Locally Advanced and Metastatic/Recurrent Cervical Cancer

신소진
계명의대 동산병원

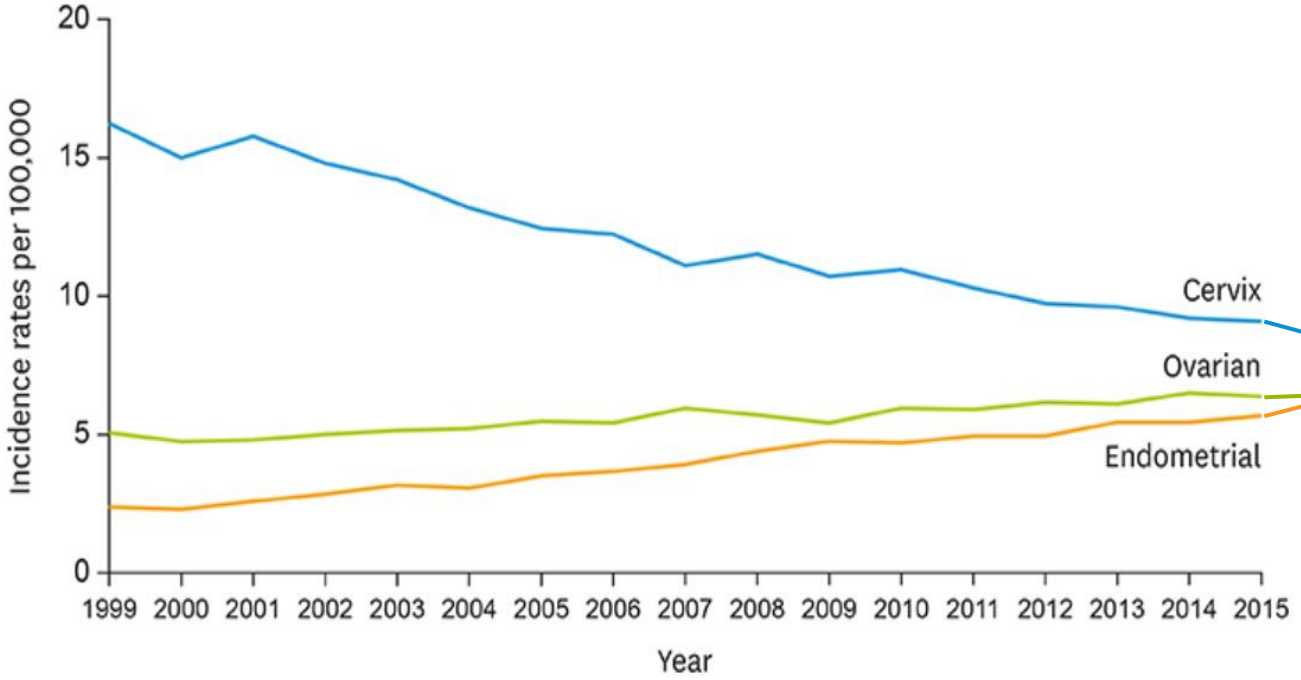
DECLARATION OF INTERESTS

Nothing to declare

CONTENTS

Background

In South Korea



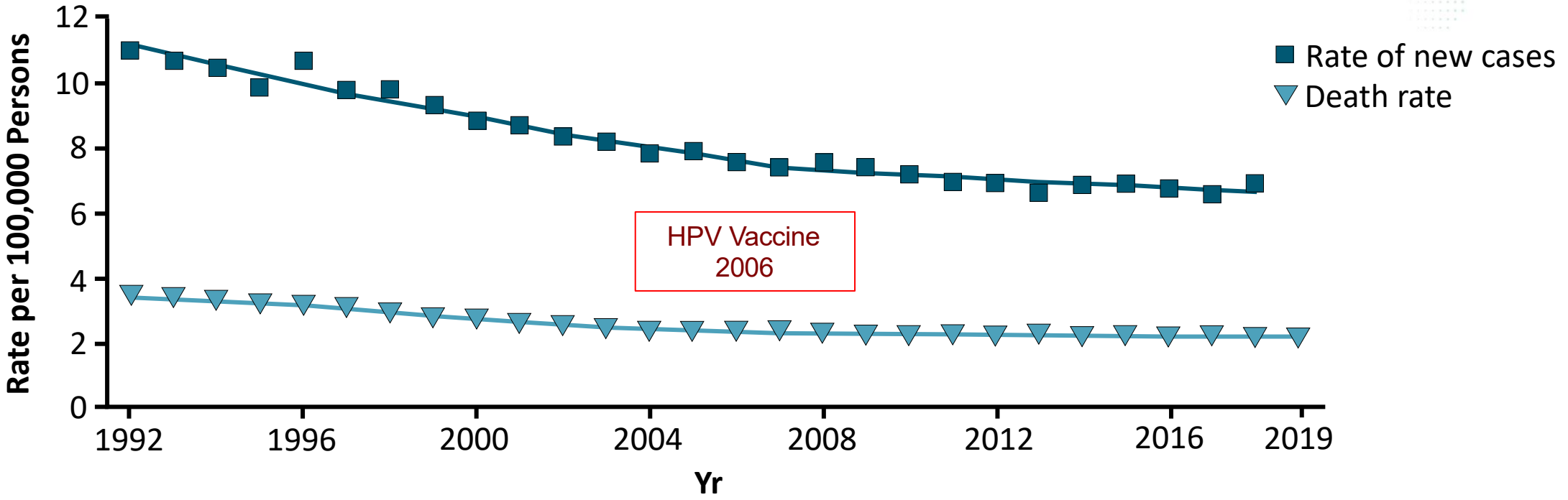
Age-standardized incidence curve for gynecologic cancers for female patients between 1999 and 2015 in the Korea Central Cancer Registry

Estimated new cases in 2025

Endometrial	4,348
Ovarian	3,580
Cervical	2,521

Background

Cervical Cancer: Challenges



- Steady **but disproportionate** decline in both the incidence and death rates in cervical cancer reflect **lack of effective salvage treatments** for those with recurrent disease

SEER Cancer Stat Facts: Cervical Cancer. National Cancer Institute. seer.cancer.gov/statfacts/html/cervix.html

Background

Cervical Cancer: FIGO 2018 staging

- Imaging and pathology information can be used to determine stage.
- Add notation of “r” for radiology-based information or “p” for pathology-based information to assigned stage.

Box 1 FIGO staging of carcinoma of the cervix uteri (2018).

Stage I:

The carcinoma is strictly confined to the cervix uteri (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[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 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 involvement
  - **IIA1** Invasive carcinoma <4 cm in greatest dimension
  - **IIA2** Invasive carcinoma ≥4 cm in greatest dimension
- **IIB** With parametrial involvement 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[c]

- **IIIA** Carcinoma involves the 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, irrespective of tumor size and extent (with r and p notations)[c]
  - **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

Background

International federation of gynecology and obstetrics (FIGO) classification

2018: FIGO updated clinical classification: images and/or pathological findings for staging.

- **Lateral extension measurement was removed from stage IA, and**
- **Stage IB: three subgroups based on tumor size (in greatest dimension):**
  - **Stage IB1 (≤ 20 mm),**
  - **Stage IB2 (>20 mm to ≤ 40 mm)**
  - **Stage IB3 (>40 mm).**
- **Incorporation of lymph node (LN) status.**
- **N +: IIIC. Pelvic LN: IIIC1. Para-aortic (PAo) LNs +: IIIC2.**
- **Notations 'r' (imaging) and 'p' (pathology) indicate the method used to stage.**
- **Four large-scale retrospective cohort studies were conducted to validate classification**

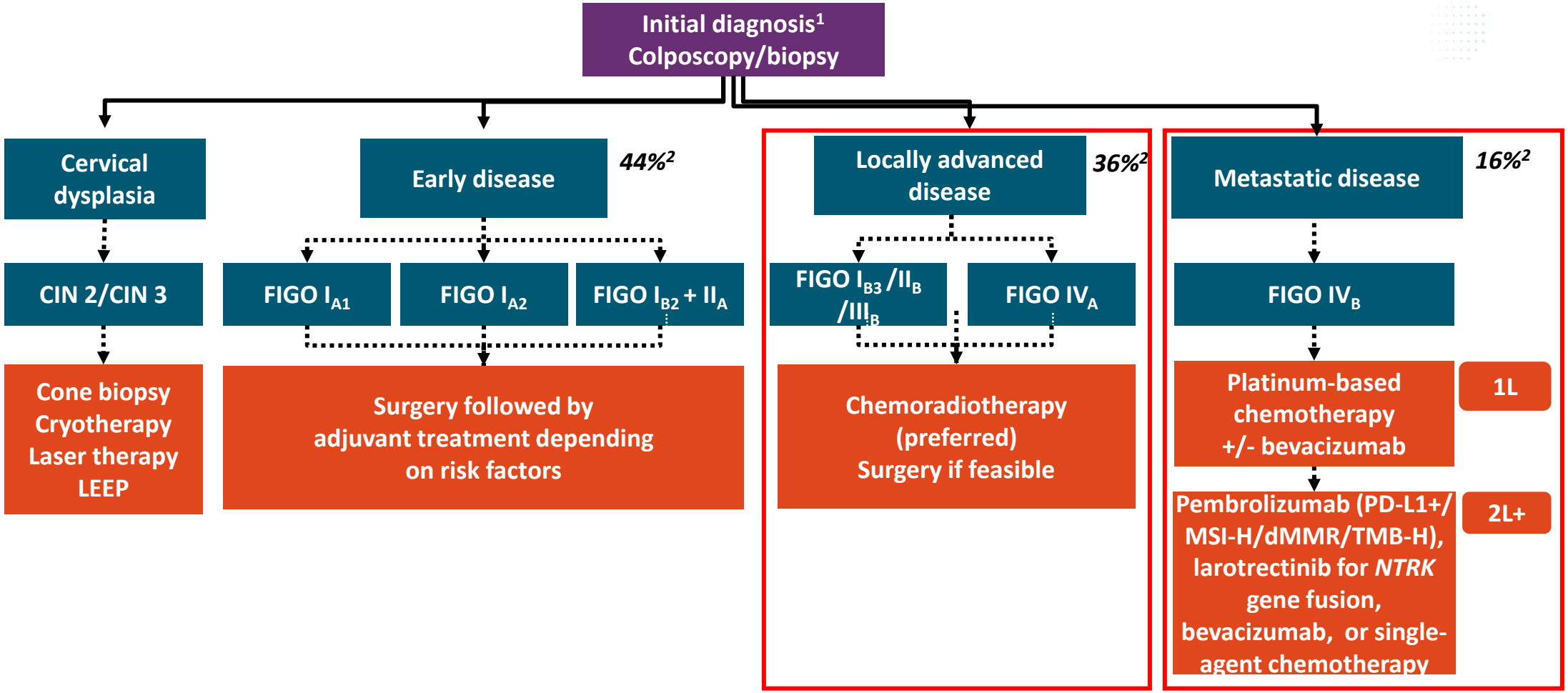
: good discrimination between the three groups in stage IB. Nodal status clearly impacts survival, with the risk of death nearly 1.5- and 2-fold greater for pelvic and PAo LN involvement, respectively.

This effect varies greatly based on local T stage, leading to survival heterogeneity in patients with stage III subgroups.

Grigsby PW, Massad LS, Mutch DG, et al. FIGO 2018 staging criteria for cervical cancer: impact on stage migration and survival. Gynecol Oncol. 2020;157(3):639–643.
Wright JD, Matsuo K, Huang Y, et al. Prognostic performance of the 2018 International federation of gynecology and obstetrics cervical cancer staging guidelines. Obstet Gynecol. 2019;134(1):49–57. Matsuo K, Machida H, Mandelbaum RS, et al. Validation of the 2018 FIGO cervical cancer staging system. Gynecol Oncol. 2019;152 (1):87–93.
McComas KN, Torgeson AM, Ager BJ, et al. The variable impact of positive lymph nodes in cervical cancer: implications of the new FIGO staging system. Gynecol Oncol. 2020;156(1):85–92.

Background

Cervical Cancer: Summary of Available Treatments



1. NCCN Cervical Cancer Guidelines v1.2021. 2. SEER Cancer Stat Facts: Cervical Cancer. National Cancer Institute. Bethesda, MD.

Background

Clinical Trials on Cervical Cancer

innovaTV 301: A Randomized, Open-Label, Phase 3 Trial

Randomized, double-blind phas

INTERLACE Trial

Key eligibility criteria

BEATcc trial design (NCT0

Open-label, multicentre, randomised, pl

- 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

Stratification factors:

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

[b]Paclitaxel 175 mg/m² da

CR = complete response; DoR

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MADRID 2023

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Key eligi

- Advance curative
- Second-
- HER2 ex
  - Local if loca cance
  - Cervic five IH
- Prior HE
- ECOG/W

*Patients were eligi excluding tumors ir ASCO, American S human epidermal g Q3W, every 3 weel

1. Hofmann M, et a

EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 Study Design* (NCT03257267)

Recurrent and metastatic cervical cancer resistant to platinum-based chemotherapy ≥2nd line ECOG PS ≤1

N=604: 477 SCC, 131 AC
Randomized 1:1
Stratified by:
- Histology (SCC/AC)
- Geographic region
- Prior bevacizumab (Y/N)
- ECOG PS (0 vs 1)

Cemiplimab 350 mg Q3W IV

IC chemotherapy

Options:
- Pemetrexed 500 mg/m² Q3W IV
- Gemcitabine 1000 mg/m² IV on Days 1 and 8 and every 21 days
- Topotecan 1 mg/m² daily IV for 5 days, every 21 days
- Irinotecan 100 mg/m2 IV weekly x 4, followed by 10–14 days rest
- Vinorelbine 30 mg/m2 IV on Days 1 and 8 and every 21 days

Treat up to 96 weeks with option for re-treatment

Tumour imaging conducted on Day 42 (±7 days) of cycles† 1–4, 6, 8, 10, 12, 14, and 16

Primary endpoint: OS

Secondary endpoints: PFS, ORR, Safety, QoL

Exploratory endpoints: PK, Immunogenicity, Biomarkers, PD

- Two interim analyses were prespecified per protocol
- At first interim analysis, IDMC recommended trial to continue
- At second interim analysis, IDMC recommended trial be stopped for efficacy; presented here

*Performed according to ENGOT Model C.[1] †To account for differences in drug administration schedules, one cycle is defined as 6 weeks.

AC, adenocarcinoma or adenosquamous carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, investigator's choice; IDMC, Independent Data Monitoring Committee; IV, intravenously; ORR, objective response rate; OS, overall survival; PD, pharmacodynamics; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; QoL, quality of life; SCC, squamous cell carcinoma.

1. Vergote I et al. *Int J Gynecol Cancer*. 2019;0:1–4.

IGCS | 2023 Annual Global Meeting

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NCCN Guidelines for Cervical Cancer

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NCCN Guidelines Version 1.2024
Cervical Cancer

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SYSTEMIC THERAPY FOR CERVICAL CANCER[a]

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

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Cervical Cancer

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SYSTEMIC THERAPY FOR CERVICAL CANCER[a,b,c]

Squamous Cell Carcinoma, Adenocarcinoma, or Adenosquamous Carcinoma		
Chemoradiation[d]	**Recurrent or Metastatic Disease**	
	First-Line Therapy[d,l]	**Second-Line or Subsequent Therapy[l,m]**
Preferred • Cisplatin + Pembrolizumab[e,f,k,1] ▸ Category 1: FIGO 2014 stage IIIA, IIIB, and IVA ▸ Category 2B: select FIGO 2018 stage III–IVA • Carboplatin + Pembrolizumab[e,f,k,1] if cisplatin intolerant ▸ Category 1: FIGO 2014 stage IIIA, IIIB, and IVA ▸ Category 2B: select FIGO 2018 stage III–IVA • Cisplatin • Carboplatin if cisplatin intolerant **Other Recommended** • If single-agent Cisplatin and Carboplatin are unavailable ▸ Capecitabine[g]/Mitomycin[2] ▸ Gemcitabine[3] ▸ Paclitaxel[4,5] • Induction chemotherapy (followed by chemoradiation) ▸ Carboplatin/Paclitaxel[h,6]	**Preferred** • PD-L1–positive tumors ▸ Cisplatin/Paclitaxel + Pembrolizumab ± Bevacizumab (category 1)[f,j,k,7] ▸ Carboplatin/Paclitaxel + Pembrolizumab ± Bevacizumab (category 1)[f,j,k,7] • Cisplatin/Paclitaxel + Bevacizumab[f,8] (category 1) • Carboplatin/Paclitaxel + Bevacizumab[f] • Cisplatin/Paclitaxel + Atezolizumab + Bevacizumab (category 1)[f,l,9] • Carboplatin/Paclitaxel + Atezolizumab + Bevacizumab (category 1)[f,l,9] **Other Recommended** • Cisplatin/Paclitaxel (category 1)[10,11] • Carboplatin/Paclitaxel[12,13] (category 1 for patients who have received prior Cisplatin therapy) • Paclitaxel/Topotecan + Bevacizumab[f,8,14] (category 1) • Paclitaxel/Topotecan[14] • Cisplatin/Topotecan[14] • Cisplatin[10] • Carboplatin[15,16]	**Preferred** • TMB-H tumors:[n] Pembrolizumab[k] • PD-L1–positive: Pembrolizumab[j,k] • MSI-H/dMMR tumors: Pembrolizumab[k,17] • Tisotumab vedotin-tftv (category 1)[18,19] **Other Recommended** • Bevacizumab • Paclitaxel[16,20] • Albumin-bound Paclitaxel • Docetaxel • Fluorouracil[g] • Gemcitabine • Pemetrexed • Topotecan • Vinorelbine • Irinotecan • Cemiplimab[21] • Ipilimumab + Nivolumab[22,23,24] **Useful in Certain Circumstances** • PD-L1–positive tumors ▸ Nivolumab[j,o,22] ▸ Pembrolizumab + Tisotumab vedotin-tftv[j,k,p,25] • HER2-positive tumors (IHC 3+ or 2+) ▸ Fam-trastuzumab deruxtecan-nxki[26] • HER2-mutant ▸ Neratinib[27] • *RET* gene fusion-positive tumors ▸ Selpercatinib • *NTRK* gene fusion-positive tumors ▸ Larotrectinib ▸ Entrectinib ▸ Repotrectinib[q,28]

Locally Advanced Cervical Cancer (LACC)

LACC

Definition : Summary FIGO staging &Treatment Option

Categorization	FIGO 2018 Stages	Description
Early-stage	IA, IB1, IB2	Invasive cervix-only disease < 5 mm deep and deeply invasive cervix-only disease smaller than 4 cm in the greatest dimensions
Locally advanced	IB3, II, III, IVA	Deeply invasive cervix-only disease larger than 4 cm, disease that invades beyond the uterus, into regional lymph nodes, and into adjacent organs
Metastatic	IVB	Cancer that extends beyond the pelvis into distant organs

Stage	Treatment Options
IB3	Chemoradiation
IIA1	Chemoradiation Surgical management
IIA2	Chemoradiation
IIB	Chemoradiation
III	Chemoradiation
IVA	Chemoradiation
IVB	Systemic therapy with or without radiation to metastatic sites for cancers with oligometastasis Systemic therapy using chemotherapy plus bevacizumab Systemic therapy using chemotherapy plus pembrolizumab with or without bevacizumab for PD-L1–expressing tumors Supportive care for all

Abbreviation: PD-L1, programmed death ligand-1.

JCO Oncology Practice,2022 (18):6

LACC

TREATMENT PHASES : CCRT –Carboplatin?

- No phase III randomized studies have compared carboplatin to cisplatin during CCRT.
- The use of carboplatin is supported by small phase I and II studies and pre-clinical evidence of synergism of this drug with RT
- A meta-analysis of 12 studies and 1698 patients suggested poorer complete response (OR 0.53) and a trend toward inferior survival (3-year OS = OR 0.70) with weekly carboplatin

Carboplatin (AUC 2) an alternative in patients unfit for cisplatin

Nam EJ, Lee M, Yim GW, et al. Comparison of carboplatin- and cisplatin-based concurrent chemoradiotherapy in locally advanced cervical cancer patients with morbidity risks. Oncologist. 2013;18 (7):843–849.
Xue R, Cai X, Xu H, et al. The efficacy of concurrent weekly carbo- platin with radiotherapy in the treatment of cervical cancer: a meta-analysis. Gynecol Oncol. 2018;150(3):412–419.

LACC

Randomized Trials in LACC

TRIAL	INTERVENTION	OUTCOME
GOG 109	Adjuvant RT vs CDDP-based RT	Superiority of Adjuvant ChemoRT
GOG 85	CDDP-based vs HU-based RT	Superiority of ChemoRT
GOG 120	CDDP-based vs HU-based RT	Superiority of ChemoRT
GOG 123	CDDP-based RT vs RT alone	Superiority of ChemoRT
RTOG 9001	CDDP+5FU-based RT vs RT alone	Superiority of ChemoRT
GOG 191	ChemoRT ± Erythropoietin	TERMINATED EARLY
GOG 219	ChemoRT ± Tirapazimine	TERMINATED EARLY
AIM2CERV	ChemoRT ± Axalimogene Filolisbac	TERMINATED EARLY
OUTBACK	ChemoRT ± consolidation ChemoRx	NEGATIVE (OS)
CALLA	ChemoRT ± anti-PD-L1 Durvalumab	NEGATIVE (PFS)
NRG-GY006	ChemoRT + Triapine	NEGATIVE (OS)
KEYNOTE-A18	ChemoRT ± anti-PD-1 Pembrolizmab	PFS significantly improved
INTERLACE	Induction ChemoRx followed by ChemoRT	OS & PFS significantly improved

RTOG 90-01: Morris M, et al. N Engl J Med 1999;340:1137-43.
GOG 120: Rose PG, et al. N Engl J Med 1999;340:1144-53.
GOG 123: Keys HM, et al. N Engl J Med 1999;340:1154-61.
GOG 85: Whitney CW, et al. J Clin Oncol 1999;17:1339-48.
GOG 109: Peters III WA, et al. J Clin Oncol 2000;18:1606-13.
OUTBACK: Mileshkin, LR, et al. Lancet Oncol 2023;24:468-82.
CALLA: Monk BJ, et al. IGCS 2022, LBA#1, NCT03830866.
NRG-GY006: Leath CA, et al. ASCO 2023, Abstract #5502, NCT02466971.
KEYNOTE-A18: Lorusso D, et al. ESMO 2023, LBA#38, NCT04221945.
INTERLACE: McCormack M, et al. ESMO 2023, LBA#8, NCT01566240.

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TREATMENT PHASES : CCRT followed by adjuvant Ctx

	LORVIDHAYA ET AL. [80]	DUENAS-GONZALEZ ET AL. [81,82]	TANG ET AL. [84]	TANGJITGAMOL ET AL. [85]
Years of enrollment	1988–1994	2002–2004	1998–2007	2015–2017
Number of patients	926	515	880	259
Stage (FIGO)	IIB to IVA	IIB to IVA	IIB to IVA	IIB to IVA
Other criteria	Stage IIB: only central tumor > 3 cm and/or half of the parametrium involved	Patients with positive PAo LN (1> cm) from imaging must be negative in biopsy	Patients with positive PAo LN from imaging received extended-field RT	Patients with PAo enlargement from imaging are excluded
Histology	SCC-ADC	SCC-ADC-ADSC and poorly differentiated	ADC-ADSC	SCC-ADC-ADSC
CCRT phase	mitomycine C + oral 5-FU	CCRT arm = cisplatin ACT arm = cisplatin + gemcitabine	cisplatin	cisplatin
ACT phase	oral 5-FU (3 cycles)	cisplatin + gemcitabine (2 cycles)	cisplatin + paclitaxel (2 cycles) + 1 cycle before CCRT	carboplatin + paclitaxel (3 cycles)
Median follow-up	89 months	46.9 months	60 months	27.4 months
Survival outcomes	DFS at 5 years = better only in CCRT arm OS = NS	PFS and OS = in favor of ACT arm	DFS = in favor of ACT arm	3-year PFS = NS 3-year OS = NS
Local relapse	Significantly higher in non-CCRT arms	NS	in favor of ACT arm	NS
Distant relapse	NS	lower in ACT arm	in favor of ACT arm	lower in ACT arm
Toxicity	increased in CCRT arm	grade 3–4 more frequent in ACT arm	leukopenia and thrombocytopenia significantly higher in ACT arm	grade 3–4 neutropenia higher in ACT arm

ACT = adjuvant chemotherapy; ADSC = adenosquamous carcinoma; ADC = adenocarcinoma; CCRT = concomitant chemoradiotherapy; DFS = disease-free survival; FIGO = International Federation of Gynecology and Obstetrics; 5-FU = 5-fluoro-uracil; LN = lymph node; NACT = neo-adjuvant chemotherapy; NS = not significant; OS = overall survival; PAo = para-aortic; PFS = progression-free survival; RT = radiotherapy; SCC = squamous cell carcinoma

Dueñas-González A, Zarbá JJ, Patel F, et al. Phase III, open-label, randomized study comparing concurrent gemcitabine plus cispla- tin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix. J Clin Oncol. 2011;29(13):1678–1685. Dueñas-González A, Orlando M, Zhou Y, et al. Efficacy in high burden locally advanced cervical cancer with concurrent gemcita- bine and cisplatin chemoradiotherapy plus adjuvant gemcitabine and cisplatin: prognostic and predictive factors and the impact of disease stage on outcomes from a prospective randomized phase III trial. Gynecol Oncol. 2012;126(3):334–340.
Tangjitgamol S, Katanyoo K, Laopaiboon M, et al. Adjuvant che- motherapy after concurrent chemoradiation for locally advanced cervical cancer. Cochrane Database Syst Rev. 2014 Dec 3;2014(12): CD010401.
Tang J, Tang Y, Yang J, et al. Chemoradiation and adjuvant che- motherapy in advanced cervical adenocarcinoma. Gynecol Oncol. 2012;125(2):297–302.
Tangjitgamol S, Tharavichitkul E, Tovanabutra C, et al. A randomized controlled trial comparing concurrent chemoradia- tion versus concurrent chemoradiation followed by adjuvant che- motherapy in locally advanced cervical cancer patients: ACTLACC trial. J Gynecol Oncol. 2019;30(4):e82.

LACC TREATMENT PHASES : CCRT followed by adjuvant Chemotherapy

OUTBACK: International, randomized phase III trial (median follow-up: 5 yr): compared efficacy and safety of standard cisplatin-based CRT followed by adjuvant carboplatin/paclitaxel vs CRT alone in women with LACC

Stratified by pelvic or common iliac node involvement; requirement for extended-field RT; FIGO 2008 stage (IB/IIA vs IIB vs IIIB/IVA); age (< vs ≥60 yrs); hospital/site

Patients with cervical cancer suitable for CRT with curative intent; FIGO 2008 stage IB1 + LN, IB2, II-IVA; squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma; no nodal disease > L3/L4; ECOG PS 0-2 (N = 926)

Concurrent CRT*
(n = 461; n = 456 in survival analyses)

Concurrent CRT*
(n = 465; n = 463 in survival analyses).

Adjuvant CT (ACT)

Carboplatin AUC 5 + **Paclitaxel** 155 mg/m² Q3W x 4 cycles
(n = 361)

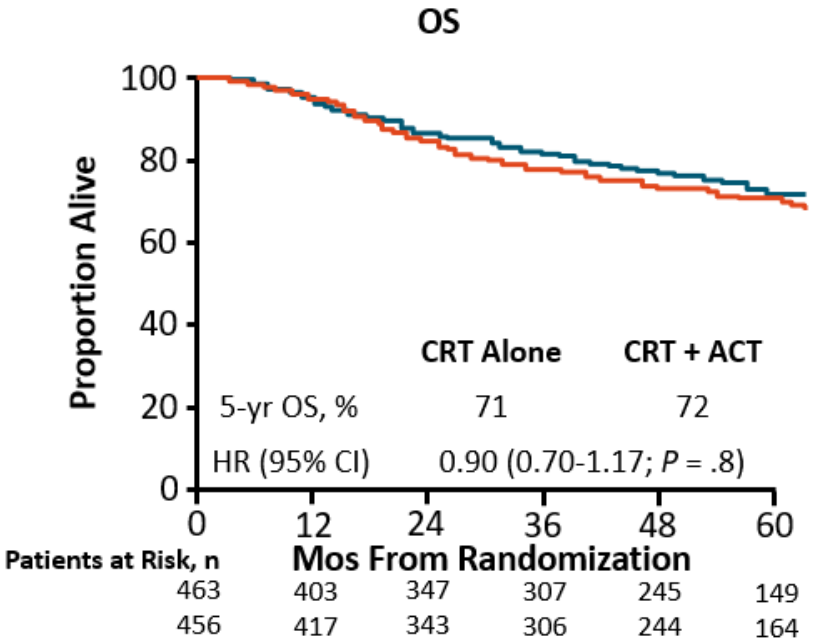
***40-45 Gy of external beam XRT in 20-25 fractions including nodal boost + brachytherapy with cisplatin 40 mg/m² weekly during XRT.**

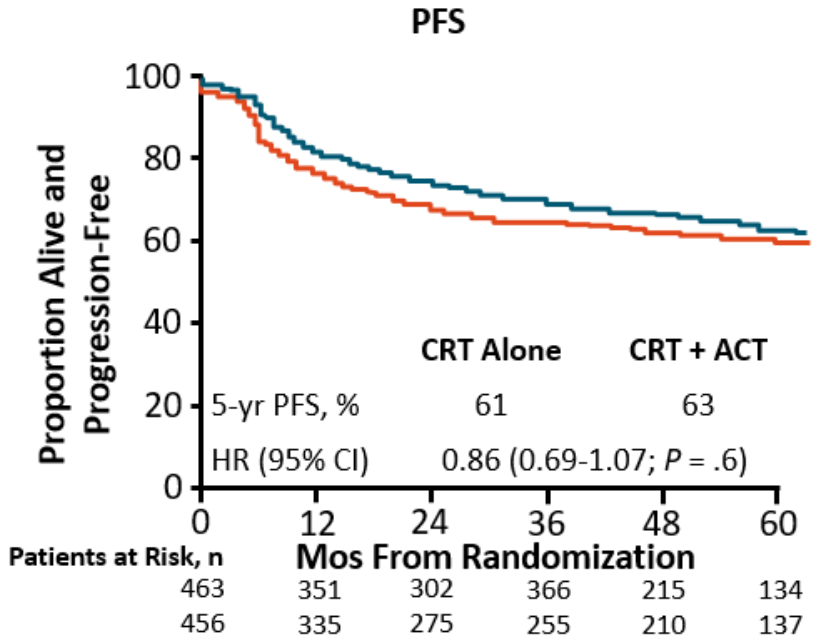
- **Primary endpoint: OS**
  - **Study protocol amended in 2016 to increase sample size from N = 780 to 900 due to nonadherence with adjuvant CT and lower event rate than anticipated (80% power and 2-sided α = 0.05 to detect 8% absolute improvement in OS at 5 yr [72% to 80%])**
- **Secondary endpoints: PFS, patterns of disease recurrence, radiation protocol compliance, PROs, safety**

Mileshkin. ASCO 2021. Abstr LBA3. NCT01414608.

LACC TREATMENT PHASES : CCRT followed by adjuvant Chemotherapy

OUTBACK: International, randomized phase III trial (median follow-up: 5 yr): compared efficacy and safety of standard cisplatin-based CRT followed by adjuvant carboplatin/paclitaxel vs CRT alone in women with LACC





- No significant improvement in 5-yr rates for OS or PFS with CRT + ACT vs CRT alone
- Sensitivity analyses found no significant differences in OS or PFS in CRT + ACT arm for those who did vs did not complete CRT
- Treatment effects consistent across subgroups except for those aged < vs ≥60 yr, where younger patients had greater OS and PFS benefit with CRT + ACT (interaction *P* = .01 and .03, respectively)

LACC

TREATMENT PHASES : Induction Chemotherapy followed by CCRT

INTERLACE: A randomized phase III trial of induction chemotherapy followed by chemoradiation compared with chemoradiation alone in locally advanced cervical cancer. (SGO 2024: Lederman et al.)

INTERLACE Trial Design

Key eligibility criteria

- Newly diagnosed histologically confirmed FIGO (2008) stages IB1 node+,IB2, II, IIIB, IVA squamous, adeno, adenosquamous cervical cancer
- No nodes above aortic bifurcation on imaging
- Adequate renal, liver & bone marrow function
- Fit for chemotherapy & radical RT
- No prior pelvic RT

RT = Radiotherapy
3D-Conformal = 3D conformal radiotherapy
IMRT = Intensity modulated radiotherapy
EBRT = External beam radiotherapy
BT = Brachytherapy
IGABT = Image-guided adaptive brachytherapy
RT QA = Radiotherapy quality assurance

Randomised (n=500)

Induction chemotherapy (n=250)
Carboplatin (AUC2) & paclitaxel (80mg/m²) given weekly for **6 weeks**

Week 7

Standard CRT (n=250)
Chemotherapy: cisplatin (40mg/m²) weekly for 5 weeks
Radiotherapy: EBRT (40-50.4Gy in 20-28 fractions) & BT to give a *minimum* total EQD2 dose of 78Gy to point A, 3D IGABT recommended
Overall treatment time ≤50days
All centres underwent RT QA

Follow-up
3-monthly for 2 years then 6-monthly for 5 years

Stratified by

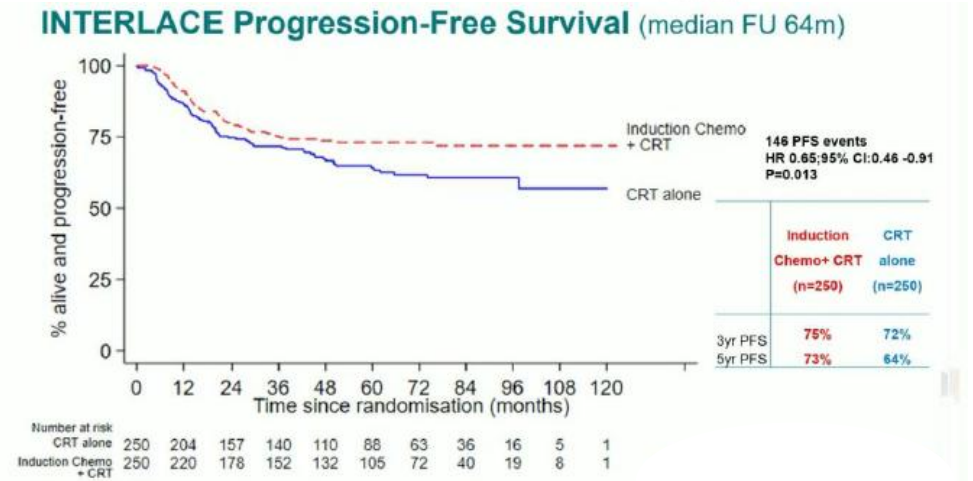
- Site
- Stage
- Nodal status
- 3D-Conformal v IMRT EBRT
- 2D v 3D BT
- Tumour size
- SCC v other

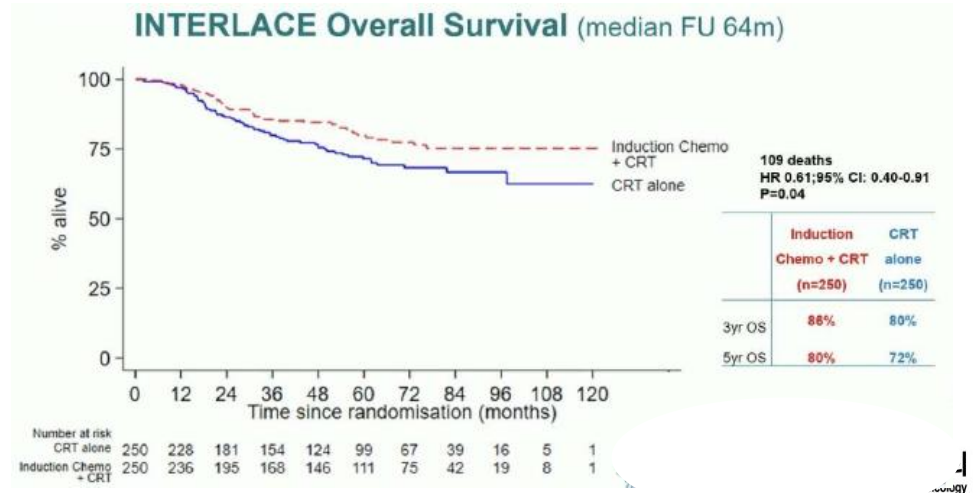
Primary endpoints

- PFS
- OS

Secondary endpoints

- Adverse events
- Pattern of relapse
- QOL
- Time to subsequent treatment





McCormack M et al. Lancet. 2024.

2025.02.20 건강보험심사평가원이 승인한 허가초과 항암요법

LACC

TREATMENT PHASES : Induction Chemotherapy followed by CCRT

INTERLACE: A randomized phase III trial of induction chemotherapy followed by chemoradiation compared with chemoradiation alone in locally advanced cervical cancer. (SGO 2024: Lederman et al.)

- Induction chemotherapy with weekly paclitaxel and carboplatin within 7 days of chemoradiotherapy (CRT) for locally advanced cervical cancer (LACC) vs standard CRT.
- Newly diagnosed FIGO 2008 stage IBI node+, IB2, II, IIIB, IVA squamous, adeno, adenosquamous carcinoma.
- No nodes above aortic bifurcation on imaging.
- Timing is strict– induction chemo x 6 weeks, then 1 week to CRT, completed in ≦50 days.
- Enrolled 500 patients (UK, Mexico, Italy, India, Brazil), 70% were stage IIB, most (95%). completed treatment within 56 days.
- Adverse events in induction arm: more neutropenia (19 v 5%) and fatigue (11 v 6%).
- Distant relapse in induction arm 12% vs. 20%.
- Induction arm:
  - PFS improved 9% (HR 0.65, 95% CI 0.46, 0.91), p=0.013
  - OS improved 8% (HR 0.61, 95% CI 0.40, 0.91), p=0.04
- Induction chemotherapy should be considered standard in LACC and is feasible across diverse healthcare settings

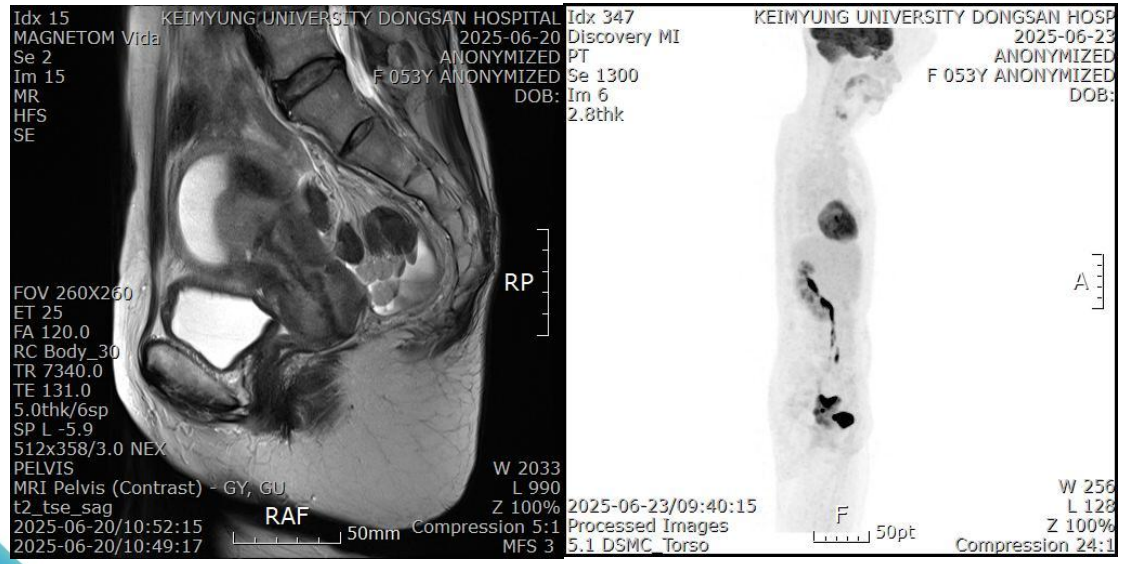
LACC

TREATMENT PHASES : Induction Chemotherapy followed by CCRT

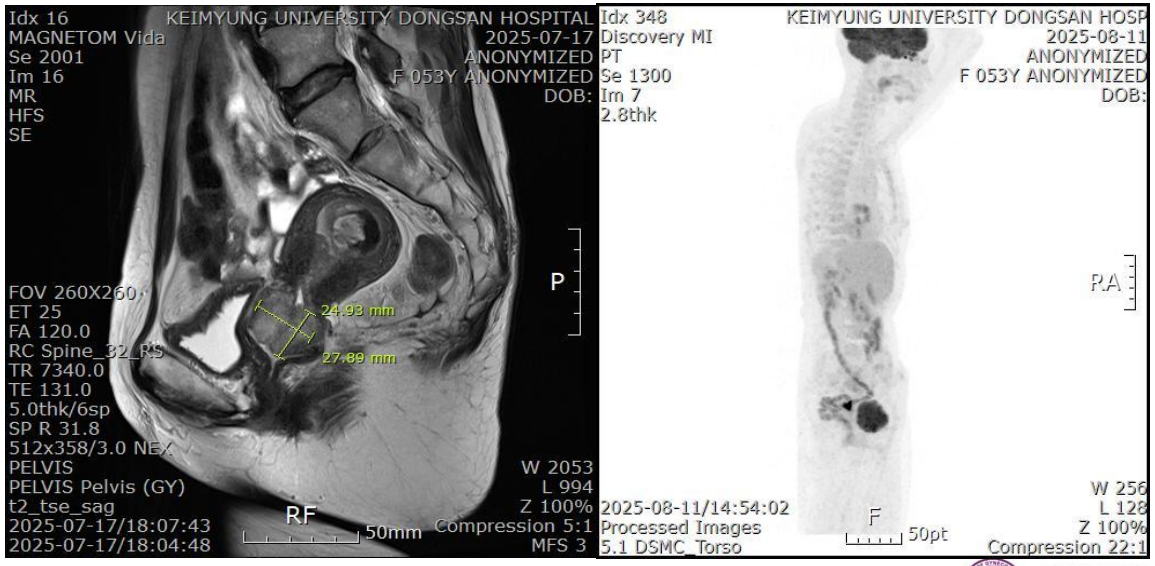
INTERLACE: A randomized phase III trial of induction chemotherapy followed by chemoradiation compared with chemoradiation alone in locally advanced cervical cancer. (SGO 2024: Lederman et al.)

Ca of Cx IIa2(carcinosarcoma)

s/p CTx(#1-6) c Neotax + carbo:2025.6.26-8.4
s/p CCRT(#1-4) c CDDP & ICR 2025.8.12-12.19(3차부터 80%, 5차부터 general weakness로 refuse)



pretreatment



induction CTx후

LACC TREATMENT PHASES : CCRT c Immunotherapy

Keynote A18 : Pembrolizumab plus chemoradiotherapy for High-Risk Locally Advanced Cervical Cancer, Randomized, Double-Blind, Phase 3 ENGOT-cx11/GOG-3047/KEYNOTE-A18 Study

D Lorusso KNA18 ESMO 2023

MADRID 2023 ESMO congress

Pembrolizumab Plus Chemoradiotherapy for High-Risk Locally Advanced Cervical Cancer: The Randomized, Double-Blind, Phase 3 ENGOT-cx11/GOG-3047/KEYNOTE-A18 Study

Domenica Lorusso,[1] Yang Xiang,[2] Kosei Hasegawa,[3] Giovanni Scambia,[4] Manuel Leiva,[5] Pier Ramos-Elias,[6] Alejandro Acevedo,[7] Julia Vizkeleti,[8] Andrea Gomes,[9] Fernando Contreras Mejia,[10] Ari Reiss,[11] Ali Ayhan,[12] Jung-Yun Lee,[13] Valeriya Saevets,[14] Flora Zagouri,[15] Kan Li,[16] Karin Yamada,[16] Sarper Toker,[16] Sandro Pignata,[17*] Linda R. Duska[18*] on behalf of the ENGOT-cx11/GOG-3047/KEYNOTE-A18 investigators

[1]Gynaecology Oncology Unit, Fondazione Policlinico Universitario A Gemelli IRCCS and Catholic University of Sacred Heart, Rome, Italy; [2]Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, National Clinical Research Center for Obstetric & Gynecologic Diseases, Beijing, China; [3]Saitama Medical University International Medical Center, Hidaka, Saitama, Japan; [4]Scientific Directorate, Fondazione Policlinico Universitario Agostino Gemelli IRCCS and Catholic University of the Sacred Heart, Rome, Italy; [5]Instituto de Oncologia y Radioterapia Clinica Ricardo Palma, Lima, Peru; [6]Integra Cancer Institute, Edificio Integra Medical Center, Guatemala City, Guatemala; [7]Oncocentro, Valparaiso, Chile; [8]National Institute of Oncology, Centre of Radiotherapy, Budapest, Hungary; [9]Liga Norte Riograndense Contra o Cancer Rio Grande do Norte, Brazil; [10]Instituto Nacional de Cancerologia, Bogota, Colombia; [11]Rambam Medical Center, Gyneco-oncology Unit, Haifa, Israel; [12]Turkish Society of Gynecologic Oncology (TRSGO), Başkent University, Ankara, Turkiye; [13]Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; [14]Chelyabinsk Regional Clinical Center Oncology and Nuclear Medicine, Chelyabinsk, Russia; [15]Alexandra Hospital, Athens, Greece; [16]Merck & Co., Inc., Rahway, NJ, USA; [17]Department of Urology and Gynecology, Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, Napoli, Italy; [18]University of Virginia School of Medicine, Charlottesville, VA, USA

*Drs. Pignata and Duska contributed equally to this presentation.

BARCELONA 2024 ESMO congress

Pembrolizumab Plus Chemoradiotherapy for High-Risk Locally Advanced Cervical Cancer: Overall Survival Results from the Randomized, Double-Blind, Phase 3 ENGOT-cx11/GOG-3047/KEYNOTE-A18 Study

Domenica Lorusso,[1] Yang Xiang,[2] Kosei Hasegawa,[3] Giovanni Scambia,[4] Manuel Leiva,[5] Pier Ramos-Elias,[6] Alejandro Acevedo,[7] Marketa Bednarikova,[8] Andrea Gomes,[9] Fernando Contreras Mejía,[10] Ari Reiss,[11] Flora Zagouri,[12] Jung-Yun Lee,[13] Valeriya Saevets,[14] Peng Liu,[15] Karin Yamada,[15] Martina Puglisi,[15] Sandro Pignata,[16*] Linda R. Duska,[17*] on behalf of the ENGOT-cx11/GOG-3047/KEYNOTE-A18 investigators

[1]Gynaecology Oncology Unit, Fondazione Policlinico Universitario A Gemelli IRCCS, Rome and Humanitas San Pio X, Milan, Italy; [2]Department of Obstetrics and Gynecology, National Clinical Research Center for Obstetric & Gynecologic Diseases, Peking Union Medical College Hospital, Beijing, China; [3]Saitama Medical University International Medical Center, Hidaka, Saitama, Japan; [4]Scientific Directorate, Fondazione Policlinico Universitario Agostino Gemelli IRCCS and Catholic University of the Sacred Heart, Rome, Italy; [5]Instituto Peruano de Oncología y Radioterapia, Lima, Perú; [6]Integra Cancer Institute, Edificio Integra Medical Center, Guatemala City, Guatemala; [7]Oncocentro, Viña Del Mar, Chile; [8]University Hospital Brno and Faculty of Medicine, Masaryk University, Brno, Czech Republic; [9]Liga Norte Riograndense Contra o Cancer, Natal, Rio Grande do Norte, Brazil; [10]Instituto Nacional de Cancerologia, Bogota, Colombia; [11]Rambam Medical Center, Gyneco-oncology Unit, Haifa, Israel; [12]Alexandra General Hospital, Athens, Greece; [13]Yonsei Cancer Center and Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; [14]Chelyabinsk Regional Clinical Center Oncology and Nuclear Medicine, Chelyabinsk, Russia; [15]Merck & Co., Inc., Rahway, NJ, USA; [16]Department of Urology and Gynecology, Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, Napoli, Italy; [17]University of Virginia School of Medicine, Charlottesville, VA, USA.

*Drs. Pignata and Duska contributed equally to this presentation.

LACC TREATMENT PHASES : CCRT c Immunotherapy

Keynote A18 : Pembrolizumab plus chemoradiotherapy for High-Risk Locally Advanced Cervical Cancer, Randomized, Double-Blind, Phase 3 ENGOT-cx11/GOG-3047/KEYNOTE-A18 Study(SGO2024, Duska et al.)

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 v1.1 measurable or non-measurable disease
- Treatment naïve

Stratification Factors

- Planned EBRT type (IMRT or VMAT vs non-IMRT or non-VMAT)
- Stage at screening (stage IB2-IIB vs III-IVA)
- Planned total radiotherapy dose (<70 Gy vs ≥70 Gy [EQD2])[a]

R
1:1
N=1060

- Cisplatin 40 mg/m^2 QW for 5 cycles[b] + 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[b] + EBRT followed by brachytherapy + Placebo Q3W for 5 cycles
- Placebo Q6W for 15 cycles

End Points[c]

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

Median (range) follow-up time from randomization to data cutoff date (Jan 9, 2023) was 17.9 (0.9-31.0) mo

LACC TREATMENT PHASES : CCRT c Immunotherapy

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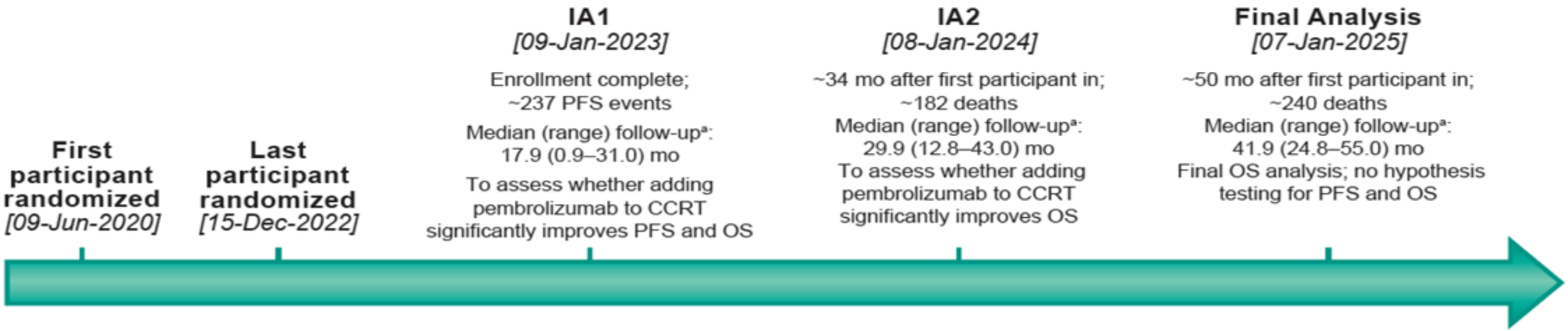

Endpoints

- Primary: PFS (per RECIST version 1.1) by investigator or histopathologic confirmation and OS
- Secondary: 24-mo PFS, 36-mo OS, ORR, patient-reported HRQoL, and safety

Multiplicity

PFS
Initial 1-sided
$\alpha = 0.025$

↓

OS
Initial 1-sided
$\alpha = 0$

Prespecified analysis plan allows alpha from successful hypothesis to be passed to the other hypothesis
Because PFS was significant at IA1 and OS was significant at IA2, the final analysis is descriptive only and no hypothesis testing was performed

HRQoL, health-related quality of life.
[a]Defined as the time from randomization to the data cutoff date.

LACC TREATMENT PHASES : CCRT c Immunotherapy

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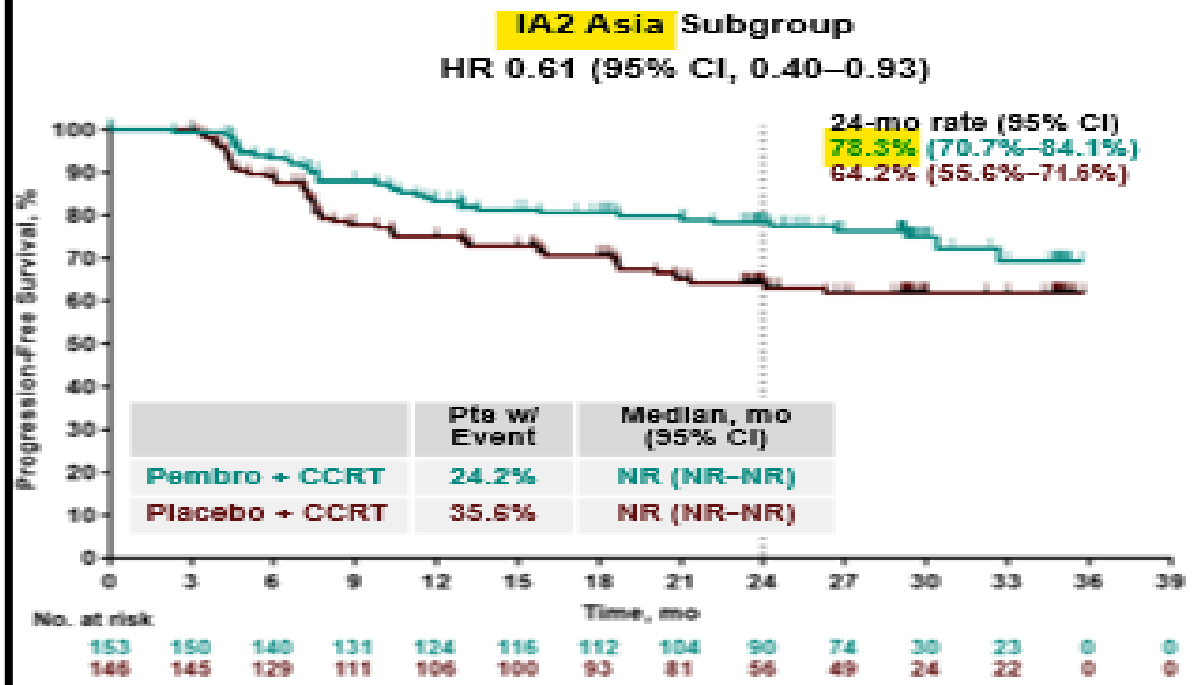
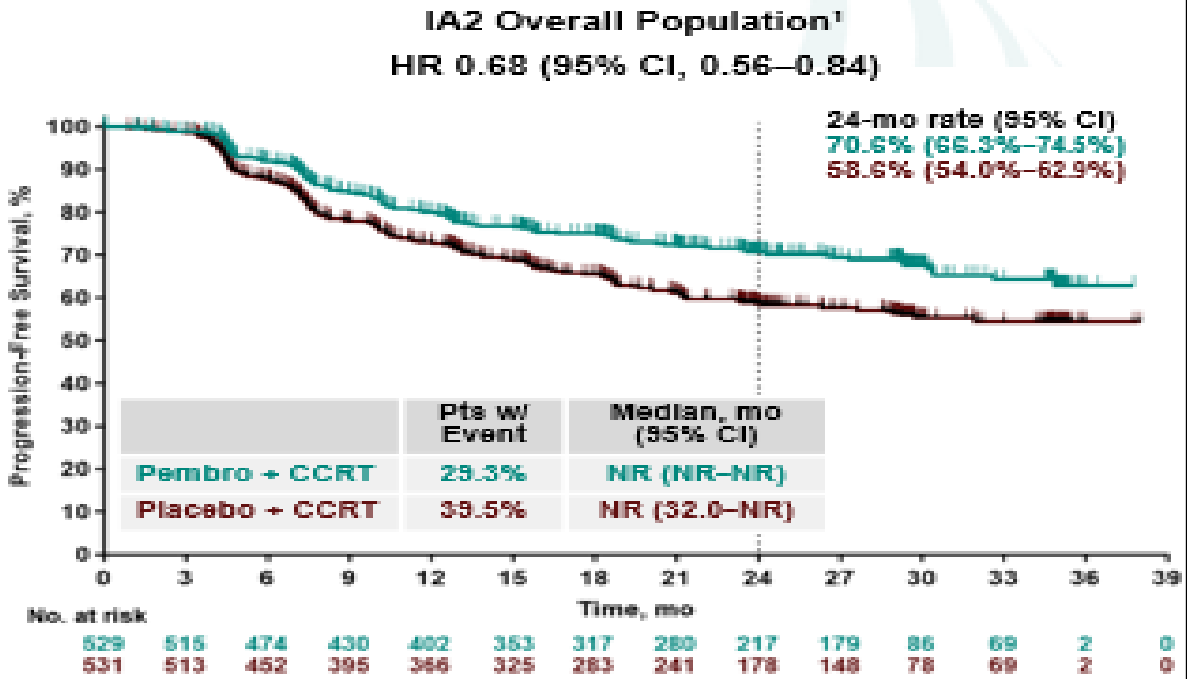
Primary Endpoint: Progression-Free Survival[a]





[a]Response assessed per RECIST v1.1 by investigator review or histopathologic confirmation. [b]Evaluated in all randomized participants. 1. Lorusso D et al. Presented at ESMO 2024. Data cutoff date: January 3, 2024.

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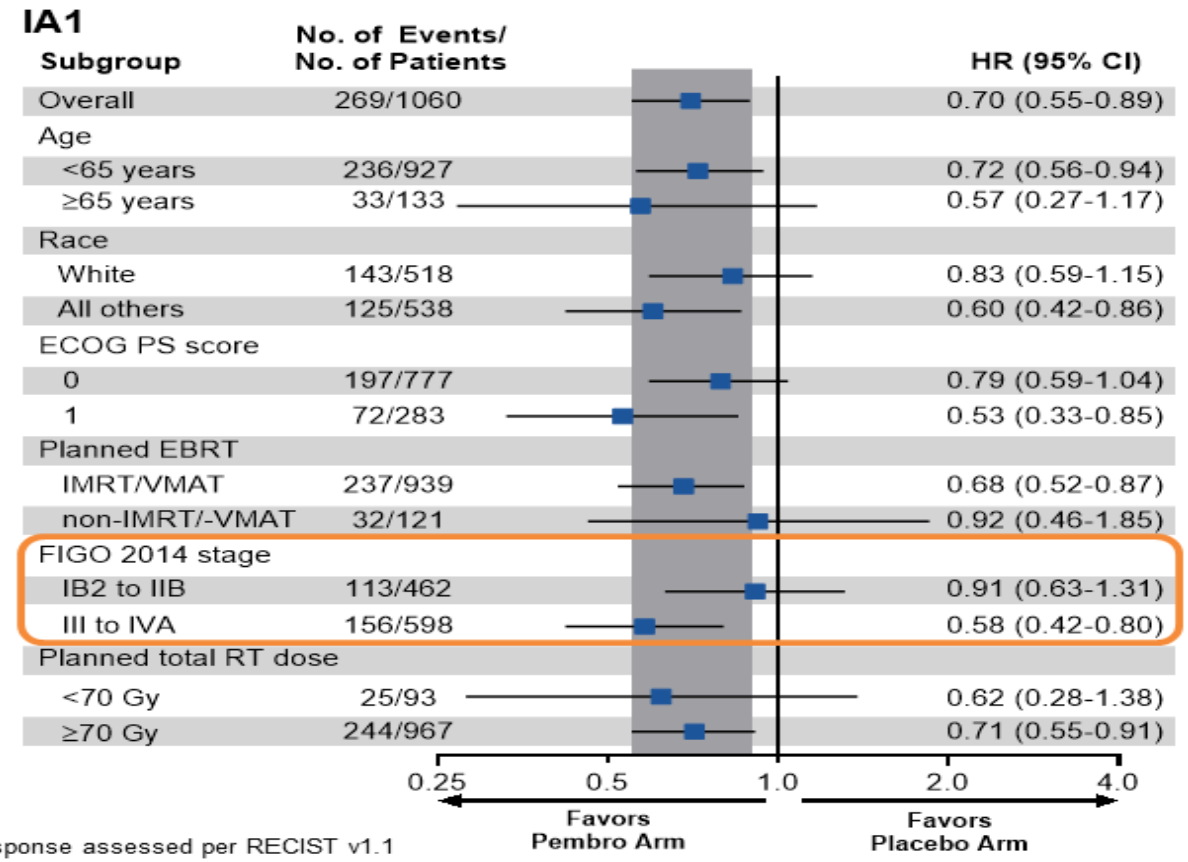
TREATMENT PHASES : CCRT c Immunotherapy

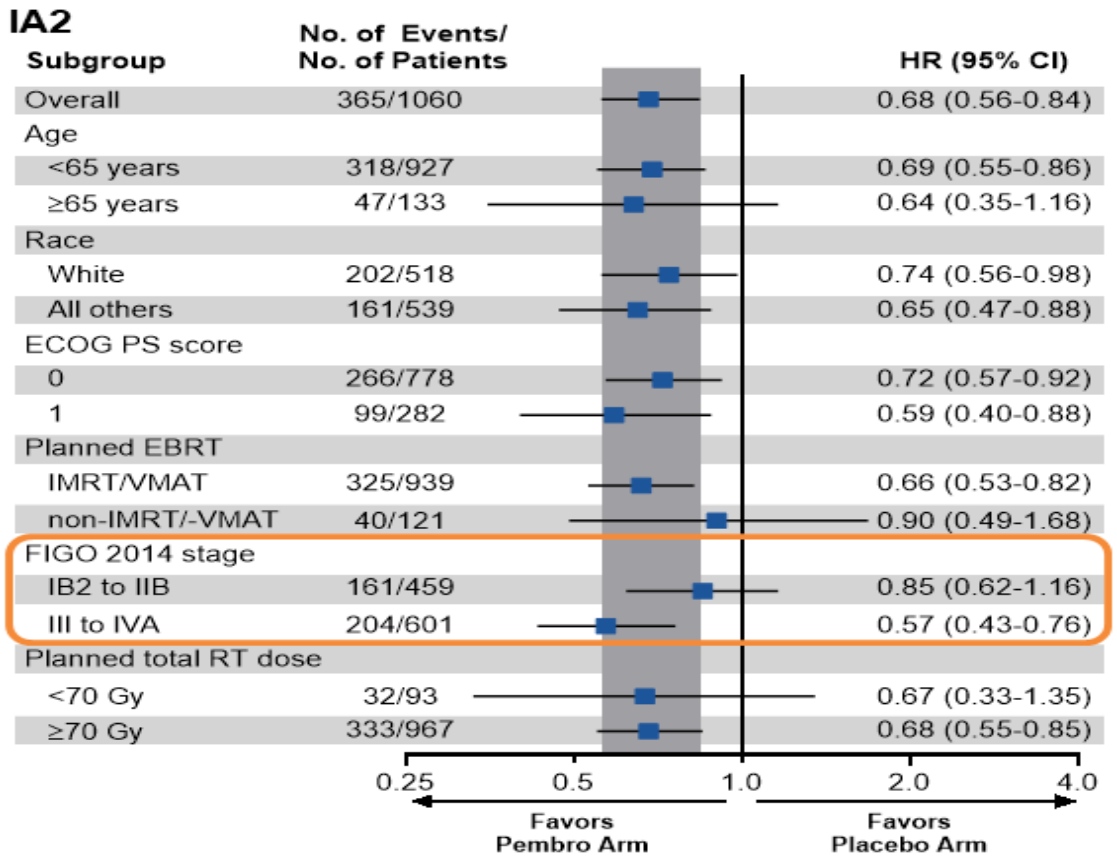
Keynote A18 : Pembrolizumab plus chemoradiotherapy for High-Risk Locally Advanced Cervical Cancer, Randomized, Double-Blind, Phase 3 ENGOT-cx11/GOG-3047/KEYNOTE-A18 Study(SGO2024, Duska et al.)

Updated Progression-Free Survival in Protocol-Specified Subgroups



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

Data cutoff date: January 9, 2023.



Data cutoff date: January 8, 2024.

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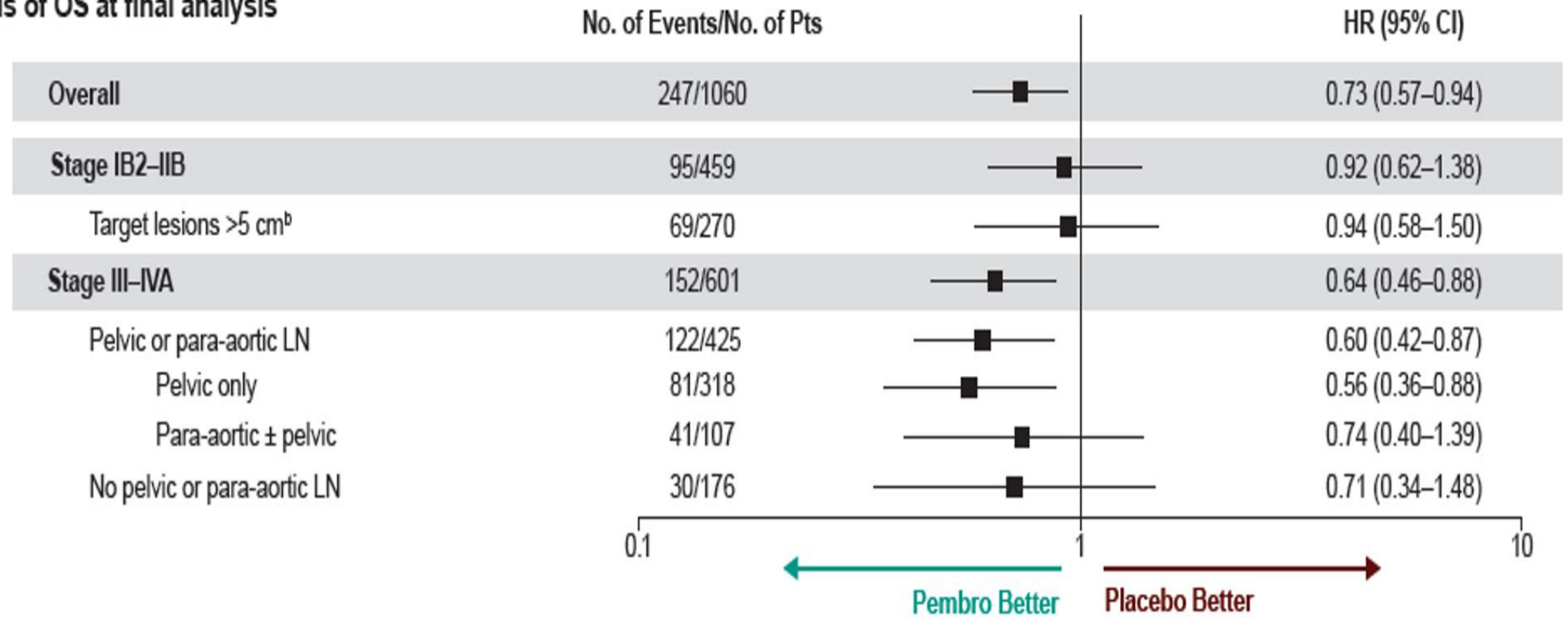
Keynote A18 : Pembrolizumab plus chemoradiotherapy for High-Risk Locally Advanced Cervical Cancer, Randomized, Double-Blind, Phase 3 ENGOT-cx11/GOG-3047/KEYNOTE-A18 Study

B. Post hoc subgroup analysis of OS at final analysis



ESMO2025

LACC TREATMENT PHASES : CCRT c Immunotherapy

Keynote A18 : Pembrolizumab plus chemoradiotherapy for High-Risk Locally Advanced Cervical Cancer, Randomized, Double-Blind, Phase 3 ENGOT-cx11/GOG-3047/KEYNOTE-A18 Study

Summary of AEs at Final Analysis

ESMO2025

	Pembro arm (n = 528)	Placebo arm (n = 530)
All-cause AEs	**528 (100.0)**	**526 (99.2)**
Grade ≥3	418 (79.2)	373 (70.4)
Serious	175 (33.1)	153 (28.9)
Led to death	6 (1.1)	7 (1.3)
Led to discontinuation		
Any treatment	112 (21.2)	79 (14.9)
All treatment	1 (0.2)	2 (0.4)
Treatment-related AEs[a]	**512 (97.0)**	**513 (96.8)**
Grade ≥3	367 (69.5)	326 (61.5)
Serious	104 (19.7)	72 (13.6)
Led to death	2 (0.4)[b]	2 (0.4)[c]
Led to discontinuation		
Any treatment	100 (18.9)	69 (13.0)
All treatment	0	1 (0.2)
Immune-mediated AEs[d]	**210 (39.8)**	**93 (17.5)**
Grade ≥3	27 (5.1)	7 (1.3)
Serious	21 (4.0)	6 (1.1)
Led to death	1 (0.2)[e]	0
Led to discontinuation		
Any treatment	16 (3.0)	4 (0.8)
All treatment	0	0

Data are n (%).
[a]Per investigator assessment.
[b]Immune-mediated gastritis and large intestine perforation.
[c]Bone marrow failure and neutropenic colitis.
[d]Events were based on a list of preferred terms intended to capture the known risks of pembrolizumab and considered regardless of attribution to treatment by the investigator.
[e]Immune-mediated gastritis.

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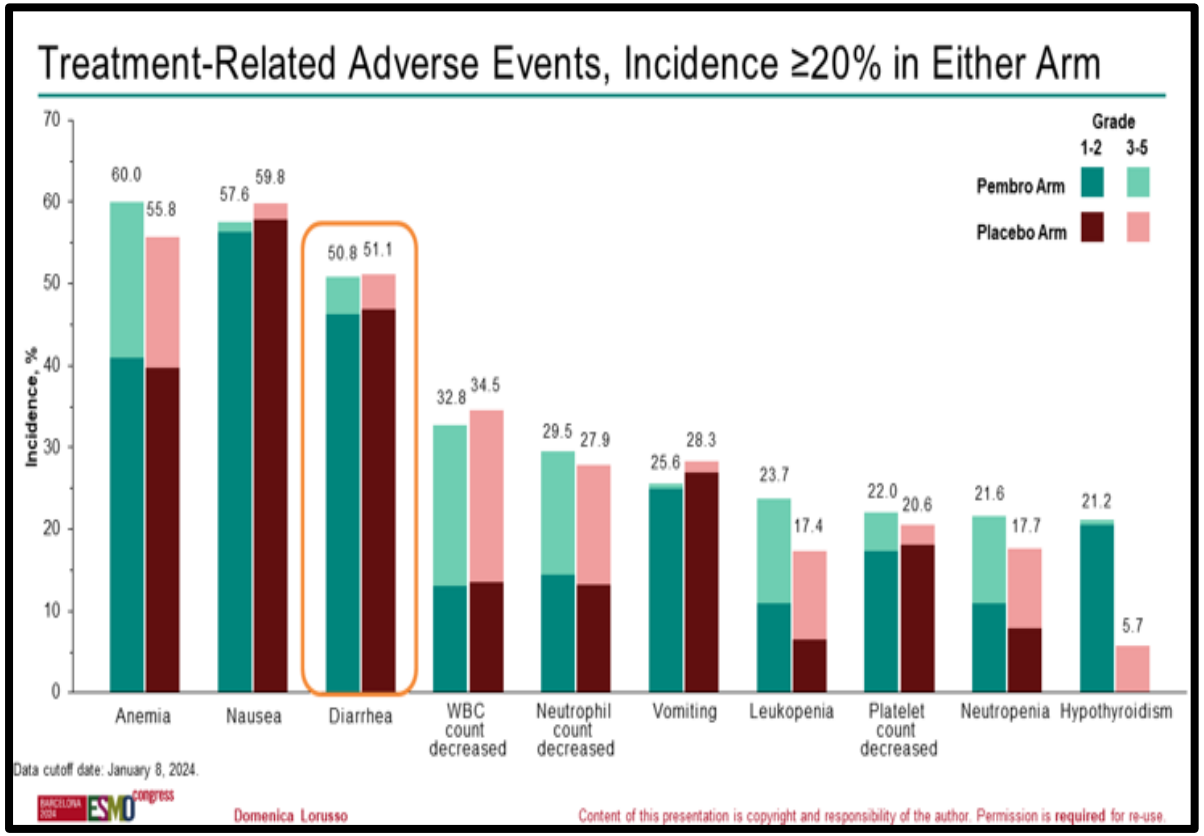

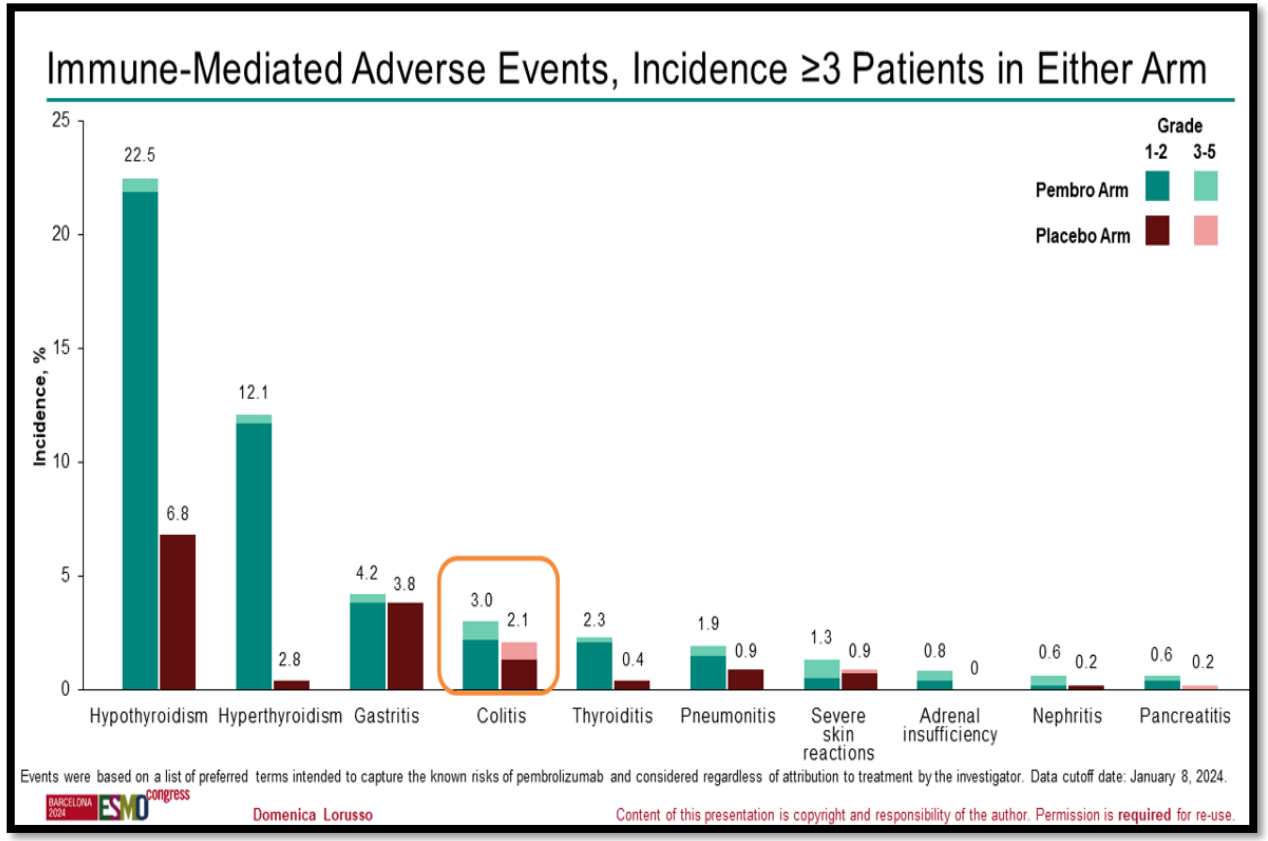

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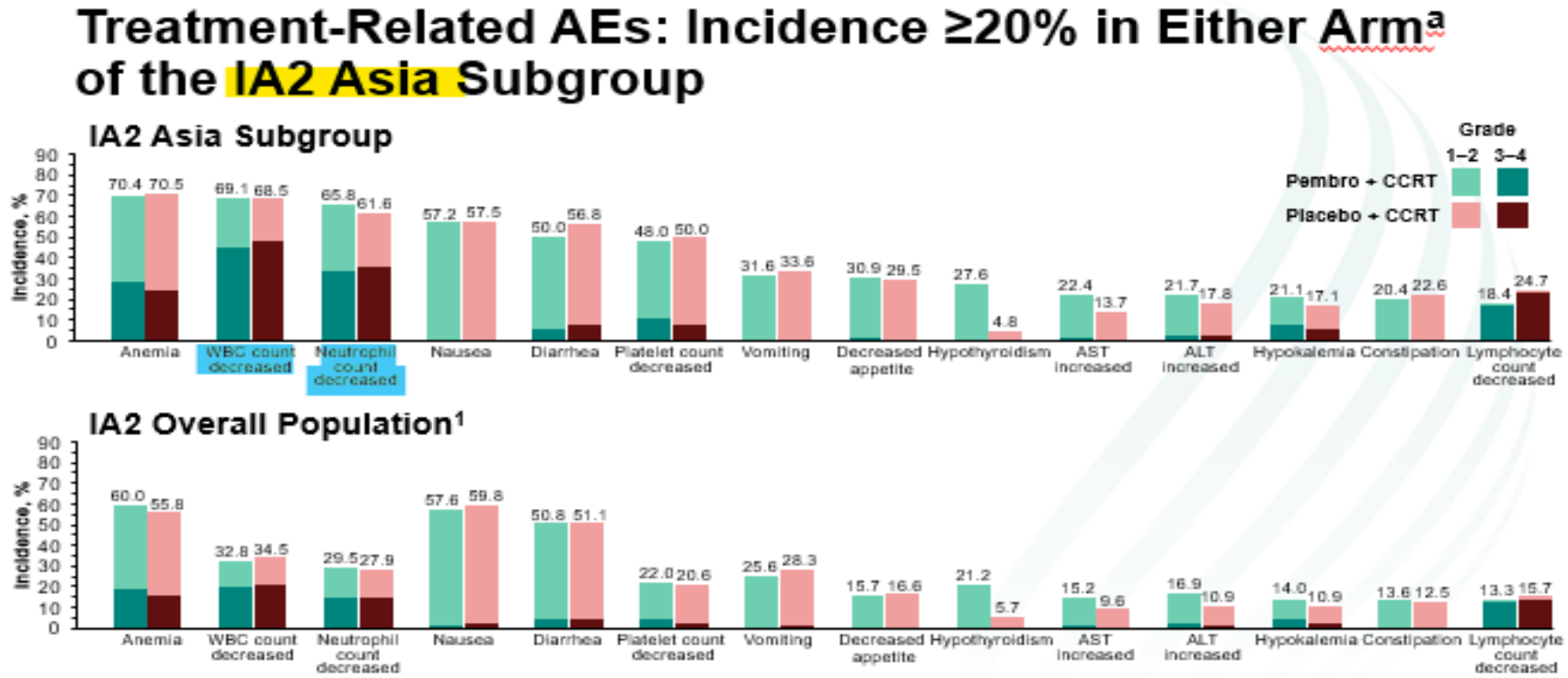
TREATMENT PHASES : CCRT c Immunotherapy

Keynote A18 : Pembrolizumab plus chemoradiotherapy for High-Risk Locally Advanced Cervical Cancer, Randomized, Double-Blind, Phase 3 ENGOT-cx11/GOG-3047/KEYNOTE-A18 Study(SGO2024, Duska et al.)



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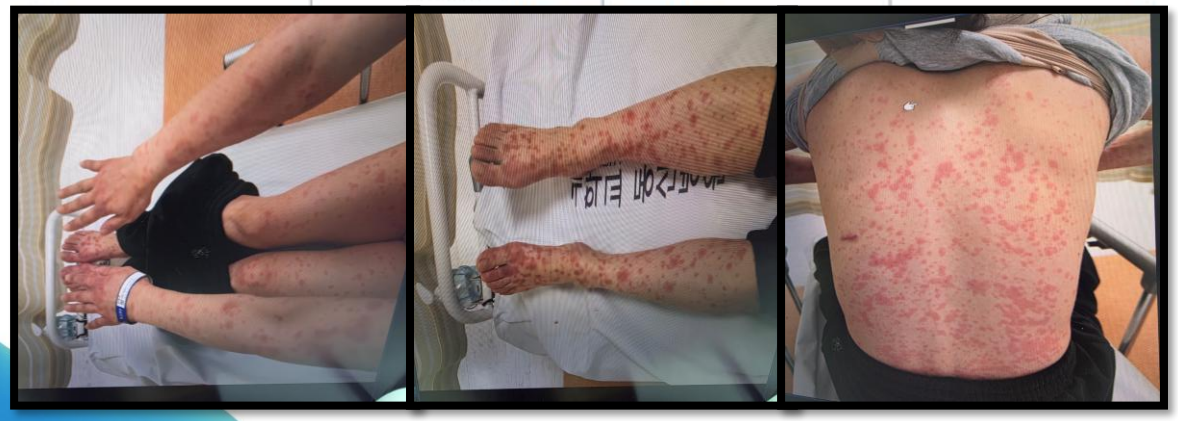
TREATMENT PHASES : CCRT c Immunotherapy

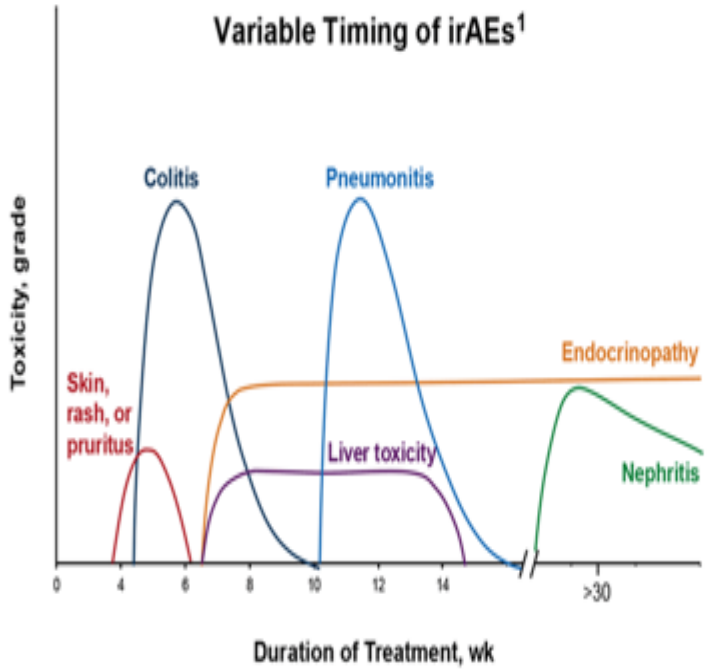
Keynote A18

irAEs From Immune Checkpoint Inhibitors Can Affect Any Organ System[1]

Dermatologic	Gastrointestinal	Endocrine	Pulmonary
Rash, pruritus	Diarrhea, nausea, vomiting	Hypothyroidism	Pneumonitis



Immune-Related Adverse Events Can Occur at Any Time



Patient Communication Is Essential

- Discuss potential onset, duration, and symptoms of irAEs
- Patients may be more likely to adhere to treatment when they have a full picture of irAEs

Martins F, et al. Nat Rev Clin Oncol.2019

LACC

TREATMENT PHASES : CCRT c Immunotherapy

Keynote A18

- After an additional 12 months of median follow-up, pembrolizumab plus CCRT followed by pembrolizumab continued to show clinically meaningful improvements in PFS and OS vs CCRT in participants with newly diagnosed, high-risk LACC
- In post hoc analyses
  - Pembrolizumab plus CCRT improved PFS and OS vs CCRT in participants with FIGO 2014 stage III–IVA LACC, regardless of pelvic/para-aortic LN involvement
  - PFS benefit was also seen with pembrolizumab plus CCRT in participants with stage IB2–IIB disease with target lesions >5 cm
- The safety profile of pembrolizumab plus CCRT was manageable and consistent with the known profiles of the individual therapies, with no new safety signals after longer follow-up
- These data are consistent with the prior interim analyses results and provide further support for pembrolizumab plus CCRT as the new standard of care for this population

LACC

TREATMENT PHASES : CCRT c Immunotherapy

Keynote A18

12th January 2024

NEWS RELEASE

FDA Approves Merck's KEYTRUDA® (pembrolizumab) Plus Chemoradiotherapy as Treatment for Patients With FIGO 2014 Stage III-IVA Cervical Cancer

1/12/2024

KEYTRUDA is the first and only anti-PD-1 therapy approved in combination with chemoradiotherapy for these patients

Approval marks third FDA-approved indication for KEYTRUDA in cervical cancer and 39th indication for KEYTRUDA in the US

RAHWAY, N.J.–(BUSINESS WIRE)– Merck (NYSE: MRK), known as MSD outside of the United States and Canada, today announced the U.S. Food and Drug Administration (FDA) has approved KEYTRUDA, Merck's anti-PD-1 therapy, in combination with chemoradiotherapy (CRT) for the treatment of patients with FIGO (International Federation of Gynecology and Obstetrics) 2014 Stage III-IVA cervical cancer. The approval is based on data from the Phase 3 KEYNOTE-A18 trial, in which KEYTRUDA plus CRT demonstrated an improvement in progression-free survival (PFS), reducing the risk of disease progression or death by 41% (HR=0.59 [95% CI, 0.43-0.82]) compared to placebo plus CRT in patients with FIGO 2014 Stage III-IVA disease. Median PFS was not reached in either group. This approval marks the third indication for KEYTRUDA in cervical cancer and the 39th indication for KEYTRUDA in the U.S.

2024년 4월 15일 기준
-→100/100 전액본인부담

FIGO 2014 III-IVA기 자궁경부암 환자의 치료로서 화학방사선요법과의 병용 요법

III	The carcinoma has extended onto the pelvic sidewall. On rectal examination, there is no cancer-free space between the tumor and pelvic sidewall. The tumor involves the lower third of the vagina.
IIIA	Involvement of the lower vagina but no extension onto pelvic sidewall
IIIB	Extension onto the pelvic sidewall, or hydronephrosis/ nonfunctioning kidney
IV	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum.
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

CPS = combined positive score; PD-L1 = programmed death ligand 1.
1. 키트루다 허가사항, 식품의약품안전처

LACC- Updated NCCN guidelines

KEYNOTE-A18

INTERLACE

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2026
Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR CERVICAL CANCER[a,b,c]

Squamous Cell Carcinoma, Adenocarcinoma, or Adenosquamous Carcinoma

Chemoradiation[d]	Recurrent or Metastatic Disease	
	First-Line Therapy[d,i]	Second-Line or Subsequent Therapy[i,m]
Preferred • Cisplatin + Pembrolizumab[e,f,k,1] ▸ Category 1: FIGO 2014 stage IIIA, IIIB, and IVA ▸ Category 2B: select FIGO 2018 stage III–IVA • Carboplatin + Pembrolizumab[e,f,k,1] if cisplatin intolerant ▸ Category 1: FIGO 2014 stage IIIA, IIIB, and IVA ▸ Category 2B: select FIGO 2018 stage III–IVA • Cisplatin • Carboplatin if cisplatin intolerant **Other Recommended** • If single-agent Cisplatin and Carboplatin are unavailable ▸ Capecitabine[g]/Mitomycin[2] ▸ Gemcitabine[3] ▸ Paclitaxel[4,5] • Induction chemotherapy (followed by chemoradiation) ▸ Carboplatin/Paclitaxel[h,6]	**Preferred** • PD-L1–positive tumors ▸ Cisplatin/Paclitaxel + Pembrolizumab ± Bevacizumab (category 1)[f,j,k,7] ▸ Carboplatin/Paclitaxel + Pembrolizumab ± Bevacizumab (category 1)[f,j,k,7] • Cisplatin/Paclitaxel + Bevacizumab[f,8] (category 1) • Carboplatin/Paclitaxel + Bevacizumab[f] • Cisplatin/Paclitaxel + Atezolizumab + Bevacizumab (category 1)[f,l,9] • Carboplatin/Paclitaxel + Atezolizumab + Bevacizumab (category 1)[f,l,9] **Other Recommended** • Cisplatin/Paclitaxel (category 1)[10,11] • Carboplatin/Paclitaxel[12,13] (category 1 for patients who have received prior Cisplatin therapy) • Paclitaxel/Topotecan + Bevacizumab[f,8,14] (category 1) • Paclitaxel/Topotecan[14] • Cisplatin/Topotecan[14] • Cisplatin[10] • Carboplatin[15,16]	**Preferred** • TMB-H tumors:[n] Pembrolizumab[k] • PD-L1–positive: Pembrolizumab[j,k] • MSI-H/dMMR tumors: Pembrolizumab[k,17] • Tisotumab vedotin-tftv (category 1)[18,19] **Other Recommended** • Bevacizumab • Paclitaxel[16,20] • Albumin-bound Paclitaxel • Docetaxel • Fluorouracil[g] • Gemcitabine • Pemetrexed • Topotecan • Vinorelbine • Irinotecan • Cemiplimab[21] • Ipilimumab + Nivolumab[22,23,24] **Useful in Certain Circumstances** • PD-L1–positive tumors ▸ Nivolumab[j,o,22] ▸ Pembrolizumab + Tisotumab vedotin-tftv[j,k,p,25] • HER2-positive tumors (IHC 3+ or 2+) ▸ Fam-trastuzumab deruxtecan-nxki[26] • HER2-mutant ▸ Neratinib[27] • *RET* gene fusion-positive tumors ▸ Selpercatinib • *NTRK* gene fusion-positive tumors ▸ Larotrectinib ▸ Entrectinib ▸ Repotrectinib[q,28]

NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer.

Metastatic / Recurrent Cervical Cancer

Metastatic Cervical Cancer

Keynote 826: A randomized phase III trial of induction chemotherapy followed by chemoradiation compared with chemoradiation alone in locally advanced cervical cancer. (SGO 2024: Lederman et al.)

IGCS 2025
Annual Global Meeting
CAPE TOWN
November 5 - 7

Kosei Hasegawa, MD, PhD
Saitama Medical University
International Medical Center

November 7, 2025

Pembrolizumab Plus Chemotherapy With or Without Bevacizumab in Participants With Persistent, Recurrent, or Metastatic Cervical Cancer: 5-Year Follow-Up Results From KEYNOTE-826

pTEP

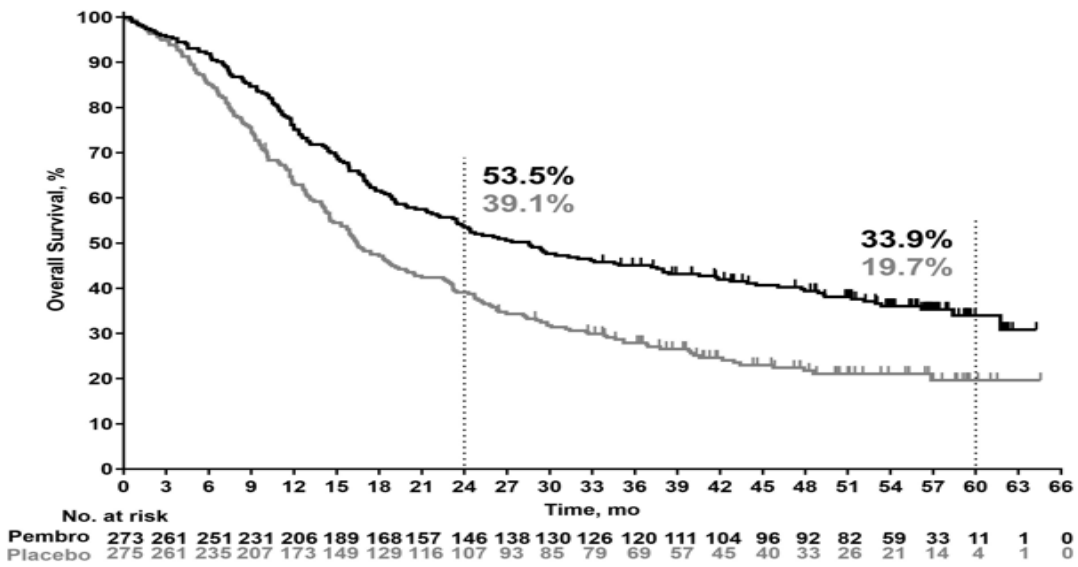
Kosei Hasegawa,[1] Nicoletta Colombo,[2] Krishnansu S. Tewari,[3] Coraline Dubot,[4] M. Valeria Cáceres,[5] Domenica Lorusso,[6] Ronnie Shapira-Frommer,[7] Pamela Salman,[8] Eduardo Yañez,[9] Mahmut Gumus,[10] Mivael Olivera Hurtado de Mendoza,[11] Vanessa Samouëlian,[12] Vincent Castonguay,[13] Alexander Arkhipov,[14] Cumhur Tekin,[15] Kan Li,[15] Sarper Toker,[15] Bradley J. Monk[16]

Metastatic Cervical Cancer

Keynote 826: The randomized, double-blind, phase 3 assessed the addition of pembro vs placebo to chemo ± bev as first-line treatment in participants with persistent, recurrent, or metastatic cervical cancer. (IGCS 2025)

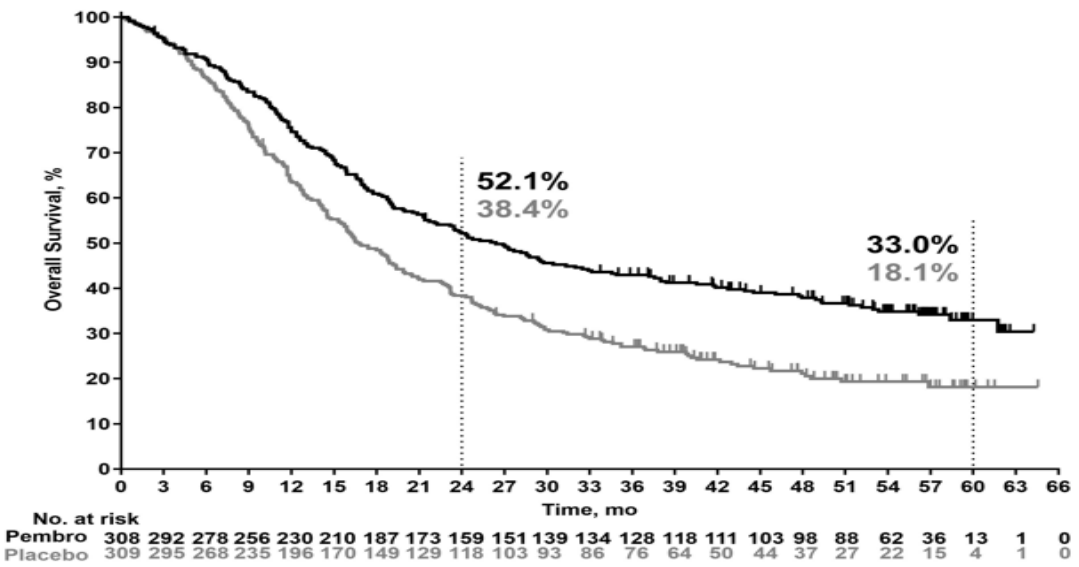
Overall Survival at 5 Years

PD-L1 CPS ≥1



	Pembro Arm[a]	Placebo Arm[a]
No. of events (%)	174 (63.7)	211 (76.7)
Median (95% CI), mo	28.6 (22.1–38.0)	16.5 (14.5–19.9)
HR (95% CI)	0.62 (0.50–0.76)	

All-Comers



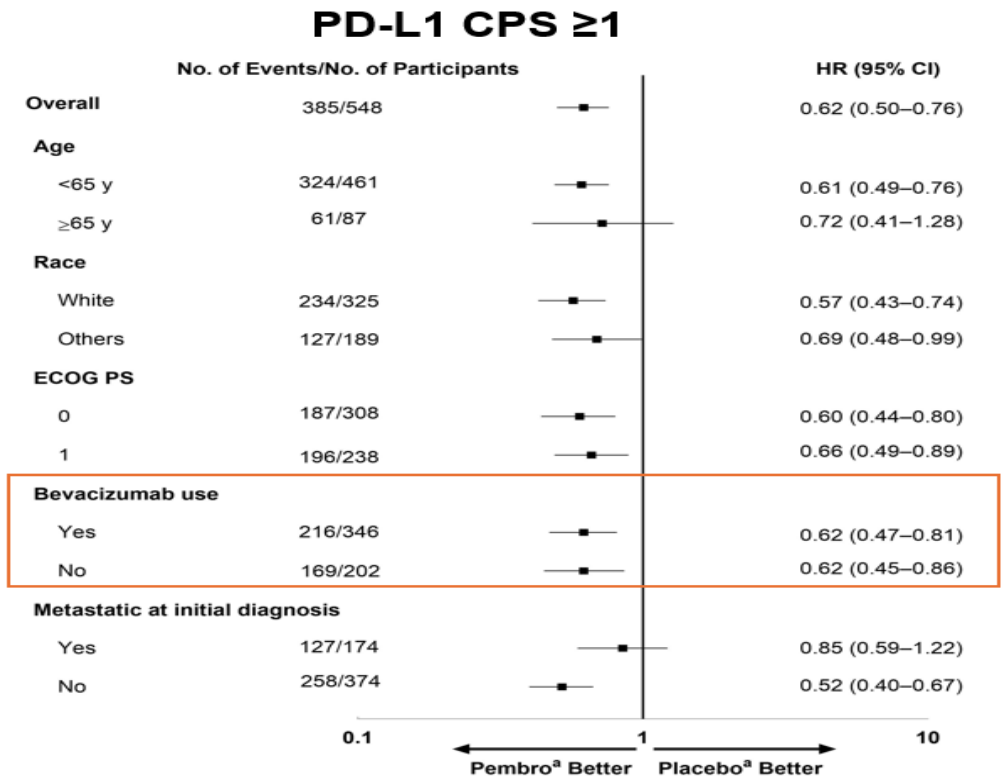
	Pembro Arm[a]	Placebo Arm[a]
No. of events (%)	199 (64.6)	241 (78.0)
Median (95% CI), mo	26.4 (21.3–32.5)	16.8 (14.6–19.4)
HR (95% CI)	0.64 (0.53–0.78)	

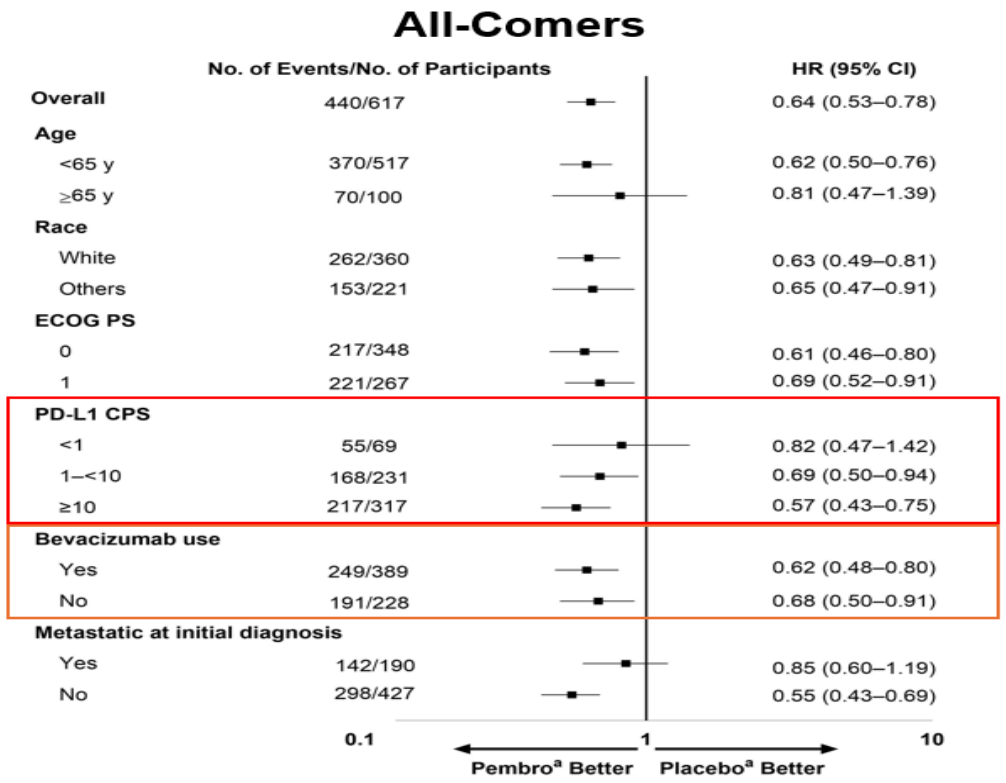
[a]The treatment regimen in each arm included chemo ± bev.
Data cutoff date: June 4, 2024.

Metastatic Cervical Cancer

Keynote 826: The randomized, double-blind, phase 3 assessed the addition of pembro vs placebo to chemo ± bev as first-line treatment in participants with persistent, recurrent, or metastatic cervical cancer. (IGCS 2025)

Overall Survival in Subgroups at 5 Years





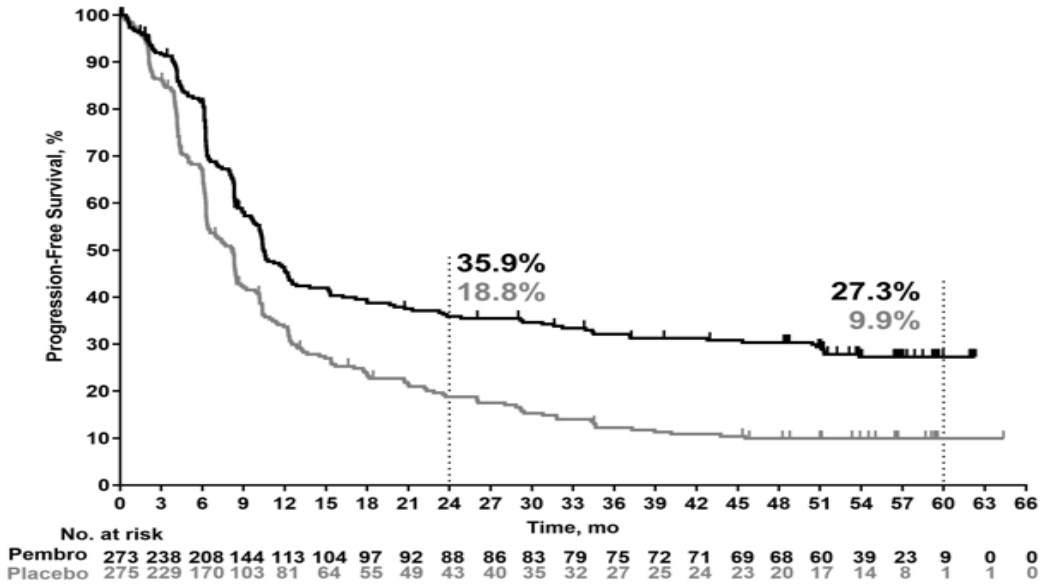
[a]The treatment regimen in each arm included chemo ± bev.
Data cutoff date: June 4, 2024.

Metastatic Cervical Cancer

Keynote 826: The randomized, double-blind, phase 3 assessed the addition of pembro vs placebo to chemo ± bev as first-line treatment in participants with persistent, recurrent, or metastatic cervical cancer. (IGCS 2025)

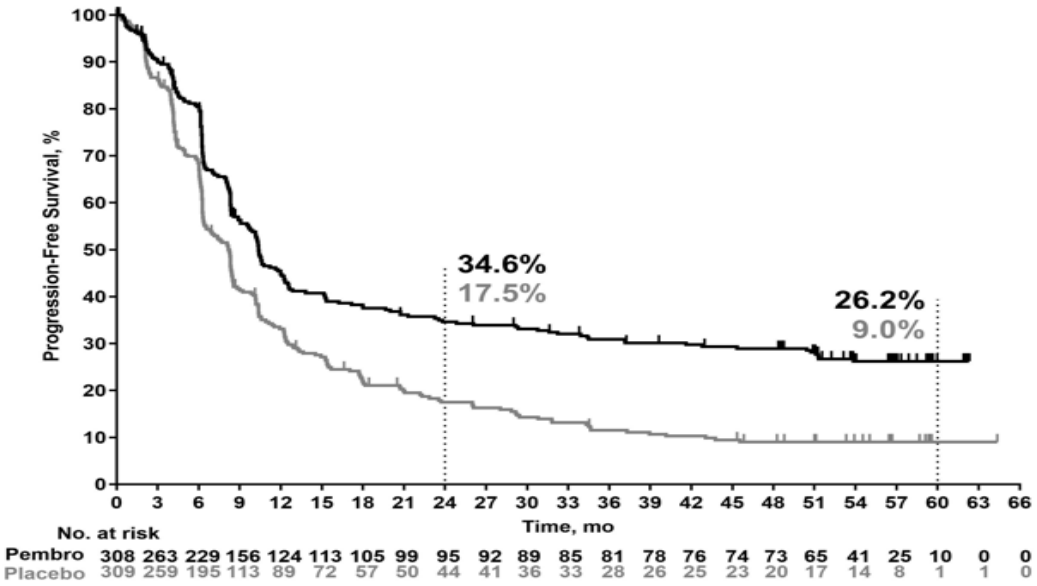
Progression-Free Survival at 5 Years

PD-L1 CPS ≥1



	Pembro Arm[a]	Placebo Arm[a]
No. of events (%)	181 (66.3)	224 (81.5)
Median (95% CI), mo	10.5 (9.7–12.3)	8.2 (6.3–8.5)
HR (95% CI)	0.58 (0.48–0.71)	

All-Comers



	Pembro Arm[a]	Placebo Arm[a]
No. of events (%)	206 (66.9)	253 (81.9)
Median (95% CI), mo	10.4 (9.1–12.2)	8.2 (6.4–8.4)
HR (95% CI)	0.61 (0.51–0.74)	

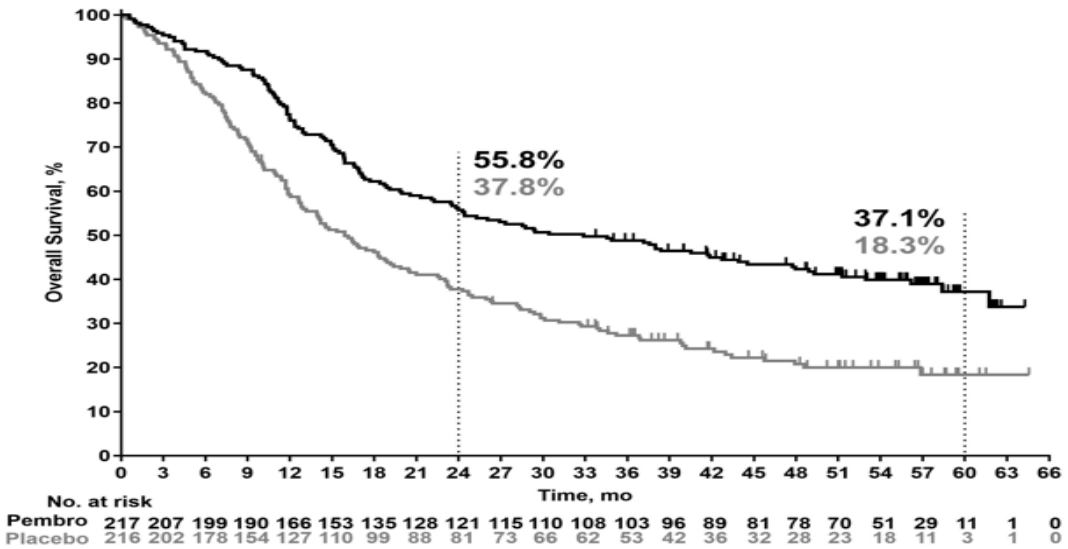
[a]The treatment regimen in each arm included chemo ± bev.
Data cutoff date: June 4, 2024

Metastatic Cervical Cancer

Keynote 826: The randomized, double-blind, phase 3 assessed the addition of pembro vs placebo to chemo ± bev as first-line treatment in participants with persistent, recurrent, or metastatic cervical cancer. (IGCS 2025)

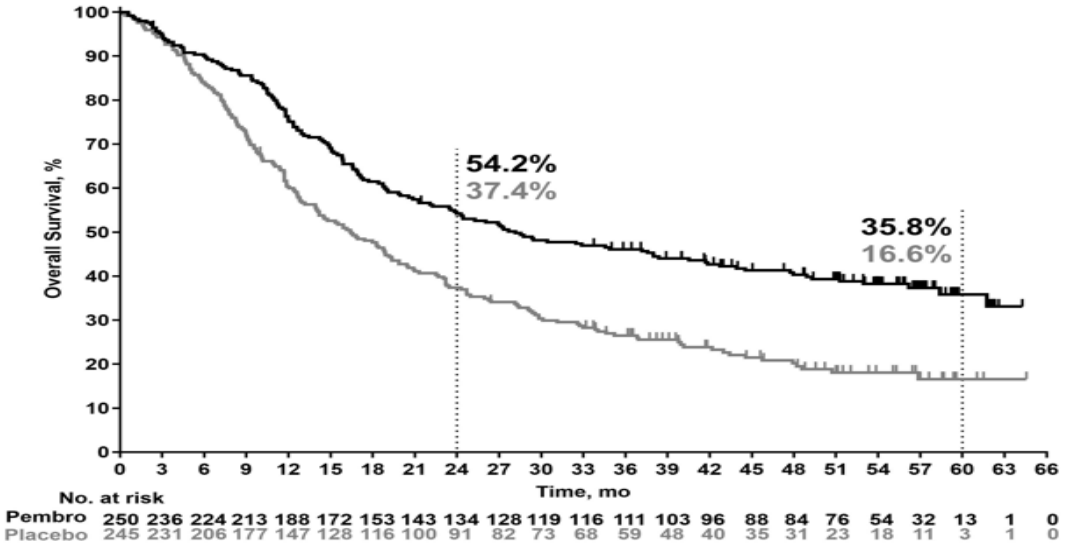
Post Hoc Analysis of Overall Survival at 5 Years in Participants With Persistent/Recurrent Disease

PD-L1 CPS ≥1



	Pembro Arm[a]	Placebo Arm[a]
No. of events (%)	131 (60.4)	168 (77.8)
Median (95% CI), mo	32.9 (23.5–44.5)	15.9 (12.8–19.2)
HR (95% CI)	0.57 (0.45–0.72)	

All-Comers



	Pembro Arm[a]	Placebo Arm[a]
No. of events (%)	154 (61.6)	194 (79.2)
Median (95% CI), mo	28.2 (22.1–40.5)	16.5 (13.2–19.4)
HR (95% CI)	0.59 (0.48–0.74)	

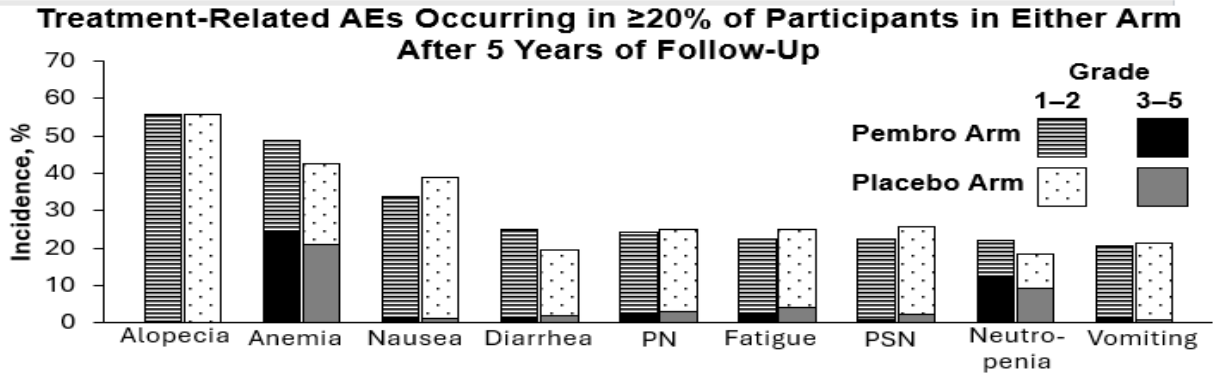
[a]The treatment regimen in each arm included chemo ± bev.
Data cutoff date: June 4, 2024

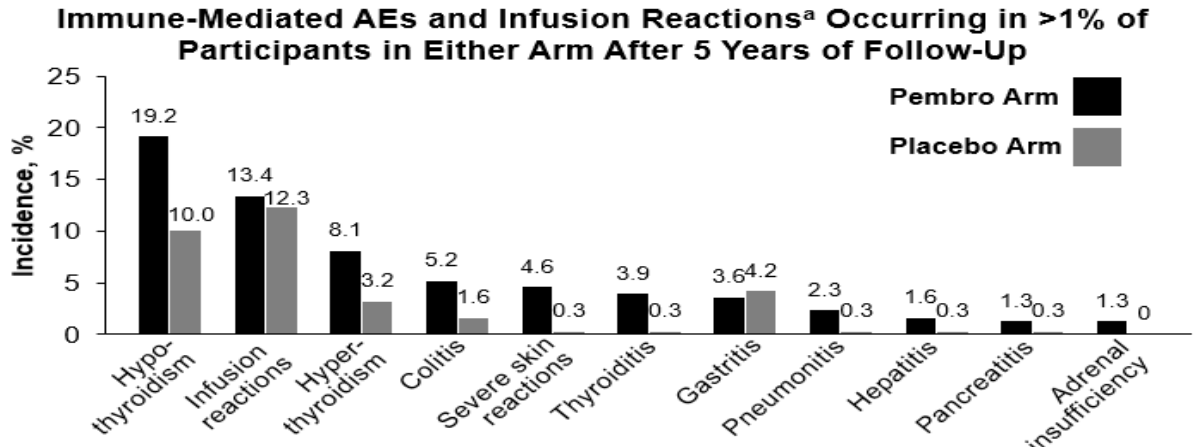
Metastatic Cervical Cancer

Keynote 826: The randomized, double-blind, phase 3 assessed the addition of pembro vs placebo to chemo ± bev as first-line treatment in participants with persistent, recurrent, or metastatic cervical cancer. (IGCS 2025)

Treatment Exposure and Adverse Event Summary, As-Treated Population

	Final analysis[1]		5 years of follow-up	
	Pembro Arm (n = 307)	Placebo Arm (n = 309)	Pembro Arm (n = 307)	Placebo Arm (n = 309)
Duration of therapy, median (range), mo	10.0 (0.03–43.7)	7.7 (0.03–43.9)	10.0 (0.03–61.9)	7.7 (0.03–63.2)
Treatment-related AEs, n (%)	298 (97.1)	300 (97.1)	297 (96.7)	300 (97.1)
Grade ≥3	212 (69.1)	201 (65.0)	213 (69.4)	202 (65.4)
Led to death[a]	2 (0.7)[b]	4 (1.3)[b]	2 (0.7)[b]	4 (1.3)[b]
Led to discontinuation of any study treatment	102 (33.2)	77 (24.9)	103 (33.6)	78 (25.2)
Immune-mediated AEs and infusion reactions,[c] n (%)	128 (41.7)	84 (27.2)	134 (43.6)	92 (29.8)
Grade ≥3	43 (14.0)	16 (5.2)	45 (14.7)	16 (5.2)
Led to death[a]	2 (0.7)[d]	0	2 (0.7)[d]	0
Led to discontinuation of any study treatment	30 (9.8)	11 (3.6)	31 (10.1)	11 (3.6)





PN, peripheral neuropathy; PSN, peripheral sensory neuropathy. [a]No additional deaths reported since the final analysis. [b]Encephalitis and intestinal perforation (n = 1 each) in pembro arm; embolism, female genital tract fistula, large intestine perforation, and pulmonary sepsis (n = 1 each) in placebo arm. [c]Immune-mediated AEs and infusion reactions were based on a list of preferred terms intended to capture known risks of pembrolizumab and were considered regardless of attribution to study treatment by the investigator. [d]Encephalitis and pancreatitis (n = 1 each). Data cutoff date: final analysis, October 3, 2022; 5-year follow-up, June 4, 2024. 1. Monk BJ, et al. *J Clin Oncol*. 2023;41:5505–5511.

Metastatic Cervical Cancer

Keynote 826: The randomized, double-blind, phase 3 assessed the addition of pembro vs placebo to chemo ± bev as first-line treatment in participants with persistent, recurrent, or metastatic cervical cancer. (IGCS 2025)

건강보험심사평가원 공고 제2025-272호

「국민건강보험 요양급여의 기준에 관한 규칙」 제5조제4항 규정에 따라 암환자에게 처방·투여하는 약제 중 보건복지부장관이 정하여 고시하는 약제(보건복지부 고시 제2025-73호, 2025.5.1.)에 대한 '요양급여의 적용기준 및 방법에 관한 세부사항(건강보험심사평가원 공고 제2025-256호, 2025.11.25.)'을 다음과 같이 개정 공고합니다.

2025년 12월 30일
건강보험심사평가원장

암환자에게 처방·투여하는 약제에 대한
요양급여의 적용기준 및 방법에 관한 세부사항 중 개정

암환자에게 처방·투여하는 약제에 대한 요양급여의 적용기준 및 방법에 관한 세부사항을 다음과 같이 변경한다.

부 칙(2025.12.30.)

① (시행일) 이 공고는 2026년 1월 1일부터 시행한다.

11. 자궁경부암 (Cervical Cancer)

1. 고식적요법(palliative)

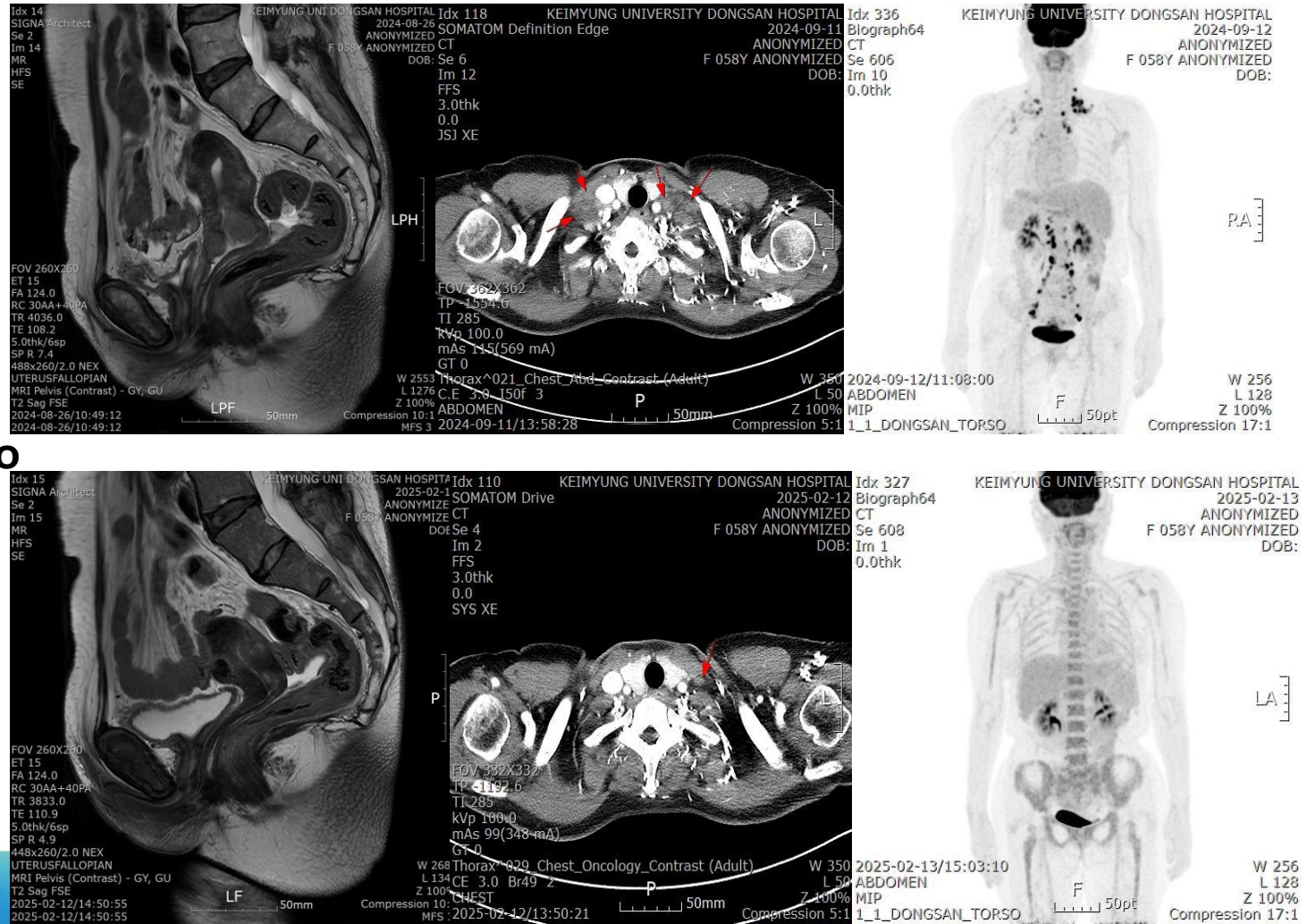
연번	항암요법	투여대상	투여단계
14	pembrolizumab[주1] + paclitaxel + cisplatin ± bevacizumab	PD-L1 발현 양성(CPS≥1[주2])이며 수술 또는 방사선 치료가 부적합한 지속성(persistent)*, 재발성 또는 전이성(IVB) 자궁경부암	1차
15	pembrolizumab[주1] + paclitaxel + carboplatin ± bevacizumab	* '지속성(persistent)'은 방사선 치료 후 3개월에 질환이 완전 관해(completely regression)되지 않는 경우를 의미함 ※ 이전 PD-1 inhibitor 등 면역관문억제제 치료를 받지 않은 경우에 한함	

Metastatic Cervical Cancer

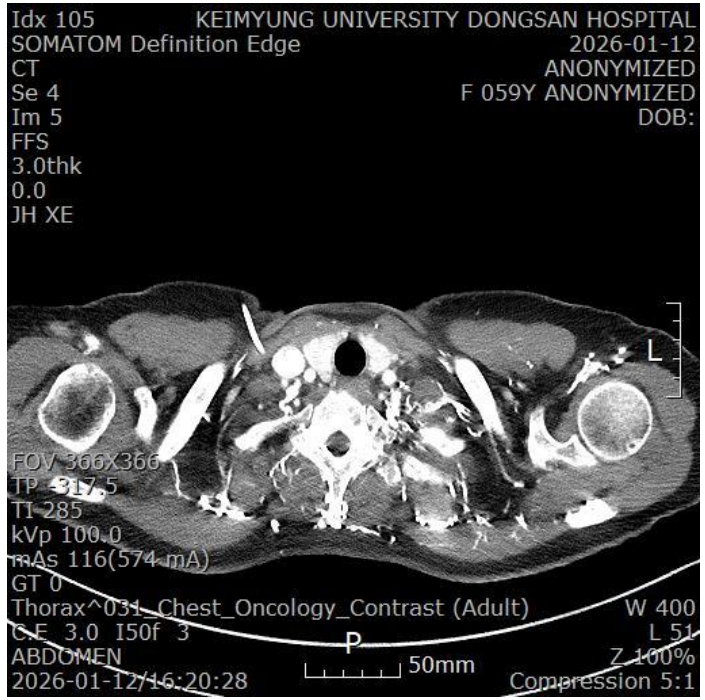
Keynote 826: The randomized, double-blind, phase 3 assessed the addition of pembro vs placebo to chemo ± bev as first-line treatment in participants with persistent, recurrent, or metastatic cervical cancer. (IGCS 2025)

<진단>

<PCB +pembro #6>



<ongoing pembro >



대한부인종양학회
Korean Society of Gynecologic Oncology

Metastatic Cervical Cancer – 1st line (Atezolizumab + bev + T/C or T/P)

Phase 3 BEATcc: A randomized phase 3 trial of first line atezolizumab combined with bevacizumab and a platinum doublet for metastatic (stage IVB), persistent or recurrent cervical cancer (SGO 2024, Oaknin et al)

- Open-label, multicenter, randomized, phase 3 trial in an all-comer population

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

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

R 1:1

N = 410

Atezolizumab 1200 mg + 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

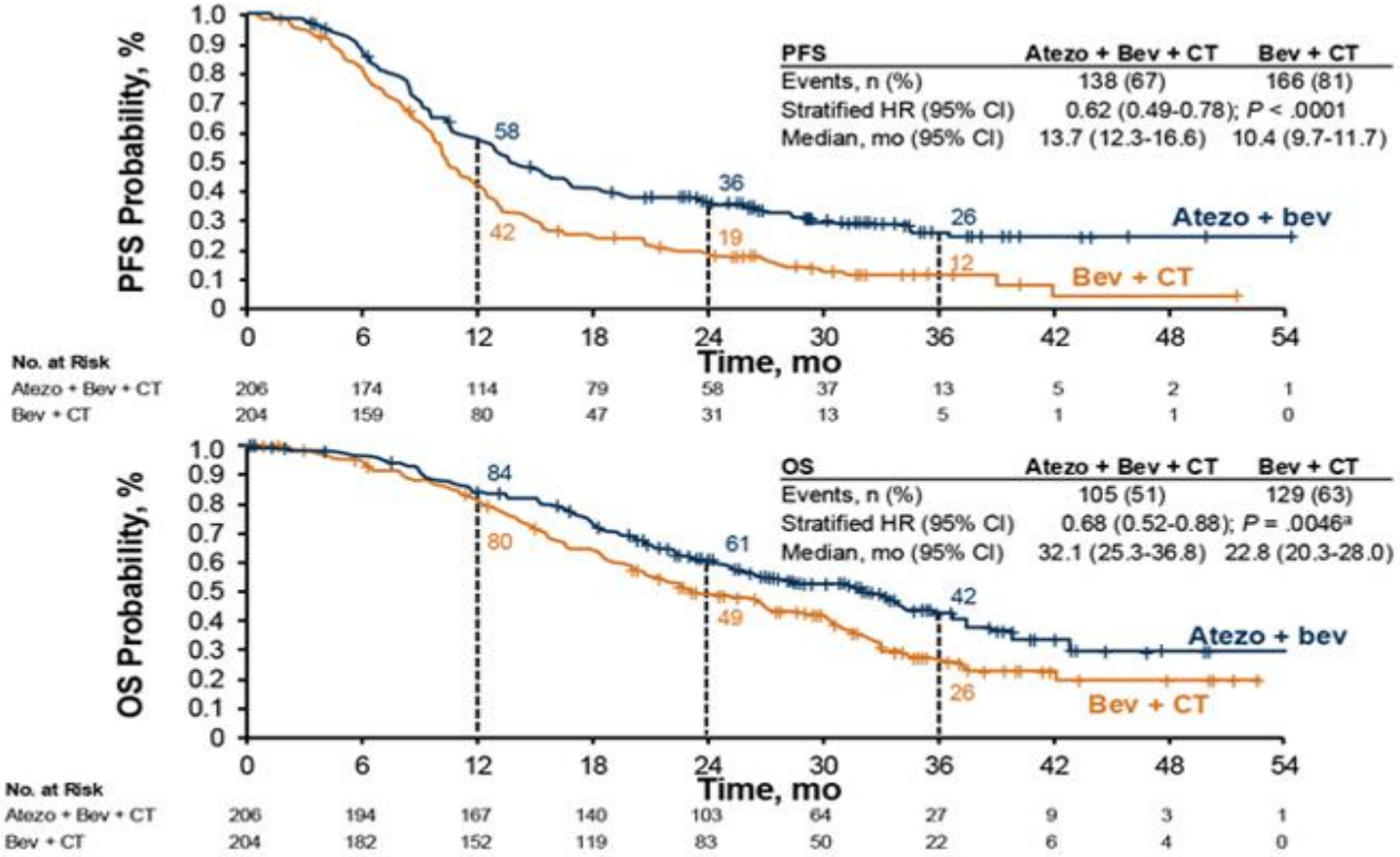
Bevacizumab 15 mg/kg + paclitaxel + cis/carboplatin[a] all IV Q3W

Dual primary endpoints
- Investigator-assessed PFS (RECIST 1.1)
- OS

Key secondary endpoints
- ORR (RECIST v1.1)
- DOR (RECIST v1.1)
- TFST
- PFS2
- Safety

Metastatic Cervical Cancer – 1st line (Atezolizumab + bev + T/C or T/P)

Phase 3 BEATcc: A randomized phase 3 trial of first line atezolizumab combined with bevacizumab and a platinum doublet for metastatic (stage IVB), persistent or recurrent cervical cancer (SGO 2024, Oaknin et al)



PFS	Atezo + Bev + CT	Bev + CT
Events, n (%)	138 (67)	166 (81)
Stratified HR (95% CI)	0.62 (0.49-0.78); *P* < .0001	
Median, mo (95% CI)	13.7 (12.3-16.6)	10.4 (9.7-11.7)

Statistically significant 38% reduction in risk of progression or death

OS	Atezo + Bev + CT	Bev + CT
Events, n (%)	105 (51)	129 (63)
Stratified HR (95% CI)	0.68 (0.52-0.88); *P* = .0046[a]	
Median, mo (95% CI)	32.1 (25.3-36.8)	22.8 (20.3-28.0)

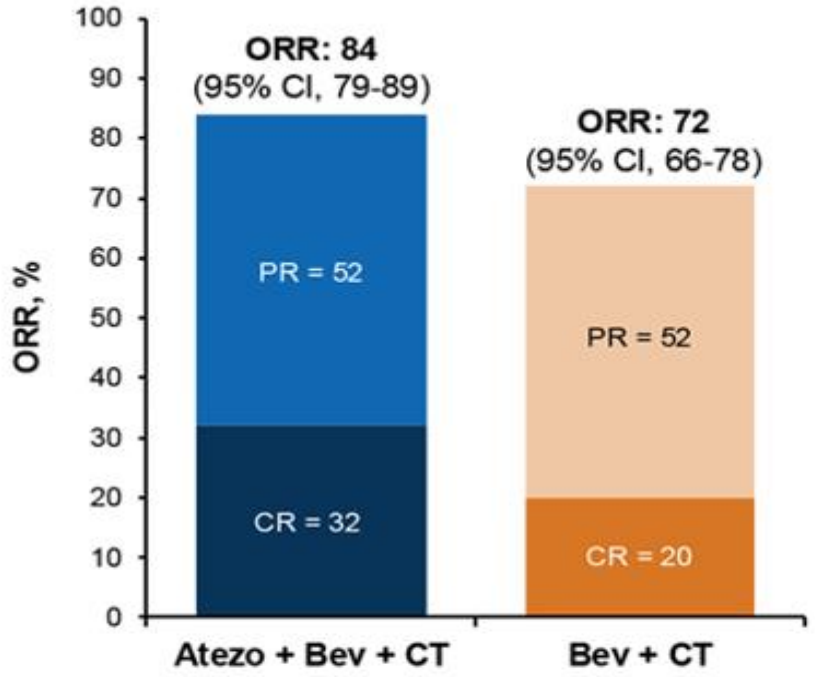
Statistically significant 32% reduction in risk of death (interim analysis[b])

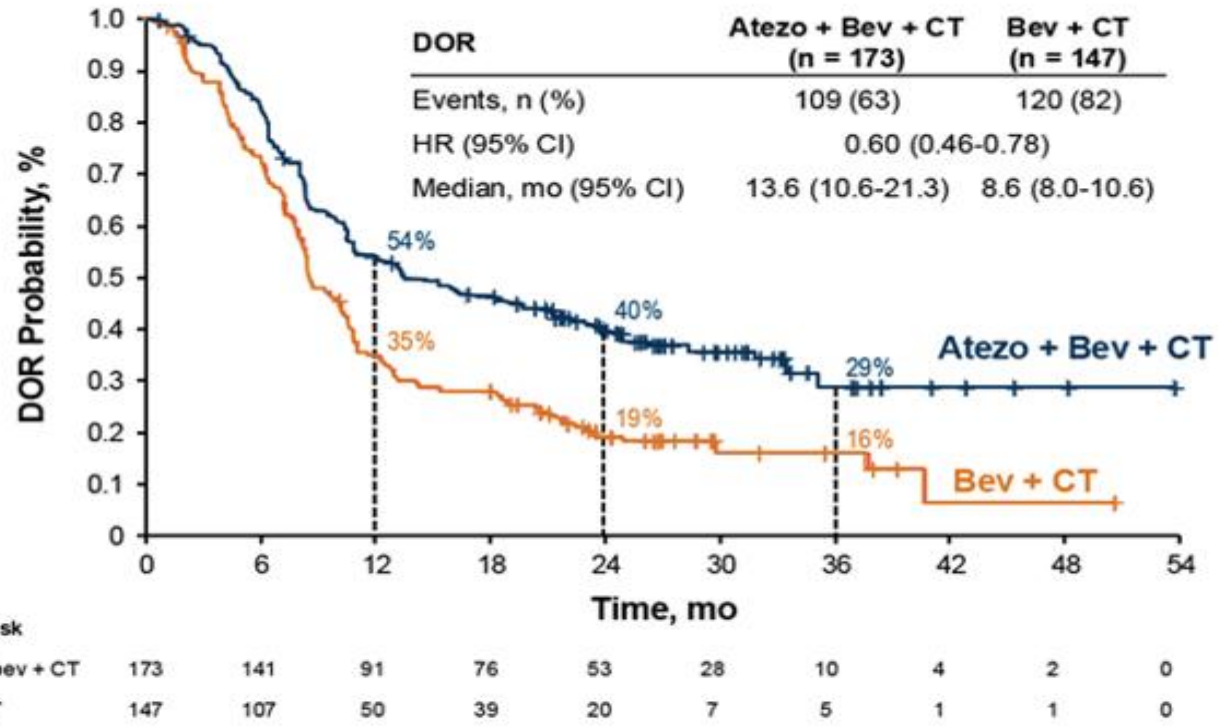
[a] Data cut-off: July 17, 2023 (median follow-up: 32.9 months; 95% CI, 31.2-34.6 months). [b] Interim OS was statistically significant, crossing the boundary of *P* = .0238.

1. Oaknin A et al. *Lancet*. 2024;403:31-43.

Metastatic Cervical Cancer – 1st line (Atezolizumab + bev + T/C or T/P)

Phase 3 BEATcc: A randomized phase 3 trial of first line atezolizumab combined with bevacizumab and a platinum doublet for metastatic (stage IVB), persistent or recurrent cervical cancer (SGO 2024, Oaknin et al)





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

1. Oaknin A et al. *Lancet*. 2024;403:31-43.

Metastatic Cervical Cancer – 1st line (Atezolizumab + bev + T/C or T/P)

Evolution of Treatment of Stage 4B, Persistent, Recurrent Cervical Cancer (1L)

The Past

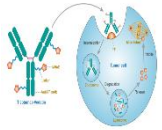
- GOG 204 (cisplatin + paclitaxel)
- JCOG 0505 (noninferiority of carboplatin and 3 hour paclitaxel)
- GOG 240 (addition of bevacizumab)

The Present

- KEYNOTE-826 (addition of pembrolizumab)
- BEATcc (addition of atezolizumab)

➢ Every patient in the first-line setting should, if they are checkpoint-naïve, be offered immune therapy

Metastatic Cervical Cancer



InnovaTV 205/GOG-3024/ENGOT-cx8 Study

:Phase 2 of this open-label multicenter study (NCT03786081) included dose-expansion

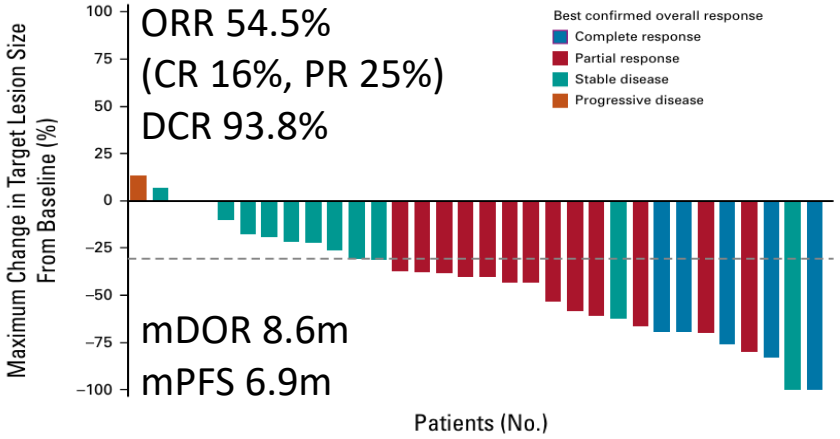
Key Eligibility Criteria

- Recurrent/metastatic cervical cancer
- Measurable disease per RECIST v1.1

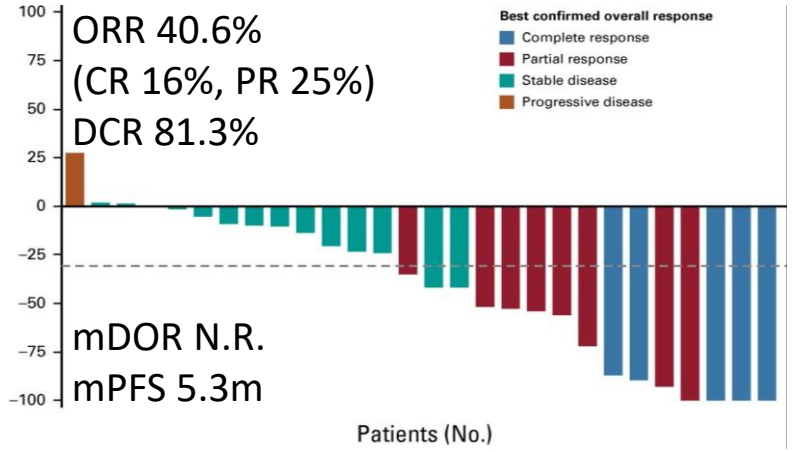
Dose Expansion

Patients with no prior systemic therapy	Arm D: 1L TV + carbo	n = 33	TV 2.0 mg/kg IV (Q3W) + carbo AUC 5 IV (Q3W)
	Arm E: 1L TV + pembro	n = 33	TV 2.0 mg/kg IV (Q3W) + pembro 200 mg IV (Q3W)
Patients with disease progression on or after 1–2 prior systemic therapies	Arm F: 2L/3L TV + pembro	n = 35	TV 2.0 mg/kg IV (Q3W) + pembro 200 mg IV (Q3W)

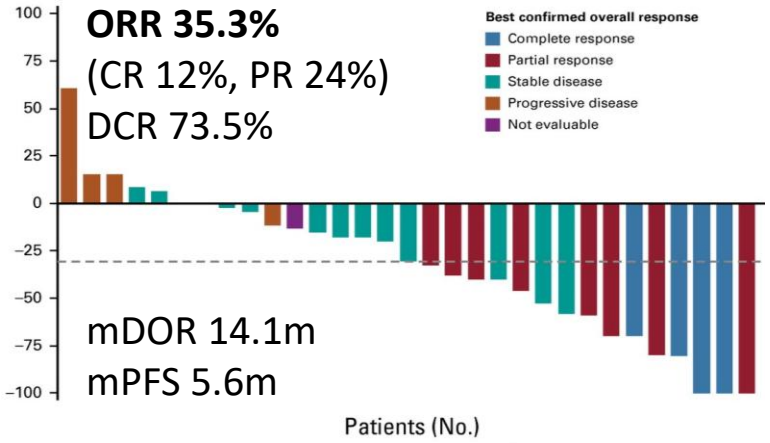
1L TV + Carbo (n = 33)



1L TV + Pembro (n = 32)



2/3L TV + Pembro (n = 34)



Vergote I, et al. J Clin Oncol. 2023.

Reccurent ,Metastatic Cervical Cancer

Updated NCCN guidelines

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2026
Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR CERVICAL CANCER[a,b,c]

Squamous Cell Carcinoma, Adenocarcinoma, or Adenosquamous Carcinoma

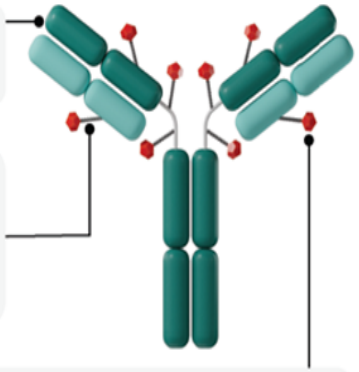
Chemoradiation[d]	Recurrent or Metastatic Disease	
	First-Line Therapy[d,i]	Second-Line or Subsequent Therapy[i,m]
Preferred • Cisplatin + Pembrolizumab[e,f,k,1] KEYNOTE-826 ▸ Category 1: FIGO 2014 stage IIIA, IIIB, and IVA ▸ Category 2B: select FIGO 2018 stage III–IVA • Carboplatin + Pembrolizumab[e,f,k,1] if cisplatin intolerant ▸ Category 1: FIGO 2014 stage IIIA, IIIB, and IVA ▸ Category 2B: select FIGO 2018 stage III–IVA • Cisplatin • Carboplatin if cisplatin intolerant BEATcc **Other Recommended** • If single-agent Cisplatin and Carboplatin are unavailable ▸ Capecitabine[g]/Mitomycin[2] ▸ Gemcitabine[3] ▸ Paclitaxel[4,5] • Induction chemotherapy (followed by chemoradiation) ▸ Carboplatin/Paclitaxel[h,6]	**Preferred** • PD-L1–positive tumors ▸ Cisplatin/Paclitaxel + Pembrolizumab ± Bevacizumab (category 1)[f,j,k,7] ▸ Carboplatin/Paclitaxel + Pembrolizumab ± Bevacizumab (category 1)[f,j,k,7] • Cisplatin/Paclitaxel + Bevacizumab[f,8] (category 1) • Carboplatin/Paclitaxel + Bevacizumab[f] • Cisplatin/Paclitaxel + Atezolizumab + Bevacizumab (category 1)[f,l,9] • Carboplatin/Paclitaxel + Atezolizumab + Bevacizumab (category 1)[f,l,9] **Other Recommended** • Cisplatin/Paclitaxel (category 1)[10,11] • Carboplatin/Paclitaxel[12,13] (category 1 for patients who have received prior Cisplatin therapy) • Paclitaxel/Topotecan + Bevacizumab[f,8,14] (category 1) • Paclitaxel/Topotecan[14] • Cisplatin/Topotecan[14] • Cisplatin[10] • Carboplatin[15,16]	**Preferred** • TMB-H tumors:[n] Pembrolizumab[k] • PD-L1–positive: Pembrolizumab[j,k] • MSI-H/dMMR tumors: Pembrolizumab[k,17] • Tisotumab vedotin-tftv (category 1)[18,19] **Other Recommended** • Bevacizumab • Paclitaxel[16,20] • Albumin-bound Paclitaxel • Docetaxel • Fluorouracil[g] • Gemcitabine • Pemetrexed • Topotecan • Vinorelbine • Irinotecan • Cemiplimab[21] • Ipilimumab + Nivolumab[22,23,24] **Useful in Certain Circumstances** • PD-L1–positive tumors ▸ Nivolumab[j,o,22] ▸ Pembrolizumab + Tisotumab vedotin-tftv[j,k,p,25] InnovaTV 205 • HER2-positive tumors (IHC 3+ or 2+) ▸ Fam-trastuzumab deruxtecan-nxki[26] • HER2-mutant ▸ Neratinib[27] • *RET* gene fusion-positive tumors ▸ Selpercatinib • *NTRK* gene fusion-positive tumors ▸ Larotrectinib ▸ Entrectinib ▸ Repotrectinib[q,28]

대한부인종양학회 Korean Society of Gynecologic Oncology

NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer.

Efficacy and Safety of Sacituzumab Tirumotecan (Sac-TMT) Monotherapy in Advanced/Metastatic Cervical Cancer: Results From the Phase 1/2 Study 2870-001/KL264-01

Sac-TMT design



Monoclonal antibody
- Sacituzumab, a humanized anti-TROP2 antibody with high affinity for TROP2

Unique, bifunctional linker
- Maximizes payload delivery to tumor cells
- Irreversible connection with the antibody ensures minimal payload loss in the circulation
- pH-sensitive cleavage from the payload in the lysosome ensures payload release in the tumor cell

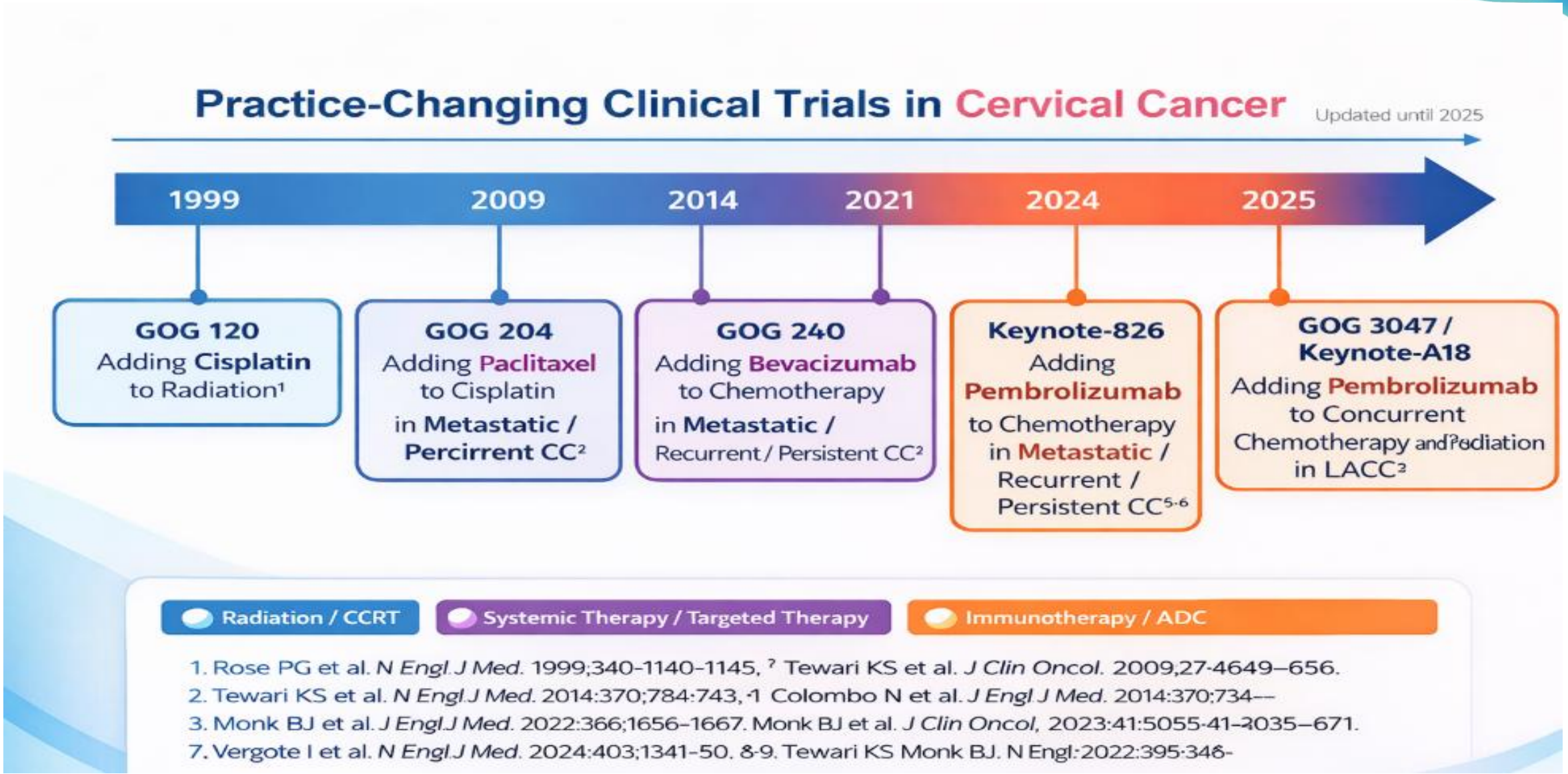
Cytotoxic payload
- Novel, belotecan-derived topoisomerase I inhibitor payload
- Average DAR of 7.4 (range, 7–8)
- Membrane permeability elicits a bystander effect in nearby tumor cells

Key eligibility criteria

- Aged ≥18 y
- Histologically or cytologically confirmed locally advanced or metastatic cervical cancer
- Progressed on/after at least 1 prior line of platinum-based therapy and received anti–PD-(L)1 inhibitor therapy[a]
- Measureable lesion by CT or MRI
- ECOG PS 0 or 1

→ **Sac-TMT 4 mg/kg IV Q2W until PD, unacceptable toxicity, or participant withdrawal**

Summary



1. Rose PG et al. *N Engl J Med*. 1999;340-1140-1145, 7 Tewari KS et al. *J Clin Oncol*. 2009,27-4649–656.
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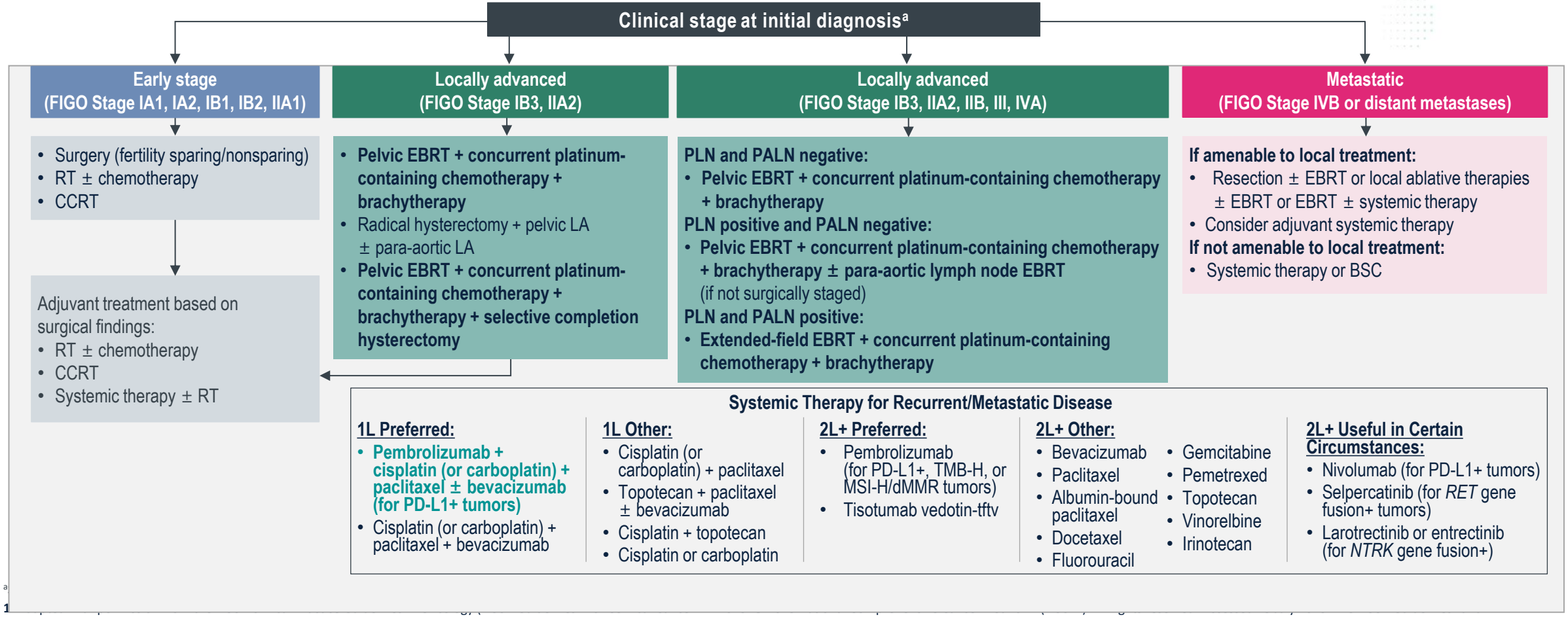
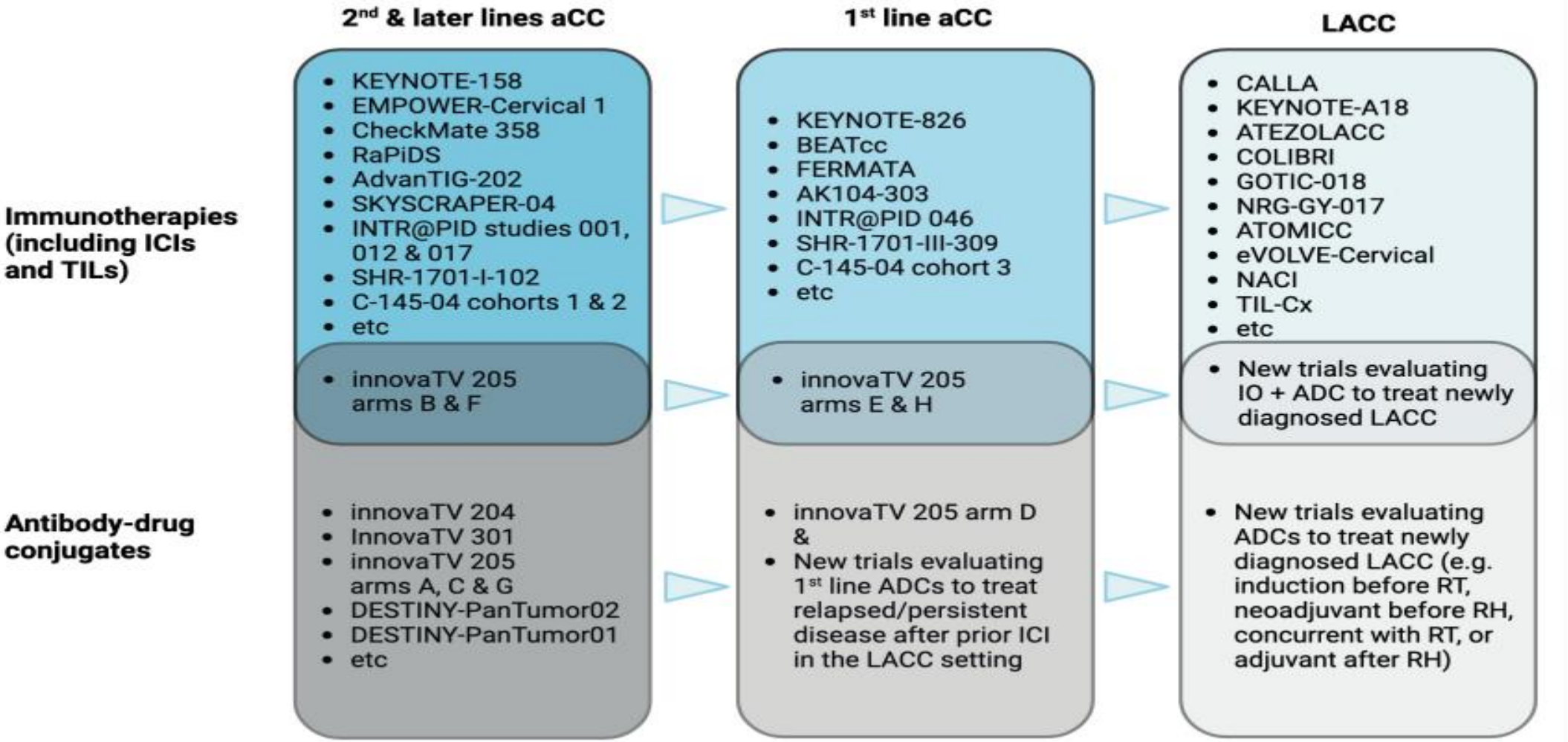
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for the Management of Cervical Cancer



Prospective evolution of the clinical development of immunotherapies and antibody-drug conjugates in cervical cancer



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Thank you for your attention!

대한부인종양학회
Korean Society of Gynecologic Oncology