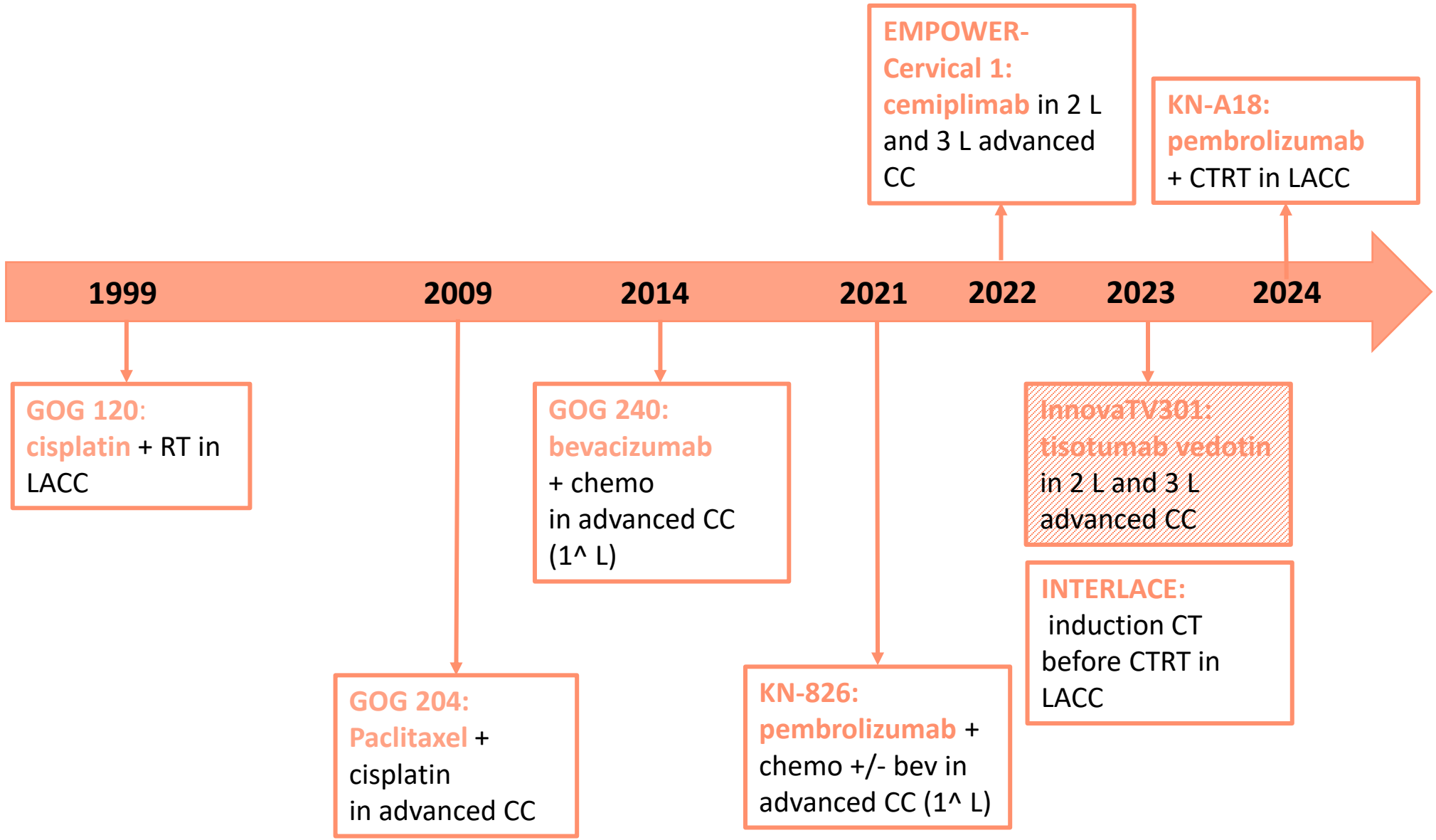
Il trattamento del carcinoma della cervice: dagli stadi iniziali alla malattia metastatica

Giulia Tasca
UOC Oncologia 2
Istituto Oncologico Veneto IRCCS Padova

Practice changing trials in cervical cancer



Rose PG et al, N Engl J Med. 1999; Monk BJ et al, J Clin Oncol. 2009; Tewari KS et al, N Engl J Med. 2014; Colombo N et al, N Engl J Med. 2021; Tewari ST et al, N Engl J Med. 2022; Vergote I et al, N Engl J Med. 2024; Lorusso D et al, Lancet. 2024

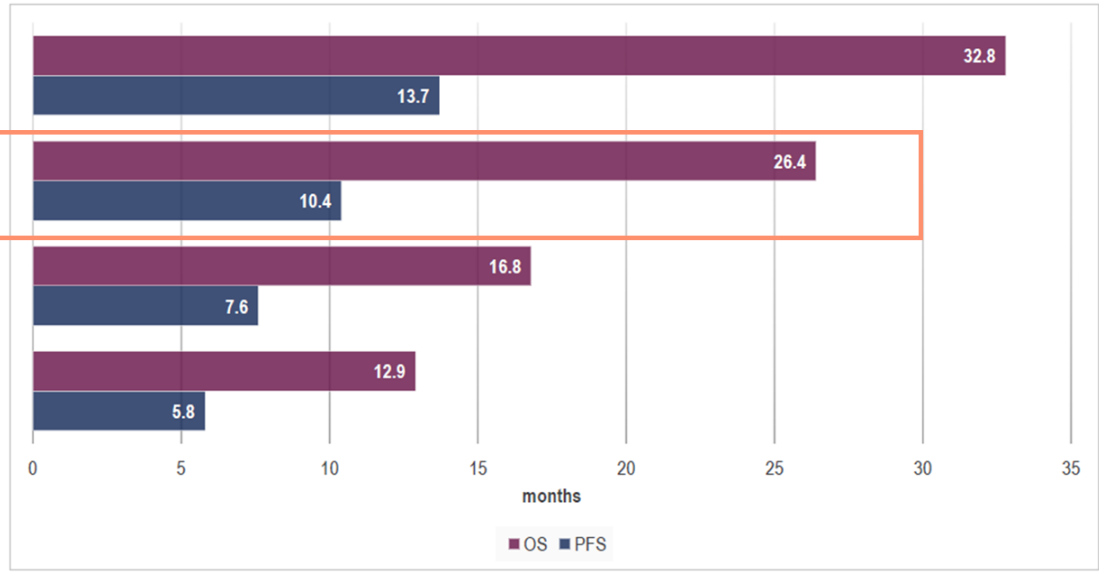
Evolution in the treatment of advacend disease: First Line

BEATcc
Chemo + atezolizumab + bevacizumab

KEYNOTE 826
Chemo + pembrolizumab +/- bevacizumab

GOG 240
Chemo + bevacizumab

GOG 204
CDDP + paclitaxel



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

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

R 1:1

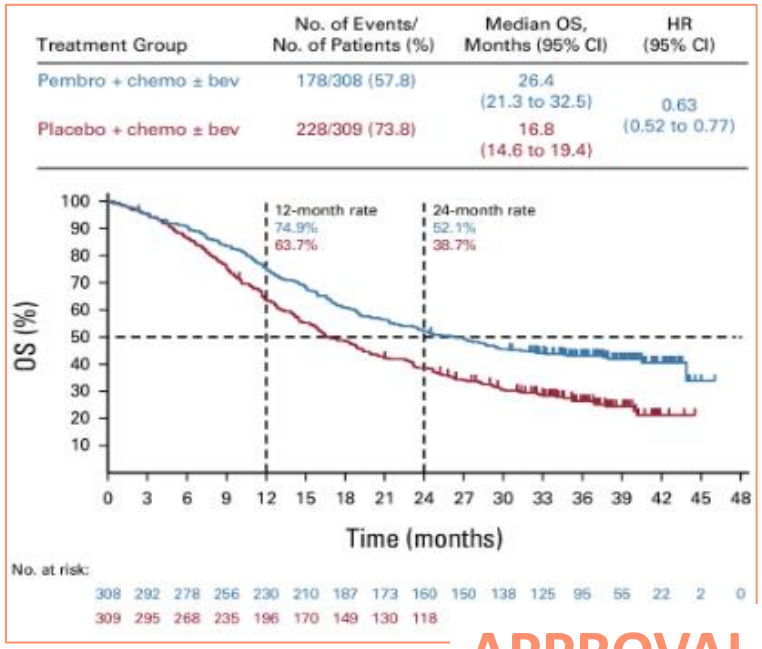
Pembrolizumab 200 mg IV Q3W
for up to 35 cycles
+
Paclitaxel + Cisplatin or Carboplatin IV Q3W
for up to 6 cycles[a]
±
Bevacizumab 15 mg/kg IV Q3W

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

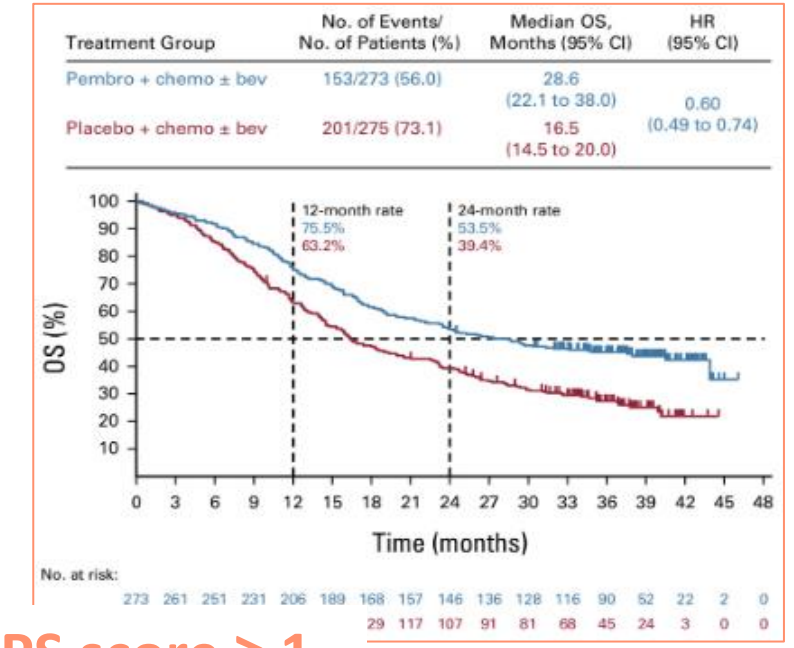
End Points
- **Dual primary:** OS and PFS per RECIST v1.1 by investigator
- **Secondary:** ORR, DOR, 12-mo PFS, and safety

Monk BJ et al, J Clin Oncol. 2009; Tewari KS et al, N Engl J Med. 2014; Colombo N et al, N Engl J Med. 2021; Oaknin A et al, Lancet 2024

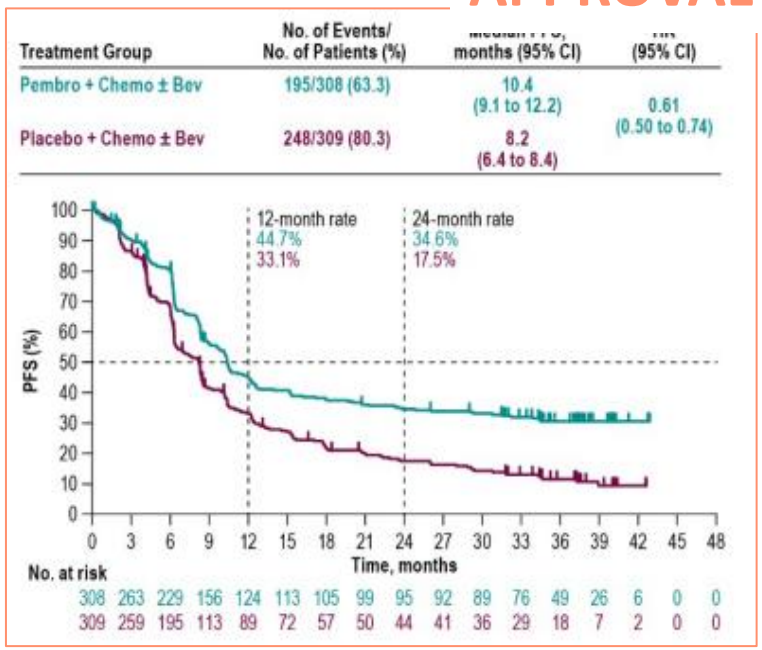
Overall population

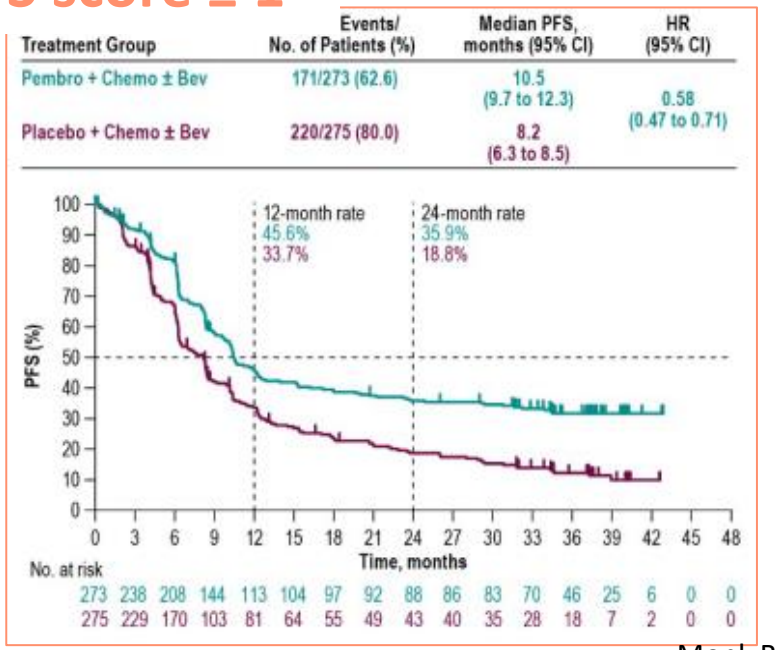


CPS ≥ 1 population



APPROVAL FOR PD-L1 CPS score ≥ 1





Monk BJ et al, J Clin Oncol. 2023

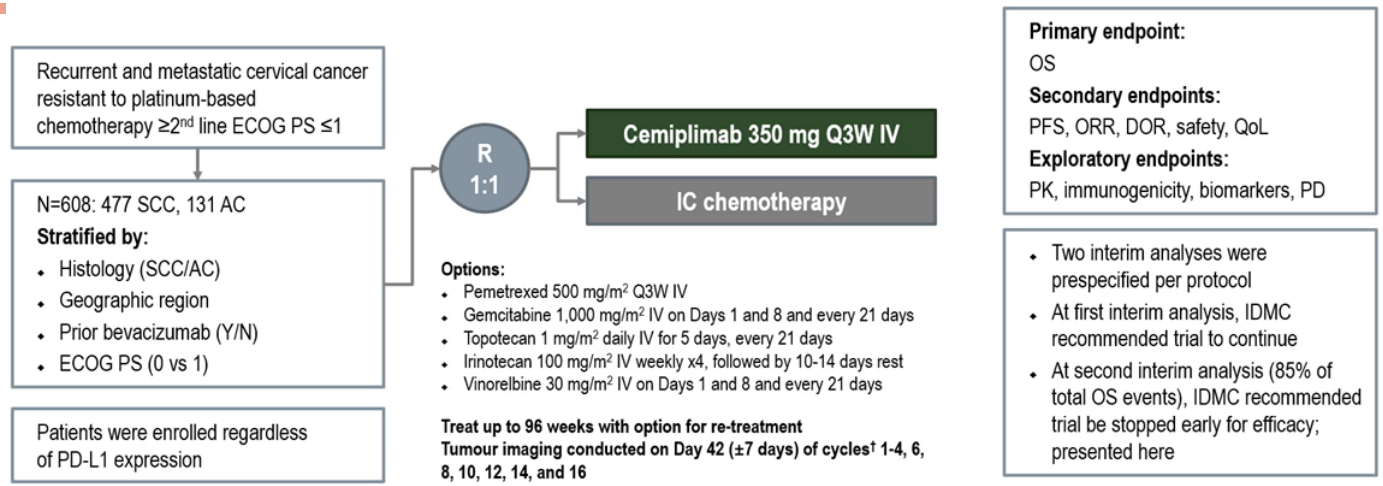
Evolution in the treatment of advacend disease: Second line and beyond

Agent	n	Response	PFS	OS
Bevacizumab	46	11	3.4	7.3
Topotecan	94	13-19	2.1-2.4	6.4-6.6
Vinorelbine	44	14	-	-
Gemcitabine	22	5	2.1	6.5
Albumin-bound paclitaxel	35	29	5.0	9.4
Docetaxel	23	9	3.8	7.0
Pemetrexed	72	14-15	2.5-3.1	7.4-8.8
Irinotecan	42	21	4.5	6.4
Pegylated liposomal doxorubicin	27	11	3.2	8.9
Pazopanib	74	9	4.5	12.7
Lapatinib	78	5	4.2	9.7
Erlotinib	28	0	1.9	5.0

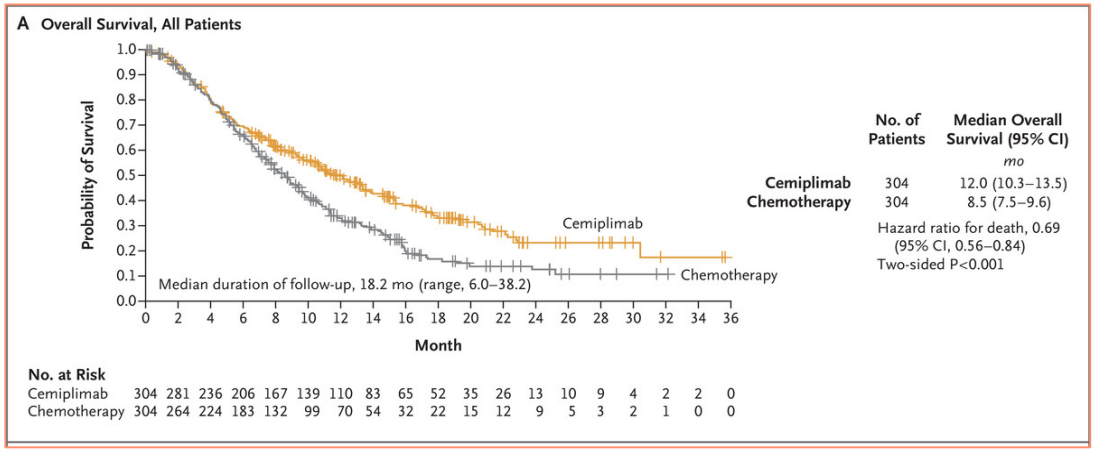
No standard of care

Limited activity of single agent chemotherapy

RR: 0-29%
PFS: 2-5 months
OS: 5-12 months



Data cutoff date: 4 Jan 2021
*Performed according to ENGOT Model C. †To account for differences in drug administration schedules, one cycle is defined as 6 weeks.

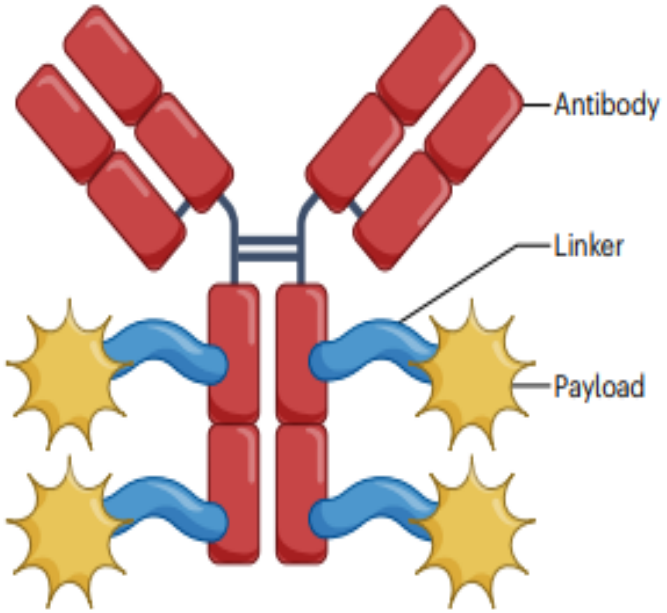


ORR: 16.4% vs 6.3%
TPS≥1%: 18% vs 7.5%
TPS<1%: 11% vs 8.3%

Tewari ST et al, N Engl J Med. 2022

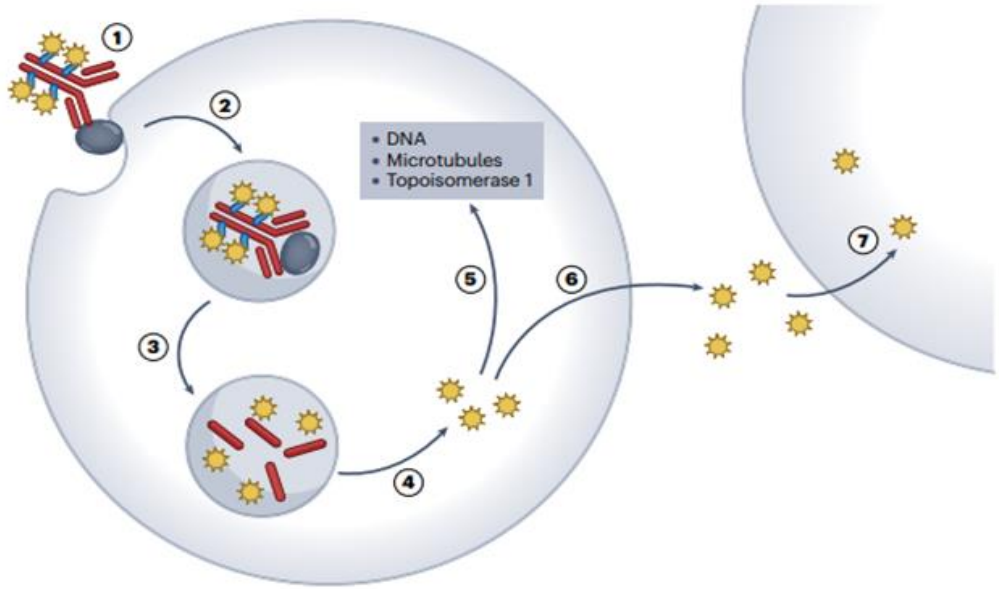
Antibody Drug Conjugates (ADCs)

Ehrlich's magic bullet concept: delivering a toxic drug to tumour cells while sparing the others



Cytotoxic activity

- Binding to specific cell-surface proteins, antibody engagement leads to ADC complex internalization;
- The payload is released in the cytoplasm and takes its effect on the cell, leading to cell death.



Bystander effect:
menbrane-permeable payloads enter neighbouring cells regardless of target expression and can also kill these cells

Target:
cell-surface proteins that are higly exspressed on tumour cells but non on non-malignant cells

- Homogeneous target expression on tumour cells
- Rate of target turnover, internalization and lysosomal processing

Antitumour effects of Ab:

- enhancement of antitumour immunity though the induction of Ab-dependent cytotoxicity.
- Inhibition of oncogenic signaling pathways.

Dumontet C, et al; Nature Reviews Drug Discovery 2023

InnovaTV301: planned iterim analysis

Key Eligibility Criteria

- Recurrent or metastatic cervical cancer
- Disease progression on or after chemotherapy doublet ± bevacizumab and an anti-PD-(L)1 agent, if eligible and available
- ≤2 prior lines
- Measurable disease per RECIST v1.1
- ECOG PS 0-1

Randomization 1:1

N=502

Stratified by:

- ECOG PS (0 vs 1)
- Prior bevacizumab (yes vs no)
- Prior anti-PD-(L)1 therapy (yes vs no)
- Geographic region (US, Europe, Other)

Treatment

Tisotumab Vedotin (n=253)

2.0 mg/kg IV Q3W

IC Chemotherapy[a] (n=249)

- Topotecan
- Vinorelbine
- Gemcitabine
- Irinotecan
- Pemetrexed

Outcomes/Endpoints

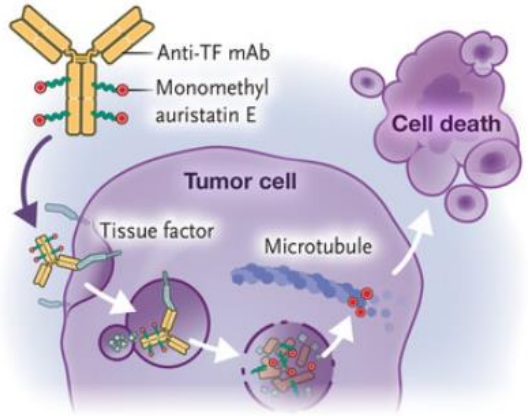
Primary Endpoint

- OS[b]

Key Secondary Endpoints

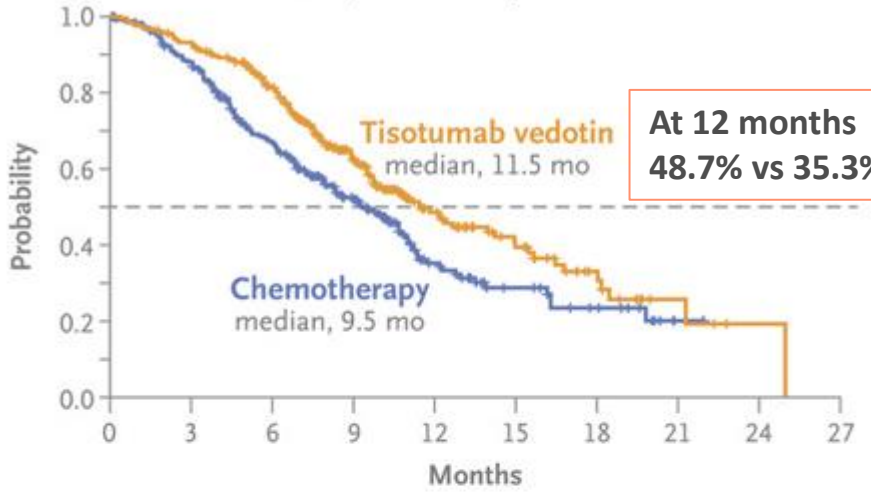
- PFS[c]
- ORR[c]
- Safety

Mechanism of Action



Overall Survival

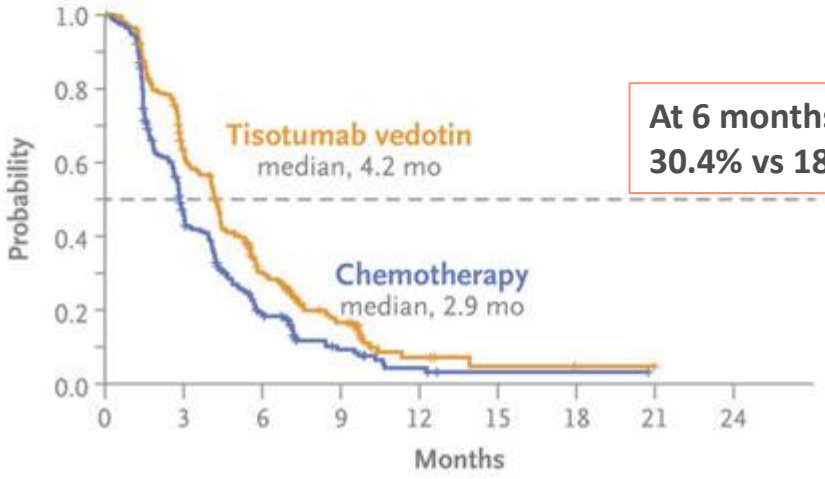
Hazard ratio for death, 0.70 (95% CI, 0.54–0.89)
P=0.004 by stratified log-rank test



At 12 months
48.7% vs 35.3%

Progression-free Survival

Hazard ratio for disease progression or death, 0.67 (95% CI, 0.54–0.82)
P<0.001 by stratified log-rank test



At 6 months
30.4% vs 18.9%

Vergote I et al, N Engl J Med. 2024

DESTINY PanTumor 02

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer guidelines[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1

T-DXd
5.4 mg/kg
q3w

n≈40 per cohort planned

(Cohorts with no objective responses in the first 15 patients were to be closed)

- Cervical cancer
- Endometrial cancer
- Ovarian cancer
- Biliary tract cancer
- Pancreatic cancer
- Bladder cancer
- Other tumors[b]

Primary endpoint

- Confirmed ORR (investigator)[c]

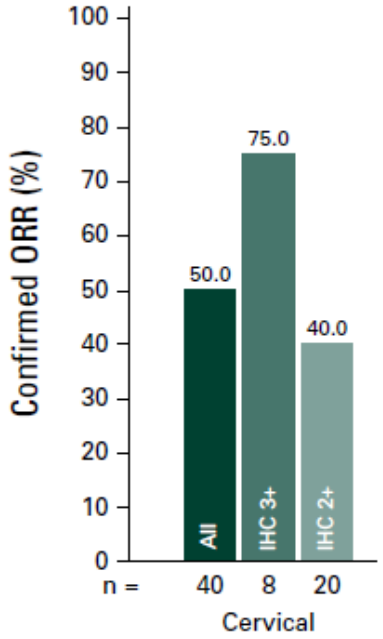
Secondary endpoints

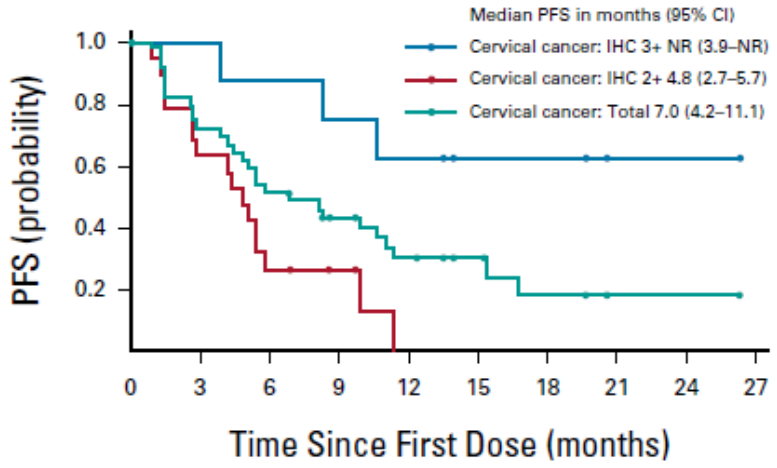
- DOR[c]
- DCR[c]
- PFS[c]
- OS
- Safety

Data cut-off for analysis:

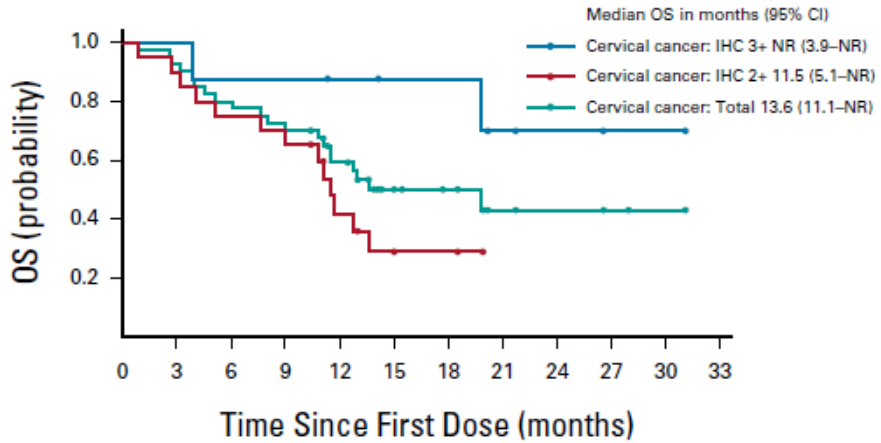
- Nov 16, 2022

FDA accelerated approval for T-DXd in metastatic HER2-positive solid tumors





No. at risk:										
Cervical cancer: IHC 3+	8	8	7	6	5	3	3	1	1	0
Cervical cancer: IHC 2+	20	12	5	3	0					
Cervical cancer: Total	40	28	20	14	9	6	3	1	1	0



No. at risk:												
Cervical cancer: IHC 3+	8	8	7	7	6	5	5	3	2	1	1	0
Cervical cancer: IHC 2+	20	18	15	14	7	3	3	0				
Cervical cancer: Total	40	37	32	29	21	11	9	4	3	2	1	0

Meric-Bernstam et al, J Clin Onco 2023

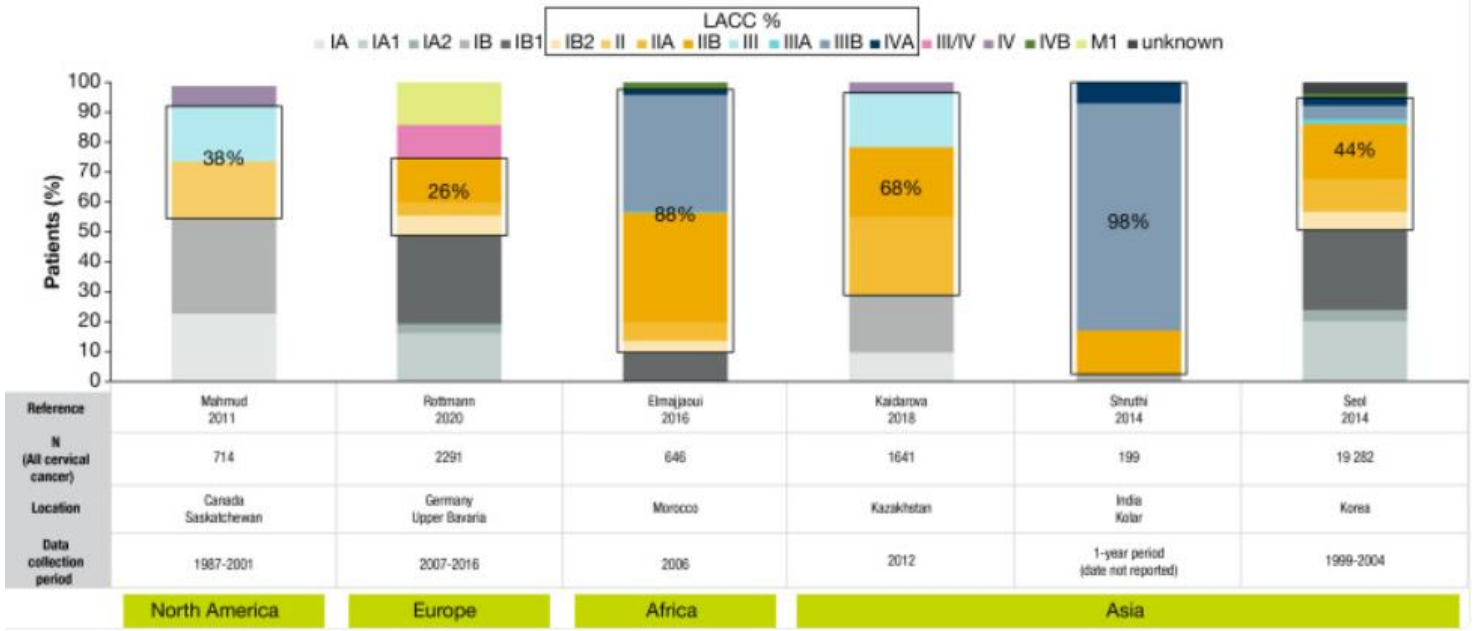
Antibody-drug conjugates: our next future

ADCs could be well placed in the post immune setting and where ICIs are less effective

Target	Name	Payload	Payload	DAR	Linker	Development stage
HER2	Trastuzumab deruxtecan	Topo1i	deruxtecan	8	Cleavable	Phase II – FDA acc appr
	DB-1303 (BNT323)	Topo1i	P1003	8	Cleavable	Phase I/IIA – FDA BTD
	Trastuzumab duocarmazine	DNA alkylating	duocarmazine	2.8	Cleavable	Phase II
	Disitamab vedotin (RC48)	Anti-microtubule	MMAE	4	Cleavable	Phase II
FRα	Mirvetuximab soravtansine	Anti-microtubule	DM4	3.5	Cleavable	Phase II
	Farletuzumab ecteribulin (MORAb-202)	Anti-microtubule	Eribulin mesylate	4	Cleavable	Phase I/II
	Luveltamab tazevibulin (STRO-002)	Anti-microtubule	SC209	4	Cleavable	Phase I/IIA
	Rinatabart sesutecan (Rina-S, PRO1184)	Topo1i	exatecan	8	Cleavable	Phase I/II
	AMT-151	Undisclosed		?	?	Phase I
	IMGN151	Anti-microtubule	DM21	3.5	Cleavable	Phase I
TROP2	Sacituzumab govitecan (IMMU-132)	Topo1i	SN38	7.6	Cleavable	Phase II
	Sacituzumab tirumotecan (MK-2870)	Topo1i	tirumotecan	7.4	Cleavable	Phase III
	Datopotamab deruxtecan (DS-1062)	Topo1i	deruxtecan	4	Cleavable	Phase II
	LCB84	Anti-microtubule	MMAE	4	Cleavable	Phase I/II
B7-H4	SGN-B7H4V	Anti-microtubule	MMAE	4	Cleavable	Phase I
	HS-20089	Topo1i	undisclosed	6	Cleavable	Phase II
	XMT-1660	Anti-microtubule	MMAF	6	Cleavable	Phase I
	AZD8205	Topo1i	AZ14170133	8	Cleavable	Phase I/IIA
B7-H3	Ifinatamab veruxtecan (DS-7300a)	Topo1i	deruxtecan	4	Cleavable	Phase I
TF	Tisotumab vedotin	Anti-microtubule	MMAE	4	Cleavable	Phase II
	XB002	Anti-microtubule	MMAE	3.3	Cleavable	Phase I
AXL	Enapotamab vedotin	Anti-microtubule	MMAE	4	Cleavable	Phase I/II
Claudin6	TORL-1–23	Anti-microtubule	MMAE	?	Cleavable	Phase I

Locally advanced cervical cancer

The estimated median proportion of LACC was 37%

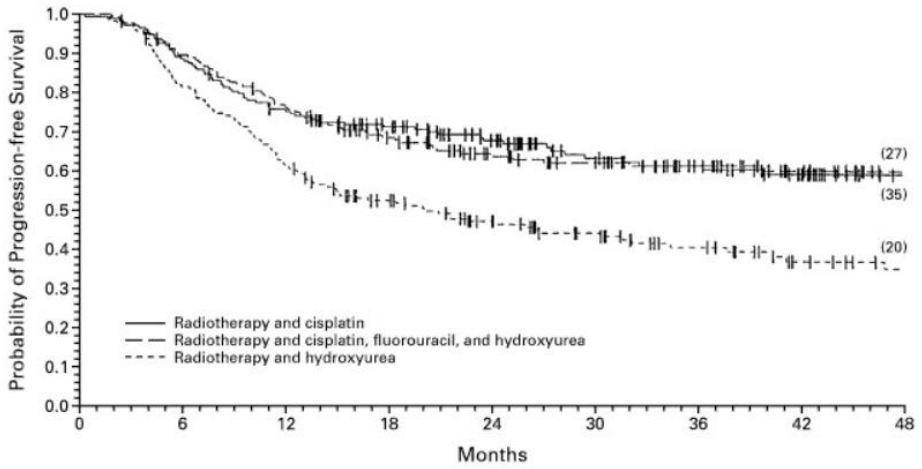


The New England Journal of Medicine

CONCURRENT CISPLATIN-BASED RADIOTHERAPY AND CHEMOTHERAPY FOR LOCALLY ADVANCED CERVICAL CANCER

PETER G. ROSE, M.D., BRIAN N. BUNDY, PH.D., EDWIN B. WATKINS, M.D., J. TATE THIGPEN, M.D., GUNTHER DEPPE, M.D., MITCHELL A. MAIMAN, M.D., DANIEL L. CLARKE-PEARSON, M.D., AND SAM INSALACO, M.D.

Regimens of radiotherapy and chemotherapy that contain cisplatin improve the rates of OS and PFS among women with LACC



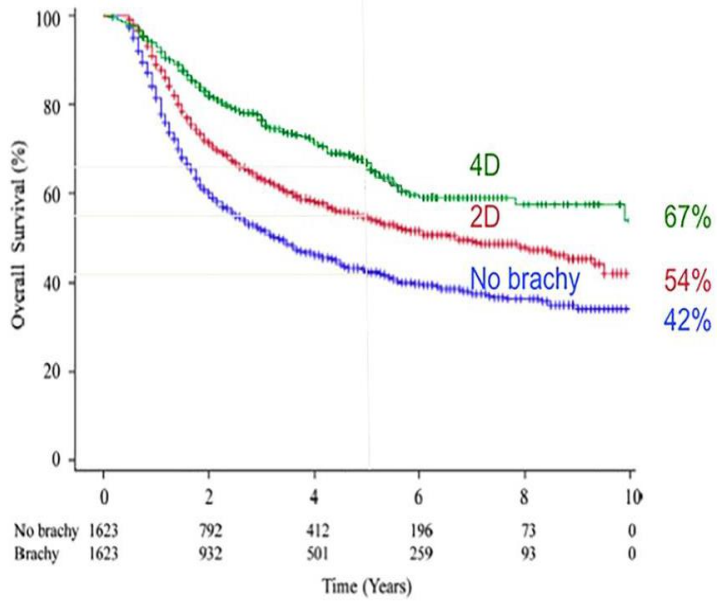
Monk BJ et al, Int J Gynecol Cancer 2022; Rose PG et al, N Engl J Med. 1999;

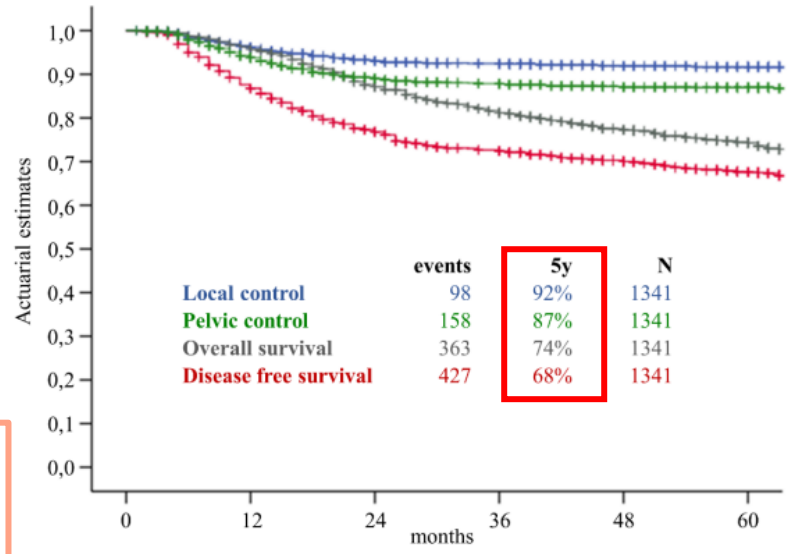
Concurrent CT/RT in LACC and RT evolution

Individual patient data meta-analysis (15 RCT; 3452 women)

	HR(95%CI)	P-value	Absolute benefit (5 years)
Overall disease-free survival	0.78 (0.70-0.87)	0.000005	8%
Locoregional disease-free survival	0.76 (0.68-0.86)	0.000003	9%
Metastases-free survival	0.81 (0.72-0.91)	0.0004	7%
Locoregional disease-free interval	0.74 (0.64-0.86)	0.00009	6%
Metastases-free interval	0.83 (0.71-0.99)	0.037	4%

5-years OS improvement 6%
5-years DFS improvement 8%

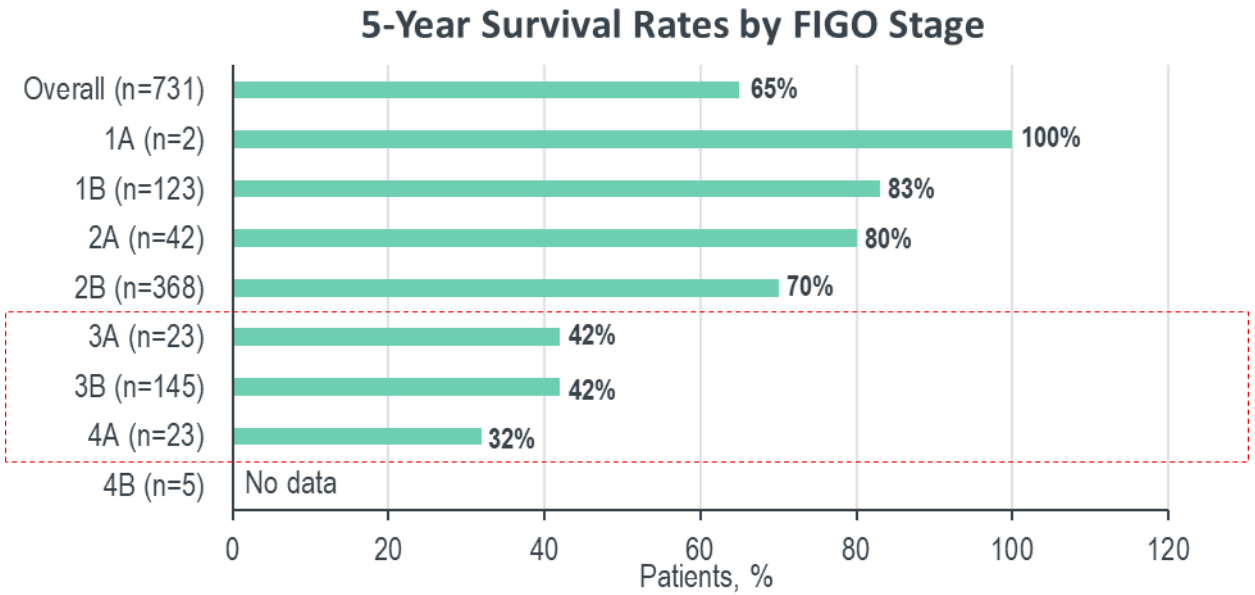




EMBRACE-I
Recommended total cervix EQD2 dose: 85-90 Gy.
Recommended total treatment duration: 56 days.

Cochrane Database Syst Rev. 2010; Han et al, Int J Radiation Oncol Biol Phys 2013; Potter R et al, The lancet 2021

Concurrent CT/RT in LACC



~~Addition of adjuvant chemotherapy post CT-RT (>2000 pts)~~

~~Neoadjuvant chemotherapy before surgery (>1000 pts)~~

Sturdza A et al, Radiother Oncol. 2016; Horeweg et al,Critical Review Onc Hem 2022; Mileskhinet al, Lancet Oncol 2023; Gupta et al, JCO 2018; Kenter JJ et al, JCO 2023.

FIGO 2018 classification

In 2018, FIGO revised the 2014 staging system of cervical cancer:

- Stage IB tumors into three substages based on tumor size (IB1–IB3);
- Patients with regional lymph node metastasis:
  - Stage IIIC1: patients with pelvic lymph node metastasis only
  - Stage IIIC2: patients with positive para-aortic lymph node

- Stage IIIC of the new staging system doesn't take primary tumor size and extent into consideration.

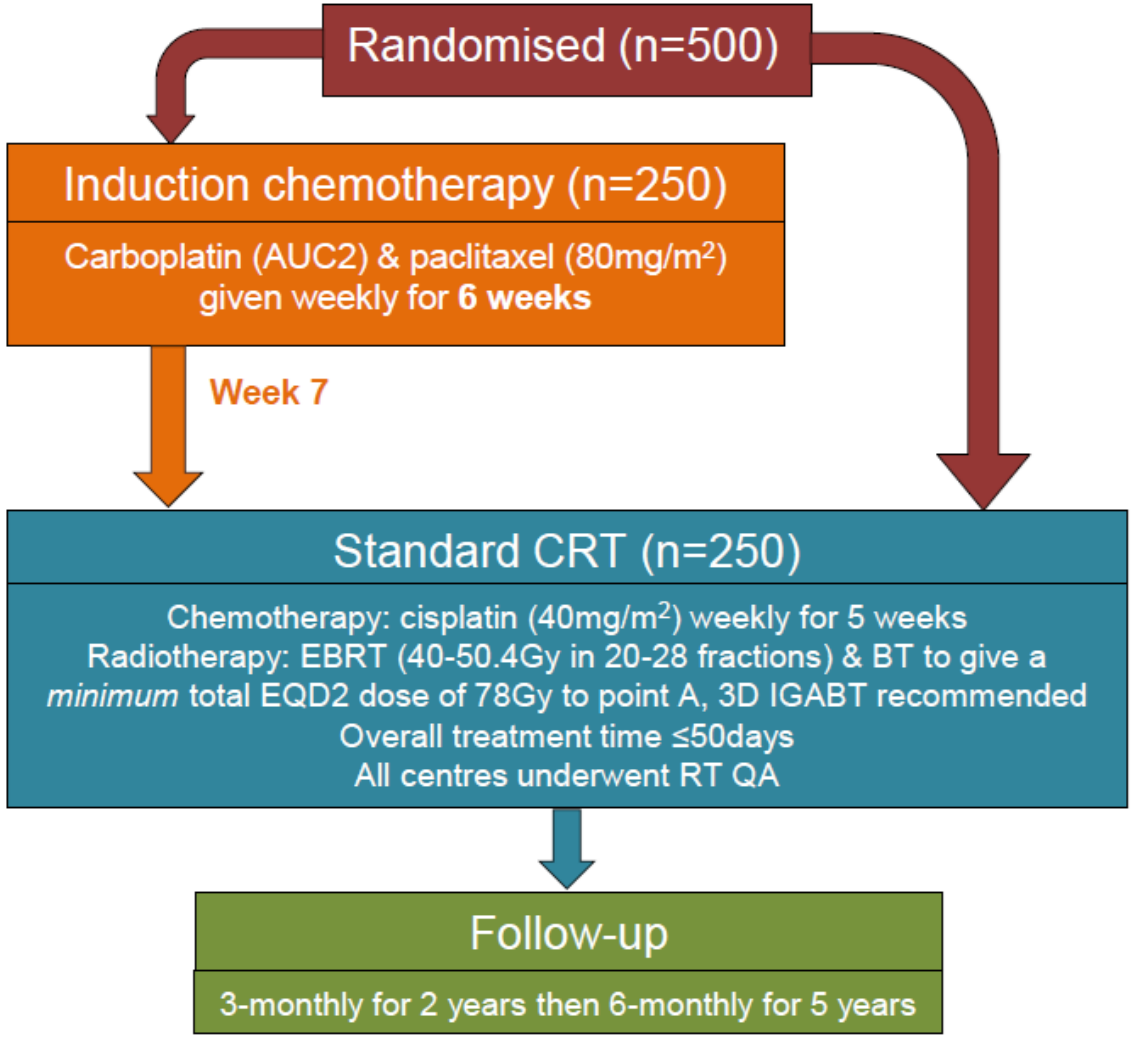
Stage	2018 FIGO Definition
I	Carcinoma is strictly confined to the cervix uteri
IA	Maximum depth of invasion <5 mm
IA1	Maximum depth of invasion <3 mm[b]
IA2	Maximum depth of invasion ≥3 mm and <5 mm
IB	Maximum depth of invasion ≥5 mm, lesion limited to cervix uteri[c]
IB1	Maximum depth of invasion ≥5 mm and <2 cm in the greatest dimension
IB2	Maximum lesion size of ≥2 cm and <4 cm in the greatest dimension
IB3	Maximum lesion size of ≥4 cm in the greatest dimension
II	Carcinoma extends beyond the uterus but not to the pelvic wall or to the lower one-third of the vagina
IIA	Involves upper two-thirds of the vagina; no parametrial invasion
IIA1	Invasive carcinoma <4 cm in the greatest dimension
IIA2	Invasive carcinoma ≥4 cm in the greatest dimension
IIB	Parametrial invasion but not up to the pelvic wall
III	Tumor extends to the lower one-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[d]
IIIA	Involves lower one-third of the vagina with no extension to the pelvic wall
IIIB	Extension to pelvic wall and/or hydronephrosis or nonfunctioning kidney
IIIC	Pelvic and/or para-aortic lymph node involvement (irrespective of tumor size and extent)[d]
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	Carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum
IVA	Spread of the growth to adjacent organs
IVB	Spread of the growth to distant organs

The GCIG INTERLACE trial

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



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, The Lancet 2024

The GCIG INTERLACE trial

Disease Characteristics at Baseline

	CRT alone (N=250)	Induction Chemo + CRT (N=250)
FIGO stage (2008)	**No. of patients (%)**	
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		
Non-squamous	45 (18)	44 (18)
Squamous	205 (82)	206 (82)
Nodal status		
Negative	142 (57)	146 (58)
Positive	108 (43)	104 (42)
Longest tumour diameter, cm median (range)	4.9 (1.8-12.8)	4.8 (1.3-13.5)

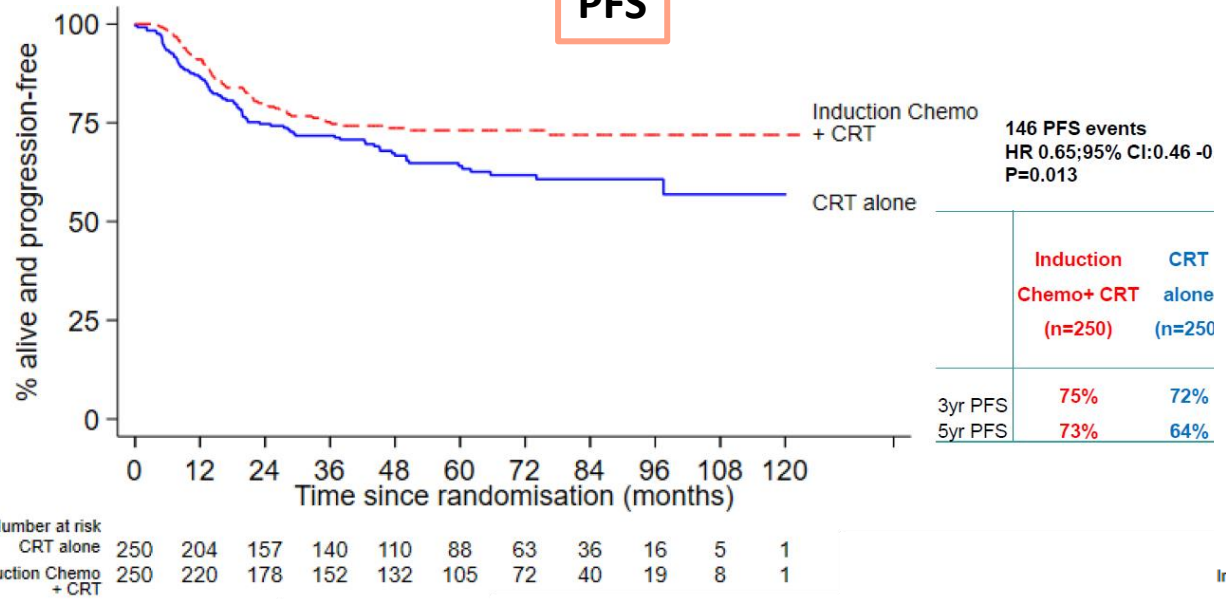
No para-aortic lymphnodes

	CRT alone (n=250)	Induction Chemo + CRT (n=250)
	No. of patients (%)	
Received external beam radiotherapy	**231 (92)**	**242 (97)**
IMRT	93 (40)	102 (42)
3D conformal	138 (60)	140 (58)
Received brachytherapy	**223 (97)**	**238 (98)**
2D point A	49(22)	46 (19)
3D point A	106 (48)	120 (51)
3D HRCTV D90	68 (30)	72 (30)
Median overall treatment time days(range)	**45 (37-88)**	**45 (36-70)**

The GCIG INTERLACE trial

Induction chemotherapy prior to CRT led to a 9% improvement in PFS rate and an 8% improvement in OS rate at 5 years.

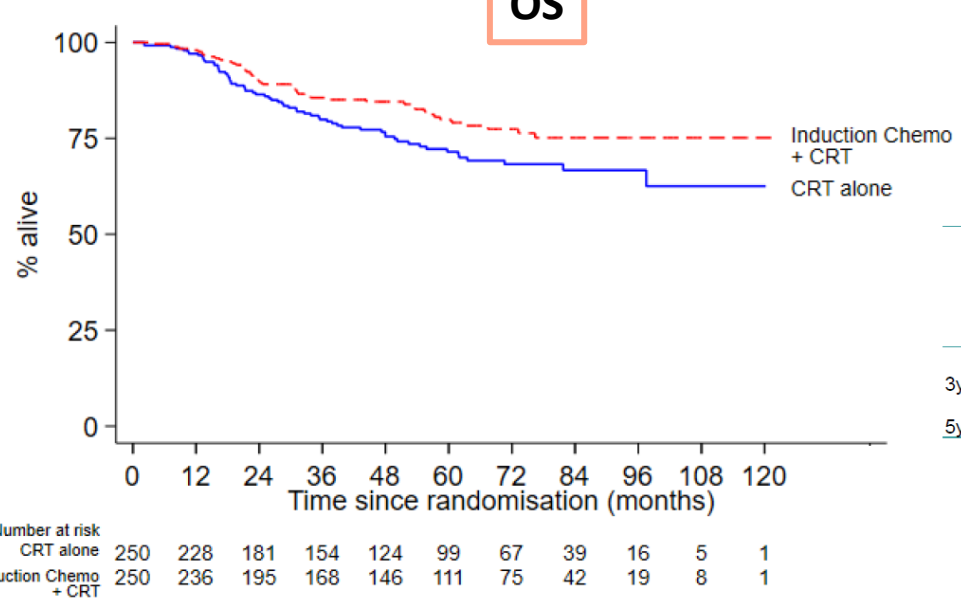
PFS



146 PFS events
HR 0.65;95% CI:0.46 -0
P=0.013

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

OS



109 deaths
HR 0.61;95% CI: 0.40-0.91
P=0.04

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

	CRT alone (n=250)	Induction Chemo + CRT (n=250)
	No. of patients (%)	
Total local/pelvic relapses	41 (16)	40 (16)
Total distant relapses	50 (20)	30 (12)

Local control 84%

Hematological toxicity was greater in the IC/CRT arm but this did not significantly compromise the delivery of radiotherapy

KEYNOTE-A18 (ENGOT-cx11 / GOG-3047)

Radiation has immunomodulatory effects!

FIGO 2018 Stage III-IVA node positive or negative disease

Patients (N=1060)

- Age ≥18 years
- High-risk, locally advanced SCC, adenocarcinoma, or adenosquamous carcinoma of the cervix
- LACC stage:FIGO 2014
  - Stage IB2–IIB with node-positive disease
  - Stage III–IVA with either node-positive or node-negative disease
- Immunotherapy naive and no prior definitive surgical, radiation, or systemic therapy for cervical cancer
- Radiographically evaluable disease by local assessment
- ECOG PS 0–1
- Available tumor lesion biopsy sample

Stratification

- Planned type of EBRT (IMRT or VMAT vs non-IMRT or non-VMAT)
- Stage at screening (FIGO 2014 Stage IB2–IIB vs Stage III–IVA)
- Planned total radiotherapy dose (<70 Gy vs ≥70 Gy)

R 1:1

Pembrolizumab 200 mg IV Q3W + SOC CRT[d] (5 cycles)[e] → **Pembrolizumab 400 mg IV Q6W (15 cycles)**

Placebo IV Q3W + SOC CRT[a] (5 cycles) → **Placebo IV Q6W (15 cycles)**

Primary Endpoints

- PFS
- OS

Secondary Endpoints

- PFS
- PFS at Month 24
- OS at Month 36
- CR rate at Week 12
- ORR
- PFS in PD-L1+ patients
- OS in PD-L1+ patients
- PFS after next-line treatment
- PRO
- Safety and tolerability

[a]SOC chemoradiotherapy regimen includes cisplatin 40 mg/m^2 IV QW for 5 or 6 weeks + EBRT followed by brachytherapy with minimum total radiotherapy dose of 80 Gy for volume-directed and 75 Gy for point-directed given with the total duration of radiation treatment not to exceed 50 days (with an extension to a maximum of 56 days for unforeseen delays).

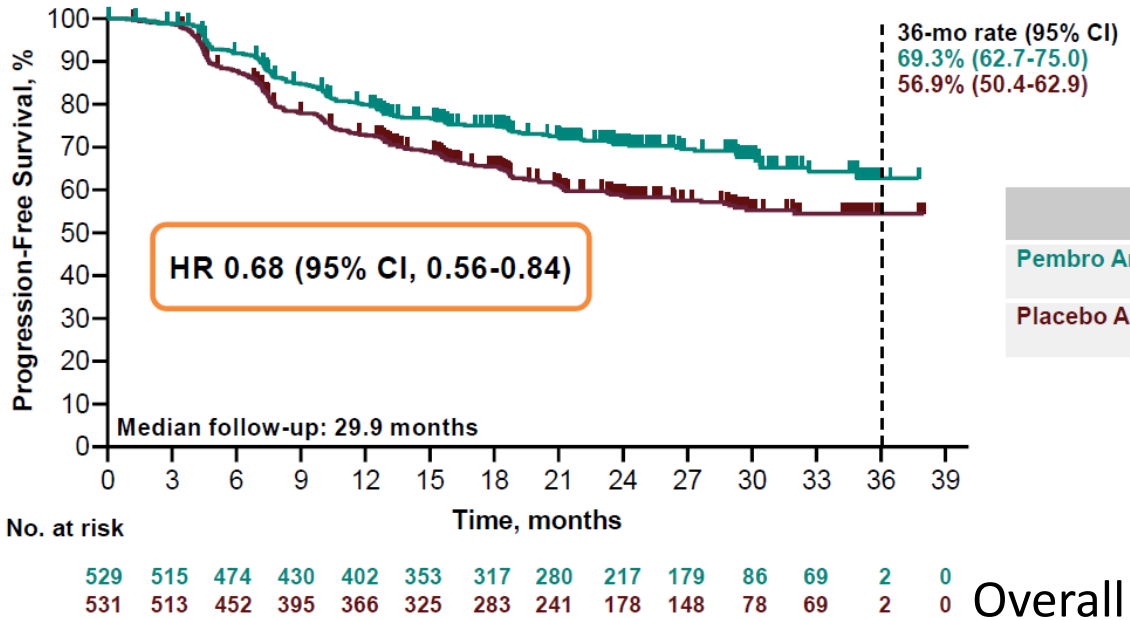
KEYNOTE-A18 (ENGOT-cx11 / GOG-3047)

Baseline Patient Characteristics

	Pembro Arm (n = 529)	Placebo Arm (n = 531)
Age, median (IQR)	49 (40–57)	50 (41–59)
Race		
White	254 (48.0%)	264 (49.7%)
Asian	155 (29.3%)	148 (27.9%)
Multiple	78 (14.7%)	86 (16.2%)
American Indian or Alaska Native	24 (4.5%)	22 (4.1%)
Black or African American	14 (2.6%)	8 (1.5%)
Native Hawaiian or Other Pacific Islander	2 (0.4%)	1 (0.2%)
PD-L1 CPS		
<1	22 (4.2%)	28 (5.3%)
≥1	502 (94.9%)	498 (93.8%)
Missing	5 (0.9%)	5 (0.9%)
ECOG PS 1	149 (28.2%)	134 (25.2%)
Squamous cell carcinoma	433 (81.9%)	451 (84.9%)

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

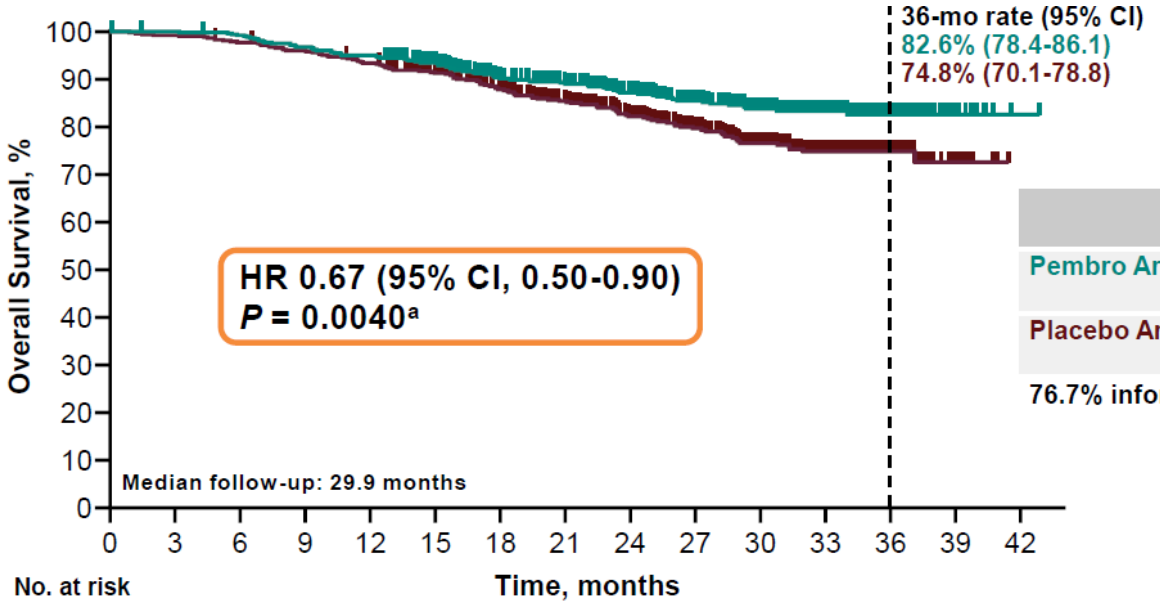
Progression-Free Survival



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

FDA approved pembrolizumab with chemoradiotherapy for patients with FIGO 2014 Stage III-IVA cervical cancer.

Overall Survival



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

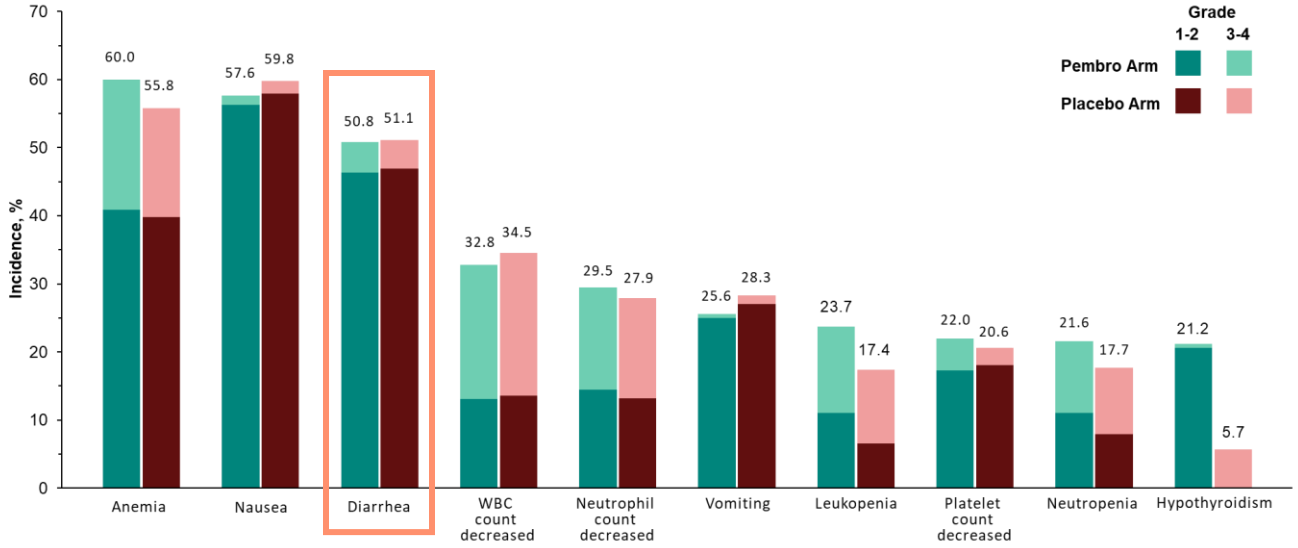
76.7% information fraction[a]

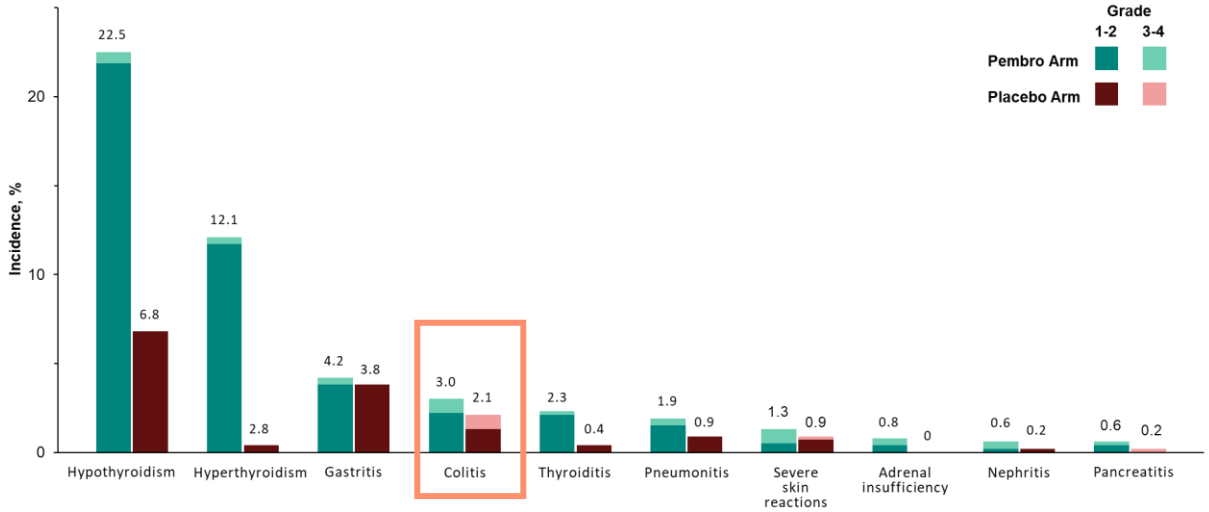
Response assessed per RECIST v1.1 by investigator.
Data cutoff date: January 8, 2024

KEYNOTE-A18 (ENGOT-cx11 / GOG-3047)

Adverse event and treatment-related AEs

	All-Cause AEs		Treatment-Related AEs[a]		Immune-Mediated AEs[b]	
	Pembro Arm (N = 528)	Placebo Arm (N = 530)	Pembro Arm (N = 528)	Placebo Arm (N = 530)	Pembro Arm (N = 528)	Placebo Arm (N = 530)
Any grade	528 (100.0%)	526 (99.2%)	512 (97.0%)	513 (96.8%)	206 (39.0%)	90 (17.0%)
Grade ≥3	413 (78.2%)	371 (70.0%)	365 (69.1%)	325 (61.3%)	25 (4.7%)	7 (1.3%)
Serious	172 (32.6%)	151 (28.5%)	102 (19.3%)	71 (13.4%)	20 (3.8%)	6 (1.1%)
Led to death	5 (0.9%)	7 (1.3%)	2 (0.4%)[c]	2 (0.4%)[d]	1 (0.2%)[e]	0
Led to discontinuation						
Any treatment	109 (20.6%)	79 (14.9%)	99 (18.8%)	69 (13.0%)	16 (3.0%)	4 (0.8%)
All treatment	1 (0.2%)	2 (0.4%)	0	1 (0.2%)	0	0





Lorusso D et al, The Lancet 2024

Conclusions:

- In **first line** advanced-metastatic cervical cancer the **platinum-based backbone chemotherapy** is the main pillar of systemic treatment;
- The addition of **immune-checkpoint inhibitors +/- bevacizumab** have provided PFS and OS benefit;
- In second line there is limited effect of chemotherapy and immune check point inhibitors;
- **ADCs** represent a new hope for patients.

- The main treatment of LACC remains concomitant **concurrent CTRT and brachytherapy with modern RT approach**;
- **Pembrolizumab in combination with CTRT + BT increased PFS and OS in high-risk, locally advanced disease** → it is becoming the new standard in this setting;
- **Induction CT before CTRT + BT** could be an option **in low risk LACC**;
- New strategies, particularly neoadjuvant immunotherapy, are under investigation.

GRAZIE PER L'ATTENZIONE!