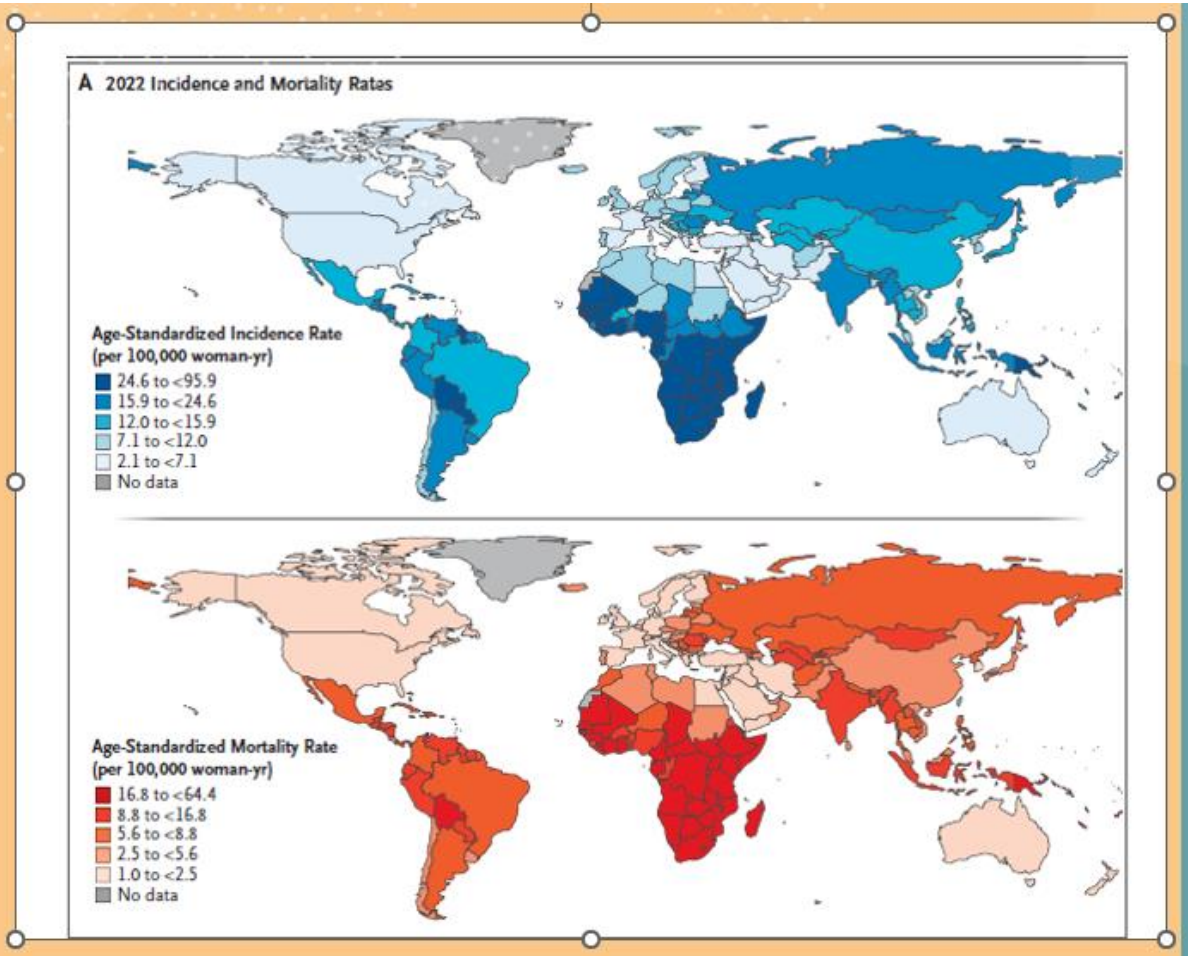
Incorporating Immunotherapy in the Management of Cervical Cancer

Susana Campos MD, MPH
Dana Farber Cancer Institute
Harvard Medical School
Boston Mass

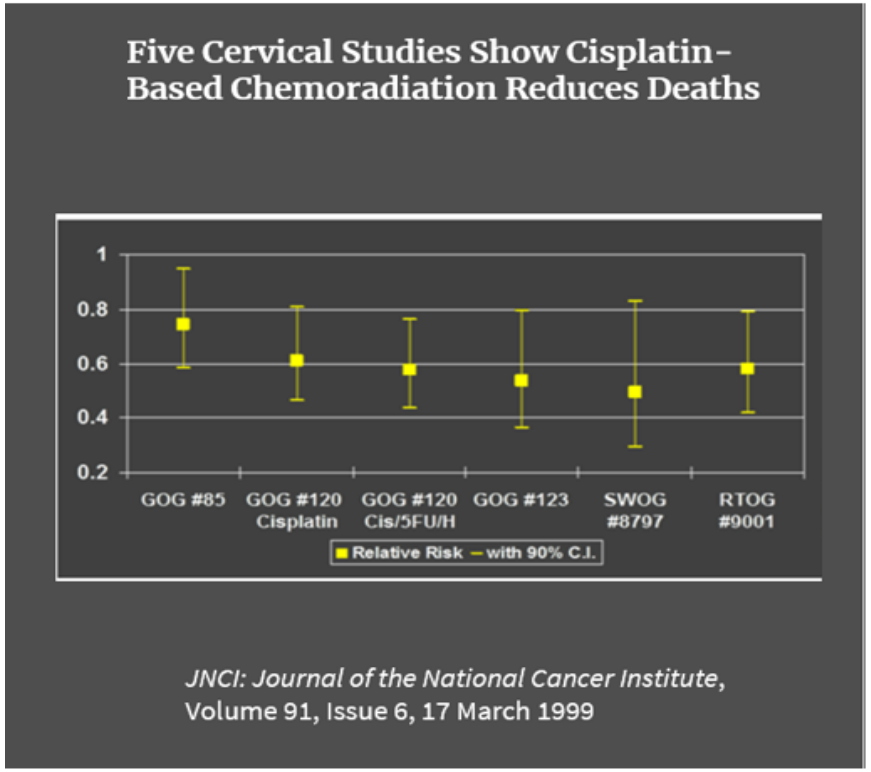
2022 Incidence and Mortality Cervical Cancer[1]

Estimated number of new cases (13,360) and deaths (4320) US 2025[2]



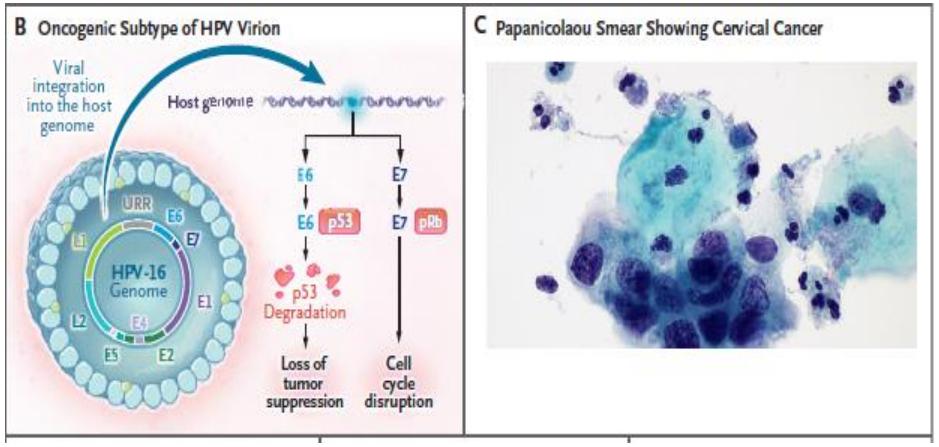
[1]Tewari KS et al, NEJM 2025;
[2]Siegel RL, et al Cancer Statistics 2025

Landmarks in Cervical Cancer

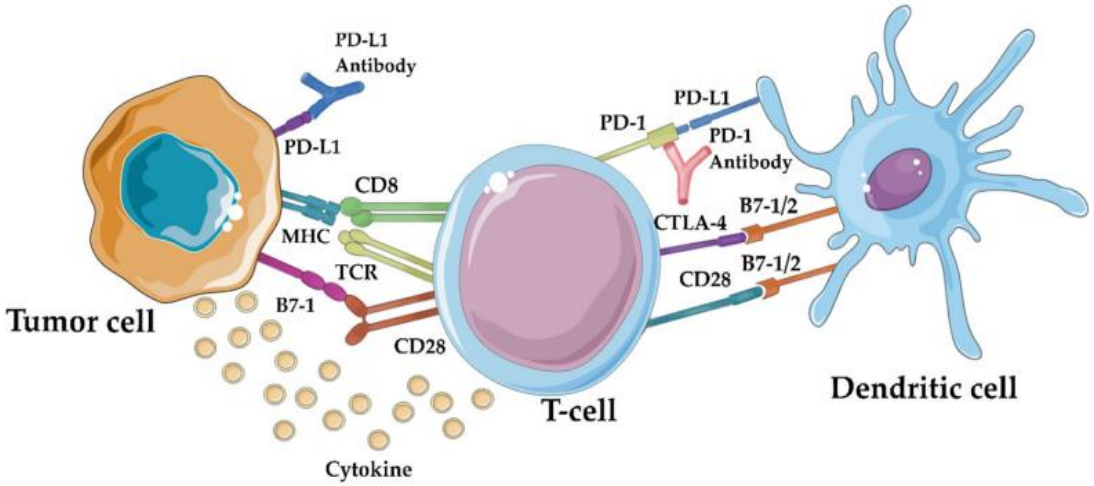


Landmarks in Cervical Cancer

- GOG 85 Whitney CW et al, JCO 1999
- RTOG 9001 Morris M et al, NEJM 1999
- GOG120 Rose P et al, NEJM 1999
- SWOG 8797 Peters WA et al, JCO 2000
- GOG 123 Keys H et al, NEJM 1999

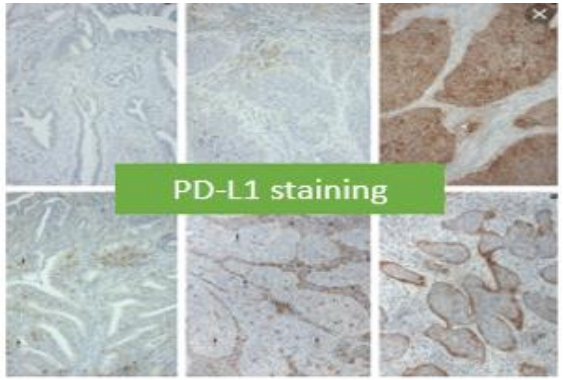


Immunotherapy: The New Landmark



Immune checkpoint inhibitors' mechanism of action: by blocking the PD-1/PD-L1 interaction, immune checkpoint inhibitors like anti-PD-1 and anti-PD-L1 antibodies can "release the brakes" on the immune system, enabling it to recognize and attack tumor cells more effectively [20]. Figure 1. Immune checkpoint inhibitors' mechanism of action: by blocking the PD-1/PD-L1 interaction, immune checkpoint inhibitors like anti-PD-1 and anti-PD-L1 antibodies can "release the brakes" on the immune system, enabling it to recognize and attack tumor cells more effectively *Life* **2024**, *14*(3), 344; **https://doi.org/10.3390/life14030344**

PD-L1 expression in cervical cancer: 64 %[1]



$$\text{CPS} = \frac{\text{PD-L1 positively stained cells (tumor cells, lymphocytes, macrophages)}}{\text{all vital tumor cells}} \times 100$$

[1]Baek MH, et al. Gyn Onc 2024

Shades of Stages: Cervical Cancer

2014

Table 2
FIGO staging of cervical cancer

Stage	
I	Lesion is confined to cervix
IA	No visual lesion identifiable, but only by microscopic examination. Depth of invasion is no greater than 5 mm and lesion is no wider than 7 mm in diameter.
IA1	Stromal invasion is no greater than 3 mm in depth and no wider than 7 mm
IA2	Stromal invasion between 3 and 5 mm in depth and is no wider than 7 mm
IB	Lesion is visible and confined to the cervix or is preclinical but larger than the limits of stage IA
IB1	Lesion is no larger than 4 cm
IB2	Lesion is larger than 4 cm
II	Lesion extends into the vagina but no further than the upper two-thirds and or extends into the parametria but not to the pelvic side wall
IIA	Lesion extends into the upper two thirds of the vagina; no parametrial involvement
IIB	Obvious parametrial involvement: does not extend to pelvic sidewall
III	Lesion extends into lower one-third of the vagina or extends to pelvic sidewall; or there is evidence of hydronephrosis or a nonfunctioning kidney without a noncancerous cause
IIIA	Lesion extends into the lower one-third of the vagina but not to pelvic sidewall
IIIB	Lesion extends to pelvic sidewall or hydronephrosis or nonfunctioning kidney
IV	Tumor extends beyond true pelvis or clinically involves the mucosa of the bladder or rectum
IVA	Tumor has spread to adjacent organs
IVB	Tumor has spread to distant organs

FIGO Committee on Gynecologic Oncology. FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. Int J Gynaecol Obstet. 2014 May;125(2):97-8.

2018

Box 1

Stage I:
The carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded).
- **IA** Invasive carcinoma that can be diagnosed only by microscopy with maximum depth of invasion ≤5 mm[a]
  - **IA1** Measured stromal invasion ≤3 mm in depth
  - **IA2** Measured stromal invasion >3 mm and ≤5 mm in depth
- **IB** Invasive carcinoma with measured deepest invasion >5 mm (greater than stage IA); lesion limited to the cervix uteri with size measured by maximum tumor diameter[b]
  - **IB1** Invasive carcinoma >5 mm depth of stromal invasion and ≤2 cm in greatest dimension
  - **IB2** Invasive carcinoma >2 cm and ≤4 cm in greatest dimension
  - **IB3** Invasive carcinoma >4 cm in greatest dimension

Stage II:
The cervical carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
- **IIA** Involvement limited to the upper two-thirds of the vagina without parametrial invasion
  - **IIA1** Invasive carcinoma ≤4 cm in greatest dimension
  - **IIA2** Invasive carcinoma >4 cm in greatest dimension
- **IIB** With parametrial invasion but not up to the pelvic wall

Stage III:
The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or paraaortic lymph nodes
- **IIIA** Carcinoma involves lower third of the vagina, with no extension to the pelvic wall
- **IIIB** Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause)
- **IIIC** Involvement of pelvic and/or paraaortic lymph nodes **(including micrometastases)**[c], irrespective of tumor size and extent (with r and p notations)[d]
  - **IIIC1** Pelvic lymph node metastasis only
  - **IIIC2** Paraaortic lymph node metastasis

Stage IV:
The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to stage IV.
- **IVA** Spread of the growth to adjacent organs
- **IVB** Spread to distant organs

- [a] Imaging and pathology can be used, when available, to supplement clinical findings with respect to tumor size and extent, in all stages. **Pathological findings supercede imaging and clinical findings.**
- [b] The involvement of vascular/lymphatic spaces should not change the staging. The lateral extent of the lesion is no longer considered.
- [c] Isolated tumor cells do not change the stage but their presence should be recorded

Int J Gynecol Obstet 145(2019) 129–135

CALLA and A18:Locally Advanced Cervical Cancer: opposing views

	CALLA[1]	A18[2]
Eligibility (stage)	FIGO 2009 stage IB2-IIB (node positive disease) or ≥ stage III	FIGO 2014 stage IB2-IIB (node-positive disease) or stage III-IVA
Eligibility (nodes)	Allows 1 pelvic node+	Must have two pelvic or aortic node+ but allows PET SUV 2.5+
Lymph node size	Amendment: downsized LN size in short axis for CT (from 1.5 cm to 1 cm)	Remained unchanged for LN size per RECIST 1.1 (≥1.5 cm shortest dimension)
Target	PD-L1	PD1
Agent	Durvalumab	Pembrolizumab
Chemo for CRT	Cisplatin or carboplatin	Cisplatin only
Primary end point(s)	PFS	PFS/OS
Stratification factors	Stage	IMRT/VMAT vs. non
	Region of world	Total RT dose <70 vs. ≥70 Gy
		Stage (1B2-IIB node+ vs. III/IVA node+/-)
Enrollment	N = 770, 120 sites, 15 countries	N = 1060, 176 sites, 30 countries

Abbreviations: CRT, chemoradiation; CT, computed tomography scan; Gy, gray; IMRT, intensity modulated radiation therapy; LN, lymph node; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; RT, radiation therapy; SUV, standardized uptake value; VMAT, volumetric modulated arc therapy.

[1]Monk B et al, Lancet Oncol 2023;[2] Lorusso D, et al Lancet 2024

Durvalumab versus placebo with chemoradiotherapy for locally advanced cervical cancer (CALLA): a randomised, double-blind, phase 3 trial

Bradley J Monk, Takafumi Toita, Xiaohua Wu, Juan C Vázquez Limón, Rafał Tarnawski, Masaki Manda, Ronnie Shapira-Frommer, Umesh Mahantshetty, María del Pilar Estevez Diz, Qi Zhou, Sewanti Limaye, Francisco J Ramírez Godínez, Christina Oppermann Kessler, Sofiia Varga, Natalia Valdivieso, Daisuke Aoki, Manuel Leiva, Jung-Yun Lee, Raymond Sukop, Yulia Kreynina, Wen-Fang Chang, Felipe Rey, Yi Kong, Guihua Ke, Sophie Wildsmith, Andrew Lloyd, Hannah Dry, Ana Tabilente Nunes, Jyoti Mayadev

Summary

Background Concurrent chemoradiotherapy has been the standard of care for locally advanced cervical cancer for over 20 years; however, 30–40% of treated patients have recurrence or progression within 5 years. Immune checkpoint inhibition has improved outcomes for patients with PD-L1 positive metastatic or recurrent cervical cancer. We assessed the benefit of adding durvalumab, a PD-L1 antibody, with and following chemoradiotherapy for locally advanced cervical cancer.

Methods The CALLA randomised, double-blind, phase 3 trial included 105 hospitals across 15 countries. Patients aged at least 18 years with previously untreated locally advanced cervical cancer (adenocarcinoma, squamous, or adenosquamous; International Federation of Gynaecology and Obstetrics [FIGO] 2009 stage IB2–IIB lymph node positive, stage ≥III any lymph node status) and WHO or Eastern Cooperative Oncology Group performance status of 0 or 1 were randomly assigned (1:1) through an interactive web response system using a permuted block size of 4 to receive durvalumab (1500 mg intravenously once every 4 weeks) or placebo with and following chemoradiotherapy, for up to 24 cycles. Chemoradiotherapy included 45 Gy external beam radiotherapy at 5 fractions per week concurrent with intravenous cisplatin (40 mg/m² or carboplatin (area under the concentration-time curve 2) once weekly for 5 weeks, followed by image-guided brachytherapy (high-dose rate, 27·5–30 Gy or low-dose/pulse-dose rate, 35–40 Gy). Randomisation was stratified by disease stage status (FIGO stage and node status) and geographical region. Chemoradiotherapy quality was continuously reviewed. The primary endpoint was progression-free survival, assessed by the investigator using Response Evaluation Criteria in Solid Tumors, version 1.1, in the intention-to-treat population. Safety was assessed in patients who received at least one dose of study treatment. This study is registered with ClinicalTrials.gov, NCT03380676.

Findings Between Feb 15, 2019, and Dec 10, 2020, 770 women were randomly assigned (385 to durvalumab and 385 to placebo; median age 49 years [IQR 41–57]). Median follow-up was 18·5 months (IQR 13·2–23·5) in the durvalumab group and 18·4 months (13·2–23·7) in the placebo group. At data cutoff, median progression-free survival had not been reached (95% CI not reached–not reached) for either group (HR 0·84; 95% CI 0·65–1·08; p=0·17); 12-month progression-free survival was 76·8% (71·3–80·9) with durvalumab and 73·3% (68·4–77·5) with placebo. The most frequently reported grade 3–4 adverse events in both groups were anaemia (76 [20%] of 385 in the durvalumab group *vs* 56 [15%] of 384 in the placebo group) and decreased white blood cells (39 [10%] *vs* 49 [13%]). Serious adverse events occurred for 106 (28%) patients who received durvalumab and 89 (23%) patients who received placebo. There were five treatment-related deaths in the durvalumab group (one case each of urinary tract infection, blood loss anaemia, and pulmonary embolism related to chemoradiotherapy only; one case of endocrine disorder related to durvalumab only; and one case of sepsis related to both durvalumab and chemoradiotherapy). There was one treatment-related death in the placebo group (pneumonia related to chemoradiotherapy).

Interpretation Durvalumab concurrent with chemoradiotherapy was well tolerated in participants with locally advanced cervical cancer, however it did not significantly improve progression-free survival in a biomarker unselected, all-comers population. Concurrent durvalumab plus chemoradiotherapy warrants further exploration in patients with high tumoral PD-L1 expression. Rigorous monitoring ensured high chemoradiotherapy compliance with advanced technology and allowed patients to receive optimal care.

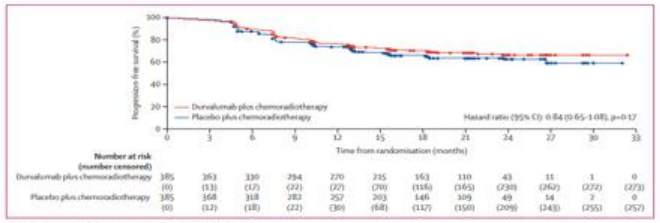


Figure 2: **Kaplan-Meier plot of progression-free survival**
Progression-free survival, as per Response Evaluation Criteria in Solid Tumors version 1.1 as assessed by investigator or histopathological confirmation of local tumour progression. Data maturity was 31%.

Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): a randomised, double-blind, phase 3 clinical trial

Domenica Lorusso, Yang Xiang, Kosei Hasegawa, Giovanni Scambia, Manuel Leiva, Pier Ramos-Elias, Alejandro Acevedo, Vladyslav Sukhin, Noelle Cloven, Andrea J Pereira de Santana Gomes, Fernando Contreras Mejía, Ari Ratos, Ali Ayhan, Jung-Yun Lee, Valeriya Saevets, Flora Zagouri, Lucy Gilbert, Jalid Sehouli, Ekkasit Tharavichitkul, Kristina Lindemann, Roberta Lazzari, Chih-Long Chang, Rudolf Lampé, Hong Zhu, Ana Oaknin, Melissa Christiaens, Stephan Polterauer, Tomoko Usumi, Kan Li, Karin Yamada, Sarpar Toker, Stephen M Keefe, Sandro Pignata*, Linda R Duska*, *on behalf of the ENGOT-cx11/GOG-3047/KEYNOTE-A18 investigators†*

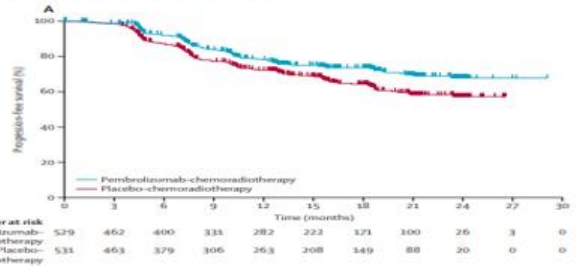
Summary

Background Pembrolizumab has shown efficacy in persistent, recurrent, or metastatic cervical cancer. The effect of chemoradiotherapy might be enhanced by immunotherapy. In this phase 3 trial, we assessed the efficacy and safety of adding pembrolizumab to chemoradiotherapy in locally advanced cervical cancer.

Methods In this randomised, double-blind, placebo-controlled, phase 3 ENGOT-cx11/GOG-3047/KEYNOTE-A18 clinical trial, adults (age ≥18 years) at 176 medical centres in 30 countries with newly diagnosed, high-risk, locally advanced cervical cancer were randomly assigned (1:1) using an interactive voice-response system with integrated web response to receive 5 cycles of pembrolizumab (200 mg) or placebo every 3 weeks plus chemoradiotherapy, followed by 15 cycles of pembrolizumab (400 mg) or placebo every 6 weeks. Randomisation was stratified by planned external beam radiotherapy type (intensity-modulated radiotherapy or volumetric-modulated arc therapy *vs* non-intensity-modulated radiotherapy or non-volumetric-modulated arc therapy), cervical cancer stage at screening (International Federation of Gynecology and Obstetrics 2014 stage IB2–IIB node positive *vs* stage III–IVA), and planned total radiotherapy (external beam radiotherapy plus brachytherapy) dose (<70 Gy *vs* ≥70 Gy equivalent dose in 2 Gy fractions). Primary endpoints were progression-free survival per Response Evaluation Criteria in Solid Tumours version 1.1—by investigator or by histopathologic confirmation of suspected disease progression—and overall survival. Primary analysis was conducted in the intention-to-treat population, which included all randomly allocated participants. Safety was assessed in the as-treated population, which included all randomly allocated patients who received at least one dose of study treatment. This study is registered with ClinicalTrials.gov, NCT04221945, and is closed to new participants.

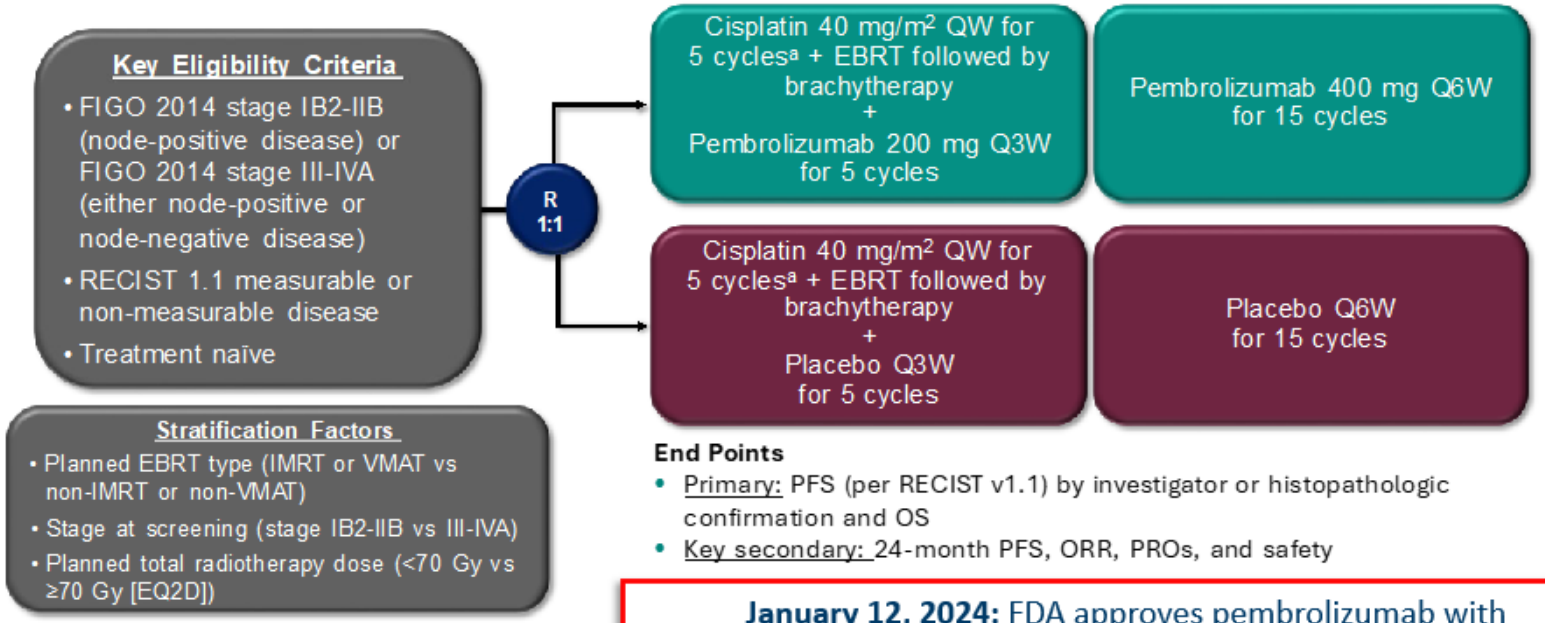
Findings Between June 9, 2020, and Dec 15, 2022, 1060 participants were randomly assigned to treatment, with 529 assigned to the pembrolizumab–chemoradiotherapy group and 531 to the placebo-chemoradiotherapy group. At data cutoff (Jan 9, 2023), median follow-up was 17·9 months (IQR 11·3–22·3) in both treatment groups. Median progression-free survival was not reached in either group; rates at 24 months were 68% in the pembrolizumab–chemoradiotherapy group versus 57% in the placebo-chemoradiotherapy group. The hazard ratio (HR) for disease progression or death was 0·70 (95% CI 0·55–0·89, p=0·0020), meeting the protocol-specified primary objective. Overall survival at 24 months was 87% in the pembrolizumab–chemoradiotherapy group and 81% in the placebo–chemoradiotherapy group (information fraction 42·9%). The HR for death was 0·73 (0·49–1·07); these data have not crossed the boundary of statistical significance. Grade 3 or higher adverse event rates were 75% in the pembrolizumab–chemoradiotherapy group and 69% in the placebo–chemoradiotherapy group.

Interpretation Pembrolizumab plus chemoradiotherapy significantly improved progression-free survival in patients with newly diagnosed, high-risk, locally advanced cervical cancer.



KEYNOTE-A18: Pembrolizumab + chemoradiotherapy for high-risk, locally advanced cervical cancer

Study Schema



End Points

- Primary: PFS (per RECIST v1.1) by investigator or histopathologic confirmation and OS
- Key secondary: 24-month PFS, ORR, PROs, and safety

January 12, 2024: FDA approves pembrolizumab with chemoradiotherapy for FIGO 2014 Stage III-IVA cervical cancer (irrespective of PD-L1 status)

Lorusso D, et al, The Lancet 2024

Baseline Characteristics

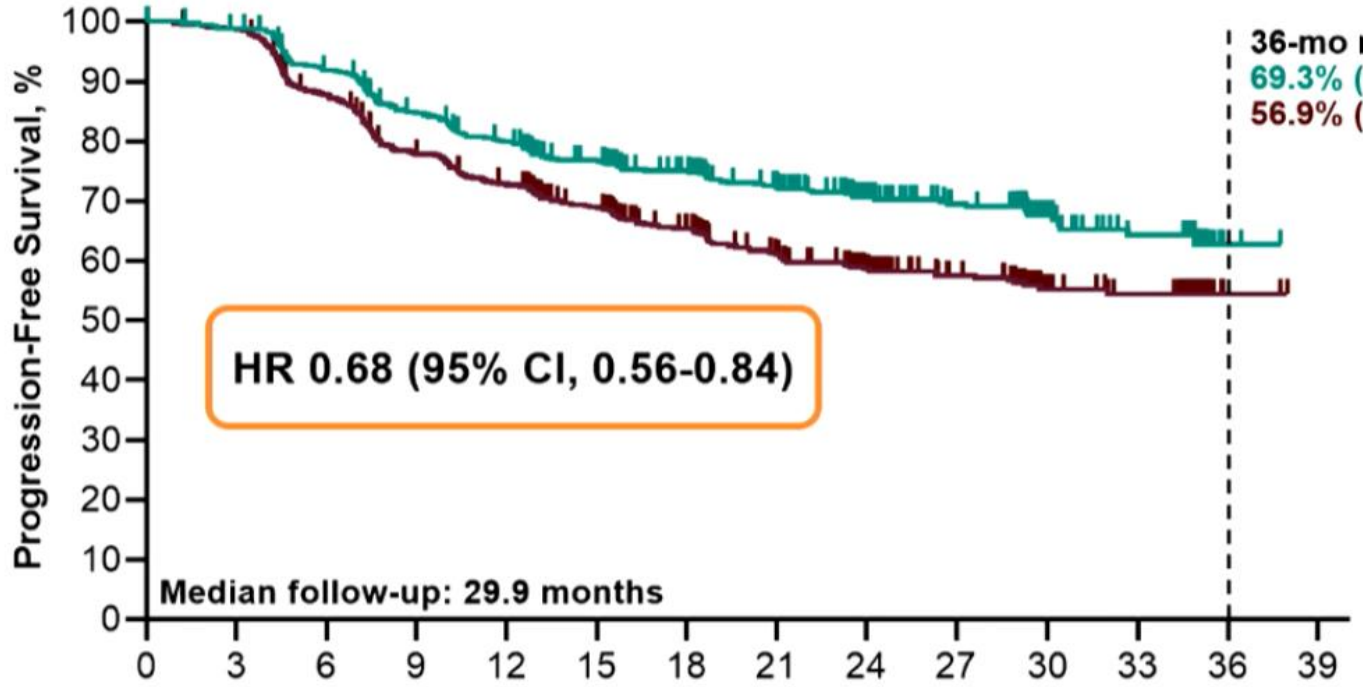
	Pembro Arm (N = 529)	Placebo Arm (N = 531)
Age, median (range)	49 y (22-87)	50 y (22-78)
Race[a]		
White	254 (48.0%)	264 (49.7%)
Asian	156 (29.5%)	148 (27.9%)
Multiple	78 (14.7%)	86 (16.2%)
American Indian or Alaska Native	24 (4.5%)	22 (4.1%)
Black or African American	14 (2.6%)	8 (1.5%)
Native Hawaiian 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%)	133 (25.0%)
Squamous cell carcinoma	434 (82.0%)	451 (84.9%)

134	Pembro Arm (N = 529)	Placebo Arm (N = 531)
Stage at screening (FIGO 2014 criteria)		
IB2-IIB	233 (44.0%)	226 (42.6%)
III-IVA	296 (56.0%)	305 (57.4%)
Lymph node involvement[b]		
Positive pelvic only	327 (62.2%)	324 (61.0%)
Positive para-aortic only	14 (2.6%)	10 (1.9%)
Positive pelvic and para-aortic	104 (19.7%)	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]3 patients (0.3%) had missing information for race, 1 (0.2%) in the pembro arm and 2 (0.4%) in the placebo arm. [b]Per protocol, a positive lymph node is defined as ≥1.5 cm shortest dimension by MRI or CT.
Data cutoff date: January 8, 2024.

Lorusso et al, Lancet 2024

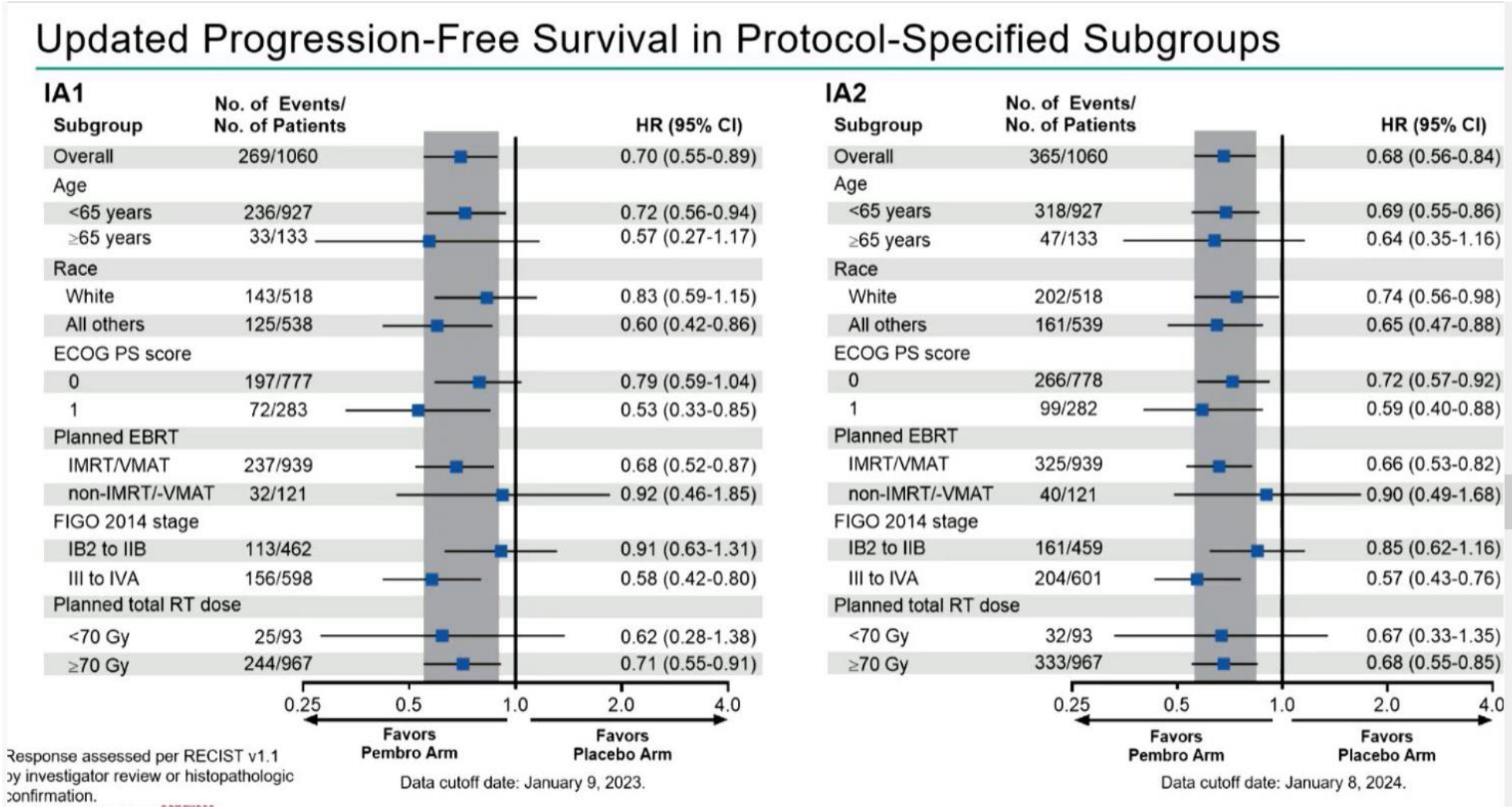
Updated Progression-Free Survival at IA2



	Pts w/ Event	Median, mo (95% CI)
Pembro Arm	29.3%	NR (NR-NR)
Placebo Arm	39.5%	NR (32.0-NR)

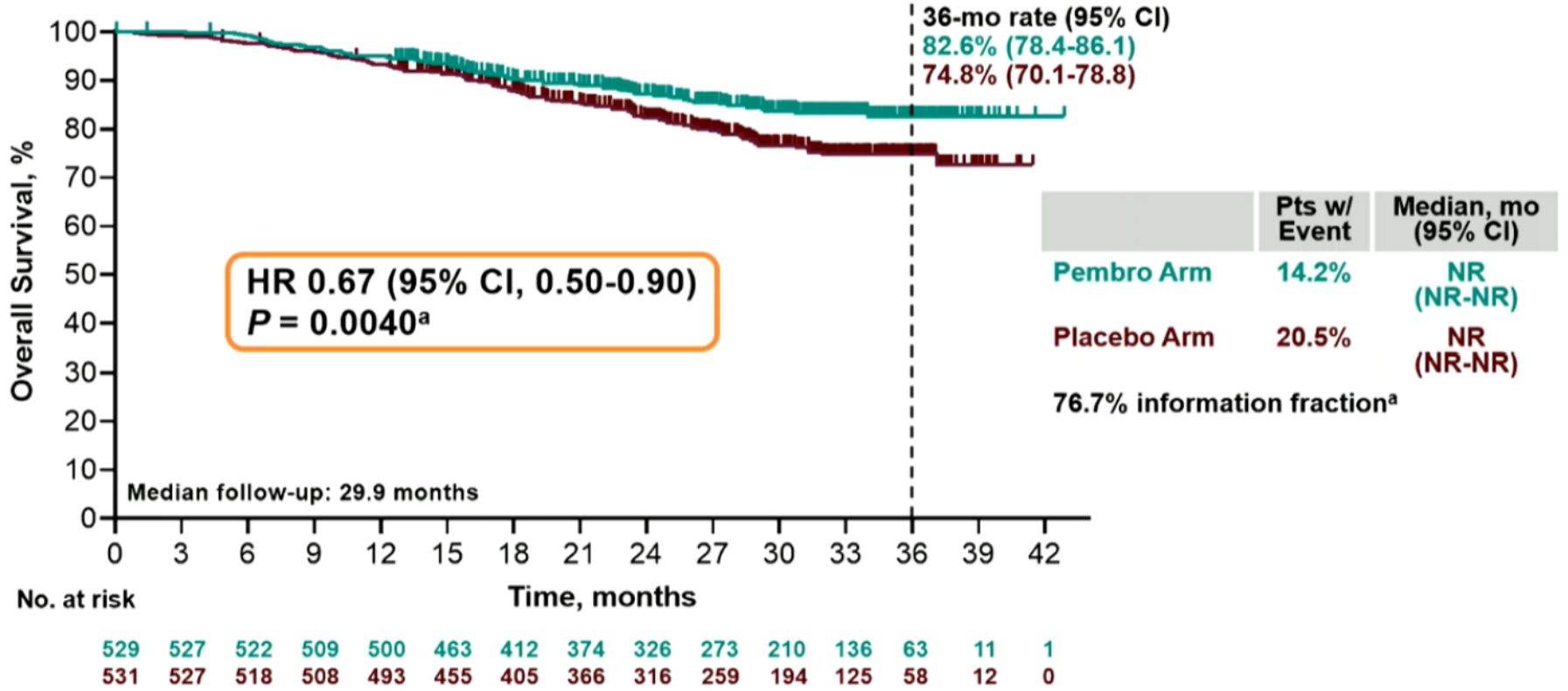
Lorusso et al, Lancet 2024

Updated Progression-Free Survival in Protocol-Specified Subgroups



Lorusso et al, Lancet 2024

Primary Endpoint: Overall Survival at IA2



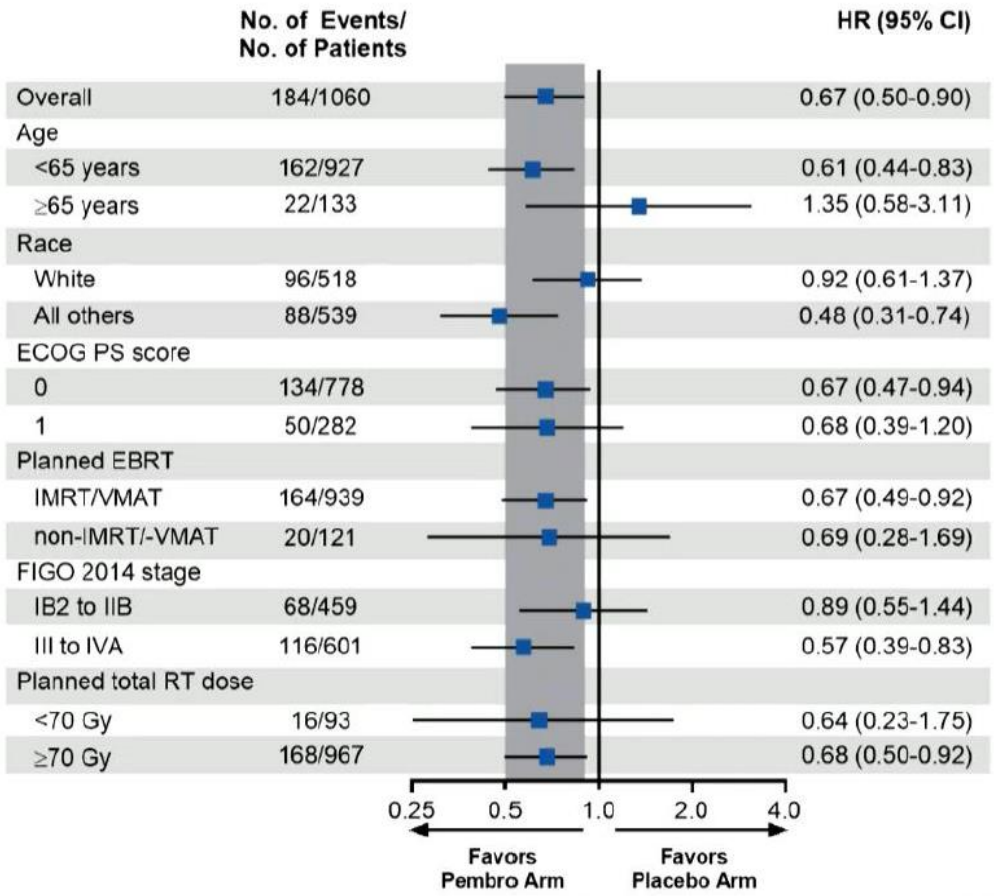
	Pts w/ Event	Median, mo (95% CI)
Pembro Arm	14.2%	NR (NR-NR)
Placebo Arm	20.5%	NR (NR-NR)

76.7% information fraction[a]

[a]With 184 of the 240 deaths expected at the final analysis (76.7% information fraction), the observed *P* = 0.0040 (1-sided) crossed the prespecified nominal boundary of 0·01026 (1-sided) at this plannec interim analysis. At this time, 66 patients had received immunotherapy as post-progression treatment, including 15/138 patients (10.9%) in the pembro arm and 51/193 patients (26.4%) in the placebo ar 10 (7.2%) and 41 (21.2%), respectively, had received pembro. Data cutoff date: January 8, 2024.

Lorusso et al, Lancet 2024

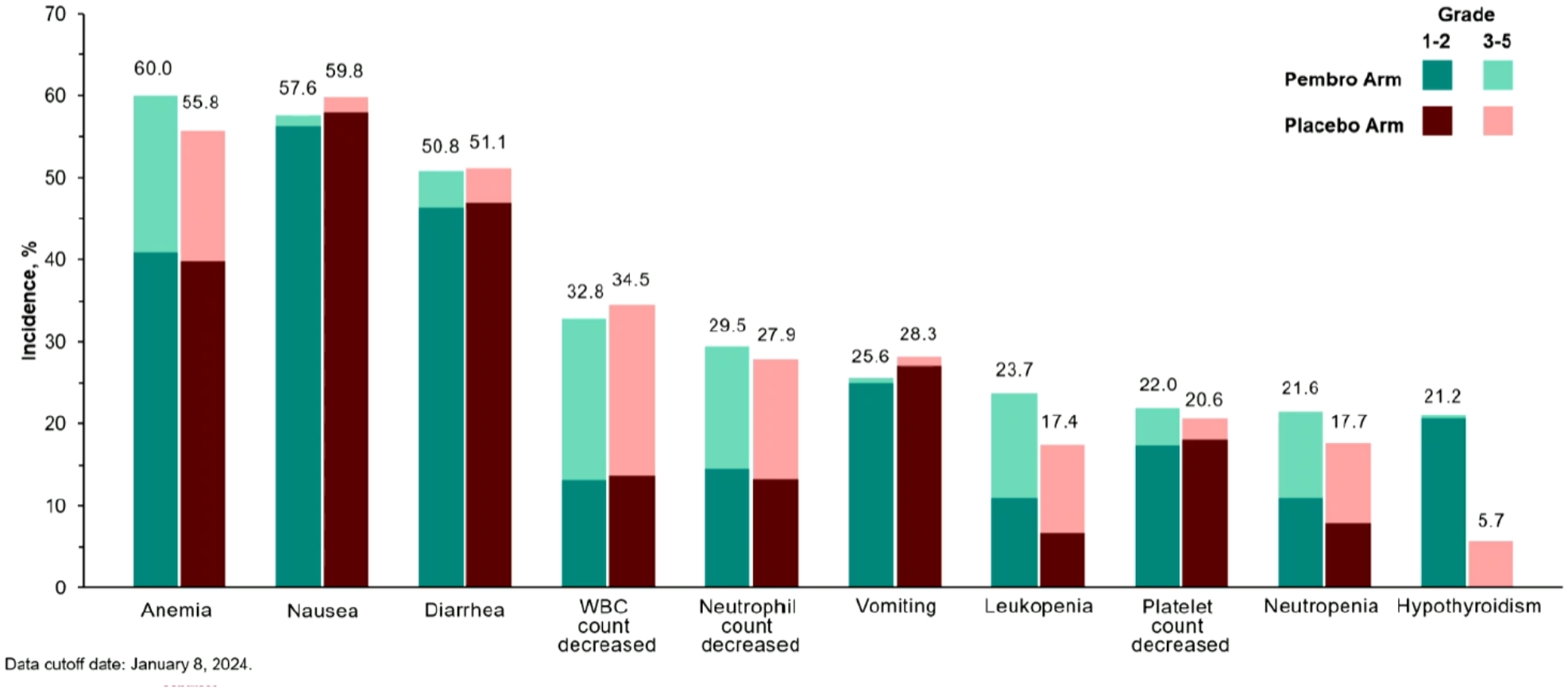
Overall Survival in Protocol-Specified Subgroups



Data cutoff date: January 8, 2024.

Lorusso et al, Lancet 2024

Treatment-Related Adverse Events, Incidence ≥20% in Either Arm



Data cutoff date: January 8, 2024.

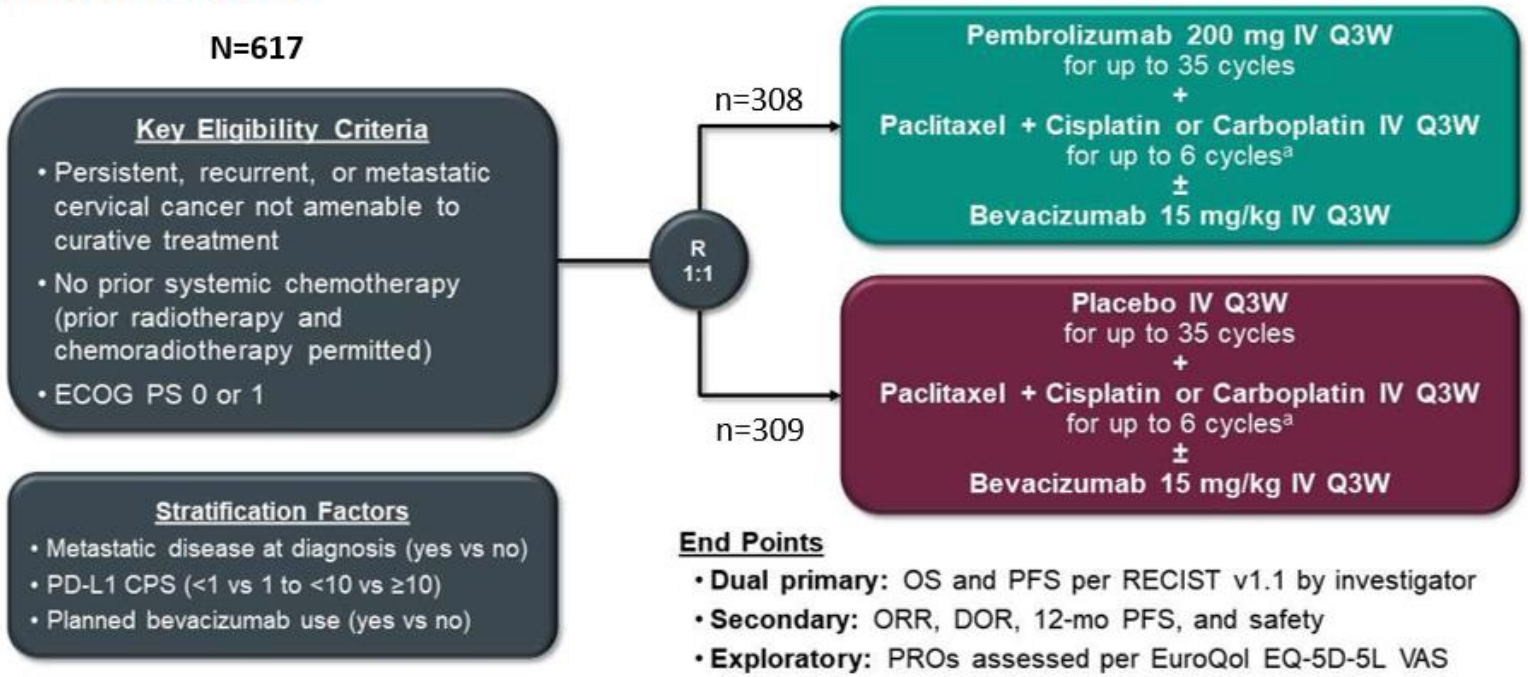
Lorusso et al, Lancet 2024

Recurrent/Persistent Metastatic Cervical Cancer : 1st Line

Keynote 826
Beat CC

KEYNOTE-826: Pembrolizumab + chemo ± bev vs chemo ± bev for persistent, recurrent, or metastatic cervical cancer

Study Schema



End Points

- **Dual primary:** OS and PFS per RECIST v1.1 by investigator
- **Secondary:** ORR, DOR, 12-mo PFS, and safety
- **Exploratory:** PROs assessed per EuroQol EQ-5D-5L VAS

October 12, 2021: Accelerated approval for 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.

Monk B et al, JCO 2023; Colombo N et al, NEJM 2021

KEYNOTE-826

Baseline Characteristics (All-Comers)

Characteristic	Pembro (n = 308)	Placebo (n = 309)
Median age, yr (range)	51 (25-82)	50 (22-79)
ECOG PS 1, n (%)	128 (41.6)	139 (45.0)
Squamous cell carcinoma, n (%)	235 (76.3)	211 (68.3)
PD-L1 CPS, n (%)		
▪ <1	35 (11.4)	34 (11.0)
▪ 1 to <10	115 (37.3)	116 (37.5)
▪ ≥10	158 (51.3)	159 (51.5)
Prior therapy, n (%)		
▪ Chemoradiation or radiation with surgery	71 (23.1)	79 (25.6)
▪ Chemoradiation or radiation only	156 (50.6)	142 (46.0)
▪ Surgery only	23 (7.5)	24 (7.8)
▪ None	58 (18.8)	64 (20.7)

Characteristic, n (%)	Pembro (n = 308)	Placebo (n = 309)
Stage at diagnosis*		
▪ I	67 (21.8)	58 (18.8)
▪ II	85 (27.6)	93 (30.1)
▪ III	5 (1.6)	8 (2.6)
▪ IIIA	4 (1.3)	8 (2.6)
▪ IIIB	46 (14.9)	42 (13.6)
▪ IVA	7 (2.3)	4 (1.3)
▪ IVB	94 (30.5)	96 (31.1)
Disease status at study entry		
▪ Metastatic	58 (18.8)	64 (20.7)
▪ Persistent or recurrent with distant metastases	199 (64.6)	179 (57.9)
▪ Persistent or recurrent without distant metastases	51 (16.6)	66 (21.4)
Bevacizumab used during study	196 (63.6)	193 (62.5)

*Per FIGO 2009/NCCN 2017 criteria.

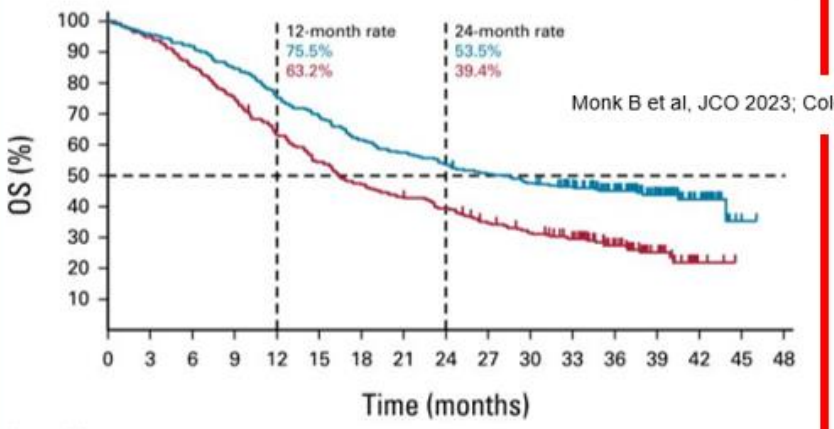
Monk B et al, JCO 2023; Colombo N et al, NEJM 2021

KEYNOTE-826

Efficacy – Overall Survival

OS: PD-L1 CPS ≥1 Population

Treatment Group	No. of Events/ No. of Patients (%)	Median OS, Months (95% CI)	HR (95% CI)
Pembro + chemo ± bev	153/273 (56.0)	28.6 (22.1 to 38.0)	0.60 (0.49 to 0.74)
Placebo + chemo ± bev	201/275 (73.1)	16.5 (14.5 to 20.0)	

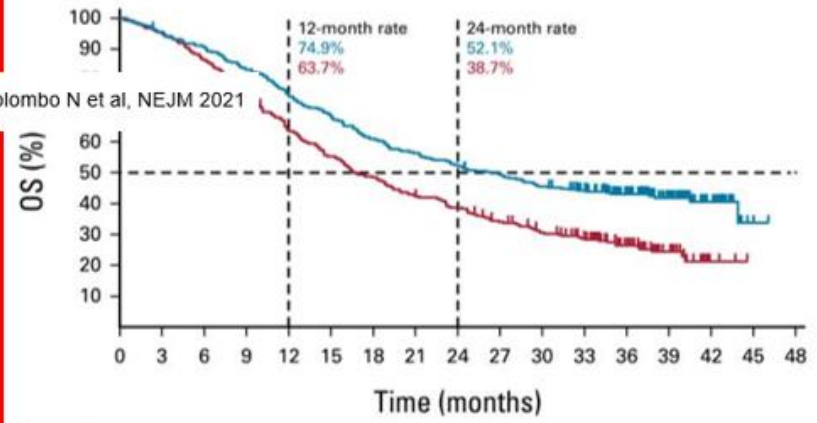


No. at risk:

273	261	251	231	206	189	168	157	146	136	128	116	90	52	22	2	0
275	261	235	207	173	149	129	117	107	91	81	68	45	24	3	0	0

OS: All-Comer Population

Treatment Group	No. of Events/ No. of Patients (%)	Median OS, Months (95% CI)	HR (95% CI)
Pembro + chemo ± bev	178/308 (57.8)	26.4 (21.3 to 32.5)	0.63 (0.52 to 0.77)
Placebo + chemo ± bev	228/309 (73.8)	16.8 (14.6 to 19.4)	



No. at risk:

308	292	278	256	230	210	187	173	160	150	138	125	95	55	22	2	0
309	295	268	235	196	170	149	130	118	101	87	72	48	26	3	0	0

Monk B et al, JCO 2023; Colombo N et al, NEJM 2021

Monk B et al, JCO 2023; Colombo N et al, NEJM 2021

KEYNOTE-826

Safety

Outcome, n (%)	Pembro (n = 307)	Placebo (n = 309)
All-cause AE	305 (99.3)	307 (99.4)
▪ Grade ≥3	253 (82.4)	233 (75.4)
▪ Serious	157 (51.1)	132 (42.7)
▪ Led to death	16 (5.2)	15 (4.9)
▪ Led to d/c of any treatment	125 (40.7)	91 (29.4)
▪ Led to d/c of all treatment	17 (5.5)	15 (4.9)
TRAEs	298 (97.1)	300 (97.1)
▪ Grade ≥3	212 (69.1)	201 (65.0)
▪ Serious	94 (30.6)	73 (23.6)
▪ Led to death	2 (0.7)	4 (1.3)
▪ Led to d/c of any treatment	102 (33.2)	77 (24.9)
▪ Led to d/c of all treatment	9 (2.9)	6 (1.9)
irAEs	106 (34.5)	51 (16.5)
▪ Grade ≥3	37 (12.1)	9 (2.9)
▪ Serious	24 (7.8)	7 (2.3)
▪ Led to death	2 (0.7)	0
▪ Led to d/c of any treatment	20 (6.5)	1 (0.3)
▪ Led to d/c of all treatment	2 (0.7)	0

Treatment parameter	Pembro (n = 307)	Placebo (n = 309)
Median number of cycles		
▪ Any treatment	14	11
▪ Pembro or placebo	13	11
▪ Chemotherapy	6	6
▪ Bevacizumab	13	11
Median treatment duration, mo	10.0	7.7
Mean treatment duration, mo	14.4	10.8

Monk B et al, JCO 2023; Colombo N et al, NEJM 2021

BEATcc: Platinum Chemo + Paclitaxel with Bevacizumab and Atezolizumb in Metastatic Cervical Cancer

Study Schema

- Metastatic, persistent or recurrent cervical cancer not amenable to curative therapy
- GOG/ECOG PS ≤1
- No prior systemic anti-cancer therapy for R/M CC
- In patients with pelvic disease, no bladder or rectal mucosa involvement
- Available archival or fresh tumour sample for PD-L1 expression

R 1:1

N=410

Atezolizumab 1200 mg + bevacizumab 15 mg/kg + paclitaxel + cis/carboplatin[a] all IV q3w

Bevacizumab 15 mg/kg + paclitaxel + cis/carboplatin[a] all IV q3w

- Continued until disease progression/unacceptable toxicity
- Patients with CR after ≥6 cycles could stop chemotherapy and continue biological therapy alone
- Crossover from standard arm at progression not permitted

Dual primary endpoints

- Investigator-assessed PFS (RECIST 1.1)
- OS

Stratification factors:

- Prior concurrent chemoradiation (yes vs no)
- Histology (squamous cell carcinoma vs adenocarcinoma[b] including adenosquamous carcinoma)
- Chemotherapy backbone (cisplatin vs carboplatin)

Oaknin A et al, The Lancet 2024

BEATcc

Baseline Characteristics

Characteristic		Control Arm (n = 204)	Atezo Arm (n = 206)
Median age, yr (range)		52.5 (21-79)	51.0 (24-90)
▪ Age <65, n (%)		168 (82)	171 (83)
GOG ECOG PS,* n (%)	▪ 0	128 (63)	138 (67)
	▪ 1	73 (36)	68 (33)
Race, n (%)	▪ White	113 (55)	111 (54)
	▪ Other†	42 (21)	45 (22)
	▪ Not available	49 (24)	50 (24)
Histology, (%)	▪ SCC	157 (77)	164 (80)
	▪ AC/ASC	47 (23)	42 (20)

Characteristic, n (%)		Control Arm (n = 204)	Atezo Arm (n = 206)
Disease status	▪ Metastatic/stage IVB	47 (23)	43 (21)
	▪ Recurrent	151 (74)	150 (73)
	▪ Persistent	6 (3)	13 (6)
Disease location at screening	▪ Pelvic + distant	90 (44)	102 (50)
	▪ Distant only	74 (36)	71 (34)
	▪ Pelvic only	40 (20)	33 (16)
Primary treatment	▪ cCRT	85 (42)	70 (34)
	▪ Surgery + CRT	44 (22)	64 (31)
	▪ Surgery and/or RT	28 (14)	16 (8)
	▪ None	47 (23)	56 (27)

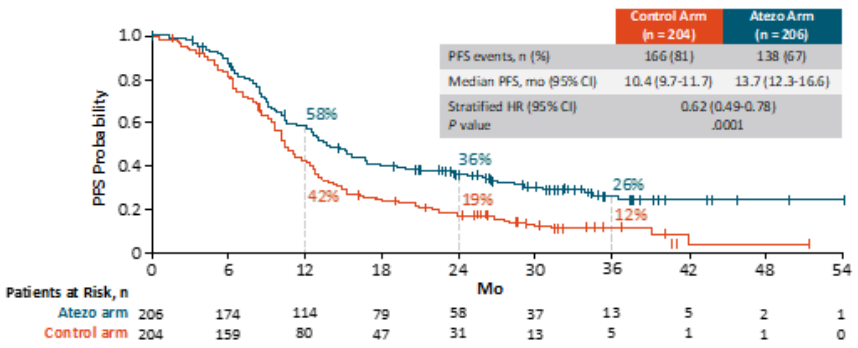
*Missing 3 patients. †Asian (n = 58), Latina (n = 18), Black (n = 5), Gypsy (n = 1).

Oaknin A et al, The Lancet 2024

BEATcc

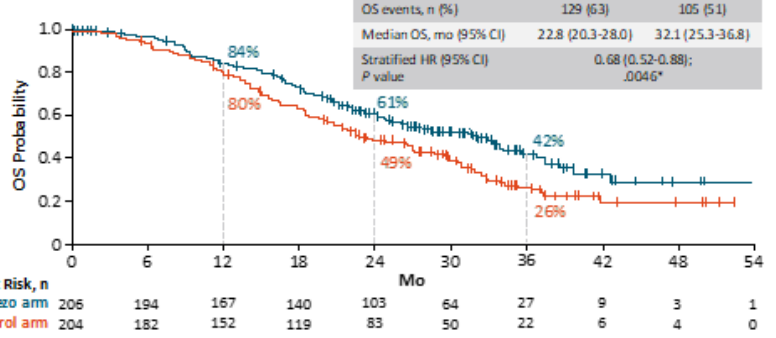
Efficacy – PFS and OS

PFS



	Control Arm (n = 204)	Atezo Arm (n = 206)
PFS events, n (%)	166 (81)	138 (67)
Median PFS, mo (95% CI)	10.4 (9.7-11.7)	13.7 (12.3-16.6)
Stratified HR (95% CI) *P* value	0.62 (0.49-0.78) .0001	

OS



	Control Arm (n = 204)	Atezo Arm (n = 206)
OS events, n (%)	129 (63)	105 (51)
Median OS, mo (95% CI)	22.8 (20.3-28.0)	32.1 (25.3-36.8)
Stratified HR (95% CI) *P* value	0.68 (0.52-0.88); .0046*	

Oaknin A et al, The Lancet 2024

BEATcc

Efficacy – Subgroup Analyses

PFS

Subgroup	No. events/patients	HR (95% CI)
Overall	304/410	0.62 (0.49–0.78)
Age, years		
<65	246/339	0.66 (0.51–0.85)
≥65	58/71	0.45 (0.26–0.78)
GOG/ECOG PS		
0	187/266	0.66 (0.49–0.87)
1	114/141	0.60 (0.42–0.88)
Race		
White	162/224	0.61 (0.45–0.83)
Other	66/87	0.64 (0.46–0.89)
Disease status		
Metastatic	66/90	0.71 (0.43–1.16)
Persistent/recurrent	238/320	0.59 (0.46–0.76)
Chemotherapy backbone		
Carboplatin	118/167	0.58 (0.40–0.84)
Cisplatin	186/243	0.66 (0.49–0.88)
Prior chemoradiotherapy		
Yes	197/263	0.55 (0.42–0.73)
No	107/147	0.77 (0.52–1.12)
Histology		
Adenocarcinoma	73/89	0.59 (0.45–0.76)
Squamous cell carcinoma	231/321	0.75 (0.47–1.19)

OS

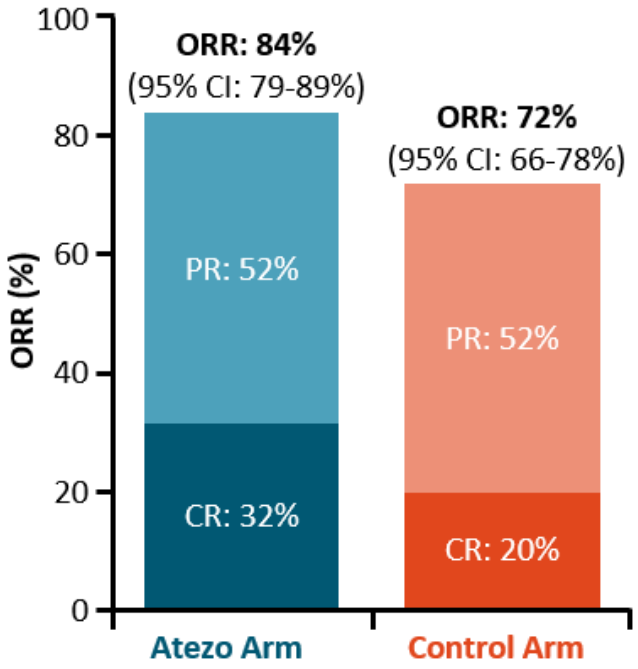
Subgroup	No. events/patients	HR (95% CI)
Overall	234/410	0.68 (0.52–0.88)
Age, years		
<65	187/339	0.72 (0.54–0.96)
≥65	47/71	0.55 (0.31–0.99)
GOG/ECOG PS		
0	139/266	0.73 (0.52–1.02)
1	93/141	0.63 (0.42–0.95)
Race		
White	128/224	0.72 (0.51–1.02)
Other	47/87	0.65 (0.45–0.96)
Disease status		
Metastatic	50/90	0.85 (0.49–1.49)
Persistent/recurrent	184/320	0.65 (0.49–0.87)
Chemotherapy backbone		
Carboplatin	91/167	0.57 (0.38–0.87)
Cisplatin	143/243	0.78 (0.56–1.08)
Prior chemoradiotherapy		
Yes	156/263	0.61 (0.45–0.84)
No	78/147	0.86 (0.55–1.34)
Histology		
Adenocarcinoma	55/89	0.62 (0.36–1.06)
Squamous cell carcinoma	179/321	0.72 (0.54–0.97)

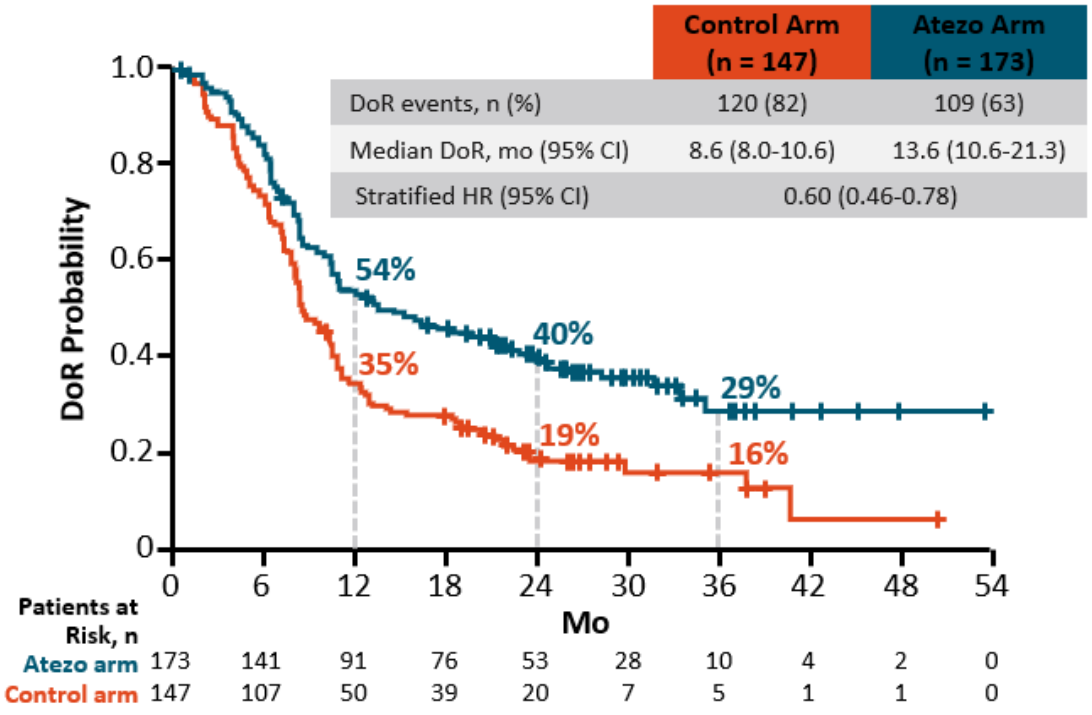
Data cut-off: 17 Jul 2023 (median follow-up: 32.9 months; 95% CI, 31.2–34.6 months)

Oaknin, A et al, The Lancet , 2024

BEATcc

Efficacy – ORR and DOR

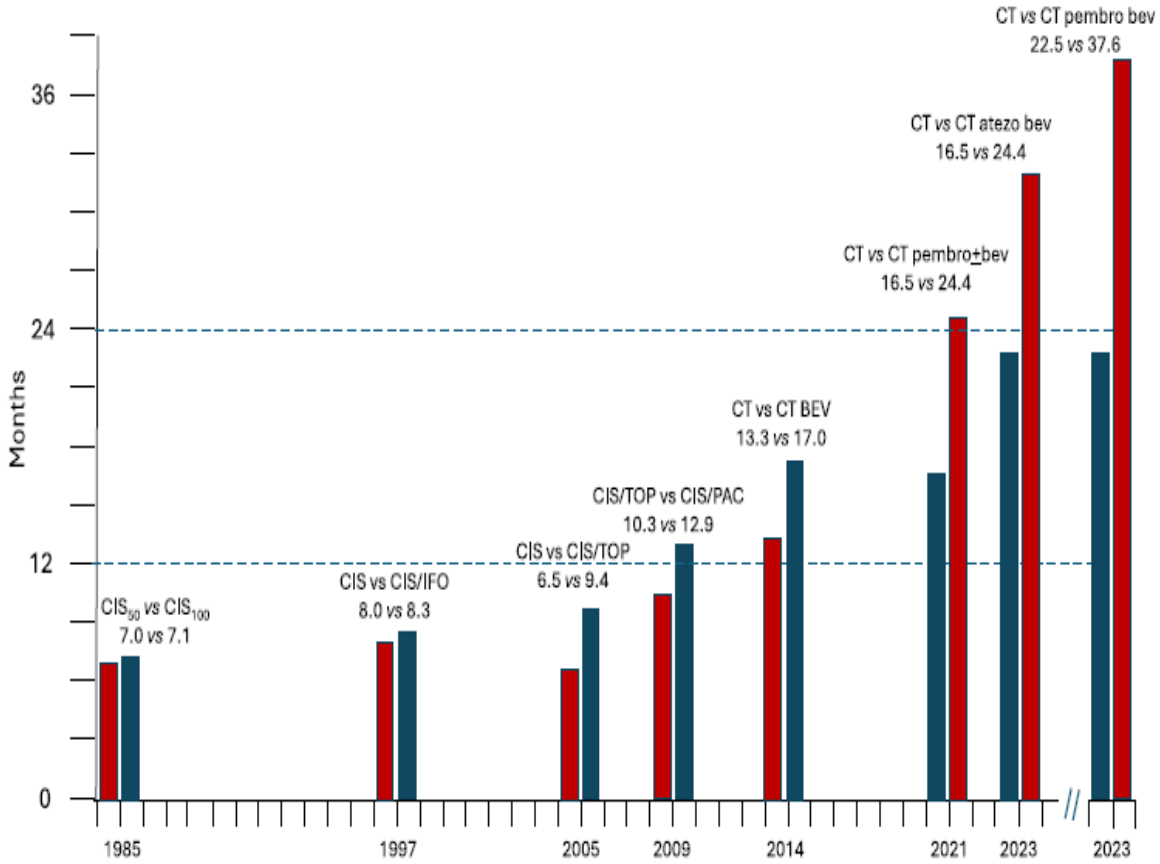




	Control Arm (n = 147)	Atezo Arm (n = 173)
DoR events, n (%)	120 (82)	109 (63)
Median DoR, mo (95% CI)	8.6 (8.0-10.6)	13.6 (10.6-21.3)
Stratified HR (95% CI)	0.60 (0.46-0.78)	

Oaknin A , et al , The Lancet 2024

Summary of median overall survival gains in first line recurrent/metastatic cervical cancer over time.



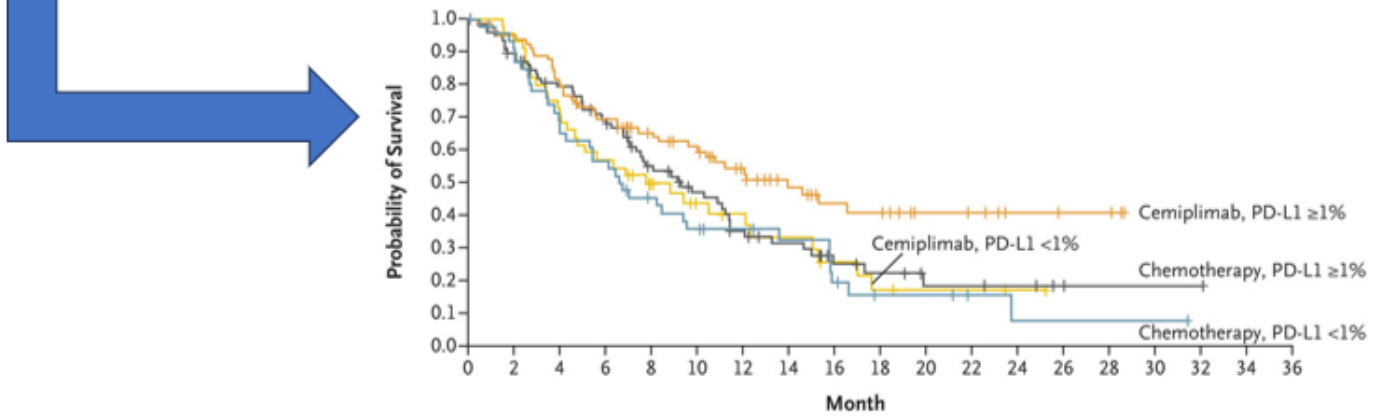
Duska LR, Podwika SE, Randall LM. *Cancer*. 2024;130(15):2571-2576.

Metastatic Cervical Cancer : Second Line

Options

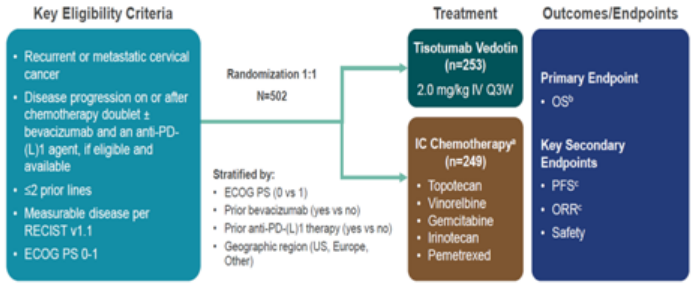
Limited Role for IO in the 2L+ R/M CC Setting

Study	Anti-PD-1	N	ORR in PD-L1+	mPFS	mOS
KEYNOTE-158	Pembrolizumab	98	17%	3	11
NCT03495882	Balstilimab	155	33%	~3mo	~12mo
EMPOWER CERVICAL-1	Cemiplimab	304	21%	2.9	12



Chung JCO 2019, O'Malley Gyn Oncol 2021; Tewari NEJM 2022

Phase 3 InnovaTV 301 /ENGOT-cx12/GOG-3057 Trial: Study Design

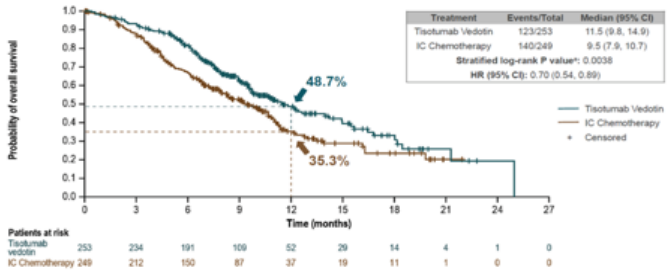


– Data presented herein are a planned interim analysis

IC, investigator's choice; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks.
End of treatment visit occurred 30 days after the last dose of treatment.
Survival follow-up occurred every 60 days after the last dose of treatment.
[a]Chemotherapy regimens were administered at the following doses: topotecan, 1 or 1.25 mg/m^2 IV, on Day 1 to 5 of a 21-day cycle; vinorelbine, 30 mg/m^2 IV on Days 1 and 8 of a 21-day cycle; gemcitabine, 1000 mg/m^2 IV on Days 1 and 8 of a 21-day cycle; irinotecan 100 or 125 mg/m^2 IV QW x 28 days every 42 days; pemetrexed 500 mg/m^2 on Day 1 of a 21-day cycle. [b]OS was defined as the time from the date of randomization to the date of death due to any cause. [c]Assessed by investigator.

Vergote I, et al, NEJM 2024

InnovaTV 301: Primary Endpoint Overall Survival



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

Vergote I, et al, NEJM 2024

InnovaTV 205/GOG-3024 ORR

First-Line Median Follow-Up: 18.8 Months	
Efficacy Parameter	**Tisotumab + Pembrolizumab (N=32[a])**
Confirmed ORR, % [95% CI]	40.6 [23.7-59.4]
• Complete Response	5 (15.6)
• Partial Response	8 (25.0)
• Stable Disease	14.8 (43.8)
• Progressive Disease	1 (3.1)
• Not Evaluable	4 (12.5)
DCR[a], % [95% CI]	84.4 [67.2 – 94.7]
Median DOR[b], months (range)	NR (2.8-21.9+)

First-Line Median Follow-Up: 14.6 Months	
Efficacy Parameter	**Tisotumab + Carboplatin (N=33[a])**
Confirmed ORR, % [95% CI]	54.5 [36.4-71.9]
• Complete Response	4 (12.1)
• Partial Response	14 (42.4)
• Stable Disease	12 (36.4)
• Progressive Disease	2 (6.1)
• Not Evaluable	1 (3.0)
DCR[a], % [95% CI]	90.9 [75.7-98.1]
Median DOR[b], months (range)	8.6 (4.2-11.5)

Second-or-Third Line Median Follow-Up: 15.0 Months	
Efficacy Parameter	**Tisotumab + Pembrolizumab (N=34[a])**
Confirmed ORR, % [95% CI]	38.2 [22.2 – 56.4]
• Complete Response	3 (8.8)
• Partial Response	10 (29.4)
• Stable Disease	12 (35.3)
• Progressive Disease	7 (20.6)
• Not Evaluable	2 (5.9)
DCR[a], % [95% CI]	73.5 [55.6-87.1]
Median DOR[b], months (range)	14.0 (2.8-NR)

Vergote I, et al, JCO, 2023

NR, not reached
[a]One patient was excluded from the full analysis set as he/she had no target lesions at baseline
[b]Defined as stable disease (SD), at least 5 weeks after the first dose of study treatment, or confirmed CR or PR

NCCN guidelines 2025

SYSTEMIC THERAPY FOR CERVICAL CANCER[a,b]

Squamous Cell Carcinoma, Adenocarcinoma, or Adenosquamous Carcinoma		
Chemoradiation[c]	**Recurrent or Metastatic Disease**	
	First-line Therapy[c,g]	**Second-line or Subsequent Therapy[g,j]**
Preferred Regimens • Cisplatin + pembrolizumab[d,e,f,1] ▸ category 1: FIGO 2014 Stage III–IVA ▸ category 2B: FIGO 2018 stage III–IVA • Carboplatin + pembrolizumab[d,e,f,1] if cisplatin intolerant ▸ category 1: FIGO 2014 Stage III–IVA ▸ category 2B: FIGO 2018 stage III–IVA • Cisplatin • Carboplatin if cisplatin intolerant **Other Recommended Regimens (if single agent cisplatin and carboplatin are unavailable)** • Capecitabine/mitomycin[2] • Gemcitabine[3] • Paclitaxel[4,5]	**Preferred Regimens** • PD-L1–positive tumors ▸ Pembrolizumab + cisplatin/paclitaxel ± bevacizumab (category 1)[e,f,h,6] ▸ Pembrolizumab + carboplatin/paclitaxel ± bevacizumab (category 1)[e,f,h,6] • Cisplatin/paclitaxel/bevacizumab[e,7] (category 1) • Carboplatin/paclitaxel/bevacizumab[e] • Atezolizumab + cisplatin/paclitaxel + bevacizumab (category 1)[e,f,i,8] • Atezolizumab + carboplatin/paclitaxel + bevacizumab (category 1)[e,f,i,8] **Other Recommended Regimens** • Cisplatin/paclitaxel (category 1)[9,10] • Carboplatin/paclitaxel[11,12] (category 1 for patients who have received prior cisplatin therapy) • Topotecan/paclitaxel/bevacizumab[e,7,13] (category 1) • Topotecan/paclitaxel[13] • Cisplatin/topotecan[13] • Cisplatin[9] • Carboplatin[14,15]	**Preferred Regimens** • Pembrolizumab for TMB-H tumors[f,k] or PD-L1–positive[h] or MSI-H/dMMR tumors[f,16] • Tisotumab vedotin-tftv (category 1)[17,18] **Other Recommended Regimens** • Bevacizumab • Paclitaxel[15,19] • Albumin-bound paclitaxel • Docetaxel • Fluorouracil • Gemcitabine • Pemetrexed • Topotecan • Vinorelbine • Irinotecan • Cemiplimab[f,20] **Useful in Certain Circumstances** • PD-L1–positive tumors ▸ Nivolumab[f,h,21] ▸ Tisotumab vedotin-tftv + pembrolizumab[h,l,22] • HER2-positive tumors (IHC 3+ or 2+) ▸ Fam-trastuzumab deruxtecan-nxki[23] • HER2-mutant ▸ Neratinib[24] • *RET* gene fusion-positive tumors ▸ Selpercatinib • *NTRK* gene fusion-positive tumors ▸ Larotrectinib ▸ Entrectinib ▸ Repotrectinib[m,25]

Answers : YES …. Coupled with Questions

Does A18 apply to all all-Stage III patients ?

01

What is the role of IO therapy after IO therapy ?

02

What are some novel combinations with IO therapy ?

03

Which ADC is best to combine with IO in cervical cancer ?

04

How can we promote prevention of this disease ?

Thank you