Cervical and Uterine Cancers: Novel Advances in Personalized Medicine in 2024

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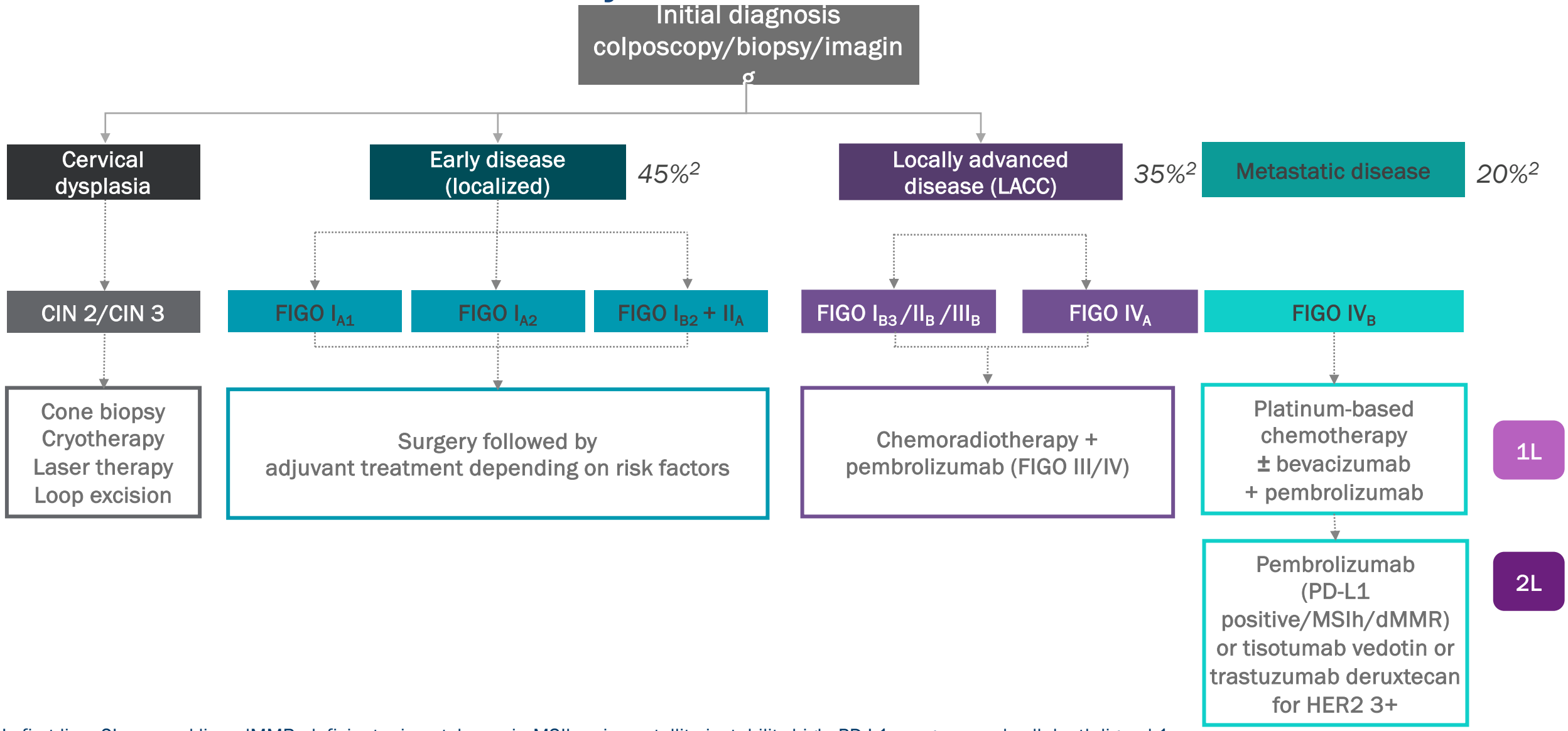
Cervical Cancer: Summary of Treatment[1,2]



1L, first line; 2L, second line; dMMR, deficient mismatch repair; MSIh, microsatellite instability high; PD-L1, programmed cell death-ligand 1.

1. National Comprehensive Cancer Network. Cervical Cancer, Version 1.2022. October 26, 2021; 2. PDQ Adult Treatment Editorial Board. Cervical Cancer Treatment (PDQ®). National Cancer Institute. January 20, 2022.

Trial Schema

Low-risk cervical cancer as defined by

- Squamous cell, adenocarcinoma, adenosquamous carcinoma
- Stage IA2 and IB1
- <10 mm stromal invasion on LEEP/cone
- <50% stromal invasion on MRI
- Max dimension of ≤20 mm
- Grade 1–3 or not assessable

Stratification:

1. **Cooperative Group**
2. **Sentinel node mapping** (Yes vs No)
3. **Stage** (IA2 vs IB1)
4. **Histologic type** (squamous vs adenocarcinoma/adenosquamous)
5. **Grade** (1–2 vs 3 vs not assessable)

RANDOMIZE 1:1

Arm 1 (Control)
Radical Hysterectomy[a]

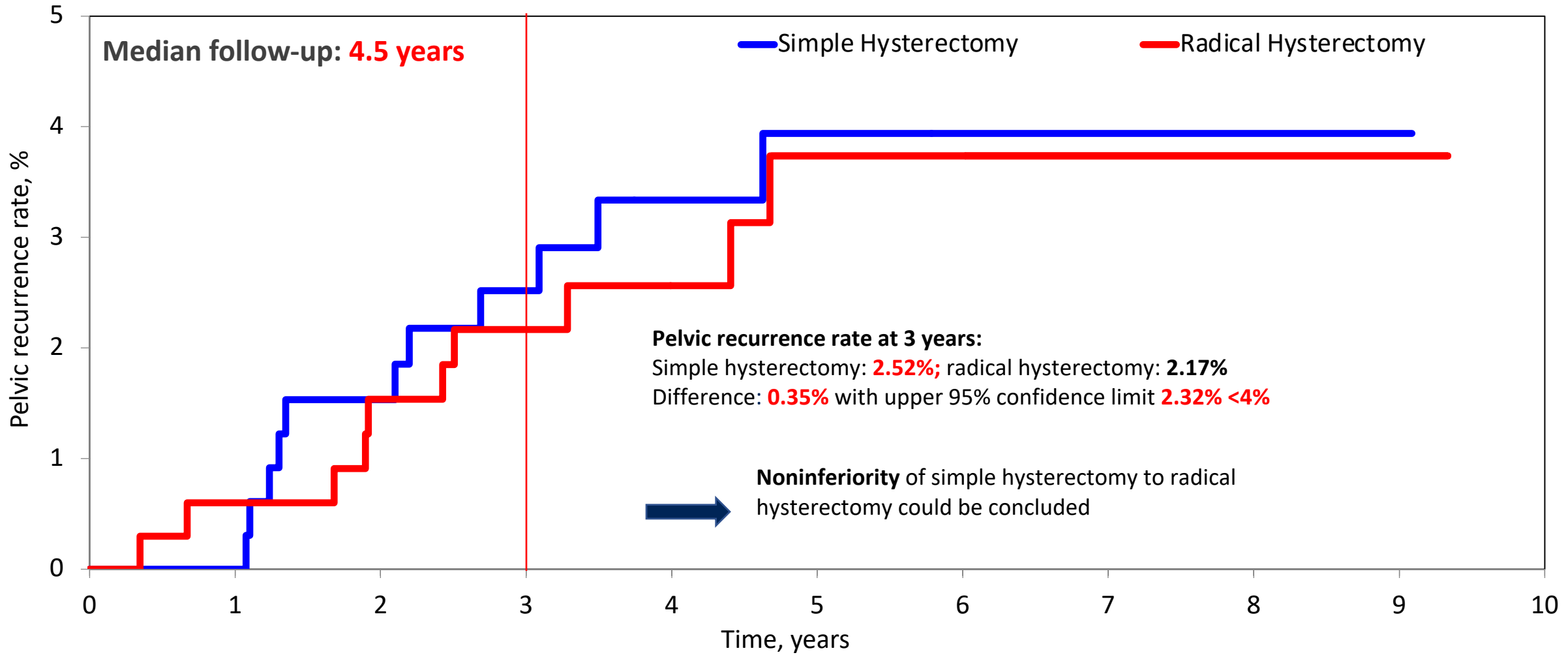
Arm 2 (Experimental)
Simple Hysterectomy[a]

Pelvic recurrence rate at 3 years

[a]Regardless of treatment assignment, surgery will include **pelvic lymph node dissection** with optional sentinel lymph node (SN) mapping. If SN mapping is to be done, the mode is optional, but the laparoscopic approach is preferred.

Plante M, et al. ASCO 2023. Abstract LBA5511.

Pelvic Recurrence Rate (ITT)



Simple	350	328	311	273	204	133	61	31	14	4	0
Radical	350	329	315	286	208	132	66	31	16	2	0

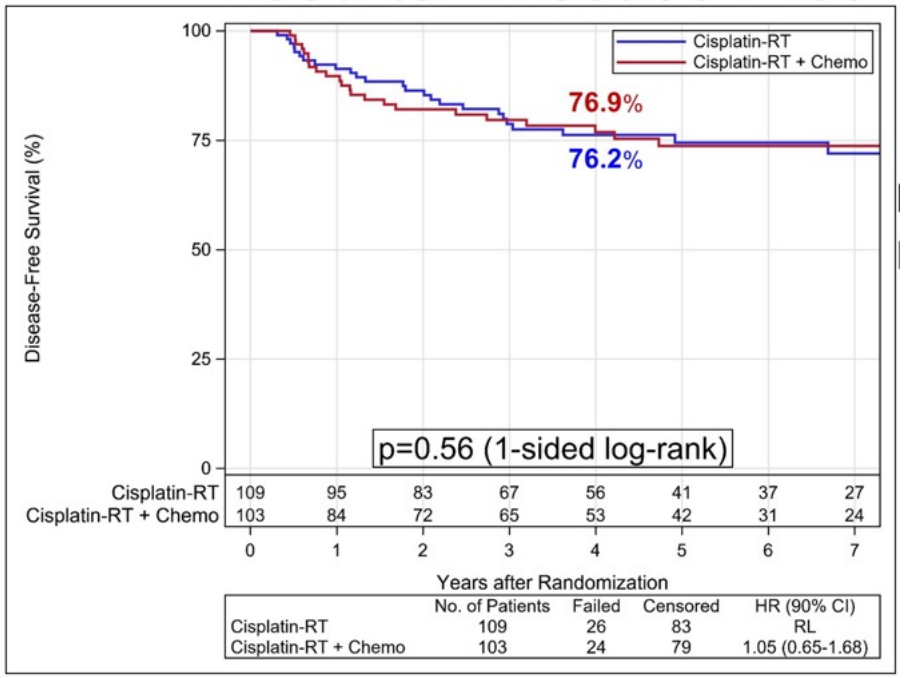
Plante M, et al. ASCO 2023. Abstract LBA5511.

RTOG0724 Schema

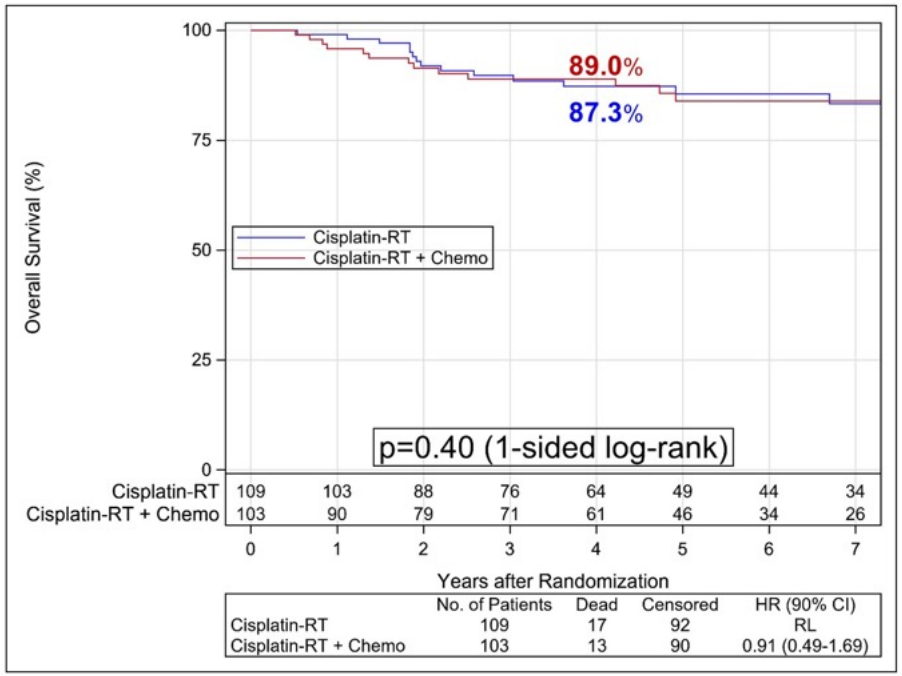
- **Clinical stage IA2, IB, or IIA with high risk factors after surgery**
- **Radical hysterectomy – positive nodes and/or positive parametrium**

STRATIFY	RANDOMIZE
Intention To Use Brachytherapy 1. No 2. Yes **RT Modality** 1. Standard RT 2. IMRT **Radiation Therapy Dose** 1. 45 Gy 2. 50.4 Gy	**Arm 1** **Concurrent weekly cisplatin and RT ± brachytherapy** **Versus** **Arm 2** **Concurrent weekly cisplatin and RT ± brachytherapy** **FOLLOWED BY** **Carboplatin and paclitaxel**

Results



Most common site of disease recurrence was distant 37/50 (74%)



26% of patients in ARM2 did not receive adjuvant chemotherapy

Jhingran and Gray et al. ASCO 2024

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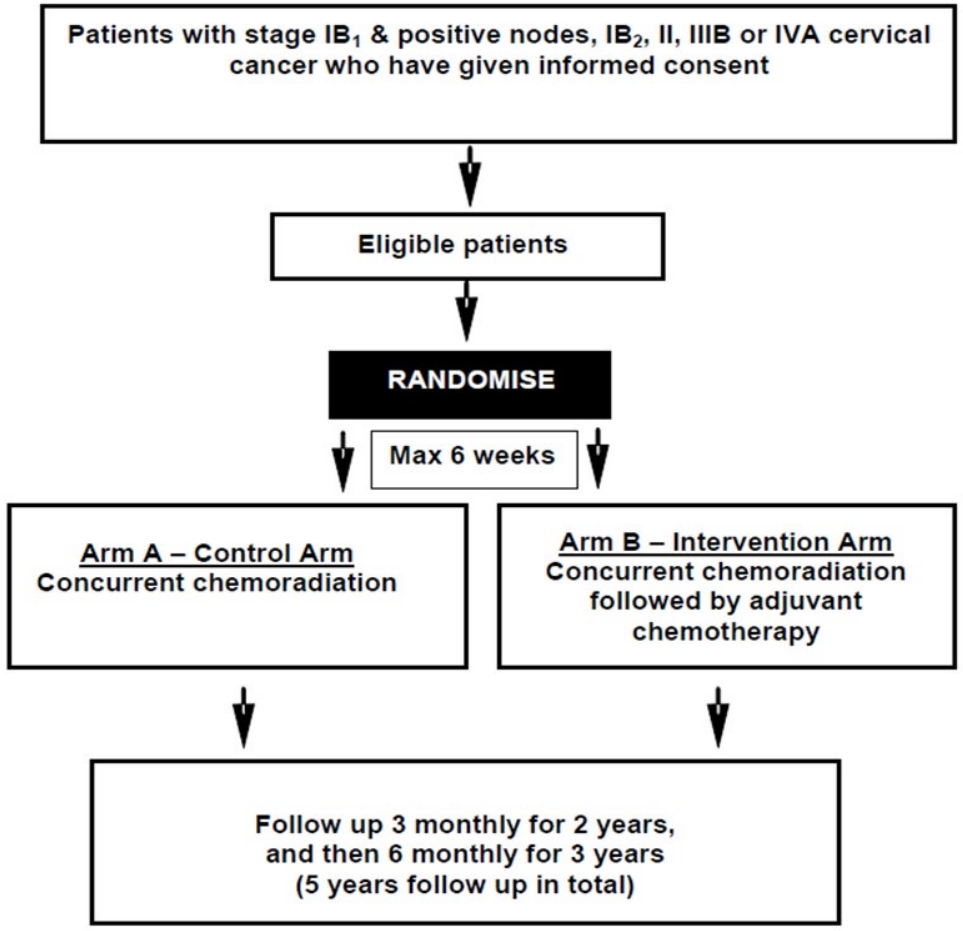
OUTBACK –chemo* after chemoradiation
Mileshkin, LR et al. Lancet Oncology 2023;24:468-482



	ChemoRT	
OS 5 years	72%	
PFS 5 years	63%	61%

27% with 0 or 1 cycle adjuvant therapy

NRG ONCOLOGY

* carboplatin and paclitaxel

NRG/RTOG 0724/GOG-0724

ENGOT-cx11/GOG-3047/KEYNOTE-A18: Randomized, Double-Blind, Phase 3 Study

Key Eligibility Criteria

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

R
1:1
N = 1060

Cisplatin 40 mg/m^2 QW for 5 cycles[a] + EBRT followed by brachytherapy
+
Pembrolizumab 200 mg Q3W for 5 cycles

Pembrolizumab 400 mg Q6W for 15 cycles

Cisplatin 40 mg/m^2 QW for 5 cycles[a] + EBRT followed by brachytherapy
+
Placebo Q3W for 5 cycles

Placebo Q6W for 15 cycles

Stratification Factors

- Planned EBRT type (IMRT or VMAT vs non-IMRT or non-VMAT)
- Stage at screening (stage IB2-IIB vs III-IVA)
- Planned total radiotherapy dose (<70 Gy vs ≥70 Gy [EQ2D])

[a]A 6th cycle was allowed per investigator discretion. EBRT, external beam radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; Gy, grays; IMRT, intensity-modulated radiotherapy; Q3W, every 3 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; VMAT, volumetric-modulated arc therapy. ENGOT-cx11/GOG-3047/KEYNOTE-A18 ClinicalTrials.gov identifier, NCT04221945.

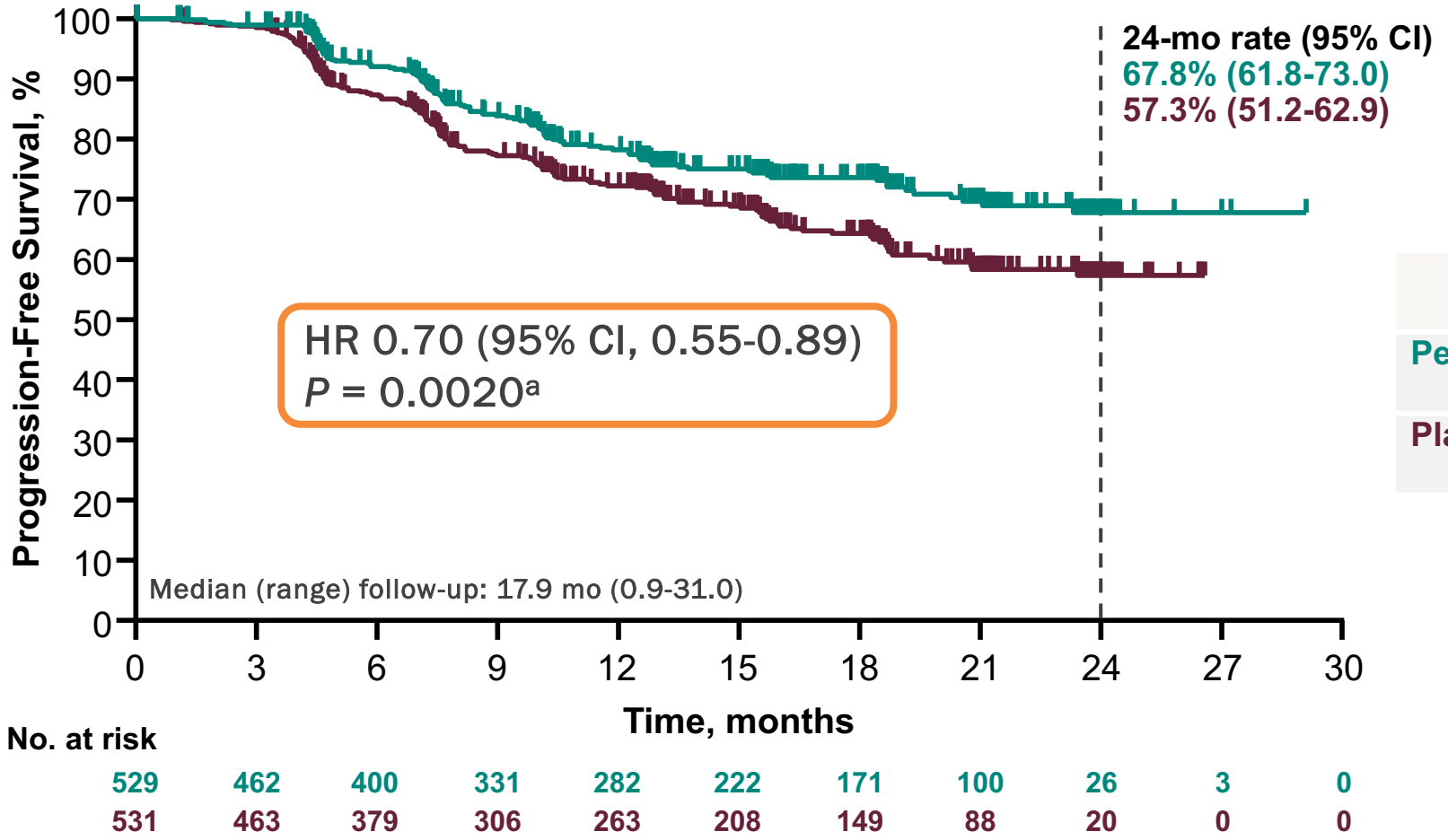
Baseline Characteristics

	Pembro Arm (N = 529)	Placebo Arm (N = 531)
Age, median (range)	49 y (22-87)	50 y (22-78)
Race[a]		
White	254 (48.0%)	264 (49.7%)
Asian	155 (29.3%)	148 (27.9%)
Multiple	78 (14.7%)	86 (16.2%)
American Indian or Alaska Native	24 (4.5%)	22 (4.1%)
Black or African American	14 (2.6%)	8 (1.5%)
Native Hawaiian or Other Pacific Islander	2 (0.4%)	1 (0.2%)
PD-L1 CPS		
<1	22 (4.2%)	28 (5.3%)
≥1	502 (94.9%)	498 (93.8%)
Missing	5 (0.9%)	5 (0.9%)
ECOG PS 1	149 (28.2%)	134 (25.2%)
Squamous cell carcinoma	433 (81.9%)	451 (84.9%)

	Pembro Arm (N = 529)	Placebo Arm (N = 531)
Stage at screening (FIGO 2014 criteria)		
IB2-IIB	235 (44.4%)	227 (42.7%)
III-IVA	294 (55.6%)	304 (57.3%)
Lymph node involvement[b]		
Positive pelvic only	326 (61.6%)	324 (61.0%)
Positive para-aortic only	14 (2.6%)	10 (1.9%)
Positive pelvic and para-aortic	105 (19.8%)	104 (19.6%)
No positive pelvic or para-aortic	84 (15.9%)	93 (17.5%)
Planned type of EBRT		
IMRT or VMAT	469 (88.7%)	470 (88.5%)
Non-IMRT and non-VMAT	60 (11.3%)	61 (11.5%)
Planned total radiotherapy dose (EQD2)		
<70 Gy	47 (8.9)	46 (8.7)
≥70 Gy	482 (91.1)	485 (91.3)

[a]In each treatment arm, 2 patients (0.4%) had missing information for race. [b]Per protocol, a positive lymph node is defined as ≥1.5 cm shortest dimension by MRI or CT. Data cutoff date: January 9, 2023.

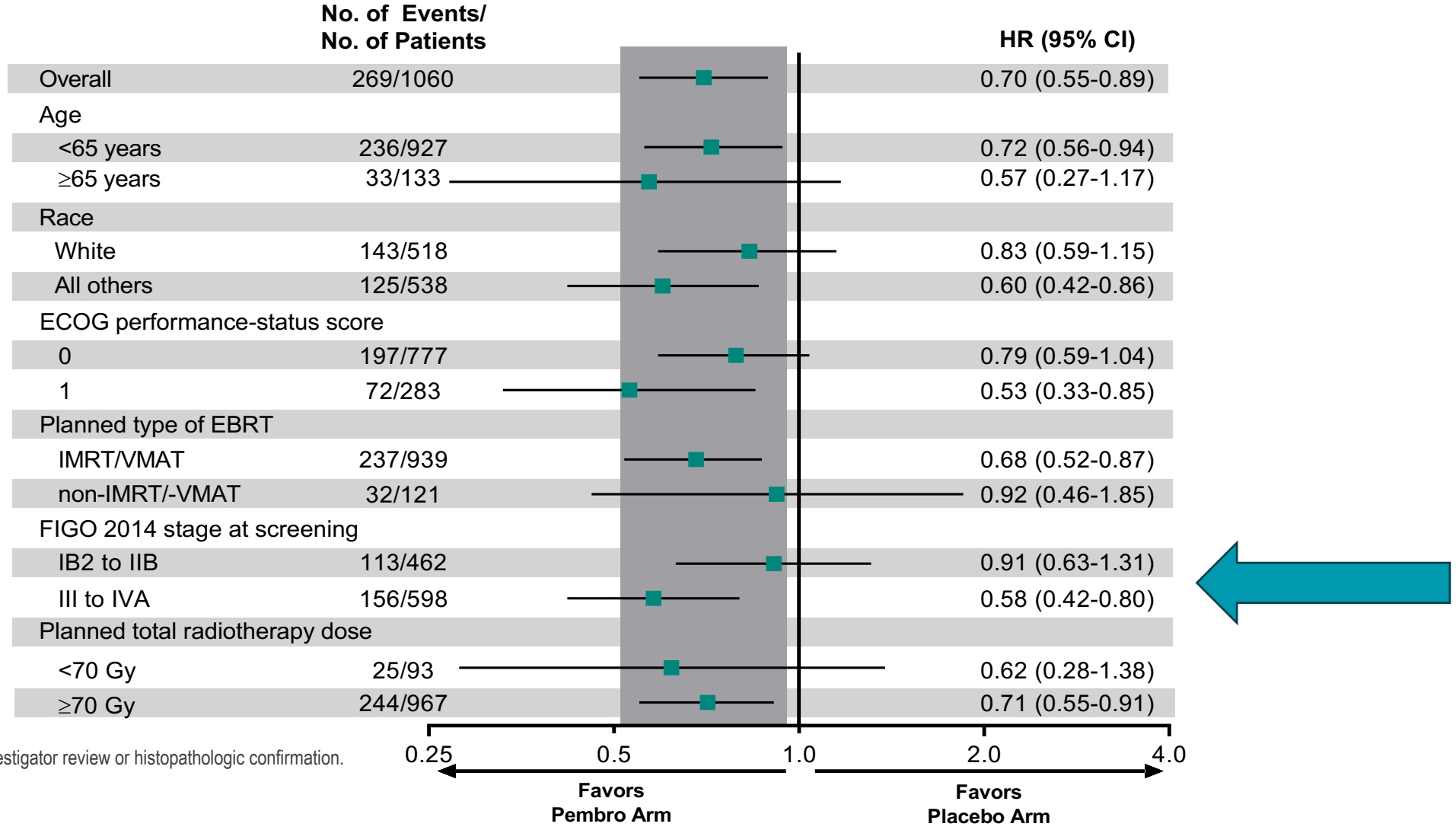
Primary Endpoint: Progression-Free Survival



	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. Data cutoff date: January 9, 2023.

Progression-Free Survival: Protocol-Specified Subgroups



Response assessed per RECIST v1.1 by investigator review or histopathologic confirmation.
Data cutoff date: January 9, 2023.

FDA approves pembrolizumab with chemoradiotherapy for FIGO 2014 Stage III-IVA cervical cancer

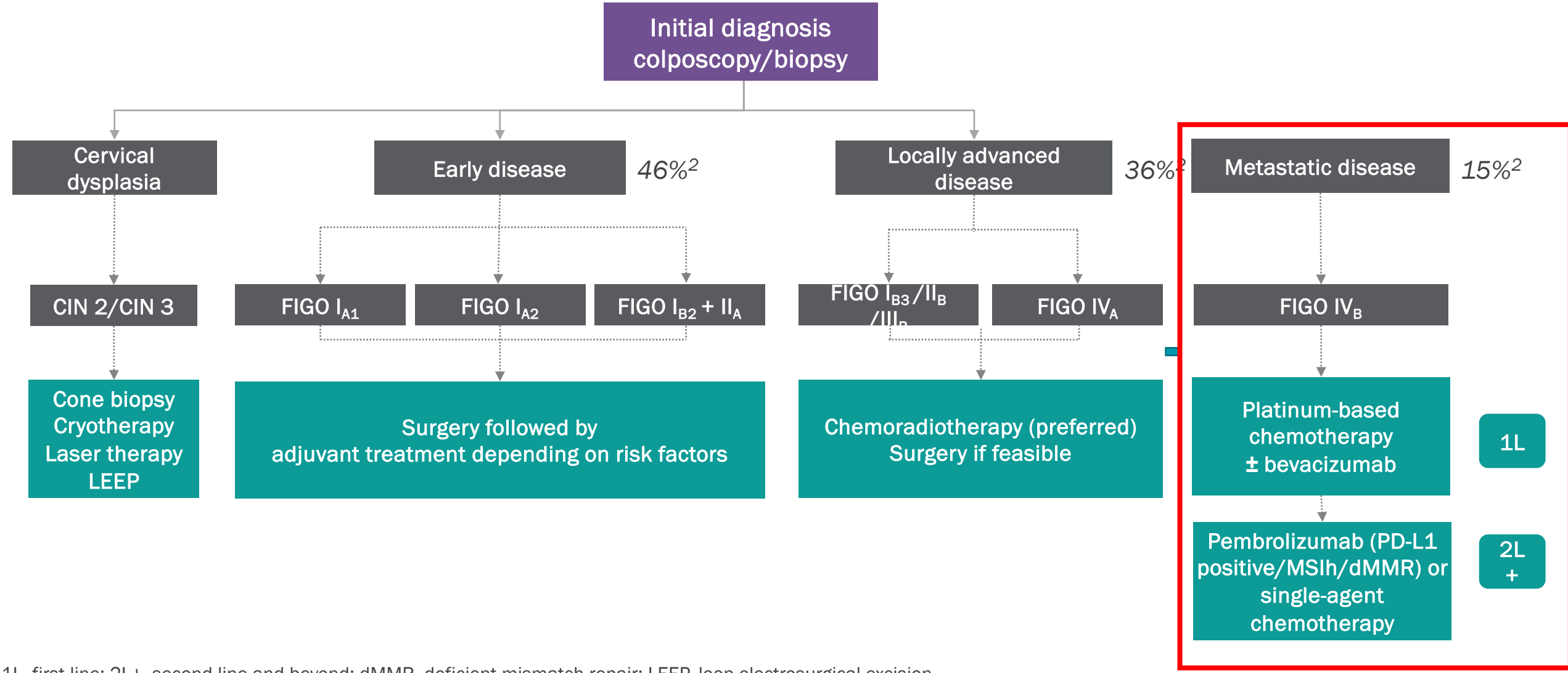
Personalization based on stage – not biomarker

On January 12, 2024, the Food and Drug Administration approved pembrolizumab with chemoradiotherapy (CRT) for patients with FIGO 2014 Stage III-IVA cervical cancer.

Full prescribing information for pembrolizumab will be posted here.

Efficacy was evaluated in KEYNOTE-A18 (NCT04221945), a multicenter, randomized, double-blind, placebo-controlled trial enrolling 1060 patients with cervical cancer who had not previously received definitive surgery, radiation, or systemic therapy. The trial included 596 patients with FIGO 2014 Stage III-IVA disease and 462 patients with FIGO 2014 Stage IB2-IIB, node-positive disease.

Cervical Cancer: Summary of Treatment

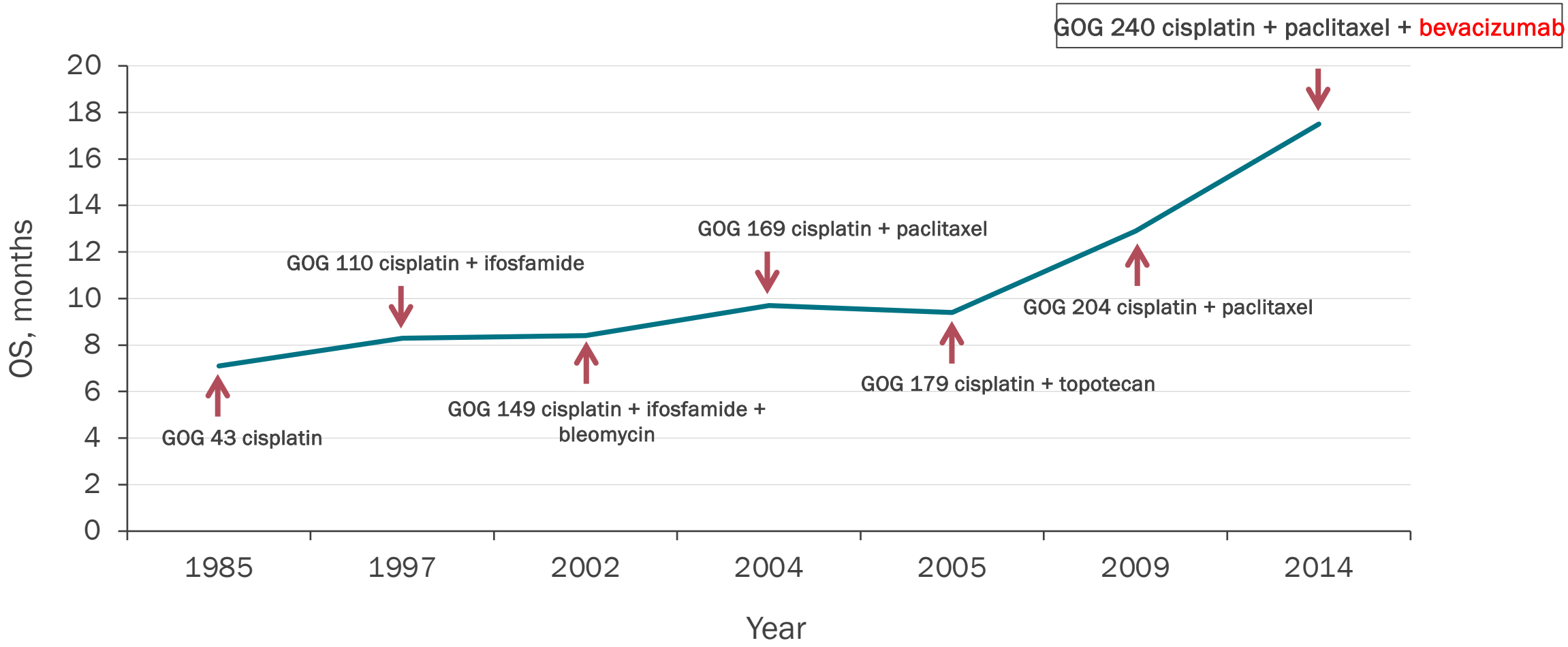


1L, first line; 2L+, second line and beyond; dMMR, deficient mismatch repair; LEEP, loop electrosurgical excision procedure; MSIh, microsatellite instability high; PD-L1, programmed death-ligand 1.

1. NCCN cervical cancer guidelines v2.2019; 2. seer cancer stat facts: cervical cancer. National cancer institute. Bethesda, MD.
Monk B, et al. ASCO 2023. Abstract 5500.

Improving OS in Recurrent or Metastatic Cervical Cancer

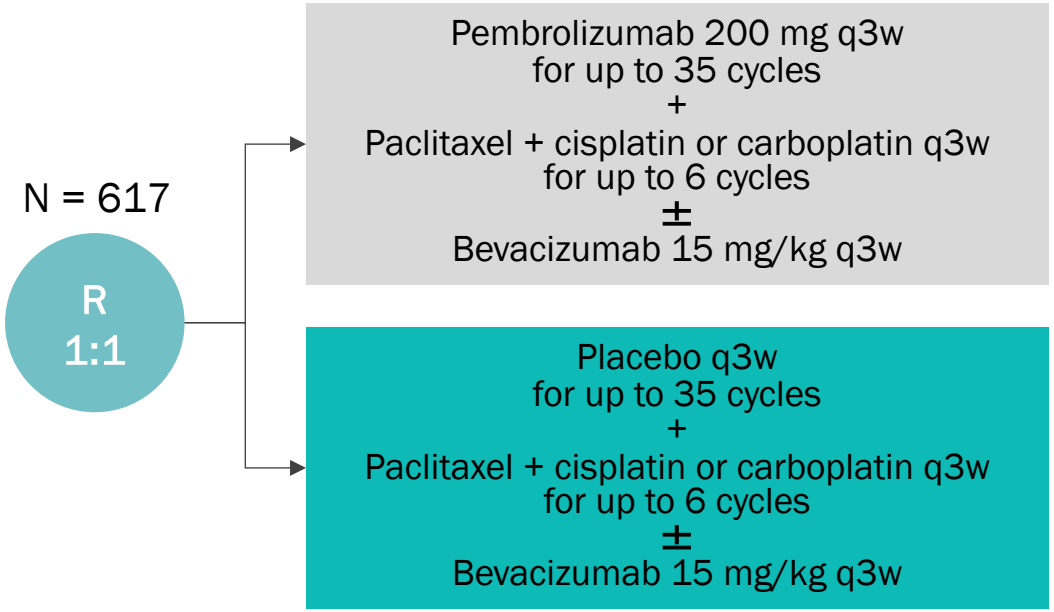
How Do We Move Forward?



Leath CA, et al. *Gynecol Oncol*. 2018;150:391-397.

KEYNOTE-826: Phase III Trial Design and Patients

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



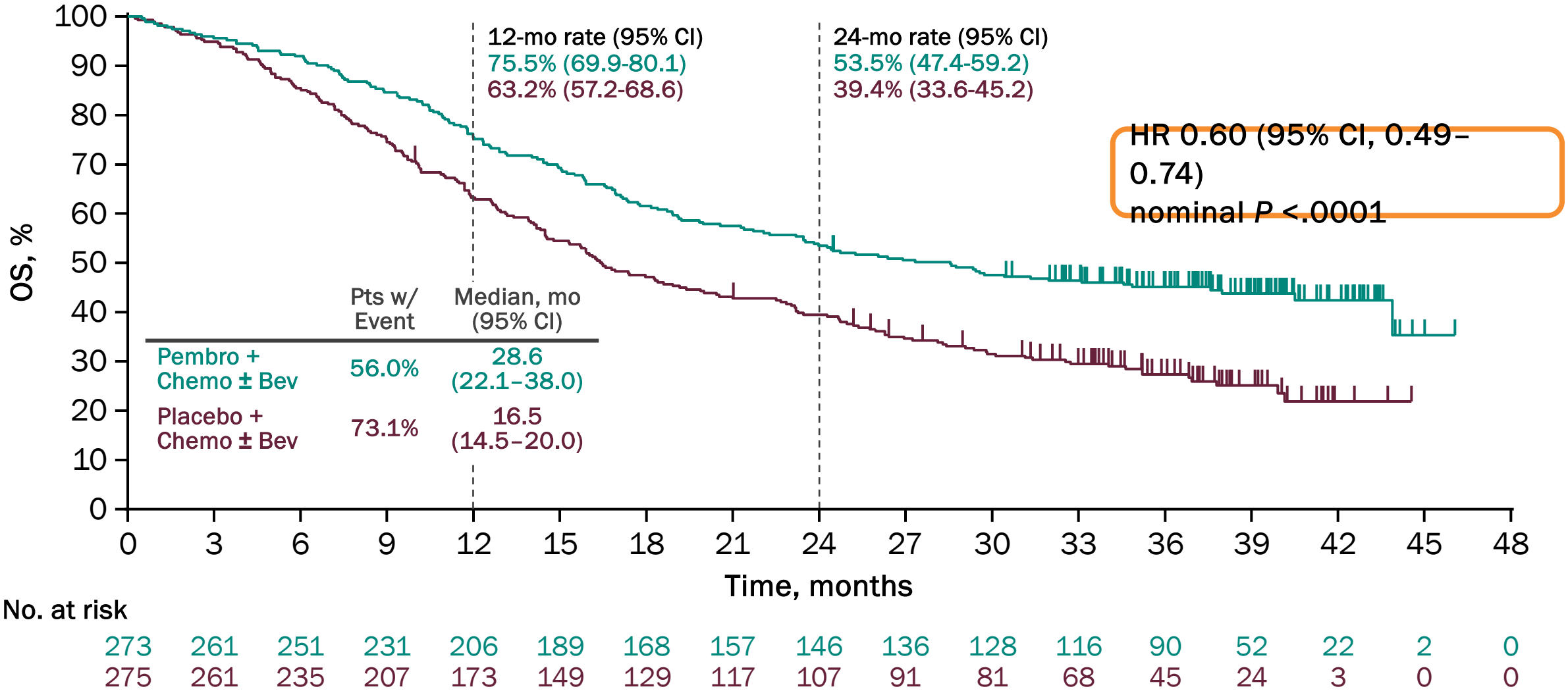
Endpoints
- Dual primary: OS and PFS
- Secondary: ORR, DOR, 12-mo PFS, and safety

	Pembrolizumab Group (n = 308)	Placebo Group (n = 309)
Age, median (range), yr	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 on 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)

Colombo N, et al. *N Engl J Med.* 2021;385:1856-1867.

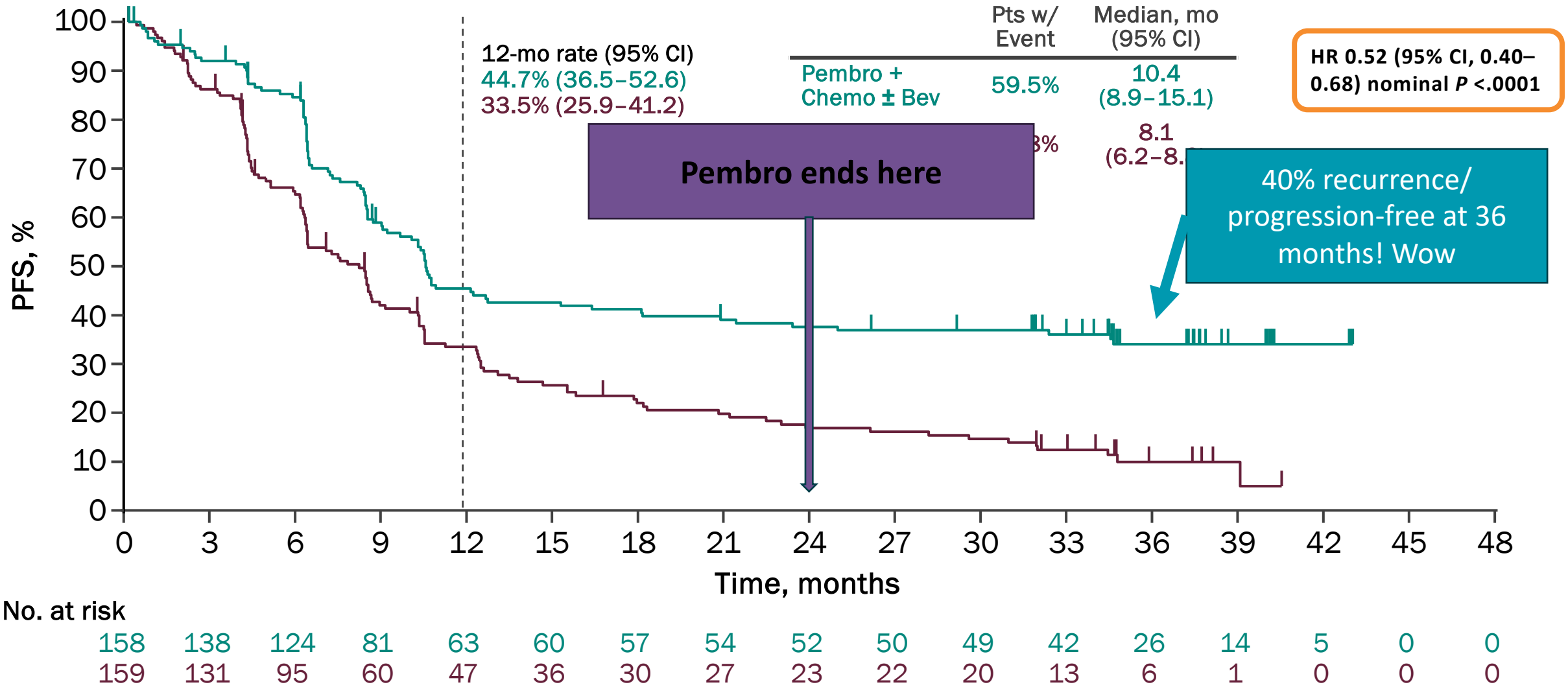
Protocol-Specified Final OS: PD-L1 CPS ≥1 Population



Monk B, et al. ASCO 2023. Abstract 5500.

Data cutoff date: October 3, 2022.

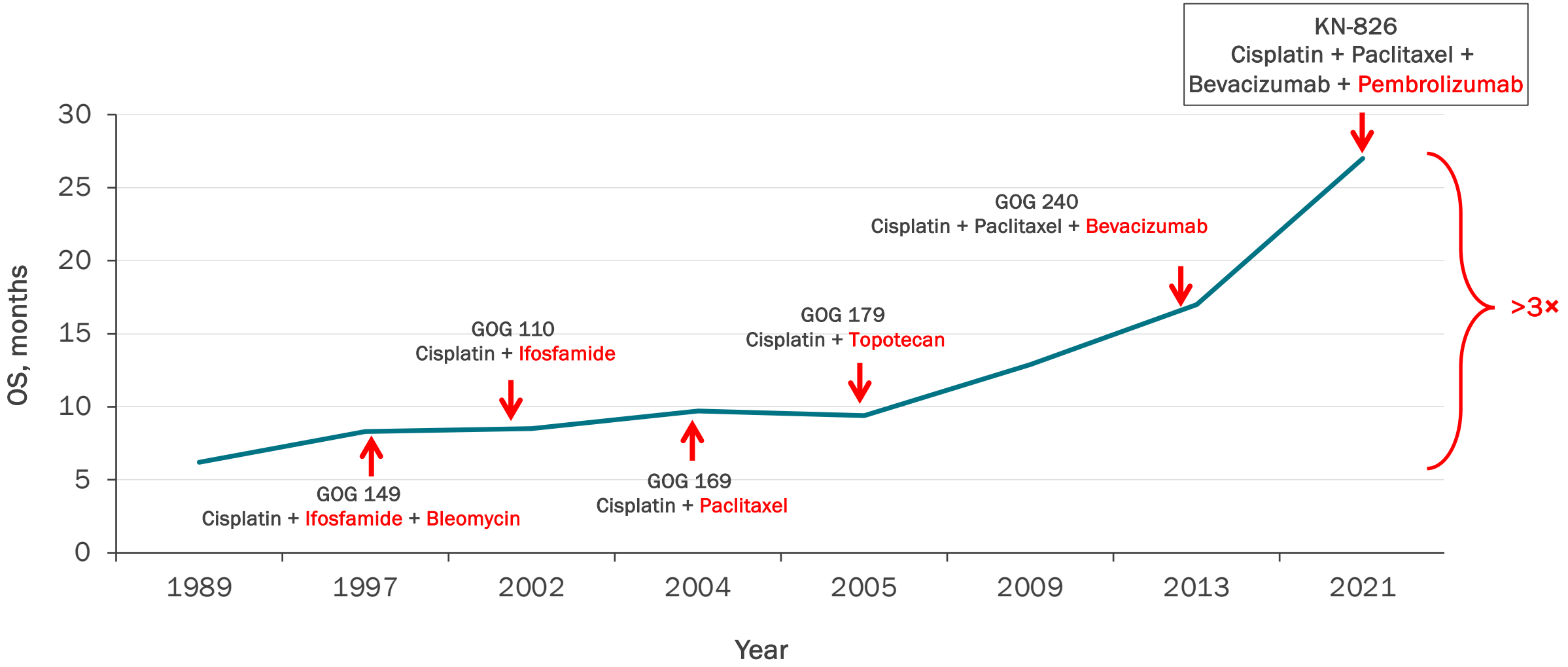
Protocol-Specified Final PFS: PD-L1 CPS ≥10 Population



Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: October 3, 2022.

Monk B, et al. ASCO 2023. Abstract 5500.

Improving OS in Recurrent or Metastatic Cervical Cancer



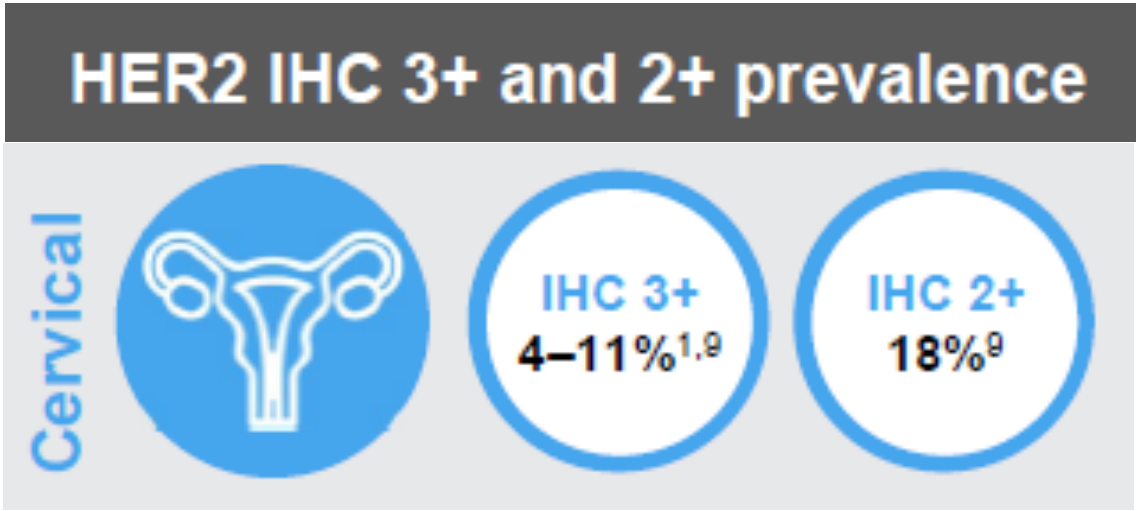
Leath CA, et al. *Gynecol Oncol*. 2018;150:391-397; Colombo N, et al. *N Engl J Med.* 2021;385:1856-1867.

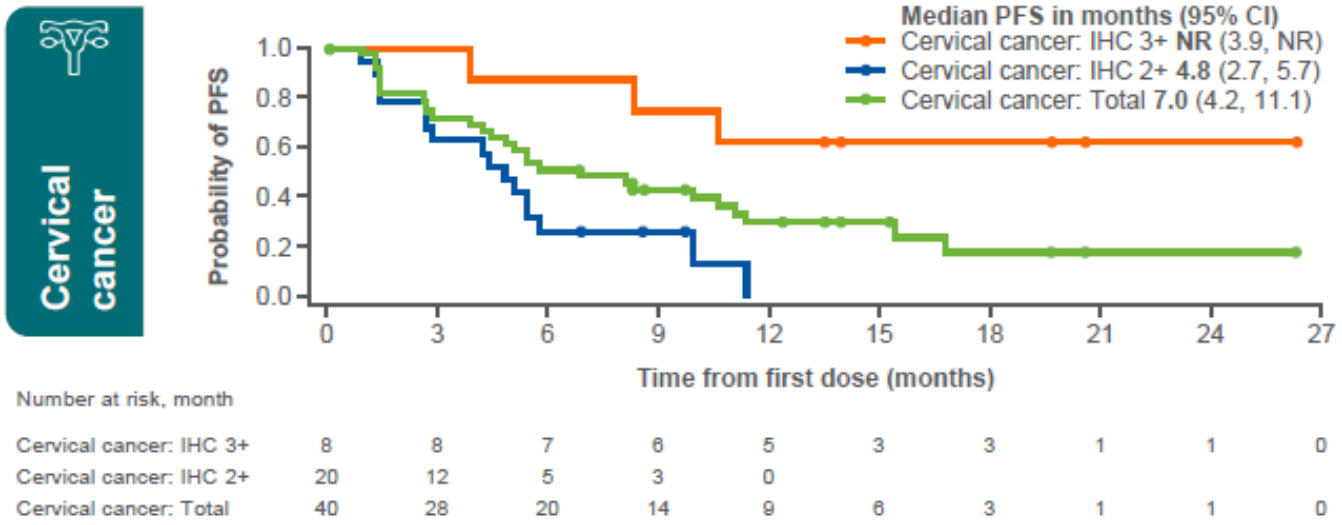
FDA approves pembrolizumab combination for the first-line treatment of cervical cancer

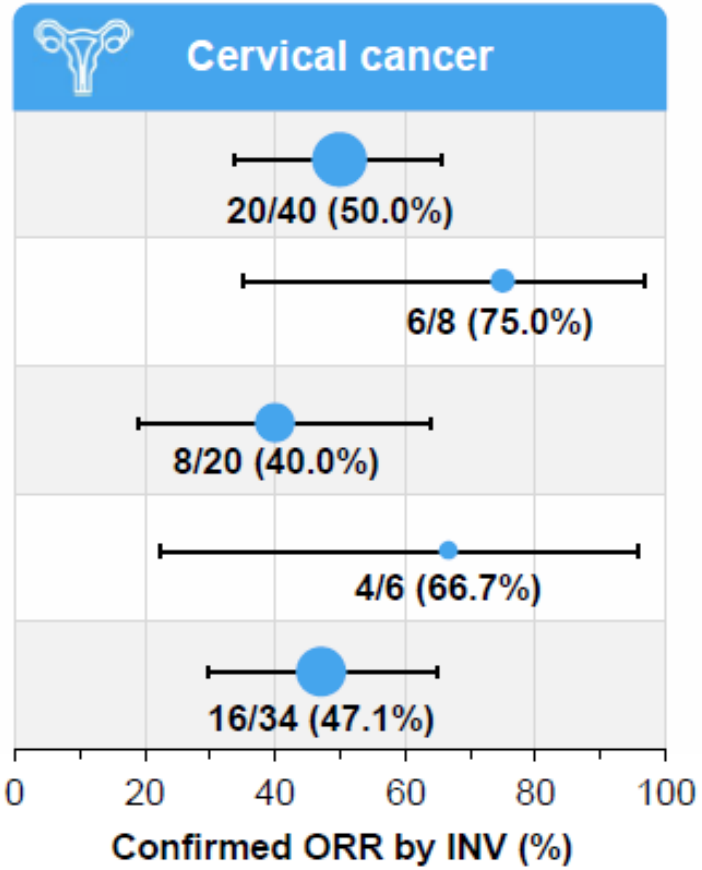
On October 13,2021, the Food and Drug Administration approved pembrolizumab in combination with chemotherapy, with or without bevacizumab, for patients with persistent, recurrent or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1), as determined by an FDA-approved test.

Personalization based on biomarker: PD-L1

Trastuzumab deruxtecan for pretreated patients with HER2-expressing solid tumors: primary analysis from the DESTINY-PanTumor02 study







Meric Bernstam et al. ESMO 2023, Makker et al SGO 2024

FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for unresectable or metastatic HER2-positive solid tumors

On April 5, 2024, the Food and Drug Administration granted accelerated approval to fam-trastuzumab deruxtecan-nxki for adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

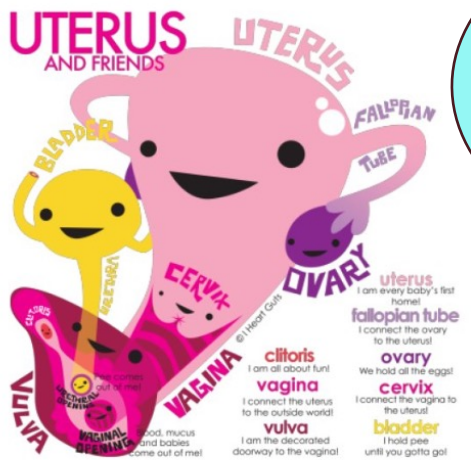
Personalization based on biomarker: HER2 IHC

Take Aways for 2024: Cervical Cancer

There is no indication for adjuvant chemotherapy following chemo/rt in any setting

Antibody Drug Conjugates (ADCs) appear poised to dominate SOC for 2L post CPI treatment

CPI + RT now FDA approved for FIGO 2014 Stage III/IV



On to highlights in uterine cancer

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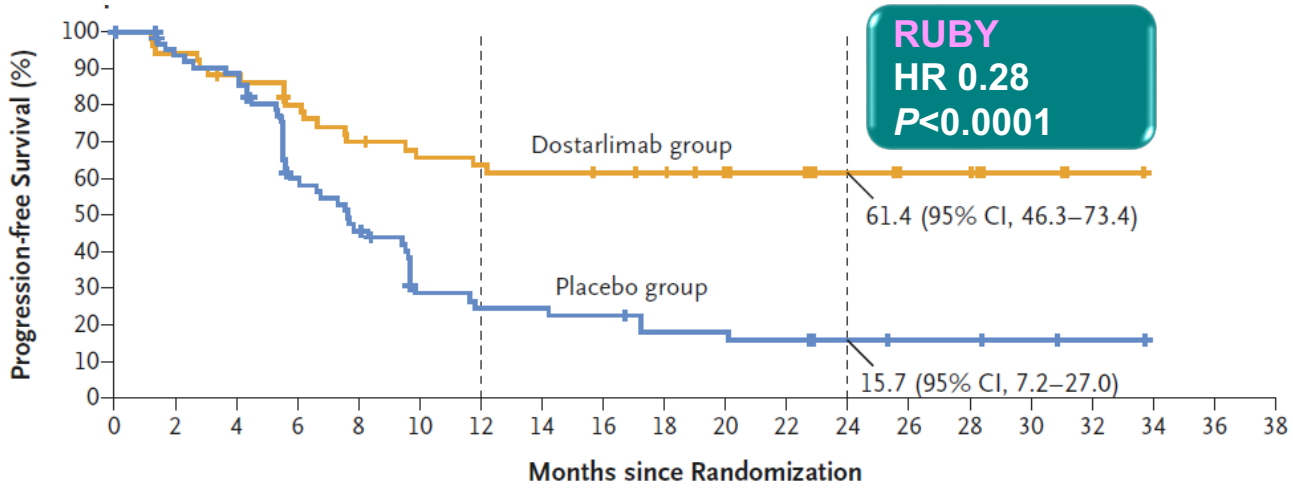
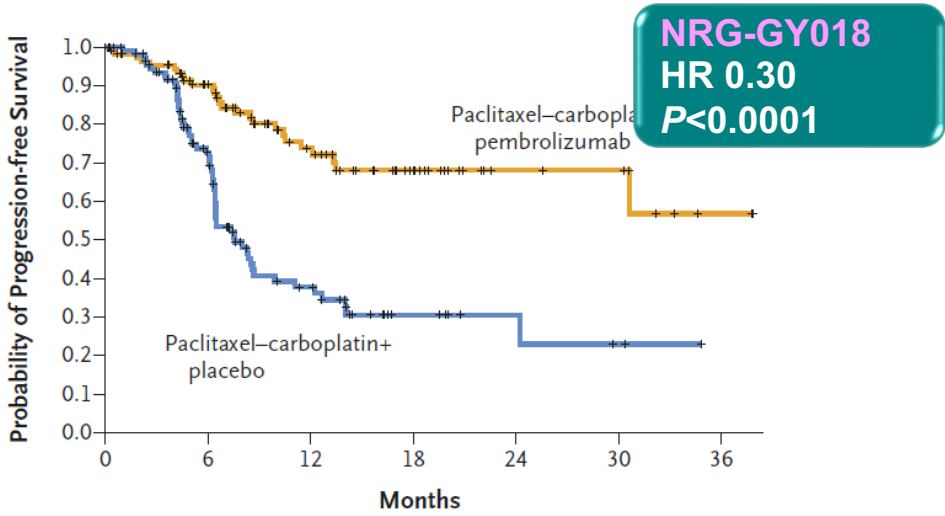
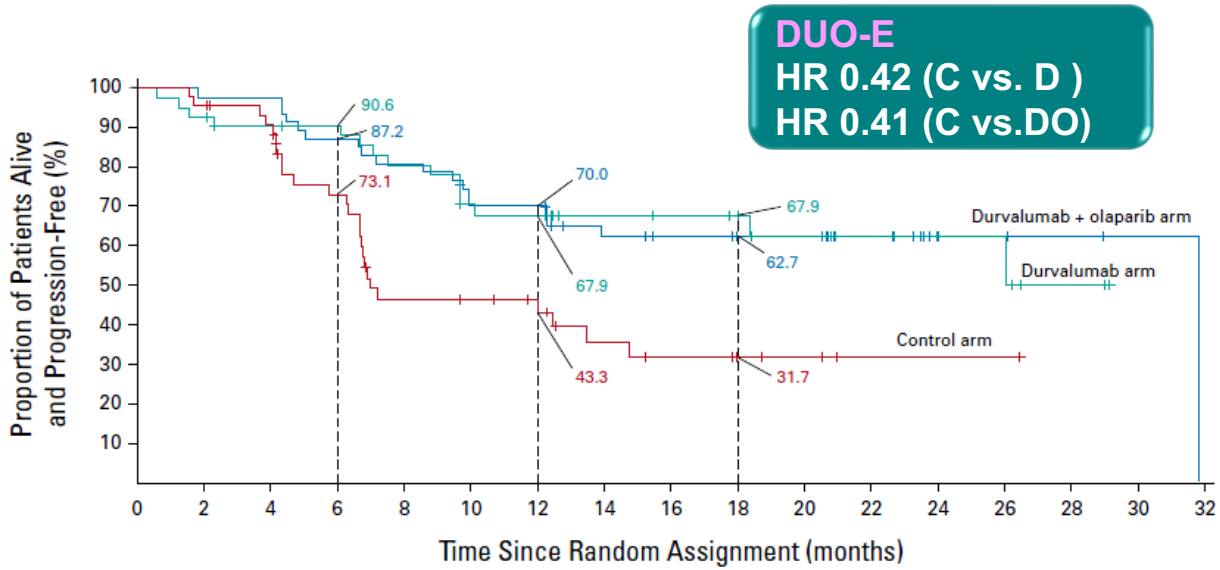
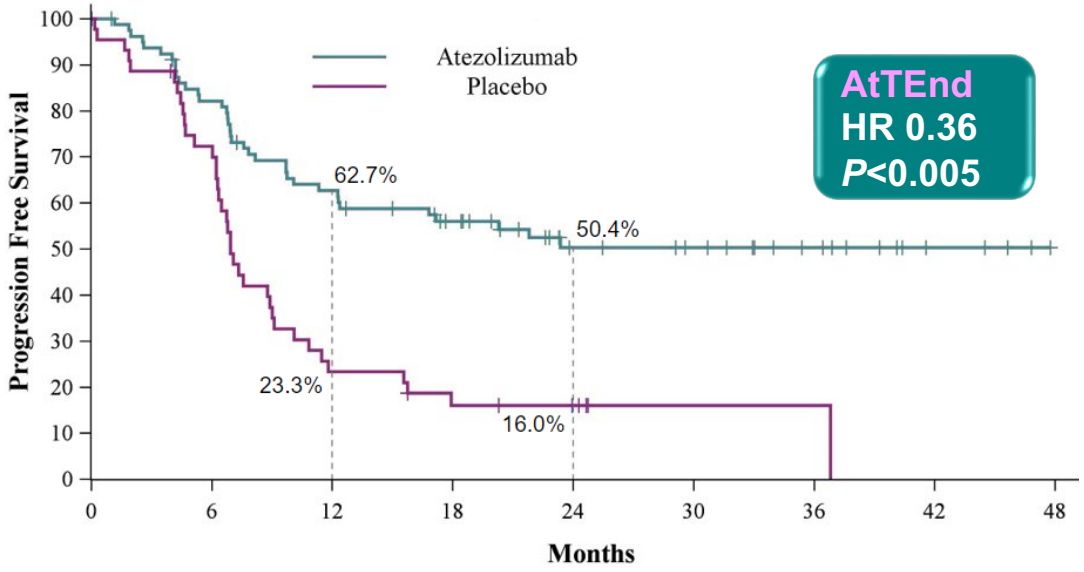
Immune Checkpoint Inhibitor plus Chemotherapy in First-line Endometrial Cancer: PFS in dMMR Tumors



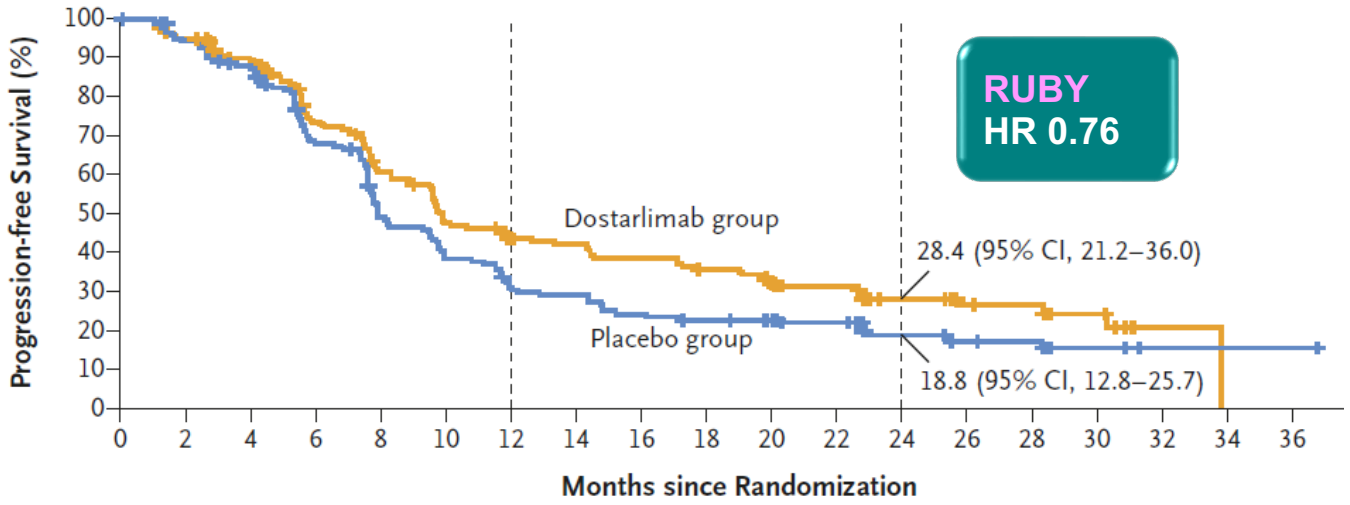




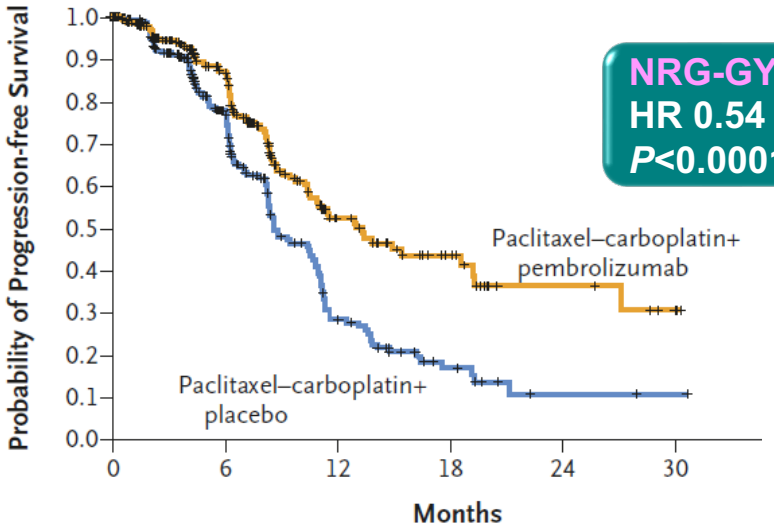


Mansoor R. Mirza et al. NEJM August 2023, Ramez N. Eskander et al. NEJM August 2023, Westin SN, et al. JCO 2023, Nicoletta Colombo et al., ESMO 2023

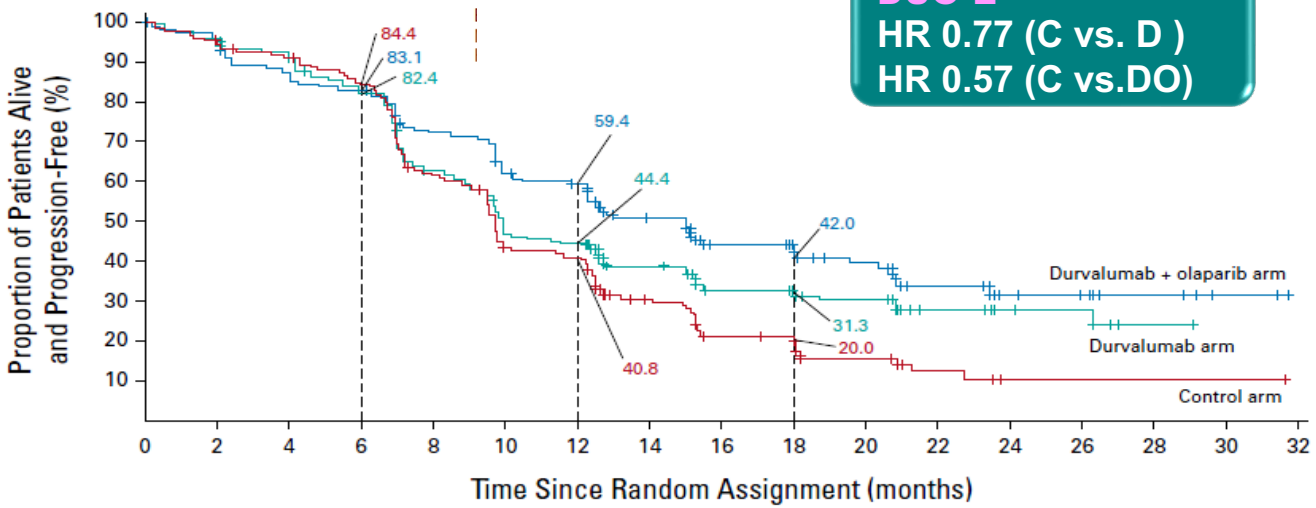
Immune Checkpoint Inhibitor plus Chemotherapy in First-line Endometrial Cancer: PFS in pMMR Tumors



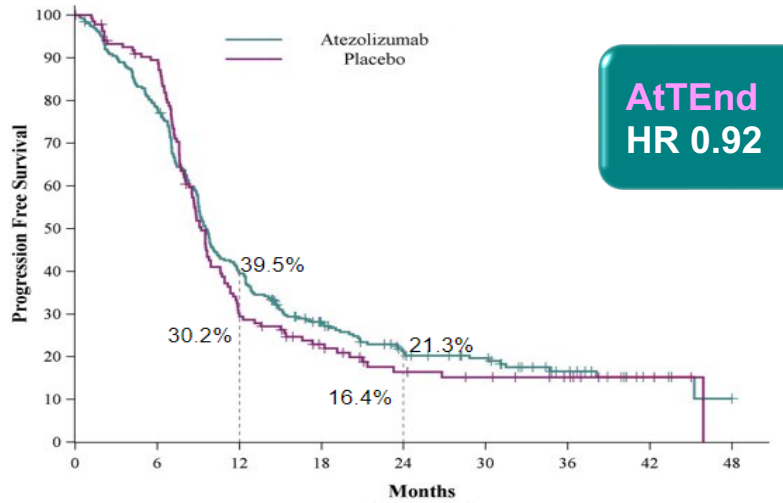
RUBY
HR 0.76



NRG-GY018
HR 0.54
***P*<0.0001**



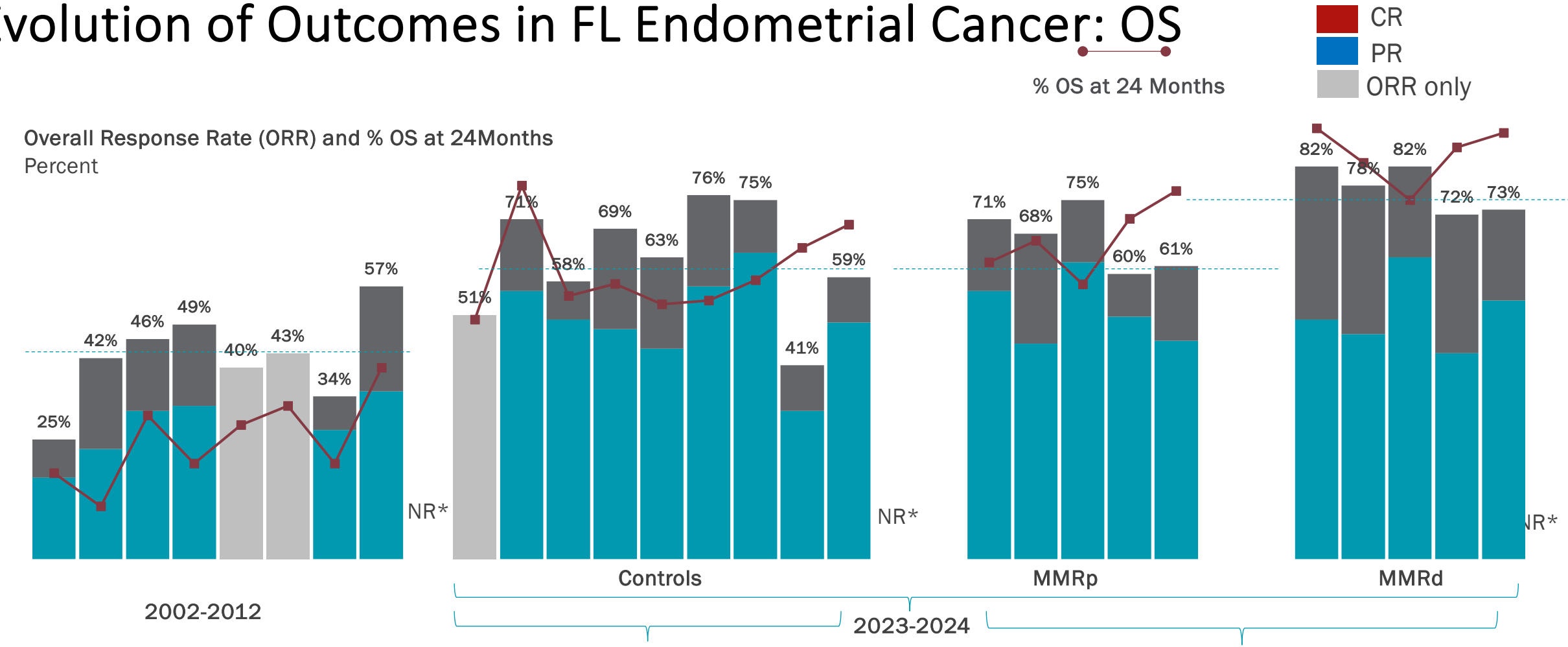
DUO-E
HR 0.77 (C vs. D)
HR 0.57 (C vs.DO)



AtTEnd
HR 0.92

Mansoor R. Mirza et al. NEJM August 2023, Ramez N. Eskander et al. NEJM August 2023, Westin SN, et al. JCO 2023, Nicoletta Colombo et al., ESMO 2023

Evolution of Outcomes in FL Endometrial Cancer: OS



Treatment with:

- doxorubicin
- doxorubicin + cisplatin
- doxorubicin + cisplatin circadian
- doxorubicin + paclitaxel
- doxorubicin + cisplatin + paclitaxel*

Control arms of Paclitaxel + Carboplatin for:

- GY018
- Ruby
- ATTEND
- DUO-E
- Ruby2*

Placlitaxel + Carbopatin + :

- pembrolizumab
- dostarlimab
- atezolizumab
- durvalumab
- durvalumab+olaparib
- dostarlimab + niraparib*

Thigpen et al. J Clin Oncol 2004, Gallion et al. J Clin Oncol 2003, Fleming et al. J Clin Oncol 2004, Fleming et al. J Clin Oncol 2004 11(22), Miller et al. J Clin Oncol 2020; Aghajanian et al. Gynecol Oncol 2018, Eskander ESMO 2023; Eskander et al. NEJM 2023; Eskander et al. SGO 2024, Mirza et al. NEJM 2023; Powell et al. SGO 2024, Colombo et al. ESMO 2023, Westin et al. ESMO 2023

DUO-E study design

Patients

- Newly diagnosed FIGO 2009 Stage III/IV or recurrent endometrial cancer
- Known MMR status
- Naïve to first-line systemic anticancer treatment for advanced disease
- Naïve to PARP inhibitors and immune-mediated therapy
- Adjuvant chemotherapy allowed if ≥12 months from last treatment to relapse
- All histologies except sarcomas

N=718

R 1:1:1

Stratified by:

- MMR status (proficient vs deficient)
- Disease status (recurrent vs newly diagnosed)
- Geographic region (Asia vs non-Asia)

	Chemotherapy phase	Maintenance phase
Control	**Carboplatin/paclitaxel** (q3w) + **Placebo** (IV q3w)	**Placebo** (IV q4w) + **Placebo** (tablets bid)
Durva	**Carboplatin/paclitaxel** (q3w) + **Durvalumab** (1120 mg IV q3w)	**Durvalumab** (1500 mg IV q4w) + **Placebo** (tablets bid)
Durva+Ola	**Carboplatin/paclitaxel** (q3w) + **Durvalumab** (1120 mg IV q3w)	**Durvalumab** (1500 mg IV q4w) + **Olaparib** (300 mg tablets bid)

Patients without disease progression

Treatment until disease progression, unacceptable toxicity or other discontinuation criteria were met

Endpoints

Primary

- PFS (RECIST per investigator) in:
  - Durva vs Control
  - Durva+Ola vs Control

Key secondary

- OS (analytical)
- Safety

Exploratory

- PFS in Durva+Ola vs durva
- Subgroup analyses of PFS
  - Including MMR, PD-L1, and HRRm

*Six cycles of carboplatin at an area under the concentration–time curve of 5 or 6 mg per mL/min and paclitaxel 175 mg/m^2.

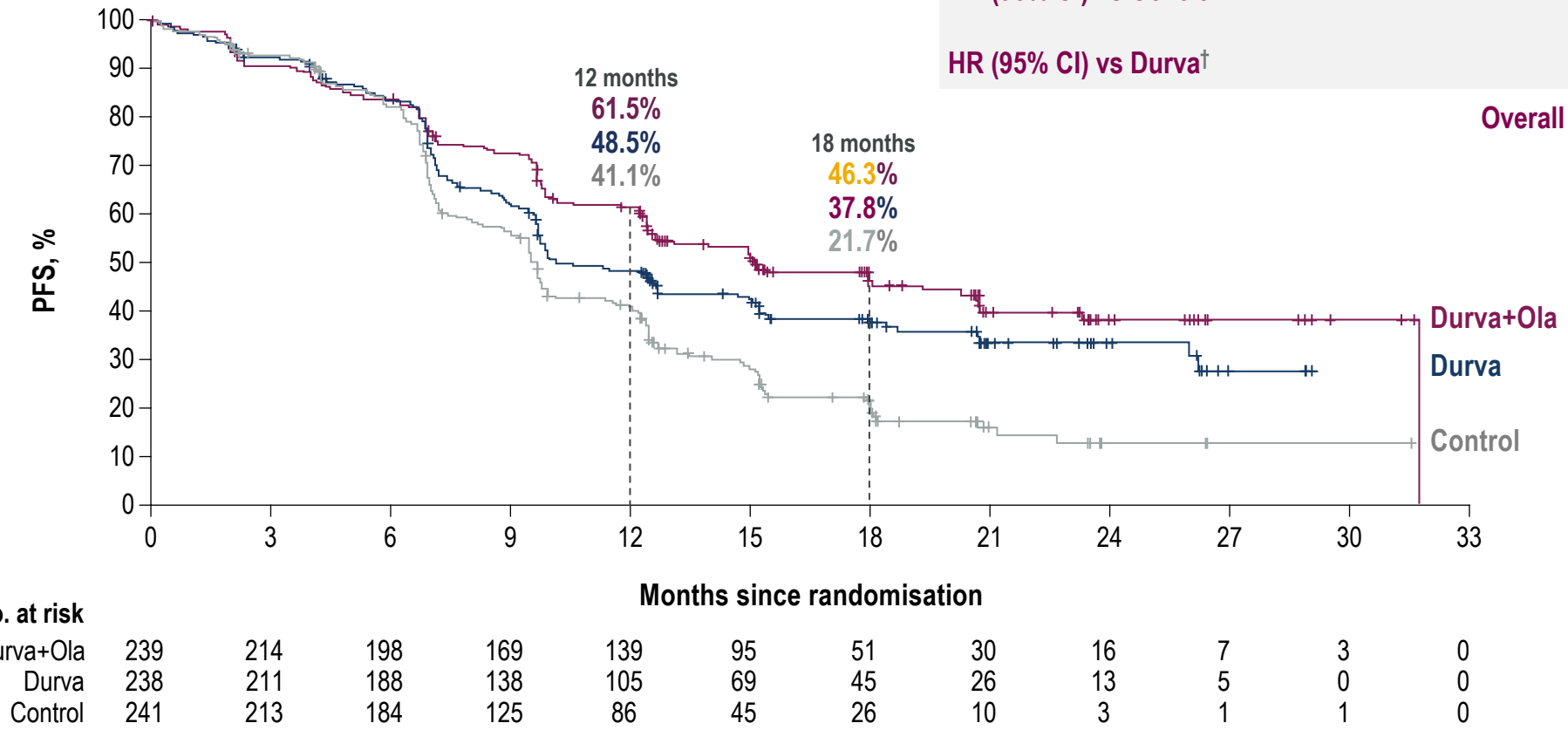
bid, twice daily; CP, carboplatin/paclitaxel; durva, durvalumab; FIGO, International Federation of Gynaecology and Obstetrics; HRRm, homologous recombination repair mutation; IV, intravenously; ola, olaparib; pbo, placebo; q3(4)w, every 3(4) weeks; R, randomisation; RECIST, Response Evaluation Criteria for Solid Tumours.

PFS: ITT population

- Primary endpoint

	Control (N=241)	Durva (N=238)	Durva+Ola (N=239)
Events, n (%)	173 (71.8)	139 (58.4)	126 (52.7)
Median PFS (95% CI),* months	9.6 (9.0–9.9)	10.2 (9.7–14.7)	15.1 (12.6–20.7)
HR (95% CI) vs Control†		**0.71** (0.57–0.89); *P*=0.003	**0.55** (0.43–0.69); *P*<0.0001
HR (95% CI) vs Durva†			0.78 (0.61–0.99)

Overall data maturity 61.0%



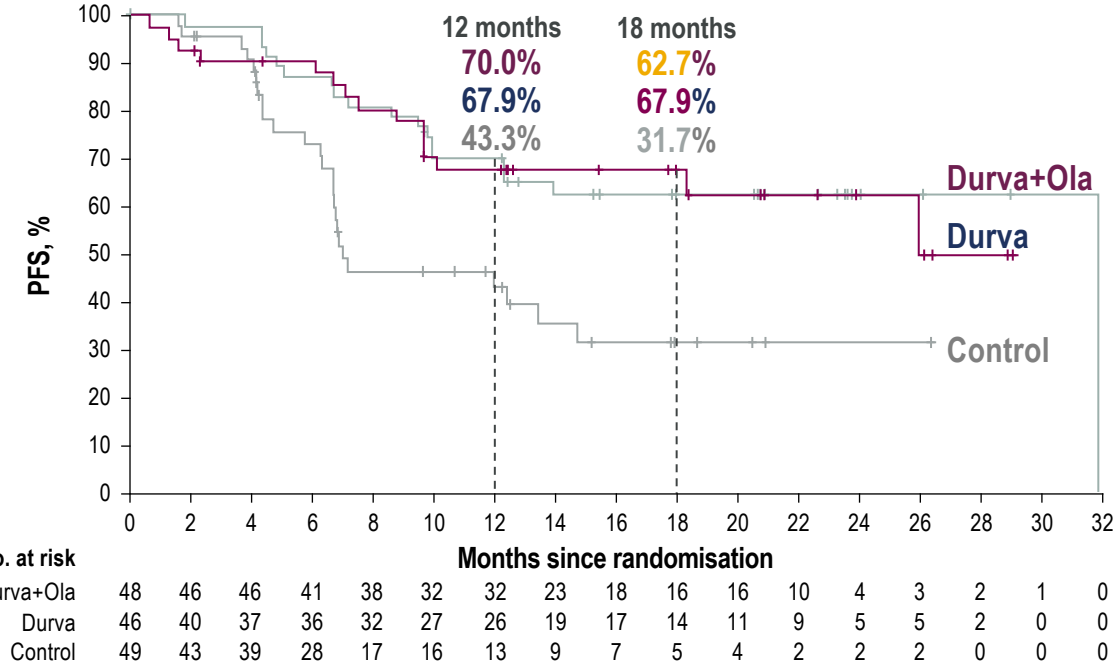
No. at risk

Durva+Ola	239	214	198	169	139	95	51	30	16	7	3	0
Durva	238	211	188	138	105	69	45	26	13	5	0	0
Control	241	213	184	125	86	45	26	10	3	1	1	0

The median (range) duration of follow-up for PFS was 12.6 (0.0–31.6), 15.4 (0.0–29.1), and 15.4 (0.0–31.7) months in censored patients for the Control, Durva, and Durva+Ola arms, respectively. PFS rates were estimated by the KM method. *CI for median PFS is derived based on the Brookmeyer–Crowley method; †The primary PFS analysis for each comparison was performed separately. The HR and CI were estimated from a Cox proportional hazards model stratified by MMR and disease status. The CI was calculated using a profile likelihood approach. The *P* value was calculated using a log-rank test stratified by MMR and disease status. ITT, intent-to-treat; KM, Kaplan–Meier.

Subgroup analysis of PFS by MMR status

dMMR (20% of population)

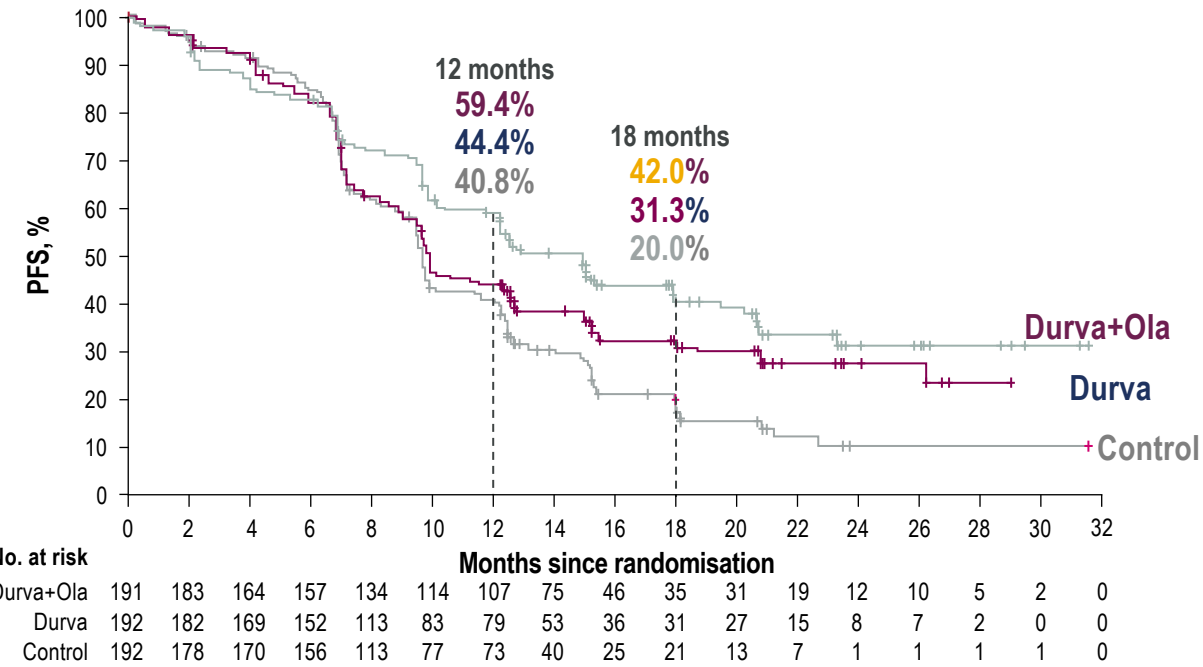


No. at risk

Durva+Ola	48	46	46	41	38	32	32	23	18	16	16	10	4	3	2	1	0
Durva	46	40	37	36	32	27	26	19	17	14	11	9	5	5	2	0	0
Control	49	43	39	28	17	16	13	9	7	5	4	2	2	2	0	0	0

	Control (N=49)	Durva (N=46)	Durva+Ola (N=48)
Events, n (%)	25 (51.0)	15 (32.6)	18 (37.5)
Median PFS (95% CI),* months	7.0 (6.7–14.8)	NR (NR–NR)	31.8 (12.4–NR)
HR (95% CI) vs Control†		**0.42 (0.22–0.80)**	**0.41 (0.21–0.75)**
HR (95% CI) vs Durva†			**0.97 (0.49–1.98)**

pMMR (80% of population)



No. at risk

Durva+Ola	191	183	164	157	134	114	107	75	46	35	31	19	12	10	5	2	0
Durva	192	182	169	152	113	83	79	53	36	31	27	15	8	7	2	0	0
Control	192	178	170	156	113	77	73	40	25	21	13	7	1	1	1	1	0

	Control (N=192)	Durva (N=192)	Durva+Ola (N=191)
Events, n (%)	148 (77.1)	124 (64.6)	108 (56.5)
Median PFS (95% CI),* months	9.7 (9.2–10.1)	9.9 (9.4–12.5)	15.0 (12.4–18.0)
HR (95% CI) vs Control†		**0.77 (0.60–0.97)**	**0.57 (0.44–0.73)**
HR (95% CI) vs Durva†			**0.76 (0.59–0.99)**

Exploratory subgroup analysis. MMR status evaluated using the Ventana immunohistochemistry MMR panel. Rates were estimated by the KM method.
*CI for median PFS was derived based on the Brookmeyer–Crowley method; †The HR and CI were estimated from an unstratified Cox proportional hazards model. NR, not reached

FDA approves pembrolizumab with chemotherapy for primary advanced or recurrent endometrial carcinoma

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On June 17, 2024, the Food and Drug Administration approved pembrolizumab with carboplatin and paclitaxel, followed by single-agent pembrolizumab, for adult patients with primary advanced or recurrent endometrial carcinoma.

All comers

Olaparib and Durvalumab *combination recommended for approval in the EU by CHMP for patients with mismatch repair proficient advanced or recurrent endometrial cancer*

PUBLISHED
1 July 2024

Imfinzi also recommended for patients with mismatch repair deficient disease

Recommendation based on DUO-E Phase III results, which showed both regimens demonstrated statistically significant and clinically meaningful improvement in progression-free survival vs. chemotherapy alone

pMMR

FDA approves durvalumab with chemotherapy for mismatch repair deficient primary advanced or recurrent endometrial cancer

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On June 14, 2024, the Food and Drug Administration approved durvalumab (Imfinzi, with carboplatin plus paclitaxel followed by single-agent durvalumab for adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair deficient (dMMR).

dMMR

FDA approves dostarlimab-gxly with chemotherapy for endometrial cancer

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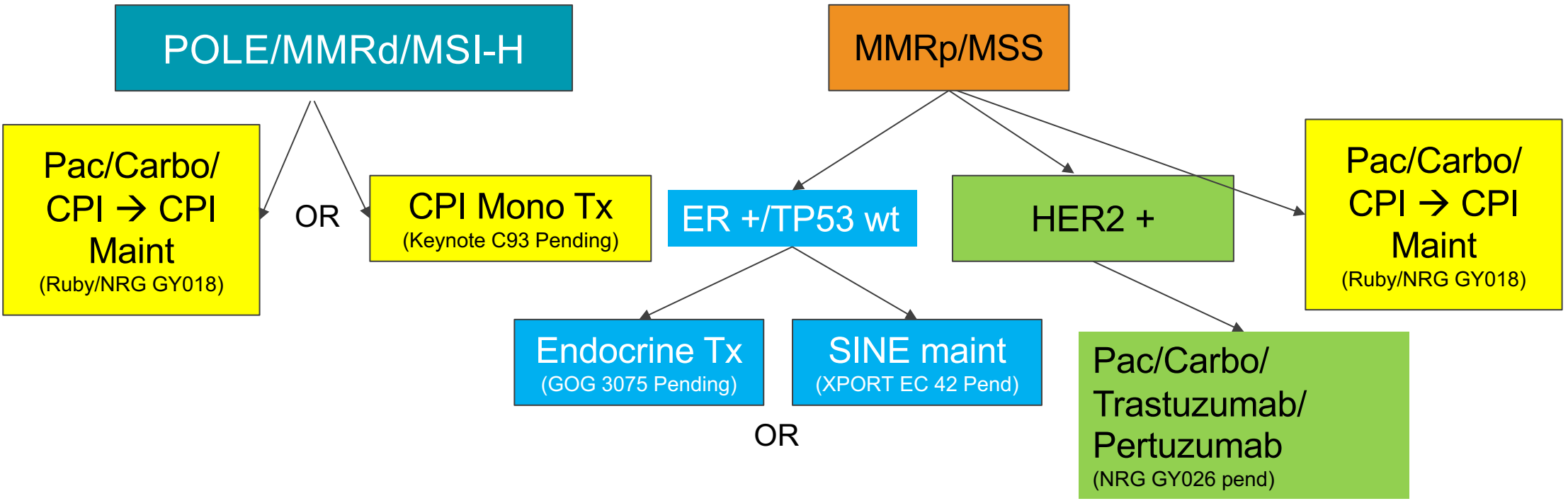
On July 31, 2023, the Food and Drug Administration approved dostarlimab-gxly with carboplatin and paclitaxel, followed by single-agent dostarlimab-gxly, for primary advanced or recurrent endometrial cancer (EC) that is mismatch repair deficient (dMMR), as determined by an FDA-approved test, or microsatellite instability-high (MSI-H).

Molecular Selection for 1L Metastatic/Recurrent EC: The Future



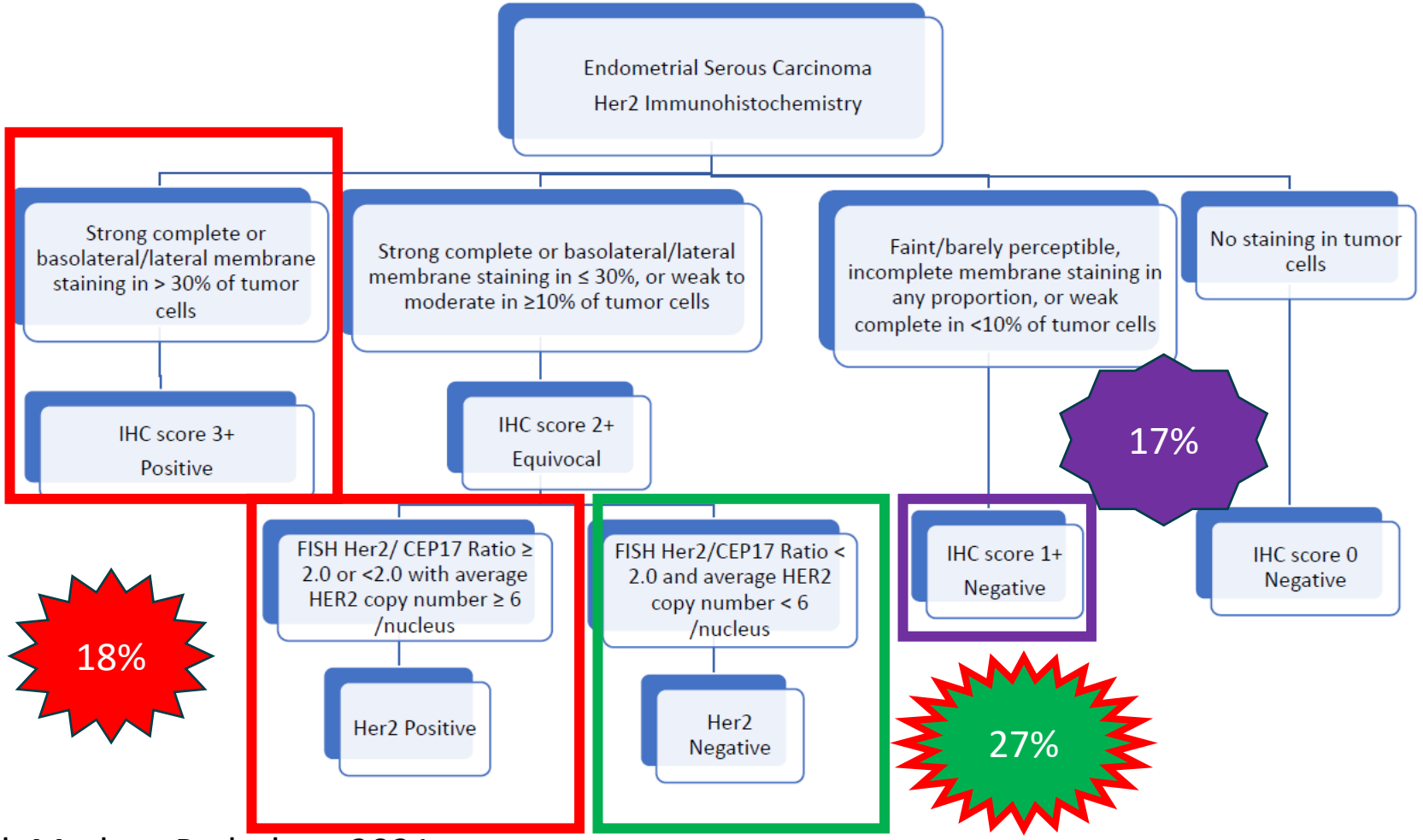
Where do PARPi Layer in (if at all)?
(DUO-E, Ruby Part 2 Pending)

What Treatment Do You Choose at Time of Recurrence?

Carbo, carboplatin; CNL, copy number low; MMRd, mismatch repair deficient; Pac, paclitaxel

IHC and FISH characterization of endometrial cancer

Addition of trastuzumab to paclitaxel and carboplatin was endorsed by the NCCN in 2019
Pathologic evaluation of tumor HER2 protein expression and gene amp is a critical part of therapeutic decision making

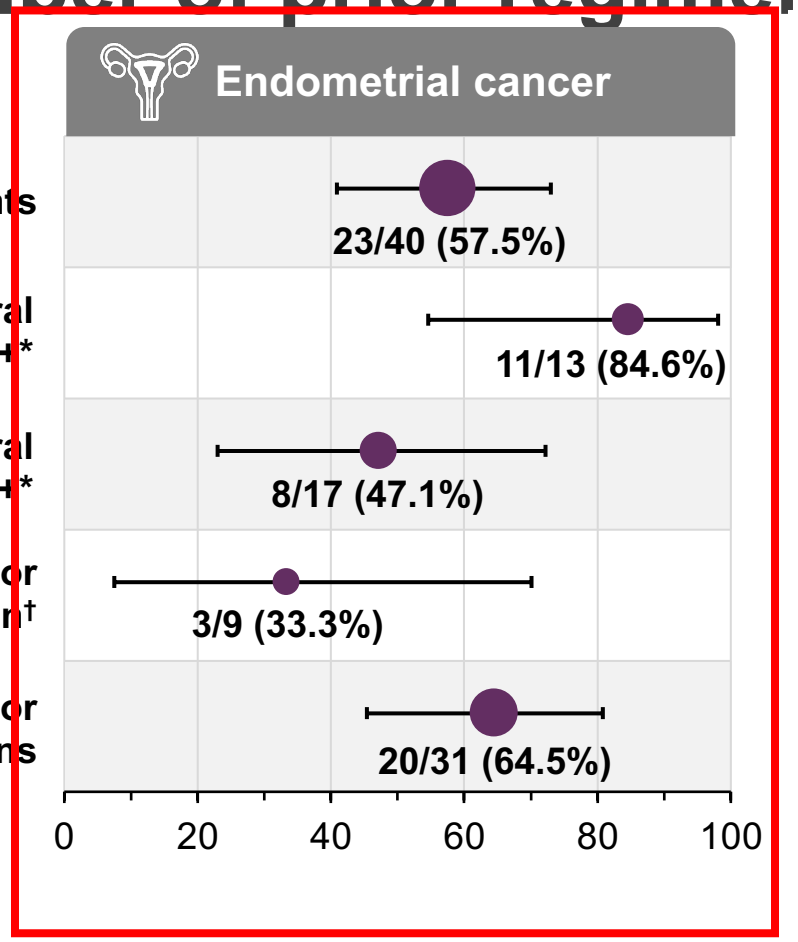


- HER2 IHC score incorporates both staining intensity and % of tumor cell staining
- Both complete and basolateral/ lateral staining patterns count towards % staining cut-off

Buza et al. Modern Pathology 2021

OU Health | Stephenson Cancer Center

TDXd ORR in all patients, and by central IHC status and number of prior regimens

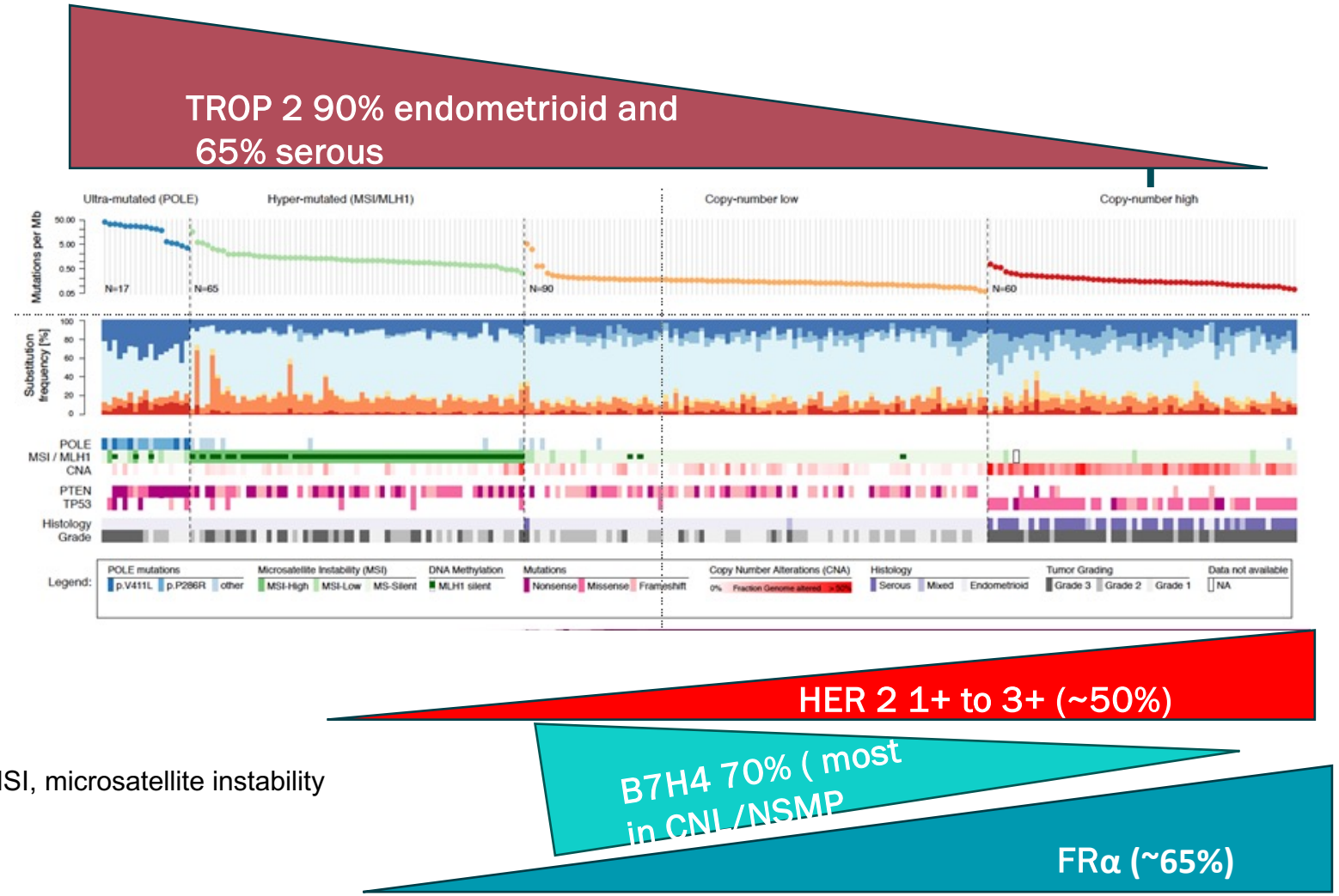


Error bars represent 95% confidence intervals

*In patients with IHC 1+/0/unknown by central testing, responses were observed in 4/10 patients with endometrial cancer, 6/12 patients with cervical cancer, and 4/10 patients with ovarian cancer; †one patient with endometrial cancer was reported to have received no prior regimens
IHC, immunohistochemistry; INV, investigator; ORR, objective response rate

Makker et al. SGO 2024

Molecular Classification of Endometrial Cancer: Layer in Tumor Associated Antigens (this is hypothetical)



MSI, microsatellite instability

We can expect a lot of overlap between tumor associated antigens across expression levels

How do we move agents forward with similar payloads and overlapping targets?

How important is the combination of target, linker, payload AND molecular setting in endometrial cancer?

We need to understand this better before we move these into front line.

The Cancer Genome Atlas Research Network. *Nature.* 2013;494(7438):506.; Soberanis Pina and Lhereux. Biologics: Targets and Therapy 2024:18 79–93

Endometrial Cancer 2024 take aways

- For FL ADV/Metastatic CPI + chemo is now FDA approved for all
- Incorporation of PARPi is pending
- 2L+ is an ADC world and biomarker interrogation is critical
- NSMP (I didn't have time to cover) is a unique subgroup where endocrine combinations are under active study – stay tuned