Cervical Cancer: Past, Present, and Future – Times They Are A-Changin'

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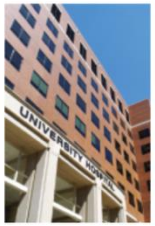



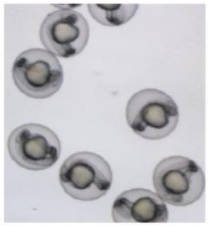


Disclosures

- Grant Support – NIH
- Consultant – AbbVie/Immunogen, Acrotech, GenMab, GSK, Merck, Pfizer/Seattle Genetics
- DSMB – Imunon
- Contracted Research – AbbVie/Immunogen, Agenus, AstraZeneca, Corcept Therapeutics, GSK, Imunon, Merck, Volastra Therapeutics

Learning Objectives

- Review the current state of cervical cancer
- Recognize the traditional treatments for cervical cancer
- Review paradigm changing clinical trials
- Explore future directions of treatment in cervical cancer

Cervical Cancer: The Past

Cervical Cancer Observation – 1960

Management of the Patient with the Positive Vaginal Cell Examination

Harry M. Nelson, M.D., Esther H. Dale, M.D. and Gerald S. Wilson, M.D.

In spite of the fact that cervical cancer is almost 100 per cent curable if found in an early stage, 15,000 women die of the disease each year. This is especially regrettable because of the easy, effective and accurate test that is available in the form of the "Pap smear" for detecting cervical cancer in an extremely early stage. In order to stimulate wider use of the test, the American Cancer Society is sponsoring a nation-wide cytology program which is designed to encourage women to have this test performed by a private physician in his own office.

One of the cancer detection centers in

pected cancer, the doctor is contacted directly without delay.

During a four and one-half year period beginning in May of 1950, 15,832 women had routine vaginal cell examinations at the Yates Clinic[1]; 160 had positive reports (Table 1). Biopsies were obtained in 140 of these women with positive cell examinations and 123 proved to have carcinoma by histological examination, an accuracy of 87.8 per cent. It deserves to be pointed out here that positive smears should always be confirmed by biopsy before therapy is initiated. Some cytologists, however, are of the opinion that the re-

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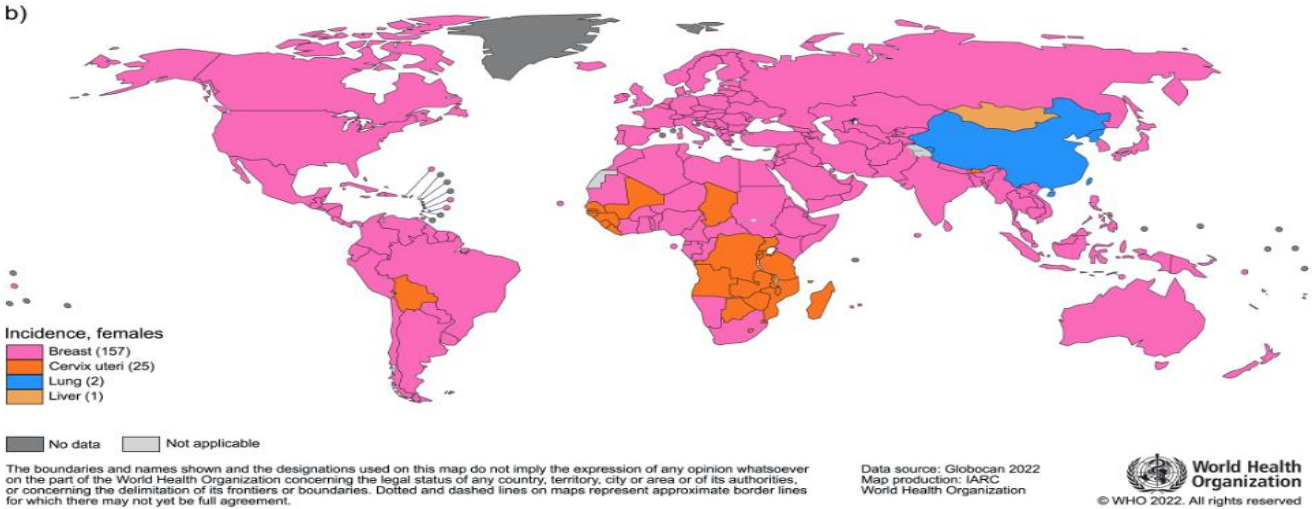
Nelson HM et al. *CA Cancer J Clin* 1960

Cervical Cancer: The Present

Cervical Cancer Worldwide – 2022

- Worldwide projected incidence: 660,000 (4th)
- Worldwide projected deaths: 350,000 (4th)
- Leading cause of death in 37 countries!!



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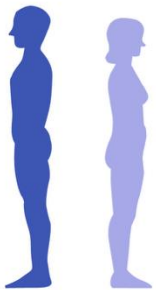
Bray F et al. *CA Cancer J Clin* 2024

Cervical Cancer Statistics – 2025

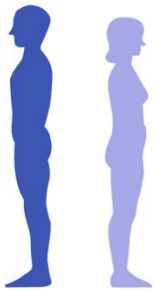
Estimated New Cases

Male			Female		
Prostate	313,780	30%	Breast	316,950	32%
Lung & bronchus	110,680	11%	Lung & bronchus	115,970	12%
Colon & rectum	82,460	8%	Colon & rectum	71,810	7%
Urinary bladder	65,080	6%	Uterine corpus	69,120	7%
Melanoma of the skin	60,550	6%	Melanoma of the skin	44,410	4%
Kidney & renal pelvis	52,410	5%	Non-Hodgkin lymphoma	35,210	4%
Non-Hodgkin lymphoma	45,140	4%	Pancreas	32,490	3%
Oral cavity & pharynx	42,500	4%	Thyroid	31,350	3%
Leukemia	38,720	4%	Kidney & renal pelvis	28,570	3%
Pancreas	34,950	3%	Leukemia	28,170	3%
All sites	**1,053,250**		**All sites**	**988,660**	



Estimated Deaths

Male			Female		
Lung & bronchus	64,190	20%	Lung & bronchus	60,540	21%
Prostate	35,770	11%	Breast	42,170	14%
Colon & rectum	28,900	9%	Pancreas	24,930	8%
Pancreas	27,050	8%	Colon & rectum	24,000	8%
Liver & intrahepatic bile duct	19,250	6%	Uterine corpus	13,860	5%
Leukemia	13,500	4%	Ovary	12,730	4%
Esophagus	12,940	4%	Liver & intrahepatic bile duct	10,840	4%
Urinary bladder	12,640	4%	Leukemia	10,040	3%
Non-Hodgkin lymphoma	11,060	3%	Non-Hodgkin lymphoma	8,330	3%
Brain & other nervous system	10,170	3%	Brain & other nervous system	8,160	3%
All sites	**323,900**		**All sites**	**294,220**	



Not in the top 10 for Incidence nor death in the United States

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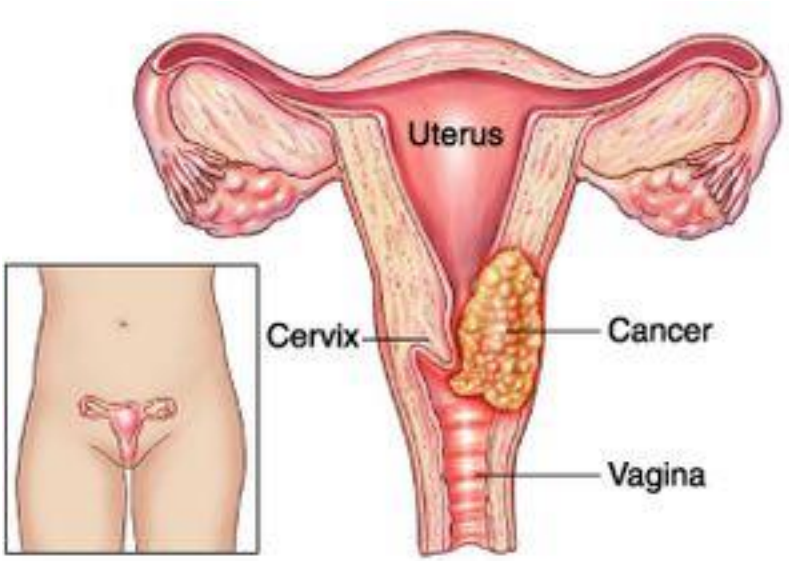
Siegel RL et al. *CA Cancer J Clin* 2025

Symptoms

- Abnormal bleeding or spotting (90%)
  - Post coital, change in menstrual characteristics
- Development of heavier menstrual cycles
- Bleeding between periods
- Vaginal discharge-NOS
- Pelvic pain
- Back pain



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UpToDate Invasive Cervical Cancer, 2024

Patient Assessment

- Tissue is the issue – A biopsy is needed
- Pap testing designed for screening asymptomatic individuals
- Pathology review
- Imaging
- Triage to appropriate treatment

Stage	Description
I	Carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only with microscopy, with maximum depth of invasion <5 mm
IA1	Stromal invasion <3 mm in depth
IA2	Stromal invasion ≥3 mm and <5 mm in depth
IB	Invasive carcinoma confined to the uterine cervix, with measured deepest invasion ≥5 mm
IB1*	Tumor measures <2 cm in greatest dimension
IB2*	Tumor measures ≥2 cm and <4 cm in greatest dimension
IB3*	Tumor measures ≥4 cm in greatest dimension
II	Carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Limited to the upper two-thirds of the vagina without parametrial involvement
IIA1	Tumor measures <4 cm in greatest dimension
IIA2	Tumor measures ≥4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	Carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes
IIIA	Involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney from tumor
IIIC*	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent†
IIIC1*	Pelvic lymph node metastasis only
IIIC2*	Para-aortic lymph node metastasis
IV	Carcinoma has extended beyond the true pelvis or has involved (biopsy-proven) the mucosa of the bladder or rectum
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

Factors that increase the risk of Cervical Cancer

- High-risk Human Papilloma Virus (HPV)
- Smoking
- Early age at sexual debut
  - RR 1.6 Ages 18-21 vs. >21
  - RR 2.24 age < 18 vs. >21
- Immunosuppression
- Multiple sexual partners
- High-risk sexual partners
- History of STIs
- First birth < age 20

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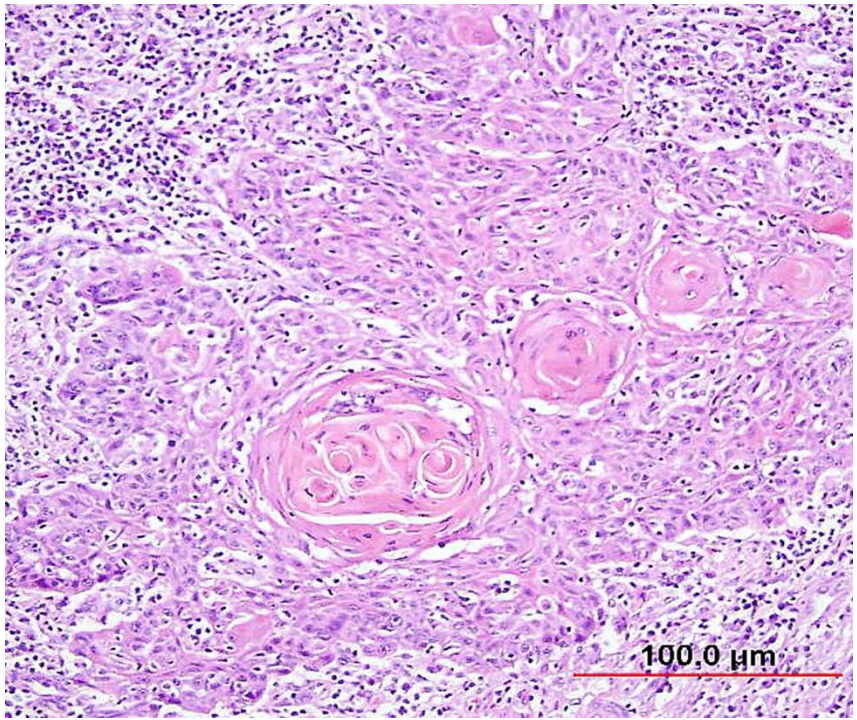
Herrero R, Murillo R. *Cervical Cancer In Cancer Epidemiology & Prevention*, 4th ed. 2017; Int J Cancer 2007 120(4);885

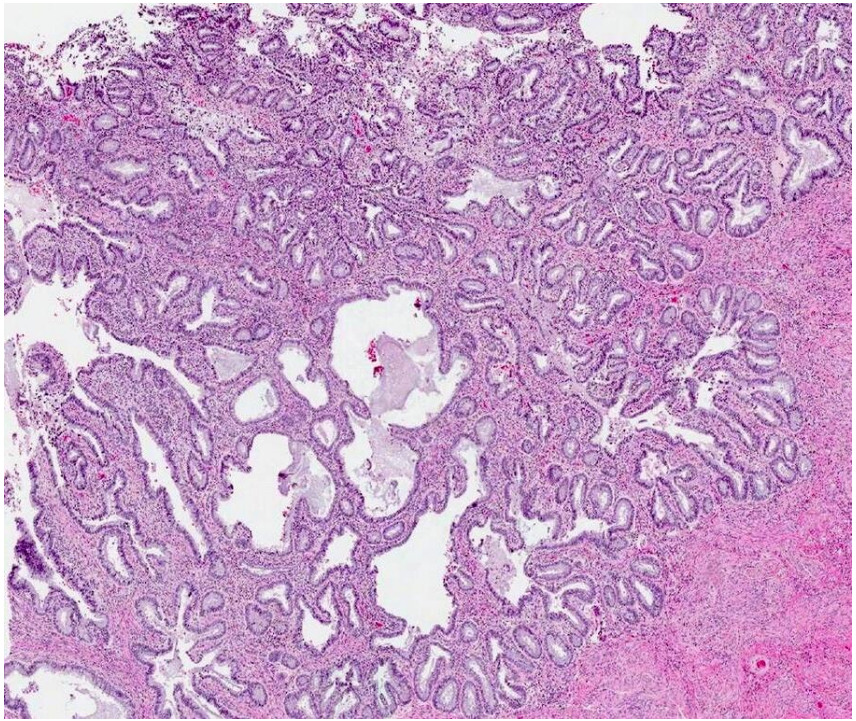
Prevention is the key!

- Primary and secondary HPV vaccination
- Pap and HPV testing options

Traditional Pathology



Squamous Cell Carcinoma



Adenocarcinoma

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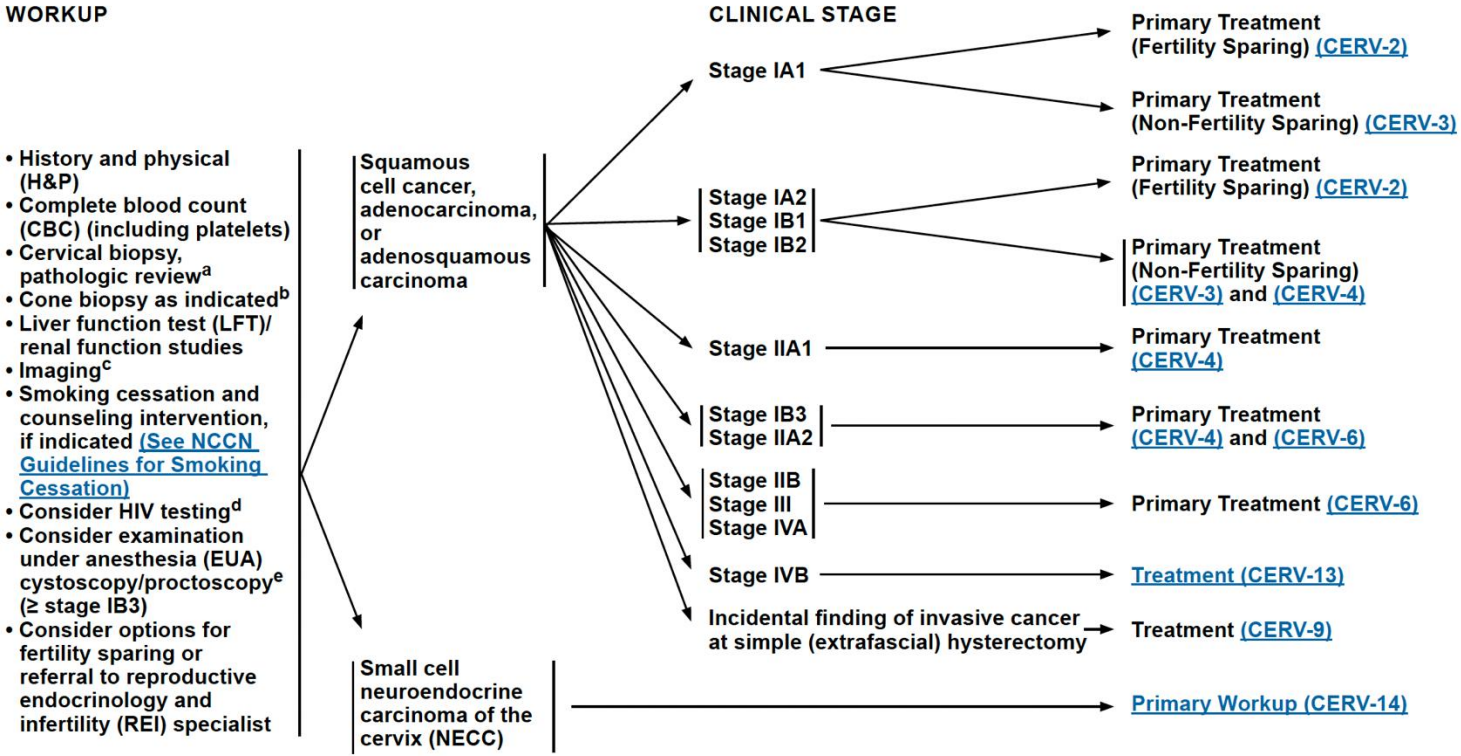
Cervical Cancer Treatment

NCCN recommendations – Treatment Overview



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Abu Rustum et al. *J Natl Compr Canc* 2024

Cervical Cancer Treatment Approaches

- Stage I Microscopic (Stage IA1 without risk factors)
  - Excisional surgical approaches
- Stage I Microscopic with risk factors / Macroscopic (Stage IA1-IB2)
  - Fertility preservation
  - Nonradical surgery
  - Radical surgery
- Locally Advanced Cervical Cancer (LACC) (Stage IB3-IVA)
  - Chemoradiation with or without immunotherapy
- Primary Metastatic (Stage IVB) / Persistent / Recurrent
  - Chemotherapy ± Bevacizumab ± Pembrolizumab (Atezolizumab)
  - Systemic therapies-NOS

What is the best treatment option for early-stage Cervical Cancer?

1. Radiation
2. Type III Open Radical Hysterectomy
3. Minimally invasive Radical Hysterectomy
4. Conization and/or simple hysterectomy with nodal assessment
5. It depends

LACC Trial

Minimally invasive vs. Open Radical hysterectomy

Non-inferiority trial

Inclusion

- Stage IA1 (+LVSI), IA2, IB1
- SCC, Adenocarcinoma, ASC

N = 631 randomized

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Open Surgery (N=312)	Minimally Invasive Surgery (N=319)
Age — yr	46.0±10.6	46.1±11.0
Body-mass index†	26.2±5.3	27.2±5.6
Histologic subtype — no. (%)		
Squamous-cell carcinoma	210 (67.3)	214 (67.1)
Adenocarcinoma	80 (25.6)	87 (27.3)
Adenosquamous carcinoma	6 (1.9)	9 (2.8)
Not reported	16 (5.1)	9 (2.8)
Stage of disease — no. (%)		
IA1: lymphovascular invasion	5 (1.6)	5 (1.6)
IA2	20 (6.4)	21 (6.6)
IB1	287 (92.0)	293 (91.8)
ECOG performance-status score — no. (%)‡		
0	289 (92.6)	292 (91.5)
1	23 (7.4)	27 (8.5)
Median length of hospital stay (range) — days	5 (0–69)§	3 (0–72)
Treatment received — no. (%)		
Open surgery	274 (87.8)	2 (0.6)
Minimally invasive surgery	8 (2.6)	289 (90.6)
Patient withdrew before surgery	19 (6.1)	12 (3.8)
Surgery was aborted	11 (3.5)	16 (5.0)

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Ramirez PT et al. *N Engl J Med* 2018

LACC Trial

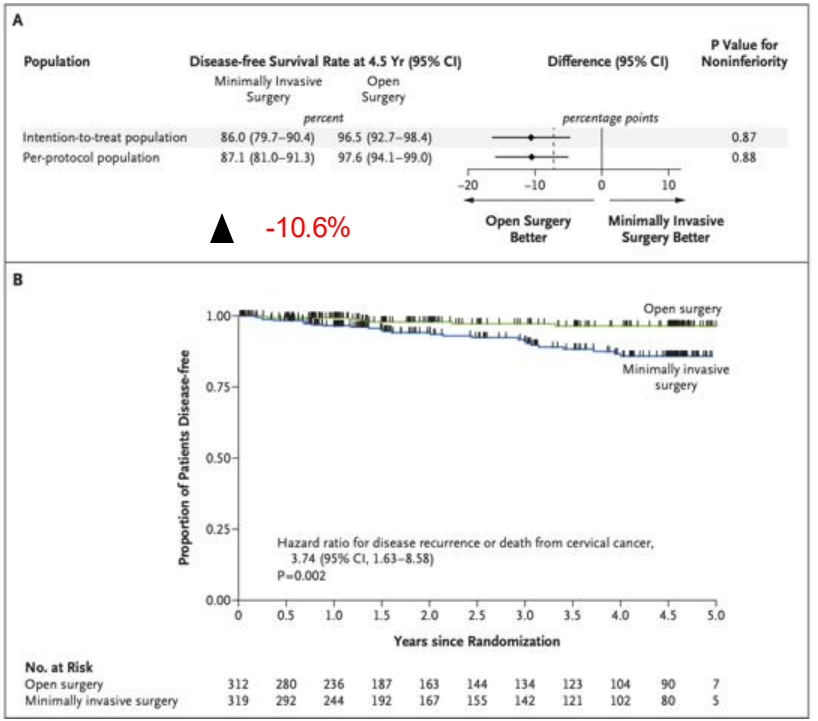
Projected 90% DFS (Open) @ 4.5 years w/ non-inferiority margin of 7.2%

Results:

- 4.5yr DFS: 86.0% v 96.5% (MIS vs Open)
- 3 yr OS: 93.8% vs 99% (MIS vs Open)
  - HR 6.0, 95% CI 1.77 to 20.30

Table 2. Adjuvant Therapy.

Adjuvant Therapy	Open Surgery (N=312)	Minimally Invasive Surgery (N=319)	P Value
	no. (%)		
Chemotherapy or radiotherapy	86 (27.6)	92 (28.8)	0.72
≥1 Cycle of chemotherapy	66 (21.2)	72 (22.6)	0.67
≥1 Dose of radiotherapy	73 (23.4)	81 (25.4)	0.56



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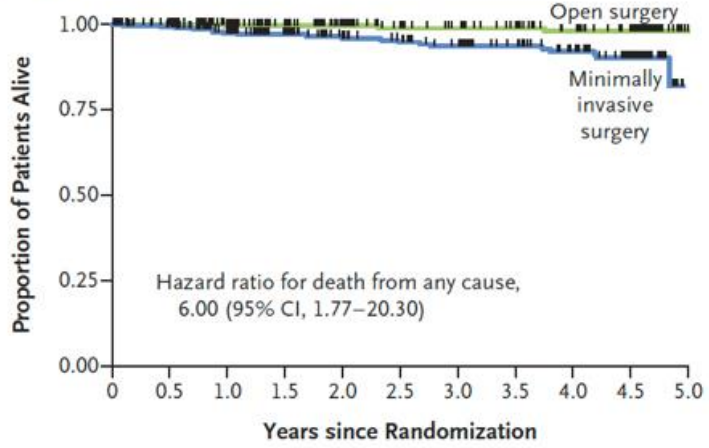
Ramirez PT et al. *N Engl J Med* 2018

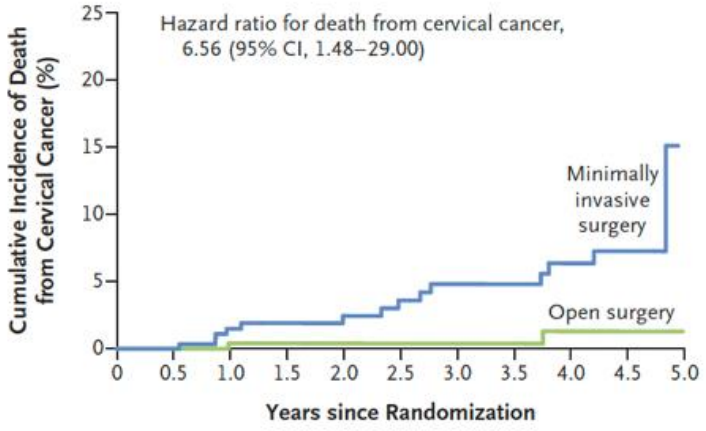
LACC Trial – OS & DSS

A Overall Survival



No. at Risk											
Open surgery	312	282	237	190	164	146	136	125	104	90	7
Minimally invasive surgery	319	297	249	198	174	163	150	133	113	87	5

B Disease-Specific Survival



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Minimally invasive surgery	319	297	249	198	174	163	150	133	113	87	5

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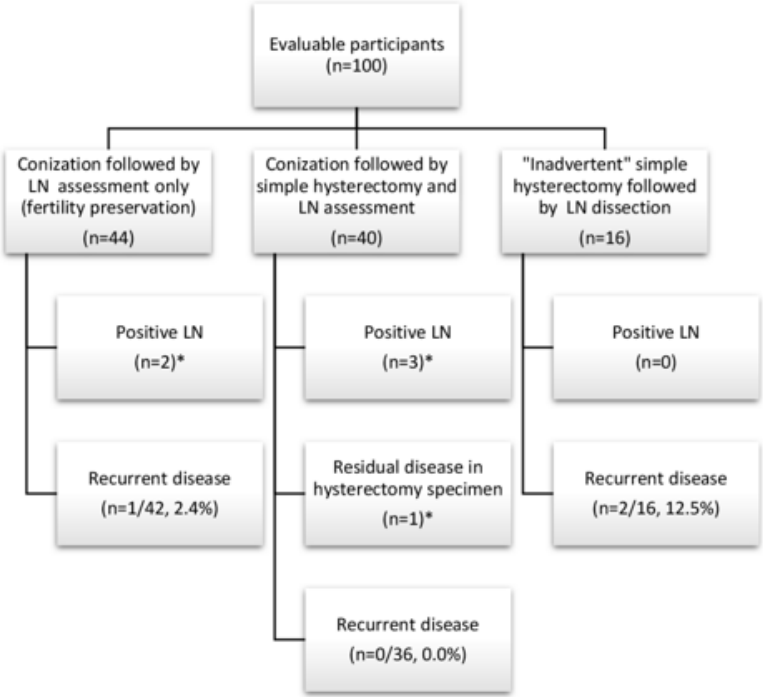
Ramirez PT et al. *N Engl J Med* 2018

ConCERV Trial

- Evaluate the feasibility of conservative surgery in women with early stage, low risk cervical cancer.
- April 2010-March 2019
- Single-arm Design
  - Patients with a cone
    - Fertility preservation option – PLND
    - Simple Hyst with LND
  - ”Inadvertent” simple hyst with diagnosis of cancer --> 2nd surgery PLND
- Inclusion
  - Stage IA2-IB1 SCC or Adenocarcinoma (gr 1 or 2)
  - <2cm tumor size, <10mm DOI
  - No LVSI
  - Negative conization margins
  - Negative imaging for metastasis



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Schmeler KM et al. *Int J Gynecol Cancer 2021*

ConCERV Trial

Table 1 Study accrual by participating site

Institution	City	Country	Number of evaluable participants
MD Anderson Cancer Center	Houston	USA	36 (36%)
Instituto de Cancerología	Medellin	Colombia	14 (14%)
Instituto Nacional de Enfermedades Neoplásicas	Lima	Perú	13 (13%)
Barretos Cancer Hospital	Barretos	Brazil	8 (8%)
Hospital Italiano	Buenos Aires	Argentina	6 (6%)
Instituto Brasileiro de Controle do Cancer	São Paulo	Brazil	6 (6%)
Hospital Erasto Gaertner	Curitiba	Brazil	5 (5%)
Instituto Nacional de Cancerologia	Mexico City	México	4 (4%)
Lyndon B. Johnson Hospital/Harris Health	Houston	USA	3 (3%)
Chulalongkorn University	Bangkok	Thailand	1 (1%)
Royal Women's Hospital	Melbourne	Australia	1 (1%)
Nebraska Methodist Health System	Omaha	USA	1 (1%)
Instituto de Ginecología de Rosario	Rosario	Argentina	1 (1%)
Fondazione Policlinico Universitario A. Gemelli IRCCS	Rome	Italy	1 (1%)

Table 2 Patient demographic and pathology information

Age at surgery (years):	
Mean	39
Median	38
Range	23–67
Stage (FIGO 2009), N (%)	
IA2	33 (33%)
IB1	67 (67%)
Histology, N (%)	
Squamous cell carcinoma	48 (48%)
Adenocarcinoma	52 (52%)
Surgical approach, N (%)	
Laparoscopic	83 (83%)
Robotic	13 (13%)
Open	4 (4%)
Lymph node assessment, N (%)	
Full lymph node dissection	58 (58%)
Sentinel lymph node biopsy+full lymph node dissection	38 (38%)
Sentinel lymph node biopsy alone	4 (4%)

Results: Median f/u 36.3mo

Disease recurrence of 3.5%
(95% CI, 0.9 – 9.0%) at 2yrs

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Schmeler KM et al. *Int J Gynecol Cancer 2021*

How about SHAPE?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Simple versus Radical Hysterectomy in Women with Low-Risk Cervical Cancer

Marie Plante, M.D., Janice S. Kwon, M.D., Sarah Ferguson, M.D., Vanessa Samouëlian, M.D., Gwenael Ferron, M.D., Amandine Maulard, M.D., Cor de Kroon, M.D., Willemien Van Driel, M.D., John Tidy, M.D., Karin Williamson, M.D., Sven Mahner, M.D., Stefan Kommoss, M.D., Frederic Goffin, M.D., Karl Tamussino, M.D., Brynhildur Eyjólfsdóttir, M.D., Jae-Weon Kim, M.D., Noreen Gleeson, M.D., Lori Brotto, Ph.D., Dongsheng Tu, Ph.D., and Lois E. Shepherd, M.D., for the CX.5 SHAPE investigators*

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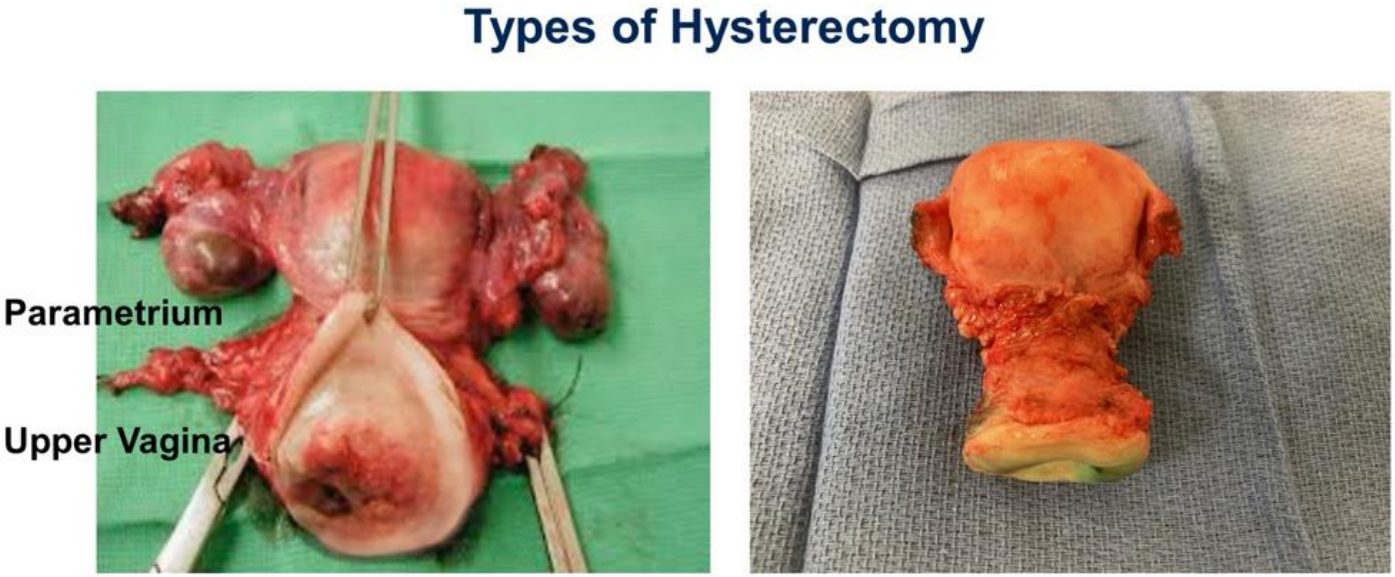
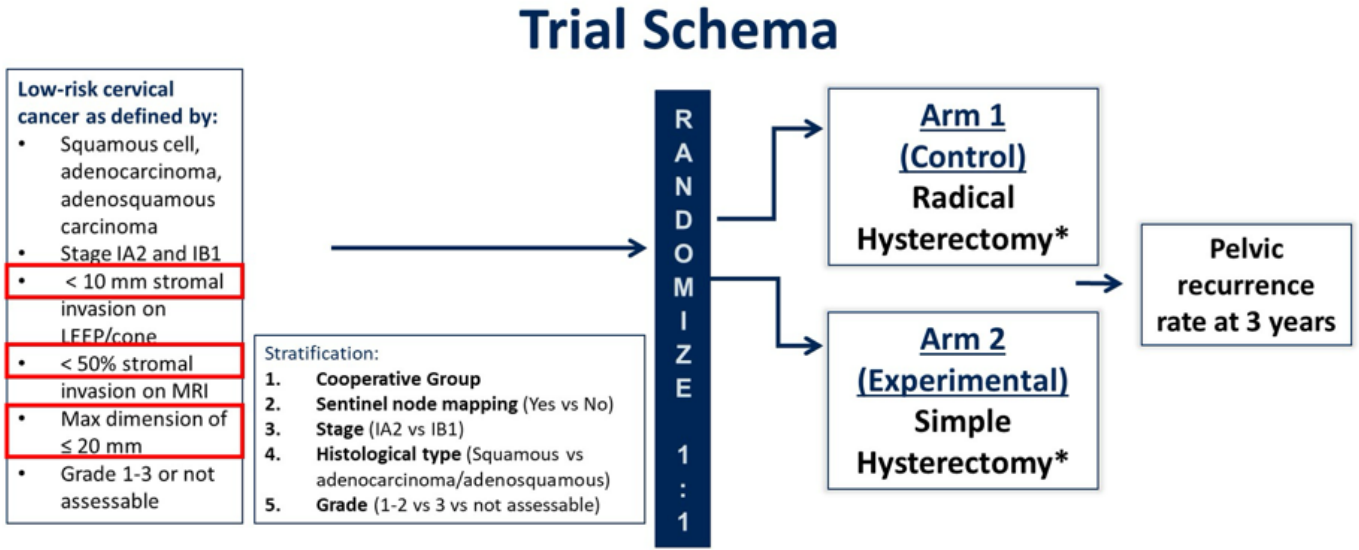
Plante M et al. *N Engl J Med 2024*

Hysterectomy Comparison



How about SHAPE?

Multicenter, randomized, noninferiority trial (margin 4%) comparing radical hysterectomy with simple hysterectomy including LN assessment in low-risk cervical cancer



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SHAPE Outcomes

- Primary Outcome: Pelvic recurrence at 3 years
- Secondary time to event outcomes:
  - Pelvic recurrence-free survival
  - Extra-pelvic recurrence-free survival
  - Recurrence-free survival
  - Overall survival
- Additional secondary outcomes
  - SLN detection
  - Parametrial involvement
  - Margins
  - PLN involvement

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SHAPE Surgical & Tumor Results

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Simple Hysterectomy (N=350)	Radical Hysterectomy (N=350)
Race or ethnic group — no. (%)†		
White	264 (75.4)	261 (74.6)
Asian	22 (6.3)	19 (5.4)
Black	3 (0.9)	5 (1.4)
American Indian or Alaska Native	2 (0.6)	1 (0.3)
Not reported	46 (13.1)	50 (14.3)
Unknown	13 (3.7)	14 (4.0)
Age		
Median (range) — yr	42 (26–77)	45 (24–80)
Distribution — no. (%)		
≤50 yr	271 (77.4)	246 (70.3)
>50 yr	79 (22.6)	104 (29.7)
ECOG performance status — no. (%)‡		
0	336 (96.0)	335 (95.7)
1	14 (4.0)	13 (3.7)
3	0	1 (0.3)
Data missing	0	1 (0.3)
Median body-mass index (range)§	25.0 (16.4–53.3)	24.8 (16.1–57.6)
Tumor histologic type — no. (%)		
Squamous-cell carcinoma	218 (62.3)	214 (61.1)
Adenocarcinoma	114 (32.6)	131 (37.4)
Adenosquamous carcinoma	18 (5.1)	5 (1.4)
Tumor FIGO stage — no. (%)		
IB_1	320 (91.4)	322 (92.0)
Tumor histologic grade — no. (%)		
1	76 (21.7)	87 (24.9)
2	129 (36.9)	123 (35.1)
3	49 (14.0)	49 (14.0)
Not assessable	96 (27.4)	91 (26.0)
Diagnostic procedure — no. (%)		
LEEP or conization with or without cervical biopsy	294 (84.0)	267 (76.3)
Cervical biopsy only	52 (14.9)	77 (22.0)
Missing	4 (1.1)	6 (1.7)

Table 2. Secondary Surgical Outcomes among Patients Who Underwent Surgery as Randomly Assigned.

Outcome	Simple Hysterectomy (N=336)	Radical Hysterectomy (N=337)	Difference (95% CI)*
	number (percent)		*percentage points*
Invasion of lymphovascular space	45 (13.4)	42 (12.5)	0.9 (−4.1 to 6.0)
specimen			
Positive nodes on final pathology specimen	11 (3.3)	14 (4.2)	−0.9 (−3.7 to 2.0)
Residual disease in hysterectomy specimen	154 (45.8)	159 (47.2)	−1.3 (−8.9 to 6.2)
Lesions >2 cm on final pathology specimen	14 (4.2)	14 (4.2)	0.0 (−3.0 to 3.0)
Parametrial involvement	0	6 (1.8)	−1.8 (−3.2 to −0.4)
Parametrial involvement and lesions >2 cm on final pathology specimen	0	2 (0.6)	

* The 95% confidence intervals (CIs) were not adjusted for multiplicity and should not be used in place of hypothesis testing.

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SHAPE Adverse Events

Intraoperative surgical complications

- 7.1% (Simple) vs. 6.4% (Radical)

All Treated Patients Post Surgery

Intraoperative complications	Simple Hysterectomy N=338 (%)	Radical Hysterectomy N=344 (%)	P-value
Intraoperative Injury	24 (7.1)	22 (6.4)	0.77
• Bladder	3	9	0.14
• Ureter	3	5	0.73
• Nerve	5	2	0.28
• Bowel	2	2	1.00
• Vein	4	1	0.21
• Other	7	3	0.22

Urinary Incontinence and Retention remained significant both <4 weeks post op to 4 weeks + post op

Table 4. Safety Outcomes.*

Outcome	Simple Hysterectomy (N=338)	Radical Hysterectomy (N=344)	P Value
	number (percent)		
Intraoperative injury			
Any intraoperative injury	24 (7.1)	22 (6.4)	0.77
Bladder	3 (0.9)	9 (2.6)	0.14
Ureter	3 (0.9)	5 (1.5)	0.73
Nerve	5 (1.5)	2 (0.6)	0.28
Bowel	2 (0.6)	2 (0.6)	1.00
Vein	4 (1.2)	1 (0.3)	0.21
Other	7 (2.1)	3 (0.9)	0.22
Surgery-related adverse event ≤4 wk after surgery†			
Any adverse event	144 (42.6)	174 (50.6)	0.04
Abdominal pain	33 (9.8)	42 (12.2)	0.33
Constipation	16 (4.7)	22 (6.4)	0.40
Fatigue	19 (5.6)	23 (6.7)	0.63
Paresthesia	14 (4.1)	22 (6.4)	0.23
Urinary incontinence	8 (2.4)	19 (5.5)	0.05
Urinary retention	2 (0.6)	38 (11.0)	<0.001
Pelvic pain	19 (5.6)	9 (2.6)	0.05
Surgery-related adverse event >4 wk after surgery†			
Any adverse event	181 (53.6)	208 (60.5)	0.08
Abdominal pain	36 (10.7)	47 (13.7)	0.24
Constipation	13 (3.8)	19 (5.5)	0.37
Fatigue	19 (5.6)	28 (8.1)	0.23
Paresthesia	17 (5.0)	22 (6.4)	0.51
Peripheral sensory neuropathy	21 (6.2)	13 (3.8)	0.16
Urinary incontinence	16 (4.7)	38 (11.0)	0.003
Urinary retention	2 (0.6)	34 (9.9)	<0.001
Dyspareunia	21 (6.2)	19 (5.5)	0.75
Pelvic pain	23 (6.8)	17 (4.9)	0.33
Lymphedema	35 (10.4)	36 (10.5)	1.00
Hot flashes	14 (4.1)	20 (5.8)	0.38

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Plante M et al. *N Engl J Med 2024*

SHAPE Recurrence

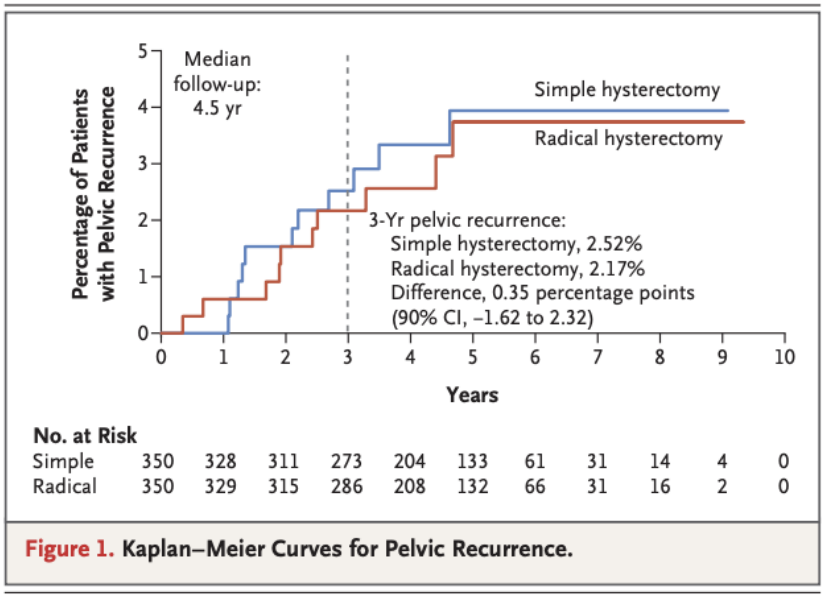

Figure 1. Kaplan–Meier Curves for Pelvic Recurrence.

Table 3. Sites of Disease Recurrence and Causes of Death.*

Event	Intention-to-Treat Analysis			Per-Protocol Analysis		
	Simple Hysterectomy (N=350)	Radical Hysterectomy (N=350)	Hazard Ratio (95% CI)	Simple Hysterectomy (N=317)	Radical Hysterectomy (N=312)	Hazard Ratio (95% CI)
	number (percent)			*number (percent)*		
Disease recurrence†	15 (4.3)	10 (2.9)	1.54 (0.69–3.45)	12 (3.8)	10 (3.2)	1.19 (0.51–2.77)
Pelvic recurrence	11 (3.1)	10 (2.9)	1.12 (0.47–2.67)	10 (3.2)	10 (3.2)	1.01 (0.42–2.44)
Vaginal vault	9 (2.6)	8 (2.3)		9 (2.8)	8 (2.6)	
Parametrium	1 (0.3)	0		1 (0.3)	0	
Lower paraaortic and common iliac lymph nodes	1 (0.3)	0		0	0	
Central pelvis	0	1 (0.3)		0	1 (0.3)	
Pelvic sidewall	0	1 (0.3)		0	1 (0.3)	
Extrapelvic recurrence	7 (2.0)	2 (0.6)	3.82 (0.79–18.4)	4 (1.3)	2 (0.6)	2.03 (0.37–11.2)
Abdomen	2 (0.6)	0		0	0	
Paraaortic lymph nodes	2 (0.6)	2 (0.6)		1 (0.3)	2 (0.6)	
Supraclavicular lymph nodes	1 (0.3)	0		1 (0.3)	0	
Interaortocaval and obturator lymph nodes and vaginal vault	1 (0.3)	0		1 (0.3)	0	
Vaginal introitus	1 (0.3)	0		1 (0.3)	0	
Death	7 (2.0)	7 (2.0)	1.09 (0.38–3.14)	3 (0.9)	4 (1.3)	0.71 (0.16–3.21)
Cervical cancer	4 (1.1)	1 (0.3)		2 (0.6)	1 (0.3)	
Other primary cancer	1 (0.3)	3 (0.9)		0	2 (0.6)	
Other medical condition	2 (0.6)	3 (0.9)		1 (0.3)	1 (0.3)	

* Hazard ratios are from stratified proportional-hazards models for secondary time-to-event outcomes (tests for superiority). The 95% CIs were not adjusted for multiplicity and should not be used in place of hypothesis testing. The intention-to-treat analysis included all patients who underwent randomization; the per-protocol analysis included all patients who met the eligibility criteria at the time of randomization, underwent randomization, underwent surgery, and had postsurgical findings that did not meet criteria for exclusion on the basis of disease severity.
† Patients may have both pelvic and extrapelvic recurrences.

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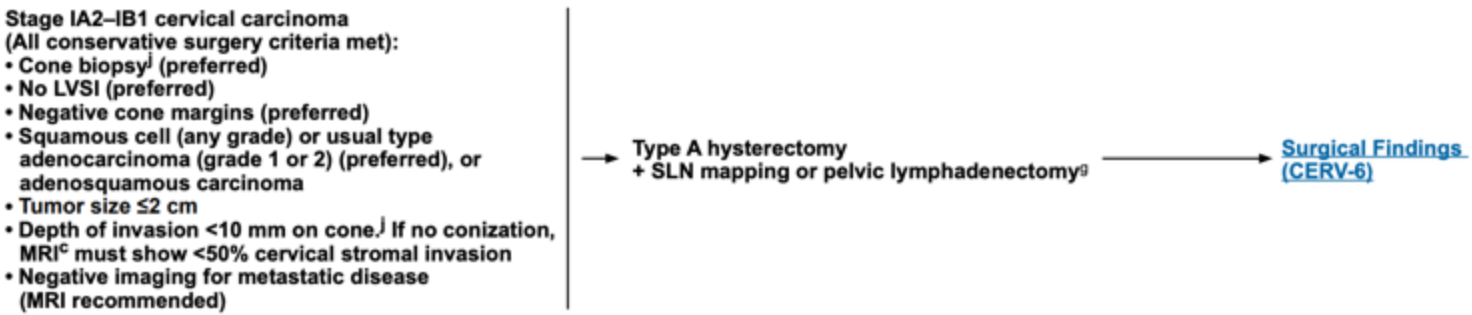
Plante M et al. *N Engl J Med 2024*

SHAPE Conclusions

- Simple hysterectomy was non-inferior to radical hysterectomy with respect to pelvic recurrence at 3 years in patients with low-risk cervical cancer
- The 3.6% overall recurrence in SHAPE was consistent with ConCerv of 3.5%.
  - This suggests that patients with LVSI and grade 3 disease with + margins on cone or LEEP could be offered conservative surgery, although small numbers in this study.



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Plante M et al. *N Engl J Med 2024*

SHAPE Limitations

- Median follow up 4.5 years
- Surgical approach e.g. open or MIS was at surgeon discretion after randomization
- Not generalizable to patients that not meeting this stringent criteria
- Black women underrepresented

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Plante M et al. *N Engl J Med 2024*

SHAPE vs. ConCERV

	ConCerv trial (2021)[1]	SHAPE trial (2024)[3]
Study design	Prospective trial	Randomized non-inferiority trial
Surgical intervention	CKC with or without simple hyst	Simple vs radical hyst
Primary outcome	Immediate failure (residual cancer in hysterectomy specimen)	Pelvic recurrence at 3y
**Lymph node assessment required in all tri*		

	ConCerv trial (2021)[1]	SHAPE trial (2024)[3]
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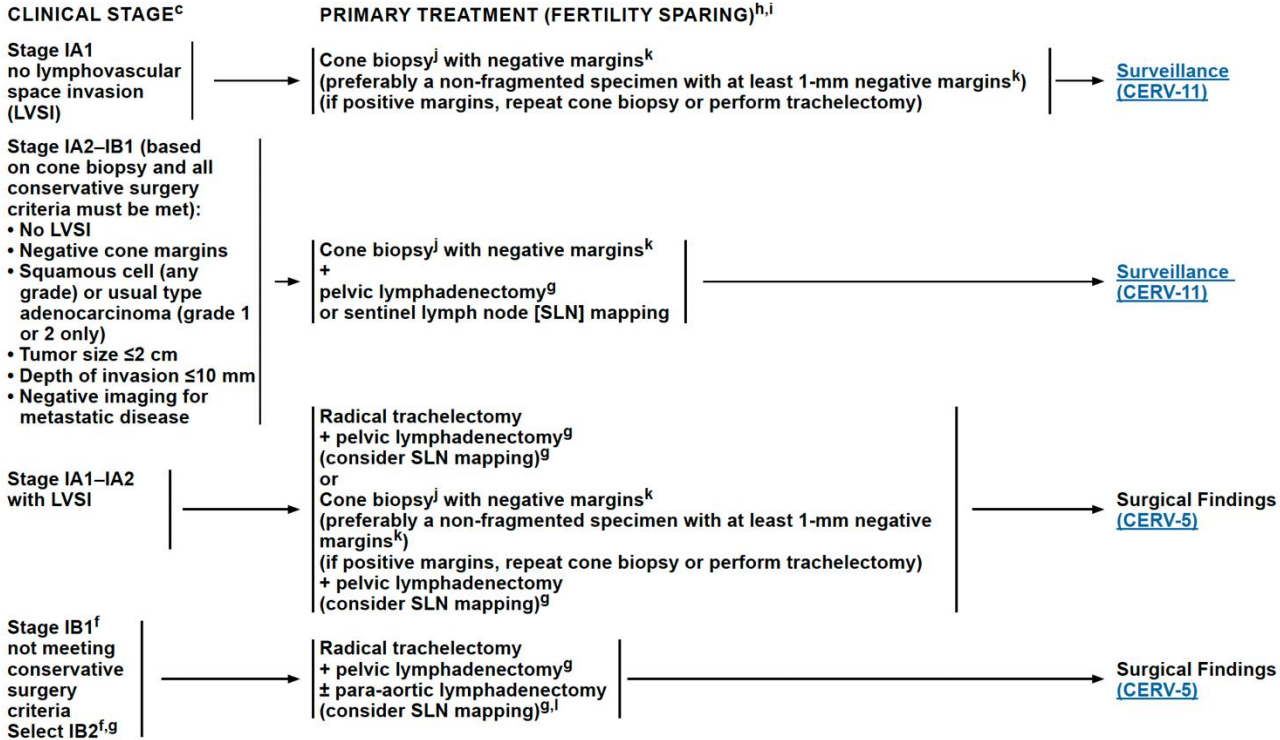
Schmeler KM et al. *Int J Gynecol Cancer 2021* Plante M et al. *N Engl J Med 2024*

Stage I Fertility Preservation



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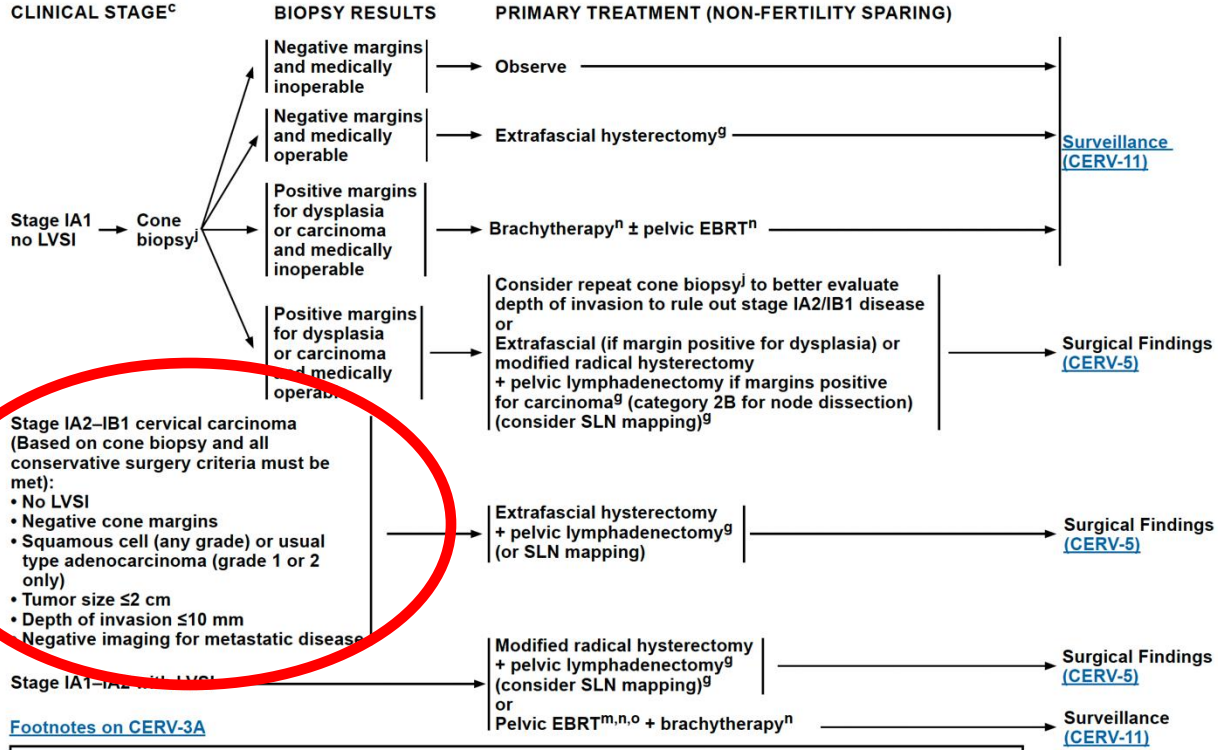
Abu Rustum et al. *J Natl Compr Canc* 2024

Stage I Non-Fertility Preservation



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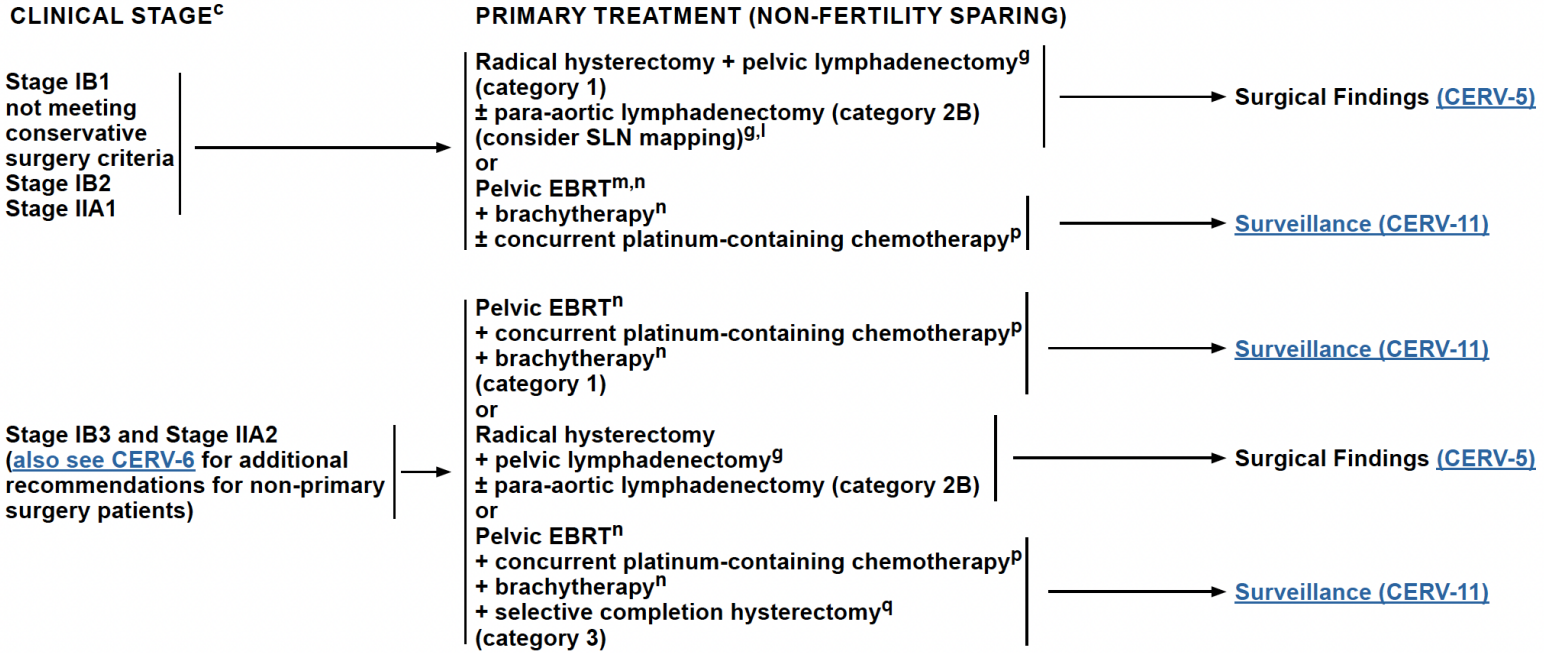
Stage I Radical Treatments



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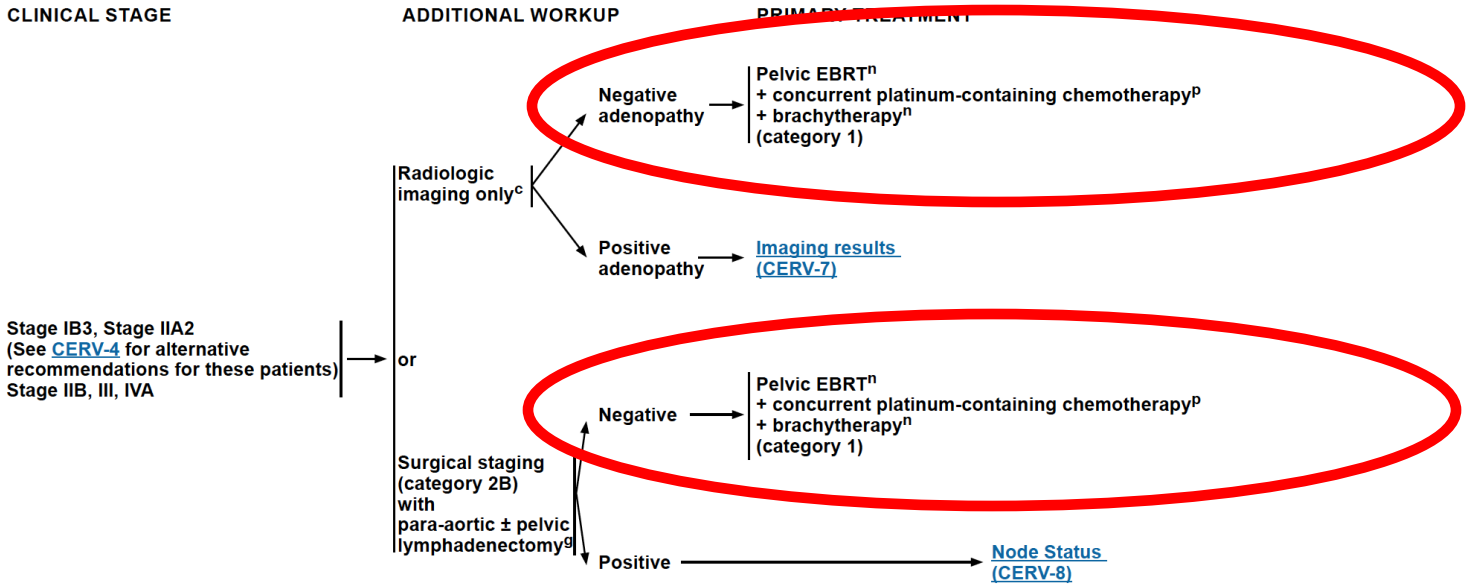
LACC Nodal Assessment Options



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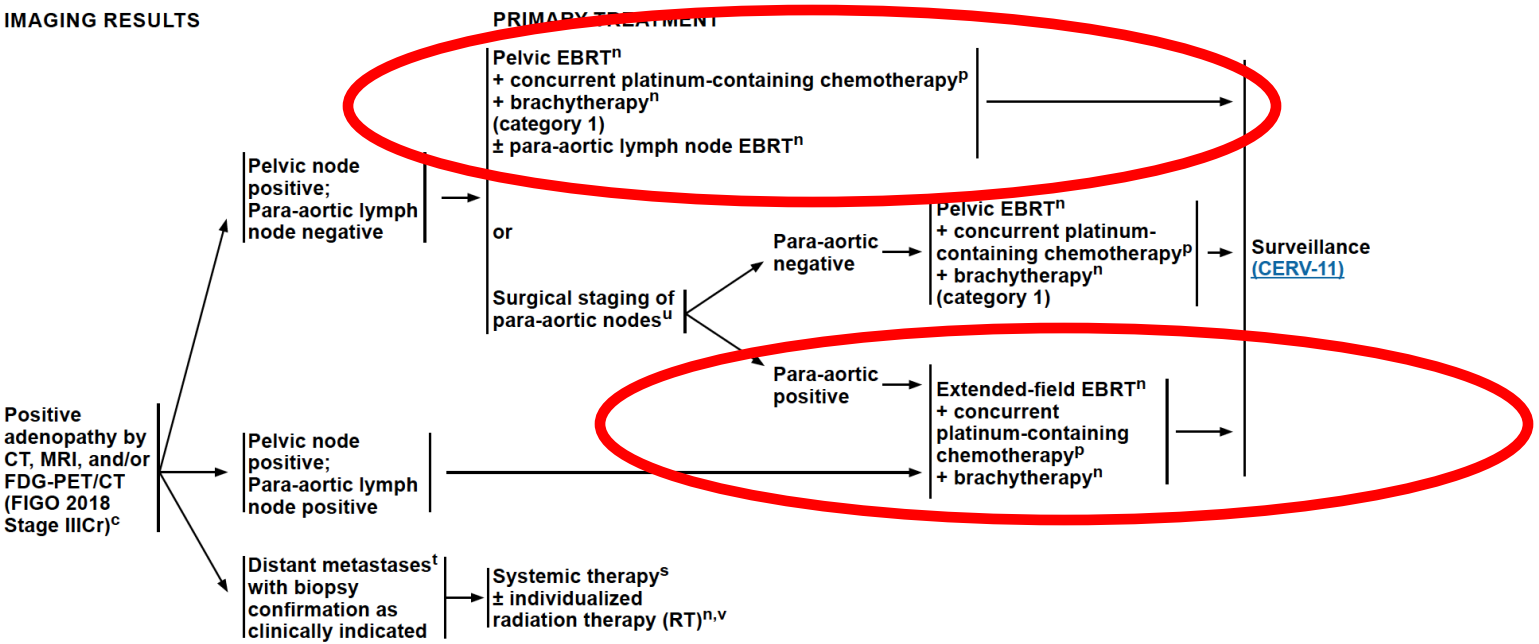
Abu Rustum et al. *J Natl Compr Canc* 2024

LACC Management – Impact of Nodal Information



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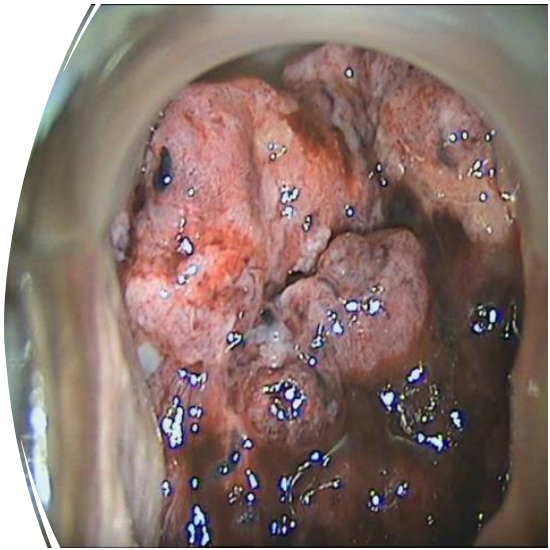
Abu Rustum et al. *J Natl Compr Canc* 2024

Impactful Clinical Trials – LACC & Metastatic

But first a case….

- 35 y/o G4P4 presents with a chief complaint of “two years of irregular bleeding” with normal ED examination and negative STI testing
- No healthcare in 6 years since birth of last child
- PMH – Hypertension
- PSH – BTL
- SH – + Tobacco
- FH – No known malignancies

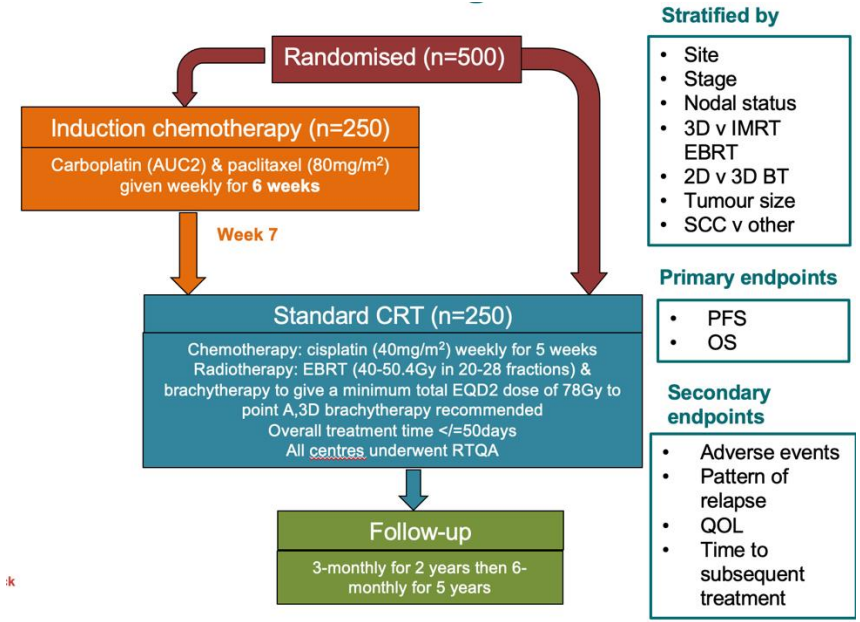
- Diagnosis – T2B lesion



Locally Advanced Cervical Cancer Treatment Options

A. Radiation with concurrent cisplatin – Post 1999 Standard
B. Radiation with concurrent cisplatin and immunotherapy – Future Standard?
C. Radiation with concurrent immunotherapy – What happened to CDDP?
D. Radiation with concurrent cisplatin and gemcitabine – Probably not
E. Neoadjuvant chemotherapy with platinum/taxane followed by surgery – EORTC-55954
F. Neoadjuvant chemotherapy with platinum/taxane followed by chemoradiation – EORTC-55954 / GCIG Interlace

GCIG INTERLACE – NACT + ChemoRT vs. ChemoRT



Design

- Open-label RCT
- IB1 node+, IB2, II, IIIB, IVA (NO + PA nodes)
- Superiority for NACT with OS HR 0.65-0.70
- 70-84% power
- Hierarchical testing type I error of 5% (PFS → OS)

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McCormack M, Gallardo D, Eminowicz G, Diez P, et al. *ESMO* 2023

GCIG INTERLACE – NACT + ChemoRT vs. ChemoRT

	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)

congress

Adherence to Cisplatin

	CRT alone (n=250)	IC+ CRT (n=250)
	No. of patients (%)	
Completed 5 cycles	197 (79)	169 (68)
Completed at least 4 cycles	224 (90)	212 (85)
Main reasons for <5 cycles:		
Adverse events leading to discontinuation:	33 (13)	68 (27)
Haematological	4	34
Non-haematological	25	20
Both	4	14
Other	20 (8)	13 (5)

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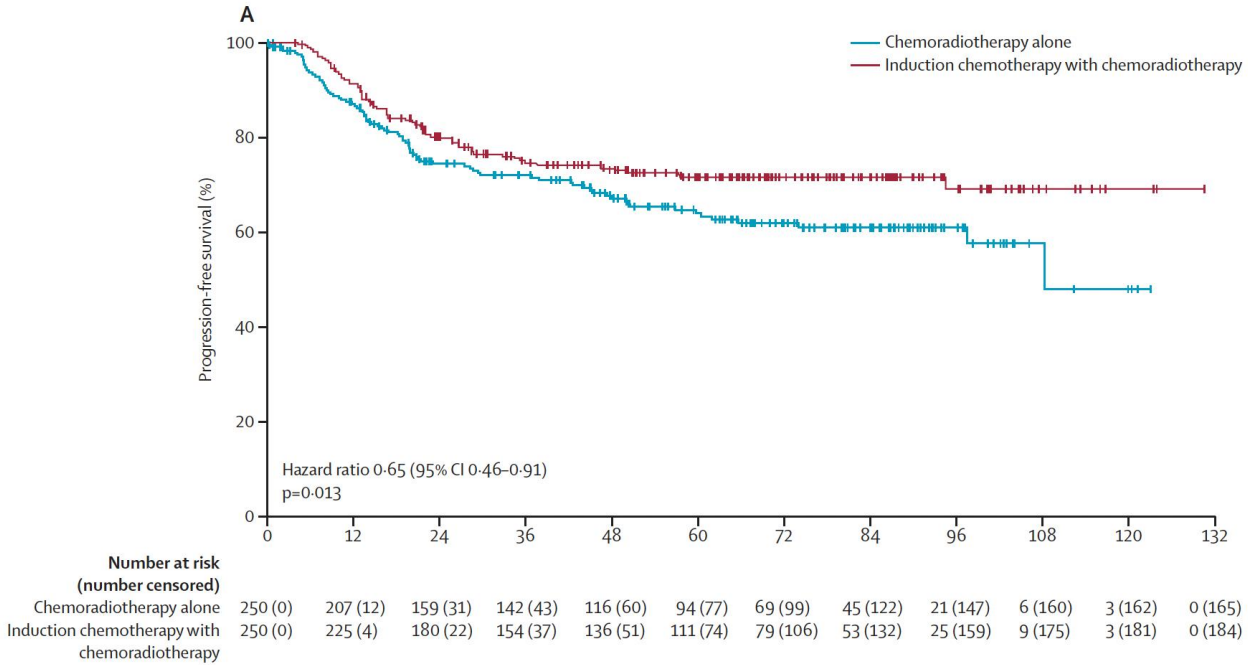
McCormack M, Gallardo D, Eminowicz G, Diez P, et al. *ESMO* 2023

GCIG INTERLACE – PFS



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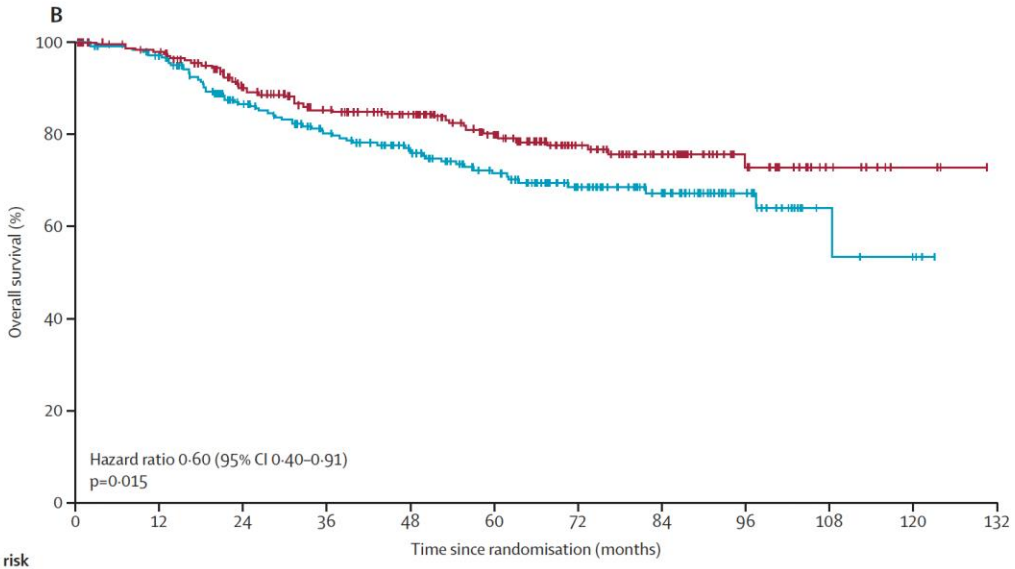
McCormack M, Gallardo D, Eminowicz G, Diez P, et al. *ESMO* 2023

GCIG INTERLACE – OS



Number at risk (number censored)												
Chemoradiotherapy alone	250 (0)	230 (13)	186 (33)	157 (49)	132 (66)	105 (86)	75 (112)	48 (138)	24 (163)	6 (179)	3 (181)	0 (184)
Induction chemotherapy with chemoradiotherapy	250 (0)	240 (5)	196 (31)	169 (48)	150 (65)	118 (90)	83 (122)	55 (148)	26 (176)	9 (193)	4 (199)	0 (202)

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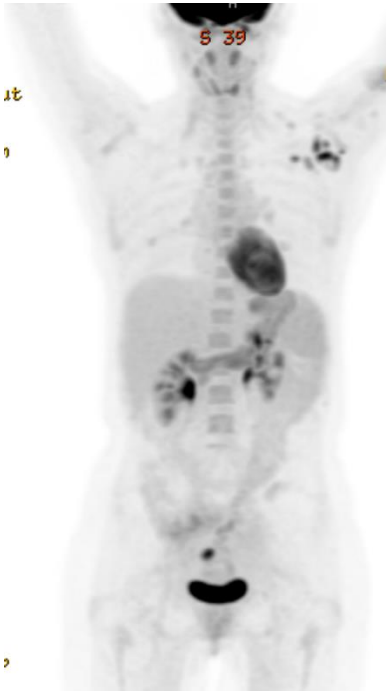
McCormack M, Gallardo D, Eminowicz G, Diez P, et al. *ESMO* 2023

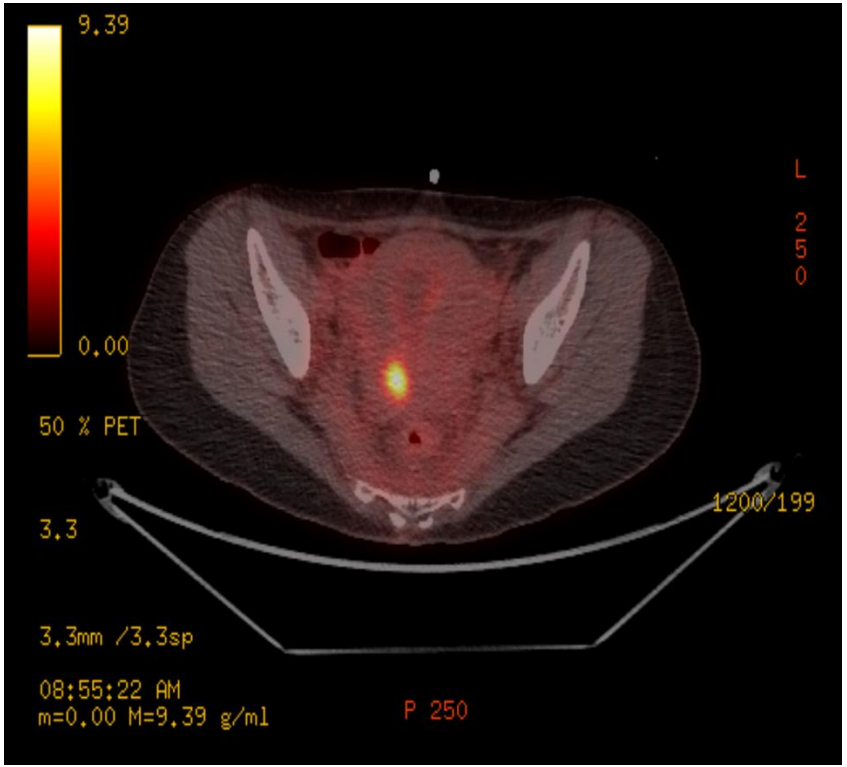
GCIG INTERLACE – Conclusions

- NACT followed by ChemoRT in predominantly Stage II node negative patients improved PFS by 9% and OS by 8% at 5 years
  - PFS HR 0.65 (95% CI, 0.46-0.91), p=0.013
  - OS: HR 0.60 (95% CI, 0.40-0.91), p=0.015
- Adherence to chemoradiation was good
- Most radiation was not IMRT

McCormack M, Gallardo D, Eminowicz G, Diez P, et al. *ESMO* 2023

Back to the Case….





Persistent Cervical Disease

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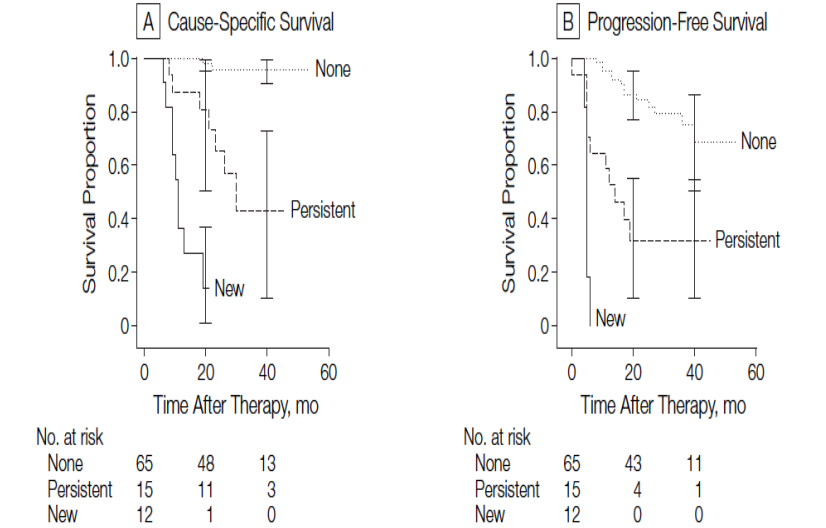
Posttreatment PET/CT in Cervical Cancer

Table 1. Baseline Characteristics

	No. (%) of Patients[a]	
	Initial Cohort (n = 152)	Prospective Cohort (n = 92)
Age, median (IQR), y	49 (41-57)	51 (42-60)
Clinical stage		
Ib1	17 (11)	13 (14)
Ib2	35 (23)	14 (15)
IIa	4 (3)	2 (2)
IIb	52 (34)	42 (46)
IIIa	2 (1)	1 (1)
IIIb	40 (26)	18 (20)
IVa	2 (1)	2 (2)
PET lymph node status		
None	48 (32)	48 (52)
Pelvic	81 (53)	30 (33)
Pelvic and para-aortic	23 (15)	14 (15)
Tumor histology		
Squamous	141 (93)	81 (88)
Adenocarcinoma	4 (3)	7 (8)
Adenosquamous	6 (4)	1 (1)
Clear cell	1 (1)	3 (3)

Abbreviations: IQR, interquartile range; PET, positron emission tomography.
[a] Unless otherwise indicated.

Figure 2. Cause-Specific and Progression-Free Survival Rates for Patients



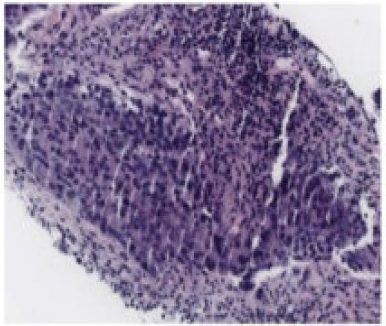
UAB MEDICINE

Schwarz JK, Siegel BA, Dehdashti F, Grigsby PW. *JAMA* 2007

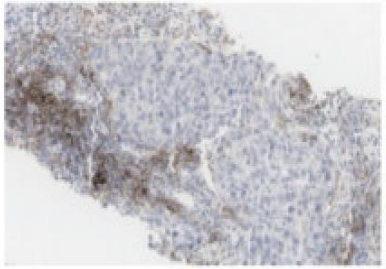
Cervical biopsy is positive for recurrent cervical cancer – Next steps?

A. Carboplatin/paclitaxel/pembrolizumab
B. Carboplatin/paclitaxel/pembrolizumab/bevacizumab
C. Carboplatin/paclitaxel/atezolizumab
D. Carboplatin/paclitaxel/atezolizumab/bevacizumab
E. Topotecan/paclitaxel/bevacizumab
F. Single agent pembrolizumab
G. Tisotumab vedotin
H. Trastuzumab deruxtecan (T-DXd)
I. Other single agent chemotherapy

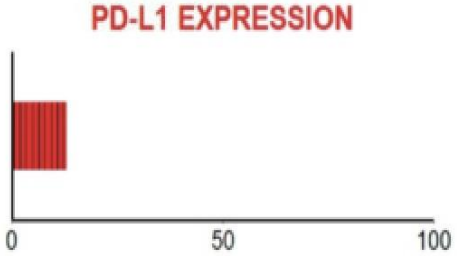
Modern “Pathologic” Assessment



H&E Image for Reference only



PD-L1 22C3 FDA (KEYTRUDA®) for Cervical: PD-L1 EXPRESSION Combined Positive Score: 13



Reference Ranges	
PD-L1 Expression	CPS >/=1
No PD-L1 Expression	CPS <1

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Recurrent Cervical Cancer Management

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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Abu Rustum et al. *J Natl Compr Canc* 2024

NCCN recommendations – Levels of Evidence

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

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Abu Rustum et al. *J Natl Compr Canc* 2021

KEYNOTE-826 – Paclitaxel, Platinum, Pembrolizumab ± Bevaciumab

Table 1. Demographic and Disease Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Pembrolizumab Group (N=308)†	Placebo Group (N=309)†
Age		
Median (range) — yr	51 (25–82)	50 (22–79)
≥65 yr — no. (%)	48 (15.6)	52 (16.8)
Race — no. (%)‡		
White	170 (55.2)	190 (61.5)
Non-White	138 (44.8)	119 (38.5)
ECOG performance-status score — no. (%)§		
0	178 (57.8)	170 (55.0)
1	128 (41.6)	139 (45.0)
Disease stage at initial diagnosis — no. (%)¶		
I	67 (21.8)	58 (18.8)
II	85 (27.6)	93 (30.1)
III	5 (1.6)	8 (2.6)
IIIA	4 (1.3)	8 (2.6)
IIIB	46 (14.9)	42 (13.6)
IVA	7 (2.3)	4 (1.3)
IVB	94 (30.5)	96 (31.1)
Disease status at trial entry — no. (%)		
Metastatic	58 (18.8)	64 (20.7)
Persistent or recurrent with distant metastases	199 (64.6)	179 (57.9)
Persistent or recurrent without distant metastases	51 (16.6)	66 (21.4)
Histologic type — no. (%)**		
Adenocarcinoma	56 (18.2)	84 (27.2)
Adenosquamous carcinoma	15 (4.9)	14 (4.5)
Squamous-cell carcinoma	235 (76.3)	211 (68.3)
PD-L1 combined positive score — no. (%)††		
<1	35 (11.4)	34 (11.0)
1 to <10	115 (37.3)	116 (37.5)
≥10	158 (51.3)	159 (51.5)
Previous therapy — no. (%)		
Chemoradiotherapy and surgery	49 (15.9)	56 (18.1)
Radiotherapy and surgery	22 (7.1)	23 (7.4)
Chemoradiotherapy only	125 (40.6)	118 (38.2)
Radiotherapy only	31 (10.1)	24 (7.8)
Surgery only	23 (7.5)	24 (7.8)
None	58 (18.8)	64 (20.7)
Bevacizumab use during the trial — no. (%)		
Yes	196 (63.6)	193 (62.5)
No	112 (36.4)	116 (37.5)

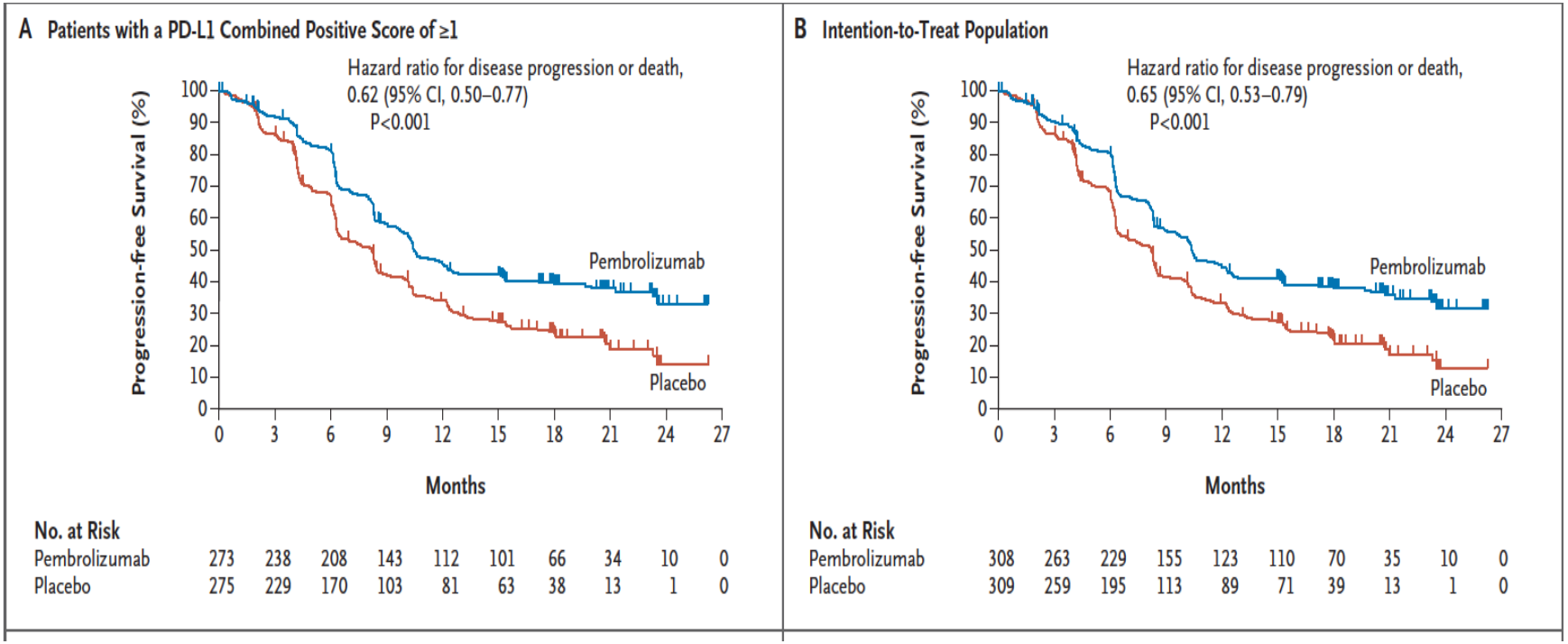
Design

- Double blind RCT
- Placebo-controlled 1:1
- Chemo + Pembro/Placebo for up to 35 cycles
- Multiple hypotheses tested
- 90%+ power for all
- PD-L1 stratification
- Accrual 15 months!
  - 11/2018 – 2/2020

UAB MEDICINE

Colombo N, Dubot C, Lorusso D et al. *N Engl J Med* 2021

KEYNOTE-826 – PFS (PD-L1 ≥ 1, ITT)



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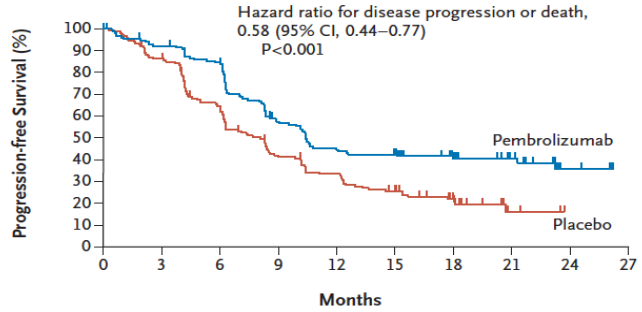
Colombo N, Dubot C, Lorusso D et al. *N Engl J Med* 2021

KEYNOTE-826 – PFS (PD-L1 ≥ 10)

C Patients with a PD-L1 Combined Positive Score of ≥10

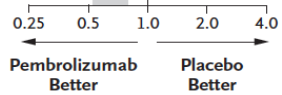


No. at Risk

Pembrolizumab	158	138	124	80	62	58	35	21	7	0
Placebo	159	131	95	60	47	35	19	3	0	0

D Subgroup Analysis in Intention-to-Treat Population

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Disease Progression or Death (95% CI)
Overall	406/617	0.65 (0.53–0.79)
Age		
<65 yr	345/517	0.63 (0.50–0.78)
≥65 yr	61/100	0.77 (0.42–1.42)
Race		
White	239/360	0.70 (0.53–0.91)
Non-White	139/221	0.64 (0.45–0.90)
ECOG performance-status score		
0	197/348	0.65 (0.48–0.87)
1	207/267	0.69 (0.52–0.93)
PD-L1 combined positive score		
<1	51/69	0.94 (0.52–1.70)
1 to <10	152/231	0.68 (0.49–0.94)
≥10	203/317	0.58 (0.44–0.77)
Concomitant bevacizumab		
Yes	234/389	0.61 (0.47–0.79)
No	172/228	0.74 (0.54–1.01)
Metastatic disease at diagnosis		
Yes	137/190	0.92 (0.64–1.30)
No	269/427	0.58 (0.45–0.75)



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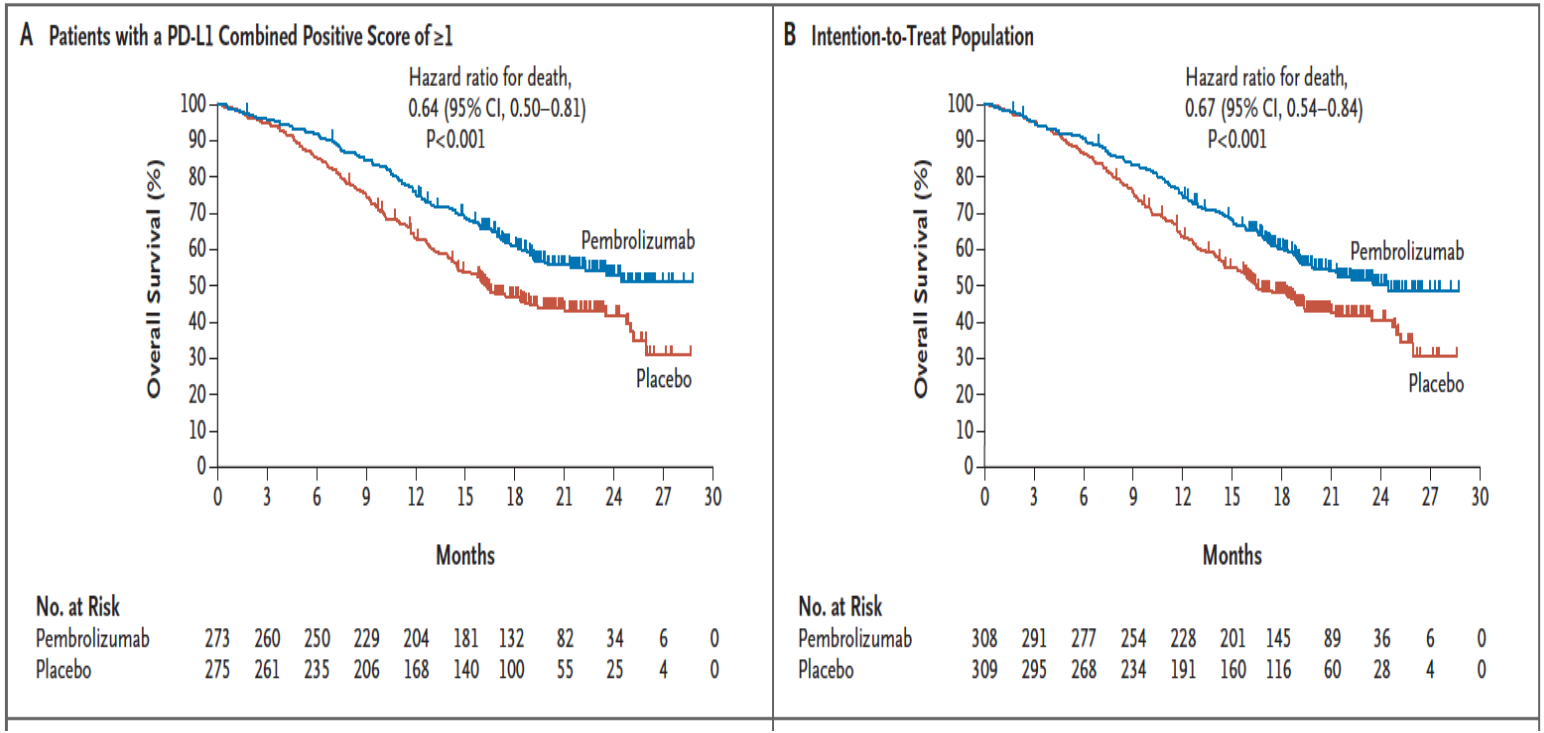
KEYNOTE-826 – Immature OS (PD-L1 ≥ 1, ITT)



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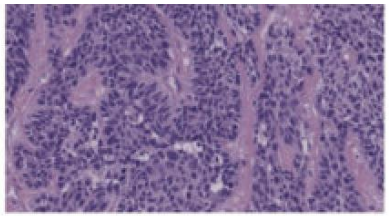
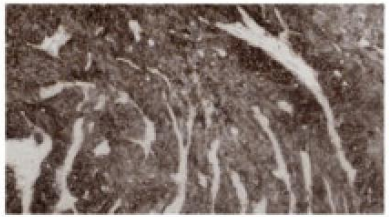
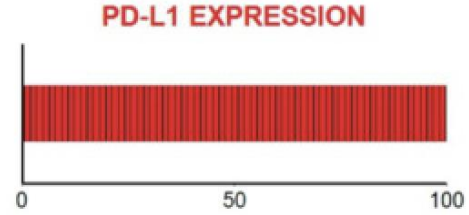
Is this Better?



H&E Image for Reference only



PD-L1 22C3 FDA (KEYTRUDA®) for Cervical: PD-L1 EXPRESSION Combined Positive Score: 100



Reference Ranges	
PD-L1 Expression	CPS >/=1
No PD-L1 Expression	CPS <1

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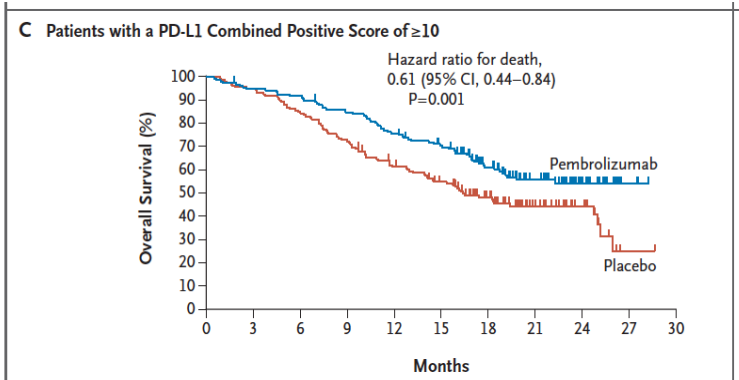
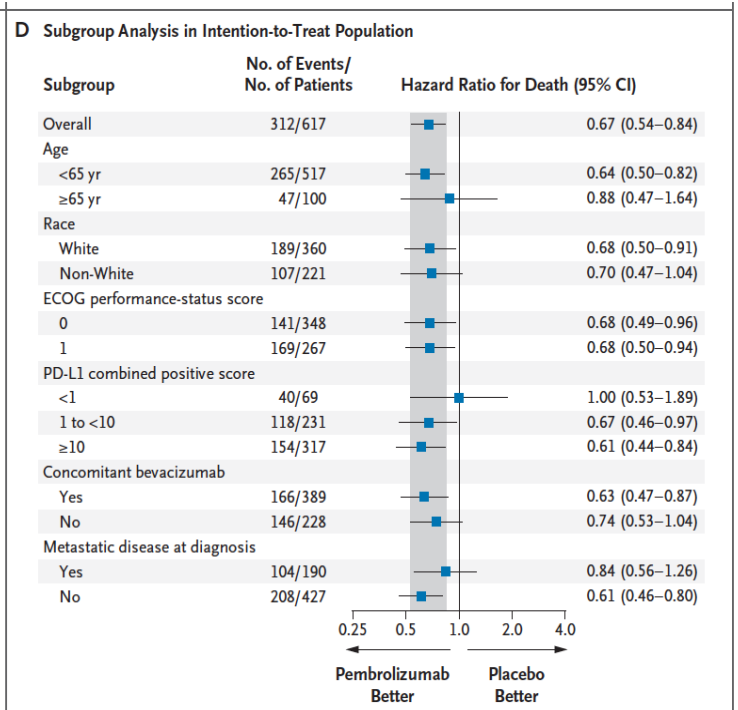
KEYNOTE-826 – Immature OS (PD-L1 ≥ 10)





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KEYNOTE-826 – Conclusions

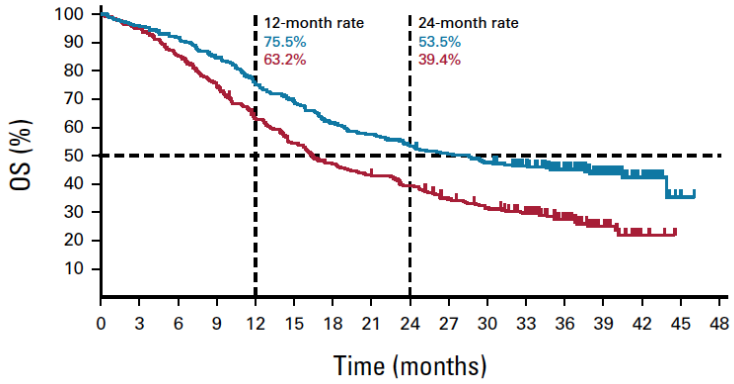
- **Improved PFS in experimental arm**
  - PD-L1 1+: 10.4 vs. 8.2 months (HR 0.62, 95% CI 0.50 – 0.77, $p<0.001$)
  - ITT: 10.4 vs. 8.2 months (HR 0.65, 95% CI 0.53 – 0.79, $p<0.001$)
  - PD-L1 10+: 10.4 vs. 8.1 months (HR 0.58, 95% CI 0.44 – 0.77, $p<0.001$)
- **Improved OS in experimental arm @ 24 months**
  - PD-L1 1+: 53% vs. 41.7% (HR 0.64, 95% CI 0.50 – 0.81, $p< 0.001$)
  - ITT: 50.4% vs. 40.4% (HR 0.67, 95% 0.54 – 0.84, $p<0.001$)
  - PD-L1 10+: 54.4 vs. 44.6% (HR 0.61, 95% CI 0.44-0.84, $p<0.001$)
- **Over 20% of patients in experimental arm with a CR!**

Colombo N, Dubot C, Lorusso D et al. *N Engl J Med* 2021

KEYNOTE-826 – OS (PD-L1 ≥ 1, ITT)

A OS: PD-L1 CPS ≥1 Population

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

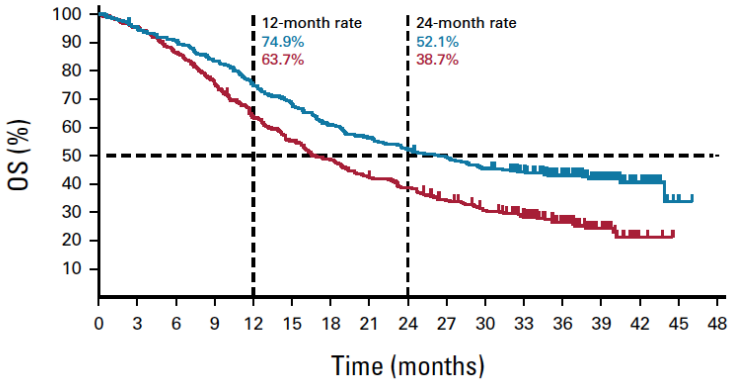


No. at risk:

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

B OS: All-Comer Population

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



No. at risk:

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

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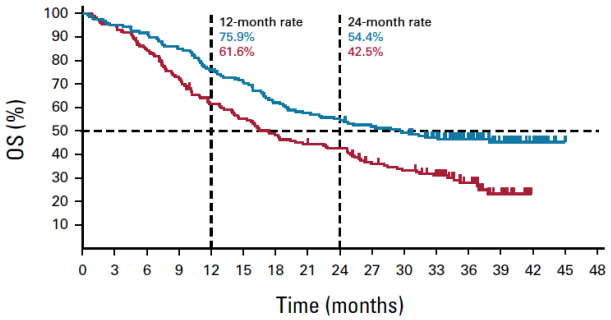
KEYNOTE-826 – OS (PD-L1 ≥ 10)

C OS: PD-L1 CPS ≥10 Population

Treatment Group	No. of Events/ No. of Patients (%)	Median OS, Months (95% CI)	HR (95% CI)
Pembro + chemo ± bev	85/158 (53.8)	29.6 (20.6 to NR)	0.58 (0.44 to 0.78)
Placebo + chemo ± bev	114/159 (71.7)	17.4 (14.0 to 24.7)	

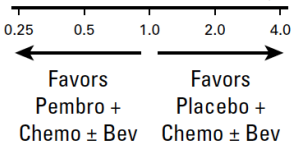


No. at risk:

158	150	145	134	120	112	98	91	86	80	76	67	51	31	15	1	0
159	151	135	116	97	87	76	70	66	53	48	39	23	10	0	0	0

D OS: Protocol-Specified Subgroups, All-Comer Population

Subgroup	No. of Events/ No. of Patients	HR (95% CI)
Overall	406/617	0.63 (0.52-0.77)
Age, years		
<65	345/517	0.60 (0.49-0.75)
≥65	61/100	0.84 (0.48-1.46)
Race		
White	238/360	0.63 (0.49-0.83)
All others	144/221	0.62 (0.44-0.87)
ECOG performance status score		
0	192/348	0.62 (0.46-0.83)
1	212/267	0.68 (0.51-0.91)
PD-L1 combined positive score		
<1	52/69	0.87 (0.50-1.52)
1 to <10	155/231	0.63 (0.45-0.86)
≥10	199/317	0.58 (0.44-0.78)
Concomitant bevacizumab		
Yes	229/389	0.61 (0.47-0.80)
No	177/228	0.67 (0.49-0.91)
Metastatic disease at diagnosis		
Yes	135/190	0.85 (0.60-1.21)
No	271/427	0.54 (0.43-0.70)



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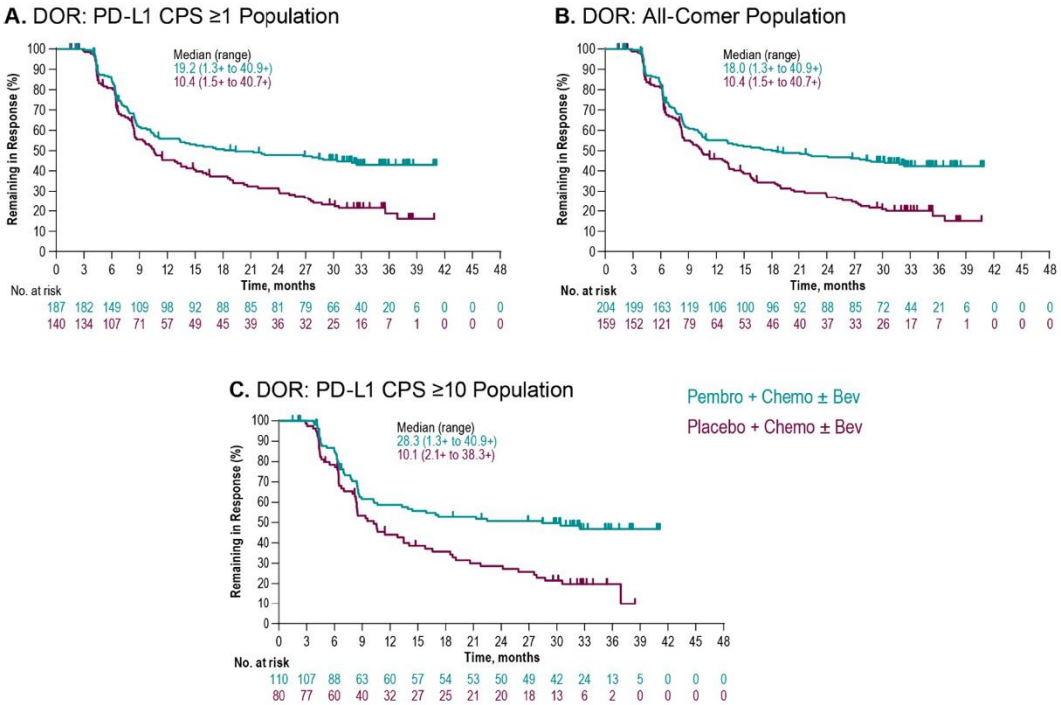
KEYNOTE-826 – OS

- **Confirmed improved OS after median follow-up of 39.1 months (range 32.1-46.5 months)**
  - PD-L1 1+: 28.6 vs. 16.5 months (HR 0.60, 95% CI 0.49 – 0.74)
  - ITT: 26.4 vs. 16.8 months (HR 0.63, 95% CI 0.52 – 0.77)
  - PD-L1 10+: 29.6 vs. 17.4 months (HR 0.58, 95% CI 0.44 – 0.78)

Monk BJ, Colombo N, Tewari KS, Dubot C et al. *J Clin Oncol* 2023

KEYNOTE-826 – DOR



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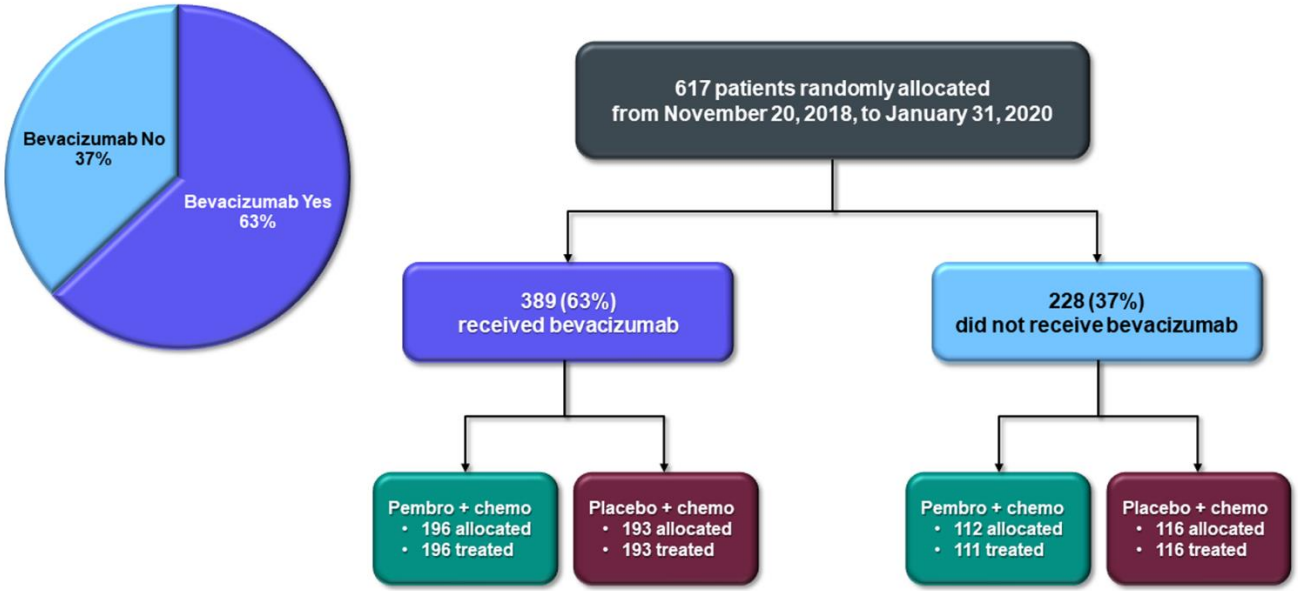
KEYNOTE-826 – Impact of Bevacizumab

Summary of Bevacizumab Use



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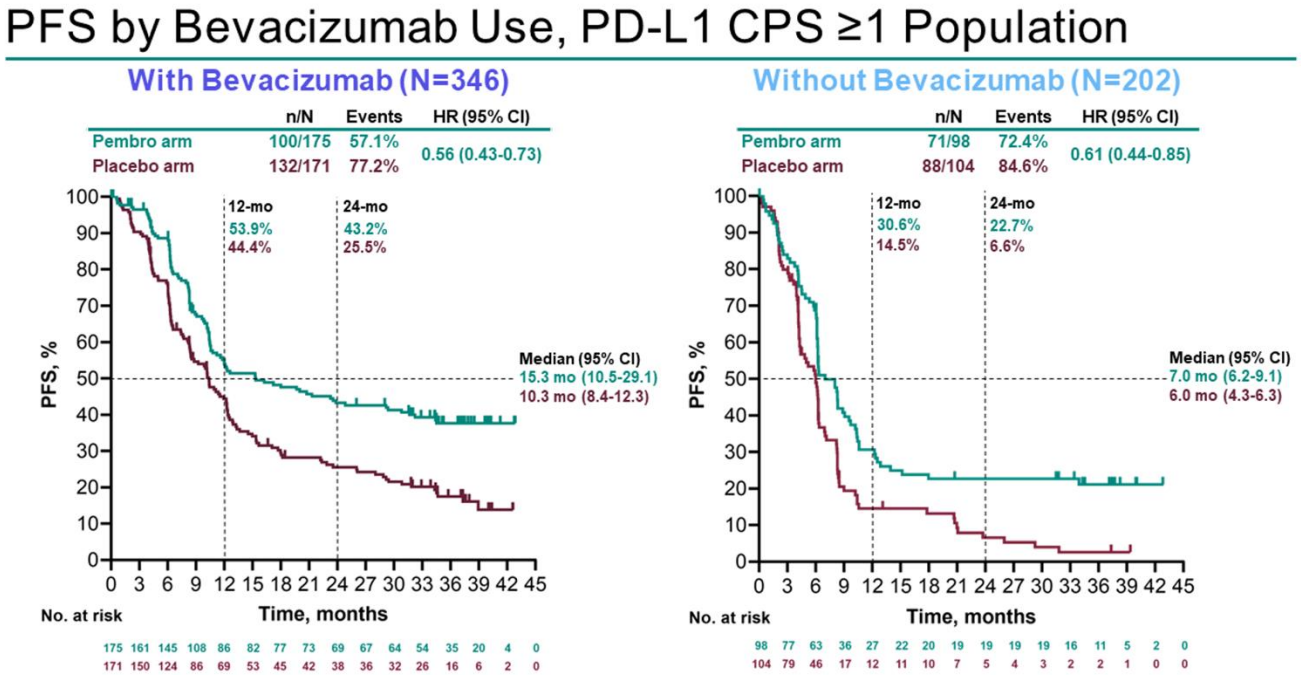
Lorusso D, Colombo N, Tewari KS, Dubot C et al. ESGO 2023

KEYNOTE-826 – Impact of Bevacizumab



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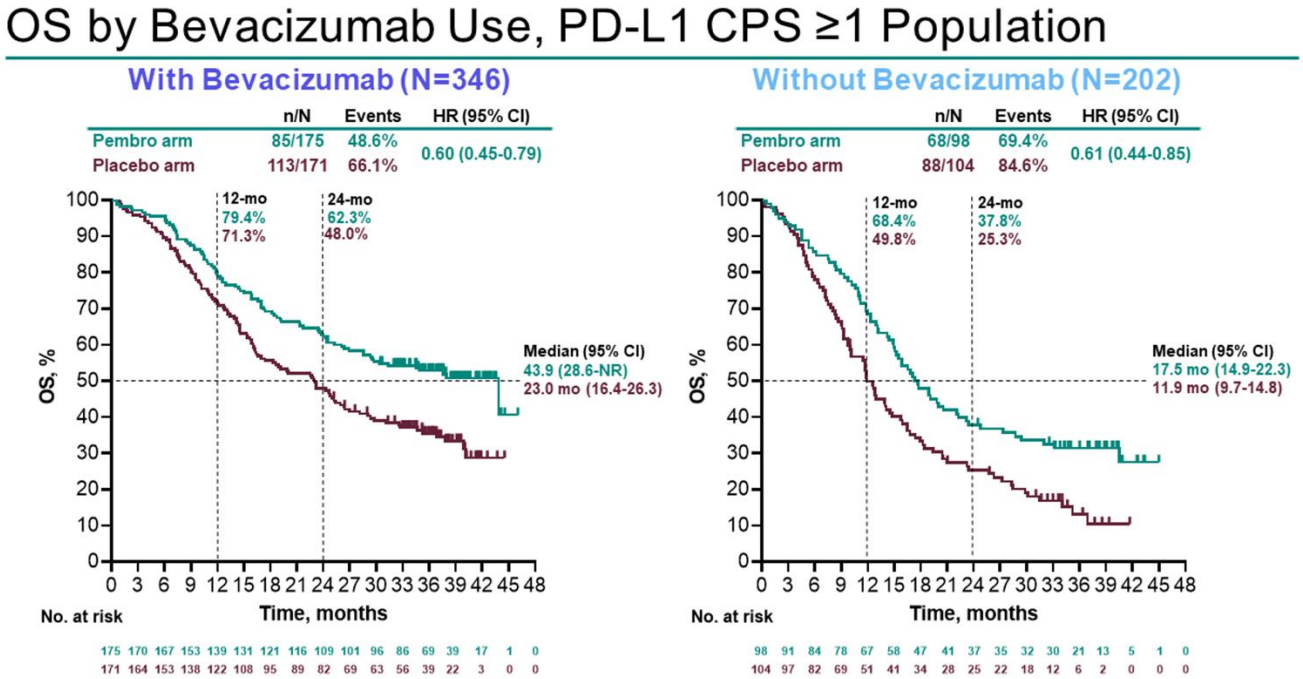
KEYNOTE-826 – Impact of Bevacizumab



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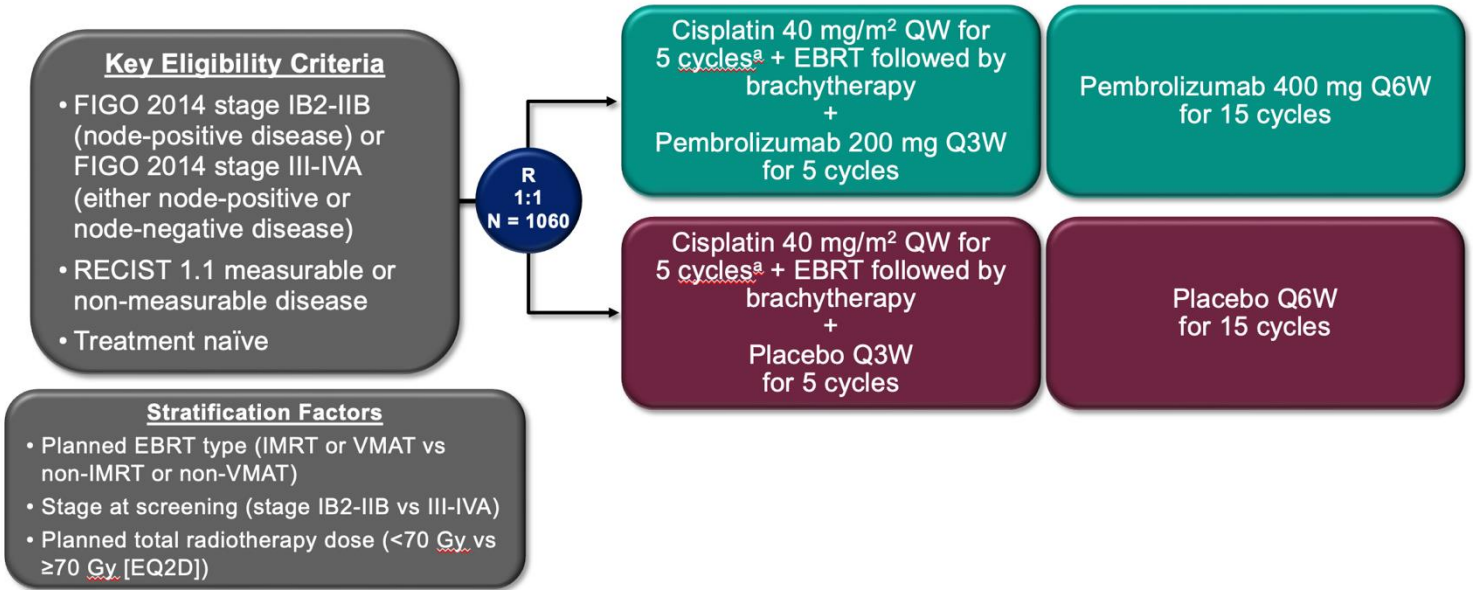
Immunotherapy Future – Impact of A18

ENGOT-cx11/GOG-3047/KEYNOTE-A18: Randomized, Double-Blind, Phase 3 Study



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A18 Patient Characteristics

	Pembrolizumab–chemoradiotherapy (n=529)	Placebo–chemoradiotherapy (n=531)
Age		
Median age, years	49 (40–57)	50 (41–59)
Participants aged ≥65 years	56 (11%)	77 (15%)
Race		
White	254 (48%)	264 (50%)
Asian	155 (29%)	148 (28%)
Multiple	78 (15%)	86 (16%)
American Indian or Alaska Native	24 (5%)	22 (4%)
Black or African American	14 (3%)	8 (2%)
Native Hawaiian or Other Pacific Islander	2 (<1%)	1 (<1%)
Missing	2 (<1%)	2 (<1%)
ECOG-PS score*		
0	380 (72%)	397 (75%)
1	149 (28%)	134 (25%)
FIGO 2014 stage at screening		
IB2 to IIB	235 (44%)	227 (43%)
III to IVA	294 (56%)	304 (57%)
Lymph node involvement†		
Positive pelvic only	326 (62%)	324 (61%)
Positive para-aortic only	14 (3%)	10 (2%)
Positive pelvic and para-aortic	105 (20%)	104 (20%)
No positive pelvic or para-aortic	84 (16%)	93 (18%)
Histology		
Non-squamous‡	96 (18%)	80 (15%)
Squamous	433 (82%)	451 (85%)
Planned type of external beam radiotherapy		
IMRT or VMAT	469 (89%)	470 (89%)
Non-IMRT and non-VMAT	60 (11%)	61 (11%)
Planned total radiotherapy dose		
<70 Gy	47 (9%)	46 (9%)
≥70 Gy	482 (91%)	485 (91%)
PD-L1 combined positive score		
<1	22 (4%)	28 (5%)
≥1	502 (95%)	498 (94%)
Missing	5 (<1%)	5 (<1%)

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Lorusso D, Xiang Y, Hasegawa K, et al. *Lancet* 2024

2014 vs. 2018 FIGO Cervical Cancer Staging

Stage 0	Carcinoma in situ, CIN
Stage I	Invasive carcinoma confined to the cervix
Stage I	Diagnosed only by microscopy
IA1	Micro-invasive carcinoma with stromal invasion <3 mm depth, <7 mm width
IA2	Micro-invasive carcinoma <5 mm depth, <7 mm width
Stage IB	Clinically visible or microscopic lesion >IA2
IB1	Clinical lesion <4 cm
IB2	Clinical lesion >4 cm
Stage II	Extension beyond cervix but not to sidewall
IIA	Involvement of upper two-thirds of vagina
IIB	Parametrial involvement
Stage III	Extension to pelvic wall and/or lower third of vagina; hydronephrosis
IIIA	Involvement of lower third of vagina
IIIB	Pelvic sidewall involvement; hydronephrosis
Stage IV	Extension beyond true pelvis or involving bladder or rectum
IVA	Involvement of bladder or rectal mucosa
IVB	Spread outside true pelvis or metastasis to distant organs

Stage	Description
I	Carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only with microscopy, with maximum depth of invasion <5 mm
IA1	Stromal invasion <3 mm in depth
IA2	Stromal invasion ≥3 mm and <5 mm in depth
IB	Invasive carcinoma confined to the uterine cervix, with measured deepest invasion ≥5 mm
IB1*	Tumor measures <2 cm in greatest dimension
IB2*	Tumor measures ≥2 cm and <4 cm in greatest dimension
IB3*	Tumor measures ≥4 cm in greatest dimension
II	Carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Limited to the upper two-thirds of the vagina without parametrial involvement
IIA1	Tumor measures <4 cm in greatest dimension
IIA2	Tumor measures ≥4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	Carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes
IIIA	Involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney from tumor
IIIC*	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent†
IIIC1*	Pelvic lymph node metastasis only
IIIC2*	Para-aortic lymph node metastasis
IV	Carcinoma has extended beyond the true pelvis or has involved (biopsy-proven) the mucosa of the bladder or rectum
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

FIGO Committee on Gynecologic Oncology *Int J Gynaecol Obstet* 2014; Bhatla N et al. Cancer of the cervix uteri *Int J Gynaecol Obstet* 2018

A18 Therapeutic Parameters

Summary of Treatment Exposure

	Pembro Arm (N = 528)	Placebo Arm (N = 530)
Total number of cycles, median (range)		
Pembro or placebo	11 (1-20)	11 (1-20)
Cisplatin[a]	5 (1-7)	5 (1-7)
Radiation therapy, median (range)[a]		
Overall treatment time (days)	52 (12-139)	52 (2-166)
Within 50 days[b], n (%)	184 (35.5%)	194 (37.2%)
Within 56 days, n (%)	386 (74.5%)	390 (74.7%)
Cervix total dose (Gy), median (range)[a]		
Total cervix physical dose	76 (14-94)	76 (3-125)
Total cervix EQD2 dose	87 (14-118)	87 (3-207)

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A18 Adverse Events – Similar in both Arms

	Pembrolizumab–chemoradiotherapy (n=528)		Placebo–chemoradiotherapy (n=530)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse event*	525 (99%)	394 (75%)	526 (99%)	364 (69%)
Treatment-related adverse event†	507 (96%)	354 (67%)	509 (96%)	321 (61%)
Anaemia	313 (59%)	99 (19%)	292 (55%)	84 (16%)
Nausea	302 (57%)	7 (1%)	315 (59%)	9 (2%)
Diarrhoea	266 (50%)	22 (4%)	271 (51%)	23 (4%)
White blood cell count decreased	172 (33%)	102 (19%)	181 (34%)	111 (21%)
Neutrophil count decreased	153 (29%)	77 (15%)	148 (28%)	78 (15%)
Vomiting	132 (25%)	3 (<1%)	150 (28%)	7 (1%)
Leukopenia	125 (24%)	67 (13%)	92 (17%)	57 (11%)
Platelet count decreased	116 (22%)	25 (5%)	108 (20%)	13 (2%)
Neutropenia	113 (21%)	56 (11%)	92 (17%)	51 (10%)
Immune-mediated adverse event‡	167 (32%)	21 (4%)	54 (10%)	5 (<1%)
Hypothyroidism	102 (19%)	3 (<1%)	24 (5%)	0
Hyperthyroidism	60 (11%)	2 (<1%)	11 (2%)	0
Colitis	14 (3%)	4 (<1%)	9 (2%)	4 (<1%)
Thyroiditis	11 (2%)	1 (<1%)	1 (<1%)	0

Data are n (%). *Listed are adverse events that occurred during the treatment period or within 30 days after the

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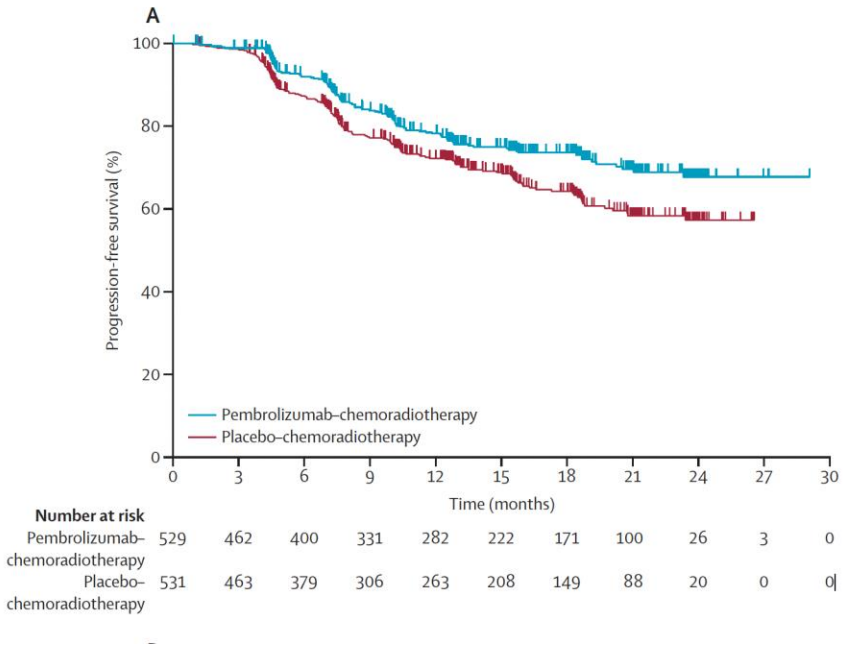
A18 PFS Interim Analysis (IA) 1

- HR: 0.70 (95% CI 0.55-0.89), *p*=0.0020
- 24-month PFS:
  - Pembro: 68% (95% CI 62-73)
  - Placebo: 57 (95% CI 51-63)



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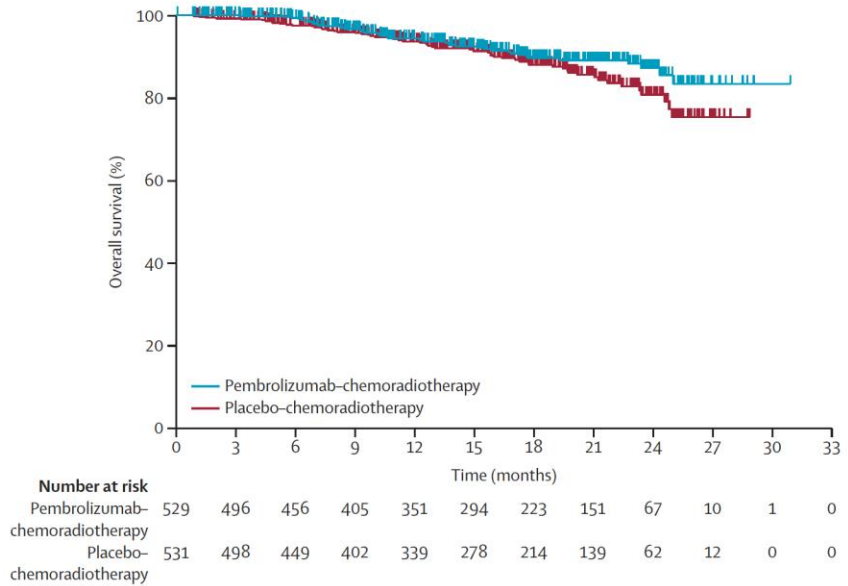
A18 OS IA1 (Immature at Publication)

- HR: 0.73 (95% CI 0.49-1.03)
  - *103 of 240 expected deaths (42.9%)*
- 24-month PFS:
  - Pembro: 87% (95%, CI 92-81)
  - Placebo: 81% (95%, CI 75-86)



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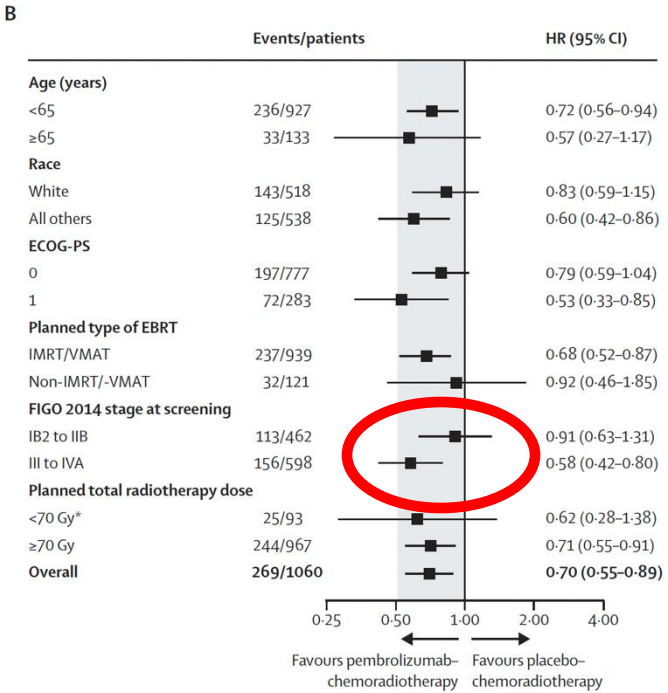
A18 IA1 Conclusions / Observations

A18 patients (N=1060)

- 529 Stage I/II (50%) – Improved outcomes but 95% CI crosses 1
  - Although multiple subgroups have 95% CI that cross 1 – Age > 65, White, ECOG = 0, Non-IMRT, and < 70 Gy Radiation Dose
- 531 Stage III/IV (50%) – More pronounced benefit



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Impact of A18

FDA approves pembrolizumab with chemoradiotherapy for FIGO 2014 Stage III-IVA cervical cancer

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On January 12, 2024, the Food and Drug Administration approved pembrolizumab (Keytruda, Merck) with chemoradiotherapy (CRT) for patients with FIGO 2014 Stage III-IVA cervical cancer.

A18 PFS IA2

- Investigator HR: 0.68 (95% CI, 0.56-0.84)
  - No formal statistical testing of PFS at IA2
- No median PFS reached in either arm
- BICR PFS HR 0.67 (95% CI, 0.53-0.85)
- 24-month PFS rate
  - Pembro: 76.1% (95% CI, 71.9-79.7)
  - Placebo: 66.9 (95% CI, 62.2-71.1)

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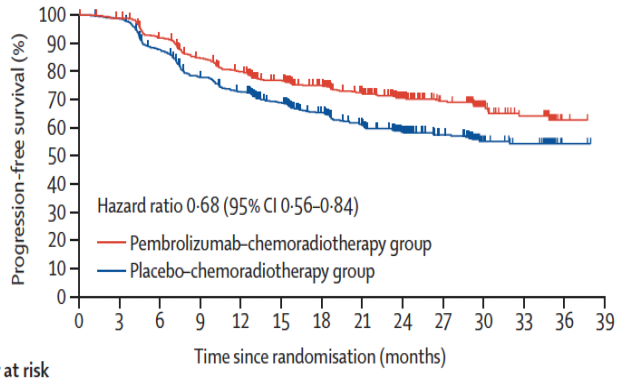

Number at risk (number censored)														
Pembrolizumab–chemoradiotherapy group	529 (0)	515 (8)	474 (13)	430 (20)	402 (24)	353 (58)	317 (86)	280 (112)	217 (169)	179 (204)	86 (293)	69 (306)	2 (372)	0 (374)
Placebo–chemoradiotherapy group	531 (0)	513 (11)	452 (16)	395 (22)	366 (26)	325 (48)	283 (74)	241 (98)	178 (152)	148 (179)	78 (244)	69 (252)	2 (319)	0 (321)

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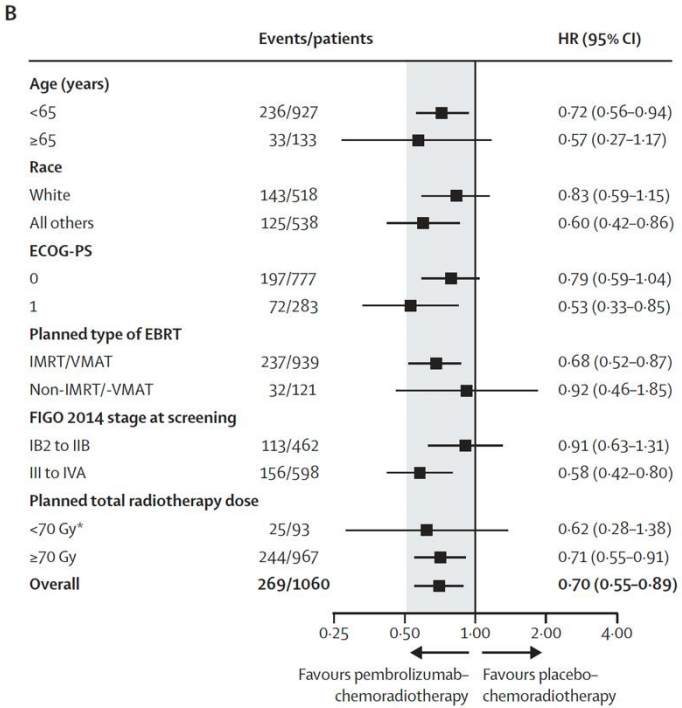
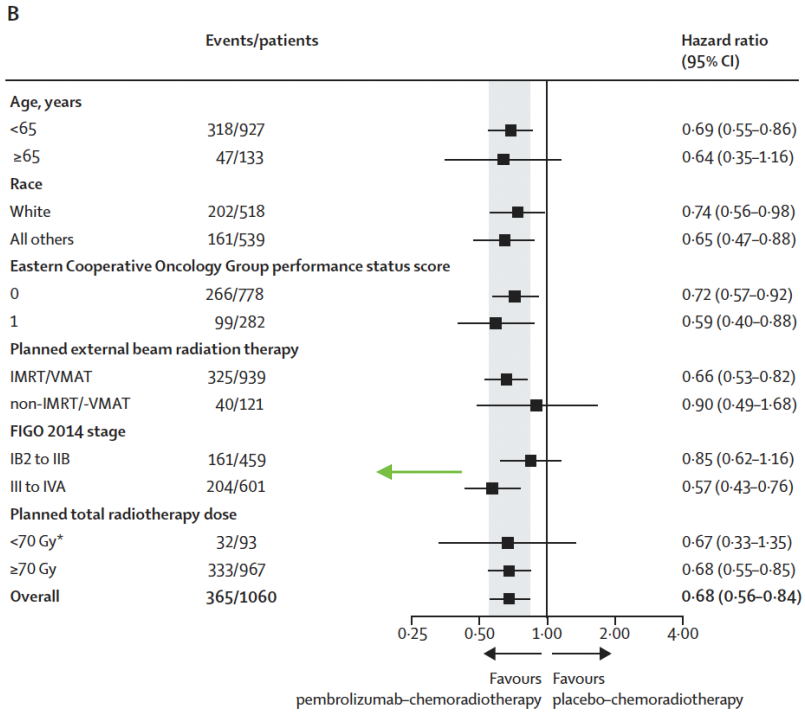
“Dynamic” A18 Subgroups





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Lorusso D, Xiang Y, Hasegawa K, et al. *Lancet* 2024 Lorusso D, Xiang Y, Hasegawa K, et al. *Lancet* 2024

A18 IA2 Conclusions / Observations

- Improved OS!
  - What else is there, really?
- 36 Month OS:
  - Pembro: 82.6% (95% CI, 78.4-86.1)
  - Placebo: 74.8% (95% CI, 70.1-78.8)
  - OS HR 0.67 (95% CI, 0.50-0.90, p=0.0040)

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Lorusso D, Xiang Y, Hasegawa K,, et al. *Lancet* 2024

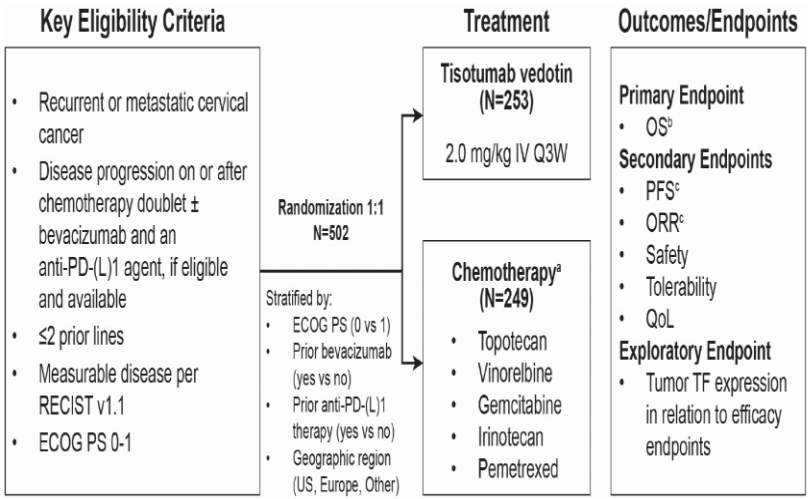
LACC Treatment Options

A. Radiation with concurrent cisplatin – Post 1999 Standard
B. Radiation with concurrent cisplatin and immunotherapy – Present and Future Standard
C. Radiation with concurrent immunotherapy – What happened to CDDP?
D. Radiation with concurrent cisplatin and gemcitabine – Probably not
E. Neoadjuvant chemotherapy with platinum/taxane followed by surgery – EORTC-55954
F. Neoadjuvant chemotherapy with platinum/taxane followed by chemoradiation – EORTC-55954 / GCIG Interlace

Immunotherapy Related Conclusions

- **Early recurrences are challenging to treat, as depicted in this case, although incorporation of immunotherapy improves outcomes**
- **Recurrent/Metastatic (PD-L1+) cervical cancers should receive immunotherapy (KEYNOTE-826, BEATcc)**
- **Results from A-18 will further impact treatment, as patients will not be CPI naïve at recurrence/progression**
- **Ongoing identification of novel agents is needed**

innovaTV 301/ENGOT-cx12/GOG-3057



Design

- Open-label 1:1 RCT
- Tisotumab vedotin (ADC to Tissue Factor) vs. Physician's choice chemotherapy (1-2 prior lines)
  - Topo, Vino, Gem, Irino, Peme
- Superiority for TV in OS HR 0.70
- 90% power
- N=502 (489 treated)
- Median OS for PCC = 9 months

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Vergote I, Gonzalez-Martin A, Fujiwara K, et al. *N Engl J Med* 2024

innovaTV 301/ENGOT-cx12/GOG-3057 Patients & AEs

Characteristic	Tisotumab Vedotin (N=253)	Chemotherapy† (N=249)	All Patients (N=502)
Median age (range) — yr	51 (26–80)	50 (27–78)	50 (26–80)
Baseline ECOG performance-status score — no. (%)‡			
0	137 (54.2)	136 (54.6)	273 (54.4)
1	116 (45.8)	113 (45.4)	229 (45.6)
Geographic region — no. (%)			
United States	16 (6.3)	14 (5.6)	30 (6.0)
Europe	106 (41.9)	104 (41.8)	210 (41.8)
Asia	85 (33.6)	88 (35.3)	173 (34.5)
Other	46 (18.2)	43 (17.3)	89 (17.7)
No. of previous lines of systemic therapy for recurrent or metastatic disease — no. of patients (%)			
1	159 (62.8)	149 (59.8)	308 (61.4)
2	93 (36.8)	100 (40.2)	193 (38.4)
Unknown	1 (0.4)	0	1 (0.2)
Previous systemic therapy or radiation for cervical cancer — no. (%)	253 (100)	249 (100)	502 (100)
Previous receipt of bevacizumab — no. (%)	164 (64.8)	157 (63.1)	321 (63.9)
Previous receipt of anti–PD-1 or anti–PD-L1 agent — no. (%)	71 (28.1)	67 (26.9)	138 (27.5)
Race or ethnic group — no. (%)§			
White	122 (48.2)	122 (49.0)	244 (48.6)
Asian	90 (35.6)	90 (36.1)	180 (35.9)
American Indian or Alaska Native	7 (2.8)	7 (2.8)	14 (2.8)
Black	4 (1.6)	6 (2.4)	10 (2.0)
Other	2 (0.8)	1 (0.4)	3 (0.6)
Native Hawaiian or other Pacific Islander	1 (0.4)	0	1 (0.2)
Not reported	19 (7.5)	17 (6.8)	36 (7.2)
Unknown	8 (3.2)	6 (2.4)	14 (2.8)
Disease status at trial entry — no. (%)			
Pelvic recurrent only	27 (10.7)	24 (9.6)	51 (10.2)
Extrapelvic metastatic	226 (89.3)	225 (90.4)	451 (89.8)
Histologic feature — no. (%)			
Squamous-cell carcinoma	160 (63.2)	157 (63.1)	317 (63.1)
Adenocarcinoma	85 (33.6)	75 (30.1)	160 (31.9)
Adenosquamous carcinoma	8 (3.2)	17 (6.8)	25 (5.0)
Evaluable biopsy sample — no. (%)¶	210 (83.0)	194 (77.9)	404 (80.5)
Positive membrane tissue factor expression — no./total no. (%)‖	194/210 (92.4)	183/194 (94.3)	377/404 (93.3)

Event	Tisotumab Vedotin (N=250)		Chemotherapy† (N=239)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any event	246 (98.4)	130 (52.0)	237 (99.2)	149 (62.3)
Nausea	83 (33.2)	1 (0.4)	96 (40.2)	5 (2.1)
Conjunctivitis	78 (31.2)	0	1 (0.4)	0
Peripheral sensory neuropathy	71 (28.4)	7 (2.8)	6 (2.5)	0
Epistaxis	65 (26.0)	0	6 (2.5)	0
Constipation	62 (24.8)	3 (1.2)	39 (16.3)	0
Alopecia	61 (24.4)	0	7 (2.9)	0
Decreased appetite	59 (23.6)	2 (0.8)	42 (17.6)	1 (0.4)
Anemia	58 (23.2)	21 (8.4)	125 (52.3)	66 (27.6)
Diarrhea	54 (21.6)	4 (1.6)	36 (15.1)	3 (1.3)
Vomiting	44 (17.6)	4 (1.6)	44 (18.4)	3 (1.3)
Pyrexia	42 (16.8)	1 (0.4)	50 (20.9)	2 (0.8)
Asthenia	40 (16.0)	5 (2.0)	38 (15.9)	5 (2.1)
Keratitis	39 (15.6)	5 (2.0)	0	0
Abdominal pain	34 (13.6)	10 (4.0)	23 (9.6)	4 (1.7)
Dry eye	33 (13.2)	0	1 (0.4)	0
Urinary tract infection	33 (13.2)	11 (4.4)	38 (15.9)	17 (7.1)
Fatigue	32 (12.8)	9 (3.6)	39 (16.3)	10 (4.2)
Pruritus	25 (10.0)	1 (0.4)	7 (2.9)	0
Vaginal hemorrhage	25 (10.0)	3 (1.2)	13 (5.4)	1 (0.4)
Increased alanine aminotransferase	18 (7.2)	4 (1.6)	26 (10.9)	5 (2.1)
Increased aspartate aminotransferase	17 (6.8)	1 (0.4)	27 (11.3)	3 (1.3)
Neutropenia	17 (6.8)	9 (3.6)	54 (22.6)	32 (13.4)
Peripheral edema	9 (3.6)	0	30 (12.6)	5 (2.1)

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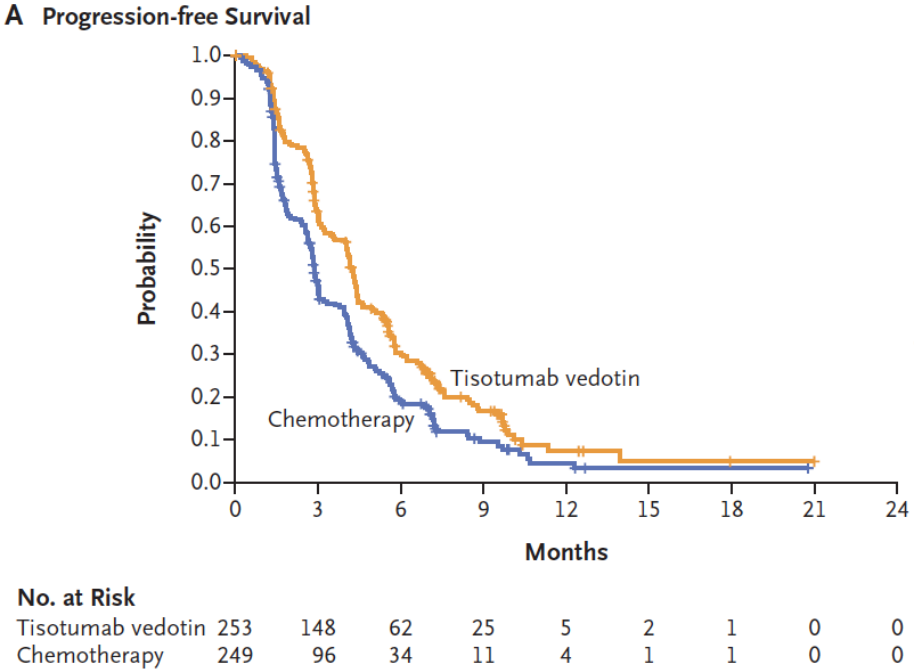
innovaTV 301/ENGOT-cx12/GOG-3057 – PFS



	No. of Events/ Total No. of Patients	Median Progression-free Survival (95% CI)
		mo
Tisotumab Vedotin	198/253	4.2 (4.0–4.4)
Chemotherapy	194/249	2.9 (2.6–3.1)

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

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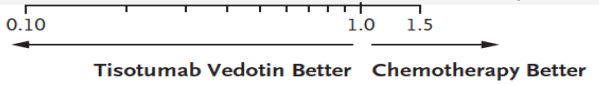
Vergote I, Gonzalez-Martin A, Fujiwara K, et al. *N Engl J Med* 2024

innovaTV 301/ENGOT-cx12/GOG-3057 – PFS Subgroups

B Subgroup Analysis

Subgroup	Tisotumab Vedotin (no. of events/total no. of patients)	Chemotherapy (no. of events/total no. of patients)	Hazard Ratio for Disease Progression or Death (95% CI)
Intention-to-treat population	198/253	194/249	0.67 (0.54–0.82)
Geographic region			
United States	13/16	8/14	0.37 (0.12–1.10)
Europe	86/106	81/104	0.71 (0.51–0.97)
Asia	69/85	73/88	0.60 (0.43–0.85)
Other	30/46	32/43	0.76 (0.44–1.30)
ECOG performance-status score at baseline			
0	104/137	106/136	0.70 (0.53–0.92)
1	94/116	88/113	0.62 (0.46–0.84)
Previous bevacizumab administration			
Yes	130/164	122/157	0.59 (0.46–0.76)
No	68/89	72/92	0.83 (0.59–1.16)
Previous anti–PD-1 or anti–PD-L1 therapy administration			
Yes	53/71	50/67	0.66 (0.44–0.99)
No	145/182	144/182	0.67 (0.53–0.85)
Histologic features			
Squamous-cell carcinoma	124/160	122/157	0.71 (0.55–0.93)
Adenocarcinoma and adenosquamous carcinoma	74/93	72/92	0.63 (0.44–0.89)
No. of previous systemic regimens for recurrent or metastatic disease			
1	123/159	119/149	0.68 (0.52–0.88)
2	74/93	75/100	0.66 (0.47–0.92)



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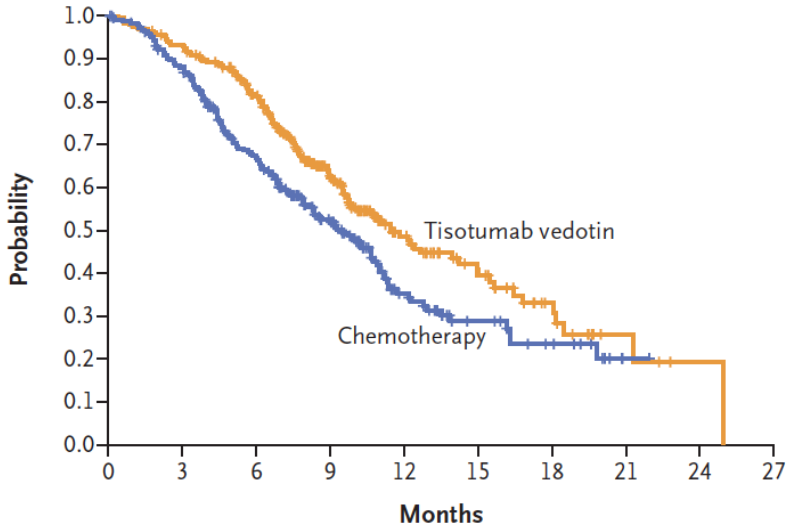
A Overall Survival



No. at Risk

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

	No. of Events/ Total No. of Patients	Median Overall Survival (95% CI)
		mo
Tisotumab Vedotin	123/253	11.5 (9.8–14.9)
Chemotherapy	140/249	9.5 (7.9–10.7)

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

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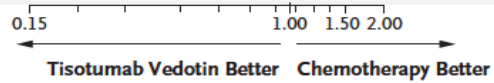
innovaTV 301/ENGOT-cx12/GOG-3057 – OS Subgroups

B Subgroup Analysis

Subgroup	Tisotumab Vedotin	Chemotherapy	Hazard Ratio for Death (95% CI)
	no. of events/total no. of patients		
Intention-to-treat population	123/253	140/249	0.70 (0.54–0.89)
Geographic region			
United States	13/16	13/14	0.47 (0.19–1.16)
Europe	52/106	51/104	0.76 (0.51–1.12)
Asia	37/85	52/88	0.63 (0.41–0.98)
Other	21/46	24/43	0.87 (0.46–1.66)
ECOG performance-status score at baseline			
0	57/137	65/136	0.74 (0.52–1.06)
1	66/116	75/113	0.67 (0.48–0.94)
Previous bevacizumab administration			
Yes	77/164	92/157	0.57 (0.42–0.78)
No	46/89	48/92	1.00 (0.66–1.50)
Previous anti–PD-1 or anti–PD-L1 therapy administration			
Yes	42/71	42/67	0.72 (0.46–1.14)
No	81/182	98/182	0.67 (0.50–0.90)
Histologic features			
Squamous-cell carcinoma	81/160	92/157	0.69 (0.50–0.94)
Adenocarcinoma and adenosquamous carcinoma	42/93	48/92	0.70 (0.45–1.10)
No. of previous systemic regimens for recurrent or metastatic disease			
1	74/159	73/149	0.83 (0.59–1.15)
2	48/93	67/100	0.56 (0.38–0.82)



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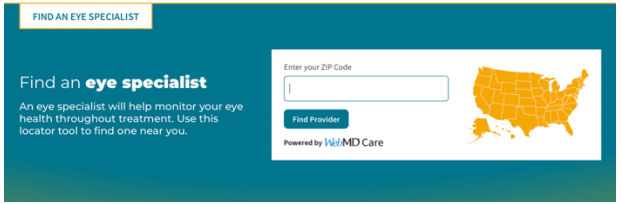
Vergote I, Gonzalez-Martin A, Fujiwara K, et al. *N Engl J Med* 2024

innovaTV 301/ENGOT-cx12/GOG-3057 Conclusions

- TV was superior to physician's choice chemotherapy in 2nd or 3rd line cervical cancer (median OS benefit of 2 months)
  - PFS HR 0.67 (95% CI, 0.54-0.82), p<0.001
  - OS: HR 0.70 (95% CI, 0.54-0.89), p=0.004
- Overall RR: 17.8 vs 5.2% (OR 4.0, 95% CI 2.1 – 7.6, p<0.001)
- Nausea (33.2%), conjunctivitis (31.2%), peripheral sensory neuropathy (28.4%) and epistaxis (26.0%) most common TV toxicities – no new safety concerns
- Support site: https://www.tivdak.com/resources-and-support/



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FDA approves tisotumab vedotin-tftv for recurrent or metastatic cervical cancer

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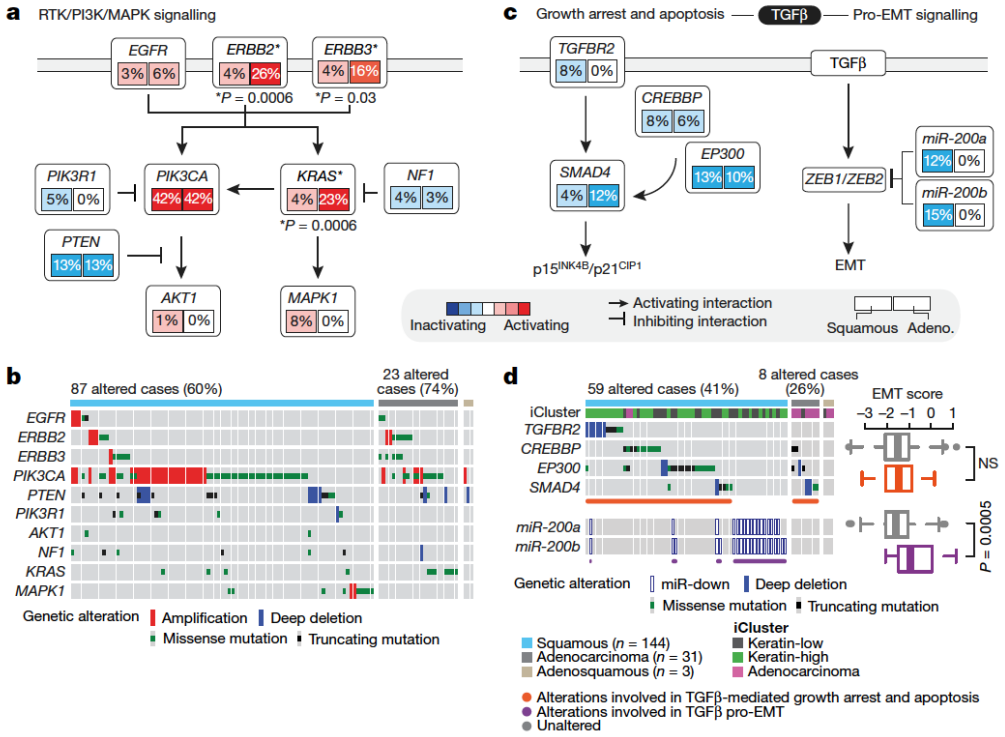
Future Directions in Cervical Cancer

Potential Cervical Cancer Targets



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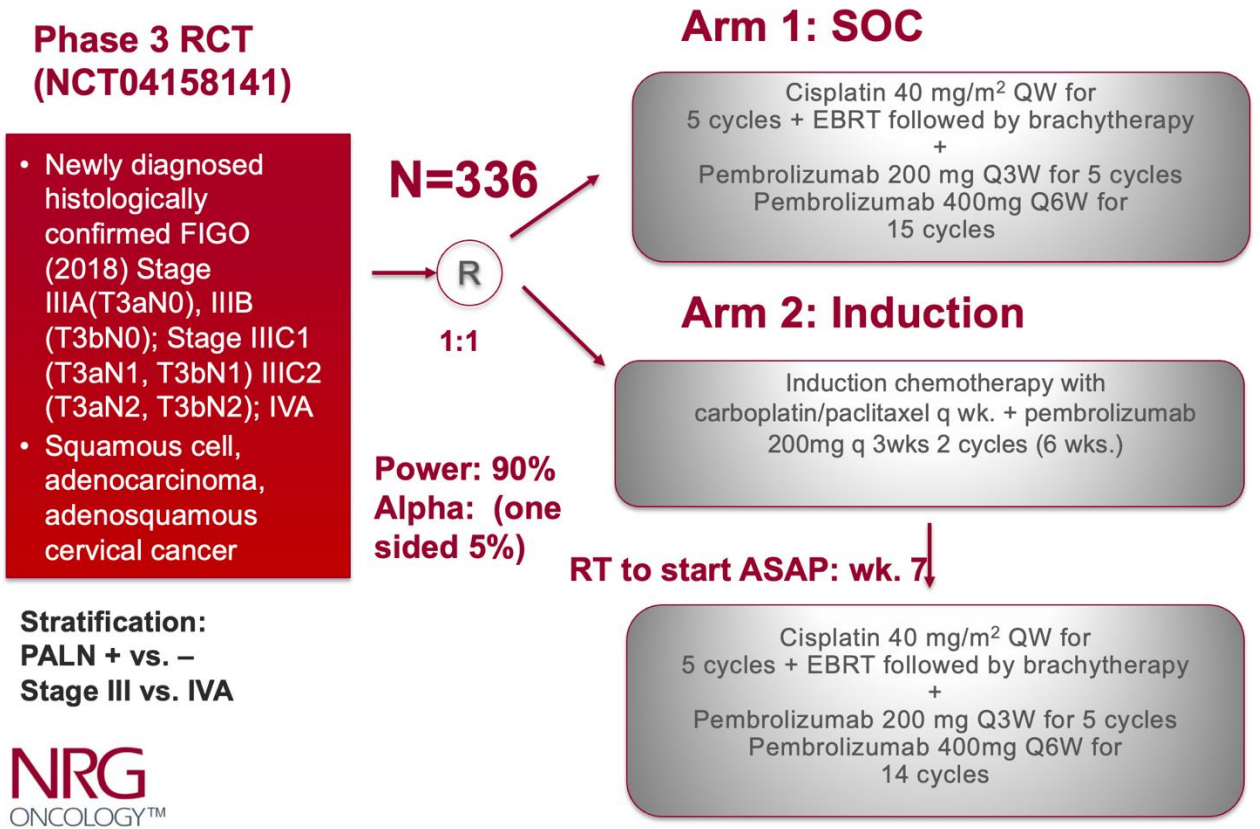
TCGA *Nature* 2017

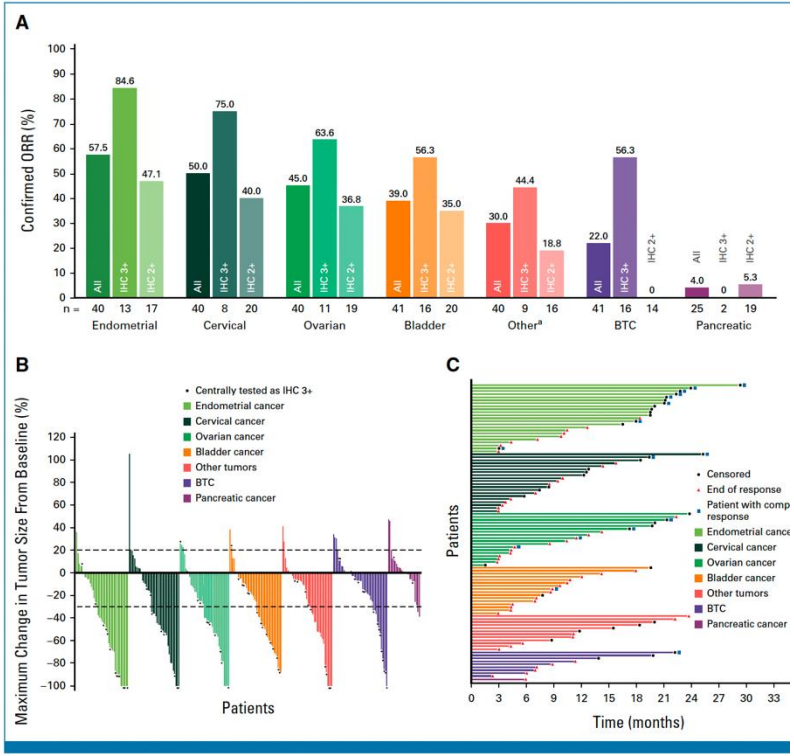
How can we Improve Outcomes?

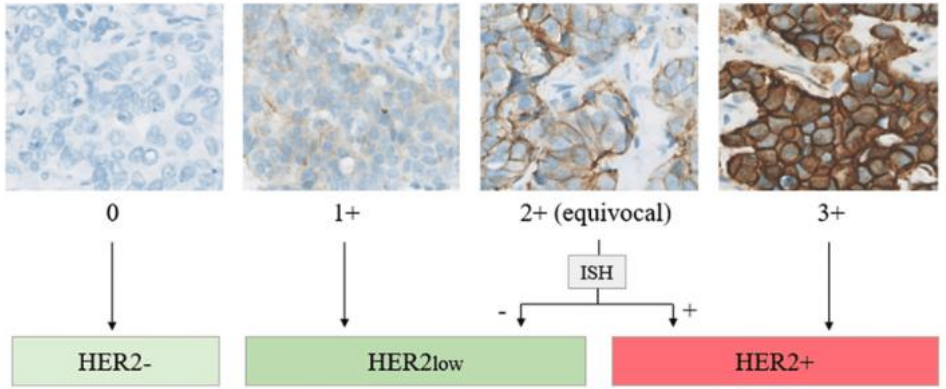
- Novel Combinations
  - NACT + CPI (CPI Naïve)
- Novel Agents / Approaches
  - CPI after CPI?
  - ADCs de jour
- Novel Targets
  - Her2
  - Trop2 (human trophoblastic cell-surface marker)
  - Various HPV related Antigens

NRG GY037 Schema



What about targeting HER2?





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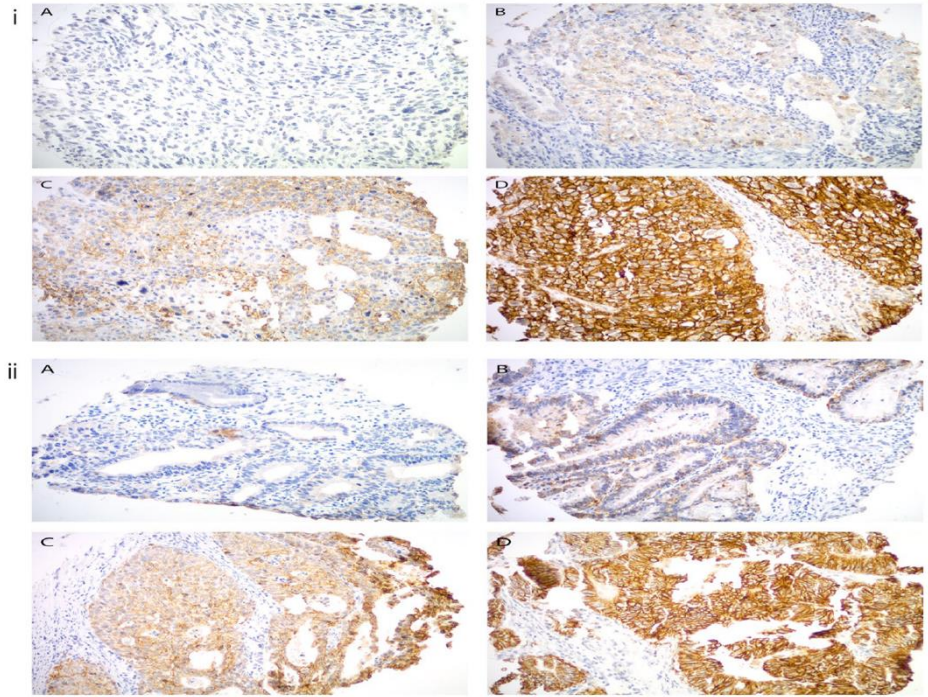
Meric-Bernstam F et al. *JCO* 2024

Trop2 as a Target



90%+ in SCC
80%+ in AC

Ongoing Ph2 trial w/
IMMU-132 at Yale
NCT05838421

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Zeybek et al. *Sci Rep* 2020

Management for CPI Naïve

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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Future Management for CPI Exposed

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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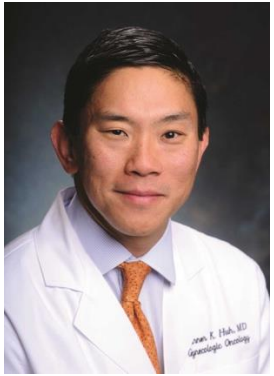
What have we learned?

- Immunotherapy is active when combined with chemotherapy in recurrent cervical cancer
- NACT as well as immunotherapy improves outcome in LACC
  - INTERLACE more applicable for T1/2 cancers?
  - A18 more applicable for T3/4 cancers?
- Novel therapies including ADCs have activity in recurrent cervical cancer
- Additional research is needed to identify novel targets and agents

UAB Gynecologic Oncology

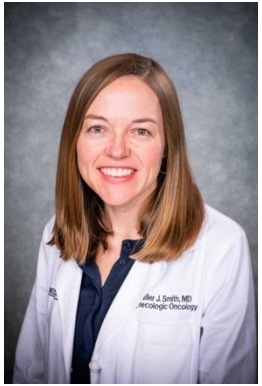
Rebecca Arend, MD, MSPH



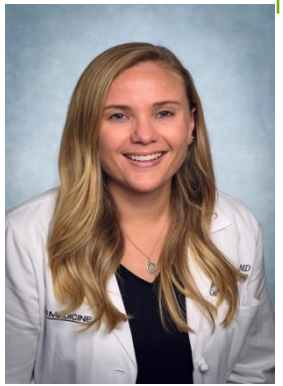
Warner Huh, MD

Trey Leath, MD, MSPH

J. Michael Straughn, MD



Haller Smith, MD



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Questions?

Thank you!