ALL HANDS ON DECK IN CERVICAL CANCER CARE

Screening, Treatment, and Equity Strategies to Improve Patient Lives

cecONCOLOGY

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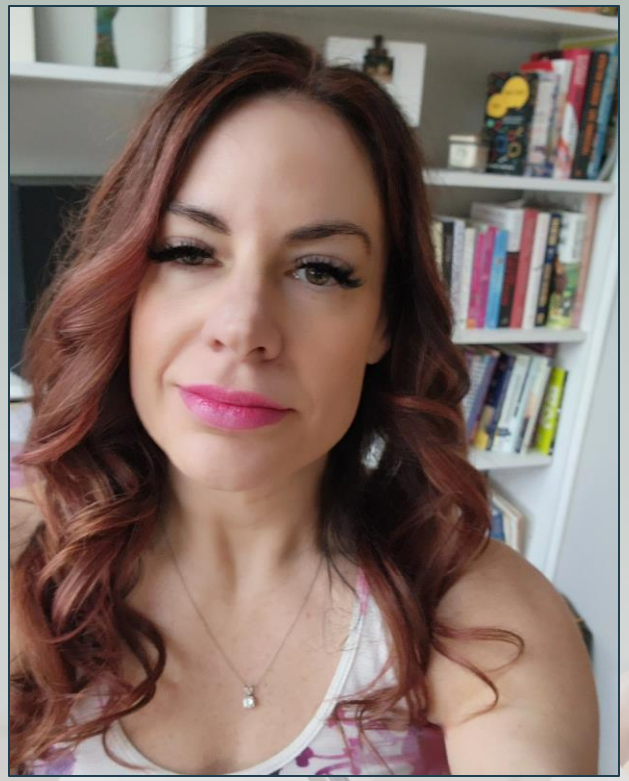

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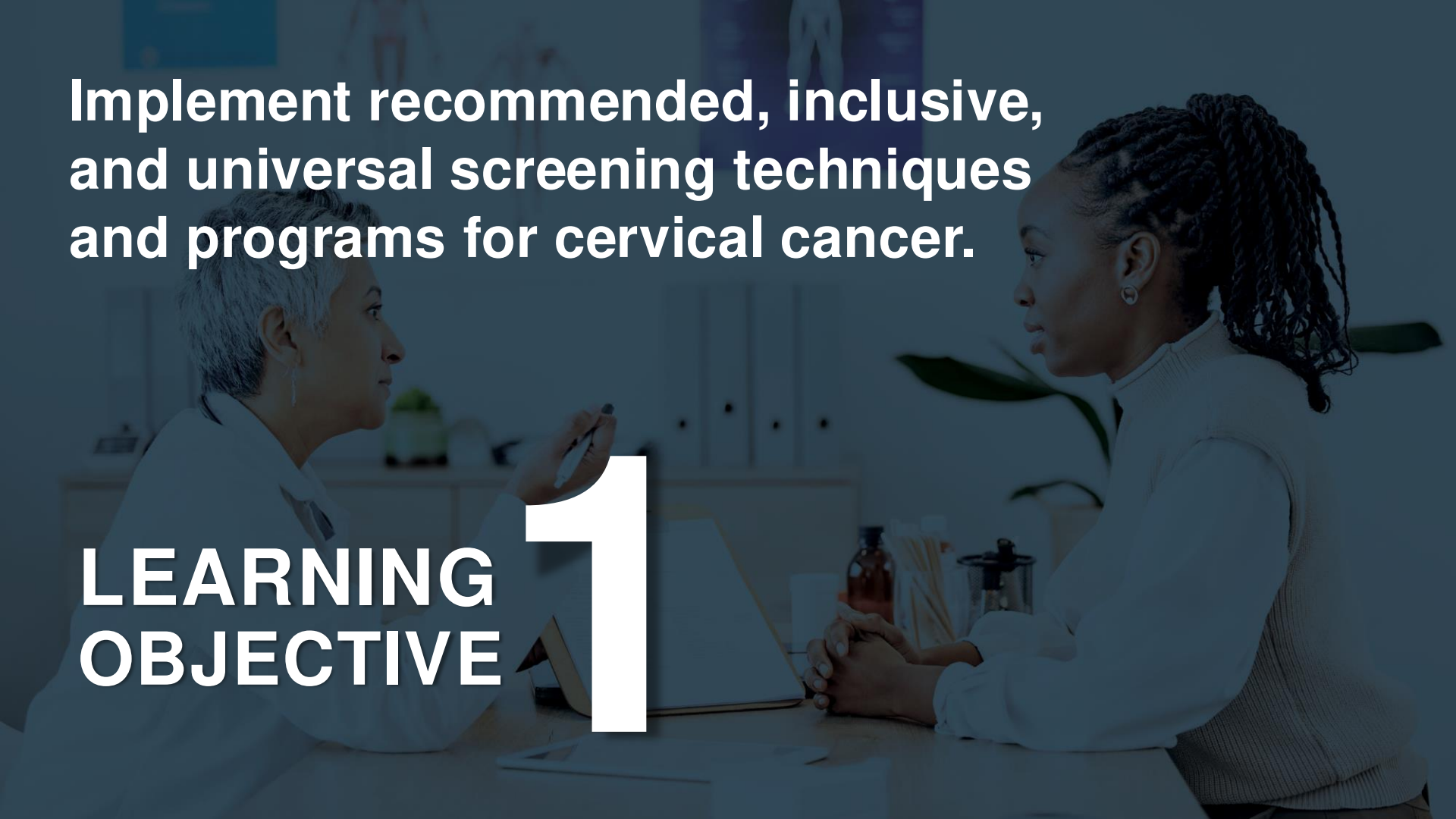
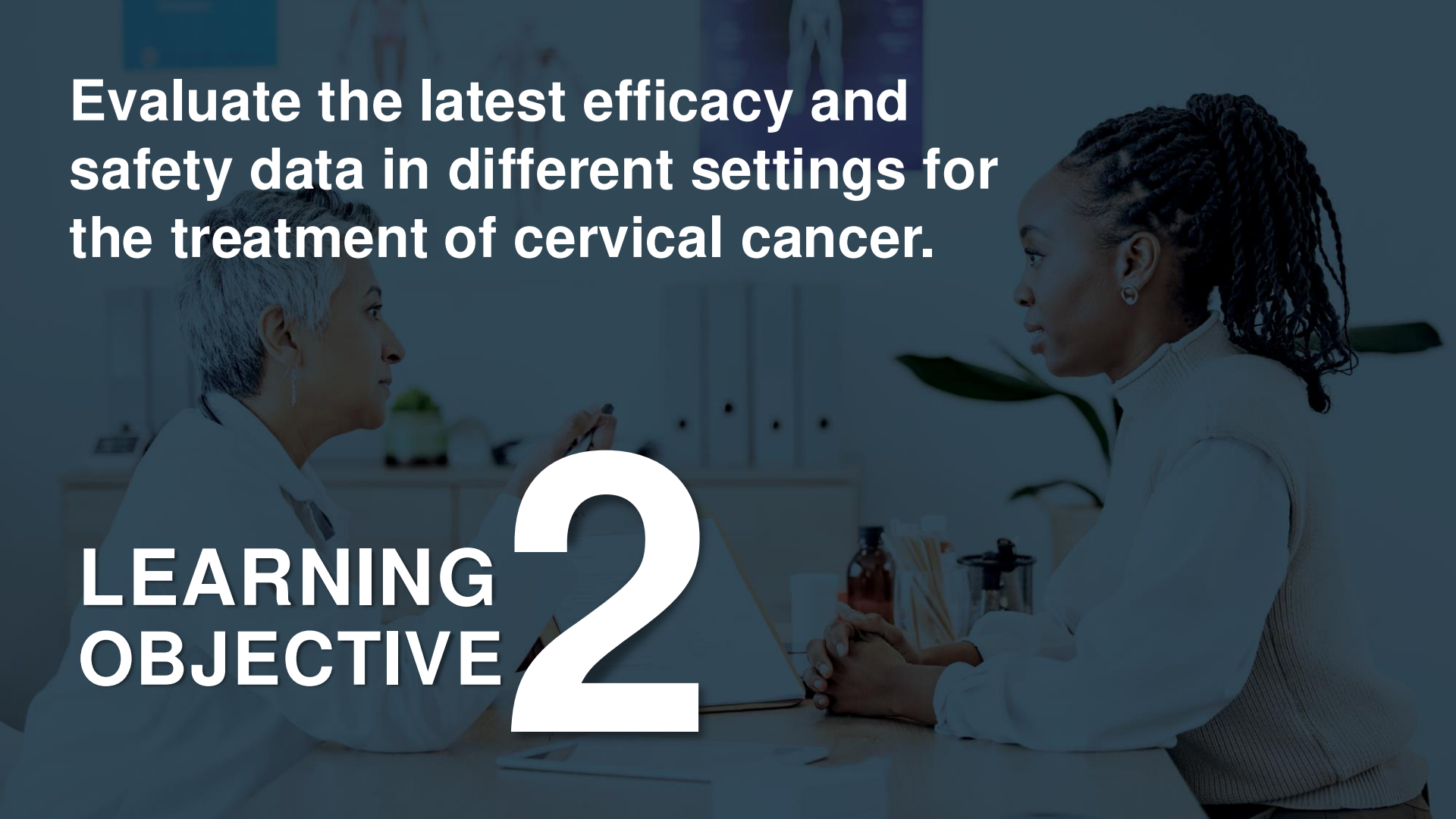


Implement recommended, inclusive, and universal screening techniques and programs for cervical cancer.

LEARNING OBJECTIVE 1


Evaluate the latest efficacy and safety data in different settings for the treatment of cervical cancer.
LEARNING OBJECTIVE 2

Incorporate actionable strategies to address disparities and unique health care needs of individuals with marginalized sexualities and genders related to cancer screening.

LEARNING OBJECTIVE 3

Cervical Cancer Screening Guidelines

	2020 ACS	2018 USPSTF
Age 21-24	No screening	Pap test every 3 years
Age 25-29	HPV test every 5 years (preferred)	Pap test every 3 years
	HPV/Pap co-test every 5 years (acceptable)	
	Pap test every 3 years (acceptable)	
Age 30-65	HPV test every 5 years (preferred)	Pap test every 3 years, HPV test every 5 years, or HPV/Pap co-test every 5 years
	HPV/Pap co-test every 5 years (acceptable)	
	Pap test every 3 years (acceptable)	
Age ≥ 65	No screening if a series of prior tests were normal	No screening if a series of prior tests were normal and not at high risk for cervical cancer

ACS = American Cancer Society; HPV = human papillomavirus; USPSTF = U.S. Preventive Services Task Force.

National Cancer Institute. 2020. https://www.cancer.gov/news-events/cancer-currents-blog/2020/cervical-cancer-screening-hpv-test-guideline.

Cervical Cancer Prevention

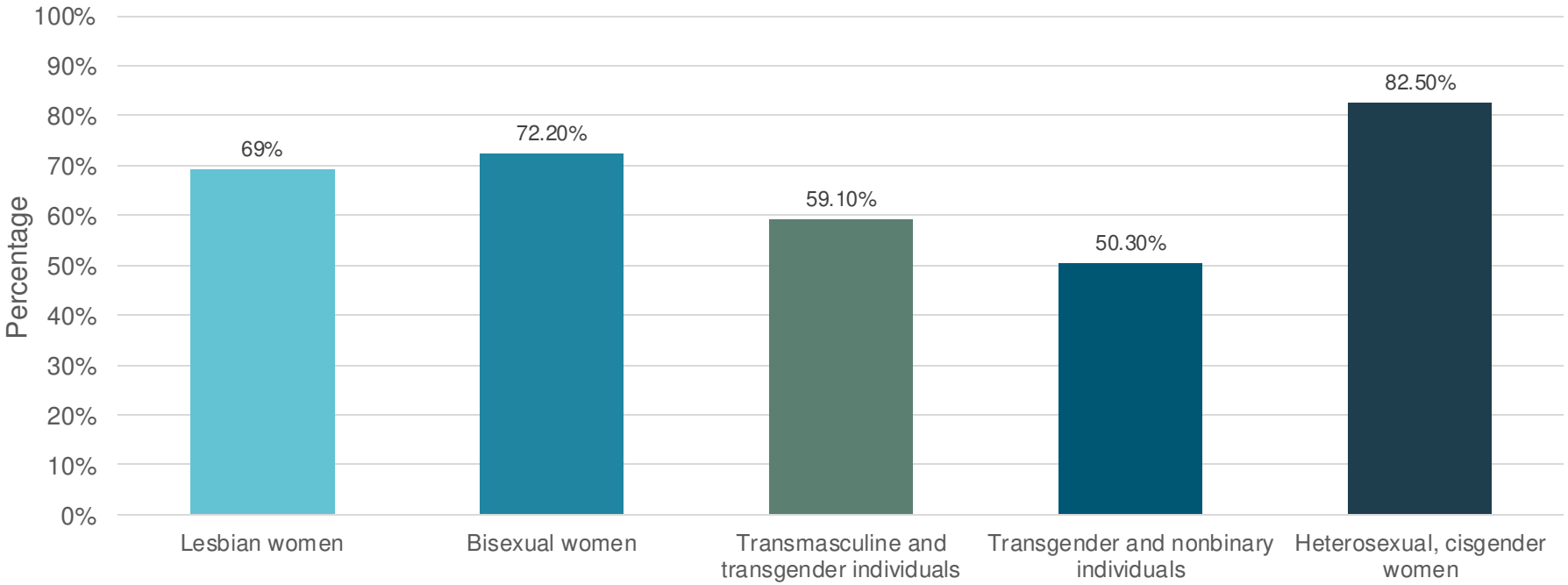
- HPV vaccination protects against the types of HPV that most often cause cervical, vaginal, and vulvar cancers
- HPV vaccination is recommended for
  - Preteens age 11-12, but can be given starting at age 9 (2 doses, 6 months apart)
  - Everyone through age 26 if they are not vaccinated already (3 doses for people who start the series after their 15th birthday)
- Some adults age 27-45 who are not already vaccinated may benefit from HPV vaccination
- HPV vaccination prevents new HPV infections but does not treat existing infections or diseases

Centers for Disease Control and Prevention [CDC]. 2023. https://www.cdc.gov/cervical-cancer/prevention/index.html.

Marginalized Sexual Orientations and Gender Identities and Cancer Screening

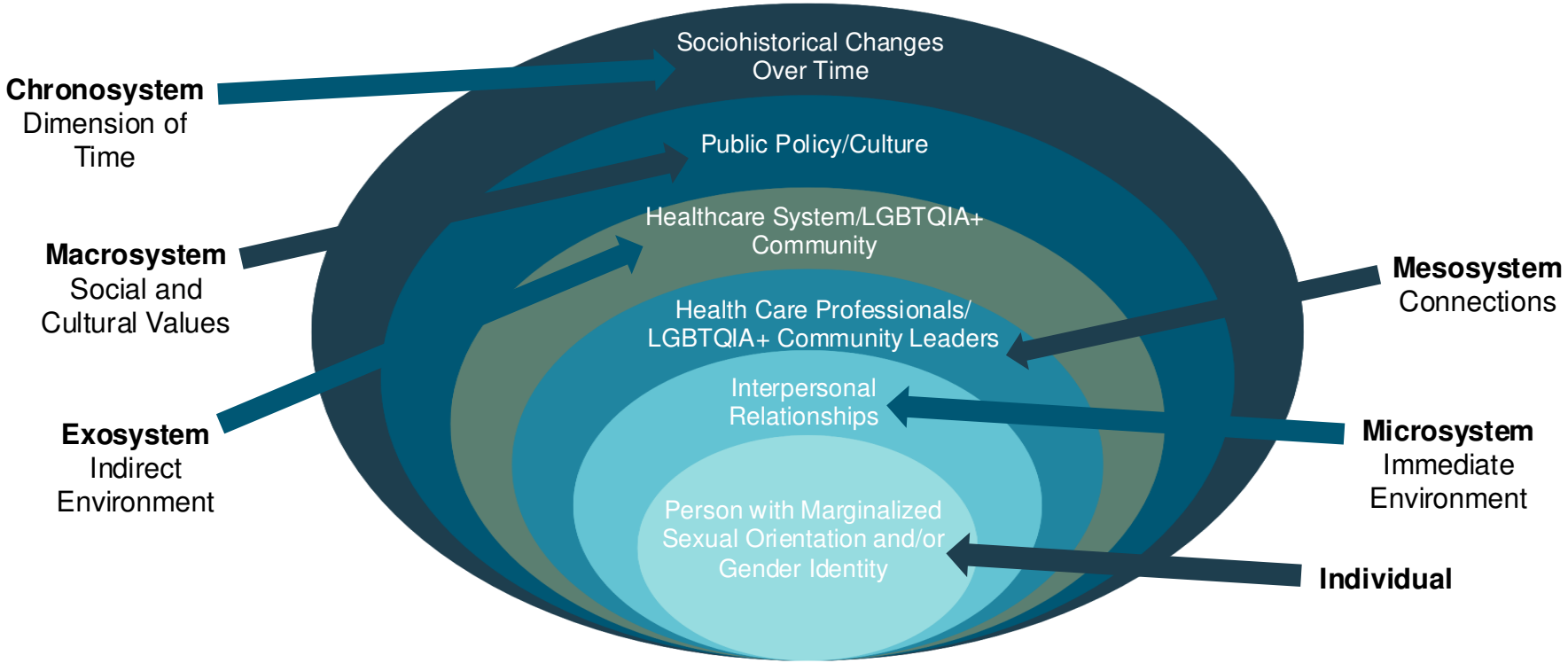
- Scope of the problem
- Misconceptions about cervical cancer risks and screening needs
- Conversations and changes are key

Up-to-Date Cervical Cancer Screening by Sexual Orientation and Gender Identity



Charkhchi P, et al. *J Am Coll Rad.* 2019;16(4PB):607-620. Grasso C, et al. *Int J Med Inform.* 2020;142:104245. Lee M, et al. *Cancer Causes Control.* 2020;31(10):951. Kiran T, et al. *Can Fam Physician.* 2019;65(1):e30-e37.

Application of the Social Ecological Model



LGBTQIA+ = Lesbian, gay, bisexual, transgender, queer/questioning, intersex, asexual, plus other identities not included in the acronym.

Stokols D. *Am Psychol.* 1992;47(1):6-22. Dhillon N, et al. *Am J Mens Health.* 2020;14(3). Milner GE, et al. *Health Psychol.* 2020;39(10):891-899. Johnson MJ, et al. *J Clin Nurs.* 2016;39(6):455-463. Johnson M, et al. *Prev Med Rep.* 2020;17:101052. Tabaac AR, et al. *LGBT Health.* 2019;6(2):77-86. Lombardo J, et al. *Cancer Causes Control.* 2022;33(4):559-582.

Common Misconceptions about Cervical Cancer Risk in Marginalized Sexuality and Gender Populations

People who are LGBTQIA+ have fewer or more sexual partners than those who are not

People who have never had penetrative vaginal sex (using fingers, sex toys, or genitals) or who have only had penetrative sex in the past are not at risk for cervical cancer

A person is at minimal risk of cervical cancer if they have never had PIV sex, and it is not important to encourage cervical cancer screening if someone has not engaged in PIV

Certain LGBTQIA+ patients only engage in certain sexual practices, altering their cervical cancer risk

PIV = penis-in-vagina.

Coughlin SS, et al. *Cancer Epidemiol Biomarkers Prev*. 2005;14(3):1143-1148. Barefoot KN, et al. *Rural Remote Health*. 2017(1):3875. Greene MZ, et al. *J Midwifery Women's Health*. 2018;63(5):550-577.

Health Care Experiences of Patients with Marginalized Sexual Orientations and/or Gender Identities

- Stigma
- Discrimination
- Lack of access to **culturally sensitive care** and to **medical and support services** that affirm sexual orientation and/or gender identity
- Heightened concerns about **confidentiality**
- Fear of being **“outed”**
- Fear of discussing sexual practices, gender identity, or sexual orientation

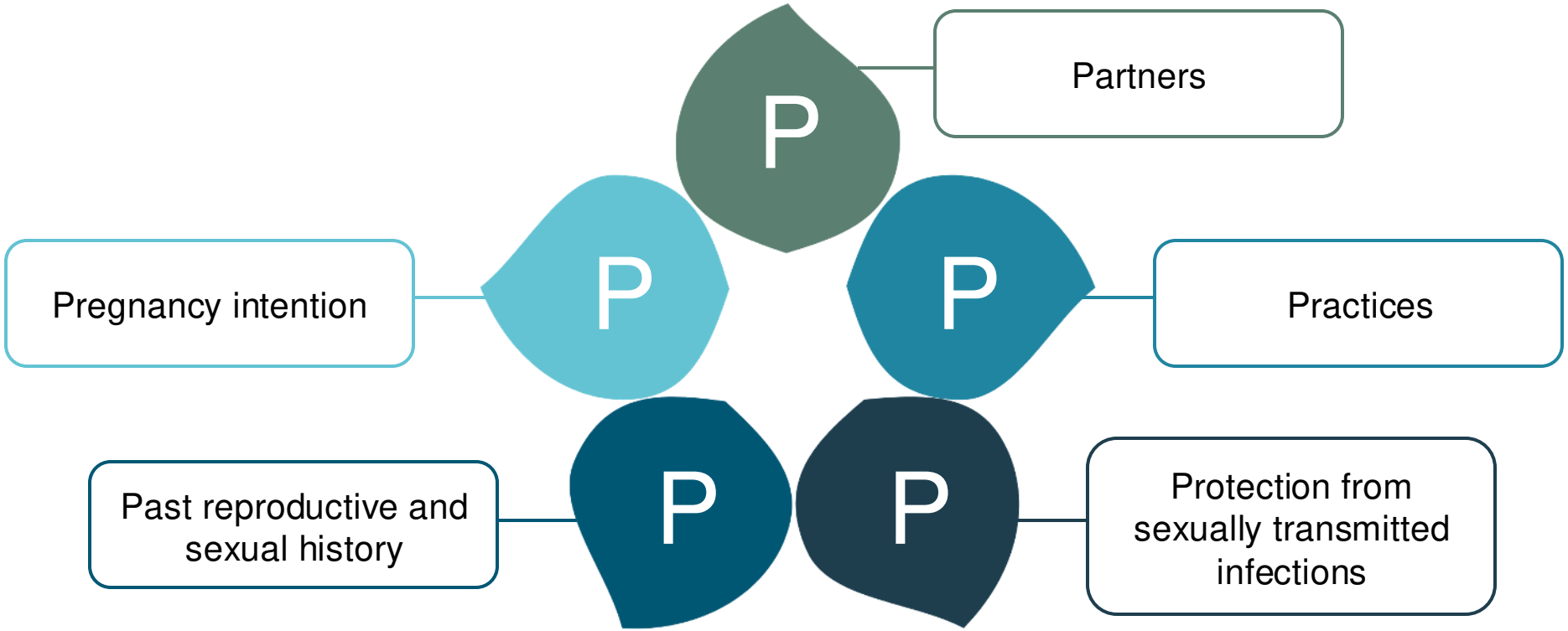
Heslin KC, et al. *Natl Health Stat Report.* 2022(171):1-16.

Terminology and Language to Use with Patients

- Though *queer* has not been formally adopted in academic or health care settings, many members of the community identify as such and **respect** for the label is thus appropriate
- Use **LGBTQIA+** as a catchall for marginalized sexual orientations and gender identities
- Use **trans** and **transgender**; avoid *trans*, transgendered,* or *transsexual*
- Use **person-centered** and **gender-neutral** language
- Use **preferred terms for patient anatomy** (e.g., *chest* instead of *breasts*) rather than anatomical terms when possible
- Respect chosen names, preferred **pronouns**, cultural identifiers, and **self-identification**

GLAAD Media Reference Guide 11th Edition. 2024. https://glaad.org/reference/.

The 5 Ps for Sexual History Dialogue



GLAAD Media Reference Guide 11th Edition. 2024. https://glaad.org/reference/.

Recommendations: Relationships Matter

The best predictors of cervical cancer screening uptake are **HCP recommendation** and the **HCP/patient relationship.**

- Positive experiences are key
- Practice affirming, patient-centered care
- Avoid assumptions
- Examine one's own biases

HCP = health care professional.

Wearn A, et al. *Psychol Health*. 2024:39(2):145-170.

10 Strategies for Creating Inclusive Health Care Environments for People with Marginalized Sexual Orientations and/or Gender Identities

1) Leadership is **actively engaged**
2) Organizational policies **protect** people with marginalized sexual orientations and/or gender identities
   - Nondiscrimination policies
   - Restroom policies
   - Family and support person policies
3) The **physical and virtual environment** welcomes marginalized sexual orientations and gender identities
4) Medical forms **affirm** people with marginalized sexual orientations and/or gender identities and their relationships
5) Partnerships are forged within the **LGBTQIA+ community**

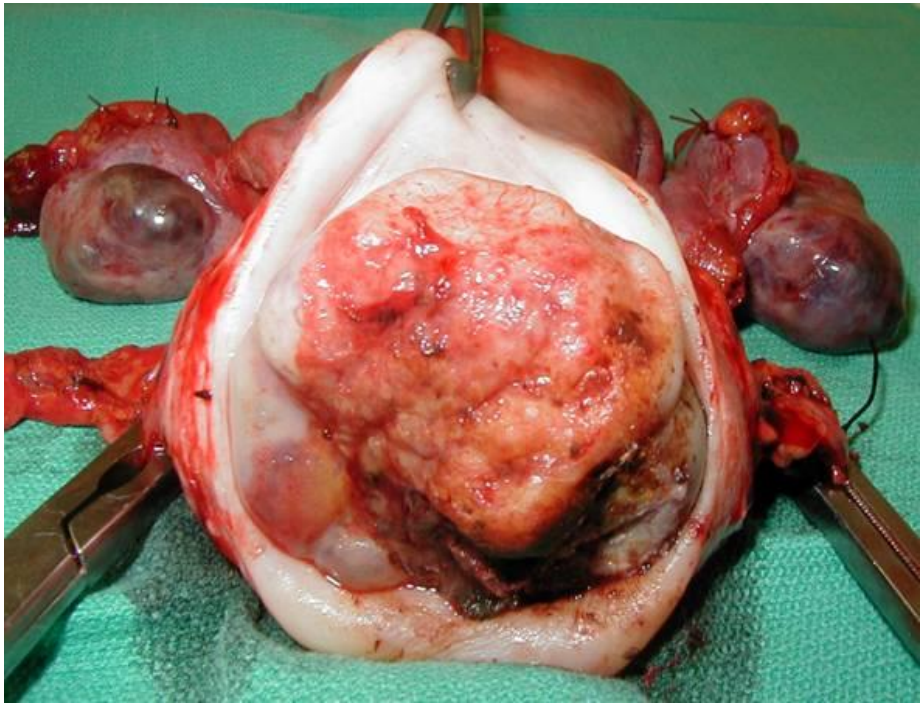
National LGBTQ+ Health Education Center. *Ten Strategies for Creating Inclusive Health Care Environments for LGBTQIA+ People.* 2021. https://www.lgbtqiahealtheducation.org/wp-content/uploads/2021/05/Ten-Strategies-for-Creating-Inclusive-Health-Care-Environments-for-LGBTQIA-People-Brief.pdf.

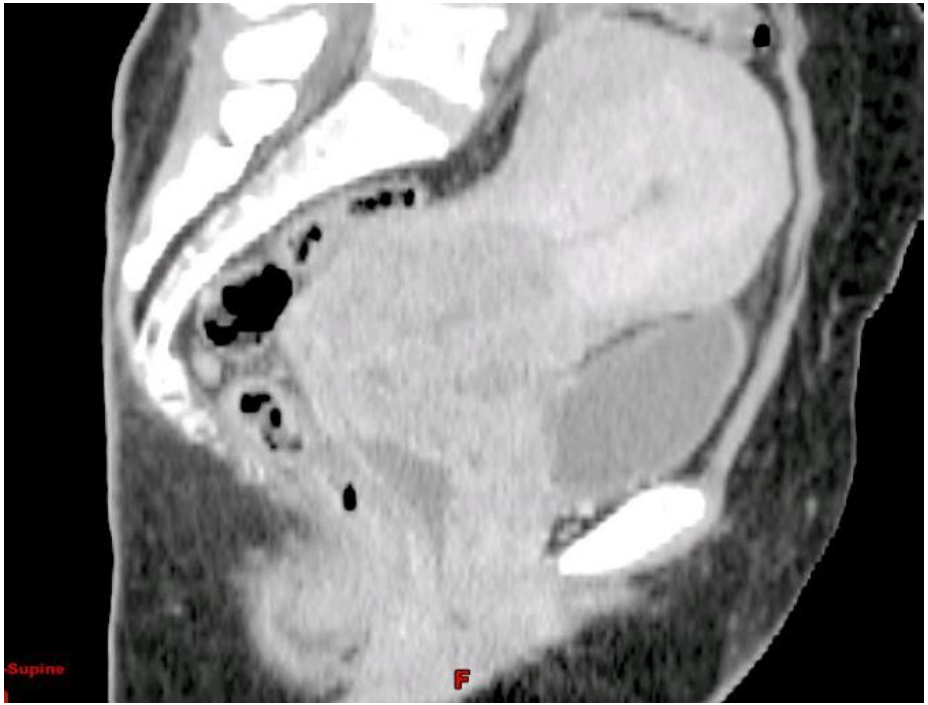
10 Strategies for Creating Inclusive Health Care Environments for People with Marginalized Sexual Orientations and/or Gender Identities

6) All staff receive training on **affirming communication** and care
7) Sexual orientation and gender identity data are collected and used to **improve health outcomes**
8) All patients receive **routine and inclusive** sexual health histories
9) Clinical care and services meet the **needs** of individuals with marginalized sexual orientations and/or gender identities
10) Members of the LGBTQIA+ community are **recruited and retained**

National LGBTQ+ Health Education Center. *Ten Strategies for Creating Inclusive Health Care Environments for LGBTQIA+ People.* 2021. https://www.lgbtqiahealtheducation.org/wp-content/uploads/2021/05/Ten-Strategies-for-Creating-Inclusive-Health-Care-Environments-for-LGBTQIA-People-Brief.pdf.

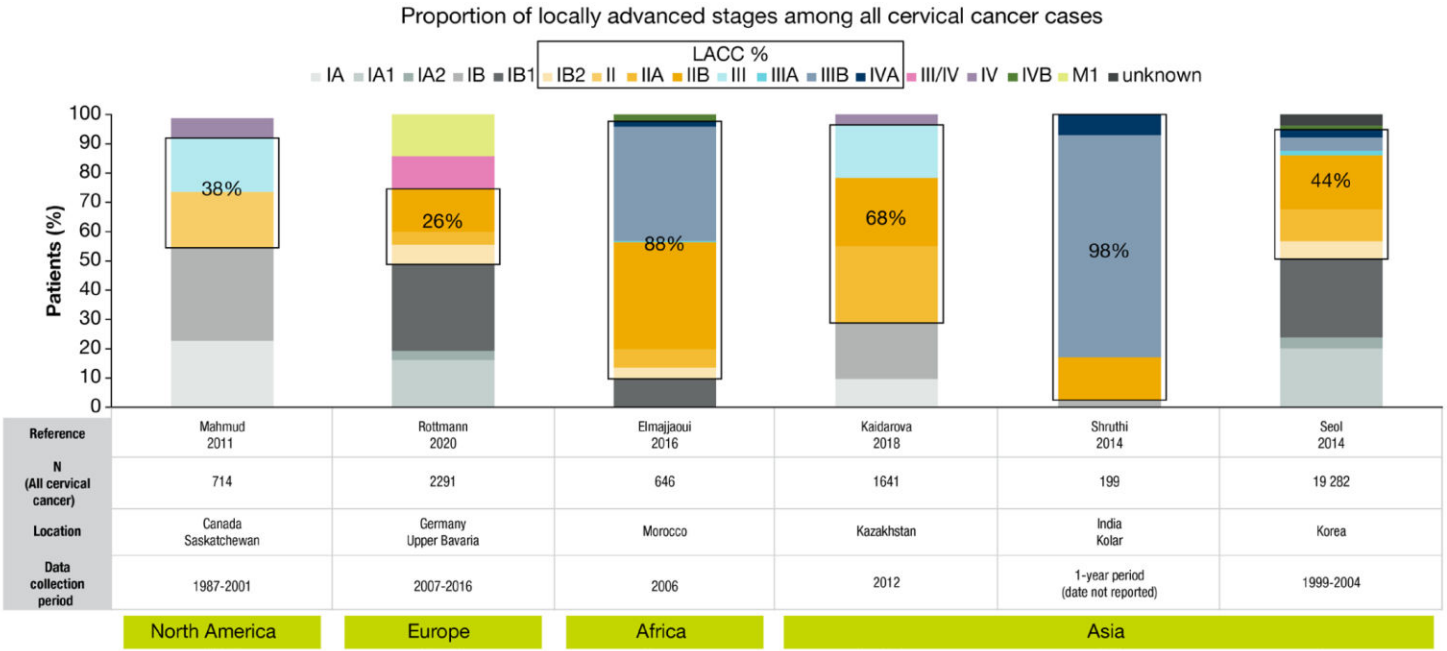
The Enemy





Photos courtesy of Dr. Bradley J. Monk.

Proportions and Incidence of Locally Advanced Cervical Cancer: A Global Systematic Literature Review



LACC = locally advanced cervical cancer.

Monk BJ, et al. *Int J Gynecol Cancer*. 2022;32(12):1531-1539.

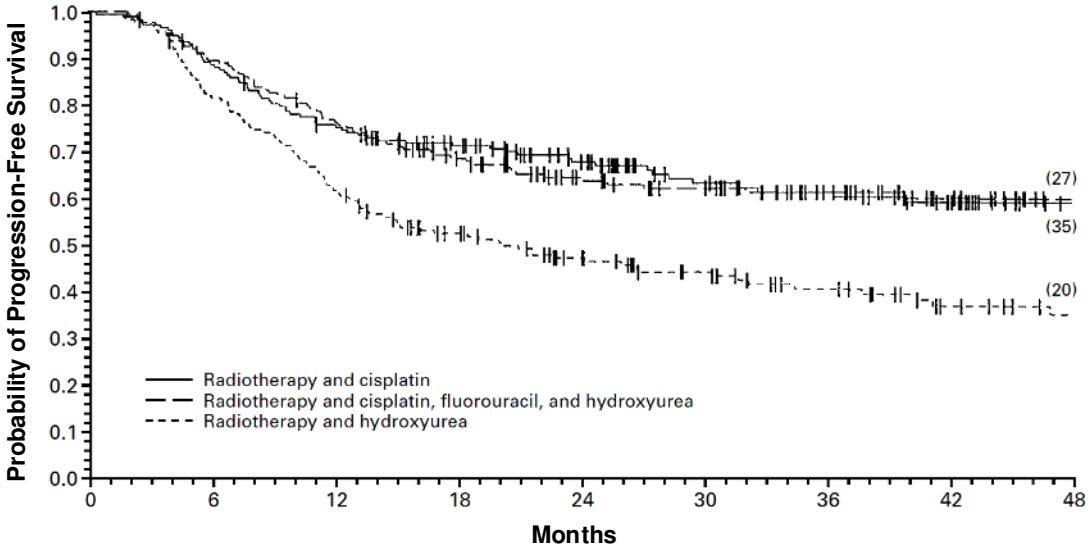
Staging and Evaluation of Locally Advanced Cervical Cancer

1. Two-handed pelvic exam
2. Pelvic MRI with IV and vaginal contrast
3. PET-CT
4. Unproven role of surgical staging
5. Little value of examination under anesthesia, proctoscopy, and cystoscopy

IV = intravenous; MRI = magnetic resonance imaging; PET-CT = positron emission tomography-computed tomography.

GOG 120 Established the Standard of Care in 1999: Cisplatin Plus RT in Locally Advanced Cervical Cancer

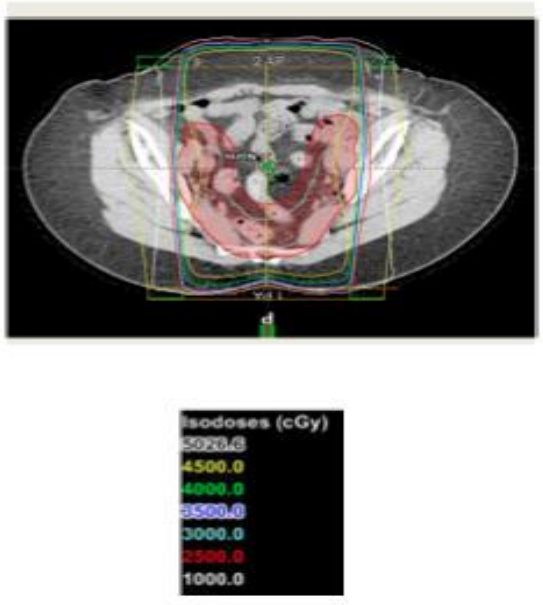
- N = 526 women
- Median duration of follow up was 35 months
- Both groups that received cisplatin had a higher rate of progression-free survival and overall survival
- At 2 years, 67% of patients were alive and progression-free with cisplatin compared to 46% with hydroxyurea



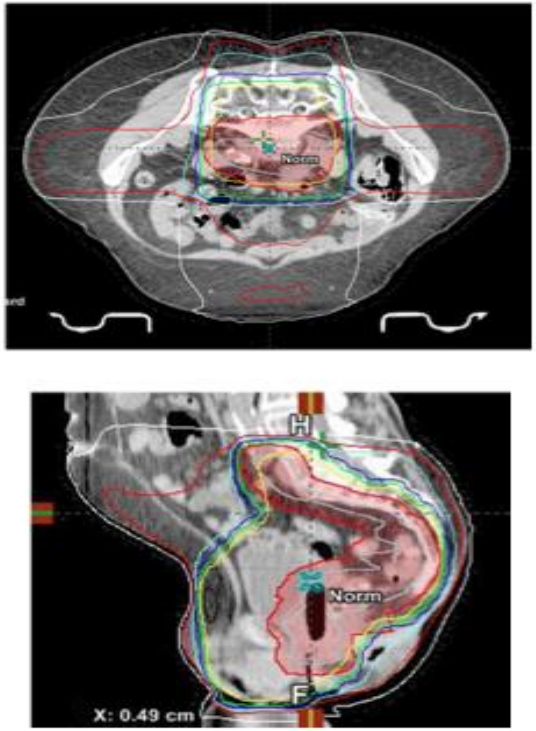
RT = radiotherapy.

Rose PG, et al. *N Engl J Med*. 1999;340(15):1144.

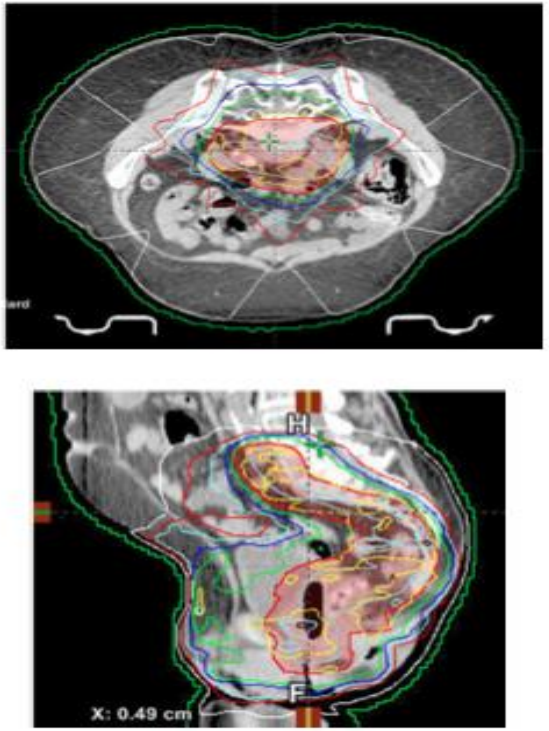
External Beam Radiation



AP/PA Fields



3D Conformal



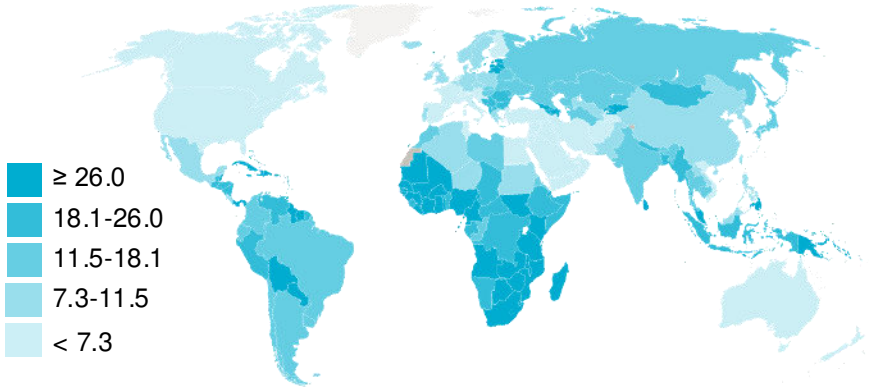
IMRT

AP/PA = anterior/posterior; IMRT = intensity-modulated radiation therapy.
Photos courtesy of Dr. Bradley J Monk.

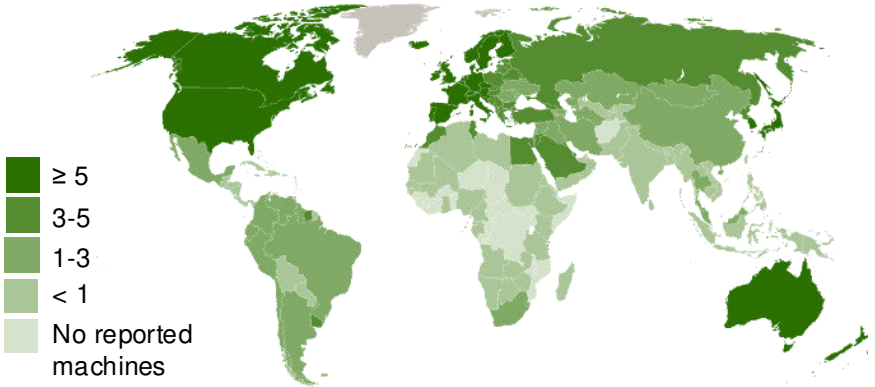
Mismatch of Radiotherapy Resources Worldwide

- Although radiation therapy is a critical part of the optimal treatment for many patients with LACC, not all countries have enough radiotherapy machines to treat patients
- In fact, due to reduced screening, many low-income countries where patients typically present with LACC also have fewer resources to provide optimal treatment for these patients
- This creates a mismatch of resources where radiotherapy machines are found primarily in high-income countries that have a lower demand for radiotherapy to treat cervical cancer due to their high vaccination and screening rates

Estimated age-standardized incidence rates of cervical cancer in women in 2018



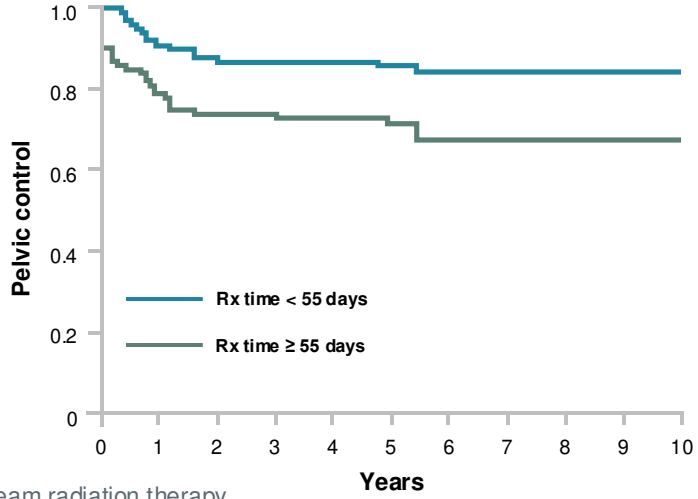
Number of radiotherapy machines per million people

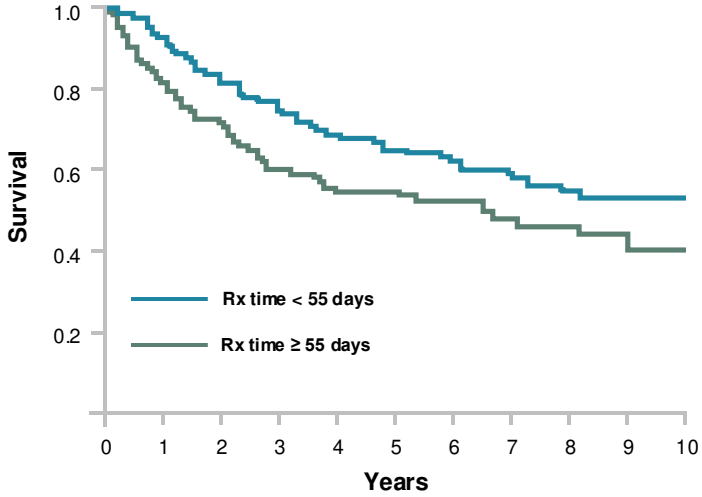


Directory of Radiotherapy Centres. 2020. https://dirac.iaea.org/Query/Map2?mapId=0. Chopra S, et al. *J Glob Oncol.* 2019;5:1-5.
Milosevic M, et al. World Cancer Congress, 2018. Abstract T3-61. https://www.worldcancercongress.org/sites/congress/files/atoms/files/T3-61.pdf. World Health Organization [WHO]. 2020. https://gco.iarc.fr/.

Effect of Treatment Timing on Pelvic Control and Survival

- Treatment delay has been correlated with higher rates of pelvic failure, and current guidelines stipulate completion of EBRT plus brachytherapy within 8 weeks
- Treatment extended beyond 8 weeks is associated with poorer outcomes
  - It is possible that prolonging treatment beyond 8 weeks allows increased repopulation of cancer cells, resulting in reduced local control rates



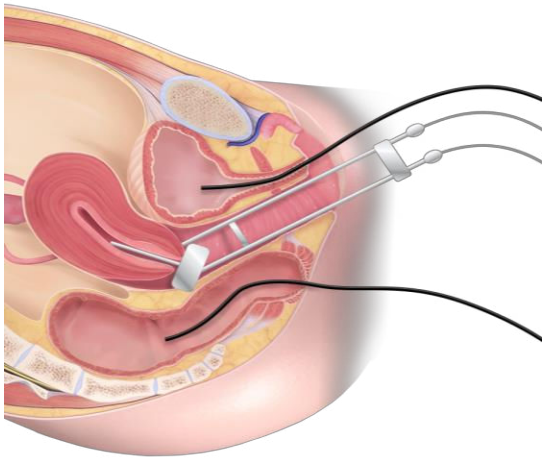


EBRT = external beam radiation therapy.

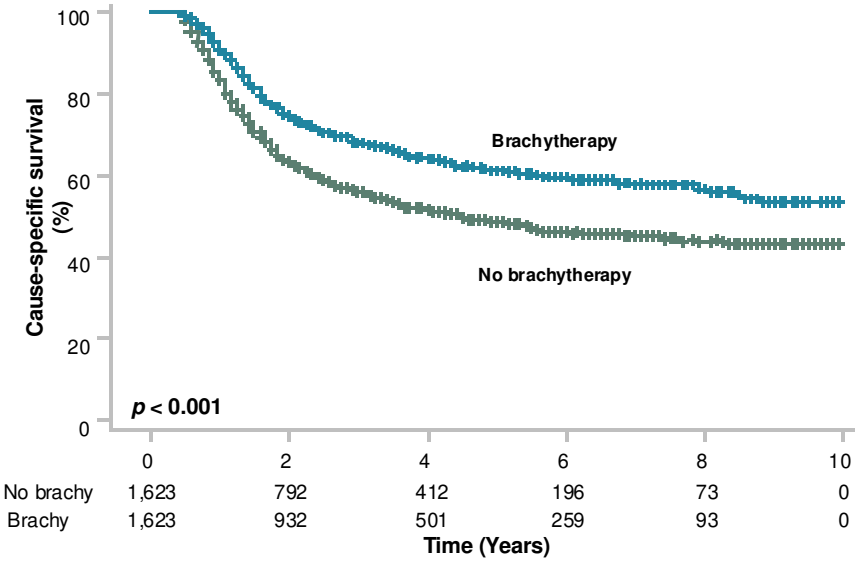
Bhatla N, et al. *Int J Gynaecol Obstet.* 2018;143:22-36. Song S, et al. *Cancer.* 2013;119:325-331. Petereit DG, et al. *Int J Radiat Oncol Biol Phys.* 1995;32:1301-1307.

Brachytherapy

- Brachytherapy (BT) is the only method demonstrated to provide the high dose of radiation needed to control cervical cancer while minimizing adverse effects on normal tissue
- Imaging can improve the efficacy of brachytherapy



A radioactive source is placed in or near the tumor, which allows for the tumor to receive a concentrated dose while relatively sparing the surrounding normal tissue

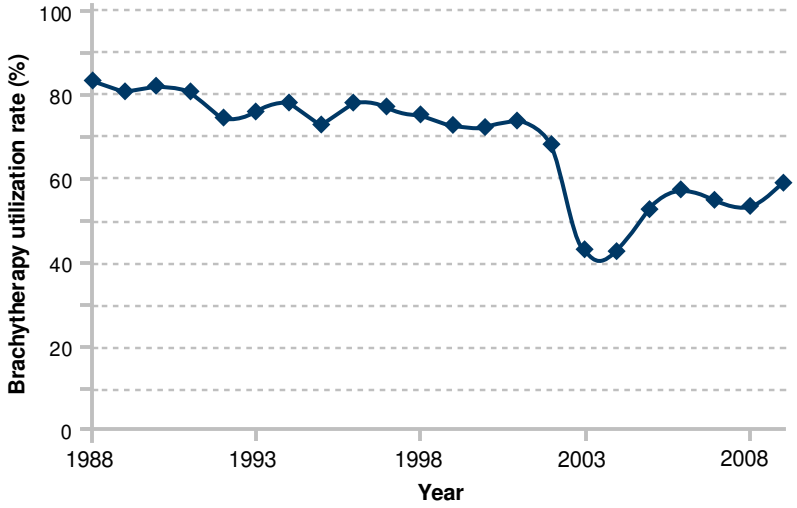


Banerjee R, Kamrava M. *Int J Women's Health.* 2014;6:555-564.
Han K, et al. *Int J Radiat Oncol Biol Phys.* 2013;87:111-119. Holschneider CH, et al. *Gynecol Oncol.* 2019;152:540–547.

Underutilization of Brachytherapy

- SEER data shows brachytherapy utilization **decreased from 83% in 1988 to 58% in 2009** ($p < 0.001$)
- Brachytherapy treatment was associated with higher 4-year cause-specific survival (64.3% vs 51.5%, $p < 0.001$) and overall survival (58.2% vs 46.2%, $p < 0.001$)

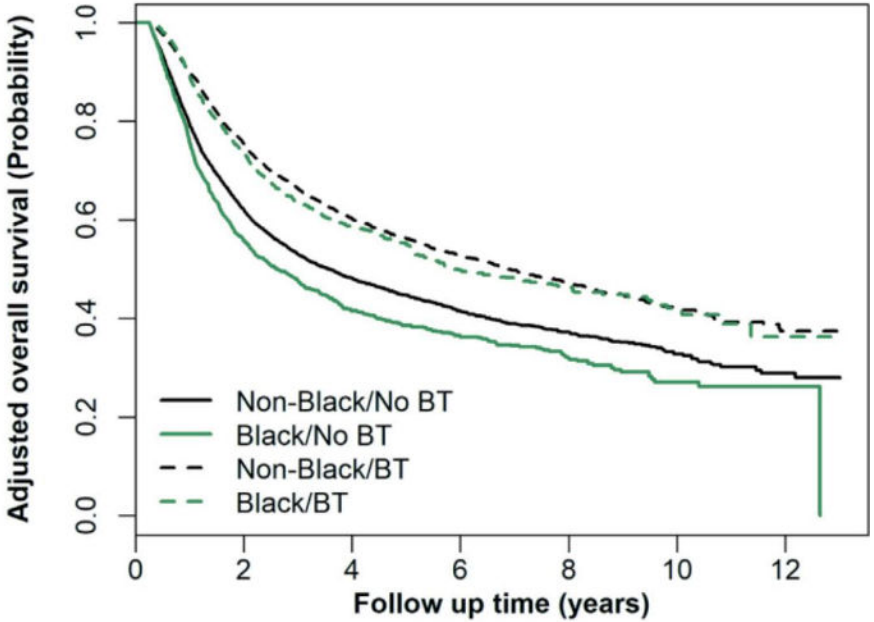
- A study of patients with cervical cancer in California showed **45% brachytherapy utilization during the study period (2004-2014)**, with a subsequent decrease in survival outcomes (HR, 1.16; 95% CI, 1.01-1.34; $p = 0.0330$) in patients who did not receive brachytherapy
- There was also a disparity in patients treated with brachytherapy:
  - Brachytherapy utilization was lower in patients age > 80 and in patients at Stage IVA
  - Black patients and those in low socioeconomic situations had worse survival



SEER = Surveillance, Epidemiology, and End Results Program.

Han K, et al. *Int J Radiation Oncol Biol Phys.* 2013;87:111-119. Mayadev J, et al. *Gynecol Oncol.* 2018;150:73-78.

Racial Disparities in Brachytherapy Administration and Survival in Women with LACC in the U.S.

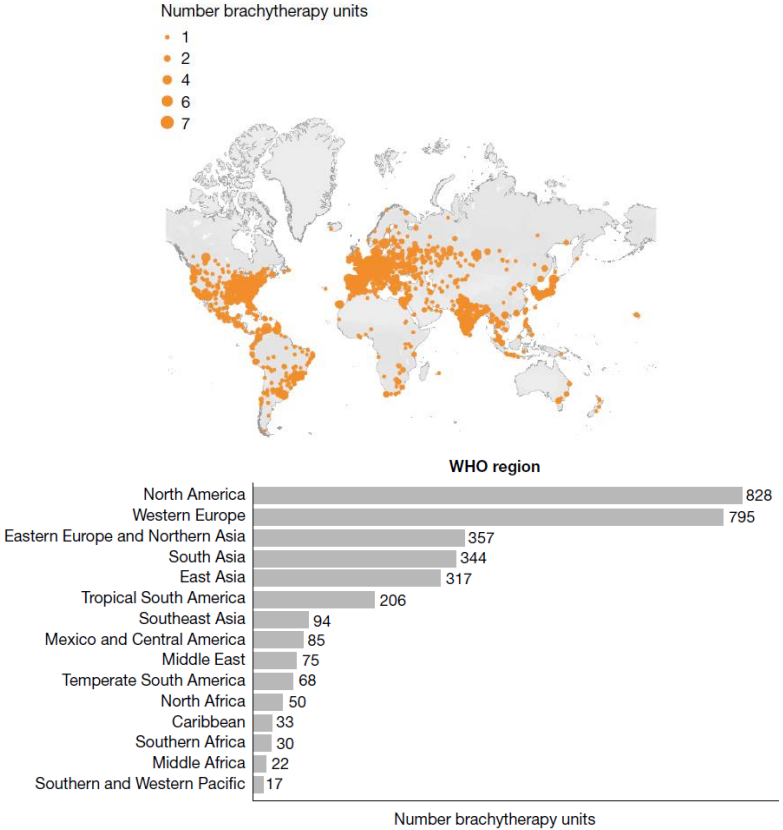


Non-Black/No BT	12725	6784	3653	1897	894	324	60
Black/No BT	3042	1458	821	396	185	63	9
Non-Black/BT	12805	8387	4644	2472	1210	484	65
Black/BT	3027	1977	1083	595	314	104	17

Alimena S, et al. *Gynecol Oncol*. 2019;154:595-601.

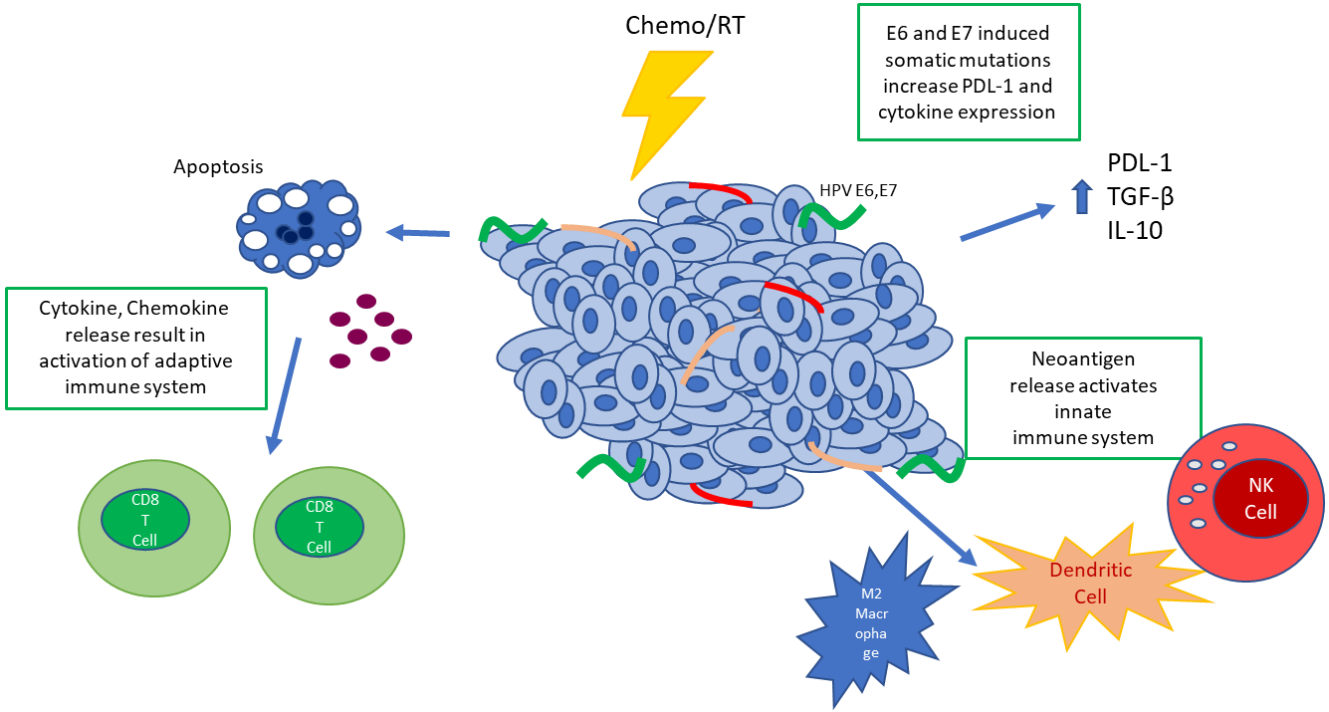
Underutilization of Brachytherapy

- In **Japan**, about 50% of patients with LACC did not receive guideline-adherent treatment, with approximately 20-25% not given brachytherapy
- Brachytherapy underutilization for LACC treatment has also been observed in **Korea**
- In 2014, 55 of 139 low- and middle-income countries (LMICs) had no radiotherapy facilities
  - Of these, 7 were in **Asia** and 6 were in **Latin America** and the **Caribbean**
- In **Latin America** and the **Caribbean**, there was only one brachytherapy machine per 2.4 million people for the entire region, with ~50% of machines in **Brazil** and **Mexico**



International Atomic Energy Agency, Directory of Radiotherapy Centres. https://dirac.iaea.org/Query/Map2?mapId=2. Watanabe T, et al. *J Gynecol Oncol* 2018;29:e83. Kim H, et al. *J Gynecol Oncol.* 2016;27:e33. Datta NR, et al. *Int J Radiat Oncol Biol Phys.* 2014;89:448-457. Bishr MK, Zaghloul MS. *Int J Radiat Oncol Biol Phys.* 2018;102:490-498.

Immune Dynamics of Cervical Cancer



IL = interleukin; NK = natural killer; PDL-1 = programmed death-ligand 1; TGF-β = transforming growth factor beta.

Yang W, et al. *J Obstet Gynaecol Res.* 2013;43(10):1602-1612. Formenti SC, et al. *J Natl Cancer Inst.* 2013;105(4):256-265. Weichselbaum RR, et al. *Nat Rev Clin Oncol.* 2017;14(6):365-379. Salama AKS, et al. *Cancer.* 2016;122(11):1659-1671. Twyman-Saint Victor C, et al. *Nature.* 2015;520(7547):373-377.

ENGOT-cx11/GOG-3047/KEYNOTE-A18: Randomized, Double-Blind, Phase III 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 [EQD2])

End Points

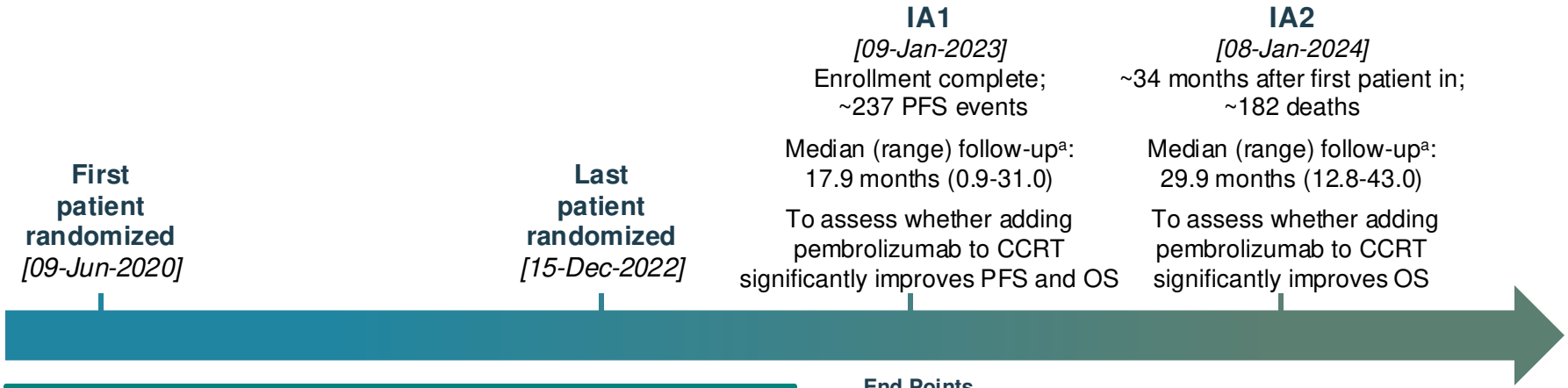
- Primary: PFS (per RECIST v1.1) by investigator or histopathologic confirmation and OS
- Secondary: 24-month PFS, 36-month OS, ORR, patient-reported HRQoL, and safety

[a]A 6th cycle was allowed per investigator discretion.

EQD2 = equivalent dose in 2Gy; FIGO = International Federation of Gynaecology and Obstetrics; Gy = gray (radiation dose); HRQoL = health-related quality of life; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; Q_W = every _ week(s); RECIST = Response Evaluation Criteria in Solid Tumors; VMAT = volumetric-modulated arc therapy.

Lorusso D, et al. *Lancet*. 2024;403(10434):1341-1350. Lorusso D, et al. *Ann Oncol*. 2023;34:S1279-S1280.

KEYNOTE-A18: Study End Points, Milestones, and Statistical Considerations



Multiplicity

PFS
Initial one-sided
α = 0.025

↓

OS
Initial one-sided
α = 0

Prespecified analysis plan allows alpha from successful hypothesis to be passed to the other hypothesis. Because PFS was significant at IA1, OS was tested at α = 0.025 at IA2 according to group sequential design.

End Points

- Primary: PFS (per RECIST v1.1) by investigator or histopathologic confirmation and OS
- Secondary: 24-month PFS, 36-month OS, ORR, patient-reported HRQoL, and safety

[a]Defined as the time from randomization to the data cutoff date.

CCRT = concurrent chemoradiotherapy.

Lorusso D, et al. *Lancet*. 2024;403(10434):1341-1350.
Lorusso D, et al. *Ann Oncol*. 2023;34:S1279-S1280.

KEYNOTE-A18: 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%)

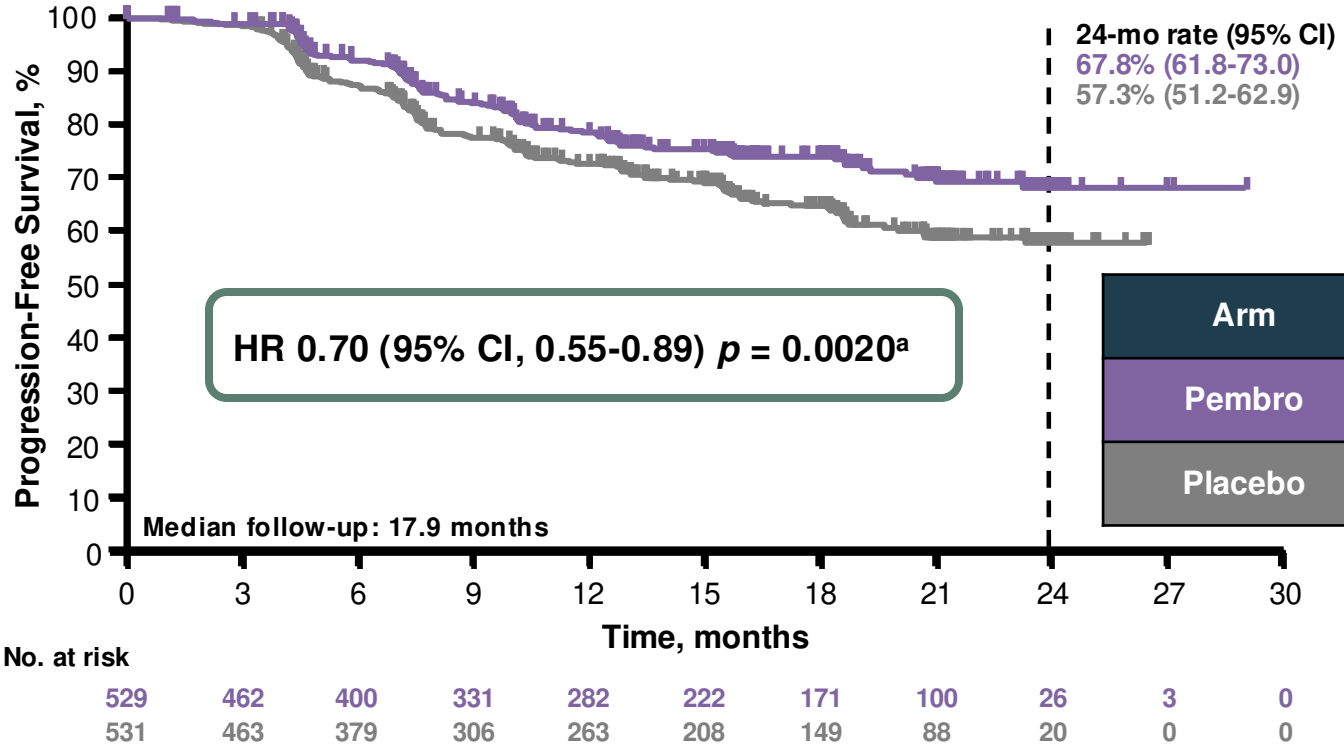
	Pembro Arm (N = 529)	Placebo Arm (N = 531)
Stage at screening (FIGO 2014 criteria)		
IB2-IIB	233 (44.0%)	226 (42.6%)
III-IVA	296 (56.0%)	305 (57.4%)
Lymph node involvement[b]		
Positive pelvic only	327 (62.2%)	324 (61.0%)
Positive para-aortic only	14 (2.6%)	10 (1.9%)
Positive pelvic and para-aortic	104 (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.

CPS = combined positive score; ECOG PS = Eastern Cooperative Oncology Group Performance Status.

Lorusso D, et al. *Lancet*. 2024;403(10434):1341-1350. Lorusso D, et al. *Ann Oncol*. 2023;34:S1279-S1280.

KEYNOTE-A18: Progression-Free Survival at IA1



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

CI = confidence interval; HR = hazard ratio; NR = not reached. Lorusso D, et al. *Lancet*. 2024;403(10434):1341-1350. Lorusso D, et al. *Ann Oncol*. 2023;34:S1279-S1280.

KEYNOTE-A18: Baseline Characteristics in Patients with FIGO 2014 Stage III-IVA Cervical Cancer

Baseline Characteristics	Patients with FIGO 2014 Stage III-IVA disease in KEYNOTE-A18 N=596
Median age, years (range)	52 (22-87)
Age ≥65 years, %	17
Race, %	
White	36
Asian	34
Black	1
Hispanic or Latino	38
ECOG PS, %	
0	68
1	32
CPS ≥1, %	93
Lymph node involvement	
Positive pelvic and/or para-aortic lymph nodes, %	70
Neither positive pelvic nor para-aortic lymph nodes, %	30
Squamous cell carcinoma	83
Non-squamous histology	17

- 85% of patients received IMRT or VMAT EBRT, and the median EQD2 dose was 87 Gy (range: 7 to 114).

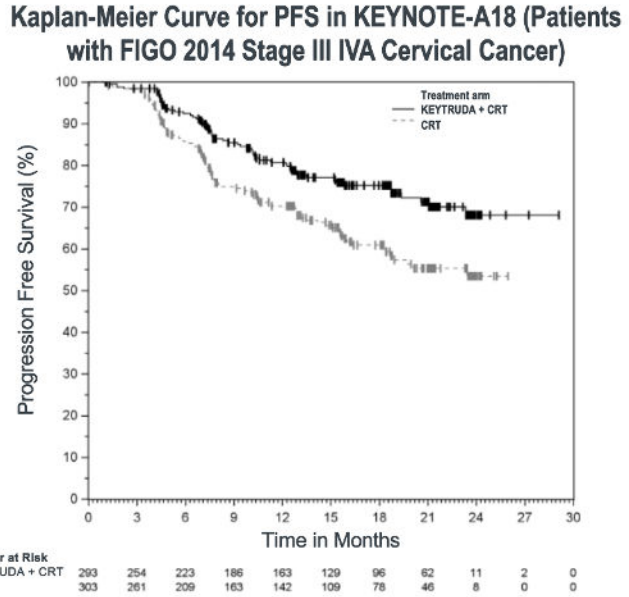
Lorusso D, et al. *Lancet*. 2024;403(10434):1341-1350. Lorusso D, et al. *Ann Oncol*. 2023;34:S1279-S1280.

KEYNOTE-A18: Efficacy in Patients with FIGO 2014 Stage III-IVA Cervical Cancer at IA1

- In an exploratory subgroup analysis for the 462 patients (44%) with FIGO 2014 stage IB2-IIB disease, the PFS HR estimate was 0.91 (95% CI: 0.63-1.31)
- OS data were not mature at the time of PFS analysis, with 10% deaths in the overall population

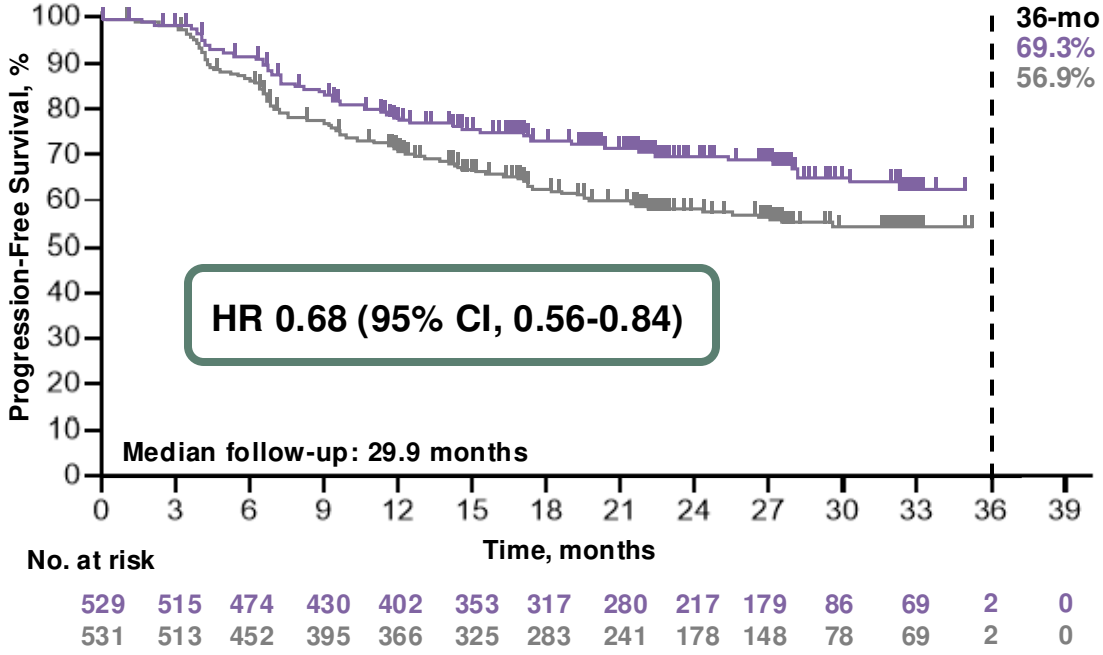
	KEYTRUDA 200 mg every 3 weeks and 400 mg every 6 weeks with CRT n=293	Placebo with CRT n=303
PFS by Investigator		
Number of patients with event (%)	61 (21%)	94 (31%)
Median in months (95% CI)	NR (NR, NR)	NR (18.8, NR)
12-month PFS rate (95% CI)	81% (75, 85)	70% (64, 76)
Hazard ratio* (95% CI)	0.59 (0.43, 0.82)	

* Based on the unstratified Cox proportional hazard model



Lorusso D, et al. *Lancet*. 2024;403(10434):1341-1350. Lorusso D, et al. *Ann Oncol*. 2023;34:S1279-S1280.

KEYNOTE-A18: Updated Progression-Free Survival at IA2



36-mo rate (95% CI)
69.3% (62.7-75.0)
56.9% (50.4-62.9)

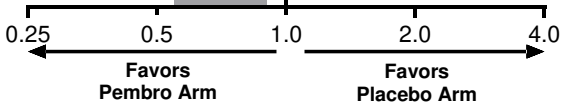
Arm	Pts w/ Event	Median, mo (95% CI)
Pembro	29.3%	NR (NR-NR)
Placebo	39.5%	NR (32.0-NR)

Response assessed per RECIST v1.1 by investigator review or histopathologic confirmation. Since the success criterion of the PFS hypothesis was met at IA1, no formal testing of PFS was performed at IA2.
Data cutoff date: January 8, 2024.

Lorusso D, et al. *Lancet*. 2024 Sept 14. [Epub ahead of print].

KEYNOTE-A18: Updated Progression-Free Survival in Protocol-Specified Subgroups

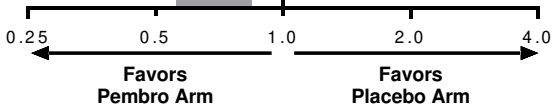
Subgroup	No. of Events/ No. of Patients	HR (95% CI)
Overall	269/1060	0.70 (0.55-0.89)
Age		
<65 years	236/927	0.72 (0.56-0.94)
≥65 years	33/133	0.57 (0.27-1.17)
Race		
White	143/518	0.83 (0.59-1.15)
All others	125/538	0.60 (0.42-0.86)
ECOG PS score		
0	197/777	0.79 (0.59-1.04)
1	72/283	0.53 (0.33-0.85)
Planned EBRT		
IMRT/VMAT	237/939	0.68 (0.52-0.87)
non-IMRT/-VMAT	32/121	0.92 (0.46-1.85)
FIGO 2014 stage		
IB2 to IIB	113/462	0.91 (0.63-1.31)
III to IVA	156/598	0.58 (0.42-0.80)
Planned total RT dose		
<70 Gy	25/93	0.62 (0.28-1.38)
≥70 Gy	244/967	0.71 (0.55-0.91)



Response assessed per RECIST v1.1 by investigator review or histopathologic confirmation.

Data cutoff date: January 9, 2023.

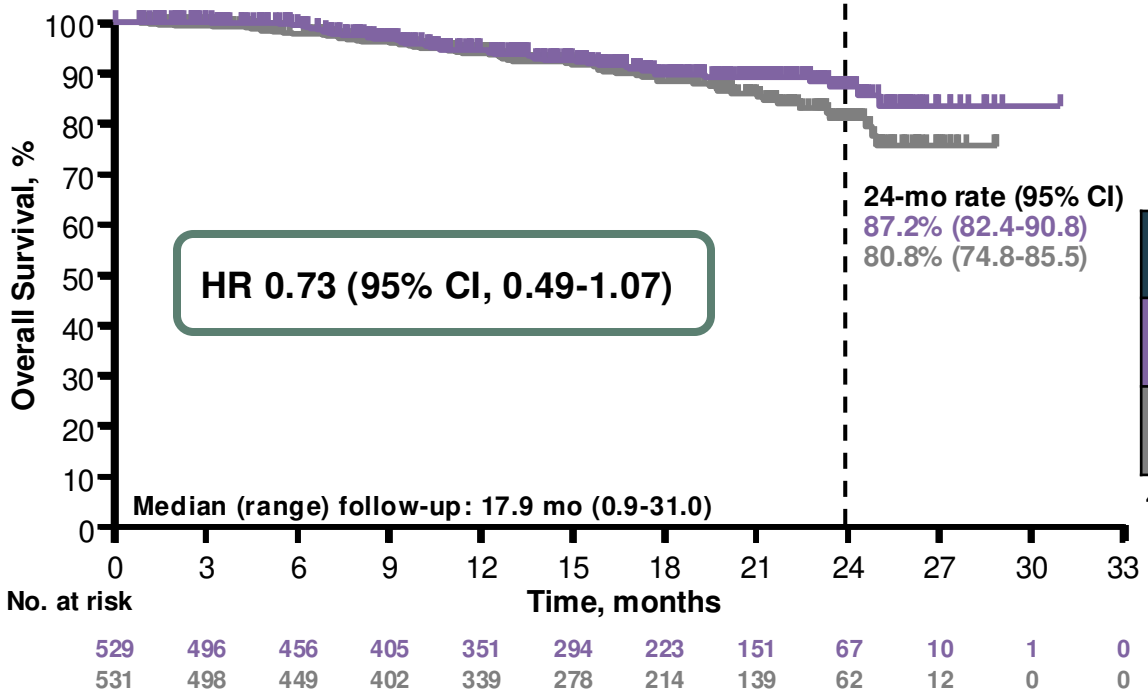
Subgroup	No. of Events/ No. of Patients	HR (95% CI)
Overall	365/1060	0.68 (0.56-0.84)
Age		
<65 years	318/927	0.69 (0.55-0.86)
≥65 years	47/133	0.64 (0.35-1.16)
Race		
White	202/518	0.74 (0.56-0.98)
All others	161/539	0.65 (0.47-0.88)
ECOG PS score		
0	266/778	0.72 (0.57-0.92)
1	99/282	0.59 (0.40-0.88)
Planned EBRT		
IMRT/VMAT	325/939	0.66 (0.53-0.82)
non-IMRT/-VMAT	40/121	0.90 (0.49-1.68)
FIGO 2014 stage		
IB2 to IIB	161/459	0.85 (0.62-1.16)
III to IVA	204/601	0.57 (0.43-0.76)
Planned total RT dose		
<70 Gy	32/93	0.67 (0.33-1.35)
≥70 Gy	333/967	0.68 (0.55-0.85)



Data cutoff date: January 8, 2023.

Lorusso D, et al. *Lancet*. 2024 Sept 14. [Epub ahead of print].

KEYNOTE-A18: Primary Endpoint: Overall Survival (Immature, IA1)



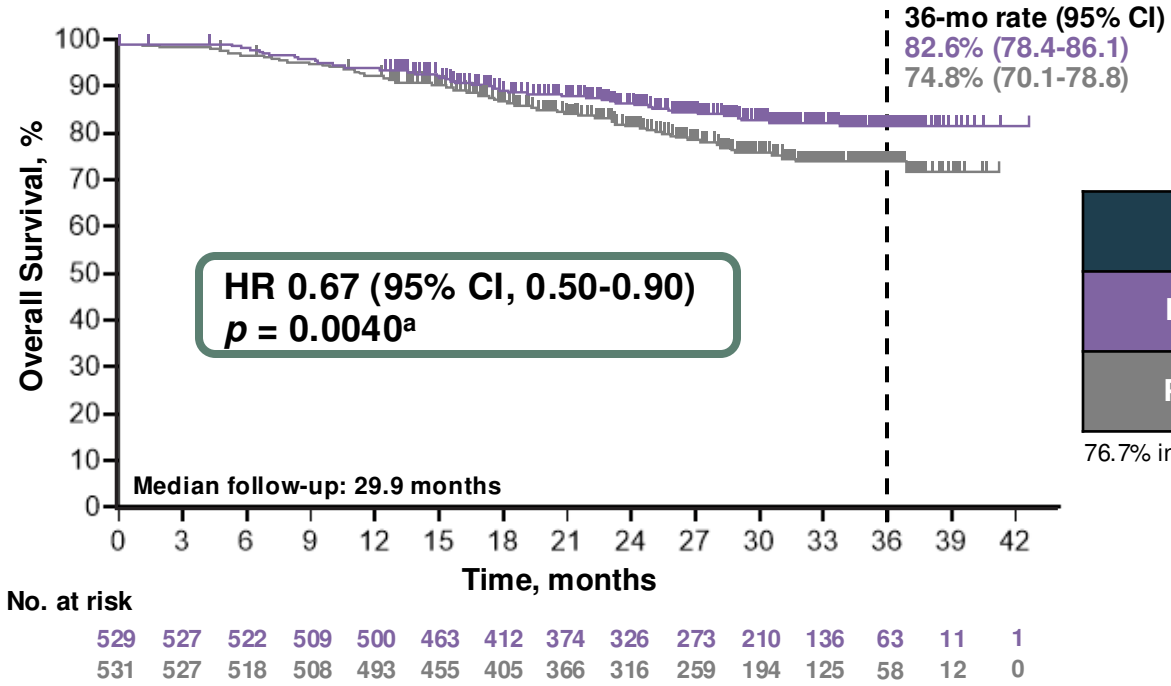
Arm	Pts w/ Event*	Median, mo (95% CI)
Pembro	8.3%	NR (NR-NR)
Placebo	11.1%	NR (NR-NR)

42.9% information fraction[a]

[a]At this analysis, 103 of the 240 deaths expected at the final analysis had occurred.
Data cutoff date: January 9, 2023.

Lorusso D, et al. *Lancet*. 2024;403(10434):1341-1350. Lorusso D, et al. *Ann Oncol*. 2023;34:S1279-S1280.

KEYNOTE-A18: Primary Endpoint: Overall Survival at IA2



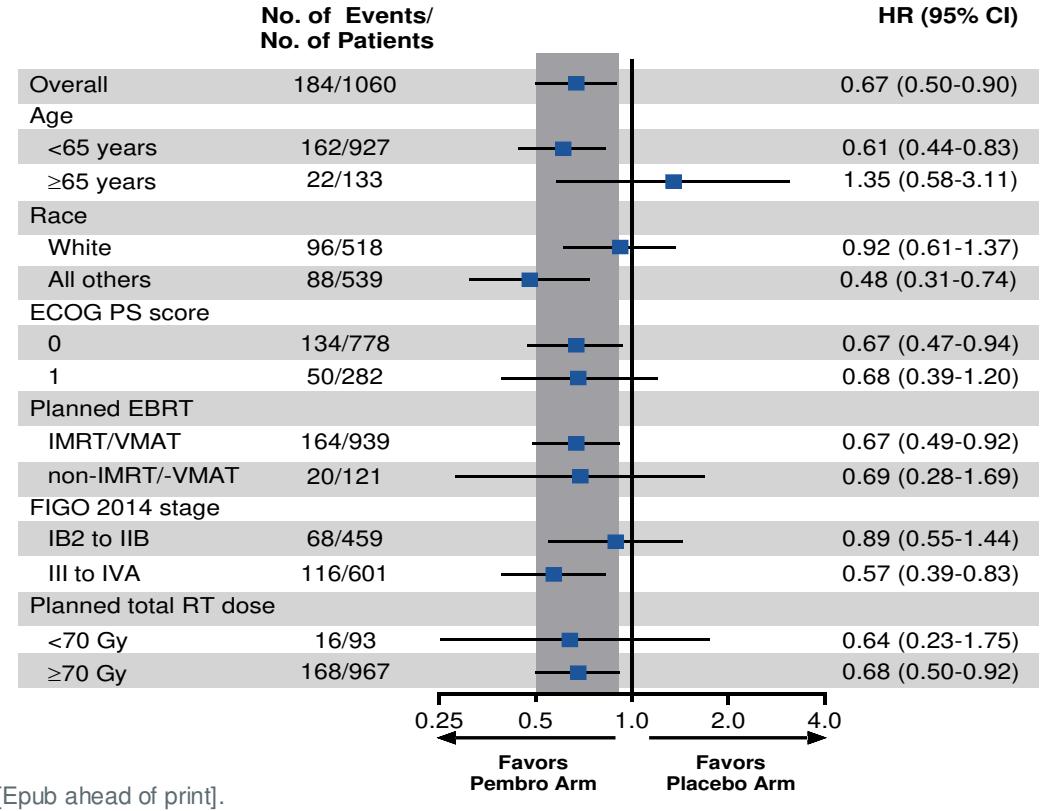
Arm	Pts w/ Event	Median, mo (95% CI)
Pembro	14.2%	NR (NR-NR)
Placebo	20.5%	NR (NR-NR)

76.7% information fraction[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 planned second 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 arm; of those, 10 (7.2%) and 41 (21.2%), respectively, had received pembro. Data cutoff date: January 8, 2024.

Lorusso D, et al. *Lancet*. 2024 Sept 14. [Epub ahead of print].

KEYNOTE-A18: Overall Survival in Protocol-Specified Subgroups at IA2

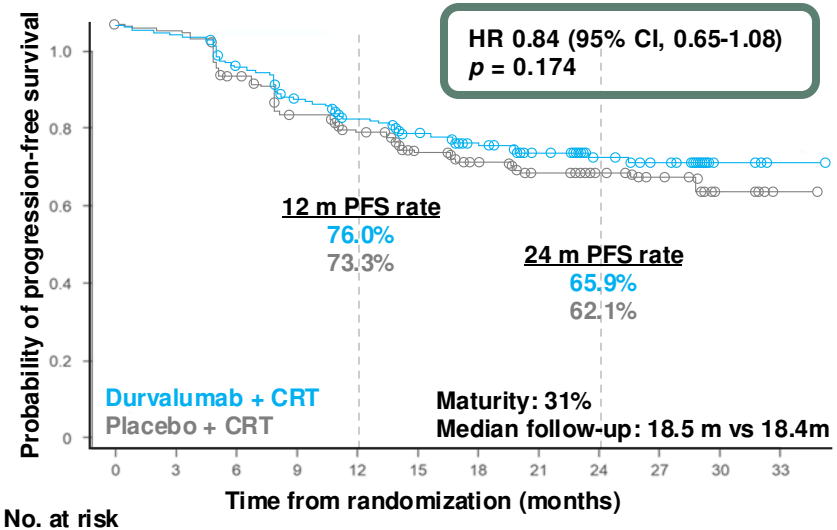


Data cutoff date: January 8, 2024.

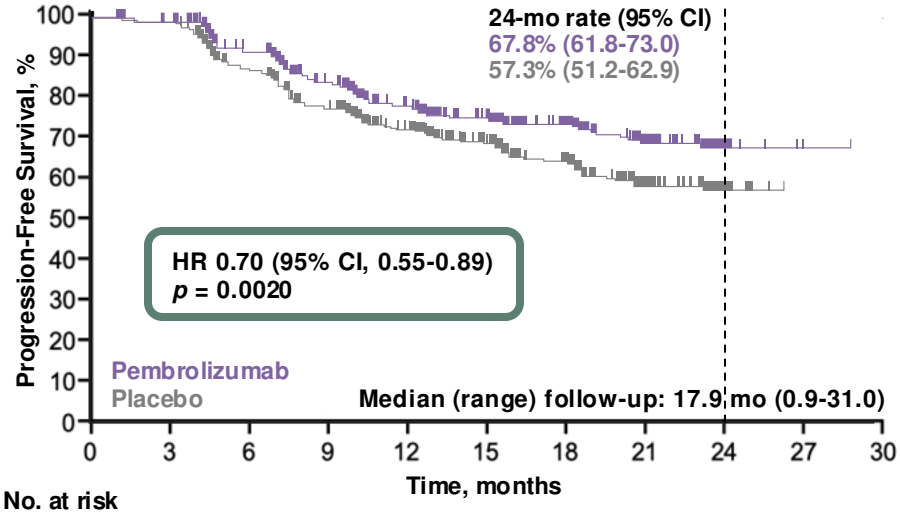
Lorusso D, et al. *Lancet*. 2024 Sept 14. [Epub ahead of print].

Adding Immune Checkpoint Inhibitors CCRT in LACC

Durvalumab in CALLA



Pembrolizumab in KEYNOTE-A18



Monk B, et al. *Int J Gynecol Cancer*. 2022;32(Suppl 3):A2. Monk BJ, et al. *Lancet Oncol*. 2023;24(12):1334-1348. Lorusso D, et al. *Lancet*. 2024;403(10434):1341-1350.

MADRID 2023 ESMO congress

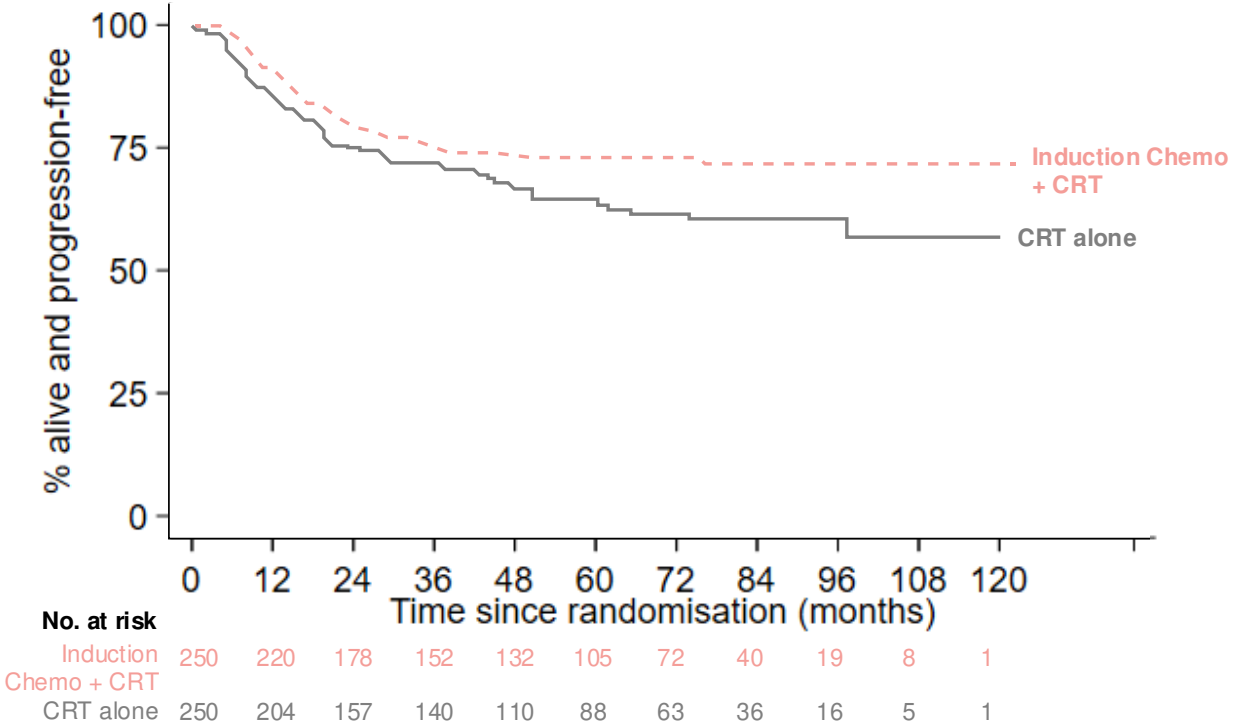
A randomised phase III trial of induction chemotherapy followed by chemoradiation compared with chemoradiation alone in locally advanced cervical cancer The GCIG INTERLACE Trial

M. McCormack[1], D. Gallardo[2], G. Eminowicz[1], P. Diez[3], L. Farrelly[4], C. Kent[5], E. Hudson[6], M. Panades[7], T. Mathew[8], A. Anand[9], M. Persic[10], J. Forrest[11], R. Bhana[12], N. Reed[13], A. Drake[14], H. Stobart[15], A. Mukhopadhyay[16], A.M. Hacker[4], A. Hackshaw[4], J.A. Ledermann[4]

[1]University College Hospital NHS Trust, London, UK; [2]INCAN, Mexico; [3]East and North Hertfordshire NHS trust, UK; [4]University College London CTC, UK; [5]University of Leicester NHS trust, UK; [6]Velindre Cancer Centre, UK; [7]United Lincolnshire Hospitals NHS Trust, UK; [8]Sheffield Teaching Hospitals NHS Trust, UK; [9]Nottingham University NHS Trust, UK; [10]University of Derby and Burton NHS Foundation Trust, UK; [11]Royal Devon and Exeter NHS Foundation Trust, UK; [12]University Hospital of North Midlands NHS Trust, UK; [13]Beatson West of Scotland Cancer Centre, UK; [14]Belfast Health and Social Care Trust, UK; [15]Independent Cancer Patients' Voice, UK; [16]Kolkata Gynaecological Oncology Trials and Translational Research Group, Kolkata India

CRUK grant number: C37815/A12832

INTERLACE: Progression-Free Survival

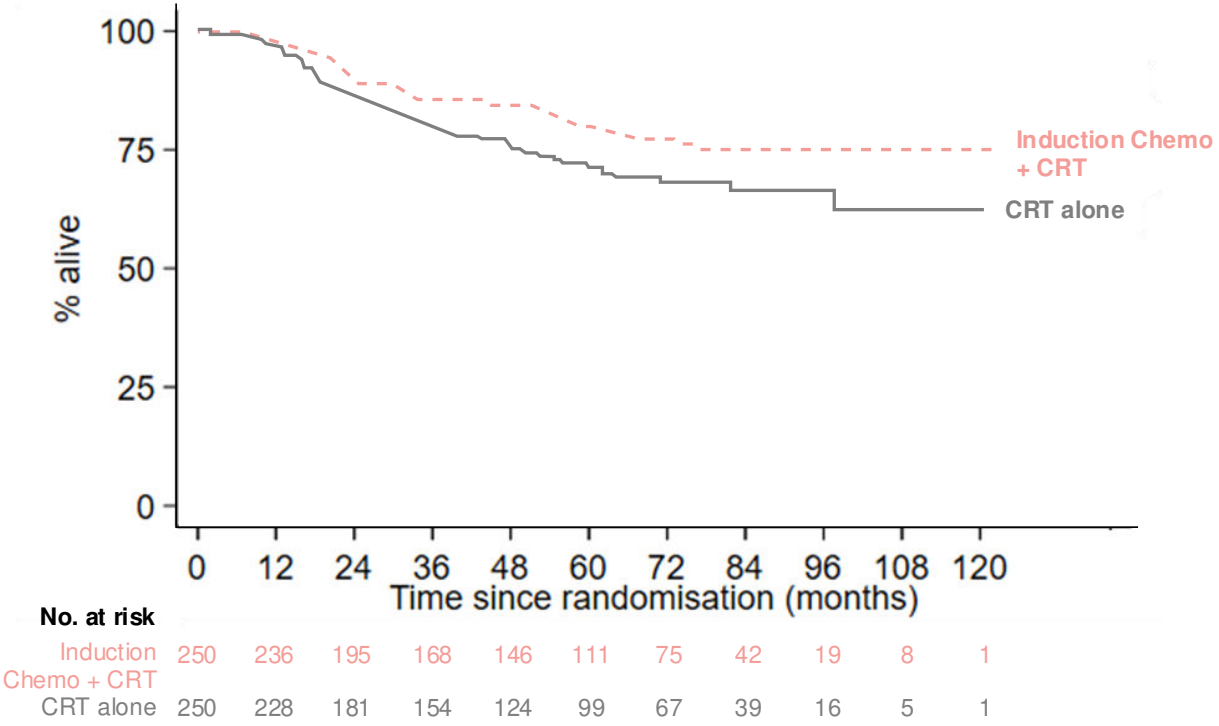


PFS	Induction Chemo + CRT (n = 250)	CRT alone (n = 250)
3-year	75%	72%
5-year	73%	64%

Median follow up 64 months
146 PFS events
HR 0.65 (95% CI: 0.46-0.91)
***p* = 0.013**

CRT = chemoradiotherapy.
McCormack M, et al. *Ann Oncol.* 2023;34:S1276.

INTERLACE: Overall Survival



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

Median follow up 64 months
109 deaths
HR 0.61 (95% CI: 0.40-0.91)
***p* = 0.04**

McCormack M, et al. *Ann Oncol.* 2023;34:S1276.

Questions That Will Likely Never Be Answered

- What is the role of surgical staging?
- What is the role of hypo-fractionization?
- What is the optimal timing of brachytherapy (after tumor shrinks to improve dosimetry vs earlier to shorten treatment time)?
- What is the role of interstitial brachytherapy?
- Why did CALLA fail while A18 succeeded? (eligibility vs anti-PD-1 vs anti-PD-L1)
  - Could this be informed by comparing BEATcc to KN-826?
- What is the most optimal surveillance (PET at 3 months or 6 months after CCRT)?

PD-1 = programmed death protein 1.

Study Design: eVOLVE-Cervical (ENGOT-cx19/GEICO/GOG-3092)

Screening Period
FIGO 2018 IIIC-IVA cervical cancer (LN involvement)

Randomization
Max 42 days after the end of CCRT

Treatment Period

Endpoints

Part I: Diagnosis (~Day -140 to Day -1)

Patient consenting process step 1:

- Tumor sample submission and analysis
  - PD-L1 expression by VENTANA PD-L1 (SP263) assay
- **Initial staging procedures** completed prior to any component of definitive treatment

Part II: Day -42 to -1

Patient consenting process step 2:

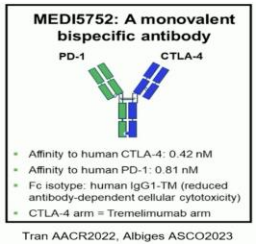
- No progression after completion of SOC platinum-based CCRT (≥ 4 cycles)
- Grade > 2 toxicities resolved prior to randomization
- ECOG 0 or 1

R 1:1

N = 1000

Arm A
Volrustomig (MEDI5752)
750 mg IV Q3W, 24 mo

Arm B
Placebo IV Q3W for 24 mo



Tran AACR2022, Albiges ASCO2023

Stratification Factors

- PD-L1 expression (PD-L1 high expression vs. others)
- Region (Asia vs. non-Asia)
- FIGO (IIIC1 vs IIIC2 and IVA)

Primary Endpoint: PFS in PD-L1 high population (Inv)

Secondary Endpoint:

Key: PFS in ITT (Inv), OS in PD-L1 high population/ITT

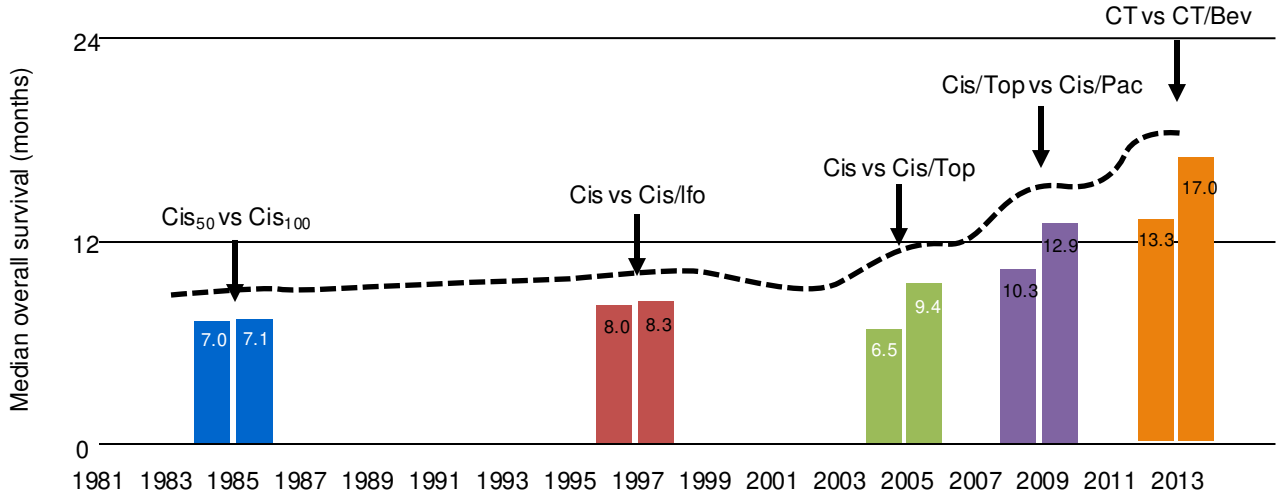
Others: PFS (BICR), 12mo-PFS, 24mo-PFS, 36mo-OS, ORR, DOR, incidence of local progression and distant disease progression, PK, ADAs, safety and tolerability, ePROs

Exploratory Endpoint: ctDNA, T cell proliferation/clonal expansion, baseline tumor immune and genomic profile

ADA = anti-drug antibody; BICR = blinded independent central review; ctDNA = circulating tumor DNA; DOR = duration of response; ePROs = electronic patient-reported outcomes; ITT = intention-to-treat; PK = pharmacokinetics.

A Phase III, Randomized, Double-blind, Placebo-controlled, Multi-centre, Global Study of Volrustomig in Women With High Risk Locally Advanced Cervical Cancer Who Have Not Progressed Following Platinum-based, Concurrent Chemoradiation Therapy (eVOLVE-Cervical) ClinicalTrials.gov Identifier: NCT06079671. 2023.

Progress in Current Treatment Approaches for First-Line Metastatic/Recurrent Cervical Cancer

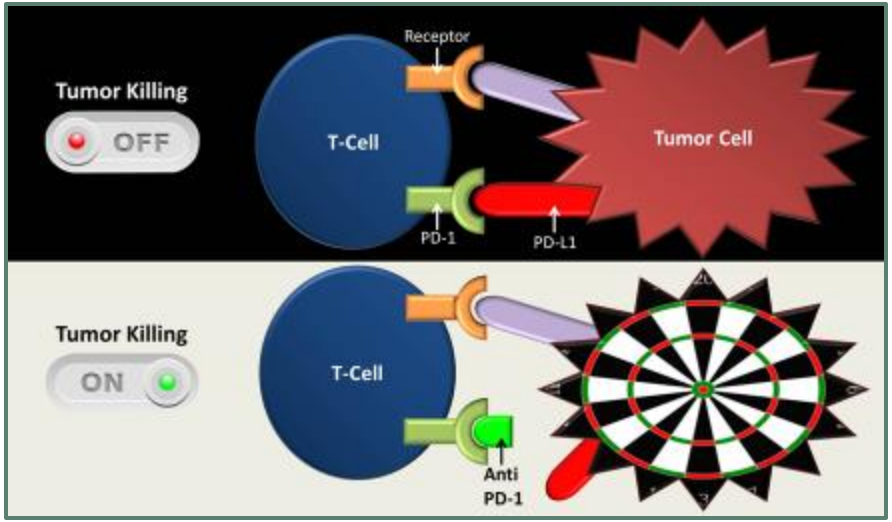


Bev = bevacizumab; Cis = cisplatin; CT = chemotherapy; Ifo = ifosfamide; Pac = paclitaxel; Top = topotecan.

Bonomi P, et al. *J Clin Oncol*. 1985;3(8):1079-1085. Moore DH, et al. *J Clin Oncol*. 2004;22(15):3113. Long HL 3rd, et al. *J Clin Oncol*. 2005;23(21):4626. Monk BJ, et al. *J Clin Oncol*. 2009;27(28):4649. Tewari KS, et al. *N Engl J Med*. 2014;370:734-743. Kitagawa R, et al. *J Clin Oncol*. 2015;33(19):2129-2135.

Immunotherapy: The Next Frontier
Anti-Programmed Death (PD)-1 Therapy for Cervical Cancer

- Human papillomavirus (HPV) infection is the cause of more than 90% of cervical cancers
- HPV+ tumor microenvironment is enriched for PD-1+ CD8+ T cells
- PD-L1 is significantly upregulated in cervical cancer and detectable by immunohistochemistry in tumor cells:
  - Squamous cervical cancer: between 54% and 80% according to different series
  - Adenocarcinoma: 14%
- PD-L1 expression reduces the immune response, since it is able to bind to PD1 on T lymphocytes and thereby inhibits their function
- These findings suggest that targeting the PD-1/PD-L1 pathway may be therapeutically effective and should be considered in the treatment of cervical cancer patients



Liu C, et al. *Mol Med Rep*. 2017;15:1063-1070. Mezache L, et al. *Mod Pathol*. 2015;28:1594-1602. Heeren AM, et al. *Mod Pathol*. 2016;29:753-763.

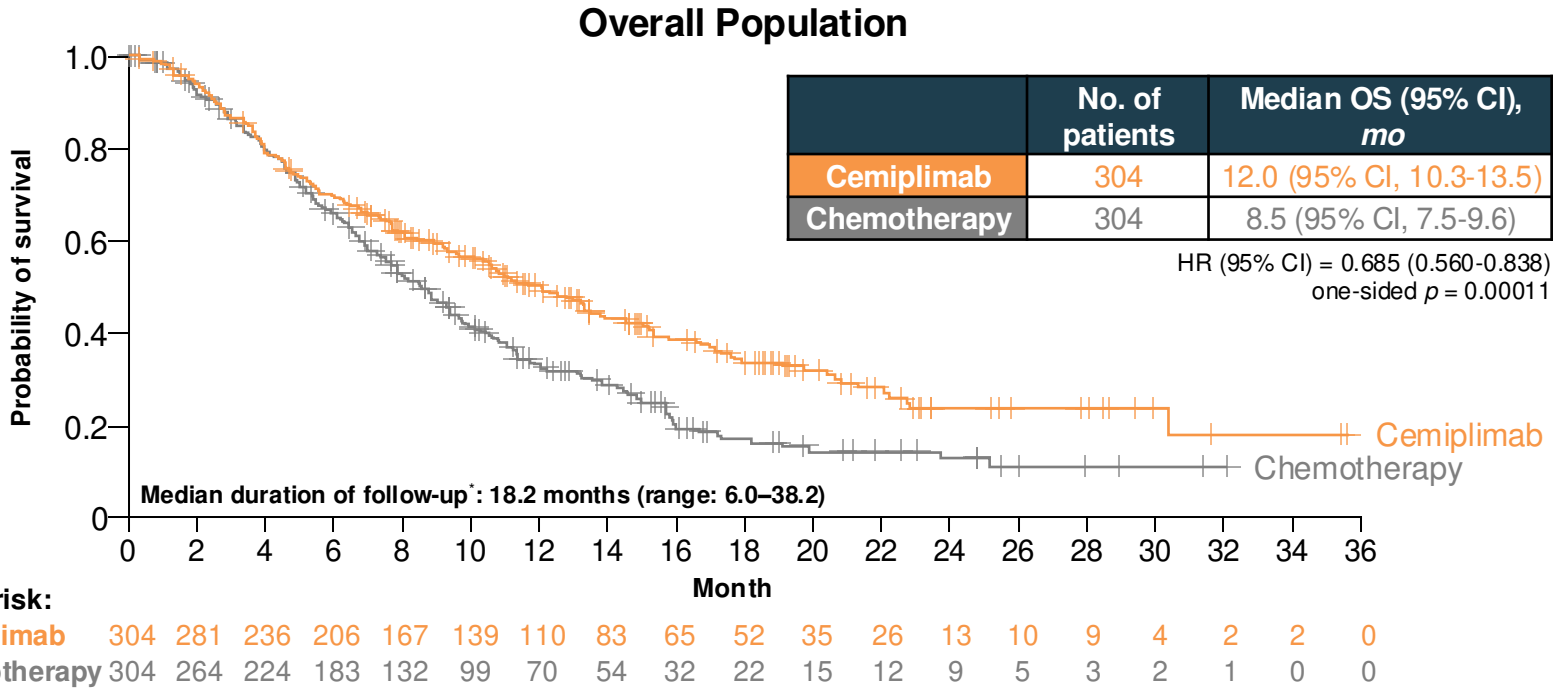
Single-Agent Anti-PD-(L)1 Activity, 2L+

Agent	N	ORR (95% CI)	ORR PD-L1+ (95% CI)	ORR PD-L1-neg (95% CI)
Pembrolizumab	98	14.3% (8.0-22.8)	17.1% (9.7-27.0)	0% (0-21.8)
Cemiplimab	304	16.4% (12.5-21.1)	18.3% (10.6-28.4)	11.4% (3.8-24.6)
Balstilimab	140	15% (10.0-21.8)	20.0% (12.9-29.7)	7.9% (NR)

Cemiplimab is not FDA-approved for the treatment of cervical cancer.

Chung H, et al. *Gynecol Oncol*. 2021;162:S27. Tewari KS, et al. *N Engl J Med*. 2022;386(6):544-555. O'Malley DM, et al. *Gynecol Oncol*. 2021;163(2):274-280.

Overall Survival
EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9*



*From randomisation to data cutoff date.

Cemiplimab is not FDA-approved for the treatment of cervical cancer. Tewari KS, et al. *N Engl J Med*. 2022;386(6):544-555.

Immuno-oncology Combinations

- PD1 inhibitors as monotherapy have modest activity
- **Combination therapies** will likely be required to enhance and broaden the anti-tumor activity of immune checkpoint inhibition in cervical cancer

KEYNOTE-826: Randomized, Double-Blind, Phase III Study

Key Eligibility Criteria

- Persistent, recurrent, or metastatic cervical cancer not amenable to curative treatment
- No prior systemic chemotherapy (prior radiotherapy and chemoradiotherapy permitted)
- ECOG PS 0 or 1

Stratification Factors

- Metastatic disease at diagnosis (yes vs no)
- PD-L1 CPS (< 1 vs 1 to <10 vs ≥ 10)
- Planned bevacizumab use (yes vs no)

R
1:1

Pembrolizumab 200 mg IV Q3W
for up to 35 cycles
+
Paclitaxel + Cisplatin or Carboplatin IV Q3W
for up to 6 cycles[a]
±
Bevacizumab 15 mg/kg IV Q3W

Placebo IV Q3W
for up to 35 cycles
+
Paclitaxel + Cisplatin or Carboplatin IV Q3W
for up to 6 cycles[a]
±
Bevacizumab 15 mg/kg IV Q3W

End Points

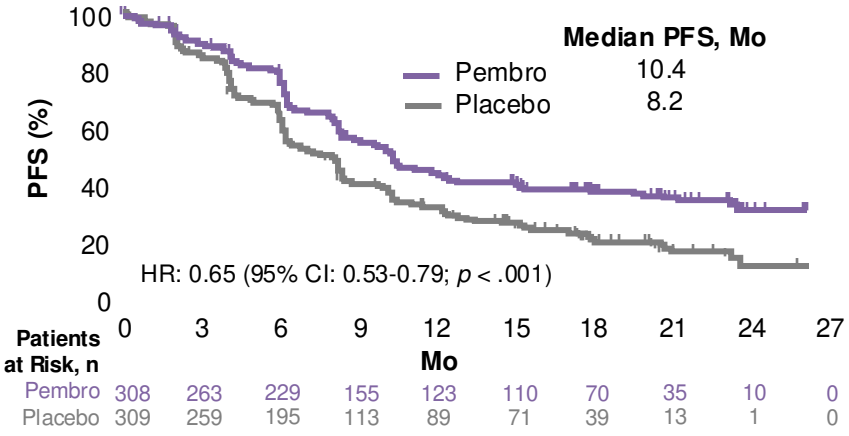
- Dual primary: OS and PFS per RECIST v1.1 by investigator
- Secondary: ORR, DOR, 12-mo PFS, and safety
- Exploratory: PROs assessed per EuroQol EQ-5D-5L VAS

- [a]Paclitaxel: 175 mg/m^2. Cisplatin: cisplatin 50 mg/m^2. Carboplatin: AUC 5 mg/mL/min. The 6-cycle limit was introduced with protocol amendment 2, although participants with ongoing clinical benefit who were tolerating chemotherapy could continue beyond 6 cycles after sponsor consultation.

CPS = combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100); VAS = visual analog scale. Colombo N, et al. *N Engl J Med*. 2021;385(20):1856-1867.

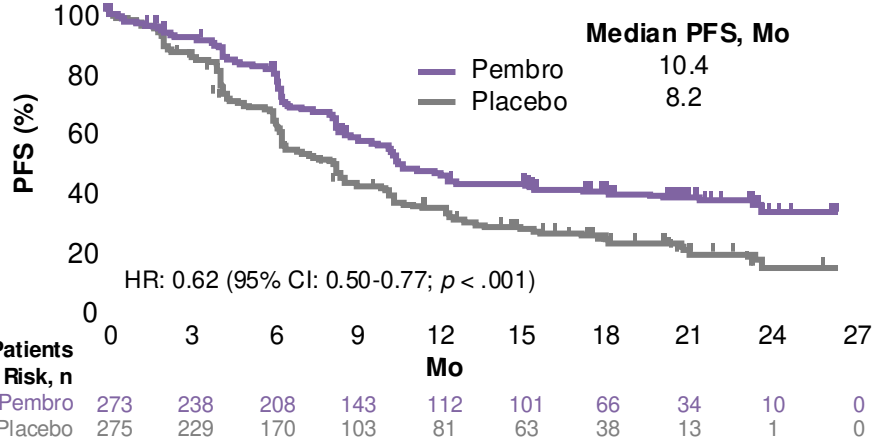
KEYNOTE-826: PFS

ITT Population



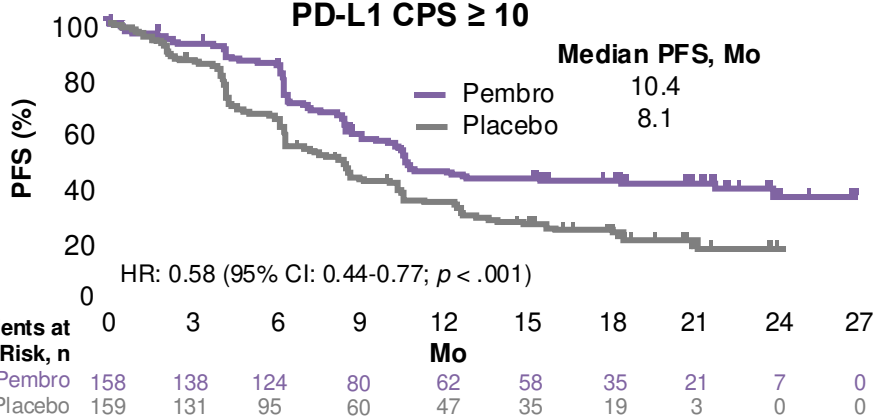
Patients at Risk, n										
Pembro	308	263	229	155	123	110	70	35	10	0
Placebo	309	259	195	113	89	71	39	13	1	0

PD-L1 CPS ≥ 1 (FDA Approval)



Patients at Risk, n										
Pembro	273	238	208	143	112	101	66	34	10	0
Placebo	275	229	170	103	81	63	38	13	1	0

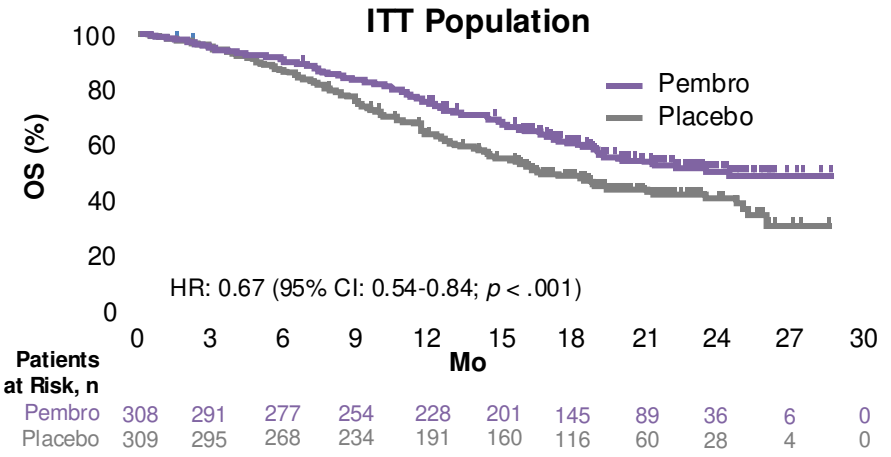
PD-L1 CPS ≥ 10

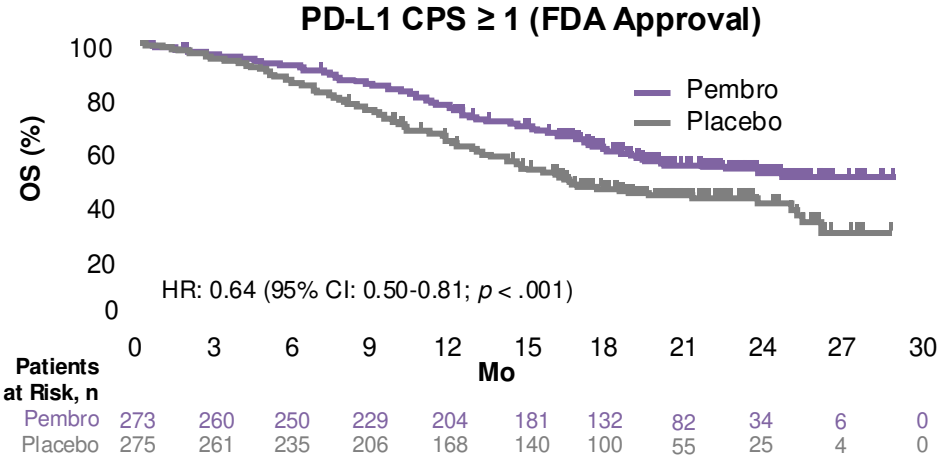


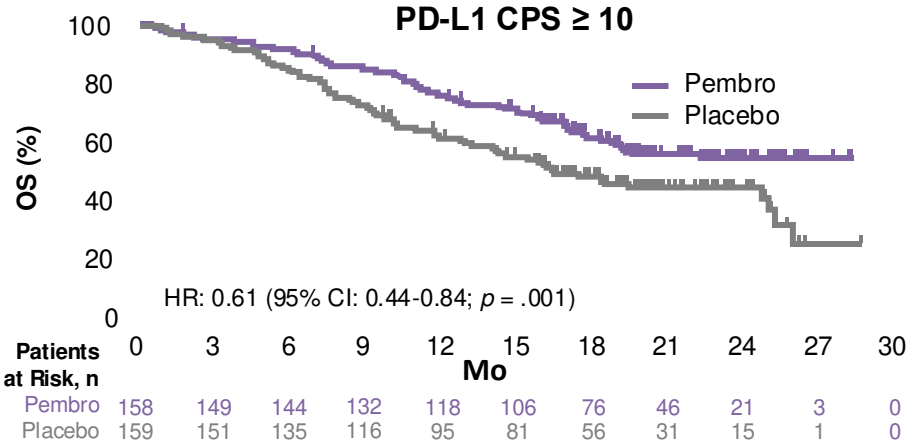
Patients at Risk, n										
Pembro	158	138	124	80	62	58	35	21	7	0
Placebo	159	131	95	60	47	35	19	3	0	0

Colombo N, et al. *N Engl J Med.* 2021;385(20):1856-1867.

KEYNOTE-826: OS

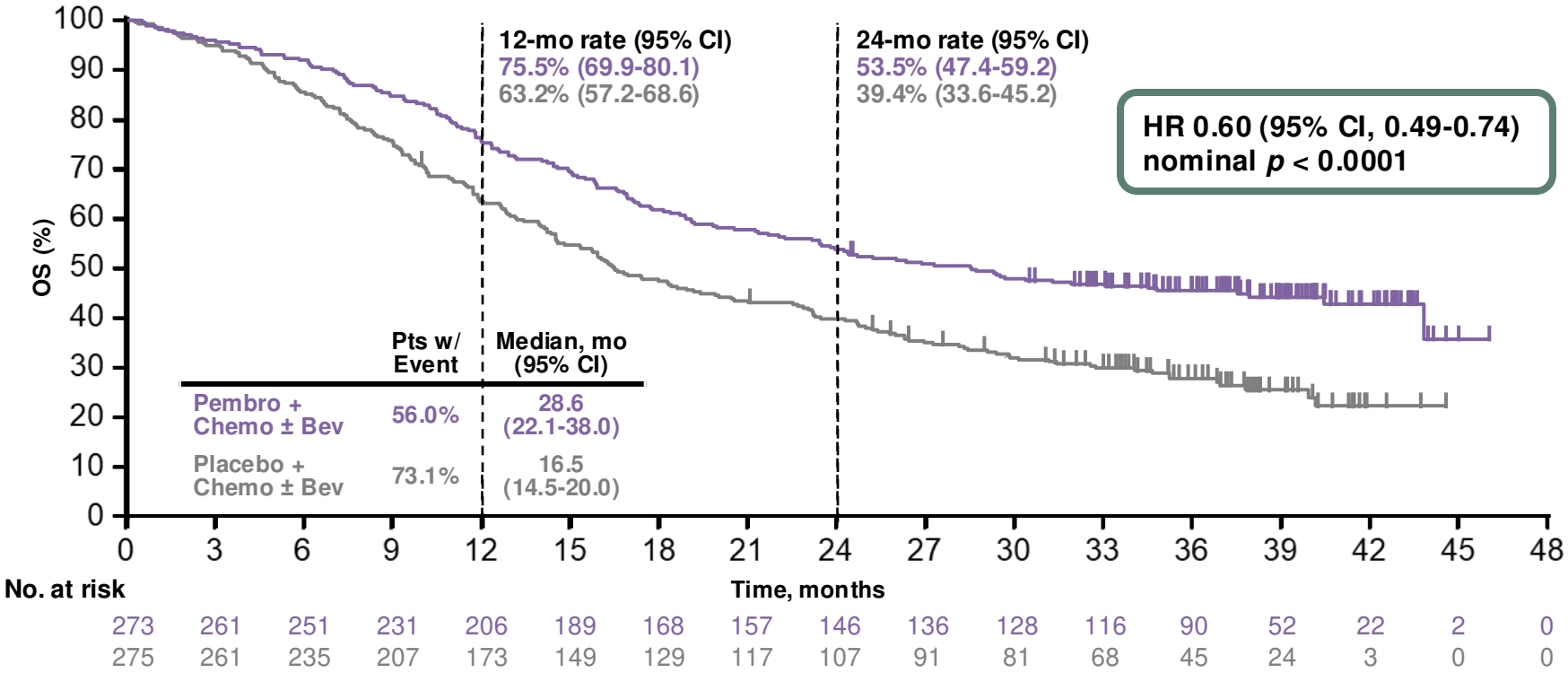






Colombo N, et al. *N Engl J Med*. 2021;385(20):1856-1867.

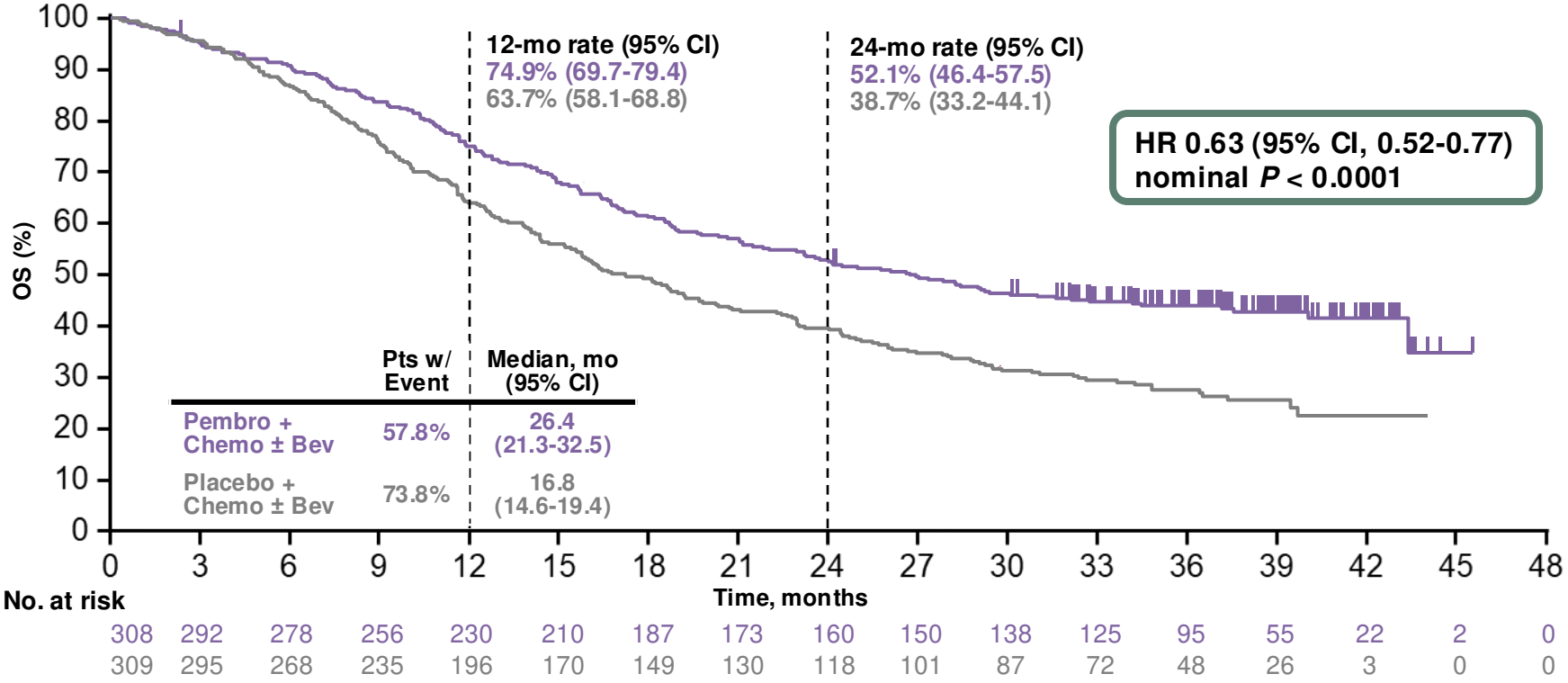
KEYNOTE-826: Protocol-Specified Final OS: PD-L1 CPS ≥ 1 Population



Data cutoff date: October 3, 2022.

Monk BJ, et al. *J Clin Oncol*. 2023;41(36):5505-5511.

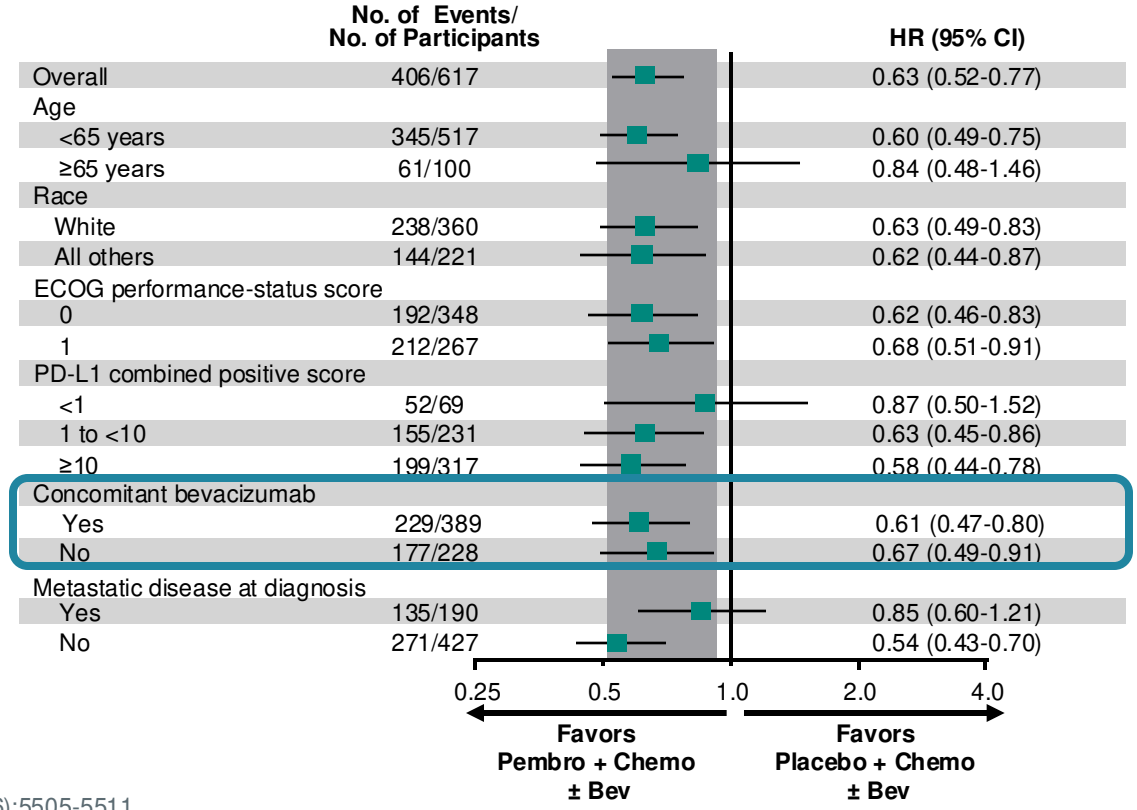
KEYNOTE-826: Protocol-Specified Final OS: All-Comer Population



Data cutoff date: October 3, 2022.

Monk BJ, et al. *J Clin Oncol*. 2023;41(36):5505-5511.

KEYNOTE-826: Protocol-Specified Final OS in Subgroups, All-Comer Population

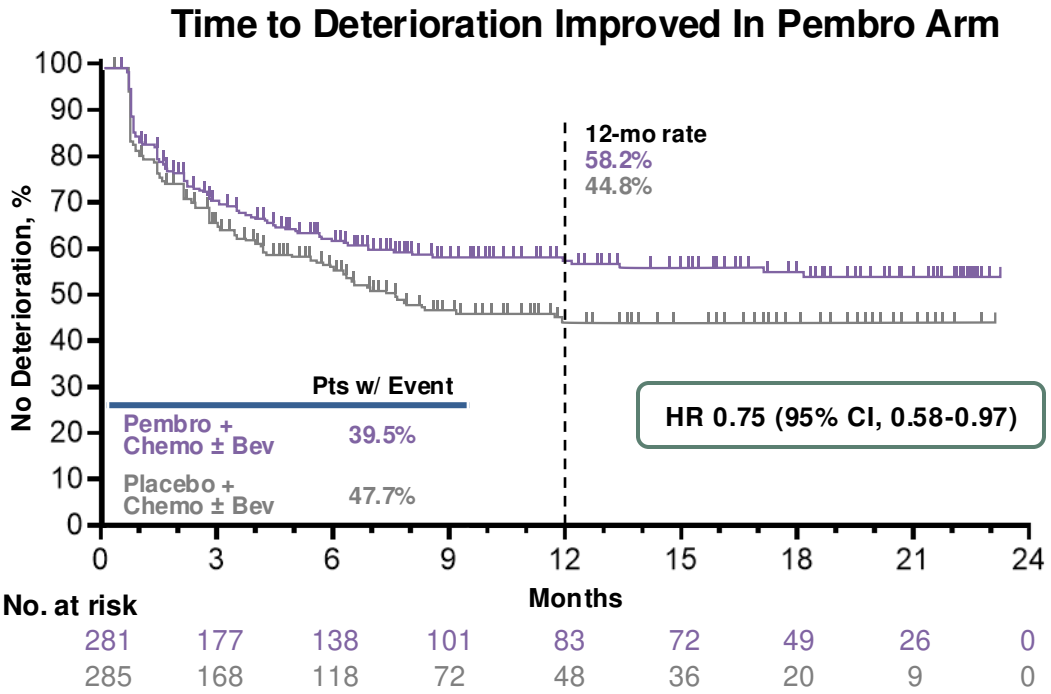


Data cutoff date: October 3, 2022.

Monk BJ, et al. *J Clin Oncol*. 2023;41(36):5505-5511.

EuroQol EQ-5D-5L VAS, All-Comer Population

- Administered before study treatment at cycles 1-14 and every other cycle thereafter
  - Compliance between baseline and wk 30a: ≥ 94.0% with pembro + chemo ± bev, ≥ 88.9% with placebo + chemo ± bev
- Analysis population: all treated participants with ≥ 1 available PRO assessment
- Time to deterioration: time from first
- EQ-5D-5L VAS assessment to first onset of a ≥ 10-point decrease in score from baseline with confirmation under the right censoring rule or death, whichever occurred first

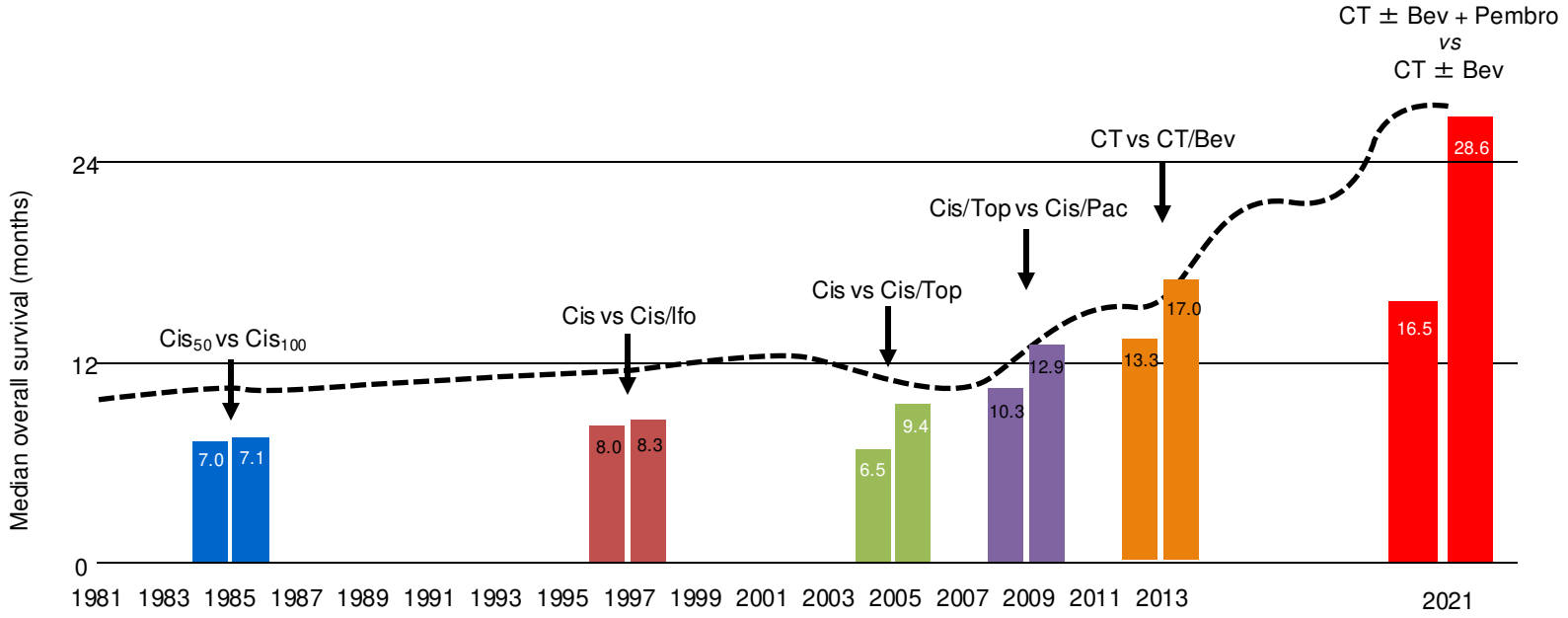


[a]Compliance was defined as the proportion of participants who completed the patient-reported outcome questionnaire among those who were expected to complete the questionnaire at the time point, excluding those missing by design; missing by design includes adverse event, death, discontinuation, translations not available, and no visit scheduled.

Data cutoff date: May 3, 2021.

Colombo N, et al. *N Engl J Med*. 2021;385(20):1856-1867. Monk B, et al. *Gynecol Oncol*. 2022;166:S18.

Progress in Current Treatment Approaches for First-Line Metastatic/Recurrent Cervical Cancer



Bonomi P, et al. *J Clin Oncol*. 1985;3(8):1079-1085. Moore DH, et al. *J Clin Oncol*. 2004;22(15):3113. Long HL 3rd, et al. *J Clin Oncol*. 2005;23(21):4626. Monk BJ, et al. *J Clin Oncol*. 2009;27(28):4649. Tewari KS, et al. *N Engl J Med*. 2014;370:734-743. Kitagawa R, et al. *J Clin Oncol*. 2015;33(19):2129-2135. Columbo N, et al. *N Engl J Med*. 2021;385(20):1856-1867. Monk BJ, et al. *J Clin Oncol*. 2023;41(36):5505-5511.

BEATcc: Study Design

- Primary stage IVB, persistent or recurrent carcinoma of the cervix
- Measurable disease by RECIST v1.1
- ECOG-PS: 0-1
- No previous systemic chemotherapy for advanced or recurrent disease
- Available tissue (archival or fresh)
- N = 404 patients

R 1:1

Control Arm

Cis- or carboplatin + paclitaxel + bevacizumab (GOG 240) until disease progression, unacceptable toxicity, death or withdrawal of consent

Experimental Arm

Cis- or carboplatin + paclitaxel + bevacizumab + atezolizumab until disease progression, unacceptable toxicity, death or withdrawal of consent

Primary Endpoint:
Overall survival (OS)

Secondary Endpoints:
- PFS
- ORR
- DOR
- Safety
- HRQoL

Stratification Factors
- Prior ChemoRT
- Histology: SCC vs Adeno (including AdenoSquamous)
- Chemotherapy Backbone: Cisplatin vs Carboplatin

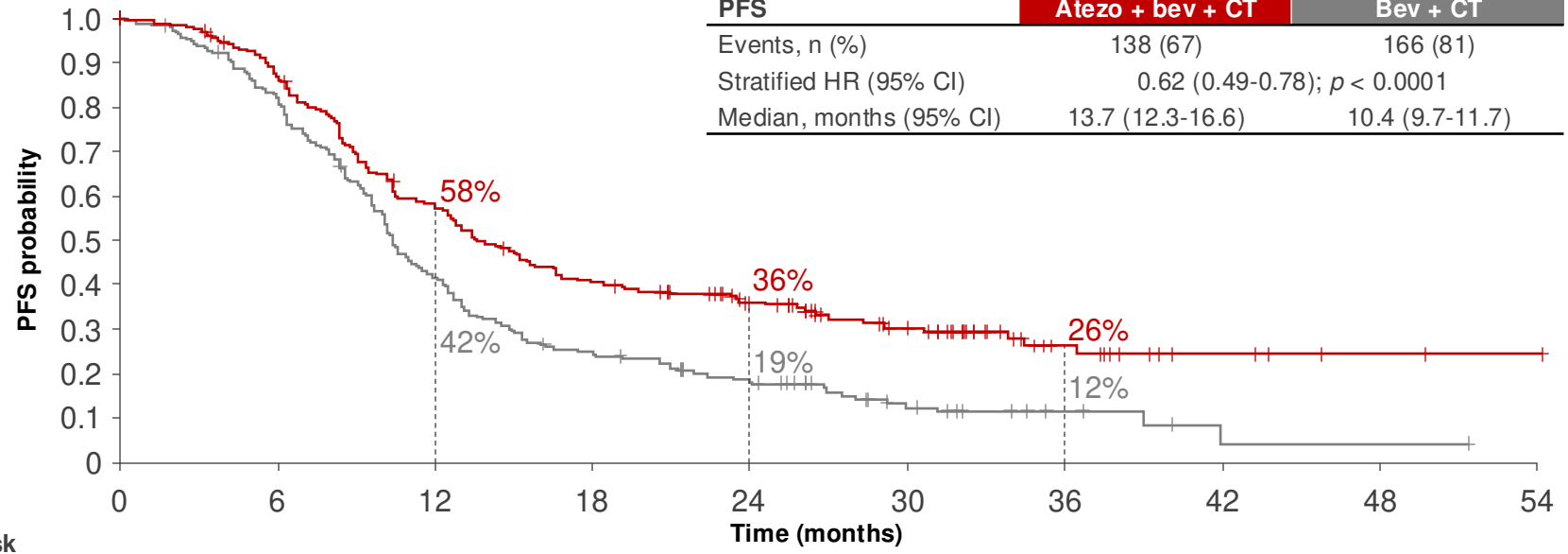
Atezolizumab is not FDA-approved for the treatment of cervical cancer. SCC = squamous cell carcinoma; Adeno = adenocarcinoma.

Oaknin, A. A Randomized Phase III Trial of Platinum Chemotherapy Plus Paclitaxel With Bevacizumab and Atezolizumab Versus Platinum Chemotherapy Plus Paclitaxel and Bevacizumab in Metastatic (Stage IVB), Persistent, or Recurrent Carcinoma of the Cervix. ClinicalTrials.gov Identifier: NCT03556839. 2018.

BEATcc: Dual Primary Endpoint, PFS

Statistically significant 38% reduction in risk of progression or death

PFS	Atezo + bev + CT	Bev + CT
Events, n (%)	138 (67)	166 (81)
Stratified HR (95% CI)	0.62 (0.49-0.78); $p < 0.0001$	
Median, months (95% CI)	13.7 (12.3-16.6)	10.4 (9.7-11.7)



No. at risk

Atezo + bev + CT	206	174	114	79	58	37	13	5	2	1
Bev + CT	204	159	80	47	31	13	5	1	1	0

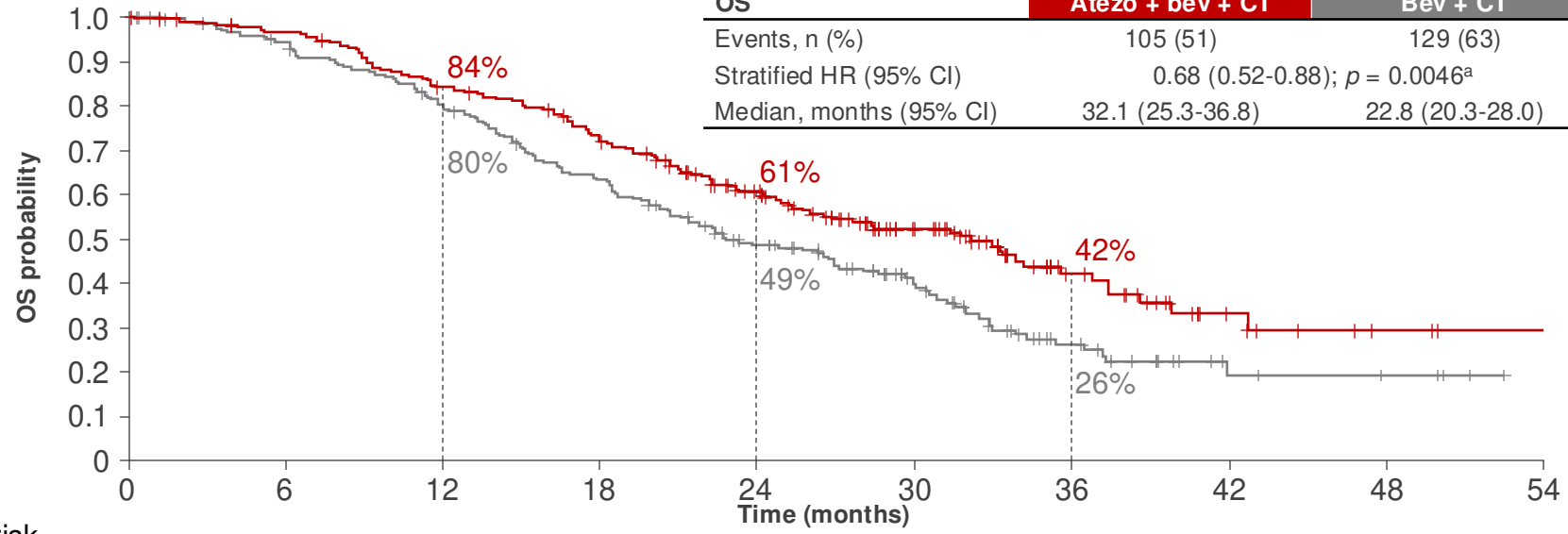
Data cut-off: July 17, 2023 (median follow-up: 32.9 months; 95% CI, 31.2–34.6 months).

Atezolizumab is not FDA-approved for the treatment of cervical cancer. Oaknin A, et al. *Lancet*. 2024;403(10421):31-43.

BEATcc: Dual Primary Endpoint, OS (Interim Analysis)

Statistically significant 32% reduction in risk of death

OS	Atezo + bev + CT	Bev + CT
Events, n (%)	105 (51)	129 (63)
Stratified HR (95% CI)	0.68 (0.52-0.88); $p = 0.0046$[a]	
Median, months (95% CI)	32.1 (25.3-36.8)	22.8 (20.3-28.0)



No. at risk

Atezo + bev + CT	206	194	167	140	103	64	27	9	3	1
Bev + CT	204	182	152	119	83	50	22	6	4	0

[a]Interim OS was statistically significant, crossing the boundary of $p = 0.0238$.
Data cut-off: July 17, 2023 (median follow-up: 32.9 months; 95% CI, 31.2–34.6 months).

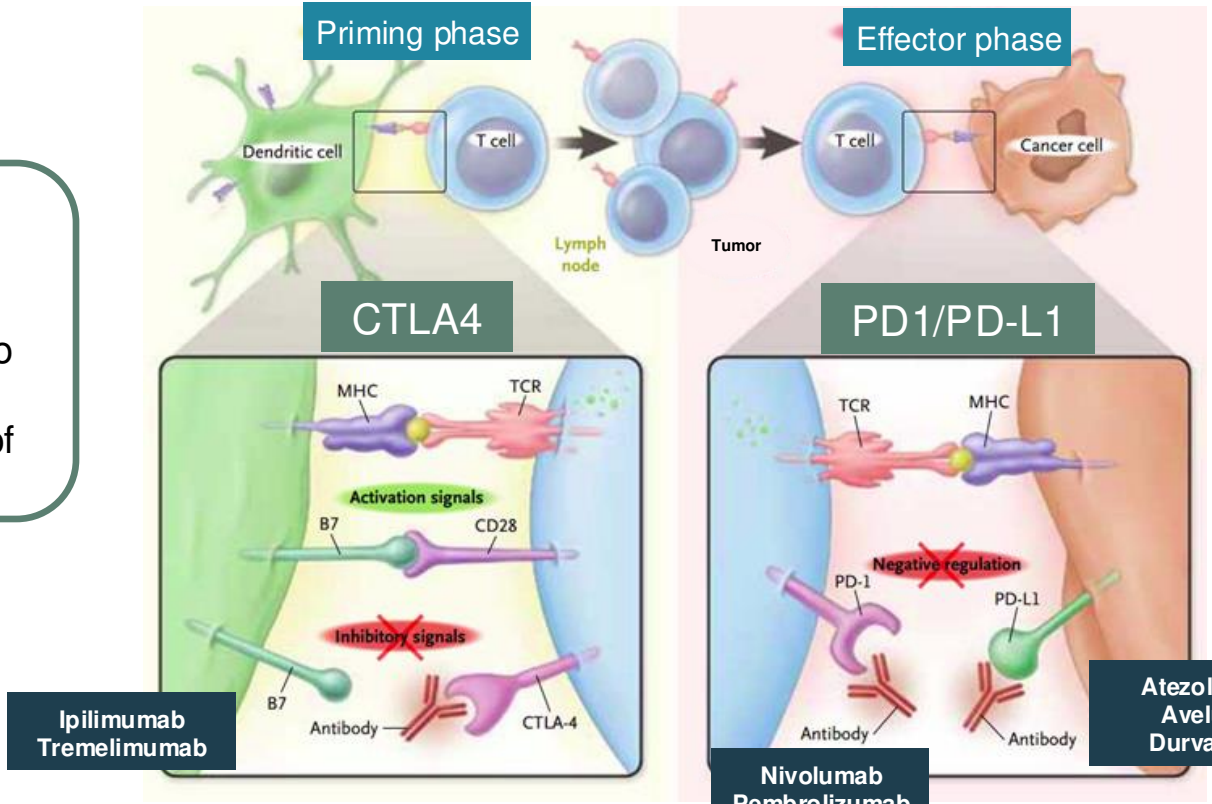
Atezolizumab is not FDA-approved for the treatment of cervical cancer. Oaknin A, et al. *Lancet*. 2024;403(10421):31-43.

What's Next?

- Dual Checkpoint Inhibition
- Therapeutic Vaccines
- Adoptive Cell Therapy
- Antibody Drug Conjugates

Blockade of PD-1/PD-L1 and CTLA-4 Signaling in Tumor Immunotherapy

- CTLA4 (cytotoxic T lymphocyte antigen 4) inhibits T cell activation
- PD-L1 (on tumor) binds to PD-1 (on effector T cell) and inhibits T cell killing of tumor cell



Adapted from Ribas A. *N Engl J Med.* 2012;366(26):2517-2519.

Anti PD-1/AntiCTLA-4 Combinations 2L+

	N	ORR (95% CI)	ORR PD-L1+ (95% CI)	ORR PD-L1- (95% CI)
Nivolumab + Ipilimumab	45	31% (18-47)	36%	20%
Nivolumab + Ipilimumab	112	38% (29-48)	36%	31%
Balstilimab + Zalifrelimab*	125	25.6% (18.8-33.9)	32.8%	9.1%
Cadonilimab	100	33% (23.9-43.1)	43.8 (31.4-56.7)	16.7 (3.6-41.4)

Nivo-IPI: Grade 3-4 TRAE: 28.9-37%
Bal-Zal: Grade 3-4 TRAE: 20%
Cadolinimab: Grade 3-4 TRAE: 27%

*FDA fast track designation in March 2020.

Balstilimab, zalifrelimab, and cadonilimab are not FDA-approved for the treatment of cervical cancer.

Oaknin A, et al. *Ann Oncol*. 2022;33:S782. O'Malley DM, et al. *J Clin Oncol*. 2022;40(7):762-771. Wu X, et al. *Gynecol Oncol*. 2022;166:S47-S48.

Therapeutic Vaccines in Immuno-oncology-Naïve Patients

	Phase	Drug	N	ORR, % (95%CI)	mDoR, mo (95%CI)	mPFS, mo 95%CI)	mOS, mo (95%CI)
VB C-02 NCT04405349	II	Atezolizumab + VB10.16	47	**19.1** (9-33)	**17.1** (2.6-NR)	**4.1** (2.1-6.2)	**16.9** (8.3-NR)
KEYNOTE-567 NCT03444376	II	Pembrolizumab + GX-188E	60	**31.7**	**12.3**	**3.0** (0.3-5.8)	**17.2** (6.6-27.8)
Study 1981 NCT04646005	II	Cemiplimab + ISA101b	113	**16.8** (9.9-23.7)	**5.6** (3.5-NR)	**3.0** (1.7-4.0)	**13.3** (10.8-16.3)
KEYNOTE-158 NCT02628067	II	Pembrolizumab	98	**12.2** (6.5-20.4)	**NR** (>3.7->18.6)	**2.1** (2.0-2.2)	**9.4** (7.7-13.1)
EMPOWER NCT03257267	III	Cemiplimab	608	**16.4** (12.5-21.1)	**16.4** (12.4-NR)	**2.8** (2.6-4.0)	**12.0** (10.3-13.5)

Atezolizumab, cemiplimab, VB10.16, GX-188E, and ISA101b are not FDA-approved for the treatment of cervical cancer.

Ryan C. OncLive Website. 2023. https://www.onclive.com/view/vb10-16-plus-atezolizumab-generates-positive-survival-data-in-pd-l1-advanced-cervical-cancer. Lee S, et al. *Ann Oncol*. 2022;33:S1398. Lorusso D, et al. *J Clin Oncol*. 2024;42(Suppl 16):5522. Chung HC, et al. *J Clin Oncol*. 2019;37(17):1470-1478. Tewari KS, et al. *N Engl J Med*. 2022;386(6):544-555.

Antibody-Drug Conjugates (ADCs) in Gynecologic Cancer: Patient and Clinician Insights

Important questions for…

Patients

- ❑ What are the benefits of ADCs?
- ❑ Which ADC is right for me?
- ❑ What are the risks of ADCs?
- ❑ Why does the provider think I should take a particular ADC?

Providers

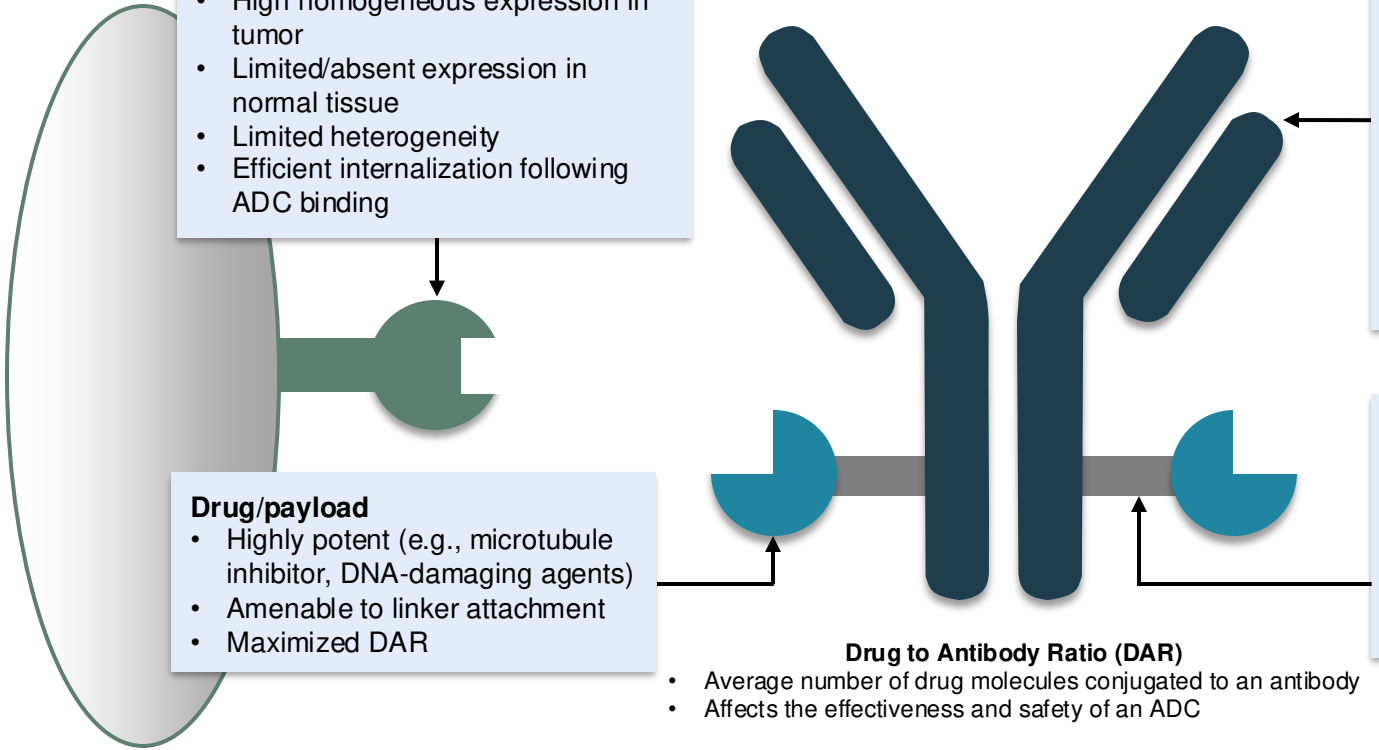
- ❑ Which ADCs are available?
- ❑ How do you integrate ADCs into clinical practice?
- ❑ How do you address workflow challenges associated with ADCs?
- ❑ How do you prevent and mitigate AEs?

AE = adverse event.

ADCs: Understanding Their Composition and Structure

Antigen target/receptor
- High homogeneous expression in tumor
- Limited/absent expression in normal tissue
- Limited heterogeneity
- Efficient internalization following ADC binding

Antibody
- High affinity and avidity for target antigen
- Long half-life
- Conjugation sites with minimal impact on ADC stability, internalization, and pharmacokinetics (e.g., cysteine, lysine)
- Chimeric or humanized (decreasing immunogenicity)



Drug/payload
- Highly potent (e.g., microtubule inhibitor, DNA-damaging agents)
- Amenable to linker attachment
- Maximized DAR

Linker
- Controlled release of payload
  - Noncleavable (e.g., lysosomal degradation of mAb)
  - Cleavable (e.g., acid/redox/lysosomal sensitive)

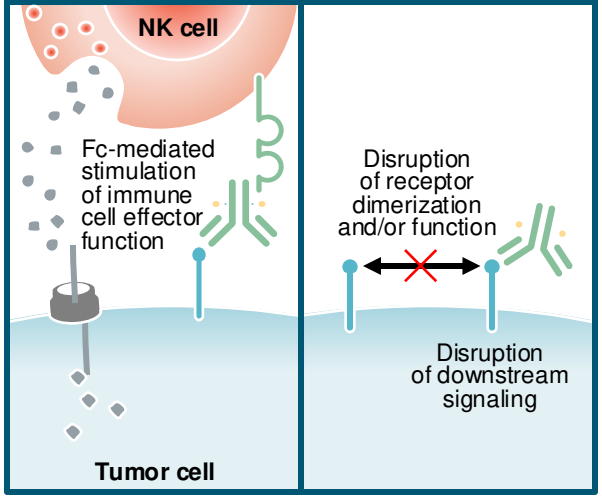
Drug to Antibody Ratio (DAR)
- Average number of drug molecules conjugated to an antibody
- Affects the effectiveness and safety of an ADC

mAb = monoclonal antibody. Marks S, Naidoo J. *Lung Cancer*. 2022;163:59-68.

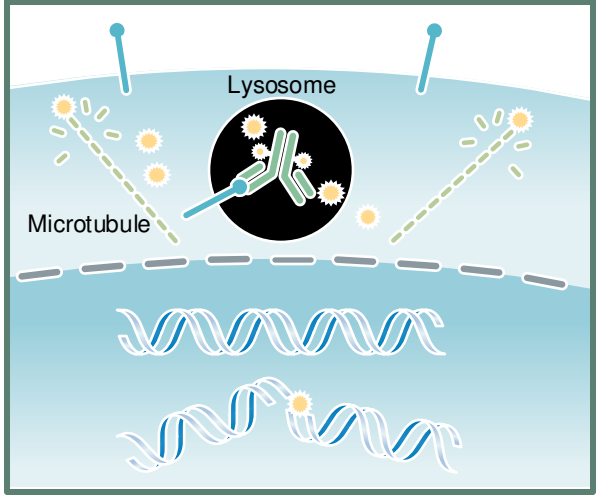
ADC Mechanisms of Action

Antibody engagement leads to payload-independent antitumor activity via several mechanisms:

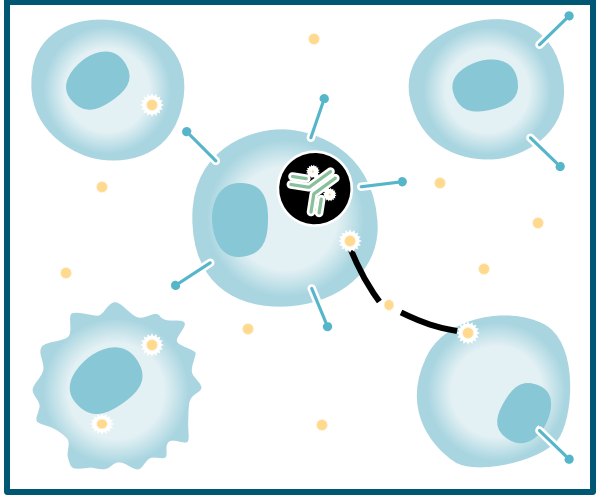
1. Fc-mediated stimulation of immune cell
2. Disruption of receptor dimerization



Most ADCs are internalized in tumor cells
The payload is released from endosomes and/or lysosomes and takes its effect on cells, leading to cell death



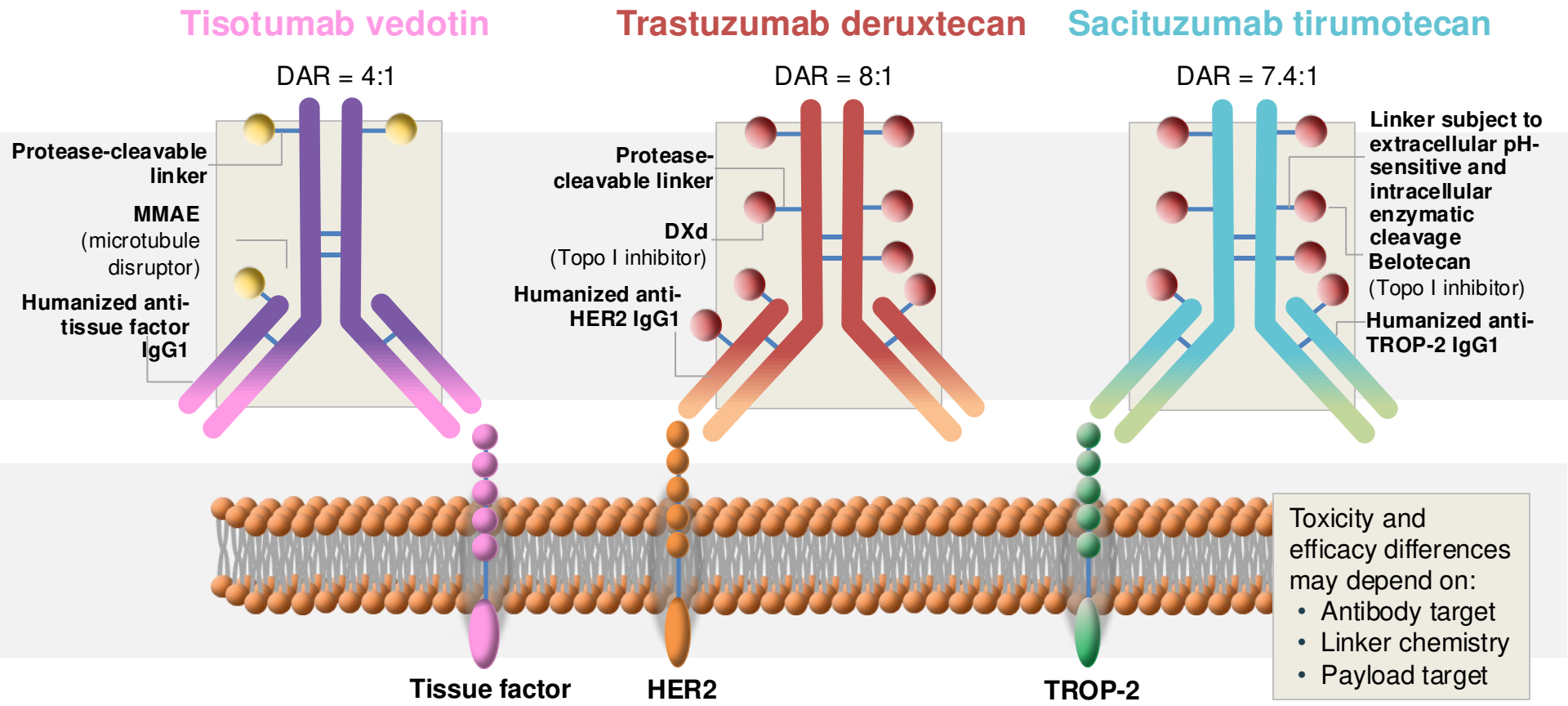
Membrane-permeable payloads enter neighboring cells regardless of target expression and can also kill these cells (bystander effect)



Fc region of the mAb component of ADCs can orchestrate antibody-dependent cellular cytotoxicity (ADCC)

Drago JZ, et al. *Nat Rev Clin Oncol*. 2021;18:327-344.

Comparison of ADCs for Cervical Cancer

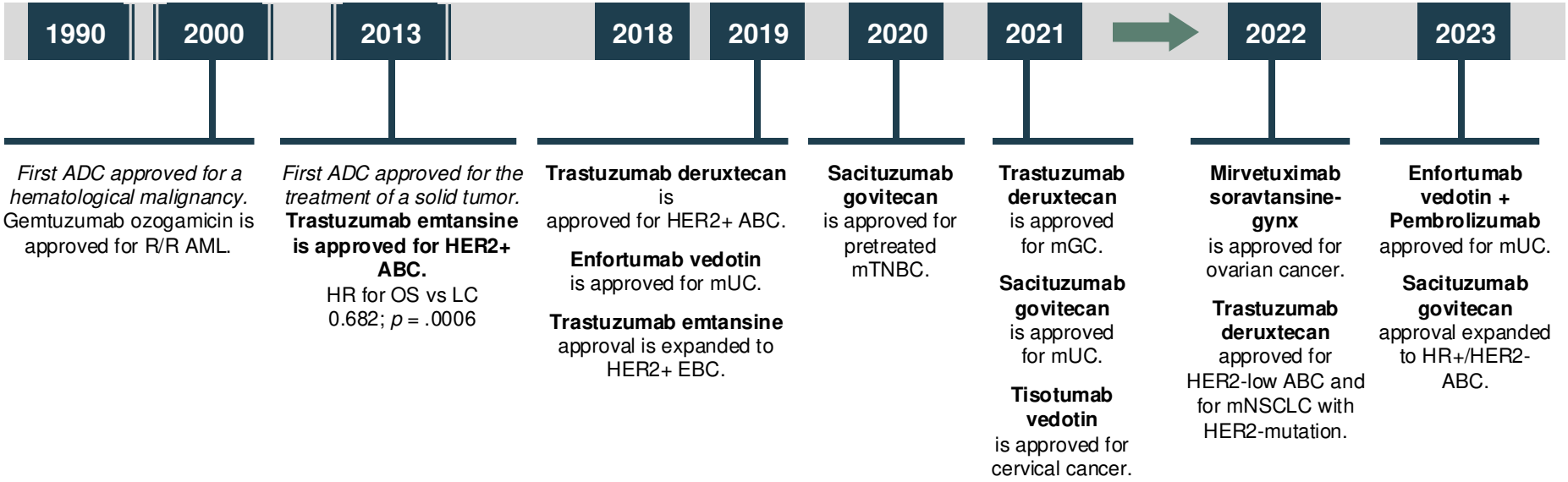


Sacituzumab tirumotecan is not FDA-approved for any indication. IgG = immunoglobulin G; Topo = topoisomerase.

Xu B, et al. *J Clin Oncol*. 2024;42(Suppl 16):104. Tisotumab vedotin-tftv [package insert]. Revised April 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761208s007lbl.pdf. Fam-trastuzumab deruxtecan-nxki [package insert]. Revised April 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s028lbl.pdf.

Pharmacodynamic Biomarkers for ADC Development

Solid tumors: **7 ADCs** today are approved for **10 solid tumor indications.**
Targets: HER2, TROP-2, nectin-4, tissue factor, FR-a



ABC = advanced breast cancer; AML = acute myeloid leukemia; EBC = early breast cancer; mGC = metastatic gastric cancer; mNSCLC = metastatic non-small cell lung cancer; mTNBC = metastatic triple-negative breast cancer; mUC = metastatic urothelial cancer; R/R = relapsed and/or refractory.

Optimal ADC Targets in Gynecologic Cancers

Tissue factor (TF) is a transmembrane receptor for coagulation factor VII/VIIa

- Under normal conditions, it is involved in the coagulation cascade
- Under oncogenic conditions, it is involved in tumor angiogenesis, proliferation, and thrombosis
- It is highly expressed in squamous cell and adenocarcinoma of the cervix

Unmet need in recurrent or metastatic cervical cancer

- Associated with a poor prognosis and a high mortality rate globally
- Fourth most deadly cancer in female patients worldwide
- Despite the addition of immunotherapy, patients who progress on/after first-line therapy continue to have a high unmet need

National Cancer Institute (NCI). 2024. https://seer.cancer.gov/statfacts/html/cervix.html. Alholm Z, et al. *Gynecol Oncol*. 2021:422-428. Tewari KS, et al. *N Engl J Med*. 2022:544-555. Sung H, et al. *CA Cancer J Clin*. 2021:209-249.

Plenty of Payloads: Multiple ADCs Are Approved and Others Are Being Actively Evaluated

ADC	Target	Antibody	Linker	Payload	Regulatory Status
Tisotumab vedotin (TV)	Tissue factor	IgG1-κ	Cleavable	MMAE	**Cervical:** Accelerated FDA approval; FDA priority review for full approval
Mirvetuximab soravtansine (MIRV)	FRα	IgG1-κ	Cleavable	DM4	**Ovarian:** Accelerated FDA approval; FDA priority review for full approval
Trastuzumab deruxtecan (T-DXd)	HER2	IgG1	Cleavable	Topoisomerase I inhibitor	**HER2 IHC3+ tumor agnostic:** FDA priority review

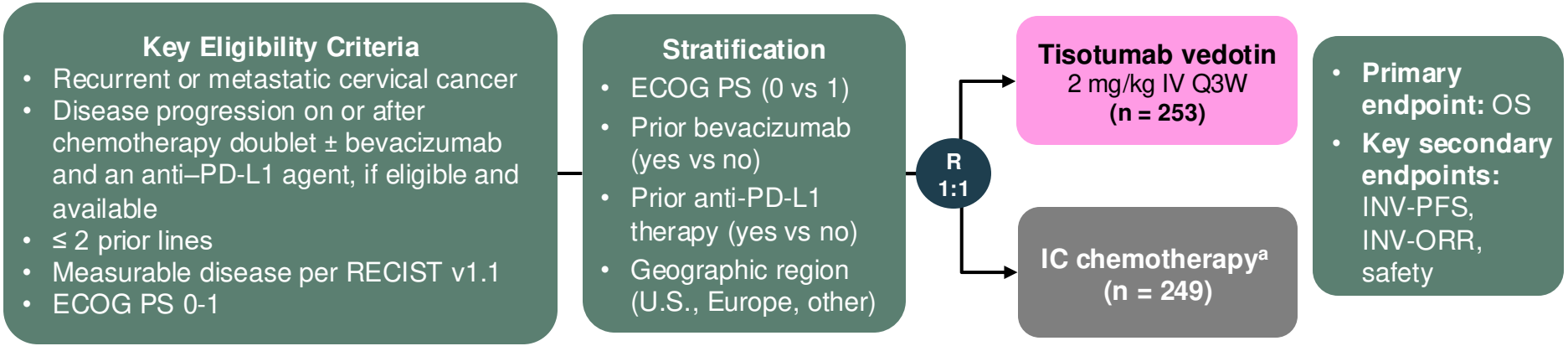
Other transmembrane glycoproteins are highly expressed in gynecologic tumors, often associated with poor prognosis, and under study as ADC targets

TROP-2 **B7-H4** **CDH6** **Mesothelin**

Tisotumab vedotin-tftv [package insert]. Revised April 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761208s007lbl.pdf.
Mirvetuximab soravtansine-gynx [package insert]. Revised March 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761310Origs005lbl.pdf.
Fam-trastuzumab deruxtecan-nxki [package insert]. Revised April 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s028lbl.pdf.

Phase III innovaTV 301: Tisotumab Vedotin in Cervical Cancer

- **2021:** Received accelerated FDA approval for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy, based on the phase II innovaTV204/GOG-3023/ENGOT-cx6 study
- **2024:** Under FDA priority review for full approval based on data from the phase III confirmatory innovaTV301/ENGOT-cx12/GOG-3057 trial

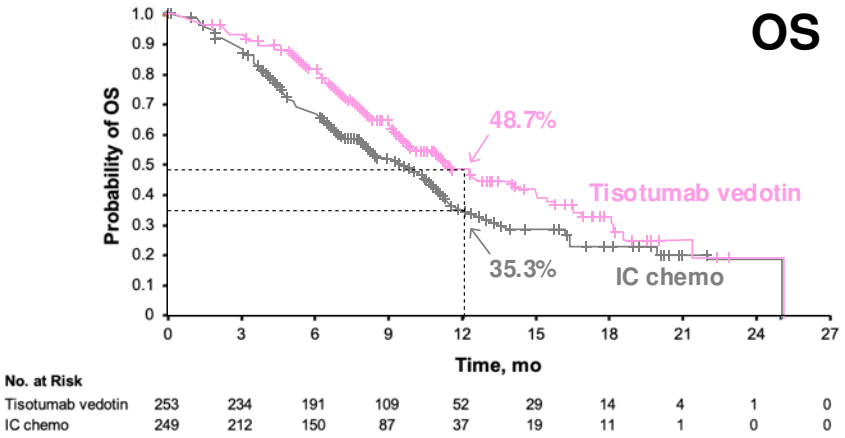


[a]Chemotherapy regimens were given at the following doses: topotecan: 1 or 1.25 mg/m^2 IV on days 1 to 5, every 21 days; vinorelbine: 30 mg/m^2 IV on days 1 and 8, every 21 days; gemcitabine: 1,000 mg/m^2 IV on days 1 and 8, every 21 days; irinotecan: 100 or 125 mg/m^2 IV weekly for 28 days, every 42 days; pemetrexed: 500 mg/m^2 on day 1, every 21 days.

Coleman RL, et al. *Lancet Oncol*. 2021;22(5):609-619. Tisotumab vedotin-tftv [package insert]. Revised April 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761208s007lbl.pdf. Vergote IB, et al. *Ann Oncol*. 2023;34:S1276-S1277.

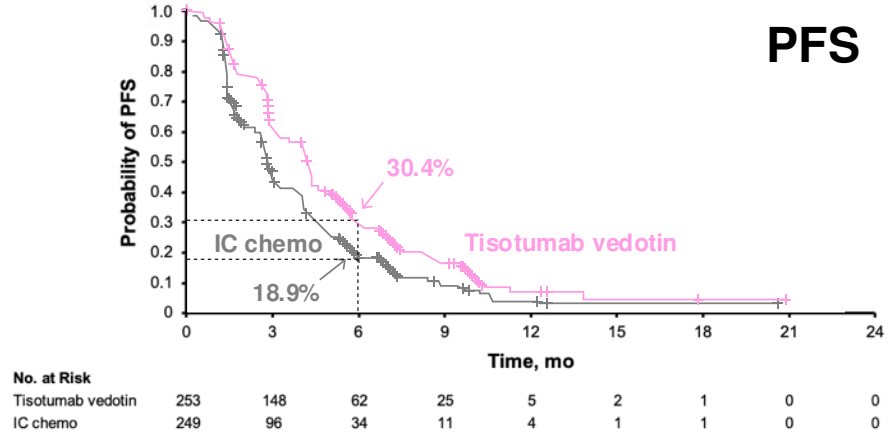
Phase III innovaTV 301: Tisotumab Vedotin in Cervical Cancer

OS



	Events/Total, n	Median OS, mo (95% CI)
Tisotumab vedotin	123/253	11.5 (9.8-14.9)
IC chemo	140/249	9.5 (7.9-10.7)
Stratified log-rank p^a = .0038		
HR = 0.70 (95% CI, 0.54-0.89)		

PFS



	Events/Total, n	Median PFS, mo (95% CI)
Tisotumab vedotin	198/253	4.2 (4.0-4.4)
IC chemo	194/249	2.9 (2.6-3.1)
Stratified log-rank p^b < .0001		
HR = 0.67 (95% CI, 0.54-0.82)		

[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 IB, et al. *Ann Oncol*. 2023;34:S1276-S1277.

innovaTV 301: 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%)

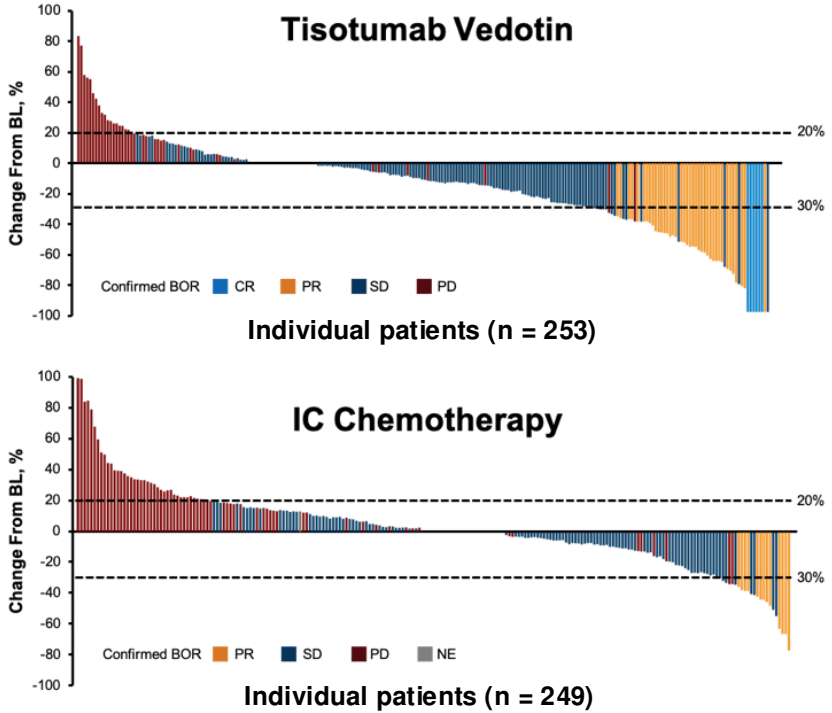
	Pembro Arm (N = 529)	Placebo Arm (N = 531)
Stage at screening (FIGO 2014 criteria)		
IB2-IIB	233 (44.0%)	226 (42.6%)
III-IVA	296 (56.0%)	305 (57.4%)
Lymph node involvement[b]		
Positive pelvic only	327 (62.2%)	324 (61.0%)
Positive para-aortic only	14 (2.6%)	10 (1.9%)
Positive pelvic and para-aortic	104 (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 D, et al. *Lancet*. 2024;403(10434):1341-1350. Lorusso D, et al. *Ann Oncol*. 2023;34:S1279-S1280.

innovaTV 301: Tisotumab Vedotin in Cervical Cancer

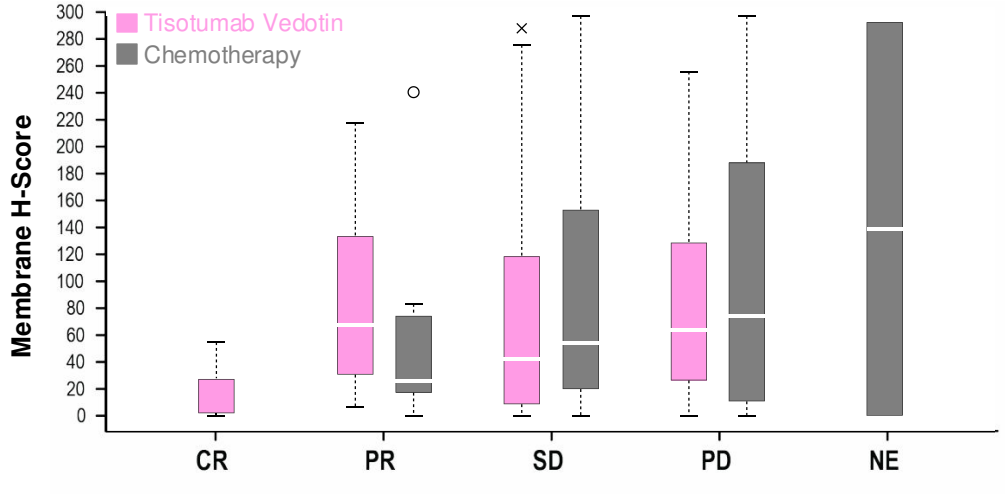
	Tisotumab Vedotin (n = 253)	IC Chemotherapy (n = 249)
ORR, % (95% CI)	17.8 (13.3-23.1)	5.2 (2.8-8.8)
Odds ratio (95% CI)	4.0 (2.1-7.6) p <.0001	
BOR, n (%)		
CR	6 (2.4)	0
PR	39 (15.4)	13 (5.2)
SD	147 (58.1)	132 (53.0)
PD	46 (18.2)	74 (29.7)
NE/NA	15 (5.9)	30 (12.0)
DCR,[a] % (95% CI)	75.9 (70.1-81.0)	58.2 (51.8-64.4)
Median DOR (95% CI)	5.3 (4.2-8.3)	5.7(2.8-NR)



BOR = best overall response; CR = complete response; DCR = disease control rate; IC = induction chemotherapy; NE/NA = not evaluable/applicable; PD = progressive disease; PR = partial response; SD = stable disease. [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 IB, et al. *Ann Oncol*. 2023;34:S1276-S1277.

innovaTV 301: Confirmed ORR Trends Were Consistent Regardless of Tissue Factor (TF) Expression

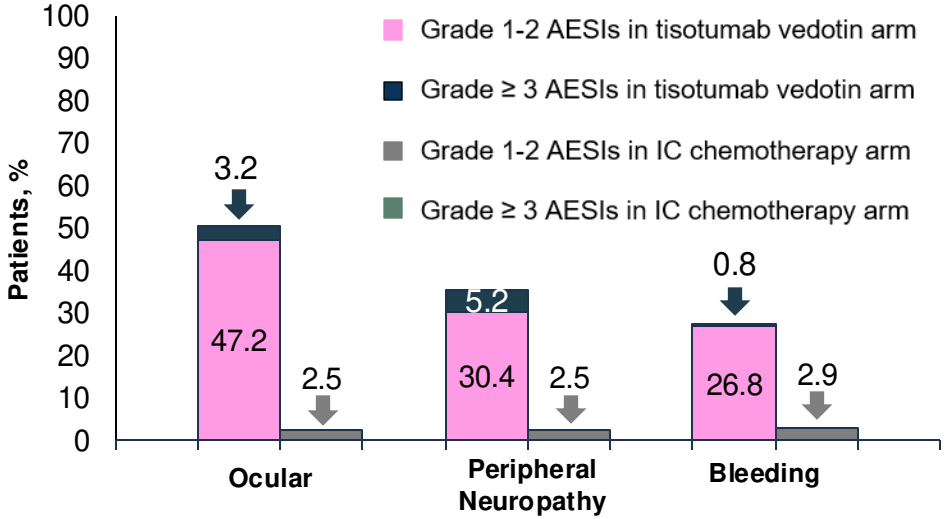


	CR	PR	SD	PD	NE
Tisotumab Vedotin (n)	6	35	120	39	0
Chemotherapy (n)	0	10	107	57	3

- 210 (83.0%) tisotumab vedotin patients and 194 (77.9%) chemotherapy patients had biopsies evaluable for TF expression
  - Of these, positive membrane TF expression was observed in 194 (92.4%) and 183 (94.3%) patients, respectively
- Comparable distribution of TF expression was observed among different confirmed best overall response groups

Vergote I, et al. *N Engl J Med.* 2024;391(1):44-55.

innovaTV 301: Treatment-Related Adverse Events of Special Interest (AESIs) for Tisotumab Vedotin



- There were no grade 4 or 5 AESIs
- Dose discontinuation because of ocular and peripheral neuropathy events occurred in 5.6% of patients for each arm

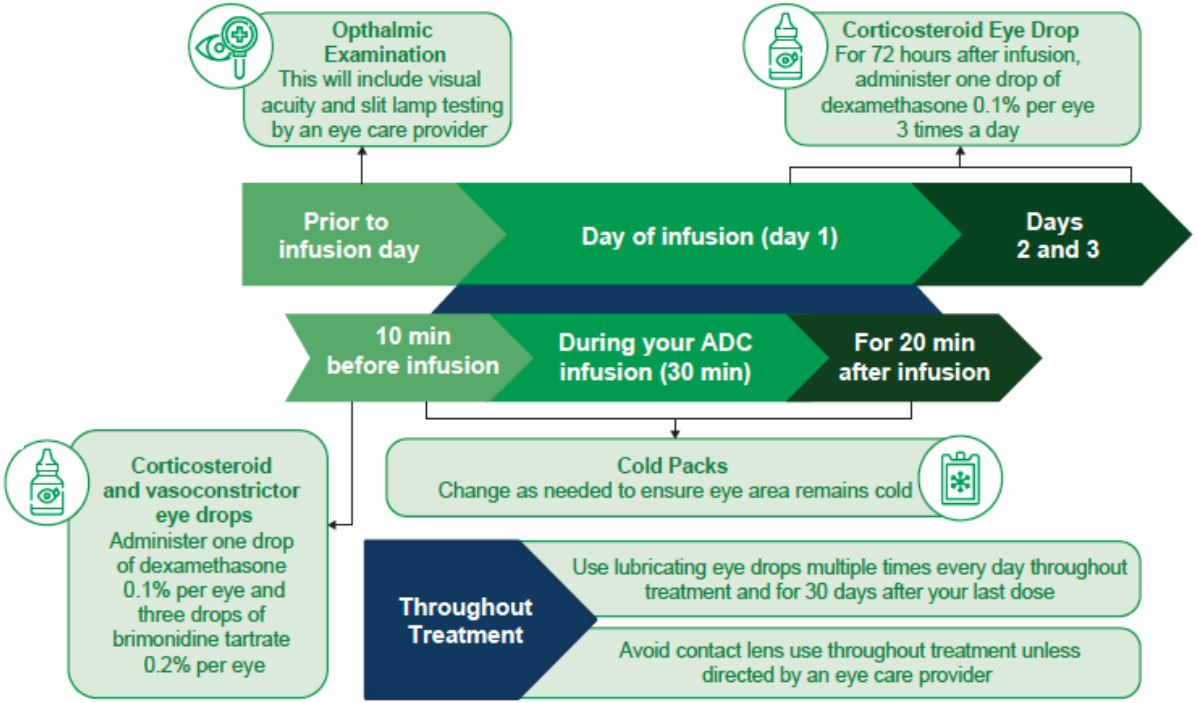
Most Common Preferred Terms for Each AESI
• **Ocular:** conjunctivitis (30.4%), keratitis (15.6%), dry eye (13.2%)
• **Peripheral neuropathy:** peripheral sensory neuropathy (26.8%), paresthesia (2.8%), muscular weakness (2.4%), peripheral sensorimotor neuropathy (2.4%)
• **Bleeding:** epistaxis (22.8%), hematuria (3.2%), vaginal hemorrhage (3.2%)

Vergote IB, et al. *Ann Oncol.* 2023;34:S1276-S1277.

Expert Insights on the Effective Implementation of Tisotumab Vedotin and Practical Tips for Its Use

Important Provider/Patient Discussion Points

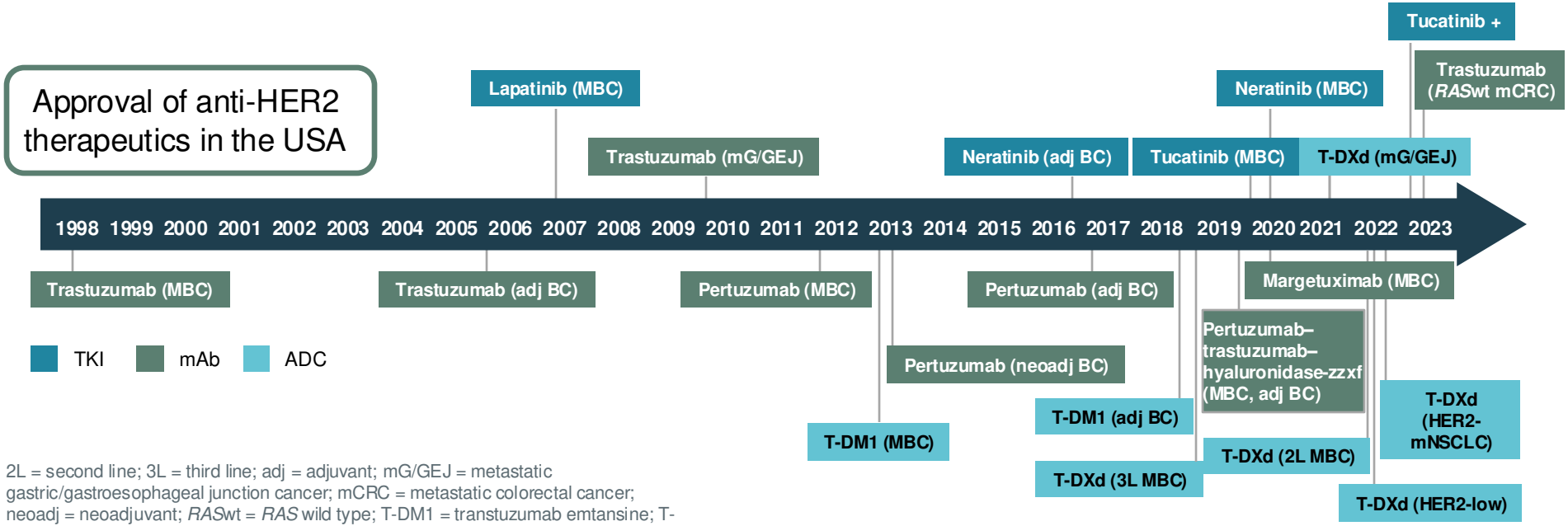
- Treatment schedule and dosing
- Management of AEs
  - Potential for dose holds or reductions
- Ocular AEs: focus on expectations, prevention, plan for eye drops/regimens
  - Timeline of eye drops (prior to infusion/day of infusion/days after infusion)
  - Types of eye drops
  - Patient reminder tools
  - Educate eye care specialists



Kim SK, et al. *Gynecol Oncol*. 2022;165:385-392. Richardson DL, et al. *Gynecol Oncol Rep*. 2023;46:101148.

History of Approvals for HER2-Targeted Therapies for Cancer

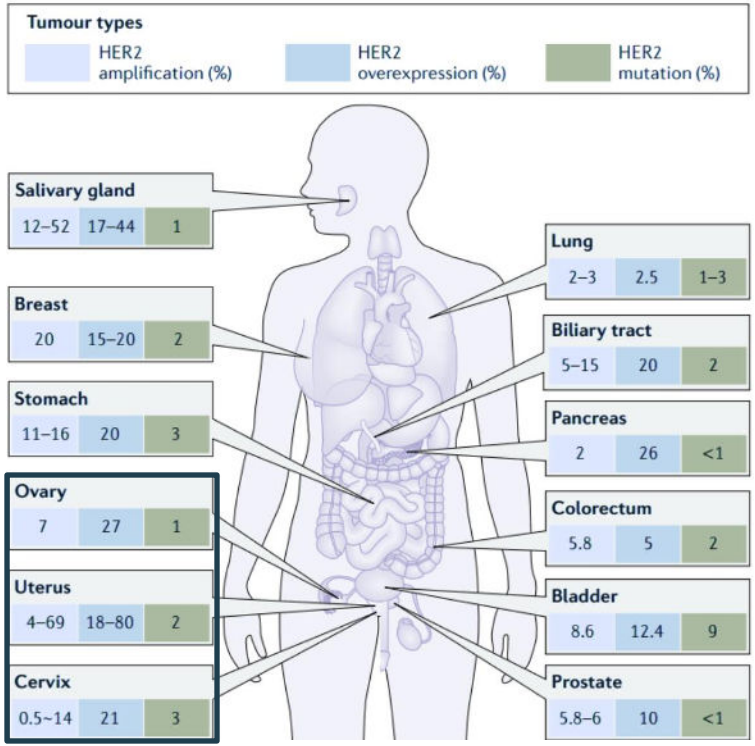
- HER2 protein expression, gene amplification, and gene mutation are therapeutic targets in several types of tumors
- HER2-directed therapy is the standard of care for HER2-expressing unresectable or metastatic breast cancer, HER2-positive locally advanced or metastatic gastric cancers, CRC and GEJ adenocarcinomas, and HER2-mutant NSCLC



2L = second line; 3L = third line; adj = adjuvant; mG/GEJ = metastatic gastric/gastroesophageal junction cancer; mCRC = metastatic colorectal cancer; neoadj = neoadjuvant; *RAS*wt = *RAS* wild type; T-DM1 = transtuzumab emtansine; T-DXd = trastuzumab deruxtecan; TKI = tyrosine kinase inhibitor.

Drugs.com. 2024. https://www.drugs.com/history/herceptin.html. Drugs.com. 2024. https://www.drugs.com/history/enhertu.html. Drugs.com. 2023. https://www.drugs.com/history/tukysa.html.

HER2 Overexpression, Amplification, and Mutations Across Tumor Types

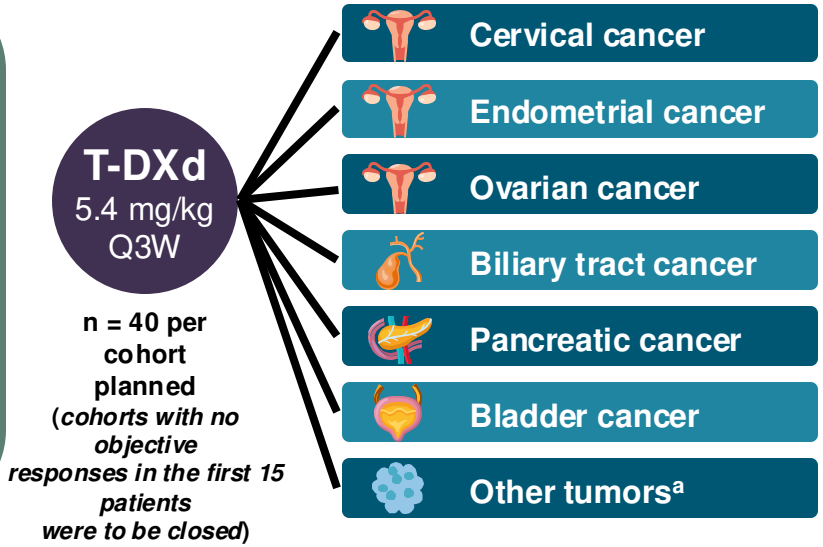


Cancer Genome Atlas Research Network. *Nat Genet*. 2013;45:1113-1120. AACR Project GENIE Consortium. *Cancer Discov*. 2017;7:818-831. Oh DY, et al. *Nat Rev Clin Oncol*. 2020;17:33-48.

Open-Label, Phase II DESTINY-PanTumor02 Study of T-DXd for HER2-Expressing Solid Tumors

Tumor types were selected based on epidemiological frequency, prevalence of HER2 expression, and unmet medical need

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by Hercep Test if local test not feasible (ASCO/CAP gastric cancer guidelines)
- Prior HER2-targeting therapy
- ECOG/WHO PS 0-1 restricted in strenuous activity



Primary endpoint
- Confirmed ORR (investigator)

Secondary endpoints
- DOR
- DCR
- PFS
- OS
- Safety

Data cut-off for analysis
- June 8, 2023
- FDA approved Apr 5. 2024

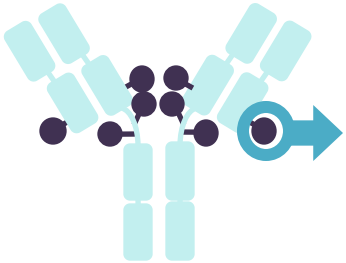
[a]Other tumors cohort: Salivary gland cancer (n = 19), malignant neoplasm of unknown primary site (n = 5), extramammary Paget disease (n = 3), cutaneous melanoma (n = 2), oropharyngeal neoplasm (n = 2), adenoid cystic carcinoma, head and neck cancer, lip and/or oral cavity cancer, esophageal adenocarcinoma, intestinal adenocarcinoma, appendiceal adenocarcinoma, esophageal squamous cell carcinoma, testicular cancer, and vulvar carcinoma (all n = 1).

ASCO/CAP = American Society of Clinical Oncology/College of American Pathologists; IHC = immunohistochemistry; WHO = World Health Organization.

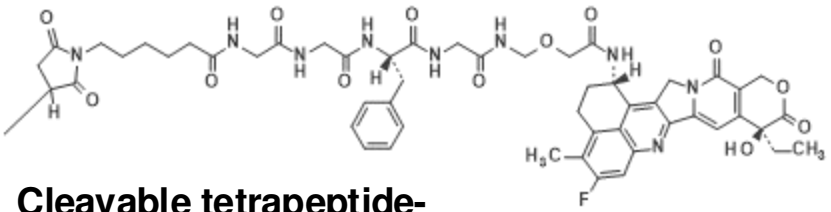
Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42:47-58. A Phase 2, Multicenter, Open-label Study to Evaluate the Efficacy and Safety of Trastuzumab Deruxtecan (T-DXd, DS-8201a) for the Treatment of Selected HER2 Expressing Tumors (DESTINY-PanTumor02) Clinicaltrials.gov Identifier: NCT04482309. 2020.

T-DXd: Structure and Key Attributes

Human anti-HER2 IgG1 mAb



Deruxtecan



Cleavable tetrapeptide-based linker

Topoisomerase I inhibitor payload (DXd)

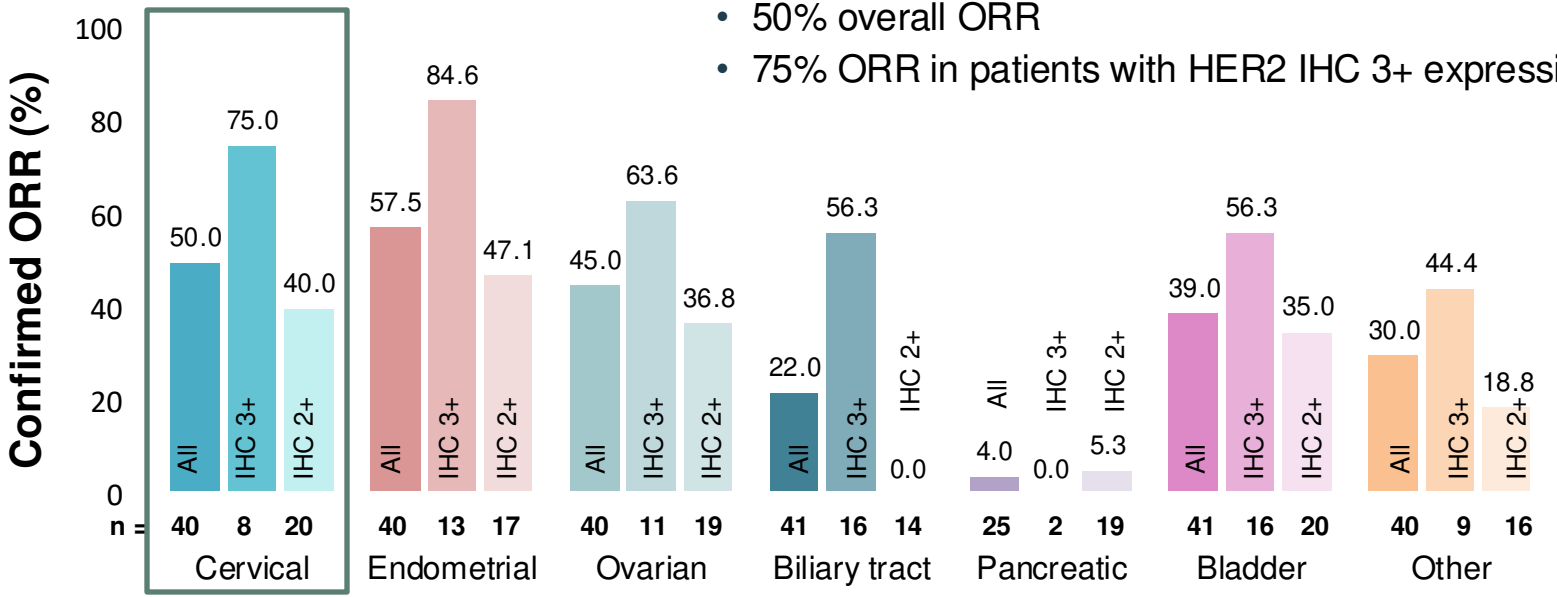
- Payload mechanism of action: topoisomerase I inhibitor*
- High potency of payload*
- High drug-to-antibody ratio ≈8*
- Payload with short systemic half-life*
- Stable linker-payload*
- Tumor-selective cleavable linker*
- Bystander antitumor effect*

*Clinical relevance under investigation.

Fam-trastuzumab deruxtecan-nxki [package insert]. Revised April 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s028lbl.pdf.

DESTINY-PanTumor02 Study: ORR by HER2 Status: Primary Analysis

- **Cervical cancer**: high mortality rate
- 50% overall ORR
- 75% ORR in patients with HER2 IHC 3+ expression



Median follow-up: 12.75 months.

Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42:47-58.

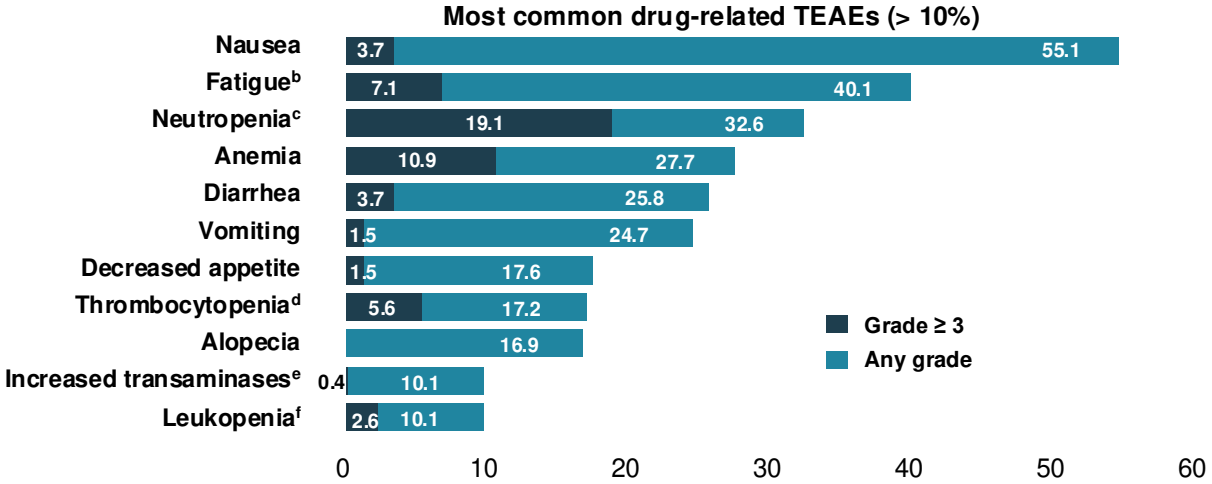
DESTINY-PanTumor02 Study: PFS and OS by Tumor Type

Efficacy by tumor cohort	Cervical cancer	Endometrial cancer	Ovarian cancer	Biliary tract cancer	Pancreatic cancer	Bladder cancer	Other tumors
Median PFS, months	7.0	11.1	5.9	4.6	3.2	7.0	8.8
PFS, 6 months	51.3	74.0	48.9	35.1	32.8	57.6	63.7
PFS, 12 months	29.9	49.2	31.6	15.1	10.9	22.8	39.8
Median OS, months	13.6	26.0	13.2	7.0	5.0	12.8	21.0
OS, 6 months	80.0	84.7	77.3	52.6	48.0	77.6	92.4
OS, 12 months	59.1	69.3	56.7	30.0	36.0	62.6	71.3

Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42:47-58.

DESTINY-PanTumor02: Safety Summary

n (%)	All patients (N = 267)
Any drug-related TEAEs	226 (84.6)
Drug-related TEAEs Grade ≥ 3	109 (40.8)
Serious drug-related TEAEs	36 (13.5)
Drug-related TEAEs associated with dose discontinuations	23 (8.6)
Drug-related TEAEs associated with dose interruptions	54 (20.2)
Drug-related TEAEs associated with dose reductions	54 (20.2)
Drug-related TEAEs associated with deaths	4 (1.5)[a]



Patients experiencing drug-related TEAEs (%)

ILD/pneumonitis adjudicated as T-DXd related, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
All patients (N = 267)	7 (2.6)	17 (6.4)	1 (0.4)	0	3 (1.1)	28 (10.5)

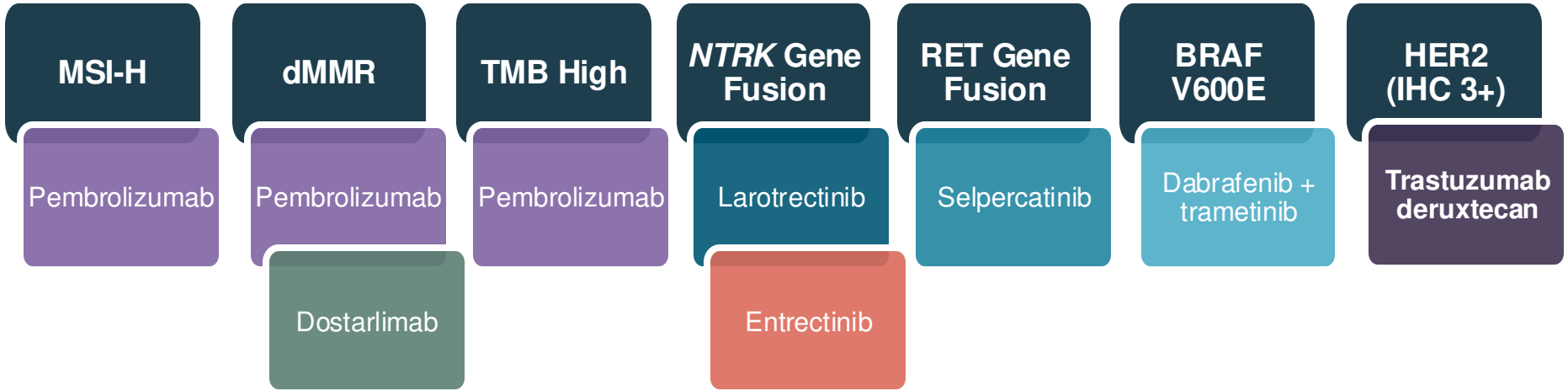
Analyses were performed in patients who received ≥1 dose of T-DXd (N=267); median total treatment duration 5.6 months (range 0.4–31.1).

[a]Included pneumonia (n = 1), organizing pneumonia (n = 1), pneumonitis (n = 1), and neutropenic sepsis (n = 1). [b]Ccategory includes the preferred terms fatigue, asthenia, and malaise. [c]Category includes the preferred terms neutrophil count decreased and neutropenia. [d]Category includes the preferred terms platelet count decreased and thrombocytopenia. [e]Category includes the preferred terms aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, hypertransaminasemia. [f]Category includes the preferred terms white blood cell count decreased and leukopenia.

ILD = interstitial lung disease; TEAE = treatment-emergent adverse event.

Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42:47-58.

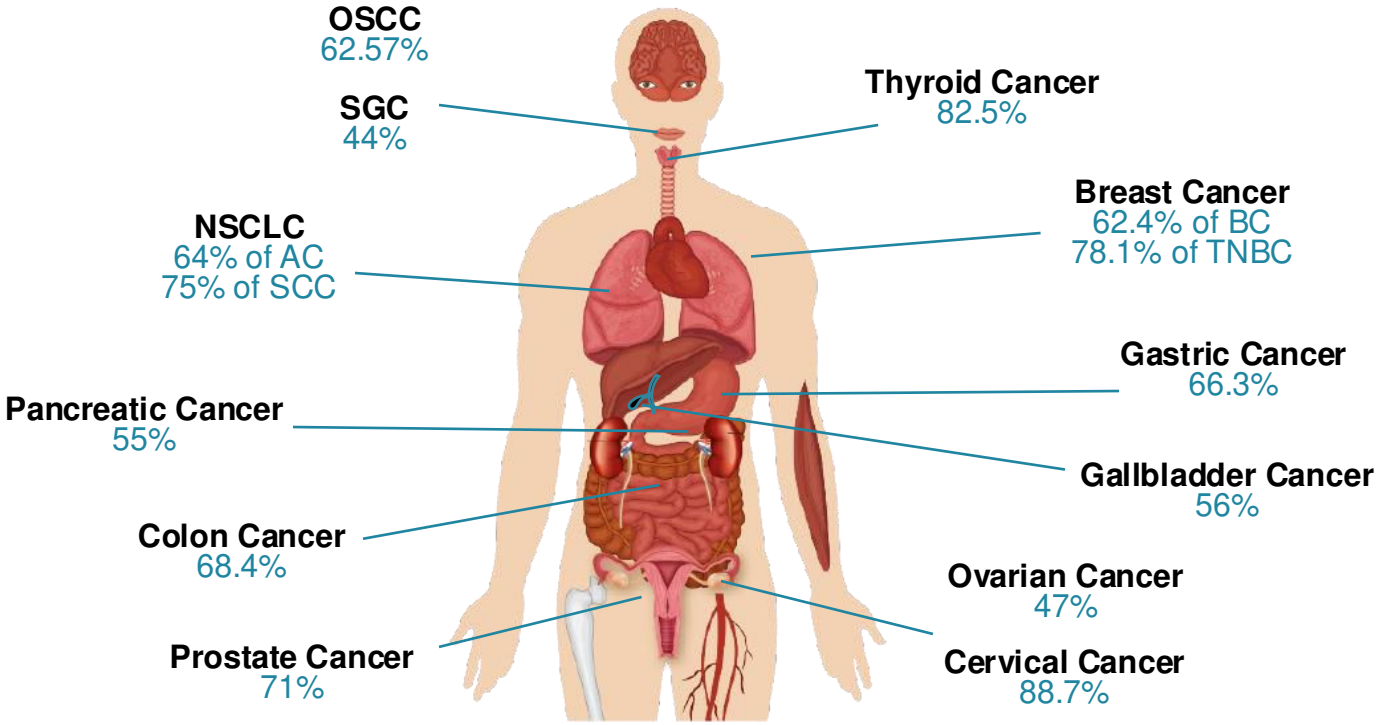
7 Drugs Are Approved By the FDA for Tumor-Agnostic Use:



dMMR = deficient mismatch repair; MSI-H = microsatellite instability-high; TMB = tumor mutation burden.

Zettler ME. *Target Oncol*. 2023;18:777-792.

TROP-2 Overexpression in Cervical and Other Cancers



OSCC = oral squamous cell carcinoma; TROP-2 = trophoblast cell-surface antigen 2; SGC = salivary gland carcinoma.

Liu X, et al. *Pharmacol Ther.* 2022;239:108296.

Anti-TROP-2 Antibody-Drug Conjugates

Characteristic	Dato-DXd	Sacituzumab Govitecan	Sacituzumab Tirumotecan
Antibody	Anti-TROP-2 IgG1	Anti-TROP-2 IgG1κ	Anti-TROP-2 IgG1
High affinity binding	+++	+++	+++
Linker	Cleavable	Cleavable	Cleavable
Payload	Deruxtecan derivative	SN-38	Belotecan derivative
DAR	4	7.6	7.4
Dose/schedule	6 mg/kg Q3W	10 mg/kg D1,8 Q3W	5 mg/kg Q2W

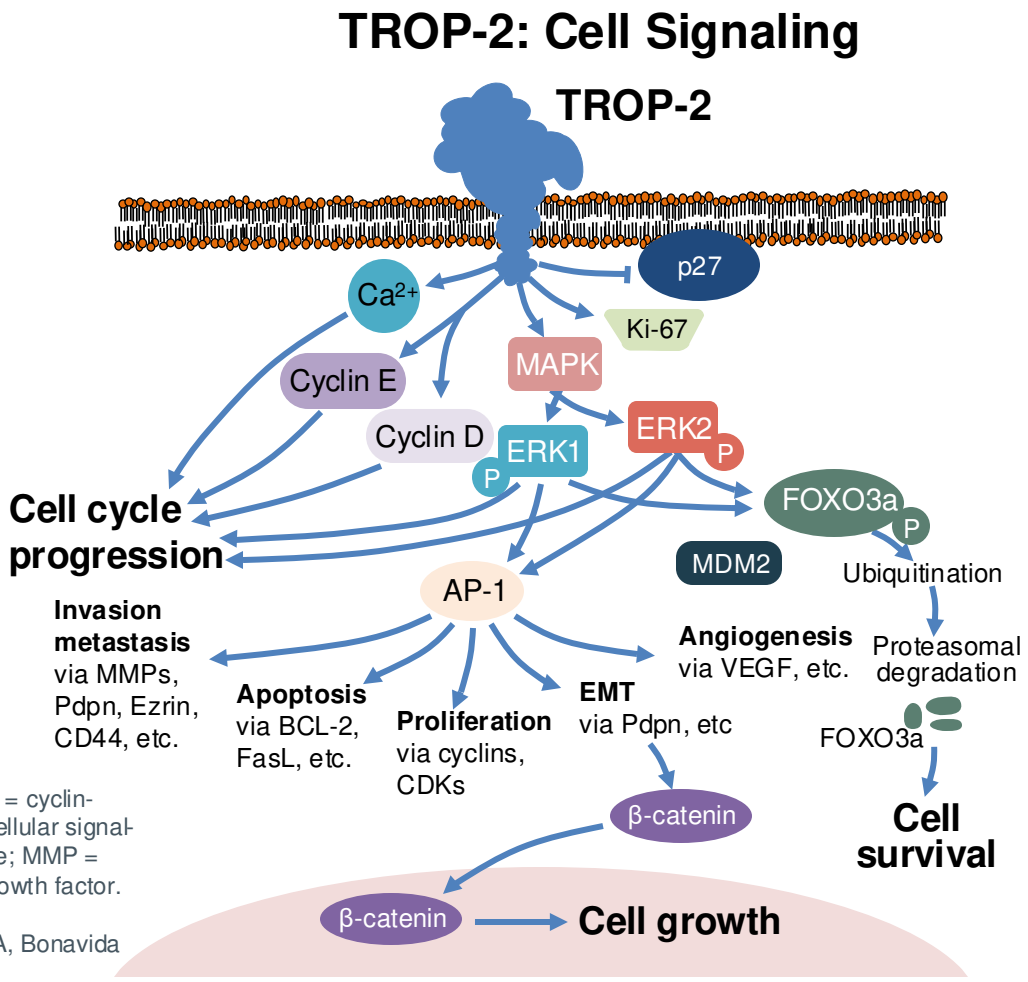
Dato-DXd, sacituzumab govitecan, and sacituzumab tirumotecan are not FDA-approved for the treatment of cervical cancer.

Dato-DXd = datopotamab deruxtecan.

Okajima D, et al. *Mol Can Ther.* 2021;20(12):2329-2340. Sacituzumab govitecan-hziy [package insert]. Revised February 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761115s035lbl.pdf. Xu B, et al. *J Clin Oncol.* 2024;42(Suppl 16):104.

TROP-2 as a Therapeutic Target

- TROP-2 is a transmembrane glycoprotein overexpressed in solid tumors, including cervical cancer
- TROP-2 is an epithelial adhesion molecule and regulates stem cell marker-associated cell regeneration



AP-1 = activator protein 1; BCL-2 = B-cell leukemia/lymphoma 2 protein; CDK = cyclin-dependent kinase; EMT = epithelial-to-mesenchymal transition; ERK = extracellular signal-regulated kinase; FasL = Fas ligand; MAPK = mitogen-activated protein kinase; MMP = matrix metalloproteinase; Pdpn = podoplanin; VEGF = vascular endothelial growth factor.

Jiang A, et al. *Oncol Lett*. 2013;6(2):375-380. Figure adapted from Shvartsur A, Bonavida B. *Genes Cancer*. 2015;6 (3-4):84-105.

Efficacy and Safety of Sacituzumab Tirumotecan (sac-TMT) Plus Pembrolizumab in Patients with Recurrent or Metastatic Cervical Cancer

Xiaohua Wu[1], Jing Wang[2], Ruifang An[3], Yi Huang[4], Jieqing Zhang[5], Jeffrey C. Goh[6], Kui Jiang[7], Guohua Yu[8], Liang Chen[9], Diane Provencher[10], Ying Tang[11], Guiling Li [12], Hui Qiu[13], Omobolaji·O. Akala[14], Elliot Chartash[14], Yiting Zhou[15], Xiaoping Jin[15], Junyou Ge[15]

[1]**Fudan University Shanghai Cancer Center, Shanghai, China;** [2]The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University/Hunan Cancer Hospital, Changsha, China; [3]The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; [4]Hubei Cancer Hospital, Wuhan,China; [5]Guangxi Medical University Cancer Hospital, Nanning, China; [6]Icon Cancer Centre Wesley, Chermside, QLD, Australia; [7]The Second Hospital of Dalian Medical University, Dalian, China; [8]Weifang People's Hospital, Weifang, China; [9]Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China; [10]CHUM – Centre Hospitalier de l'Université de Montréal, Montreal, Canada; [11]Chongqing University Cancer Hospital, Chongqing, China;
[12]Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [13]Zhongnan
Hospital of Wuhan University, Wuhan, China; [14]Merck & Co., Inc., Rahway, NJ, USA; [15]Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd., Chengdu, China

Sun, 15.09.2024, 14:55-15:00 716MO

Wang J, et al. *Ann Oncol*. 2024;35:S548-S549.

Phase II Basket Trial Sacituzumab Tirumotecan (sac-TMT) Plus Pembrolizumab in Patients with Recurrent or Metastatic Cervical Cancer

- **Sac-TMT (also known as SKB264/MK-2870)** is a TROP-2 ADC developed with a proprietary Kthiol (pyrimidine-thiol) linker conjugated to a novel topoisomerase I inhibitor (KL610023) with a DAR of 7.4
- Sac-TMT combined with a PD-L1 antibody showed a potential additive effect in NSCLC

Cohort A: 2L or 3L recurrent or metastatic CC (N = 40)

Key Inclusion Criteria

- Received 1 or 2 prior systemic regimens (prior anti-PD-1/L1 allowed) for recurrent or metastatic CC
- Progressed on or after platinum-doublet chemotherapy
- ECOG PS 0 or 1

Safety Run-In

Sac-TMT 3 or 5 mg/kg Q2W + pembrolizumab 400 mg Q6W

Expansion

Sac-TMT 5 mg/kg Q2W + pembrolizumab 400 mg Q6W

Tumor Assessment:

- Every 8 weeks for the first 12 months, and every 12 weeks thereafter

Treatment continues until

- Disease progression
- Unacceptable toxicity

Primary Endpoints

- Safety (DLT, AEs)
- ORR per RECIST v1.1

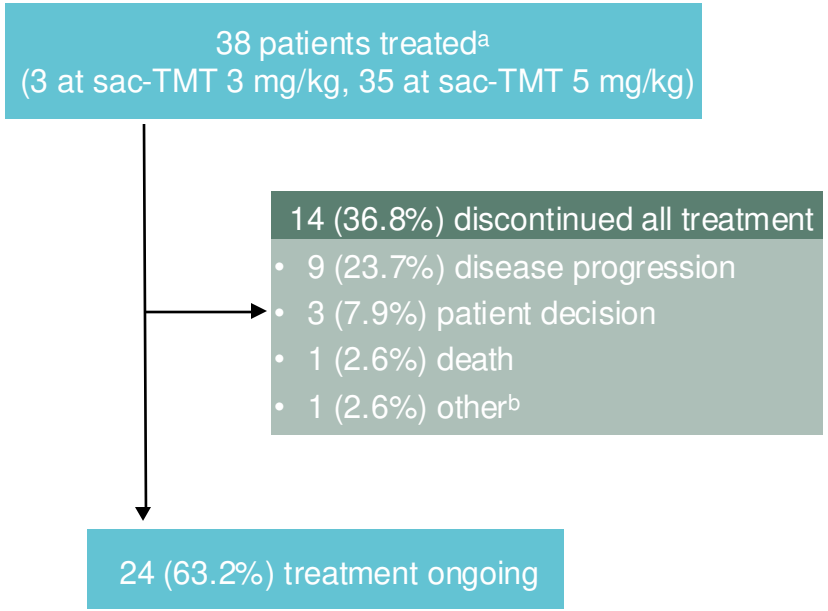
Secondary Endpoints

- DCR, DoR, PFS, OS
- PK, immunogenicity

CC = cervical cancer; DLT = dose limiting toxicity.

Fang W, et al. *J Clin Oncol*. 2024;42(Suppl 16):8502. Wang J, et al. *Ann Oncol*. 2024;35:S548-S549. Xiaoping J. A Multicenter, Open-label, Phase 2, Basket Study to Evaluate the Efficacy and Safety of SKB264 in Combination With Pembrolizumab in Subjects With Selected Solid Tumors. Clinicaltrials.gov Identifier: NCT05642780. 2022.

Sac-TMT: Baseline Characteristics and Disposition



Median follow-up was 6.2 (1.8-12.9) months

[a]38 patients were treated and followed up for at least 17 weeks or 2 tumor assessments.

[b]Start new anti-cancer therapy.

Data cutoff: March 25, 2024.

Characteristics	Sac-TMT + pembrolizumab (n = 38)
Median age (range), years	52 (33, 72)
ECOG PS, n (%)	
0	22 (57.9)
1	16 (42.1)
Histologic type, n (%)	
Squamous cell carcinoma	29 (76.3)
Adenocarcinoma	9 (23.7)
PD-L1 expression[a], n (%)	
CPS ≥ 1	14 (36.8)
CPS < 1	15 (39.5)
Unknown	9 (23.7)
Disease status, n (%)	
Recurrence	2 (5.3)
Metastases	36 (94.7)
Prior lines of systemic therapy, n (%)	
1	20 (52.6)
2	18 (47.4)
Prior anti-PD-1 based therapy, n (%)	16 (42.1)
Prior bevacizumab use, n (%)	20 (52.6)
Prior concurrent chemoradiotherapy, n (%)	16 (42.1)

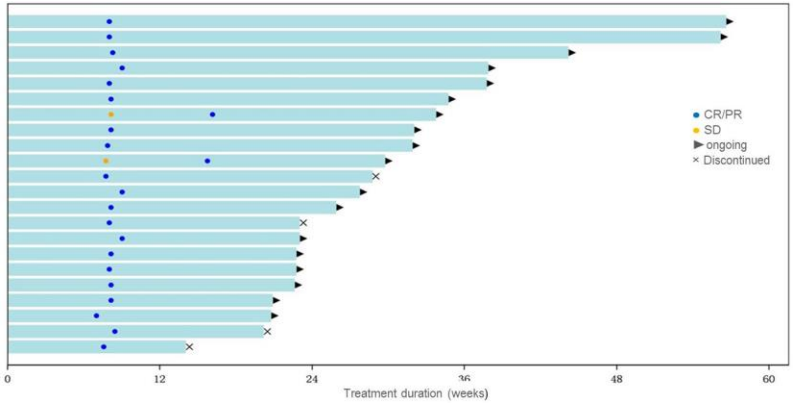
[a]PD-L1 expression level was assessed using PD-L1 IHC 22C3 pharmDx assay.

Wang J, et al. *Ann Oncol*. 2024;35:S548-S549.

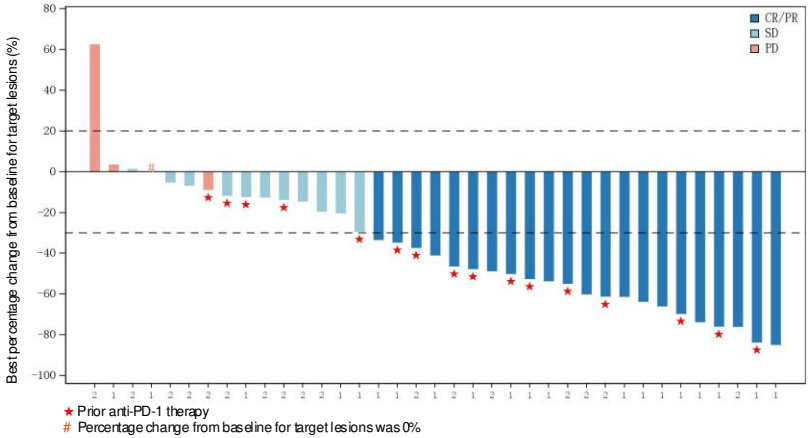
Sac-TMT: Efficacy Summary

Data cutoff: March 25, 2024.	Sac-TMT + pembrolizumab (n = 38)
ORR, n (%) (95% CI)	**22 (57.9)** (40.8, 73.7)
Confirmed ORR, n (%) (95% CI)	19 (50.0) (33.4, 66.6)
DCR, n (%)	**33 (86.8)**
CR	3 (7.9)
PR	19 (50.0)
SD	11 (28.9)
PD	4 (10.5)
NA	1 (2.6)
DoR	
Median (95% CI), months	NR (NE, NE)
6-month DoR rate, % (95% CI)	82.1 (53.9, 93.9)
PFS	
Median (95% CI), months	NR (5.6, NE)
6-month PFS rate, % (95% CI)	65.7 (45.8, 79.7)

Time to response and duration of treatment for responders



Best percentage change from baseline for target lesions



Wang J, et al. *Ann Oncol*. 2024;35:S548-S549.

Sac-TMT: Efficacy in Key Subgroups

Subgroup		N	ORR, n (%)[a]	6-month PFS rate, % (95% CI)
CPS status	CPS ≥ 1	14	7 (50.0)	68.8 (35.7, 87.3)
	CPS < 1	15	9 (60.0)	74.9 (39.1, 91.5)
	Unknown	9	6 (66.7)	43.8 (10.1, 74.2)
Prior anti-PD-1 based therapy	Yes	16	11 (68.8)	78.6 (47.2, 92.5)
	No	22	11 (50.0)	58.0 (32.4, 76.8)
Prior bevacizumab	Yes	20	12 (60.0)	67.1 (40.9, 83.7)
	No	18	10 (55.6)	67.5 (38.2, 85.2)
No. of prior systemic therapy	1	20	15 (75.0)	73.1 (46.7, 87.9)
	2	18	7 (38.9)	54.3 (21.8, 78.3)

[a]ORR including confirmed or unconfirmed responses.
Data cutoff: March 25, 2024.

Wang J, et al. *Ann Oncol*. 2024;35:S548-S549.

Sac-TMT: Frequently Reported TRAEs (≥ 20% All Grades)

Preferred terms, n (%)	All grades	Grade ≥ 3
Anemia	34 (89.5)	8 (21.1)
WBC decreased	27 (71.1)	6 (15.8)
Neutrophil count decreased	20 (52.6)	9 (23.7)
Stomatitis	13 (34.2)	2 (5.3)
Nausea	10 (26.3)	0
Lymphocyte count decreased	9 (23.7)	4 (10.5)
Alopecia	8 (21.1)	0

Data cutoff: March 25, 2024.

- The most common TRAEs were hematological toxicities (anemia, decreased WBC, decreased neutrophil count, and decreased lymphocyte count) as well as stomatitis
- Immune-mediated TRAEs occurring in ≥ 5% were hyperthyroidism and hypothyroidism
- One patient (2.6%) reported grade 2 interstitial lung disease (recovered)
- No ocular toxicity or neuropathy was reported

WBC = white blood cell. Wang J, et al. *Ann Oncol.* 2024;35:S548-S549.

Sacituzumab Tirumotecan TroFuse-020/Gog-3101/ENGOT-cx20

Key Eligibility Criteria

- Recurrent or metastatic cervical cancer that has progressed on or after treatment with 1 prior line of systemic platinum doublet chemotherapy (with or without bevacizumab) AND must have received anti-PD-1/anti-PD-L1 therapy as part of prior cervical cancer regimens
- ECOG PS 0 or 1

Stratification Factors

- Metastatic disease at diagnosis (yes vs no)
- PD-L1 CPS (< 1 vs 1 to < 10 vs ≥ 10)
- Planned bevacizumab use (yes vs no)

R
1:1

Sacituzumab tirumotecan
4 mg/kg once every 2 weeks (Q2W) IV until progressive disease or discontinuation

Treatment of physician's choice (TPC)
(pemetrexed, tisotumab vedotin, topotecan, vinorelbine, gemcitabine, or irinotecan)

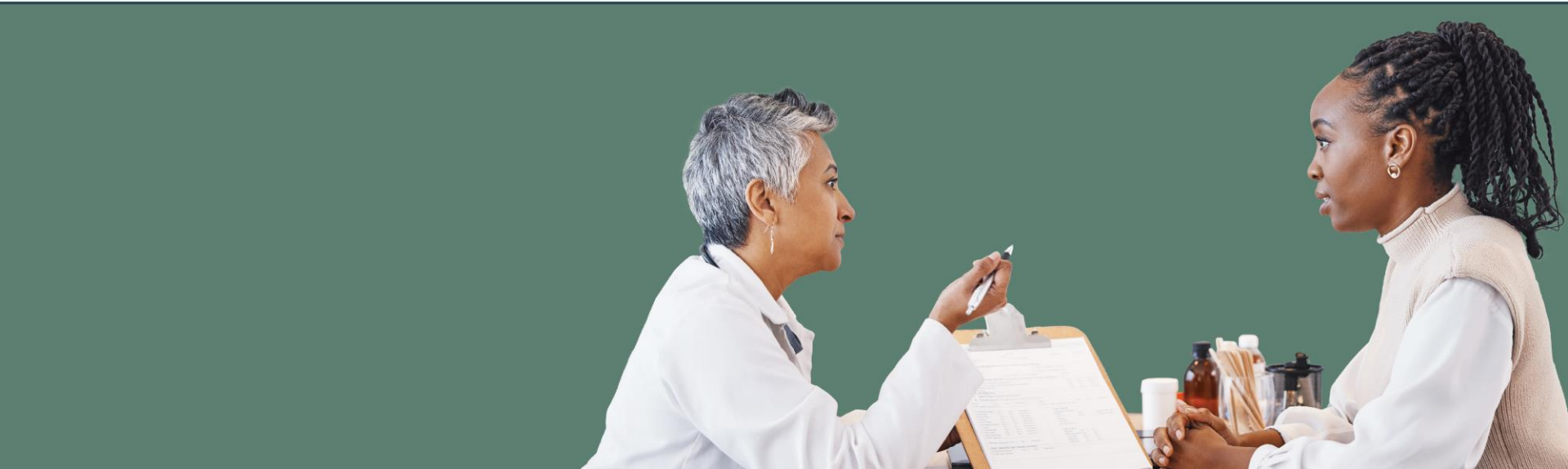
Post IO Study in 2L advanced/metastatic cancer

End Points

- Primary: ORR, safety (≥ 1 AE), sacituzumab tirumotecan discontinuation, OS
- Secondary: PFS, ORR, DOR, safety (≥ 3 AE), QoL

A Phase 3 Randomized, Active-controlled, Open-label, Multicenter Study to Compare the Efficacy and Safety of MK-2870 Monotherapy Versus Treatment of Physician's Choice as Second-line Treatment for Participants With Recurrent or Metastatic Cervical Cancer (TroFuse-020/GOG-3101/ENGOT-cx20) ClinicalTrials.gov Identifier: NCT06459180. 2024.

QUESTIONS & ANSWERS



SMART Goals

Specific, **M**easurable, **A**ttainable, **R**elevant, **T**imely

- Use inclusive language when discussing cervical cancer screening with patients
- Dispel myths about the need for cervical cancer screening in marginalized sexual orientations and gender identities
- Engage patients in shared decision-making about subsequent treatment options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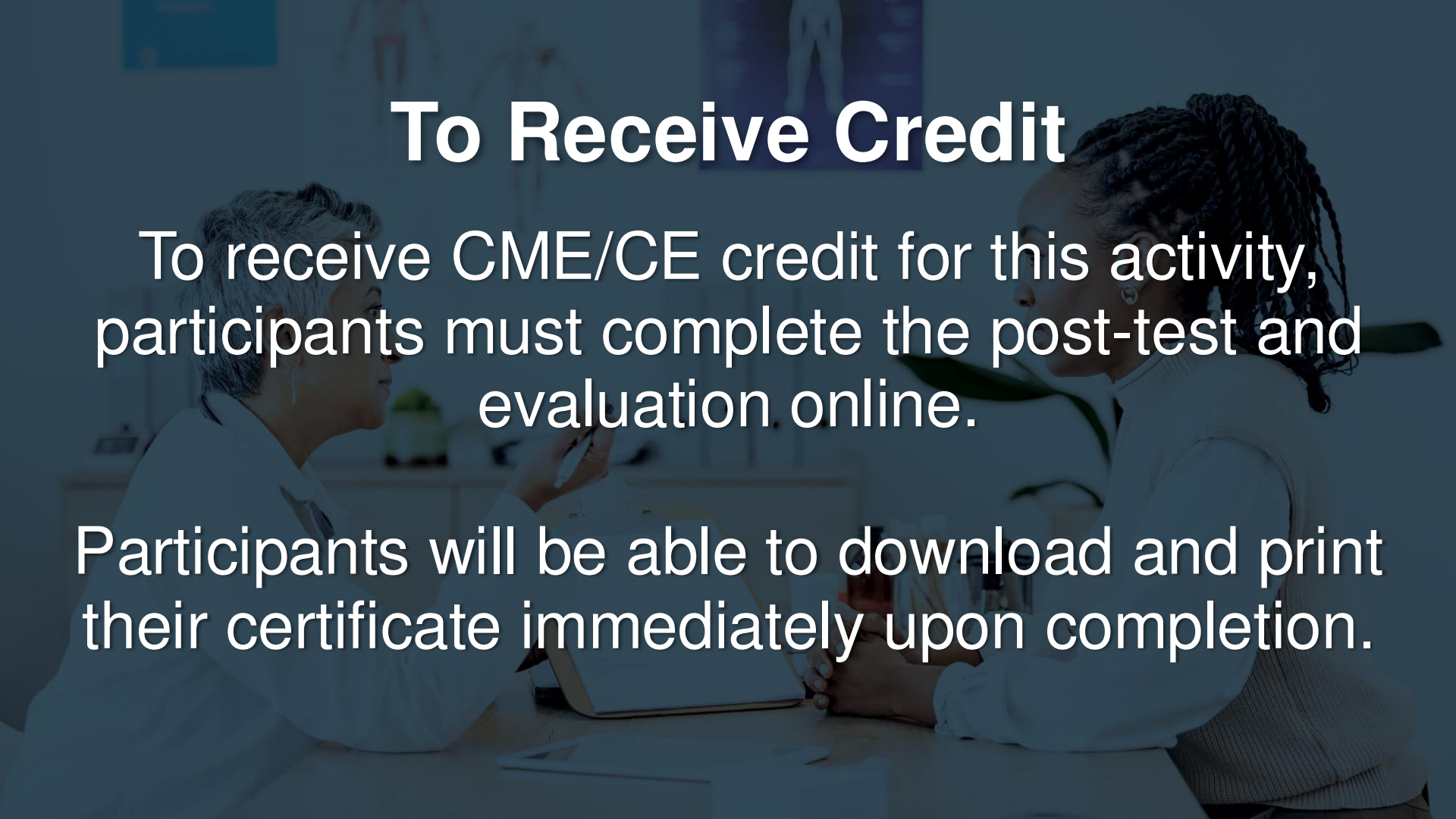

To Receive Credit

To receive CME/CE credit for this activity, participants must complete the post-test and evaluation online.

Participants will be able to download and print their certificate immediately upon completion.

ALL HANDS ON DECK IN CERVICAL CANCER CARE

Screening, Treatment, and Equity Strategies to Improve Patient Lives

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