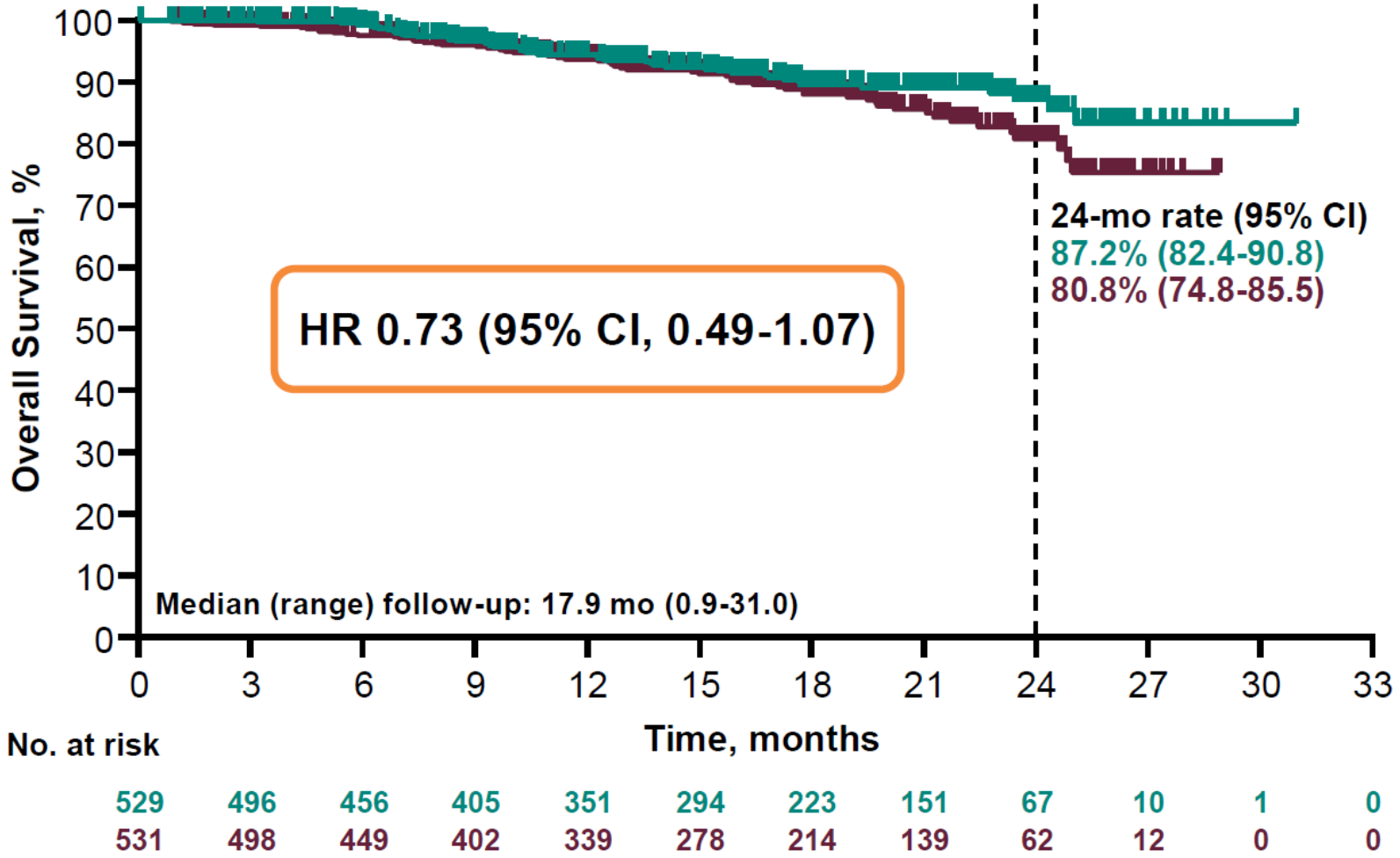


	Pts w/ Event	Median, mo (95% CI)
Pembro Arm	21.7%	NR (NR-NR)
Placebo Arm	29.0%	NR (NR-NR)

Response assessed per RECIST v1.1 by investigator review or histopathologic confirmation. [a] With 269 events (88.5% information fraction), the observed *P*=0.0020 (1-sided) crossed the prespecified nominal boundary of 0.0172 (1-sided) at this planned first interim analysis. The success criterion of the PFS hypothesis was met, and thus no formal testing of PFS will be performed at a later analysis.

Lorusso D, et al. 2023 Annual ESMO Meeting. Abstract LBA38.

KEYNOTE-A18: OS



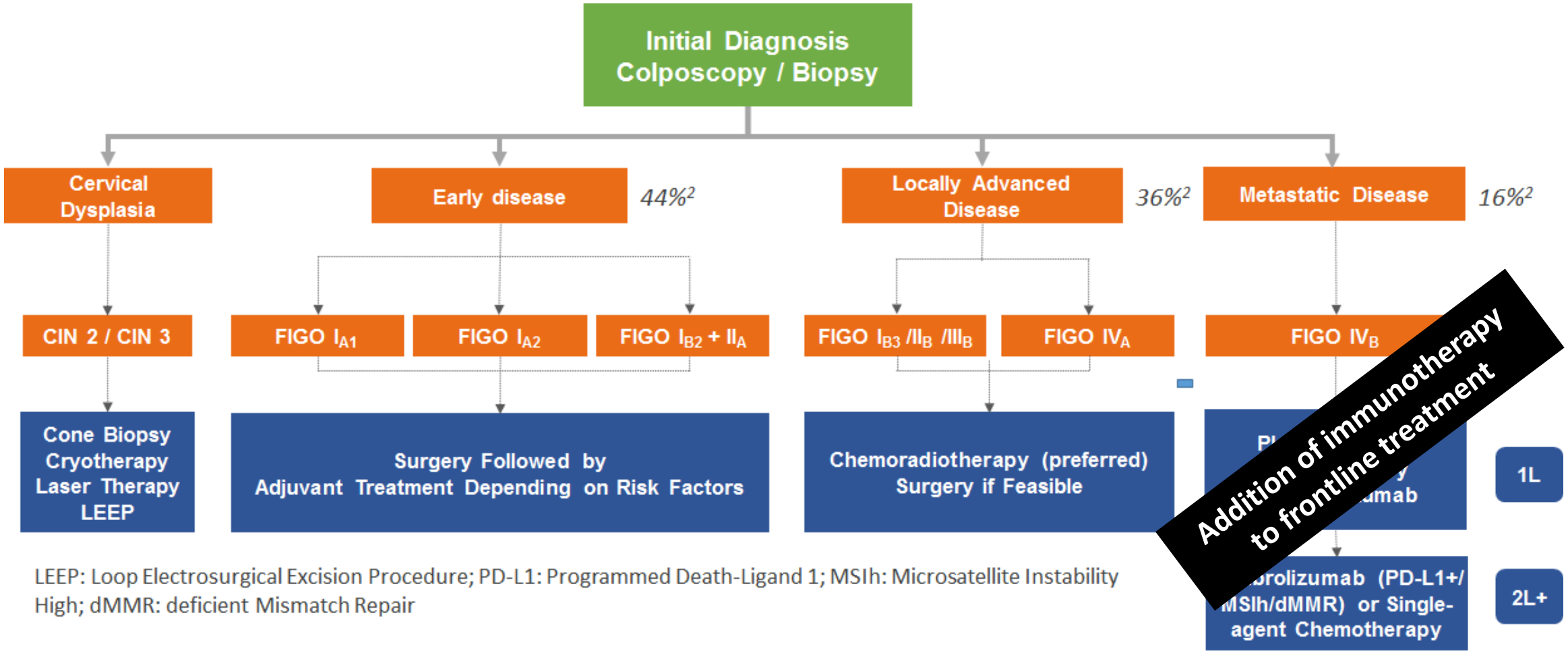
	Pts w/ Event*	Median, mo (95% CI)
Pembro Arm	8.3%	NR (NR-NR)
Placebo Arm	11.1%	NR (NR-NR)

*42.9% information fraction[a]

[a] At this analysis, 103 of the 240 deaths expected at the final analysis had occurred.

Lorusso D, et al. 2023 Annual ESMO Meeting. Abstract LBA38.

Cervical cancer treatment paradigm



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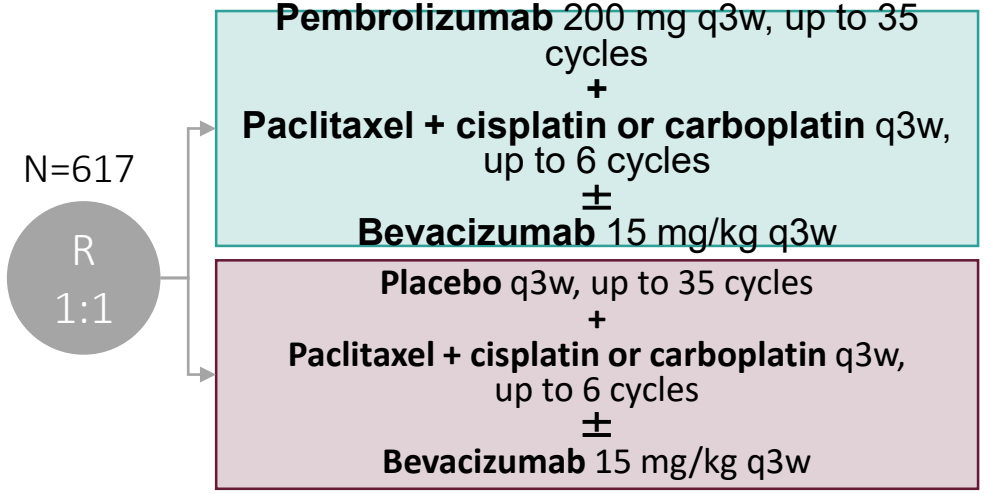
KEYNOTE 826: Phase 3 Trial of Pembro + Chemo ± Bev

- Persistent, recurrent, or metastatic cervical cancer not amenable to curative treatment
- No prior systemic chemotherapy
- ECOG PS 0-1



- Stratification factors: metastatic disease at diagnosis (yes vs no); PD-L1 CPS (<1 vs 1 to <10 vs ≥10); planned Bev use (yes vs no)

Endpoints
- Dual primary: OS and PFS
- Secondary: ORR, DOR, 12-mo PFS, and safety

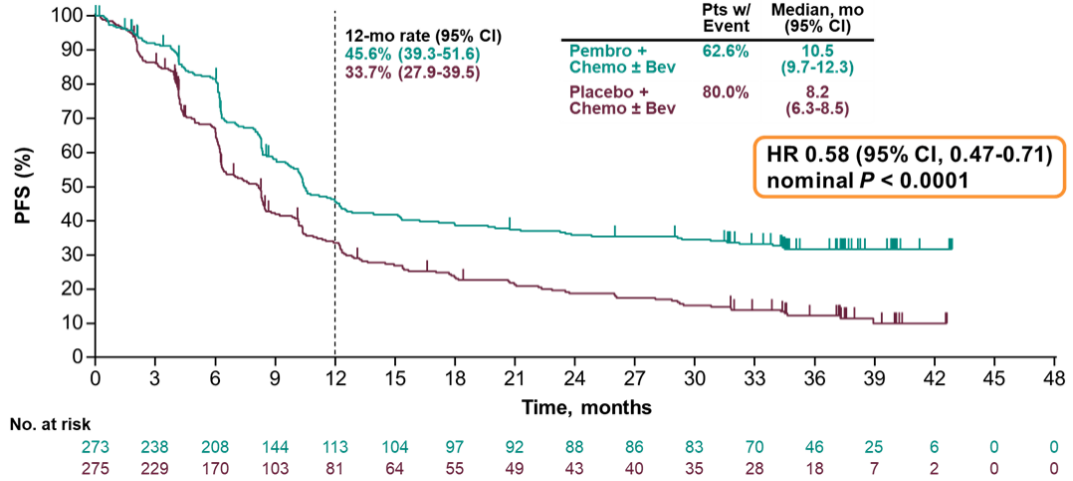
	Pembro + Chemo ± Bev (n=308)	Placebo + Chemo ± Bev (n=309)
Median age (range), y	51 (25-82)	50 (22-79)
ECOG PS 1, no. (%)	128 (42)	139 (45)
SCC, no. (%)	235 (76)	211 (68)
PD-L1 CPS, no. (%)		
<1	35 (11)	34 (11)
1 to <10	115 (37)	116 (38)
≥10	158 (51)	159 (51)
Bevacizumab use during trial, no. (%)	196 (64)	193 (62)

FDA approved October 2021 **in combination with chemotherapy, with or without bevacizumab**, for patients with persistent, recurrent, or metastatic cervical cancer **whose tumors express PD-L1 (CPS ≥1)**

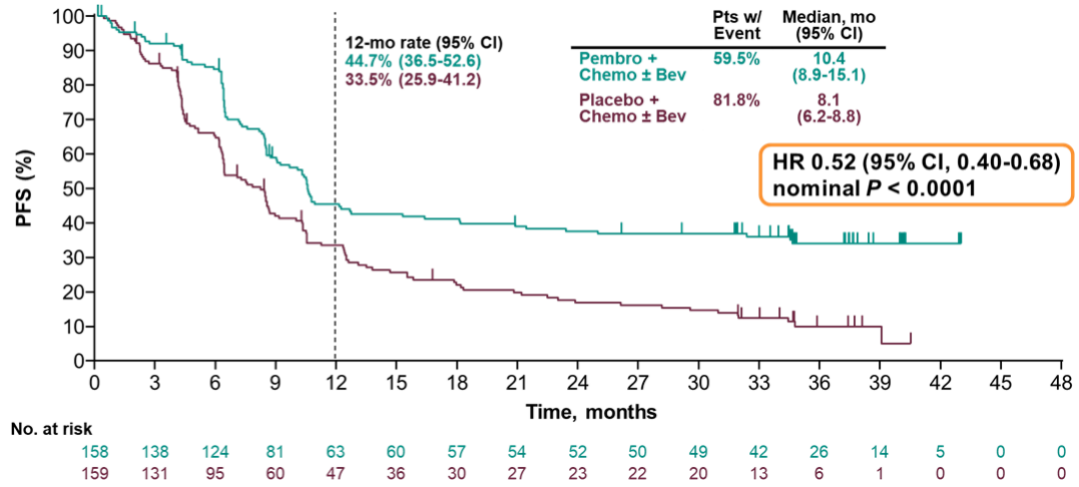
Monk BJ, et al. 2023 Annual ASCO Meeting. Abstract 5500.

KEYNOTE 826: PFS

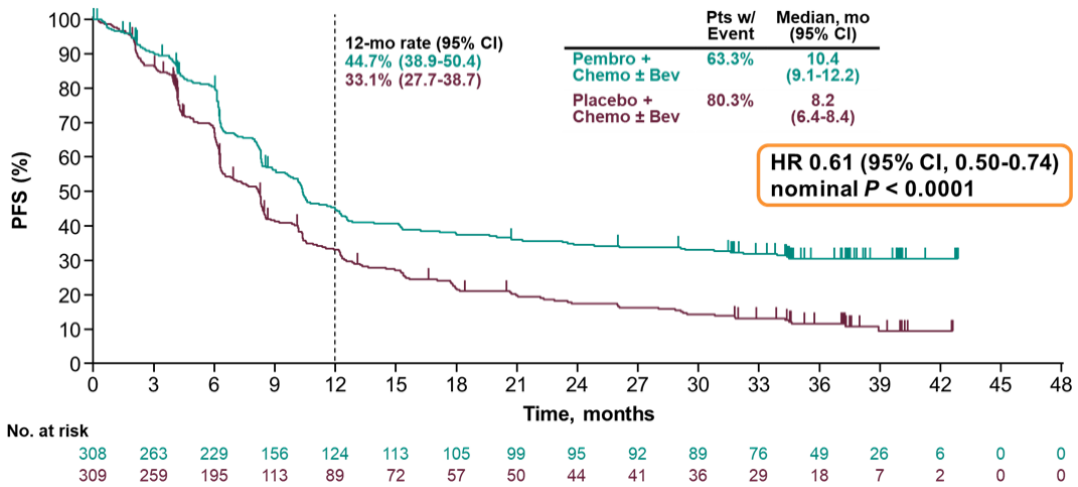
PD-L1 CPS ≥1 Population



PD-L1 CPS ≥10 Population



ITT Population



Pembrolizumab

Placebo

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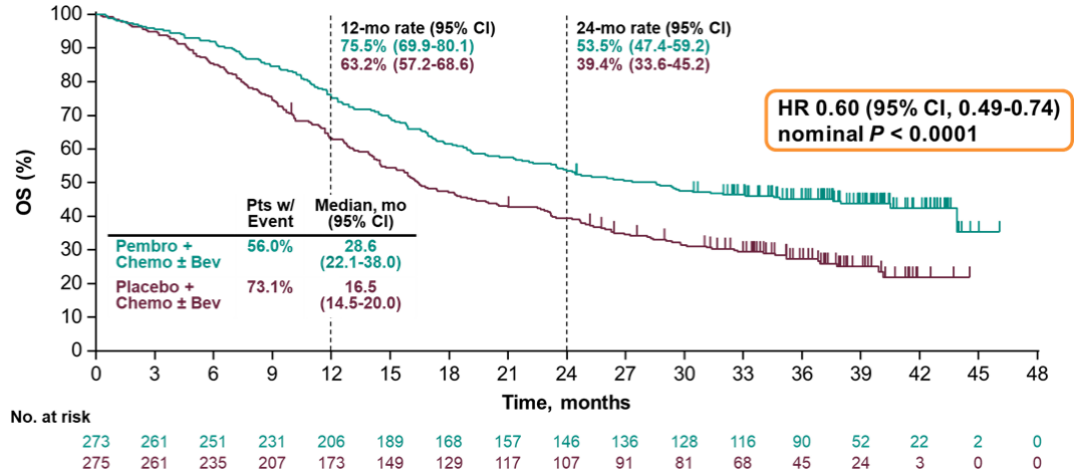
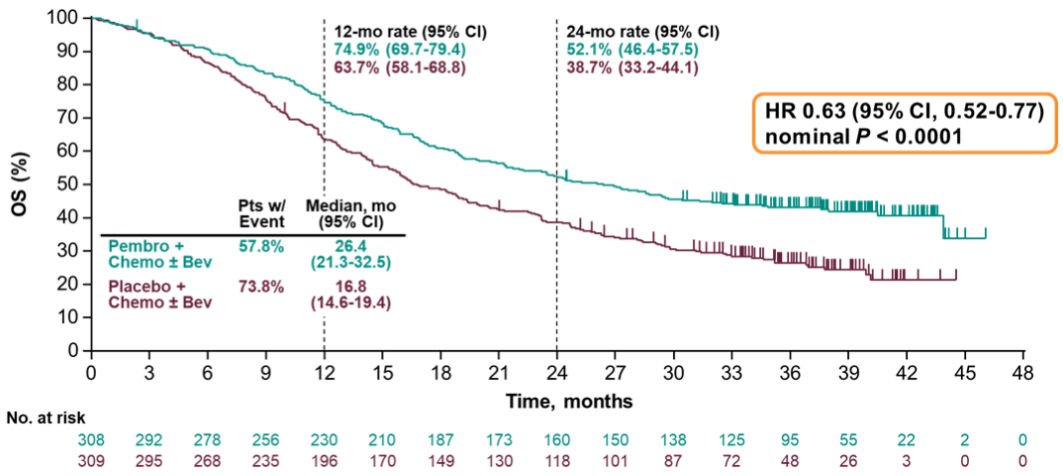
Monk BJ, et al. 2023 Annual ASCO Meeting. Abstract 5500.

KEYNOTE 826: OS

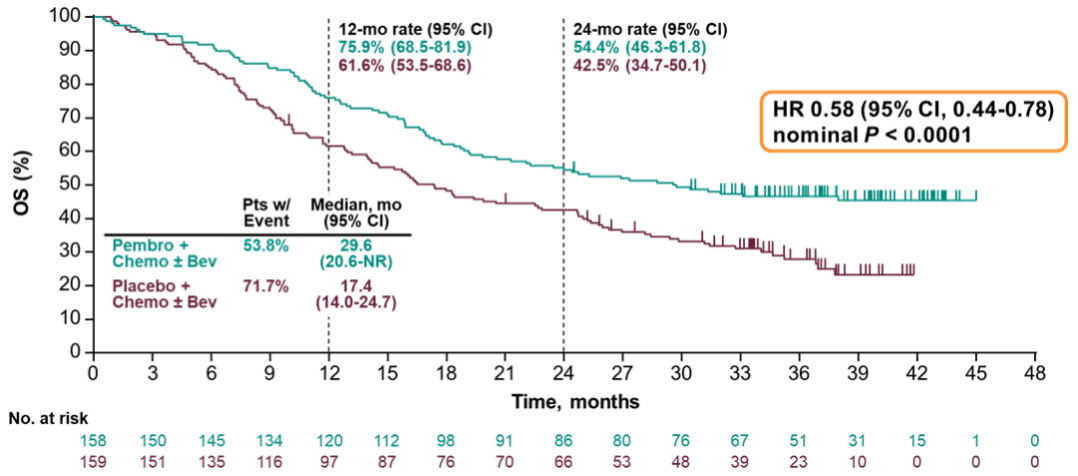
PD-L1 CPS ≥1 Population



ITT Population



PD-L1 CPS ≥10 Population



Pembrolizumab

Placebo

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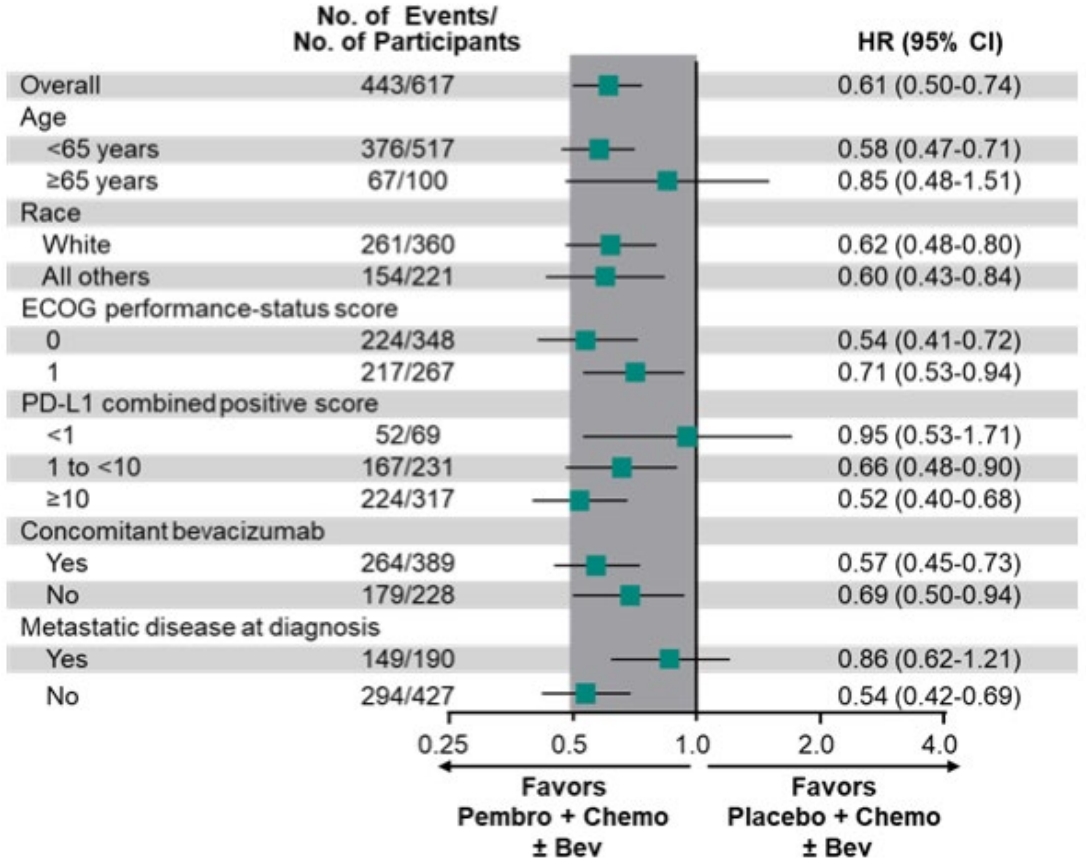
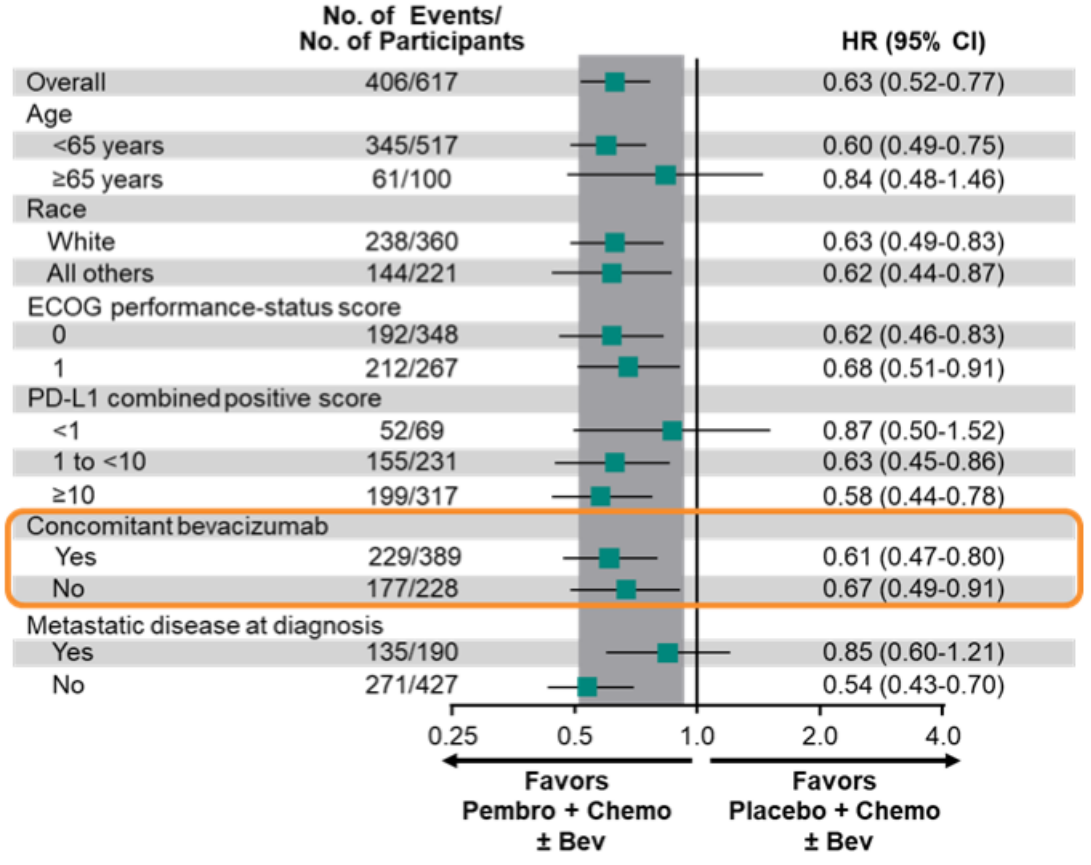
Monk BJ, et al. 2023 Annual ASCO Meeting. Abstract 5500.

KEYNOTE 826: ITT Population Subgroup Analysis

PFS



OS



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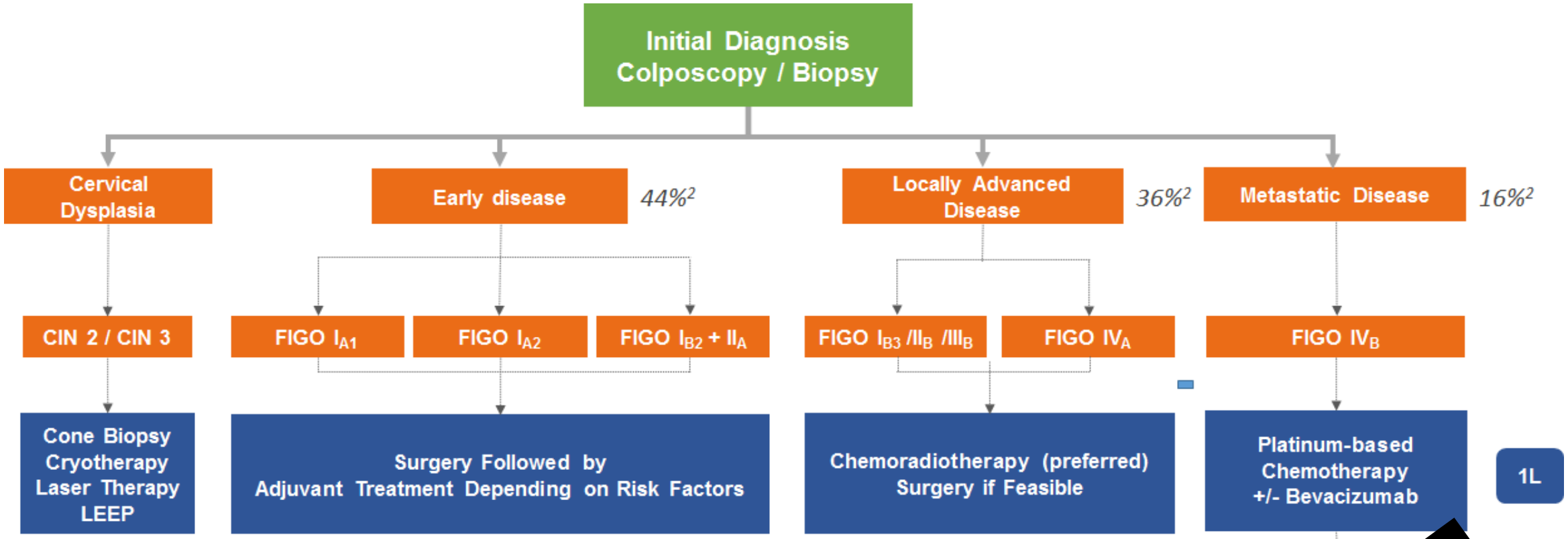
Cervical cancer treatment paradigm



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[1] NCCN Cervical Cancer Guidelines v2.2019
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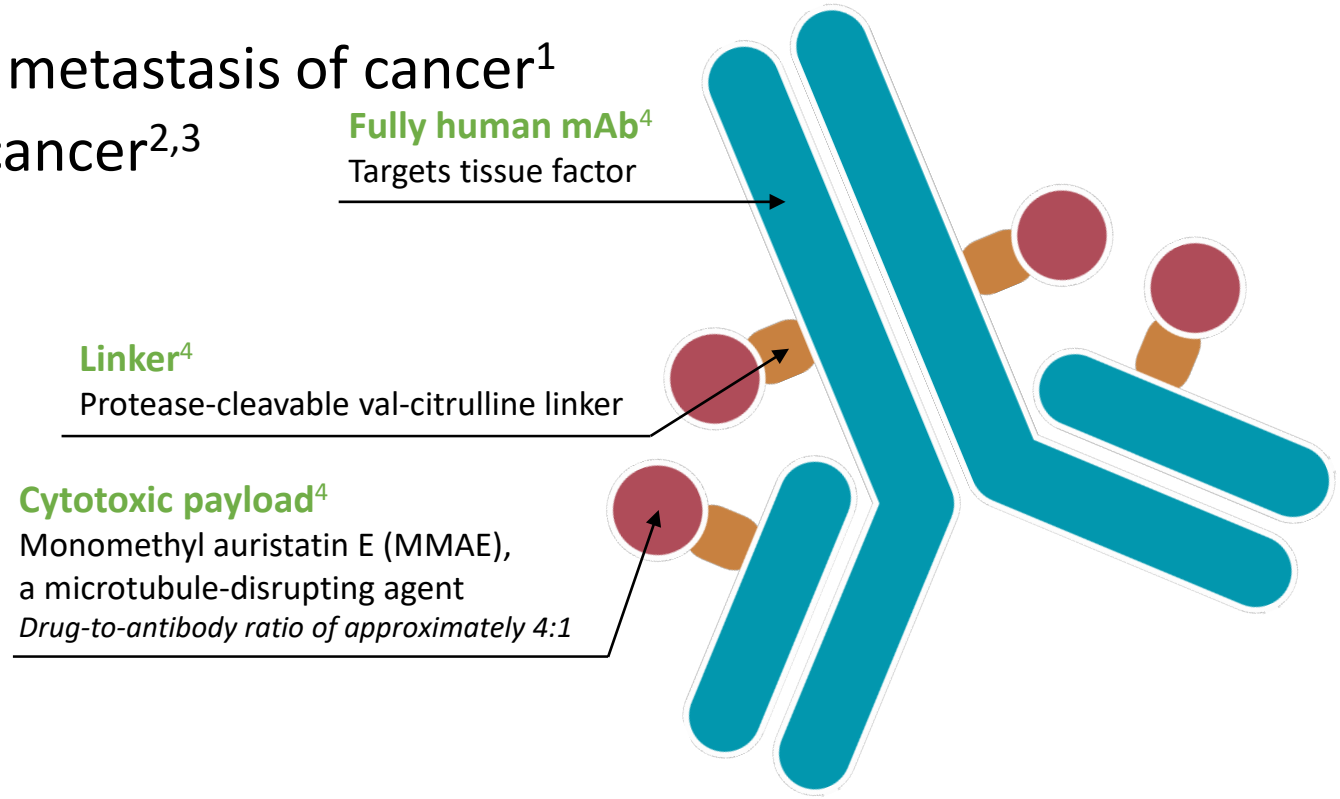
Tisotumab Vedotin (TV): A Tissue Factor-Directed ADC

- Tissue factor
  - Transmembrane protein that is the primary initiator of coagulation[1]
  - Involved in angiogenesis and metastasis of cancer[1]
  - Highly expressed in cervical cancer[2,3]



1. Versteeg HH, et al. *Semin Thromb Hemost*. 2015;41(7):747-755. **2.** Cocco E, et al. *BMC Cancer*. 2011;11:263. **3.** Zhao X, et al. *Exp Ther Med.* 2018;16(5):4075-4081. **4.** Tisotumab vedotin. Package insert. Seagen Inc.; 2023.

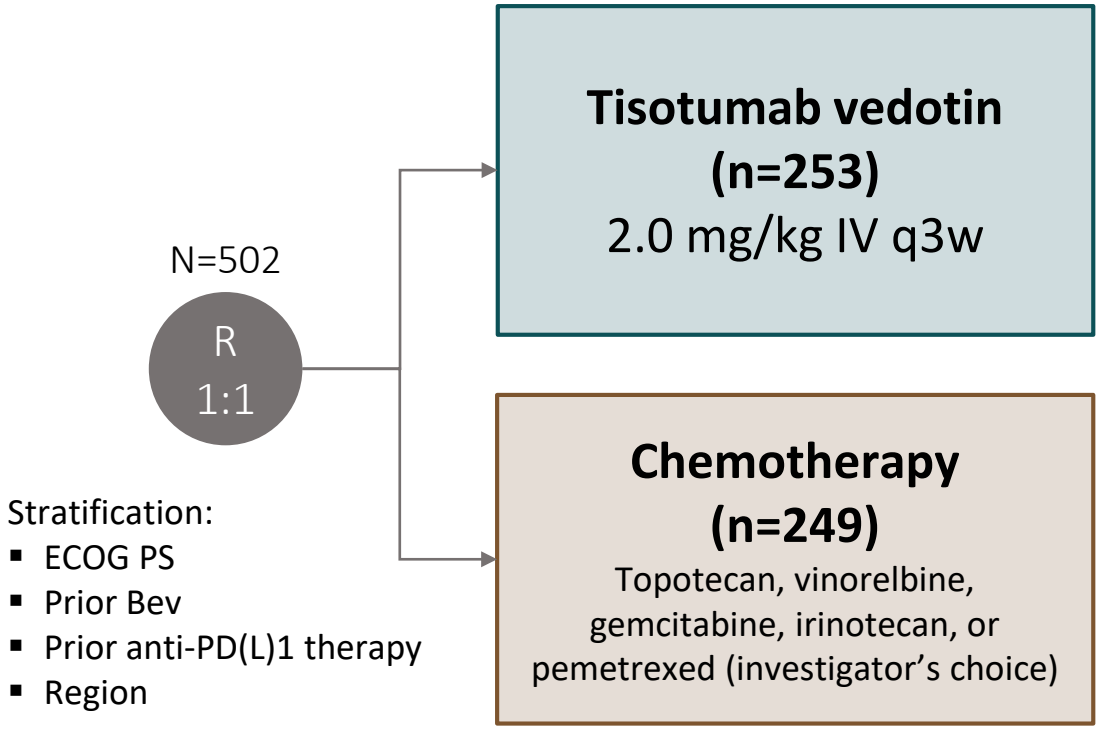
InnovaTV 301/ENGOT-cx12/GOG-3057: Phase 3 Trial of Tisotumab Vedotin vs Chemotherapy[1,2]

Key eligibility criteria

- Recurrent or metastatic cervical cancer
- Disease progression on or after chemotherapy doublet ± Bev and an anti-PD-(L)1 agent, if eligible and available
- ≤2 prior therapies for recurrent/metastatic disease
- ECOG PS 0-1

Primary endpoint: OS

Key secondary endpoints: PFS, ORR, safety



FDA approved September 2021 for the treatment of adult patients with recurrent or metastatic cervical cancer **with disease progression on or after chemotherapy**

Vergote I, et al. 2023 Annual ESMO Meeting. Abstract LBA9.

InnovaTV 301: Baseline Characteristics

	TV (N=253)	Chemo (N=249)
Median age, yrs (range)	51 (26-80)	50 (27-78)
ECOG PS, no. (%)		
0	137 (54.2)	136 (54.6)
1	116 (45.8)	113 (45.4)
Region, no. (%)		
United States	16 (6.3)	14 (5.6)
Europe	106 (41.9)	104 (41.8)
Asia	85 (33.6)	88 (35.3)
Other	46 (18.2)	43 (17.3)
Histology, no. (%)		
SCC	160 (63.2)	157 (63.1)
AC	85 (33.6)	75 (30.1)
ASC	8 (3.2)	17 (6.8)

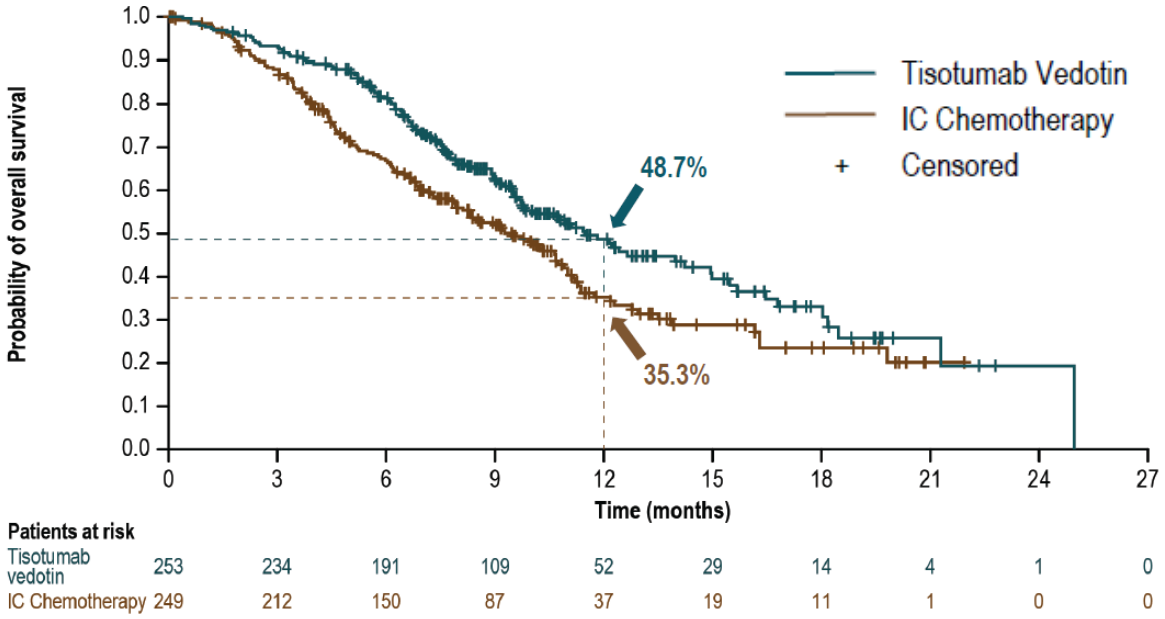
	TV (N=253)	Chemo (N=249)
Disease status at study entry, no. (%)		
Pelvic recurrent only	27 (10.7)	24 (9.6)
Extra-pelvic metastatic	226 (89.3)	225 (90.4)
Number of prior r/m systemic regimens, no. (%)		
0	159 (62.8)	149 (59.8)
1	93 (36.8)	100 (40.2)
Unknown	1 (0.4)	0
Prior Bev, no. (%)	164 (64.8)	157 (63.1)
Prior anti-PD-(L)1 therapy, no. (%)	71 (28.1)	67 (26.9)
Prior radiation therapy for cervical cancer, no. (%)	205 (81.0)	203 (81.5)
Biopsy evaluable, no. (%)	210 (83.0)	194 (77.9)
Positive membrane TF expression[a]	194 (92.4)	183 (94.3)

[a] TF expression is defined as TF membrane expression ≥1% with immunohistochemistry; percentages are calculated based on number of evaluable biopsies.

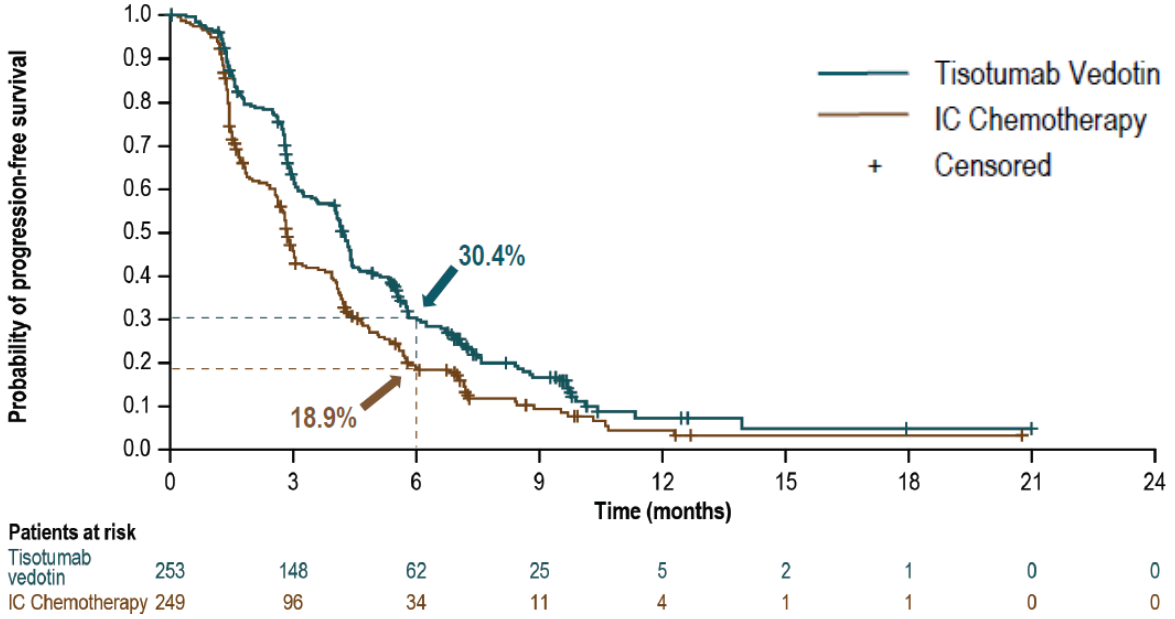
Vergote I, et al. 2023 Annual ESMO Meeting. Abstract LBA9.

InnovaTV 301: OS and PFS

	Events/ Total	mOS (95% CI)	HR (95% CI)	Stratified log-rank P value[a]
TV	123/253	11.5 (9.8-14.9)	0.70 (0.54-0.89)	0.0038
Chemo	140/249	9.5 (7.9-10.7)		



	Events/ Total	mPFS (95% CI)	HR (95% CI)	Stratified log-rank P value[b]
TV	198/253	4.2 (4.0-4.4)	0.67 (0.54-0.82)	<0.0001
Chemo	194/249	2.9 (2.6-3.1)		



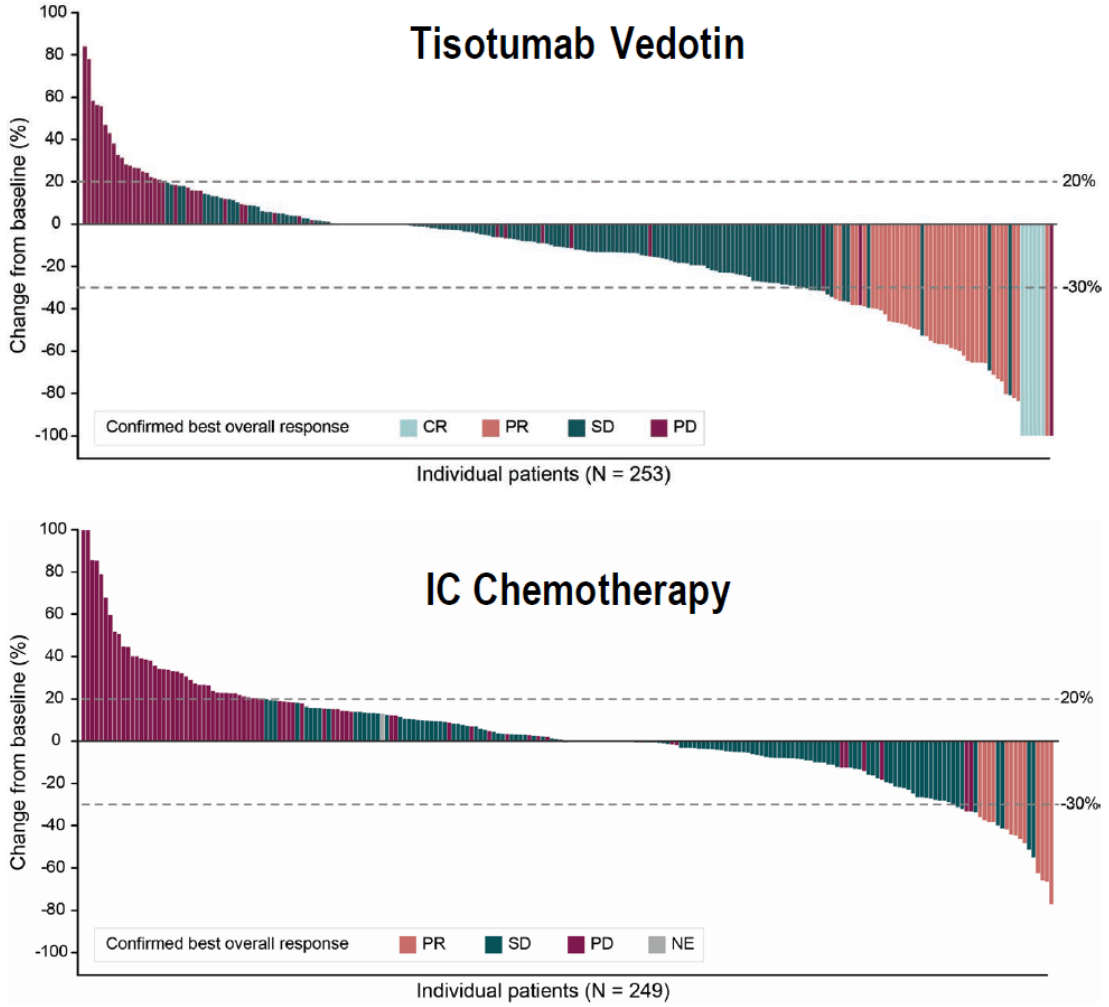
[a] The threshold for statistical significance is 0.0226 (2-sided), based on the actual number of OS events at interim analysis.

[b] The threshold for statistical significance is 0.0453 (2-sided), based on the actual number of PFS events at interim analysis.

Vergote I, et al. 2023 Annual ESMO Meeting. Abstract LBA9.

InnovaTV 301: Antitumor Activity

	TV (N=253)	Chemo (N=249)
ORR, % (95% CI)	17.8 (13.3-23.1)	5.2 (2.8-8.8)
Odds ratio (95% CI)	4.0 (2.1-7.6)	
P value	<0.0001	
Best overall response, no. (%)		
CR	6 (2.4)	0
PR	39 (15.4)	13 (5.2)
SD	147 (58.1)	132 (53.0)
PD	46 (18.2)	74 (29.7)
Not evaluable	15 (5.9)	30 (12.0)
DCR[a], % (95% CI)	**75.9** (70.1-81.0)	**58.2** (51.8-64.4)
mDOR (95% CI)	**5.3** (4.2-8.3)	**5.7** (2.8-NR)



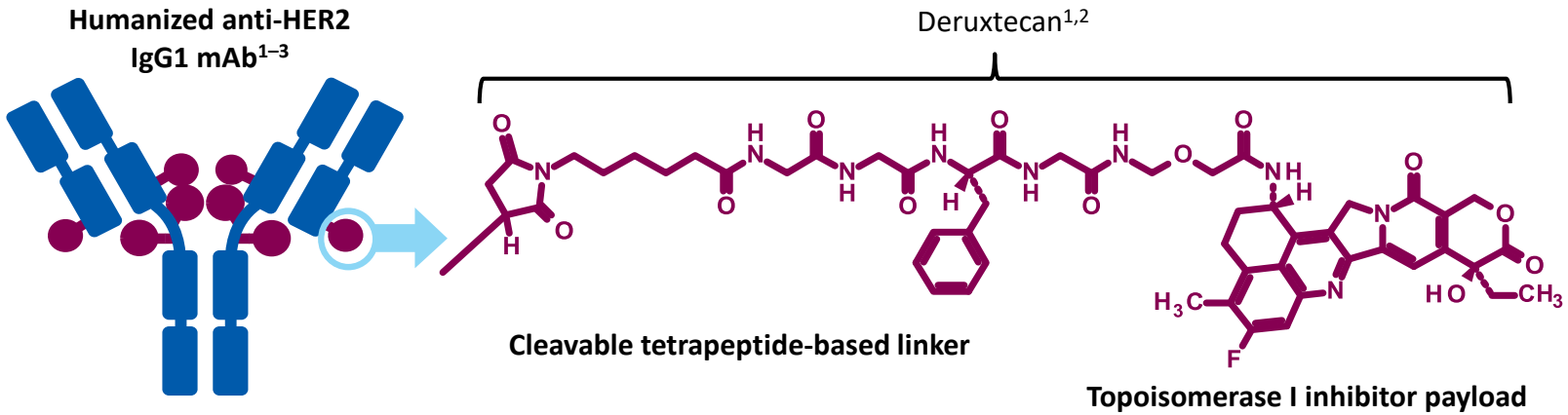
[a] DCR defined as CR+PR+SD; CR and PR were confirmed responses. The minimum criteria for SD duration was ≥5 weeks after the date of randomization.

Vergote I, et al. 2023 Annual ESMO Meeting. Abstract LBA9.

Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: DESTINY-PanTumor02 interim results

T-DXd is an ADC with three components:

1. A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
2. A topoisomerase I inhibitor payload, an exatecan derivative
3. A tetrapeptide-based cleavable linker



[a]The clinical relevance of these features is under investigation. ADC, antibody–drug conjugate; HER2, human epidermal growth factor receptor 2; IgG1, immunoglobulin G1; mAb, monoclonal antibody; T-DXd, trastuzumab deruxtecan.

1. 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.

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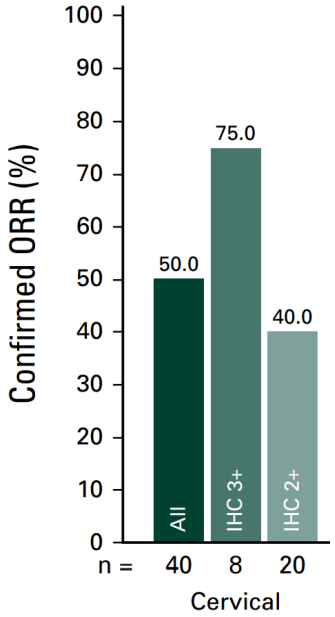
DESTINY-PanTumor02: Phase 2 Trial of T-DXd for Previously Treated HER2-Expressing Solid Tumors

Key eligibility criteria
- Locally advanced, unresectable, or metastatic solid cancers
- ≥1 prior systemic treatment
- HER2 IHC 3+ or 2+ (gastric scoring)
- ECOG PS 0-1

T-DXd
5.4 mg/kg q3w IV
(n=40 cervical)
(N=268 all cohorts)

Primary endpoint: Investigator-assessed ORR
Secondary endpoints: DOR, DCR, PFS, OS, safety

Median follow-up duration (all cohorts):
12.75 mo (range, 0.4-31.6)



	Cervical
	Total (N=40)
Best overall response, no. (%)	
CR	2 (5)
PR	18 (45)
SD	11 (27.5)
PD	7 (17.5)
NE	1 (2.5)

	Cervical		
	Total (N=40)	**IHC 3+** (n=8)	**IHC 2+** (n=20)
mDOR[a], mo (95% CI)	**14.2** (4.1-NR)	-	-
mPFS, mo (95% CI)	**7.0** (4.2-11.1)	**NR** (3.9-NR)	**4.8** (2.7-5.7)
mOS, mo (95% CI)	**13.6** (11.1-NR)	**NR** (3.9-NR)	**11.5** (5.1-NR)

Safety summary (N=267, all tumor cohorts)
- Grade ≥3 drug-related AE: 40.8%
- Drug-related ILD/pneumonitis: 10.5% [3 (1.1%) fatal]
- Drug-related AE resulting in death: 4 (1.5%)
- Drug-related AE leading to discontinuation: 8.6%

T-DXd is not FDA approved for cervical cancer; it is included in the **NCCN Guidelines®** for HER2-positive tumors **IHC 3+ or 2+**

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[a] DOR includes only patients with an objective response.

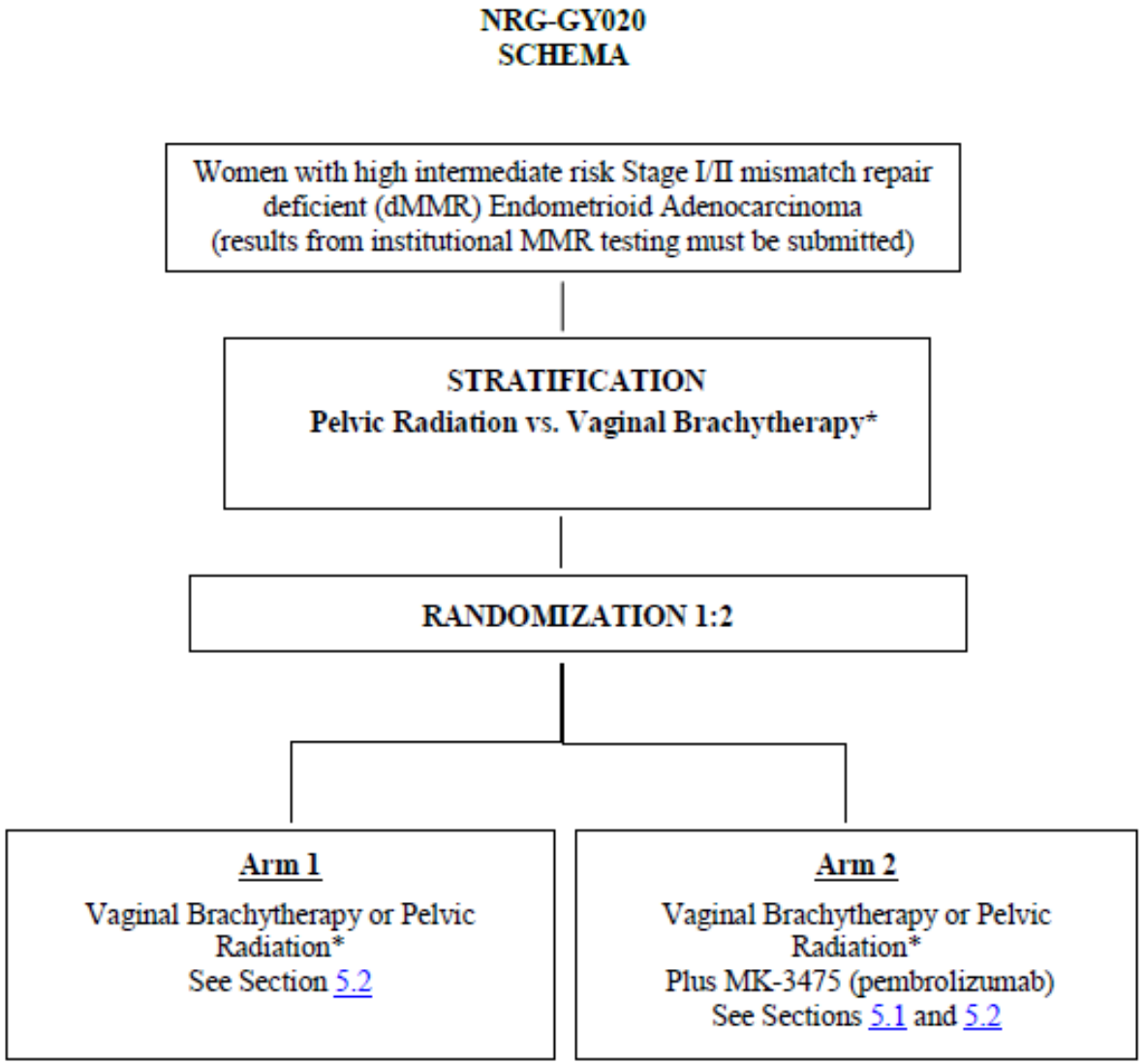
Meric-Bernstam F, et al. J Clin Oncol. 2023. DOI: 10.1200/JCO.23.02005

Endometrial cancer

- Additional of immunotherapy to first line treatment
- Antibody drug conjugates

Immunotherapy for early stage EC

GY020



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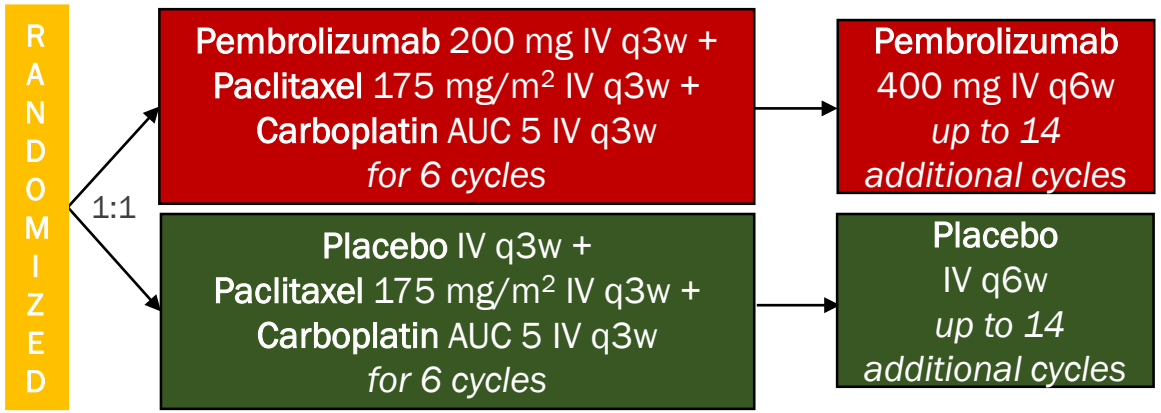
NRG GY018: Phase 3 Trial of Pembrolizumab + Chemo for Measurable Stage 3 or 4a, Stage 4b, or Recurrent EC – Study Design and Patients

Key Eligibility Criteria

- Measurable stage III/IVA or measurable/nonmeasurable stage IVB or recurrent EC
- MMR IHC testing
- ECOG PS 0-2
- No prior Chemo except adjuvant Chemo if completed ≥12 mo before study



Stratified by MMR status (pMMR vs dMMR), ECOG status, and prior adjuvant Chemo

Primary endpoints: PFS per RECIST v1.1 by INV in pMMR and dMMR cohorts
Secondary endpoints: Safety, ORR/DOR, OS, PRO/QoL, concordance of MMR testing results

Patient Characteristics, n (%)		dMMR (n=225)		pMMR (n=588)	
		Pembro + CT (n=112)	Placebo + CT (n=113)	Pembro + CT (n=293)	Placebo + CT (n=295)
Median age (range), years		67 (38-81)	66 (37-85)	66 (31-93)	65 (29-90)
ECOG PS	0	72 (64.3)	73 (64.6)	196 (66.9)	198 (67.1)
	1	39 (34.8)	35 (31.0)	88 (30.0)	88 (29.8)
	2	1 (0.9)	5 (4.4)	9 (3.1)	9 (3.1)
Histology					
Clear cell		1 (0.9)	0	17 (5.8)	20 (6.8)
Endometrioid, G1		21 (18.8)	35 (31.0)	54 (18.4)	46 (15.6)
Endometrioid, G2		52 (46.4)	41 (36.3)	51 (17.4)	58 (19.7)
Endometrioid, G3		15 (13.4)	16 (14.2)	53 (18.1)	42 (14.2)
Serous		4 (3.6)	1 (0.9)	78 (26.6)	72 (24.4)
No prior chemotherapy		107 (95.5)	105 (92.9)	221 (75.4)	218 (73.9)

Data cutoff: December 16, 2022 for dMMR; December 6, 2022 for pMMR.
Eskander R, et al. SGO 2023. Abstract 264.

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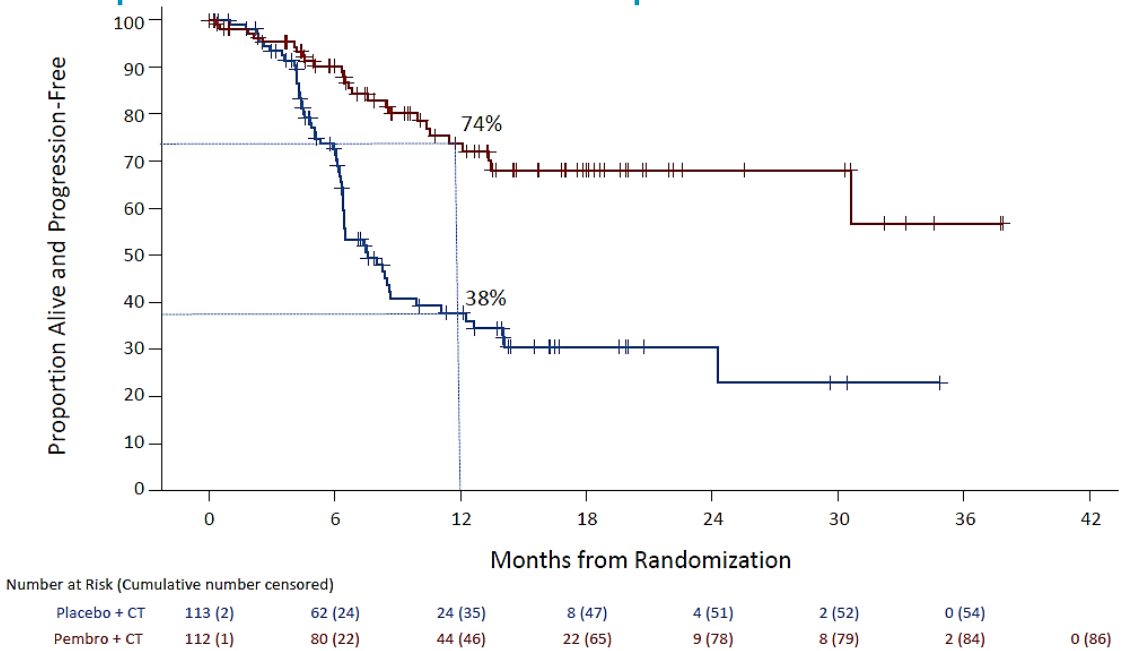
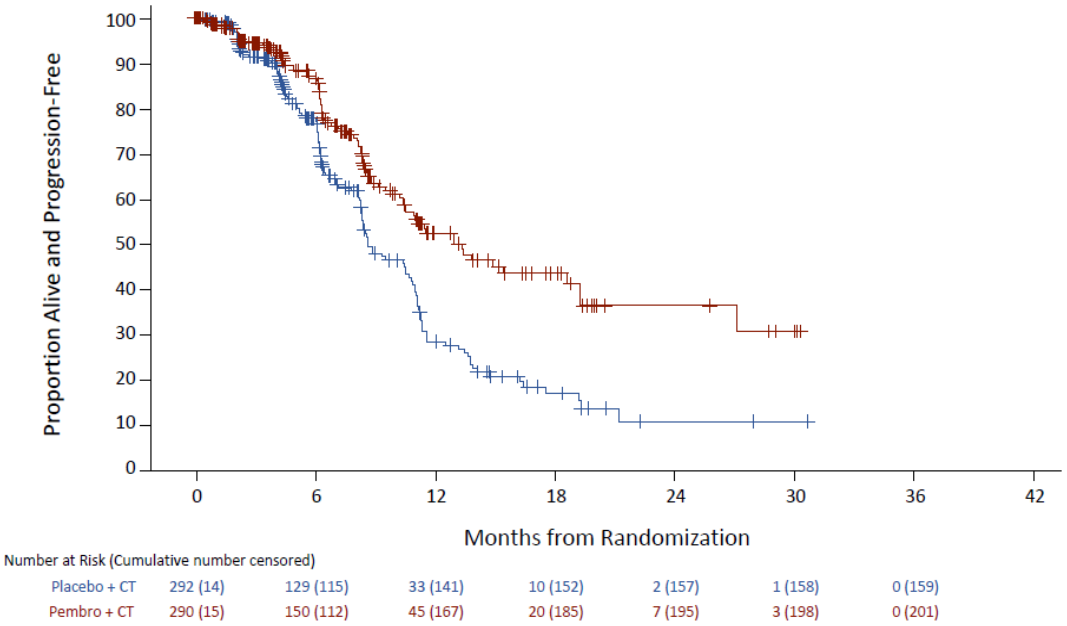
NRG GY018: Phase 3 Trial of Pembrolizumab + Chemo for Measurable Stage 3 or 4a, Stage 4b, or Recurrent EC – PFS

PFS per RECIST v1.1 in dMMR Population



	Events, n/N	Median (95% CI), mo	HR (stratified; 95% CI)
Pembro + CT	26/112	NR (30.6-NR)	**0.30 (0.19-0.48)**
Placebo + CT	59/113	7.6 (6.4-9.9)	***P*<0.00001**

PFS per RECIST v1.1 in pMMR Population



	Events, n/N	Median (95% CI), mo	HR (stratified; 95% CI)
Pembro + CT	89/290	13.1 (10.5-18.8)	**0.54 (0.41-0.71)**
Placebo + CT	133/292	8.7 (8.4-10.7)	***P*<0.00001**

- Median follow-up: 12 months for dMMR, 7.9 months for pMMR

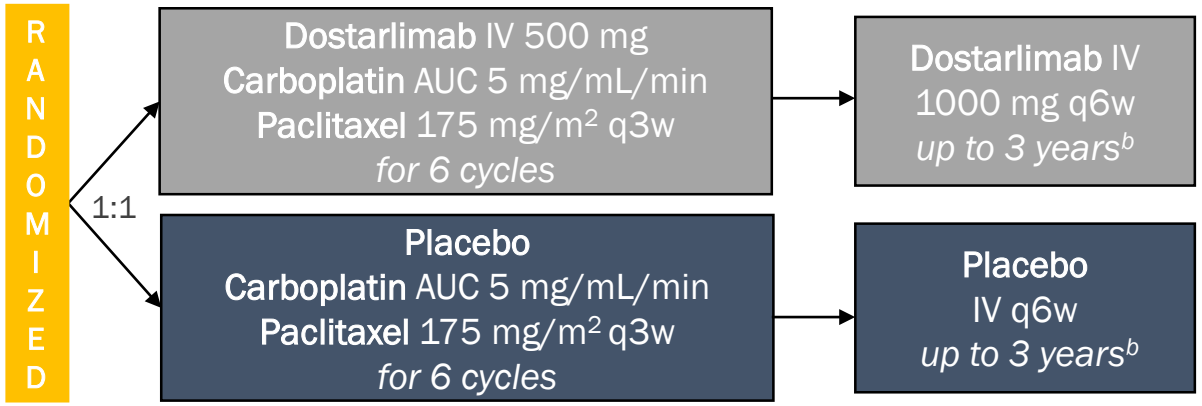
Data cutoff: December 16, 2022 for dMMR; December 6, 2022 for pMMR.
Eskander R, et al. SGO 2023. Abstract 264.

UC San Diego SCHOOL OF MEDICINE

GOG-3031/RUBY: Phase 3 Trial of Dostarlimab + Chemo for Primary Advanced/Recurrent EC – Study Design and Patients

Key Eligibility Criteria

- Histologically/cytologically proven stage III/IV or first recurrent EC
- Carcinosarcoma, clear cell, serous, or mixed histology permitted[a]
- ECOG PS 0-1
- Naive to systemic therapy or systemic anticancer therapy and had a recurrence or PD ≥6 months after completing treatment



Stratified by MMR/MSI status,[c] prior external pelvic radiotherapy, and disease status

Primary endpoints: PFS by INV, OS
Secondary endpoints: PFS by BICR, PFS2, ORR, DOR, DCR, HRQOL/PRO, safety

Patient Characteristics, n(%)		dMMR/MSI-H		Overall	
		Dostarlimab + CP (n=53)	Placebo + CP (n=65)	Dostarlimab + CP (n=245)	Placebo + CP (n=249)
Median age (range), years		61 (45-81)	66 (39-85)	64 (41-81)	65 (28-85)
ECOG PS	0	28 (53.8)	39 (60.0)	145 (60.2)	160 (65.0)
	1	24 (46.2)	26 (40.0)	96 (39.8)	86 (35.0)
Histology					
Clear cell		0	0	8 (3.3)	9 (3.6)
Carcinosarcoma		4 (7.5)	1 (1.5)	25 (10.2)	19 (7.6)
Endometrioid		44 (83.0)	56 (86.2)	134 (54.7)	136 (54.6)
Prior systemic therapy		7 (13.2)	10 (15.4)	48 (19.6)	52 (20.9)
Carboplatin/ paclitaxel		4 (7.5)	6 (9.2)	36 (14.7)	39 (15.7)
Measurable disease at baseline		49 (92.5)	58 (89.2)	212 (86.5)	219 (88.0)

•[a] Mixed histology containing at least 10% carcinosarcoma, clear cell, or serous histology. [b] Treatment ends after 3 years. [c] Patients were randomized based on either local or central MMR/MSI testing results. For local determination of MMR/MSI status, IHC, NGS, and PCR assays were accepted. For central determination of MMR/MSI status IHC per Ventana MMR RxDx Panel was used. Central testing was used when local results were not available.

•Mirza MR, et al. SGO 2023. Abstract 265.

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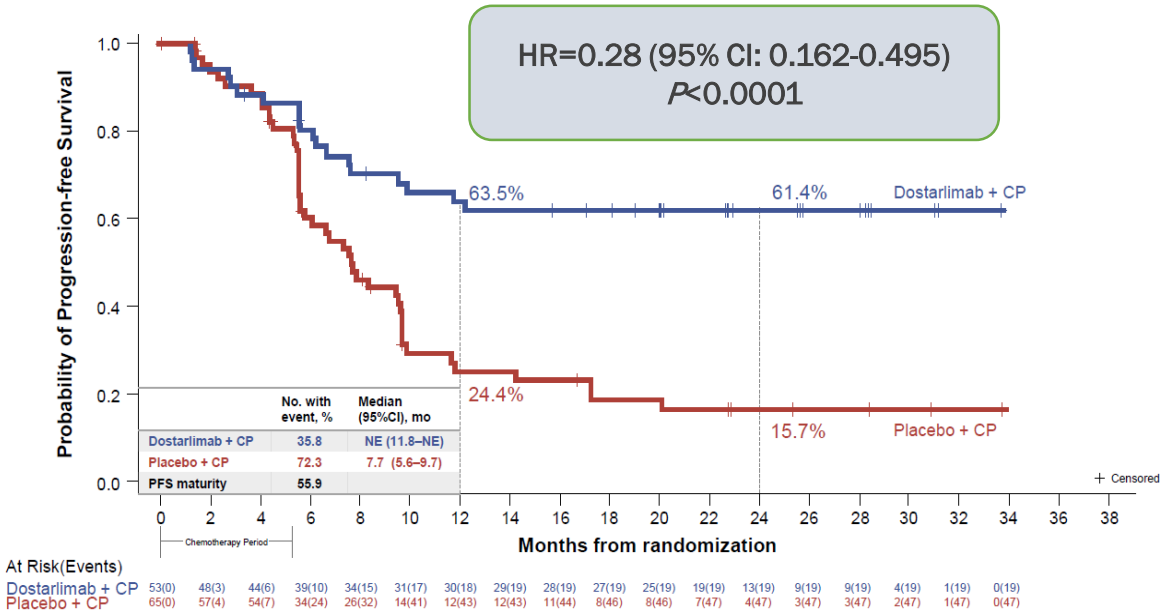
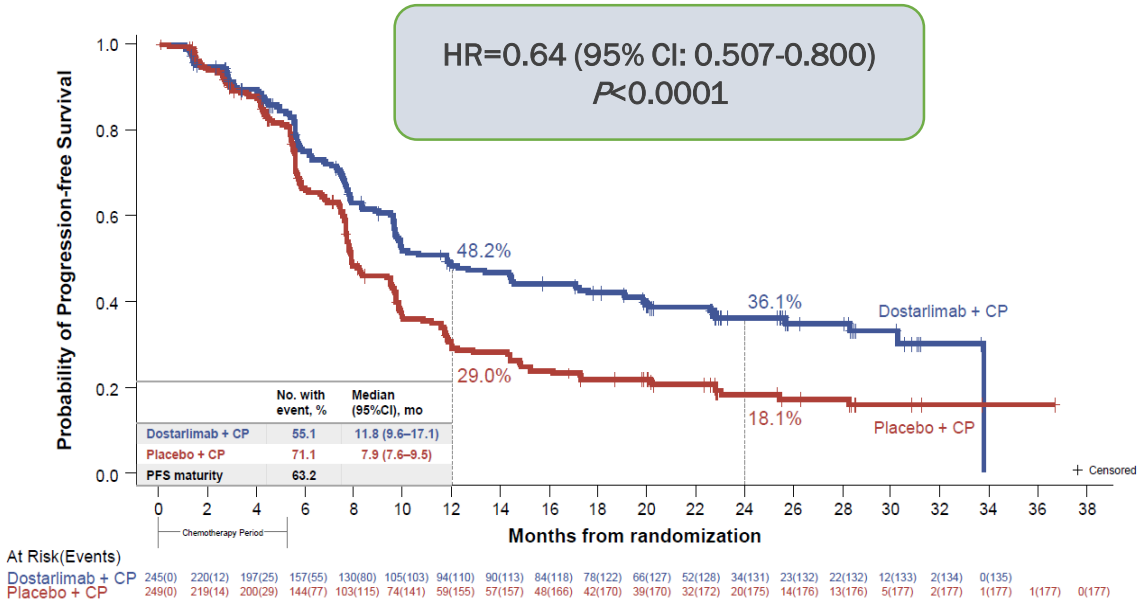
GOG-3031/RUBY: Phase 3 Trial of Dostarlimab + Chemo for Primary Advanced/Recurrent EC – PFS

PFS in dMMR/MSI-H Population



PFS in Overall Population



- Median duration of follow-up in the dMMR/MSI-H population was 24.79 months
- Median duration of follow-up in the overall population was 25.38 months

Data cutoff: September 28, 2022.
Mirza MR, et al. SGO 2023. Abstract 265.

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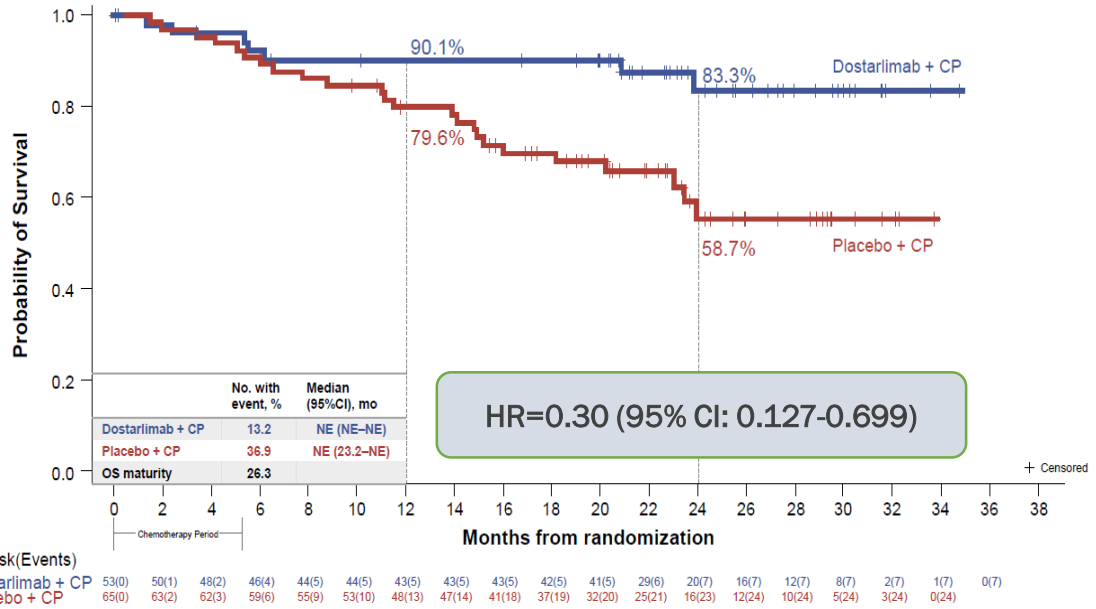
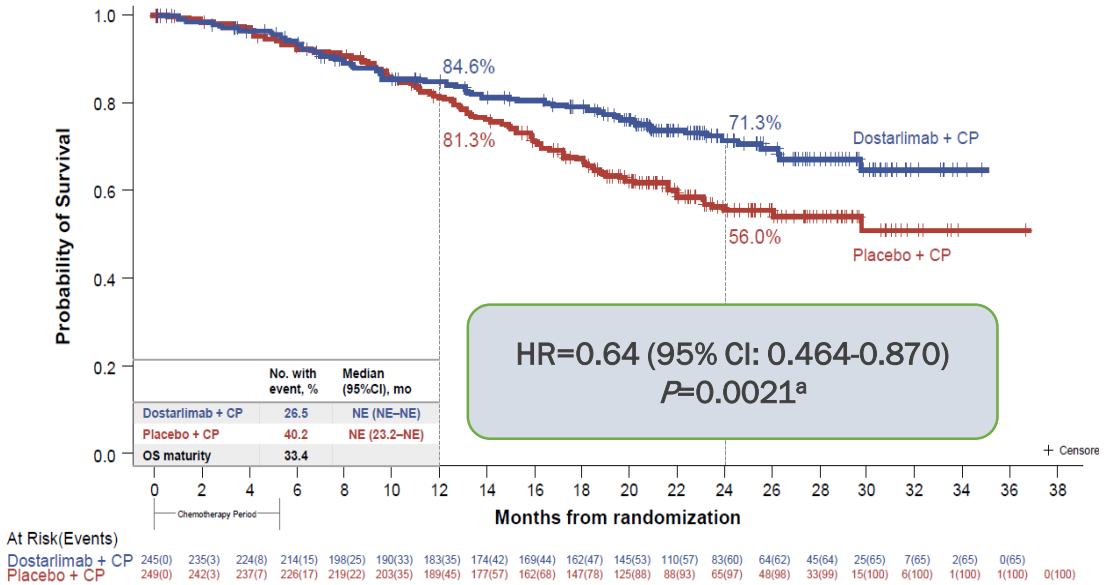
GOG-3031/RUBY: Phase 3 Trial of Dostarlimab + Chemo for Primary Advanced/Recurrent EC – OS

OS in dMMR/MSI-H Population



Received subsequent immunotherapy:
- 38.5% of patients on placebo arm
- 15.1% of patients on dostarlimab arm

OS in Overall Population (33% Maturity)



Received subsequent immunotherapy:
- 34.5% of patients on placebo arm
- 15.5% of patients on dostarlimab arm

Data cutoff: September 28, 2022. Median duration of follow-up in overall population was 25.38 months.
[a] $P \leq 0.00177$ required to declare statistical significance at first interim analysis.
Mirza MR, et al. SGO 2023. Abstract 265.

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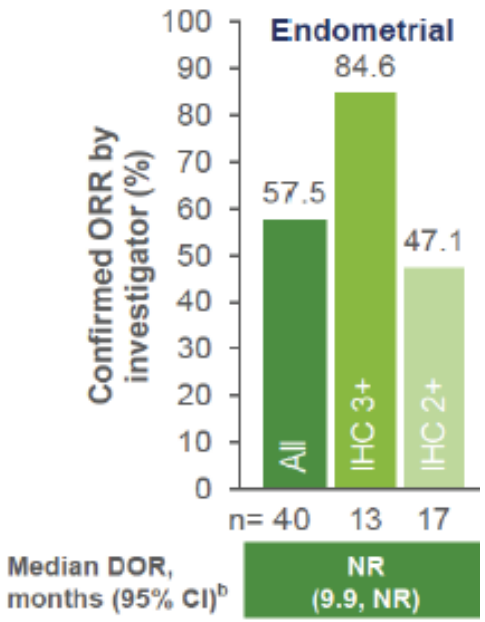
DESTINY-PanTumor02: Phase 2 Trial of T-DXd for Previously Treated HER2-Expressing Solid Tumors

Key eligibility criteria
- Locally advanced, unresectable, or metastatic solid cancers
- ≥1 prior systemic treatment
- HER2 IHC 3+ or 2+ (gastric scoring)
- ECOG PS 0-1

T-DXd
5.4 mg/kg q3w IV
(n=40 cervical)
(N=268 all cohorts)

Primary endpoint: Investigator-assessed ORR
Secondary endpoints: DOR, DCR, PFS, OS, safety

Median follow-up duration (all cohorts):
12.75 mo (range, 0.4-31.6)



	Endometrial
	Total (N=40)
Best overall response, no. (%)	
CR	7 (17.5)
PR	16 (40)
SD	13 (32.5)
PD	4 (10)
NE	0

	Endometrial		
	Total (N=40)	**IHC 3+** (n=)	**IHC 2+** (n=)
mDOR[a], mo (95% CI)	NR (9.9-NR)	-	-
mPFS, mo (95% CI)	**11.1**		
mOS, mo (95% CI)	**26**		

T-DXd is not FDA approved for endometrial cancer; it is included in the **NCCN Guidelines**® for HER2-positive tumors **IHC 3+ or 2+**

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Funda Meric-Bernstam, MD et al.
ASCO 2023

[a] DOR includes only patients with an objective response.

Meric-Bernstam F, et al. J Clin Oncol. 2023. DOI: 10.1200/JCO.23.02005

Agenda

- Cervical Cancer
  - Is conservative surgery acceptable? SHAPE and ROCC trials
  - Immunotherapy in front line treatment of metastatic or recurrent cervical cancer
  - Introduction of Antibody Drug Conjugates to the treatment of cervical cancer
- Endometrial Cancer
  - Immunotherapy in front line treatment of metastatic and recurrent endometrial cancer
  - Introduction of Antibody Drug Conjugates to the treatment of endometrial cancer

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Collaborators

Ramez Eskander, MD

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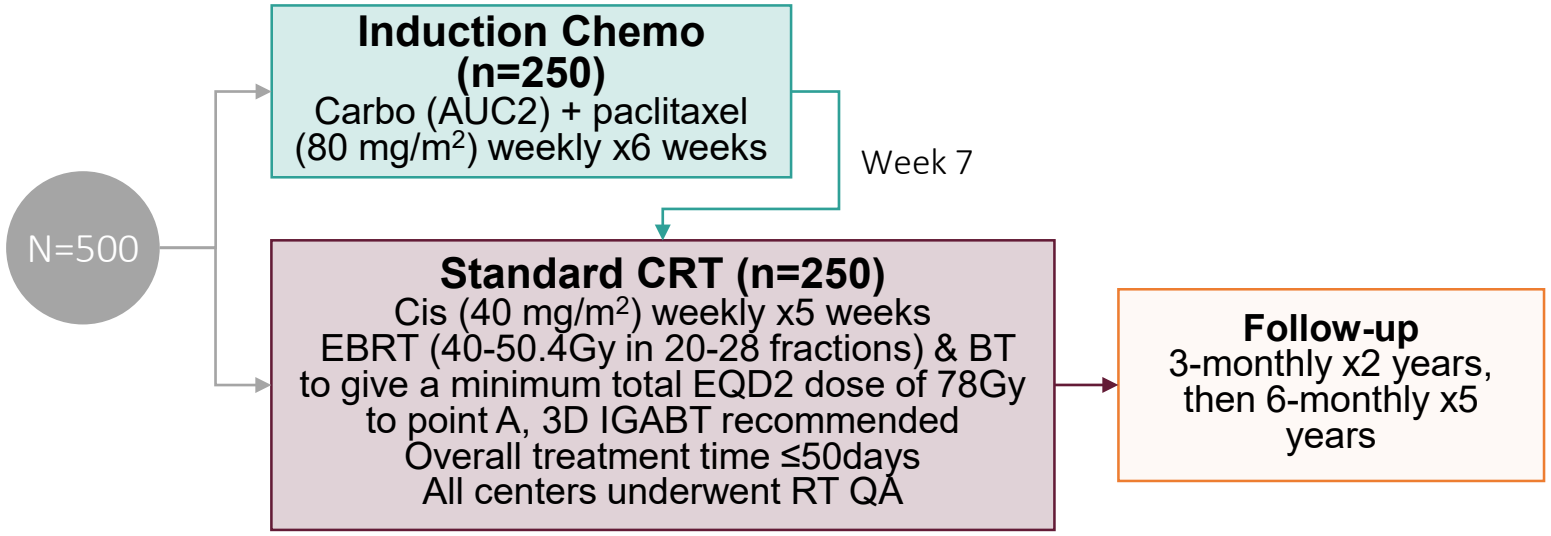
INTERLACE: Phase 3 Trial of Induction Chemo Followed by Chemoradiation

- FIGO (2008) stages IB1 node+, IB2, II, IIIB, IVA cervical cancer
- No nodes above aortic bifurcation on imaging
- Fit for Chemo and radical RT
- No prior pelvic RT

- Stratification factors: site, stage, nodal status, 3D-conformal vs IMRT EBRT, 2D vs 3D brachytherapy, tumor size, SCC vs other.

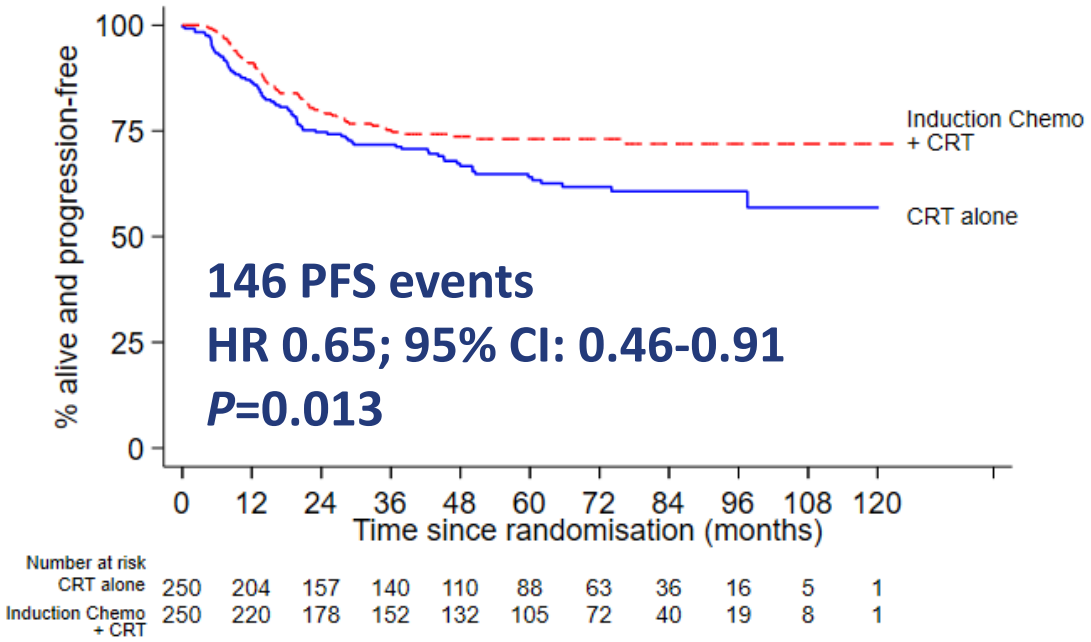


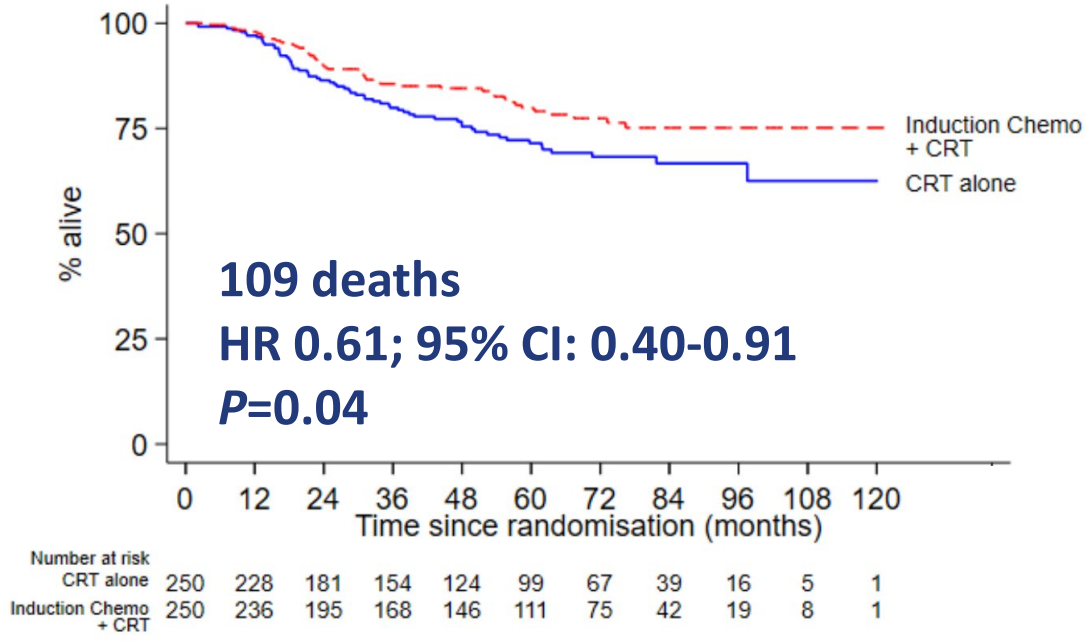
Endpoints

- Primary: PFS and OS
- Key secondary: AEs, pattern of relapse, QOL, time to subsequent treatment

McCormack M, et al. 2023 ESMO Annual Meeting. Abstract LBA8

INTERLACE: PFS and OS (median follow-up 64 mo)





	Induction Chemo + CRT (n=250)	CRT alone (n=250)
3yr PFS	75%	72%
5yr PFS	73%	64%

	Induction Chemo + CRT (n=250)	CRT alone (n=250)
3yr OS	86%	80%
5yr OS	80%	72%

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McCormack M, et al. 2023 ESMO Annual Meeting. Abstract LBA8

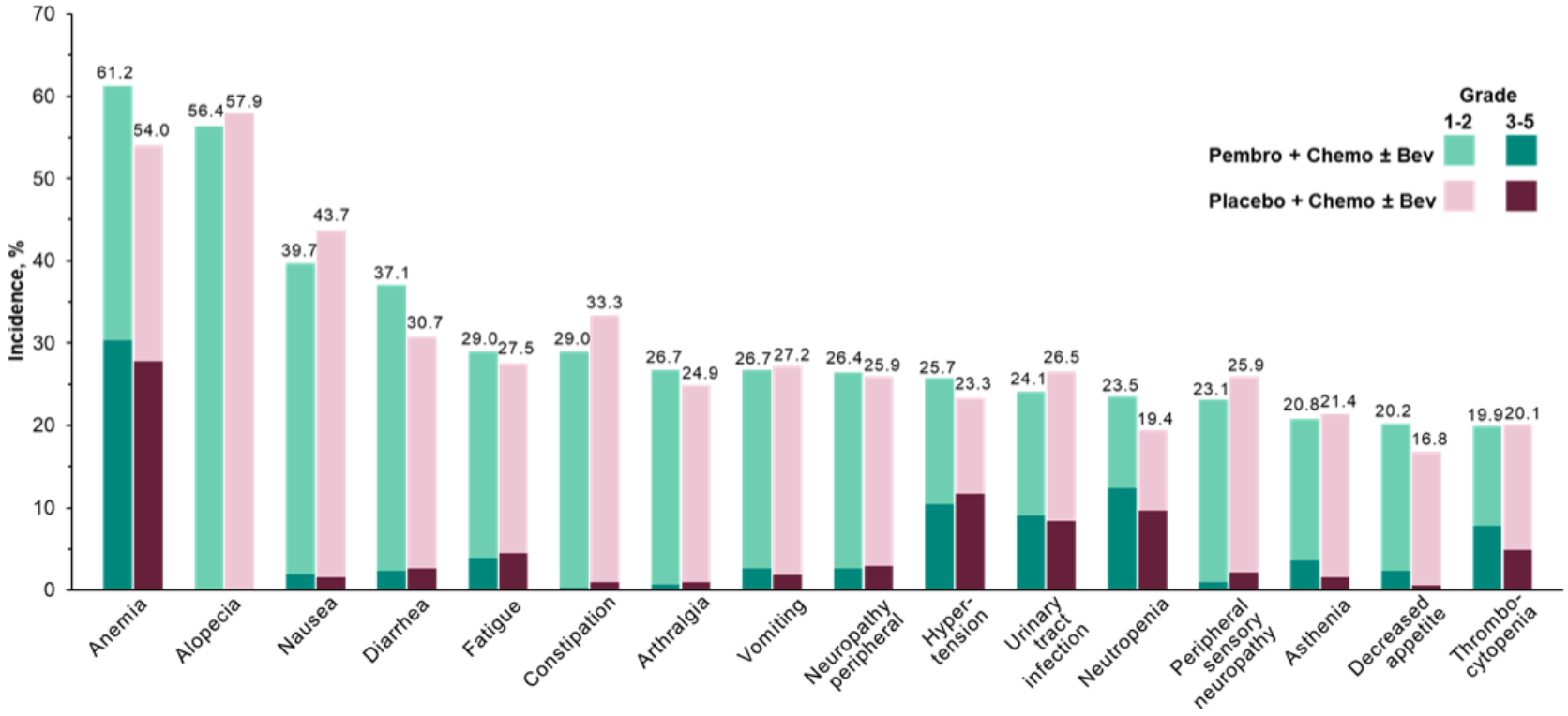
KEYNOTE-A18: Safety

	All-Cause AEs		Treatment-Related AEs		Immune-Mediated AEs	
	Pembro Arm (N=528)	Placebo Arm (N=530)	Pembro Arm (N=528)	Placebo Arm (N=530)	Pembro Arm (N=528)	Placebo Arm (N=530)
Any grade	525 (99.4%)	526 (99.2%)	507 (96.0%)	509 (96.0%)	172 (32.6%)	62 (11.7%)
Grade ≥3	394 (74.6%)	364 (68.7%)	354 (67.0%)	321 (60.6%)	22 (4.2%)	6 (1.1%)
Serious	150 (28.4%)	131 (24.7%)	91 (17.2%)	65 (12.3%)	15 (2.8%)	6 (1.1%)
Led to death	5 (0.9%)	6 (1.1%)	2 (0.4%)	2 (0.4%)	0	0
Led to discontinuation						
Any treatment	92 (17.4%)	75 (14.2%)	81 (15.3%)	67 (12.6%)	12 (2.3%)	2 (0.4%)
All treatment	1 (0.2%)	2 (0.4%)	0	1 (0.2%)	0	0

Lorusso D, et al. 2023 Annual ESMO Meeting. Abstract LBA38.

KEYNOTE 826: Adverse Events

All-Cause Adverse Events, Incidence ≥20% in Either Arm



Potentially immune-mediated AEs	
Pembrolizumab group (n=307)	
Any grade	Grade 3-5
34.5%	12.1%
Placebo group (n=309)	
Any grade	Grade 3-5
16.5%	2.9%

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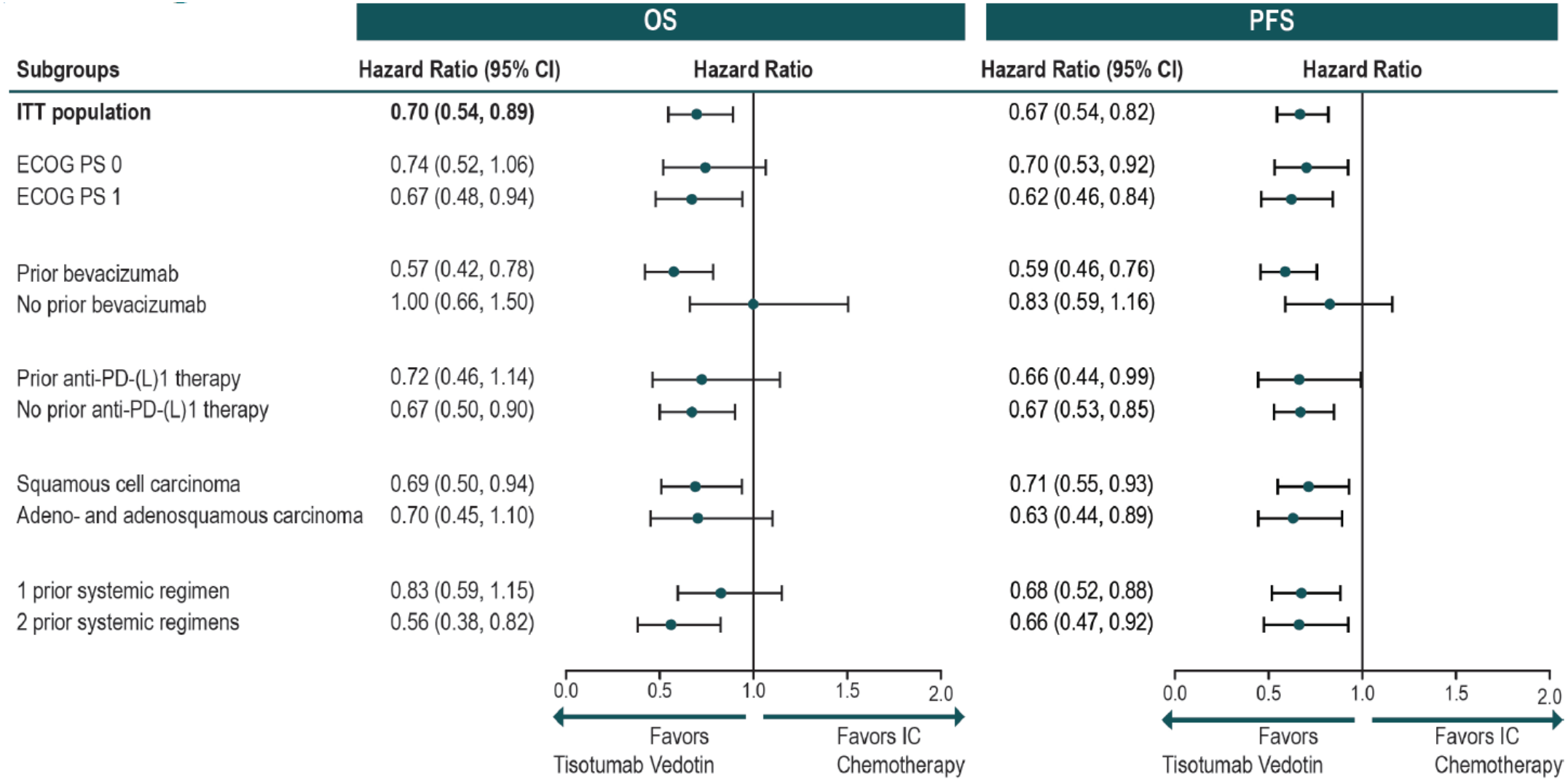
Monk BJ, et al. 2023 Annual ASCO Meeting. Abstract 5500.

InnovaTV 301: Subgroup Analysis of OS and PFS



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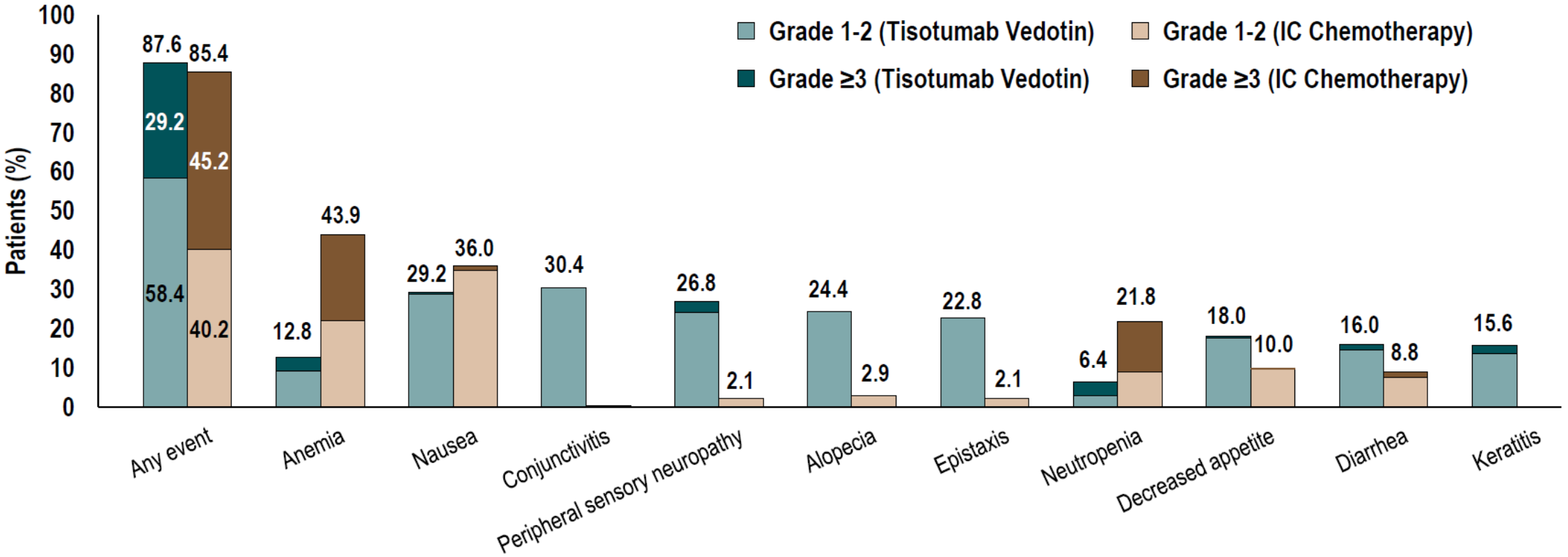
Vergote I, et al. 2023 Annual ESMO Meeting. Abstract LBA9.

InnovaTV 301: Treatment-Related AEs[a]



- Grade 5 TRAEs occurred in 2 (0.8%) and 1 (0.4%) patients in the TV and Chemo arms, respectively[b]
- Median relative dose intensity was 96.1% and 90.0% in the TV and Chemo arms, respectively

[a] TRAEs listed are those occurring in ≥15% of patients on either arm.

[b] Grade 5 TRAEs included acute kidney injury (n=1) and Stevens-Johnson syndrome (n=1) in the TV arm and pancytopenia (n=1) in the IC chemotherapy arm.

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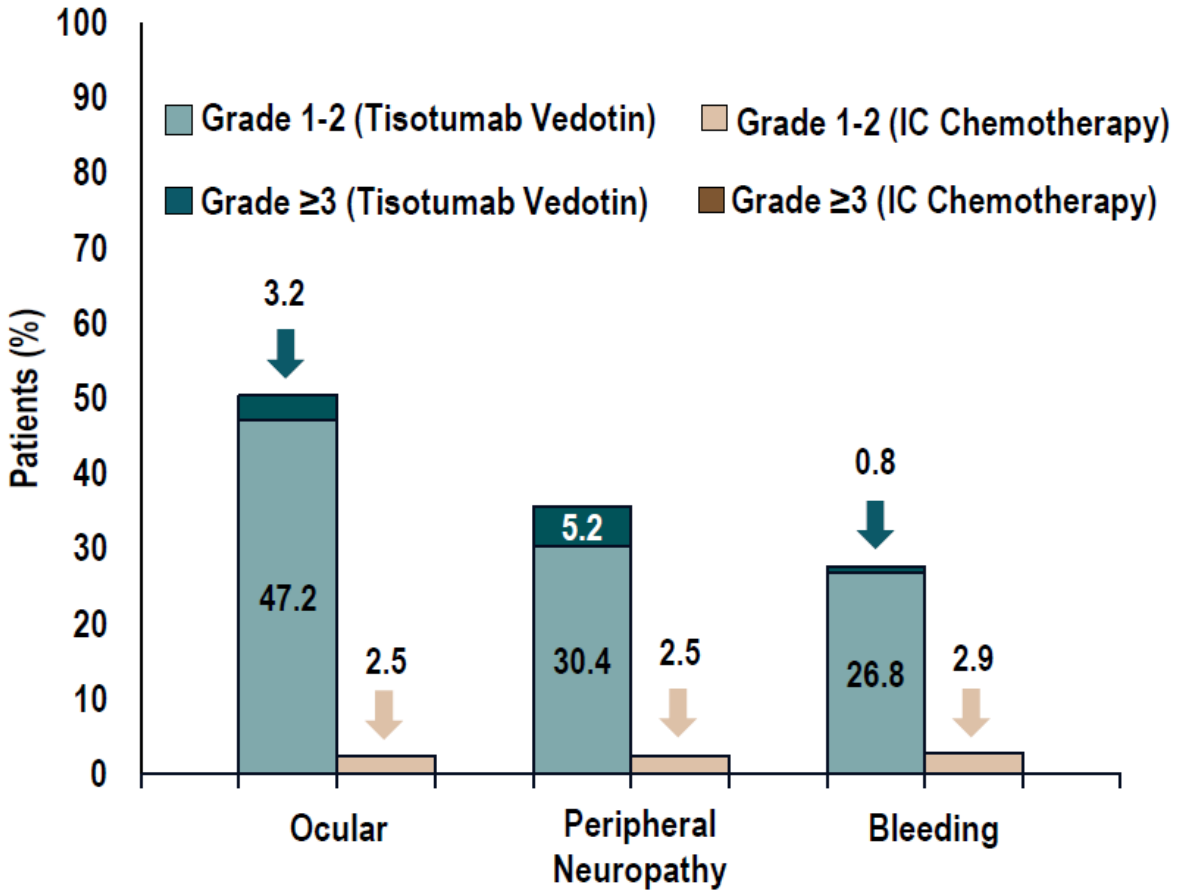
Vergote I, et al. 2023 Annual ESMO Meeting. Abstract LBA9.

InnovaTV 301: Treatment-Related AEs of Special Interest



- No grade 4 or 5 AESIs
- Dose discontinuation due to ocular and peripheral neuropathy events occurred in 5.6% of patients for each

Three most common preferred terms for each AESI

Ocular
- Conjunctivitis (30.4%)
- Keratitis (15.6%)
- Dry eye (13.2%)

Peripheral neuropathy
- Peripheral sensory neuropathy (26.8%
- Paresthesia (2.8%)
- Muscular weakness (2.4%)
- Peripheral sensorimotor neuropathy (2.4%)

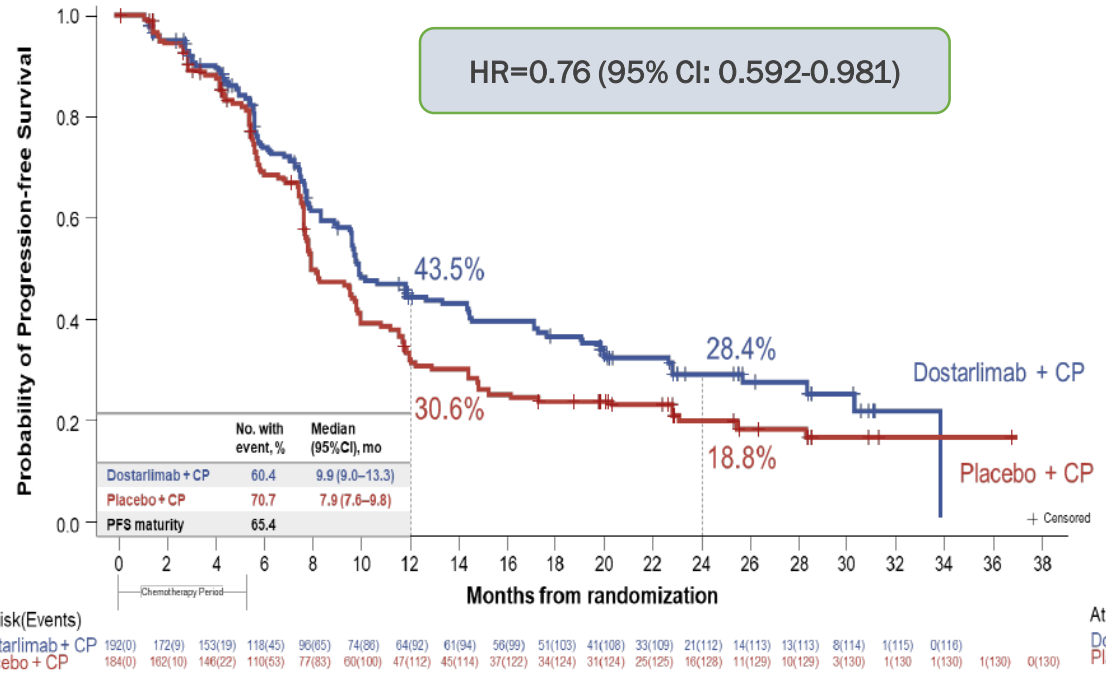
Bleeding
- Epistaxis (22.8%)
- Hematuria (3.2%)
- Vaginal hemorrhage (3.2%)

AESI, adverse event of special interest.

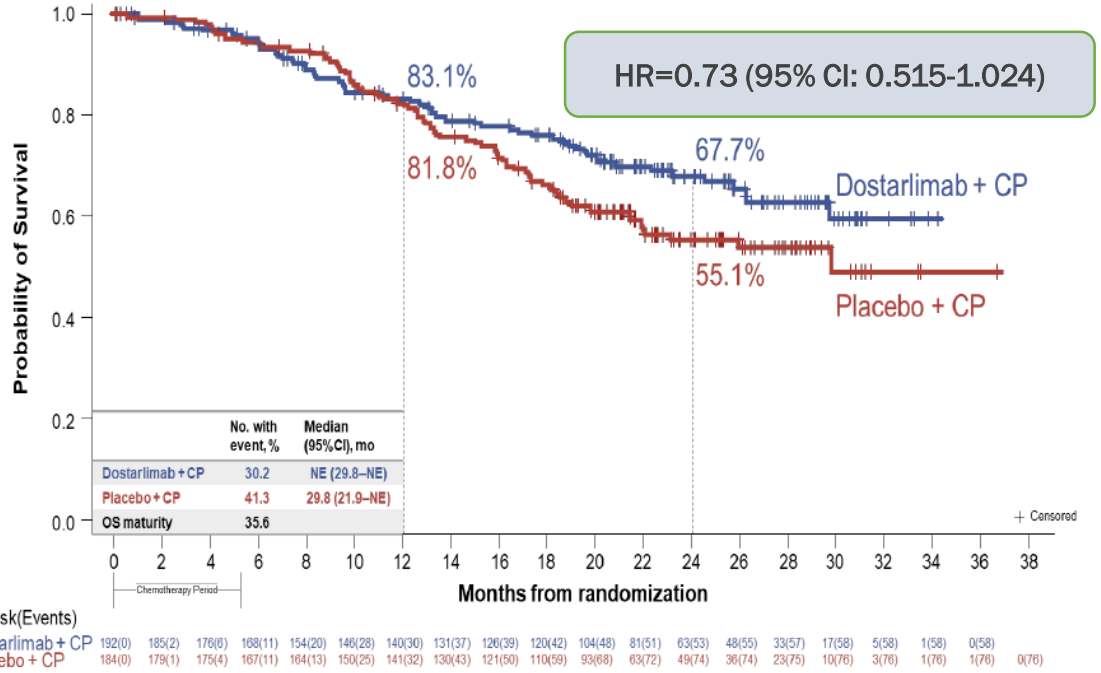
Vergote I, et al. 2023 Annual ESMO Meeting. Abstract LBA9.

GOG-3031/RUBY: Phase 3 Trial of Dostarlimab + Chemo for Primary Advanced/Recurrent EC – Efficacy in pMMR/MSS Population

PFS in pMMR/MSS Population



OS in pMMR/MSS Population



Received subsequent immunotherapy:

- 33.2% of patients on placebo arm
- 15.6% of patients on dostarlimab arm

Data cutoff: September 28, 2022.

Mirza MR, et al. SGO 2023. Abstract 265.

UC San Diego SCHOOL OF MEDICINE

GOG-3031/RUBY: Phase 3 Trial of Dostarlimab + Chemo for Primary Advanced/Recurrent EC – Safety (cont'd) and Summary

AEs, n (%)	Dostarlimab + CP (n=241)	Placebo + CP (n=246)
Any TEAE	241 (100)	246 (100)
Any grade ≥3 TEAE	170 (70.5)	147 (59.8)
Serious TEAE	91 (37.8)	68 (27.6)
Any treatment-related irAE	92 (38.2)	38 (15.4)
Any TEAE leading to discontinuation of dostarlimab or placebo	42 (17.4)	23 (9.3)
Any TEAE leading to discontinuation of carboplatin	24 (10.0)	19 (7.7)
Any TEAE leading to discontinuation of paclitaxel	24 (10.0)	23 (9.3)
Any TEAE leading to death	5 (2.1)[a]	0
Any TEAE related to dostarlimab leading to death	2 (0.8)[b]	-
Median duration of overall treatment (range), weeks	43.0 (3.0-150.9)	36.0 (2.1-165.1)

Authors' Conclusions

- Dostarlimab + CP showed:
  - Statistically significant and clinically meaningful PFS benefit
  - Early OS trend in the overall population
  - Benefit in dMMR/MSI-H patients
  - Durable benefit in MMRp/MSS patients
- The safety profile for dostarlimab + CP was manageable and consistent with individual therapies

[a] 3 deaths were not related to study treatment (opiate overdose, COVID-19, and general physical health deterioration). [b] 1 death was considered by the investigator as related to dostarlimab plus CP and occurred during the first 6 cycles (myelosuppression); 1 death was related to dostarlimab and occurred during the 90-day safety follow-up (hypovolemic shock).

Mirza MR, et al. SGO 2023. Abstract 265.

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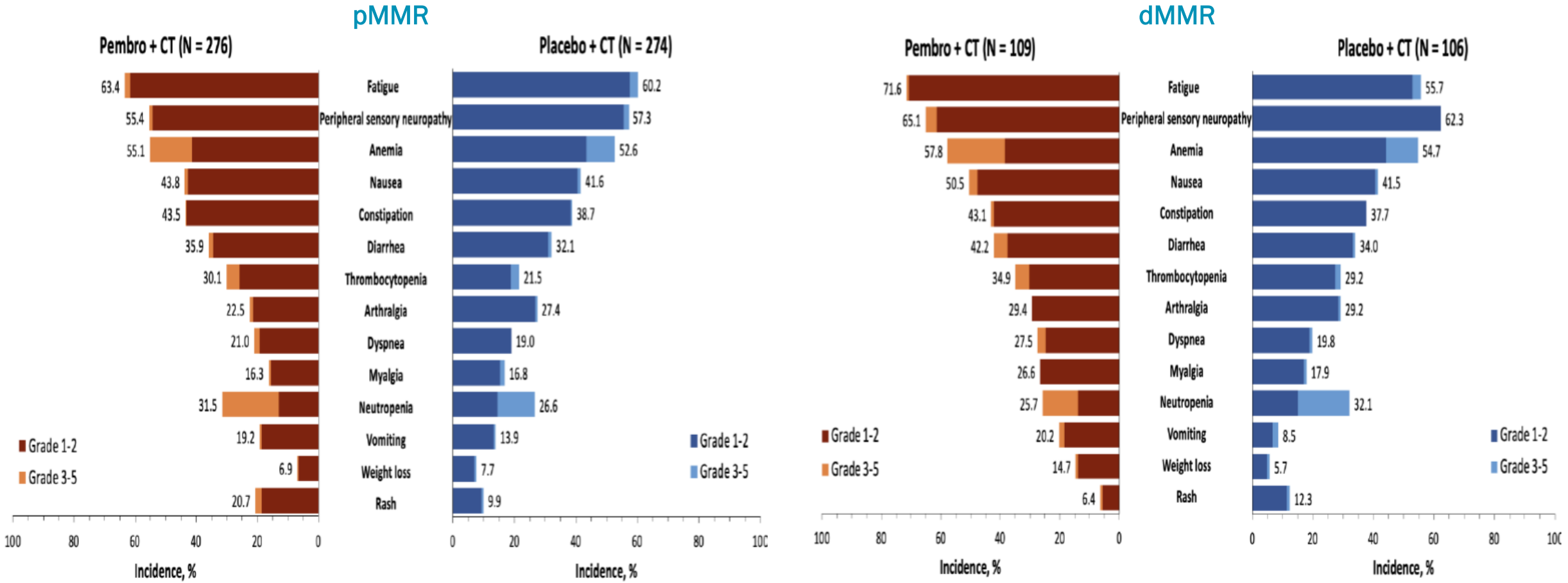
NRG GY018: Phase 3 Trial of Pembrolizumab + Chemo for Measurable Stage 3 or 4a, Stage 4b, or Recurrent EC – AEs With ≥15% Incidence



Data cutoff: December 16, 2022 for dMMR; December 6, 2022 for pMMR.
Eskander R, et al. SGO 2023. Abstract 264.

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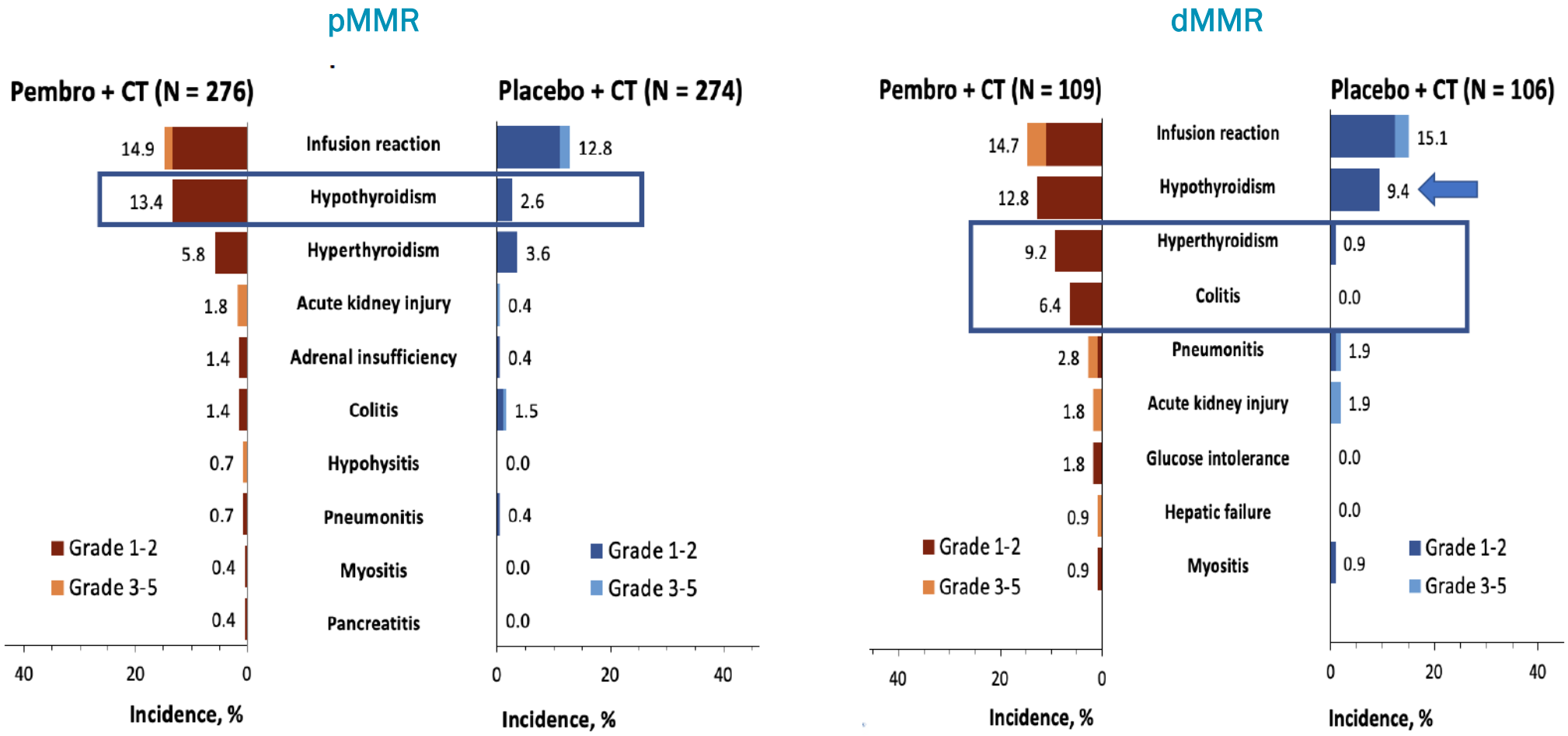
NRG GY018: Phase 3 Trial of Pembrolizumab + Chemo for Measurable Stage 3 or 4a, Stage 4b, or Recurrent EC – AEs of Interest



Data cutoff: December 16, 2022 for dMMR; December 6, 2022 for pMMR.
Eskander R, et al. SGO 2023. Abstract 264.

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