Treatment of cervical cancer

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Treatment of Cervical Cancer

Early Stage (FIGO $1B_1$-IB_2):

- Radical Hysterectomy & Lymphadenectomy plus/minus adjuvant therapy

Locally Advanced (FIGO IB_3-IVA):

- Chemoradiation plus High Dose Rate Intracavitary Brachytherapy

Isolated, Central Recurrence:

- Pelvic Exenteration with Urinary Diversion

Recurrent/Metastatic (FIGO IVB):

- Systemic Therapy + Anti-Angiogenesis Therapy + Immunotherapy

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Localized/Low –Risk Cervical Cancer

CCTG CX.5-SHAPE: Radical- vs Simple- Hysterectomy and Pelvic Node Dissection for Low-Risk Early-Stage CC

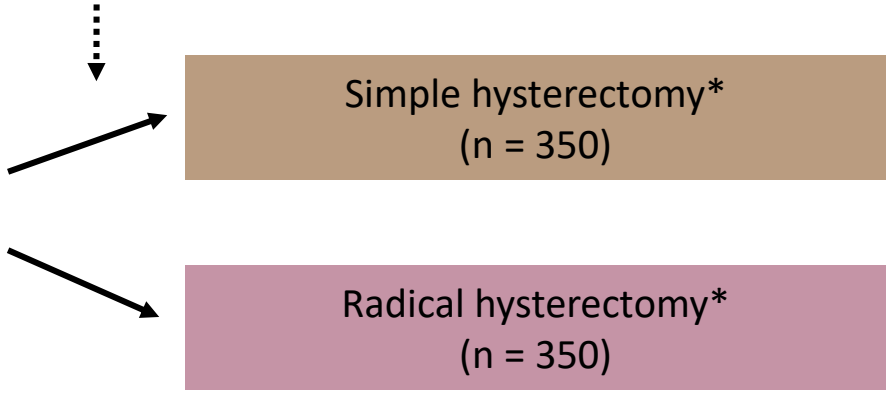
International, randomized, noninferiority phase III trial

Stratified by cooperative group, sentinel node mapping (yes vs no), stage (IA2 vs IB1), histologic type (squamous vs adenocarcinoma/ adenosquamous), grade (1/2 vs 3 vs not assessable)

Patients with low-risk cervical cancer, defined as:

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

(N = 700)



*All surgery includes pelvic lymph node dissection with optional sentinel lymph node mapping; mode for SN mapping is optional but laparoscopic approach preferred.

P**rimary endpoint:**
pelvic recurrence rate at 3 yr

CCTG CX.5-SHAPE: Baseline

Characteristic	SH (n = 350)	RH (n = 350)	All Patients (N = 700)
Median age, yr (range)	42 (26-77)	45 (24-80)	44 (24-80)
▪ ≤50 yr, n (%)	271 (77.4)	246 (70.3)	517 (73.9)
ECOG PS 0, n (%)	336 (96)	335 (95.7)	671 (95.9)
Median BMI, kg/m^2 (range)	25 (16.4-53.3)	24.8 (16.1-52)	24.8 (16.1-57.6)
Diagnostic procedure, n (%)			
▪ LEEP/cone	254 (72.6)	226 (64.6)	480 (68.6)
▪ Cervical biopsy	52 (14.9)	77 (22)	129 (18.4)
▪ Both	40 (11.4)	41 (11.7)	81 (11.6)
▪ Missing	4 (1.1)	6 (1.7)	10 (1.4)
Figo stage, n (%)			
▪ IA2	30 (8.6)	28 (8.0)	58 (8.3)
▪ IB1	320 (91.4)	322 (92.0)	642 (91.7)
Histology, n (%)			
▪ Squamous	218 (62.3)	214 (61.1)	432 (61.7)
▪ Adenocarcinoma	114 (32.6)	131 (37.4)	245 (35.0)
▪ Adenosquamous	18 (5.1)	5 (1.4)	23 (3.3)
Grade, n (%)			
▪ 1/2	205 (58.6)	210 (60.0)	415 (58.2)
▪ 3	49 (14)	49 (14)	98 (14)
▪ Not assessed	96 (27.4)	91 (26)	187 (26.7)

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CCTG CX.5-SHAPE: Surgical and Treatment Parameters

Parameter	SH (n = 338)	RH (n = 344)	P Value
Type of surgical approach,* n (%)			
▪ Abdominal	57 (16.9)	99 (28.8)	.0003
▪ Laparoscopic	188 (55.6)	152 (44.2)	.0036
▪ Robotic	82 (24.3)	87 (25.3)	.79
▪ Vaginal	11 (3.3)	4 (1.2)	.07
Sentinel node mapping, n (%)			
▪ Planned	126 (37.3)	131 (38.2)	.87
▪ Successful	78/126 (61.9)	83/131 (63.4)	.90
Key postsurgical findings on final pathology, n (%)			
▪ Residual cervical cancer detected	154 (45.6)	163 (47.4)	.65
▪ LVSI	45 (13.3)	45 (13.1)	1.00
▪ Positive nodes (sentinel or nonsentinel)	11 (3.3)	15 (4.4)	.55
▪ Positive vaginal margins	7 (2.1)	10 (2.9)	.62
▪ Positive parametrium	0	6 (1.7)	.03
▪ Lesions >2 cm	15 (4.4)	14 (4.1)	.85
Adjuvant treatment			
▪ Any, n (%)	31 (9.2)	29 (8.4)	
▪ Chemotherapy only, n	1	0	.79
▪ RT only, n	15	11	
▪ Chemoradiation, n	15	18	

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*Surgeon's discretion, not a randomization factor.

CCTG CX.5-SHAPE: Clinical Outcomes After Median Follow-up of 4.5 Yr

Outcome, %	SH (n = 350)	RH (n = 350)	HR (90% CI)	P Value
3-yr pelvic recurrence rate	2.52	2.17		
3-yr pelvic recurrence-free survival	97.5	97.8	1.12 (0.54-2.32)	.79
3-yr extrapelvic recurrence-free survival	98.1	99.7	3.82 (0.79-18.4)	.10
3-yr RFS	96.3	97.8	1.54 (0.69-3.45)	.30
3-yr OS	99.1	99.4	1.09 (0.38-3.14)	.87

Difference in 3-yr pelvic recurrence rate:

0.35

(95% CI: -1.62 to 2.32)

- 95% CI upper limit was within the <4% range to be considered noninferior

Subgroup analysis showed noninferiority of simple hysterectomy across evaluated subgroups

7 deaths in each arm

- Death from cervical cancer:
  - Simple hysterectomy: 4 (1.1%)
  - Radical hysterectomy: 1 (0.3%)

CCTG CX.5-SHAPE: Acute and Late Surgery–Related AEs

AEs Occurring in ≥5% of Patients Within 4 Wk of Surgery, n (%)	SH (n = 338)	RH (n = 344)	P Value
Any	144 (42.6)	174 (50.6)	.04
Abdominal pain	33 (9.8)	42 (12.2)	.33
Constipation	16 (4.7)	22 (6.4)	.40
Fatigue	19 (5.6)	23 (6.7)	.63
Paresthesia	14 (4.1)	22 (6.4)	.23
Peripheral sensory neuropathy	0	0	--
Urinary incontinence	8 (2.4)	19 (5.5)	.048
Urinary retention	2 (0.6)	38 (11.0)	<.0001
Dyspareunia	0	0	-
Pelvic pain	19 (5.6)	9 (2.6)	.054
Lymphedema	0	0	-
Hot flashes	0	0	-

AEs Occurring in ≥5% of Patients After 4 Wk of Surgery, n (%)	SH (n = 338)	RH (n = 344)	P Value
Any	181 (53.6)	208 (60.5)	.08
Abdominal pain	36 (10.7)	47 (13.7)	.24
Constipation	13 (3.8)	19 (5.5)	.37
Fatigue	19 (5.6)	28 (8.1)	.23
Paresthesia	17 (5.0)	22 (6.4)	.51
Peripheral sensory neuropathy	21 (6.2)	13 (3.8)	.16
Urinary incontinence	16 (4.7)	38 (11.0)	.003
Urinary retention	2 (0.6)	34 (9.9)	<.0001
Dyspareunia	21 (6.2)	19 (5.5)	.75
Pelvic pain	23 (6.8)	17 (4.9)	.33
Lymphedema	35 (10.4)	36 (10.5)	1.00
Hot flashes	14 (4.1)	20 (5.8)	.38

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Pembrolizumab + cCCRT in High-Risk LACC (KEYNOTE-A18/ENGOT-cx11/GOG-3047): Study Design

- Randomized, double-blind, placebo-controlled phase III trial

Stratified by planned EBRT (IMRT or VMAT vs non-IMRT or non-VMAT); stage (IB2-IIB vs III-IVA); and planned total radiotherapy dose (<70 Gy vs ≥70 Gy [EQ2D])

Patients with newly diagnosed, previously untreated, high-risk locally advanced cervical cancer
FIGO 2014 stage IB2-IIB; node positive or stage III-IVA;
ECOG PS ≤1
(N = 1060)

Pembrolizumab 200 mg Q3W + **cCRT*** (5 cycles)	**Pembrolizumab** 400 mg Q6W (15 cycles)
Placebo Q3W + **cCRT*** (5 cycles)	**Placebo** Q6W (15 cycles)

Protocol Amendments
- Jan 6, 2021: change of PFS by BICR to per investigator
- Nov 8, 2022: change of multiplicity strategy in SAP; prespecified α to be passed to another hypothesis (PFS, 1-sided α = 0.025 to OS, 1-sided α = 0).

- **Primary endpoints:** PFS per RECIST v1.1 by investigator (histopathologic confirmation) and OS
- **Key secondary endpoints:** 24-mo PFS, ORR, PRO, and safety

Statistical Considerations (IA1)
- Interim analysis after ~237 PD or deaths
- Cutoff date: January 9, 2023
- Interim analysis database lock: Feb 17, 2023
- Efficacy assessment in all randomized participants and safety in all participants who received 1 dose of study drug

*cCRT regimen included 5 cycles (with optional sixth dose) of cisplatin 40 mg/m^2 QW with EBRT, then followed by brachytherapy.

NCT04221945. Lorusso. ESMO 2023. Abstr LBA38.

Median follow-up: 17.9 mo

KEYNOTE-A18: Baseline Characteristics and Tx Exposure

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

Characteristic, n (%)	Placebo Arm (n = 531)	Pembro Arm (n = 529)
FIGO 2014 stage (at screening)		
▪ IB2-IIB	227 (42.7)	235 (44)
▪ III-IVA	304 (57.3)	294 (55.6)
Lymph node involvement†		
▪ Positive pelvic only	324 (61.0)	326 (61.6)
▪ Positive para-aortic only	10 (1.9)	14 (2.6)
▪ Positive pelvic and para-aortic	104 (19.6)	105 (19.8)
▪ No positive pelvic or para-aortic	93 (17.5)	84 (15.9)
Planned type of EBRT		
▪ IMRT or VMAT	470 (88.5)	469 (88.7)
▪ Non-IMRT and non-VMAT	61 (11.5)	60 (11.3)
Planned total radiotherapy dose (EQD2)		
▪ <70	46 (8.7)	47 (8.9)
▪ ≥70	485 (91.3)	482 (91.1)

- Total median number (range) of cycles with Pembro or placebo/cisplatin: 11 (1-20)/5 (1-7)
- Overall treatment days (range) with Pembro vs placebo: 52 (12-139) vs 52 (2-166); treatment within 50/56 days with Pembro vs placebo: 184/386 vs 194/390
- Median (range) radiation treatment of total cervix physical dose in Pembro vs placebo arm: 76 (14-94) vs 76 (3-125)
- Median (range) radiation treatment of total cervix EQD2 dose in Pembro vs placebo arm: 87 (14-118) vs 87 (3-207)

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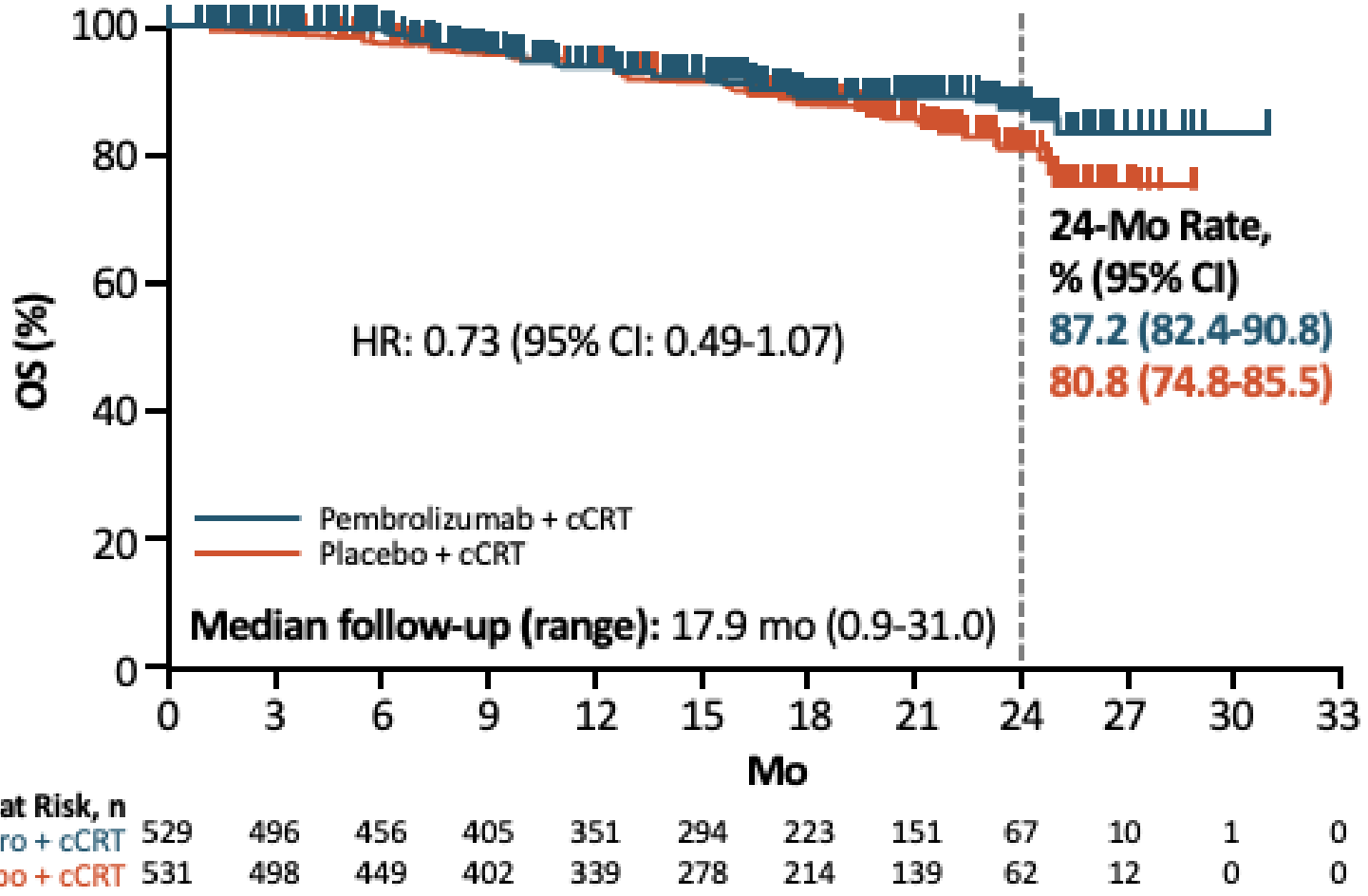
*In each treatment arm, 2 patients (0.4%) had missing information for race. †Per protocol, positive lymph node was defined as ≥1.5 cm shortest dimension by MRI or CT.

KEYNOTE-A18: OS (Coprimary Endpoint)



Characteristic	Events,* %	Median, Mo (95% CI)
Pembrolizumab	8.3	NR (NR-NR)
Placebo	11.1	NR (NR-NR)

*In this analysis, 103 of expected 240 deaths (42.9%) had occurred.

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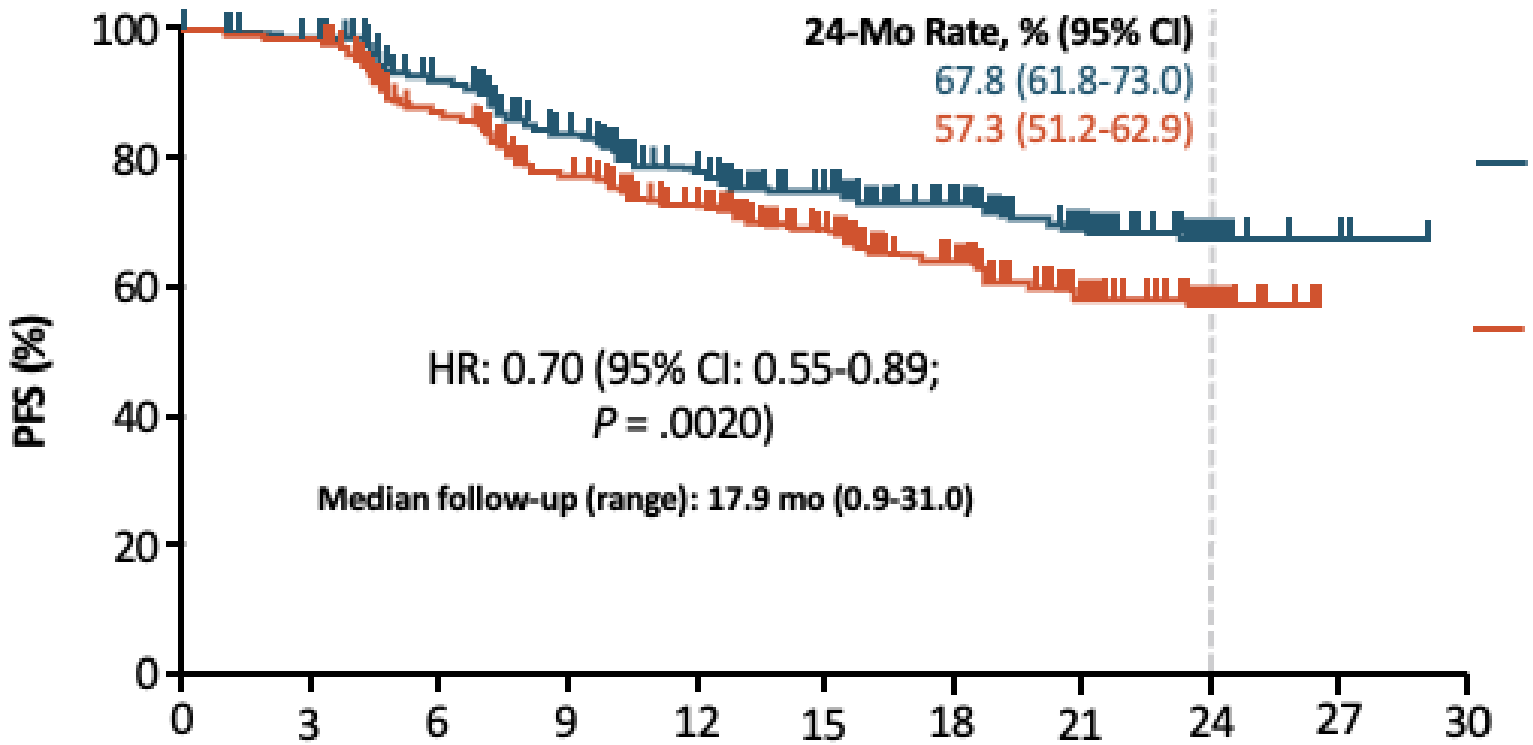
KEYNOTE-A18: PFS (Coprimary Endpoint)



Characteristic	Events, %	Median, Mo (95% CI)
Pembrolizumab	21.7	NR (NR-NR)
Placebo	29.0	NR (NR-NR)

Patients at Risk, n

Pembro + cCRT	529	462	400	331	282	222	171	100	26	3	0
Placebo + cCRT	531	463	379	306	263	208	149	88	20	0	0

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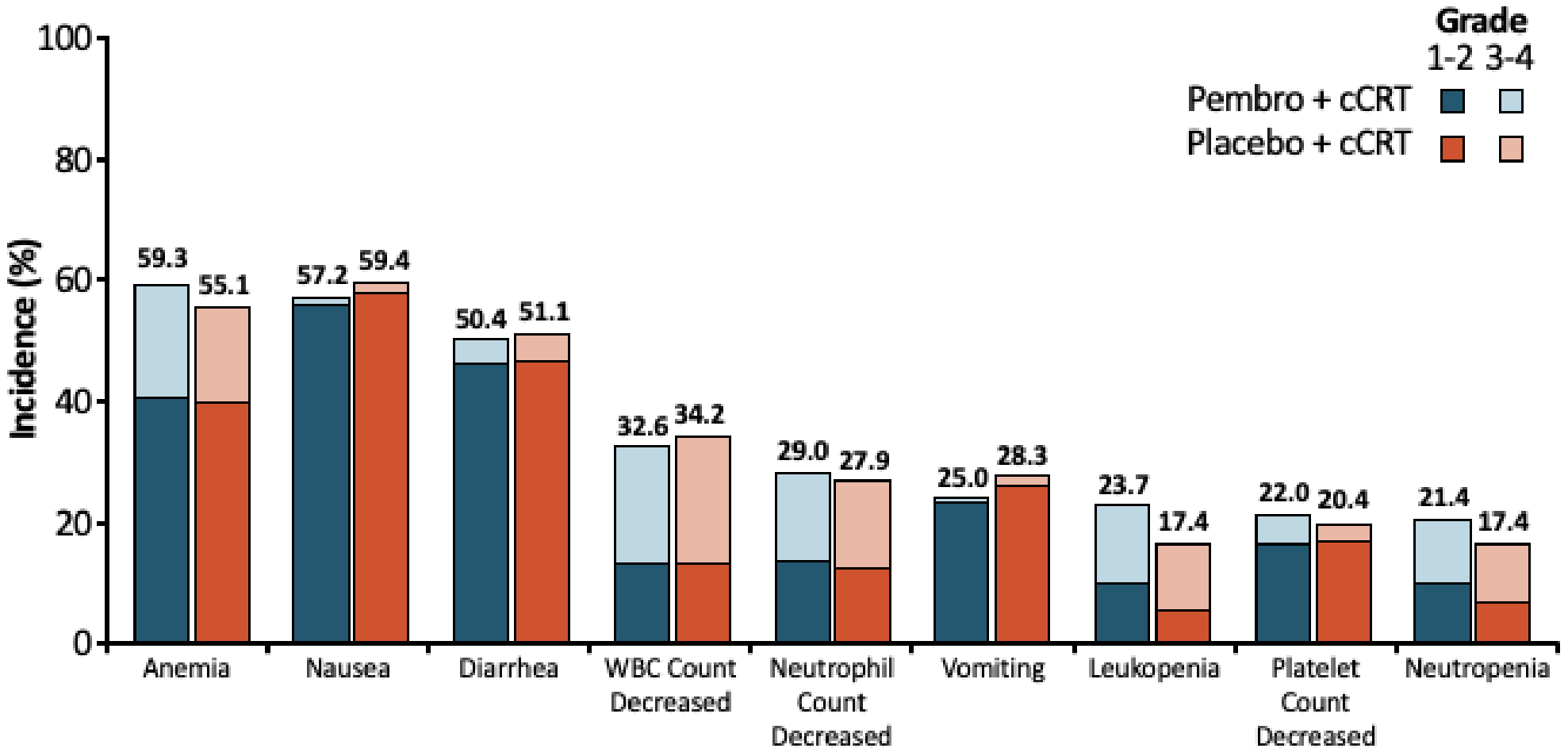
KEYNOTE-A18: Safety Summary

AEs, n (%)	All-Cause AE		Treatment-Related AEs*		Immune-Mediated AEs†	
	Placebo Arm (n = 528)	Pembro Arm (n = 530)	Placebo Arm (n = 528)	Pembro Arm (n = 530)	Placebo Arm (n = 528)	Pembro Arm (n = 530)
Any grade	**526 (99.2)**	**525 (99.4)**	**509 (96.0)**	**507 (96.0)**	**62 (11.7)**	**172 (32.6)**
▪ Grade ≥3	364 (68.7)	393 (74.6)	321 (60.6)	354 (67.0)	6 (1.1)	22 (4.2)
▪ Serious	131 (24.7)	150 (28.4)	65 (12.3)	91 (17.2)	6 (1.1)	15 (2.8)
Led to death	6 (1.1)	5 (0.9)	2 (0.4)‡	2 (0.4)	0	0
Led to discontinuation						
▪ Of any treatments	75 (14.2)	92 (17.4)	67 (12.6)	81 (15.3)	2 (0.4)	12 (2.3)
▪ Of all treatments	2 (0.4)	1 (0.2)	1 (0.2)	0	0	0

*Per investigator assessment.
†Events were considered regardless of attribution to treatment by investigator.
‡Bone marrow failure and neutropenic colitis.

KEYNOTE-A18: Treatment-Related AEs (≥20%)



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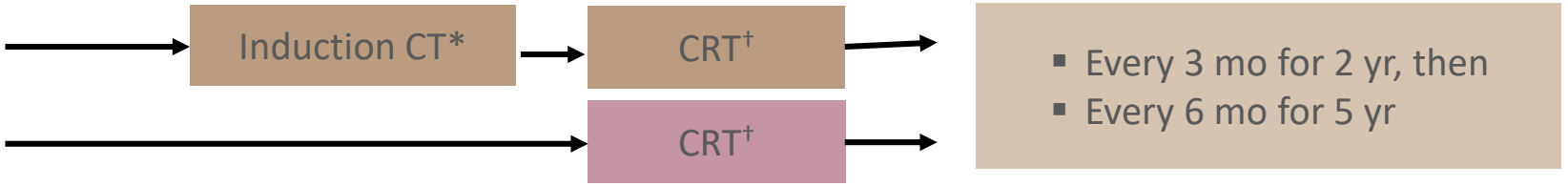
Induction CT Followed by CRT vs Chemoradiation Alone as First-line Treatment for LACC (INTERLACE): Study Design

International, randomized, multicenter phase III trial[1-4]

Previously, in meta-analysis, signal was observed for OS at 5 yr favoring short-course CT followed by CRT[1]; induction chemotherapy protocol in 46 patients further demonstrated feasibility of this approach[2]

Stratified by site, stage, nodal status, 3D-conformal vs IMRT EBRT, 2D vs 3D brachytherapy, tumor size, SCC vs other

Patients with newly diagnosed, histology-confirmed FIGO (2008) stage IB1N+, IB2, II, IIIB, IVA squamous, adeno, adenosquamous CC; no nodes above aortic bifurcation on imaging; no prior pelvic RT (N = 500)



*Induction CT consist of weekly paclitaxel 80 mg/m^2 and carboplatin AUC 2 for 6 wk (Days 1, 8, 15, 22, 29, and 36).
†CRT consists of EBRT 40-50.4 Gy in 20-28 fractions plus intracavity brachytherapy for minimum total EQD2 dose of 78 Gy to point A, 3D IGABT recommended; with weekly cisplatin 40 mg/m^2 for 5 wk and to start on first weeks of RT or as soon as blood counts have recovered from induction CT, but overall treatment time within ≤50 days.

Primary endpoints: PFS, OS

Secondary endpoints: safety, patterns of relapse, QoL, time to next treatment

Statistical considerations (target efficacy): PFS HR = 0.65 (132-168 events for 70%-80% power; OS HR = 0.65-0.70 with 70%-84% power

Error rate 5%; hierarchical sequential testing based on PFS of P <.05.

1. Neoadjuvant chemotherapy for locally-advanced cervical cancer meta-analysis collaboration. EJC. 2003; 37:2470.
2. McCormack. BJC. 2013;108:2464. 3. NCT01566240. 4. McCormack. ESMO 2023. Abstr LBA8.

INTERLACE: Demographics and Disease Characteristics

Demographics	CRT (n = 250)	Induction CT + CRT (n = 250)
Median age, yr (range)	46 (24-78)	46 (26-78)
ECOG PS, n (%)		
▪ 0	221 (88)	214 (86)
▪ 1	29 (12)	36 (14)
Country, n (%)		
▪ United Kingdom	190 (76)	190 (76)
▪ Mexico	51 (20)	49 (20)
▪ Italy	3 (1)	5 (2)
▪ India	5 (2)	5 (2)
▪ Brazil	1 (<1)	1 (<1)

Disease Characteristic	CRT (n = 250)	Induction CT + CRT (n = 250)
FIGO stage, n (%)		
▪ IB1	2 (<1)	2 (<1)
▪ IB2	23 (9)	19 (8)
▪ IIA	14 (6)	17 (7)
▪ IIB	176 (70)	178 (71)
▪ IIIB	30 (12)	26 (10)
▪ IVA	5 (2)	8 (3)
Cell type, n (%)		
▪ Nonsquamous	45 (18)	44 (18)
▪ Squamous	205 (82)	206 (82)
Nodal status, n (%)		
▪ Negative	142 (57)	44 (18)
▪ Positive	108 (43)	206 (82)
Median longest tumor diameter, cm (range)	4.9 (1.8-12.8)	4.8 (1.3-13.5)

INTERLACE: Adherence to Therapy

Adherence to Induction Chemotherapy	Paclitaxel and Carboplatin (n = 250)
Completed 6 weekly cycles, n (%)	211 (84)
Completed at least 5 cycles, n (%)	230 (92)
Main reasons for fewer than 6 cycles, n (%) ▪ AEs leading to d/c ▪ Hematologic AEs ▪ Nonhematologic AEs ▪ Hematologic and nonhematologic AEs	 29 (11) 9 (31) 17 (59) 3 (10)
Withdrawal/other, n (%)	10 (4)
Median interval from induction CT to radiotherapy, days (range)	7 (5-53)

Adherence to Cisplatin, n (%)	CRT (n = 250)	Induction CT + CRT (n = 250)
Completed 5 weekly cycles	197 (79)	169 (68)
Completed at least 4 cycles	224 (90)	212 (85)
Main reasons for fewer than 5 cycles ▪ AEs leading to d/c ▪ Hematologic AEs ▪ Nonhematologic AEs ▪ Hematologic and nonhematologic AEs ▪ Other	 33 (13) 4 (12) 25 (76) 4 (12) 20 (8)	 68 (27) 34 (50) 20 (29) 14 (21) 13 (5)

Adherence to Radiation	CRT (n = 250)	Induction CT + CRT (n = 250)
Received EBRT, n (%) ▪ IMRT ▪ 32 conformal	321 (92) 93 (40) 138 (60)	242 (97) 102 (42) 140 (58)
Received brachytherapy, n (%) ▪ 2D point A ▪ 3D point A ▪ 3D HR-CTV D90	223 (97) 49 (22) 106 (48) 68 (30)	238 (98) 46 (19) 120 (51) 72 (30)
Overall median treatment time, days (range)	45 (37-88)	45 (36-70)

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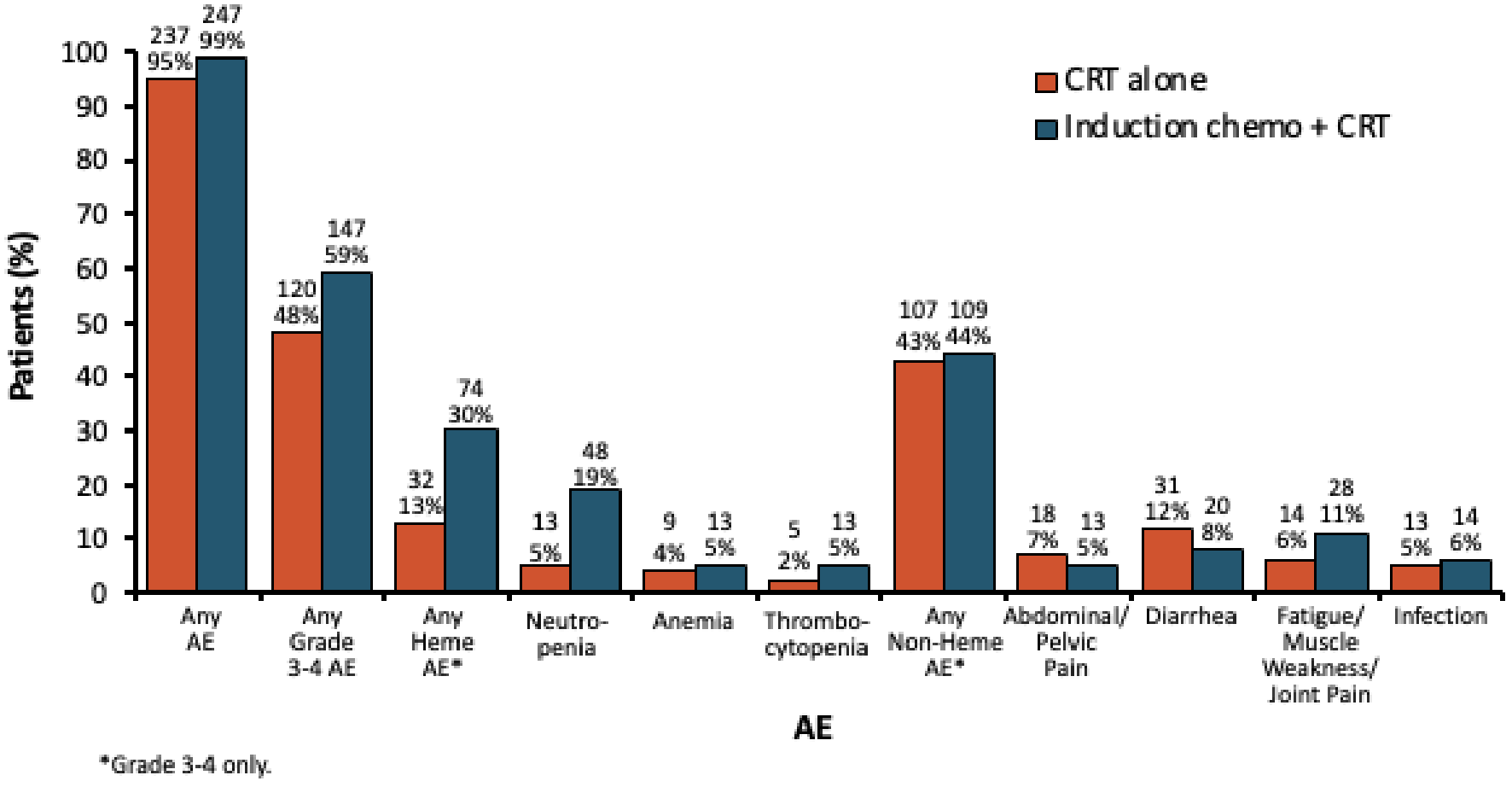
INTERLACE: Any-Grade AEs at Any Time



*Grade 3-4 only.

- Of 102 patients, 42% reported grade 2 alopecia in induction CT + CRT arm
- Total of 3 deaths were reported:
  - 2 patient deaths with CRT
  - 1 patient death with induction CT + CRT

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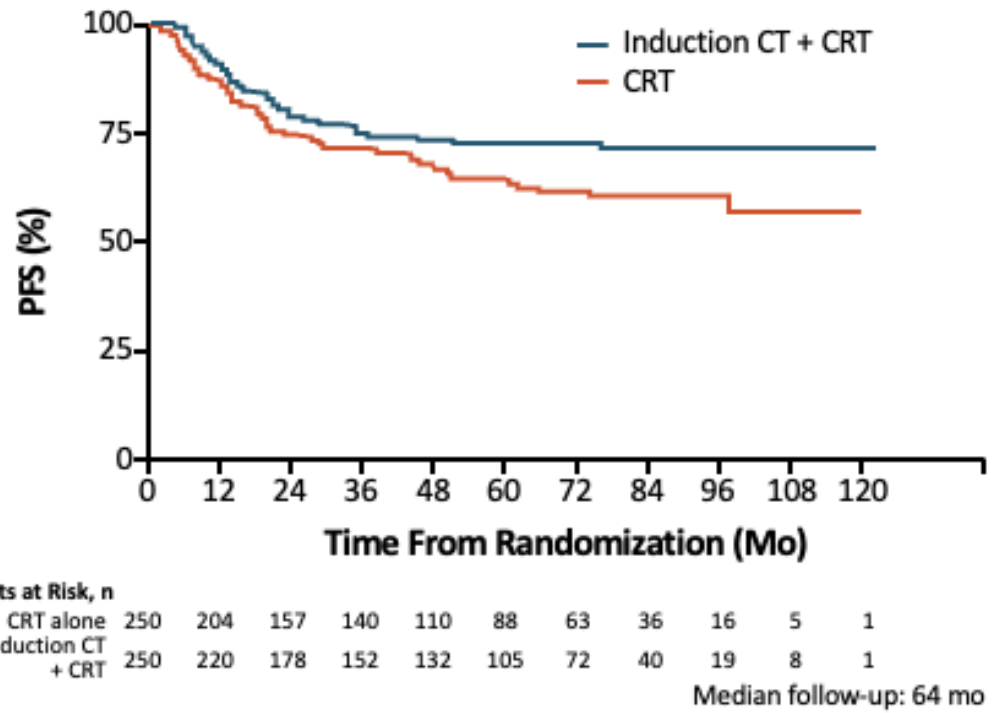
INTERLACE: PFS (Coprimary Endpoint)



	CRT (n = 250)	Induction CT + CRT (n = 250)
PFS events	146	
HR (95% CI) ▪ *P* value	0.65 (0.46-0.91) .013	
3-yr PFS rate, %	72	75
5-yr PFS rate, %	64	73

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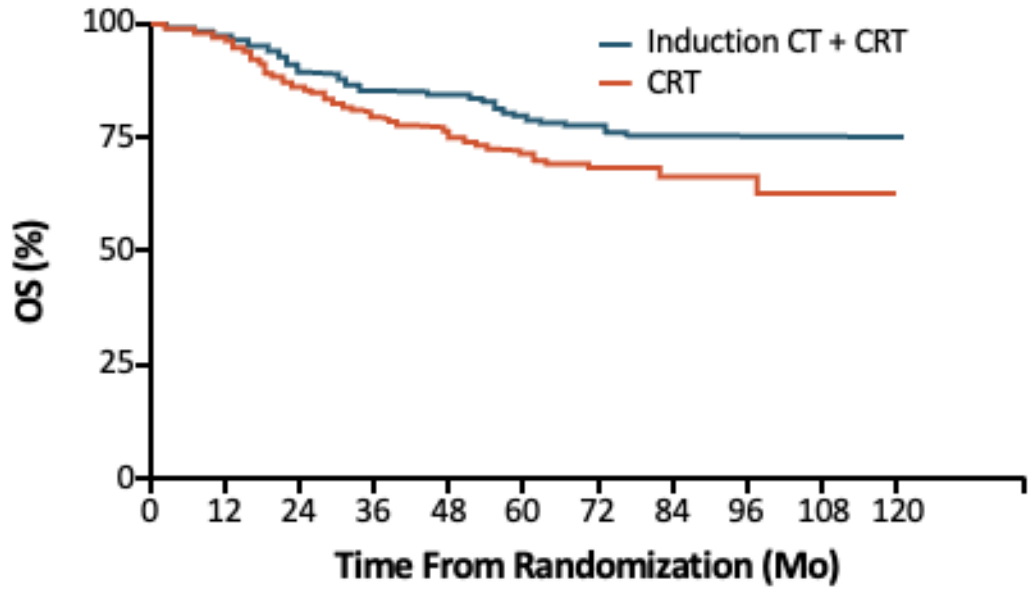
INTERLACE: OS (Coprimary Endpoint)



Patients at Risk, n

CRT alone	250	228	181	154	124	99	67	39	16	5	1
Induction CT + CRT	250	236	195	168	146	111	75	42	19	8	1

Median follow-up: 64 mo

	CRT (n = 250)	Induction CT + CRT (n = 250)
OS events	109	
HR (95% CI) ▪ *P* value	0.61 (0.40-0.91) .04	
3-yr OS rate, %	80	88
5-yr OS rate, %	72	80

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INTERLACE: Patterns of Relapse

Patterns of Relapse, n (%)	CRT (n = 250)	Induction CT + CRT (n = 250)
Local/pelvic	21 (8)	26 (10)
Local/pelvic and distant	20 (8)	14 (6)
Distant	30 (12)	16 (6)
Total local/pelvic relapses	41 (16)	40 (16)
Total distant relapses	50 (20)	30 (12)

McCormack. ESMO 2023. Abstr LBA8.

Treatment of Cervical Cancer

Early Stage (FIGO $1B_1$-IB_2):

- Radical Hysterectomy & Lymphadenectomy plus/minus adjuvant therapy

Locally Advanced (FIGO IB_3-IVA):

- Chemoradiation plus High Dose Rate Intracavitary Brachytherapy

Isolated, Central Recurrence:

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Metastatic/Persistent/Recurrent Cervical Cancer

Tisotumab Vedotin vs Investigator's Choice CT in Advanced CC (innovaTV 301 Interim Analysis): Study Design

- Global, randomized, open-label phase III study in second- or third-line recurrent/metastatic CC
  - Tisotumab vedotin showed efficacy and manageable safety profile in patients with recurrent/metastatic CC that progressed on or after chemotherapy in phase II innovaTV 204 study[1]

Stratified by ECOG PS (0 vs 1), previous bevacizumab (yes vs no), geographic region (US, Europe, other)

Patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy doubled ± bevacizumab and anti–PD-1/PD-L1 antibody, if eligible and available; measurable disease per RECIST v1.1; ECOG PS ≤0 (N = 502)

Tisotumab Vedotin 2.0 mg/kg IV Q3W

Chemotherapy Options*
- Topotecan
- Vinorelbine
- Gemcitabine
- Irinotecan
- Pemetrexed

Statistical Considerations

Hierarchical testing with boundary of significance
- OS 2-sided $P = .0226$
- PFS 2-sided $P = .0453$
- ORR 2-sided $P = .050$

Planned events for 90% power: 336; IA: 256 OS events
- Assumed HR: 0.70
- Dropout rate per yr: 5%

- **Primary endpoints:** OS†
- **Secondary endpoints:** PFS,‡ ORR,‡ safety

*Chemotherapy was given at following doses: topotecan 1 or 1.25 mg/m^2 IV on Days 1-5, Q3W; vinorelbine 30 mg/m^2 IV on Days 1 and 8, Q3W; gemcitabine 1000 mg/m^2 IV on Days 1 and 8, Q3W; irinotecan 100 or 125 mg/m^2 IV, Q3W, or every 42 wk; pemetrexed 500 mg/m^2 on Day 1, Q3W.
†Defined as time from randomization to date of death for any cause.
‡Assessed by the investigator.

1. Coleman. Lancet Oncol. 2021;22:609. 2. NCT04697628. 3. Vergote. ESMO 2023. Abstr LBA9.

innovaTV 301 Interim Analysis: Baseline Characteristics

Characteristics		CT (n = 249)	Tisotumab Vedotin (n = 253)
Median age, yr (range)		50 (27-78)	51 (26-80)
Baseline ECOG PS, n (%)	▪ 0	136 (54.6)	137 (54.2)
	▪ 1	113 (45.4)	116 (45.8)
Region, n (%)	▪ US	14 (5.6)	16 (6.3)
	▪ Europe	104 (41.8)	106 (41.9)
	▪ Asia	88 (35.3)	85 (33.6)
	▪ Other	43 (17.3)	46 (18.2)
Histology, n (%)	▪ SCC	157 (63.1)	160 (63.2)
	▪ AC	75 (30.1)	85 (33.6)
	▪ ASC	17 (6.8)	8 (3.2)
Disease status at study entry, n (%)	▪ Pelvic recurrent only	4 (9.6)	27 (10.7)
	▪ Extrapelvic metastatic	225 (90.4)	226 (89.3)

Characteristics, n (%)		CT (n = 249)	Tisotumab Vedotin (n = 253)
No of previous systemic tx	▪ 1	149 (59.8)	159 (62.8)
	▪ 2	100 (40.2)	93 (36.8)
	▪ Unknown	0	1 (0.4)
Previous bevacizumab		157 (63.1)	164 (64.8)
Previous anti–PD-1/PD-L1		67 (26.9)	71 (28.1)
Previous RT for CC		203 (81.5)	205 (81.0)
Biopsy evaluable		194 (77.9)	210 (83.0)
Positive membrane TF expression*		183 (94.3)	194 (92.4)

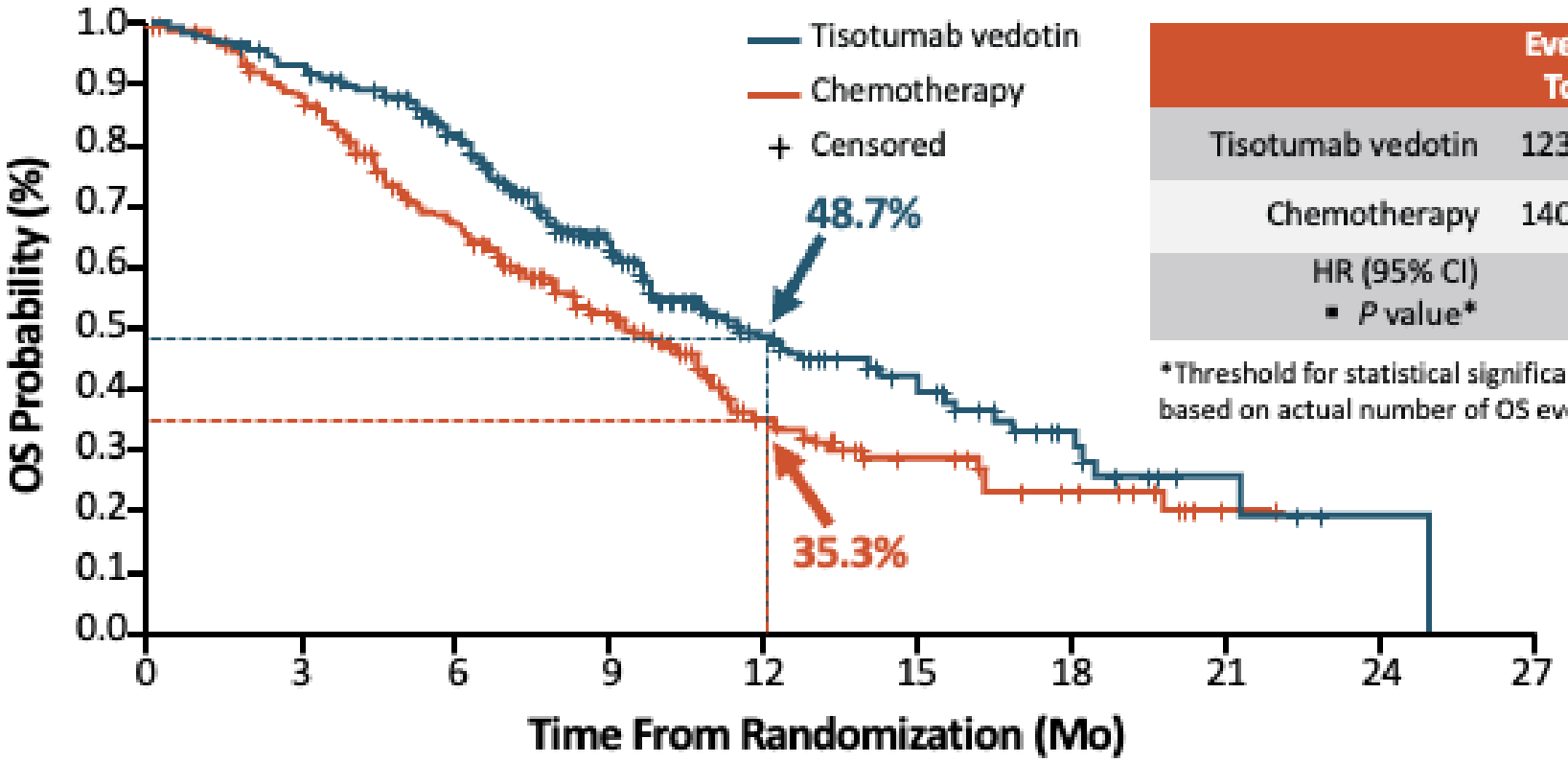
*TF expression defined as TF membrane expression ≥1% by IHC; percentages calculated based on number of evaluable biopsies.

- Data cutoff: July 24, 2023
- Median follow-up: 10.8 mo (95% CI: 10.3-11.6)

- Of 253 patients randomized to receive tisotumab vedotin, 250 received ≥1 dose
  - Discontinued treatment: 229
  - Remaining on treatment: 21
- Of 249 patients randomized to receive investigator's choice of chemotherapy, 239 received ≥1 dose
  - Discontinued treatment: 223
  - Remaining on treatment: 16

Vergote. ESMO 2023. Abstr LBA9.

innovaTV 301 Interim Analysis: OS (Primary Endpoint)



	Events/ Total	Median OS, Mo (95% CI)
Tisotumab vedotin	123/253	11.5 (9.8-14.9)
Chemotherapy	140/249	9.5 (7.9-10.7)
HR (95% CI)	0.70 (0.54-0.89)	
▪ *P* value*	.0038	

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

Patients at Risk, n

Tisotumab vedotin	253	234	191	109	52	29	14	4	1	0
IC chemotherapy	249	212	150	87	37	19	11	1	0	0

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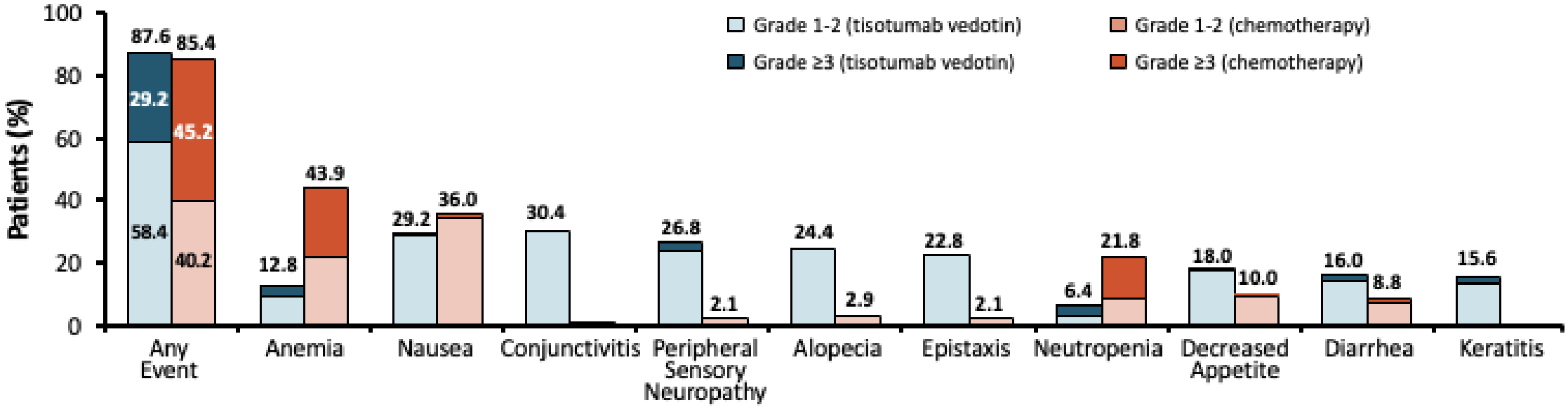
innovaTV 301 Interim Analysis: Most Common Treatment-Related AEs*



- Treatment-related deaths occurred in 0.8% and 0.4% patients in tisotumab vedotin and CT arms, respectively†
- Median relative dose intensity were 96.1% and 90.0% with tisotumab vedotin and chemotherapy arm, respectively

*Treatment-related AEs listed are those occurring in ≥15% of patients on either arm.

†Grade 5 treatment-related AE: acute kidney injury (n = 1) and Stevens-Johnson syndrome (n = 1) in tisotumab vedotin arm and pancytopenia (n = 1) in chemotherapy arm.

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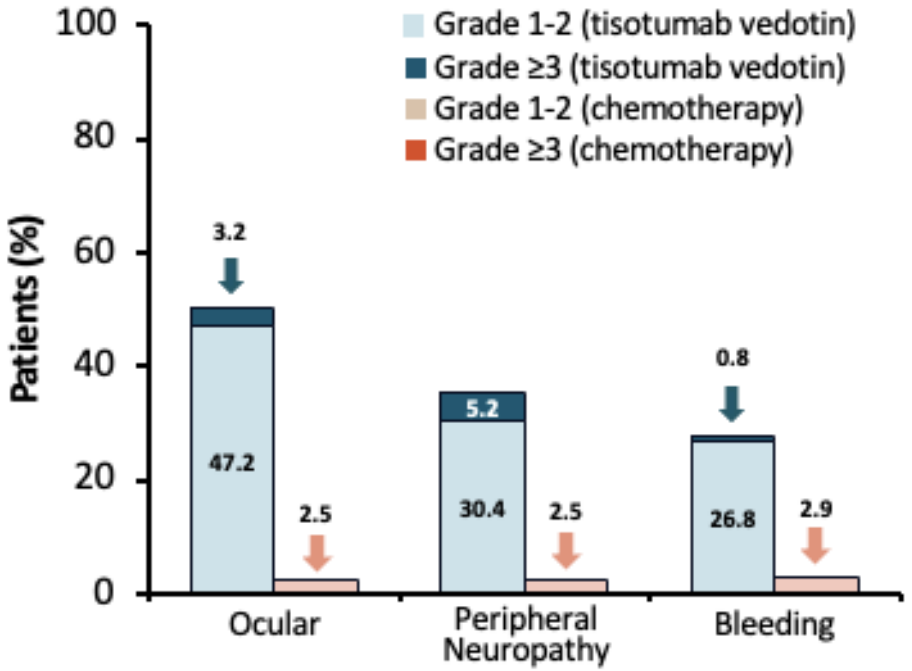
innovaTV 301 Interim Analysis: AESIs With Tisotumab Vedotin



Most Common AESI (Preferred Terms for Each)	
Ocular	▪ Conjunctivitis: 30.4% ▪ Keratitis: 15.6% ▪ Dry eye: 13.2%
Peripheral neuropathy	▪ Peripheral sensory neuropathy: 26.8% ▪ Peripheral sensorimotor neuropathy: 2.4% ▪ Paresthesia: 2.8% ▪ Muscular weakness: 2.4%
Bleeding	▪ Epistaxis: 22.8% ▪ Hematuria: 3.2% ▪ Vaginal hemorrhage: 3.2%

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

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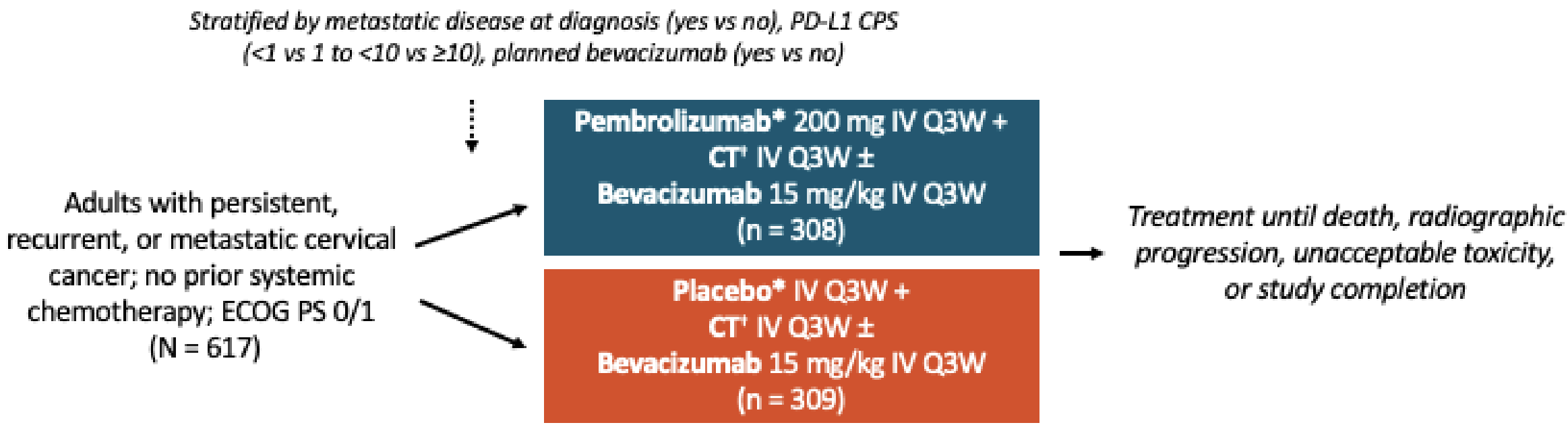
KEYNOTE-826: Study Design

- International, randomized, double-blind phase III trial



*≤35 cycles pembrolizumab/placebo. †CT: ≤6 cycles: paclitaxel 175 mg/m^2 + (cisplatin 50 mg/m^2 or carboplatin AUC 5 mg/mL/min).

- **Dual primary endpoints:** OS and PFS per RECIST v1.1 by investigator
- **Secondary endpoints:** ORR, DoR, 12-mo PFS, safety

Monk. ASCO 2022. Abstr 5500.

KEYNOTE-826: Final Analysis of PFS

Outcome	PD-L1 CPS ≥1		PD-L1 CPS ≥10		All-Comers	
	Pembro (n = 273)	Placebo (n = 275)	Pembro (n = 158)	Placebo (n = 159)	Pembro (n = 308)	Placebo (n = 309)
Median PFS, mo	10.5	8.2	10.4	8.1	10.4	8.2
	HR: 0.58 (95% CI: 0.47-0.71)*		HR: 0.52 (95% CI: 0.40-0.68)*		HR: 0.61 (95% CI: 0.50-0.74)*	
12-mo PFS, %	45.6	33.7	44.7	33.5	44.7	33.1

*Nominal *P* <.0001

KEYNOTE-826: Final Analysis of OS

Outcome	PD-L1 CPS ≥1		PD-L1 CPS ≥10		All-Comers	
	Pembro (n = 273)	Placebo (n = 275)	Pembro (n = 158)	Placebo (n = 159)	Pembro (n = 308)	Placebo (n = 309)
Median OS, mo	28.6	16.5	29.6	17.4	26.4	16.8
	HR: 0.60 (95% CI: 0.49-0.74)*		HR: 0.58 (95% CI: 0.44-0.78)*		HR: 0.63 (95% CI: 0.52-0.77)*	
12-mo OS, %	75.5	63.2	75.9	61.6	74.9	63.7
24-mo OS, %	53.5	39.4	54.4	42.5	52.1	38.7

Similar OS benefit with pembrolizumab regardless of concomitant bevacizumab

Monk. ASCO 2023. Abstr 5500.

KEYNOTE-826: Updated Safety and Treatment Exposure

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

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

Monk. ASCO 2023. Abstr 5500.

Take home messages

1. Recently, surgical treatment of early forms of cervical cancer has been changing to a less radical procedure.
2. Adding chemotherapy before radiochemotherapy improves treatment outcomes in locally advanced disease.
3. The use of immunotherapy in the treatment of advanced and recurrent cervical cancer is increasing.


Thank you