State of the Art in Treating Locally Advanced and Recurrent Cervical Cancer

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Faculty Disclosure

	No, nothing to disclose
x	Yes, please specify:

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Merck	x	x	x					
GSK	x	x	x					
AstraZeneca	x	x	x					
Regeneron		x	x					
GOG Foundation		x	x					
GNE/Roche	x	x	x					
EMD Serono		x						
Akeso Biopharma		x						

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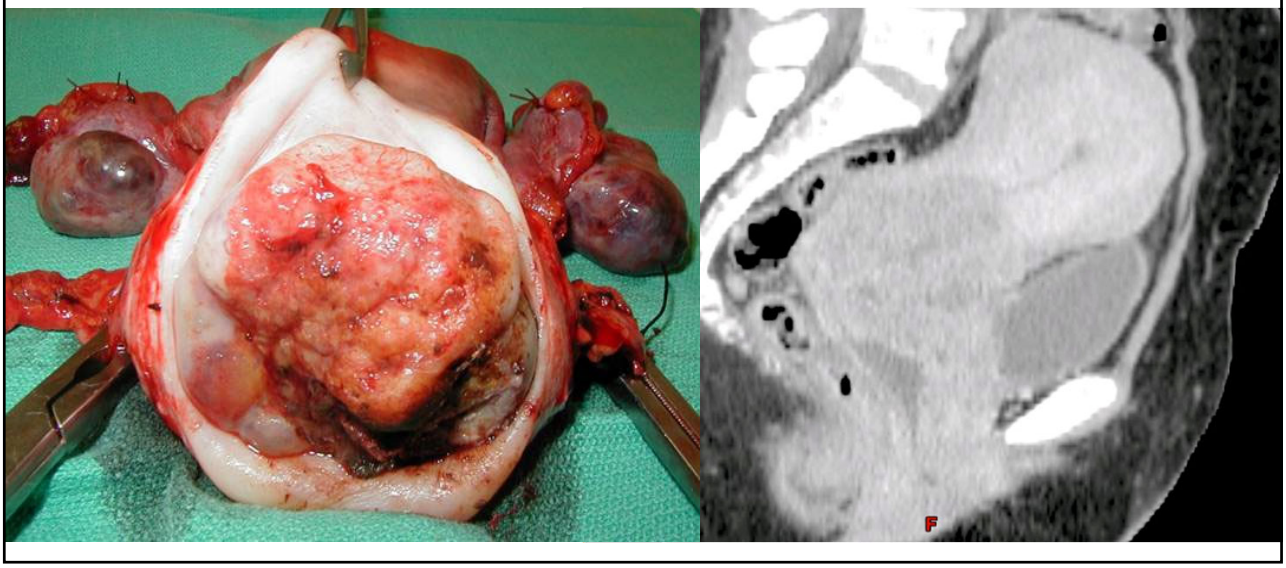
2

The Enemy



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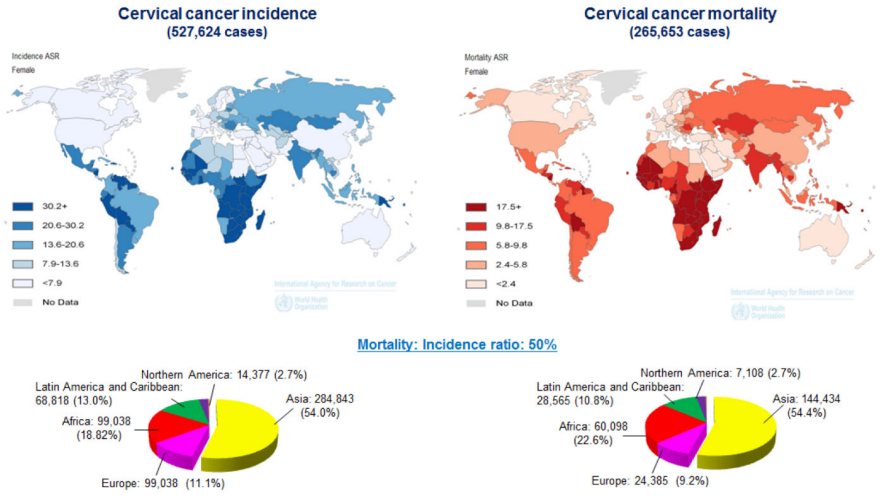
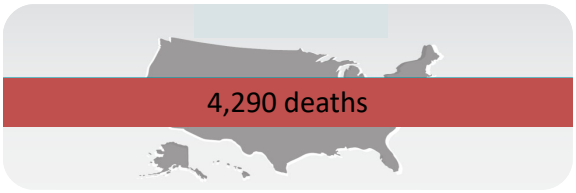
Cervical Cancer is an International Health Concern



Jung HS et al. J Clin Med. 2015. 4(5): 1126

4

An Estimated 14,480 Cases of Invasive Cervical Cancer in the US in 2020[2]



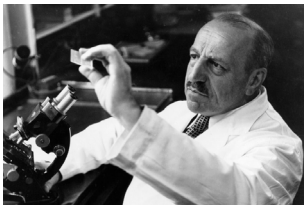
- ✓ **Death rate in 2016 (2.2 per 100,000) was less than half that in 1975 (5.6 per 100,000)**
- ✓ **From 2007 to 2016, the death rate decreased by about 1% per year in women >50 years of age and older, but was stable in <50**

1) SEER Stat Fact Sheets: Cervix Uteri Cancer. http://seer.cancer.gov/statfacts/html/cervix.html. 2) American Cancer Society. Cancer Facts & Figures 2021. Atlanta, GA: America

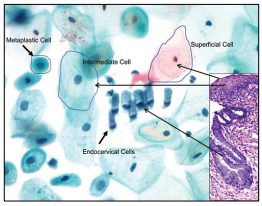
5

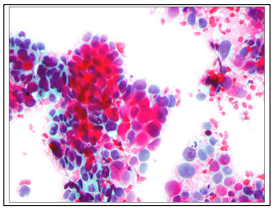
Screening for Cervical Cancer

USPSTF 2018: Cytology and/or High-Risk HPV DNA Testing

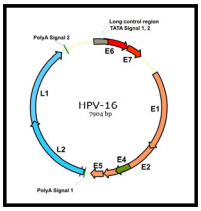


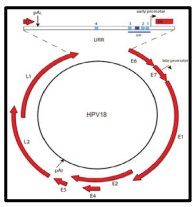
George Nicholas Papanicolaou (1883-1962)





Harald zur Hausen (b. 1936)
Nobel Prize in Medicine (2008)





Papanicolaou GN et al. *Sci USA*. 1983;80(12):3812-3815. Boshart M et al. *EMBO J*. 1984;3(5):1151-1157. Papanicolaou GN et al. *Am J Obstet Gynecol*. 1941;42(2):193-206. Dürst M et al. *Proc Natl Acad* 984;3(5):1151-1157. Wright TC et al. *Gynecol Oncol*. 2015;136(2):189-197.US Preventative Services Task Force. *JAMA*. 2018;320(7):674-686.

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Indications and Usage for HPV-9 Immunization

- Females 9 through 45 years of age for the prevention of cervical, vulvar, vaginal, anal, oropharyngeal and other head and neck cancers caused by human papillomavirus (HPV) Types 16, 18, 31, 33, 45, 52, and 58; cervical, vulvar, vaginal, and anal precancerous or dysplastic lesions caused by HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58; and genital warts caused by HPV Types 6 and 11.
- Males 9 through 45 years of age for the prevention of anal, oropharyngeal and other head and neck cancers caused by HPV Types 16, 18, 31, 33, 45, 52, and 58; anal precancerous or dysplastic lesions caused by HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58; and genital warts caused by HPV Types 6 and 11.
- Does not eliminate the necessity for vaccine recipients to undergo cancer screening

https://www.merckvaccines.com/gardasil9/

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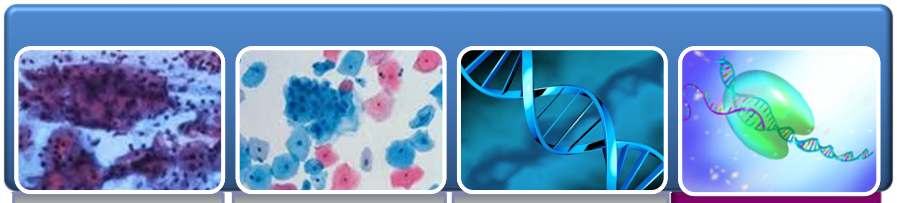
The Latest Advances in Pap and HPV:



1940s	1990s	2000s	Today
The Pap Smear:	***Liquid-Based Cytology and Cytobrush:***	***HPV DNA Testing:***	***HPV Molecular Testing:***
20-50% Sensitivity[1]	Improved sensitivity[2]	High sensitivity (Up to 100%)[4]	High sensitivity (Up to 100%)[5,6]
Frequent screening[1]	Screening every 1-3 years[3]	Screening at extended intervals[4]	Improved specificity[5,6]

1. Alliance for Cervical Cancer Prevention. Cervical Cancer Prevention Fact Sheet. http://screening.iarc.fr/doc/RH_pap_smears.pdf. Published October 2002. Accessed April 13, 2106.
2. Gibb RK, et al. The impact of liquid-based cytology in decreasing the incidence of cervical cancer. *Rev Obstet Gynecol.* 2011;4(suppl 1):S2-S11.
3. Saslow D, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *Am J Clin Pathol.* 2012;137(4):516-42. doi:10.3322/caac.21139.
4. HC2 High-Risk HPV DNA Test [package insert]. 5199-1220. Gaithersburg, MD: Digene Corporation; 2004.
5. Arbyn, et al. The APTIMA HPV assay versus the Hybrid Capture 2 test in triage of women with ASC-US or LSIL cervical cytology: a meta-analysis of the diagnostic accuracy. *Int J Cancer.* 2013;132(1):101-8. doi:10.1002/ijc.27636.
6. Aptima HPV Assay [package insert]. AW-12820. San Diego, CA: Hologic, Inc. 2015.

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The American Cancer Society (ACS) Guidelines for the Prevention and Early Detection of Cervical Cancer

- Cervical cancer testing (screening) should begin at age 25.
- Those aged 25 to 65 should have a primary HPV test* every 5 years. If primary HPV testing is not available, screening may be done with either a co-test that combines an HPV test with a Papanicolaou (Pap) test every 5 years or a Pap test alone every 3 years.

(*A primary HPV test is an HPV test that is done by itself for screening. The US Food and Drug Administration has approved certain tests to be primary HPV tests.)

https://www.cancer.org/cancer/cervical-cancer/detection-diagnosis-staging/cervical-cancer-screening-guidelines.html

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Comparison of Current and Previous ACS Guidelines for Cervical Cancer Screening

RECOMMENDATIONS FOR CERVICAL CANCER SCREENING

POPULATION	ACS 2020[a]	ACS 2012[b]
Aged <25 y	No screening	Cytology alone every 3 y starting at age 21 y
Aged 25-65 y	Starting at age 25 y, primary HPV test alone every 5 y (preferred)	Cytology alone every 3 y until age 29 y
	Use an FDA-approved HPV test for primary screening	Aged 30-65 y, switch to cotesting (preferred), cytology alone every 3 y (acceptable)[a]
	Cotesting every 5 y or cytology alone every 3 y are acceptable options[b]	*Screening by primary HPV testing alone not recommended for most clinical settings*
	Cotesting or cytology testing alone are acceptable where access to primary HPV testing is limited or not available; as the United States makes the transition to primary HPV testing, the use of cotesting or cytology alone for cervical cancer screening will not be included in future guidelines[b]	
	For management of positive results and subsequent surveillance, refer to ASCCP 2020 Risk-Based Management Consensus Guideline (Perkins, 2020[21])	
Aged >65 y	Discontinue screening if adequate negative prior screening	No screening after adequate negative prior screening
	Individuals aged >65 y without documentation of prior screening should continue screening until criteria for cessation are met	
	Adequate negative prior screening is currently defined as 2 consecutive, negative primary HPV tests, or 2 negative cotests, or 3 negative cytology tests within the past 10 y, with the most recent test occurring within the past 3-5 y, depending on the test used	
After hysterectomy	Individuals without a cervix and without a history of CIN2 or a more severe diagnosis in the past 25 y or cervical cancer ever should not be screened	No screening after hysterectomy (with removal of the cervix) for reasons not related to cervical cancer and no history of cervical cancer or serious precancer
HPV vaccinated	Follow age-specific screening recommendations (same as unvaccinated individuals)	Follow age-specific screening recommendations

Abbreviations: ASCCP, American Society of Colposcopy and Cervical Pathology; CIN2, cervical intraepithelial neoplasia grade 2; FDA, US Food and Drug Administration; HPV, human papillomavirus.
[a]Cotesting is HPV testing in combination with cytology.
[b]Individuals should not be screened more frequently than at the recommended interval for the test used and should not be screened annually at any age by any method. Annual testing may be recommended as surveillance after abnormal screening results.

https://acsjournals.onlinelibrary.wiley.com/doi/epdf/10.3322/caac.21628

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FIGO staging systems: click on the information icons to find out more about the differences between the 2009 and 2018 FIGO staging systems for cervical cancer

	FIGO 2009	FIGO 2018
I	Cervical carcinoma confined to the uterus (extension to the corpus should be disregarded)	Cervical carcinoma confined to the uterus (extension to the corpus should be disregarded)
IA	Invasive carcinoma diagnosed only by microscopy, with a maximum depth of invasion ≤5.0 mm and largest extension ≥7.0 mm	Invasive carcinoma diagnosed only by microscopy, with a maximum depth of invasion <5 mm
IA1	Measured stromal invasion with a depth of ≤3.0 mm and a horizontal spread of ≤7.0 mm	Measured stromal invasion with a depth of <3 mm
IA2	Measured stromal invasion >3.0 mm and <5.0 mm, with a horizontal spread of ≤7.0 mm	Measured stromal invasion ≥3 mm, and <5 mm in depth
IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than Stage IA	Invasive carcinoma with a maximum depth of invasion ≥5 mm (greater than Stage IA), lesion limited to the cervix uteri
IB1	Clinically visible lesion ≤4.0 cm in greatest dimension	Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension
IB2	Clinically visible lesion >4.0 cm in greatest dimension	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
IB3	N/A	Invasive carcinoma ≥4 cm in greatest dimension
II	Cervical carcinoma invading beyond the uterus but not to the pelvic wall or lower third of the vagina	Cervical carcinoma invading beyond the uterus but not to the pelvic wall or lower third of the vagina
IIA	Tumour without parametrial invasion	Tumour without parametrial invasion
IIA1	Clinically visible lesion ≤4.0 cm in greatest dimension	Invasive carcinoma <4 cm in greatest dimension
IIA2	Clinically visible lesion >4.0 cm in greatest dimension	Invasive carcinoma ≥4 cm in greatest dimension
IIB	Tumour with parametrial invasion	Tumour with parametrial invasion
III	Tumour extending to the pelvic sidewall and / or involving the lower third of the vagina and / or causing hydronephrosis or non-functioning kidney	Tumour extending to the pelvic sidewall and / or involving the lower third of the vagina and / or causing hydronephrosis or non-functioning kidney and / or involves PLN and / or PALNs
IIIA	Tumour involving the lower third of the vagina but not extending to the pelvic wall	Tumour involving the lower third of the vagina but not extending to the pelvic wall
IIIB	Tumour extending to the pelvic wall and / or causing hydronephrosis or non-functioning kidney	Tumour extending to the pelvic wall and / or causing hydronephrosis or non-functioning kidney
IIIC1/2	N/A	Involvement of the PLN and / or PALNs, irrespective of tumour size and extent (with r and p notations*)
IVA	Spread to adjacent pelvic organs	Spread to adjacent pelvic organs
IVB	Spread to distant organs	Spread to distant organs

*Notations of r (imaging) and p (pathology) indicate the findings that are used to allocate the case to Stage IIIC.

Pecorelli S. *Int J Gynaecol Obstet* 2009;105:103–104; Bhatla N, et al. *Int J Gynaecol Obstet* 2019;145:129–135.

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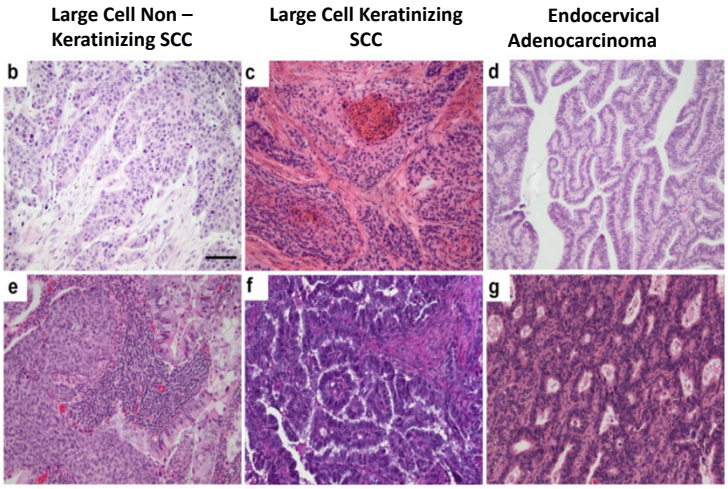
Cervical Cancer Pathology: Does Histologic Type Determine Therapy?



SCC, squamous cell carcinoma

Burk R et al. *Nature.* 2017;543:378-384.

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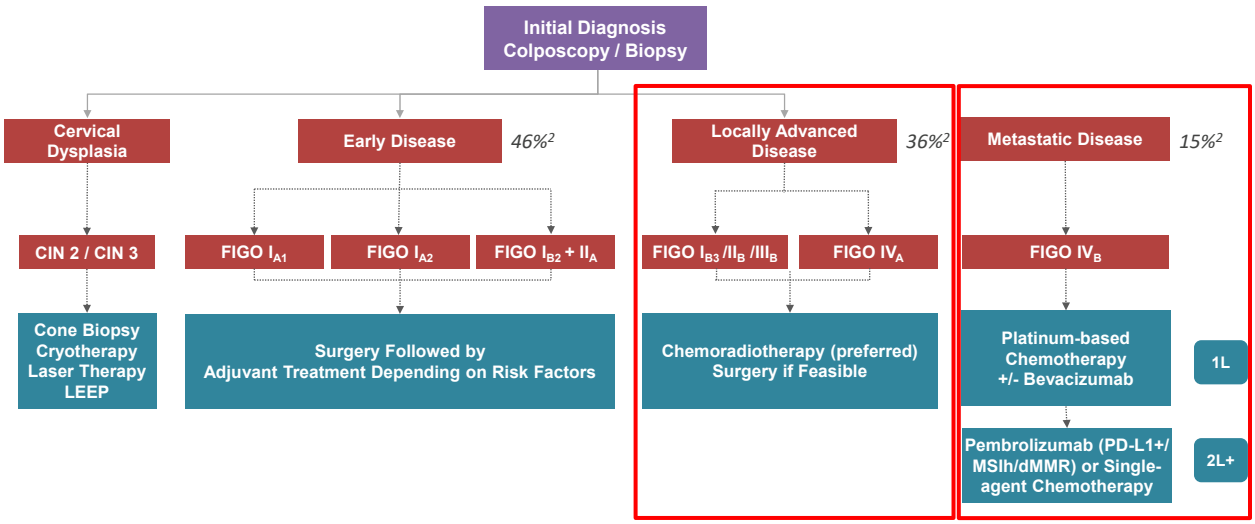
Cervical cancer: summary of treatment



LEEP: Loop Electrosurgical Excision Procedure; PD-L1: Programmed Cell Death Ligand-1; MSIh: Microsatellite Instability High; dMMR: deficient Mismatch Repair

1. National Comprehensive Cancer Network. NCCN Cervical Cancer Guidelines version 1.2021. https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf. Accessed 10 June 2021; 2. National Cancer Institute. SEER Cancer Stat Facts: Cervical Cancer. https://seer.cancer.gov/statfacts/html/cervix.html. Accessed 10 June 2021

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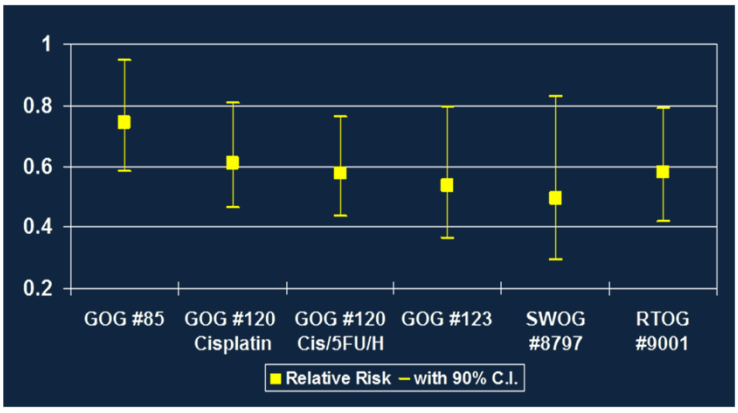
First Landmark Discovery in Cervical Cancer



- 30%-50% improvement in survival when compared with radiation alone
- Absolute benefit: Overall survival 6 %

5FU, 5-fluorouracil; CI, confidence interval; cis, cisplatin; H, hydroxyurea

Keys HM et al. *N Engl J Med.* 1999;340:1154-1161. Rose PG et al. *N Engl J Med.* 1999;340(15):1144-1153. Thomas GM. *Semin Radiat Oncol.* 2000;10(1):44-50. Peters III WA et al. *Gynecol Oncol.* 1999;72:443. Whitney CW et al. *J Clin Oncol.* 1999;17(5):1339-1348. Morris E et a. *N Engl J Med.* 1999;340(15):1137-1143.

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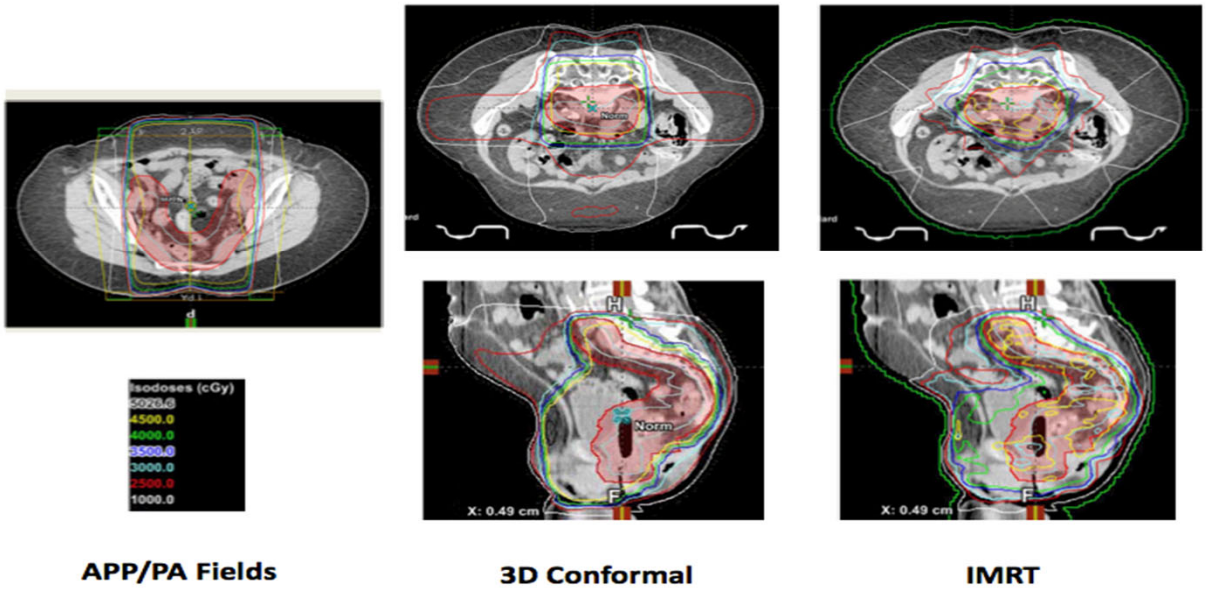
External Beam Radiation



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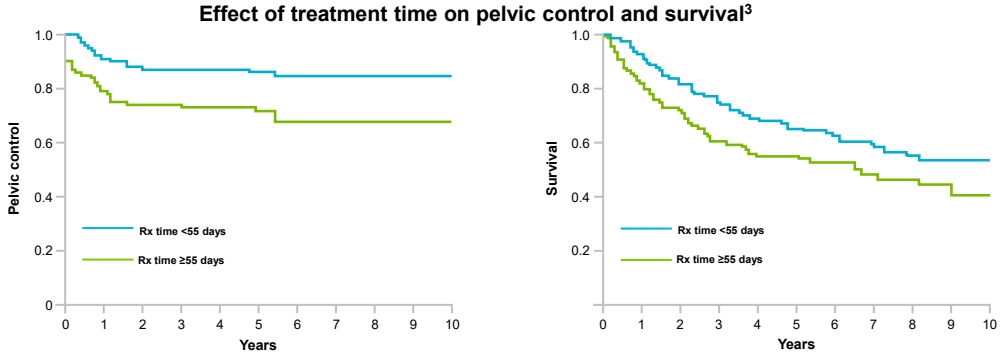
Treatment timing

- Treatment delay has been correlated with higher rates of pelvic failure, and current guidelines stipulate completion of EBRT plus brachytherapy within 8 weeks[1]
- Treatment extended beyond 8 weeks is associated with poorer outcomes[1]
  - It is possible that prolonging treatment beyond 8 weeks allows increased repopulation of cancer cells, resulting in reduced local control rates[2]

Effect of treatment time on pelvic control and survival[3]



1. Bhatla N, et al. *Int J Gynaecol Obstet* 2018;143:22–36; 2. Song S, et al. *Cancer* 2013;119:325–331; 3. Petereit DG, et al. *Int J Radiat Oncol Biol Phys* 1995;32:1301–1307.

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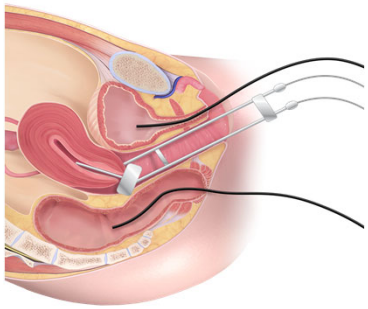
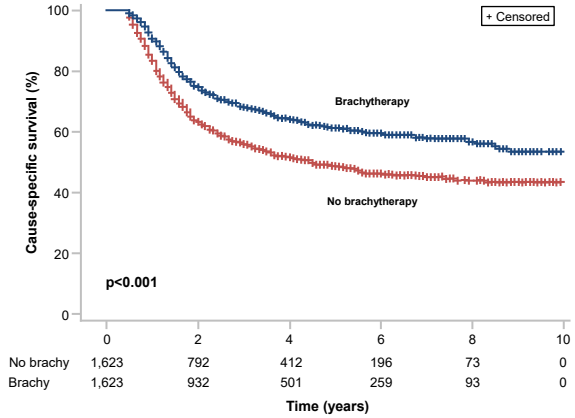
Brachytherapy

- Brachytherapy is the only method demonstrated to provide the high dose of radiation needed to control cervical cancer while minimizing adverse effects on normal tissue[1,2]
- Imaging can improve the efficacy of brachytherapy[3]



A radioactive source is placed in or near the tumor, which allows for the tumor to receive a concentrated dose while relatively sparing the surrounding normal tissue[1]



1. Banerjee R, Kamrava M. *Int J Womens Health* 2014;6:555–564; 2. Han K, et al. *Int J Radiat Oncol Biol Phys* 2013;87:111–119; 3. Holschneider CH, et al. *Gynecol Oncol* 2019;152:540–547.

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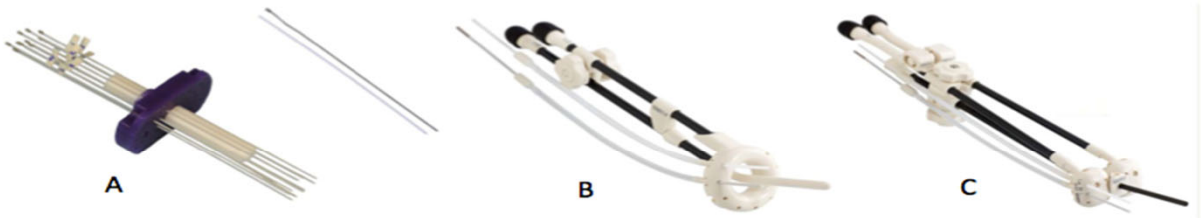
Applicators for Brachytherpay



INTERSTITIAL

Titanium needles
Non-deformable plastic catheters

Tandem and Ring

Tandem and Ovoids

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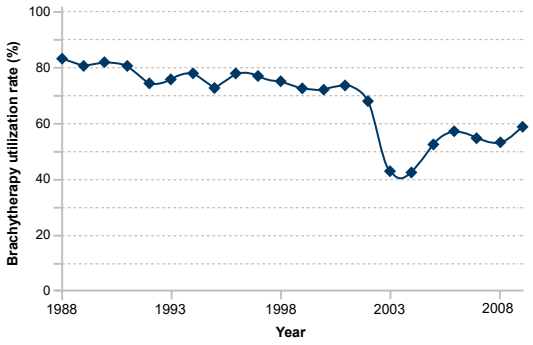
Underutilization of Brachytherapy

- SEER data shows brachytherapy **utilization decreased from 83% in 1988 to 58% in 2009** (p<0.001)[1]
- Brachytherapy treatment was associated with higher 4-year cause-specific survival (64.3% vs 51.5%, p<0.001) and overall survival (58.2% vs 46.2%, p<0.001)[1]



- A study of patients with cervical cancer in California showed **45% brachytherapy utilization during the study period (2004–2014)**, with a subsequent decrease in survival outcomes (HR, 1.16; 95% CI, 1.01–1.34; p=0.0330) in patients who did not receive brachytherapy[2]
- There was also a disparity in patients treated with brachytherapy:[2]
  - Brachytherapy utlization was lower in patients aged >80 years and in patients at Stage IVA
  - Black patients and those in low socioeconomic situations had worse survival

1. Han K, et al. *Int J Radiation Oncol Biol Phys* 2013;87:111–119; 2. Mayadev J, et al. *Gynecol Oncol* 2018;150:73–78.

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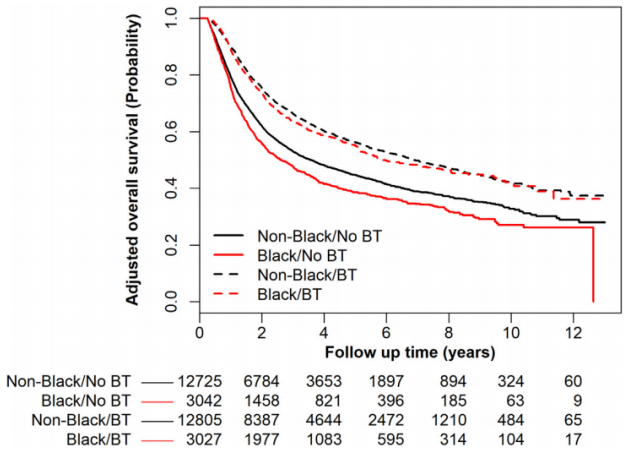
Racial Disparities in Brachytherapy Administration and Survival in Women with LACC



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

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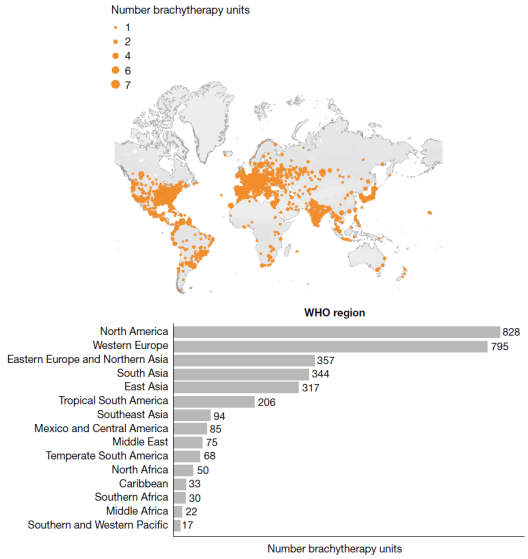
Underutilization of Brachytherapy[1]



- In **Japan**, about 50% of patients with LACC did not receive guideline-adherent treatment, with approximately 20–25% not given brachytherapy[2]
- Brachytherapy underutilization for LACC treatment has also been observed in **Korea**[3]
- In 2014, 55 of 139 low- and middle-income countries (LMICs) had no radiotherapy facilities[4]
  - Of these, 7 were in **Asia** and 6 were in **Latin America and the Caribbean**
- In **Latin America** and the **Caribbean**, there was only one brachytherapy machine per 2.4 million people for the entire region, with ~50% of machines in **Brazil** and **Mexico**[5]

1. Mayadev J, et al. *Manuscript in preparation*; 2. Watanabe T, et al. *J Gynecol Oncol* 2018;29:e83; 3. Kim H, et al. *J Gynecol Oncol* 2016;27:e33; 4. Datta NR, et al. *Int J Radiat Oncol Biol Phys* 2014;89:448–457; 5. Bishr MK, Zaghloul MS. *Int J Radiat Oncol Biol Phys* 2018;102:490–498.

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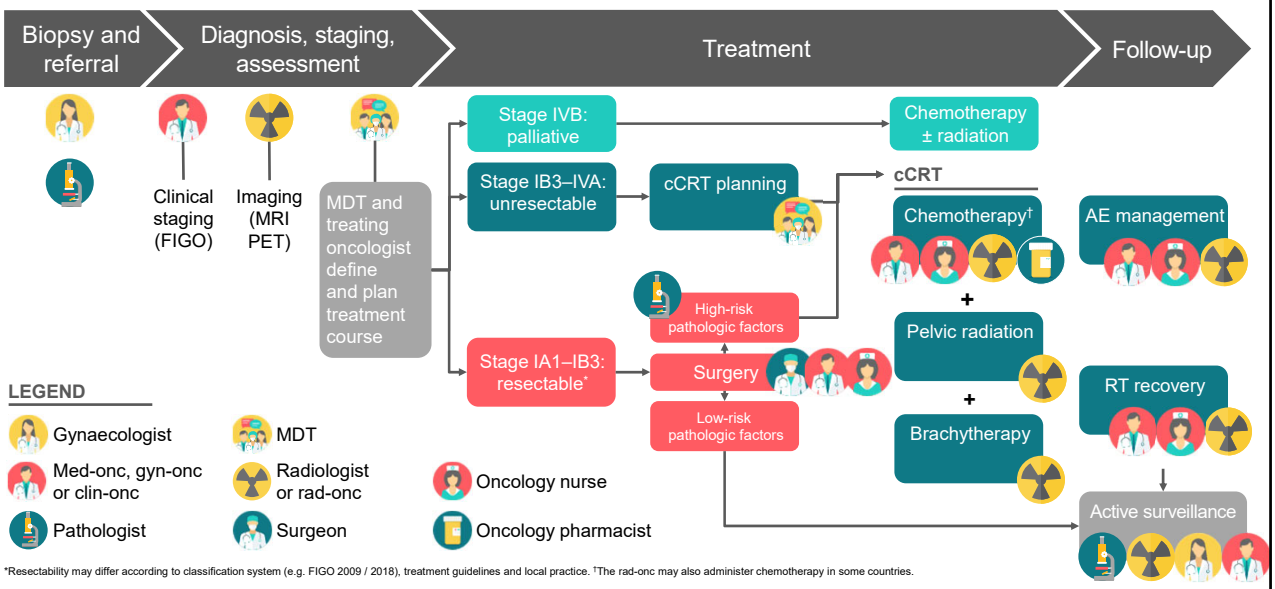
LACC Patient Journey: Current SoC



*Resectability may differ according to classification system (e.g. FIGO 2009 / 2018), treatment guidelines and local practice. †The rad-onc may also administer chemotherapy in some countries.

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US Treatment Guidelines

NCCN[1]

- Nodal disease, or with disease limited to the **pelvis only**, **pelvic EBRT with concurrent platinum-containing chemotherapy** and brachytherapy is **recommended**
- Positive **para-aortic** and pelvic lymph nodes, extended-field EBRT, concurrent platinum-containing chemotherapy and brachytherapy are r**ecommended**

ASCO[2]

- **Concurrent radiotherapy and chemotherapy** is standard in enhanced and maximal settings for women with **Stage IB–IVA**
- The addition of low-dose chemotherapy during radiotherapy, but not at the cost of delaying radiation therapy if chemotherapy is not available

ASTRO[3]

- **FIGO Stage IB3–IVA** squamous cell carcinoma or adenocarcinoma of the cervix**, radiotherapy with concurrent platinum-based chemotherapy is recommended** for definitive treatment
- For intact cervix, **brachytherapy** is recommended

1, NCCN. NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer. Version 2.2020. https://www.nccn.org/professionals/physician_gls/PDF/cervical.pdf. Accessed 19 Sept 2020.
2. Chuang LT, et al. *J Clin Oncol* 2016;34:3354–3355.
3. Chino J, et al. *Pract Radiat Oncol* 2020;10:220–234.

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EU treatment guidelines

ESMO[1]

- **Stages IB2, IIB and IIIB, cCRT** (with platinum or non-platinum-containing regimens) and tailoring of radiation according to surgical staging or imaging is **recommended**
  - **Neoadjuvant chemotherapy** followed by surgery or radiotherapy is a **lower-level recommendation**
- Adjuvant CRT is recommended in high-risk patients
- For Stage IVA, chemotherapy (with or without radiotherapy) and pelvic exenteration are recommended

ESGO / ESTRO / EGP[2]

Stage T1B2 / T2A2 and negative lymph nodes:

- **Definitive platinum-based chemoradiotherapy and brachytherapy is the preferred** treatment
- **Neoadjuvant** chemotherapy followed by radical surgery is a **controversial** alternative

Stages T1B2 / T2A2 + involved lymph nodes, and Stages T2B, T3A / T3B and T4A:

- Definitive **chemoradiotherapy and brachytherapy** is **recommended**
- An **additional radiation boost to the involved lymph nodes** should be applied

1. Marth C, et al. *Ann Oncol* 2017:28(suppl 4):iv72–iv83. 2. ESGO-ESTRO-ESP. Cervical Cancer Pocket Guidelines. https://guidelines.esgo.org/cervical-cancer/guidelines/recommendations/. Accessed 17 June 2020.

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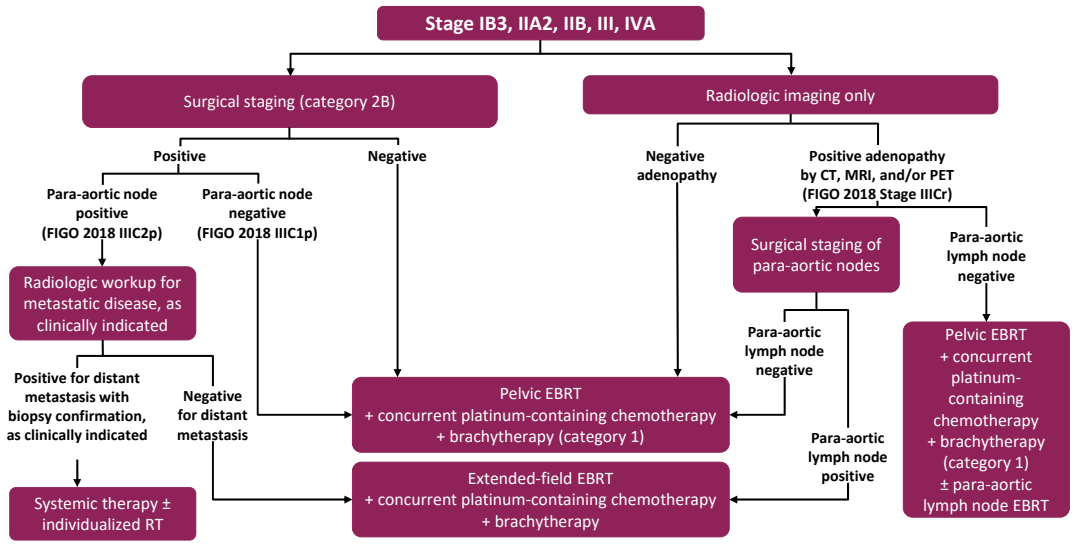
NCCN guidelines[1]



1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer. Version 2.2020. https://www.nccn.org/professionals/physician_gls/PDF/cervical.pdf. Accessed 19 September 2020.

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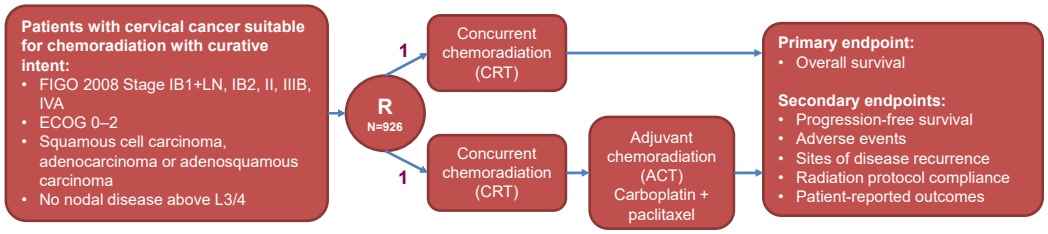
OUTBACK: randomized Phase 3 trial of adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared with chemoradiation alone

Study schema



Stratification factors:
- Pelvic or common iliac nodal involvement
- Requirement for extended-field radiotherapy
- FIGO 2008 stage: IB / IIA or IIB or IIIB / IVA
- Age <60 or ≥60 years
- Hospital / site

Mileshkin LR, et al. Presented at ASCO Annual Meeting. 4–8 June 2021. LBA3.

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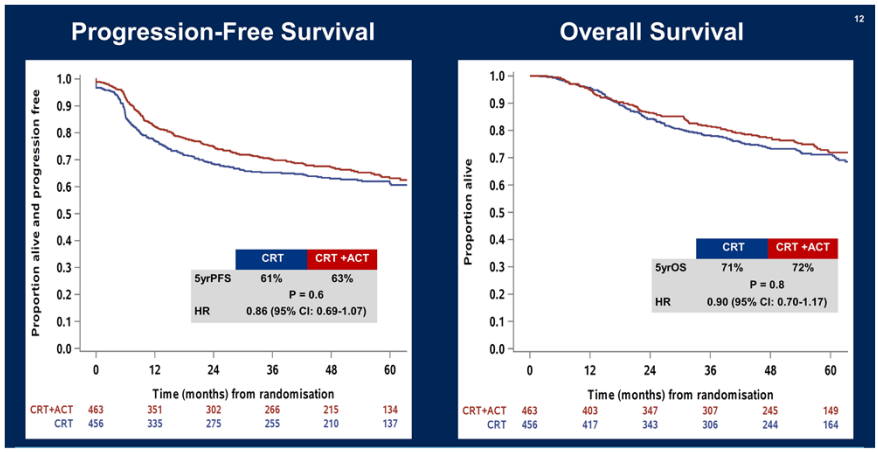
OUTBACK: Key Efficacy Outcomes



ACT **did not significantly improve** PFS or OS

Mileshkin LR, et al. Presented at ASCO Annual Meeting. 4–8 June 2021. LBA3.

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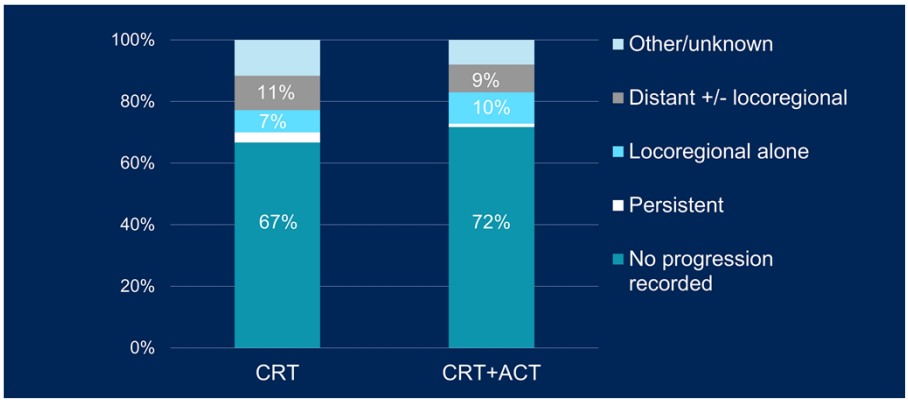
OUTBACK: Patterns of Disease Recurrence



Sites of disease progression were **not significantly different** between the treatment arms and about **two-thirds of women** did not experience recurrence

Mileshkin LR, et al. Presented at ASCO Annual Meeting. 4–8 June 2021. LBA3.

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OUTBACK: Sensitivity Analysis

	Survival Rates at 5 years (%) CRT	CRT +ACT	Difference (95% CI)	P	Hazard ratios from Cox regressions (95% CI)	P	Interaction P
Overall survival							
Completed CRT	**71%**	**74%**	**+3.3 (-4 to 11)**	**0.37**	**0.81 (0.60-1.08)**	**0.15**	0.11
Did not complete CRT	73%	64%	-9.2 (-24 to 5)	0.21	1.32 (0.77-2.25)	0.32	
Progression-Free Survival							
Completed CRT	**62%**	**66%**	**+4.8 (-3 to 12)**	**0.22**	**0.78 (0.60-1.00)**	**0.05**	0.12
Did not complete CRT	60%	51%	-8.6 (-23 to 6)	0.26	1.16 (0.75-1.80)	0.49	

There was an **absolute difference of 3% for OS**, which was not greater than expected by chance alone

Mileshkin LR, et al. Presented at ASCO Annual Meeting. 4–8 June 2021. LBA3.

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Lessons Learned from OUTBACK Trial

1. High drop out rate with switch maintenance strategy
2. With long post-progression survival, preferred endpoint is PFS
3. With almost 100% crossover, OS is not the preferred endpoint
4. Newer agents such as antiangiogenics and immunotherapy not studied

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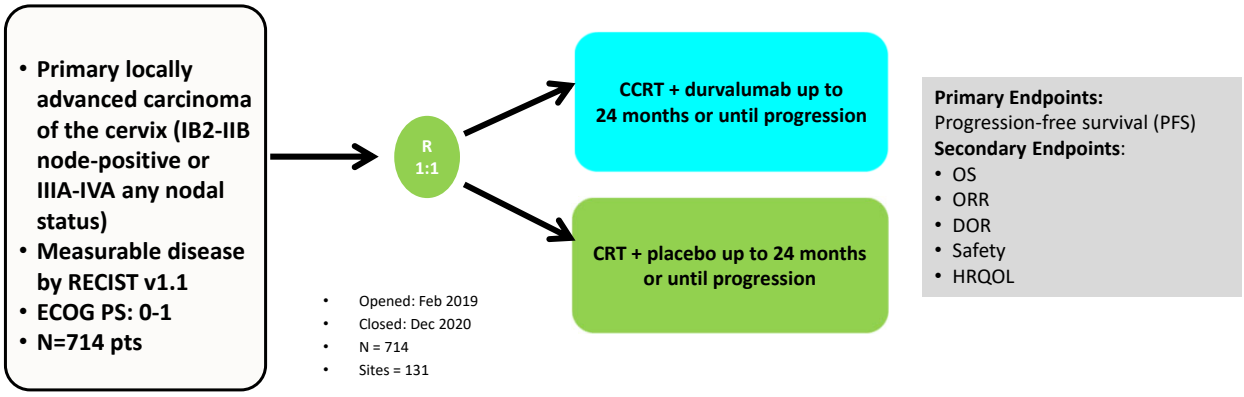
CALLA:
Durvalumab Added to Standard-of-Care CCRT



NCT03830866
CCRT = concurrent chemotherapy and radiotherapy.

DOI: 10.1200/JCO.2019.37.15_suppl.TPS5597 Journal of Clinical Oncology 37, no. 15_suppl. Published online May 26, 2019.

31

Randomized phase III ICI trials in locally-advanced setting

Frontline ICI trial	Population	Agent (n)	Design	Primary endpoint(s)
CALLA (NCT03830866)	• FIGO 2009 IB2-IIB node+ • IIIA-IVA any nodal status • Measurable RECIST v1.1 • ECOG PS: 0-1	Durva (714)	2 arm 1:1 CRT control 24 months	• PFS
KEYNOTE-A18 (NCT04221945)	• FIGO 2009 IB2-IIB node+ • IIIA-IVA any nodal status • Measurable RECIST v1.1 • ECOG PS: 0-1	Pembro (980)	2 arm 1:1 CRT control 24 months	• PFS • OS

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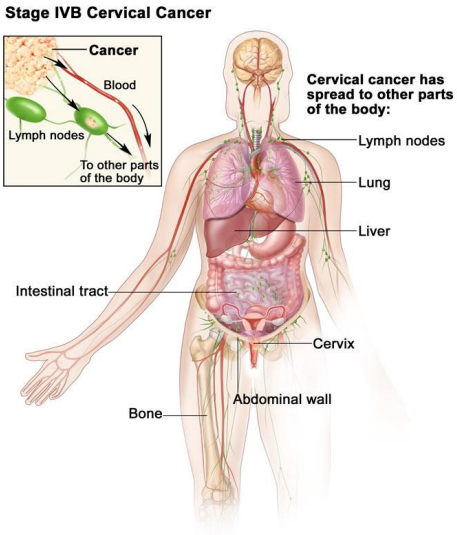
Advanced/Recurrent Cervical Cancer:
A HIGH UNMET CLINICAL NEED!



Winslow T. www.aacrfoundation.org/CancerTypes/Pages/PDQs/Cervical-Cancer-Treatment-PDQ.aspx. Accessed 15 January 2018.

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GOG-204: Study Design

A Phase III trial to assess the toxicity and efficacy of cisplatin doublet combinations in advanced and recurrent cervical cancer

GOG Gynecologic Oncology Group

Patients (N=434)

- Primary stage 4b or recurrent/persistent CC
- Measurable disease
- GOG PS 0-1
- No CNS disease
- No prior chemotherapy (unless CRT)

Randomize

Regimen 1
Paclitaxel 135 mg/m2 over 24 hours and CDDP 50 mg/m^2 q3w, 6 cycles

Regimen 2
Vinorelbine 30 mg/m2 IV bolus day1 and 8 and CDDP 50 mg/m^2 q3w, 6 cycles

Regimen 3
Gemcitabine 1000mg/m^2 IV day 1 and 8 and CDDP 50 mg/m^2 IV day q3w, 6 cycles

Regimen 4
Topotecan 0.75 mg/m^2 over 30 min days 1, 2, 3 CDDP 50 mg/m^2 IV day 1, q3w, 6 cycles

Quality of life was assessed for all regimens

Monk BJ, et al. *J Clin Oncol* 2009; 27(28):4649-4655.

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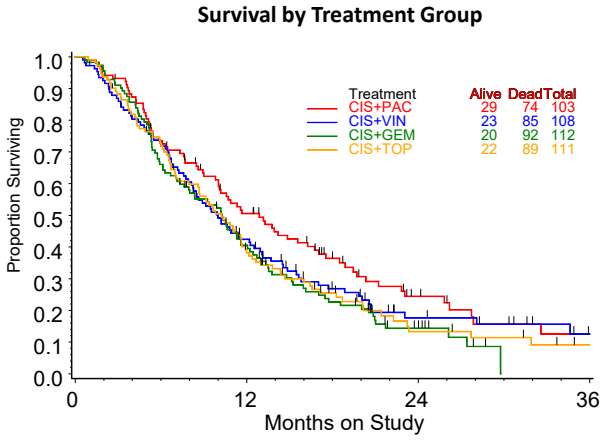
GOG-204: Results

- Response rates for PC, VC, GC and TC were 29.1%, 25.9%, 22.3%, and 23.4%.
- Comparable toxicity except for leukopenia, neutropenia, infection and alopecia



Monk BJ, et al. *J Clin Oncol* 2009; 27(28):4649-4655.

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JCOG 0505

JCOG Japan Clinical Oncology Group

Stage IVB, persistent or recurrent cervical cancer; not amenable to curative surgery / radiotherapy

*** Balancing factors:**
- Tumors outside of the prior irradiation field (yes or no)
- PS 0-1 or 2
- SCC or non-SCC
- Institution

R A N D O M I Z E*

Standard arm: TP
Paclitaxel 135 mg/m^2 24h d1
Cisplatin 50 mg/m^2 2h d2

Experimental arm: TC
Paclitaxel 175 mg/m^2 3h d1
Carboplatin AUC 5 1h d1

ClinicalTrials.gov Identifier:NCT00295789

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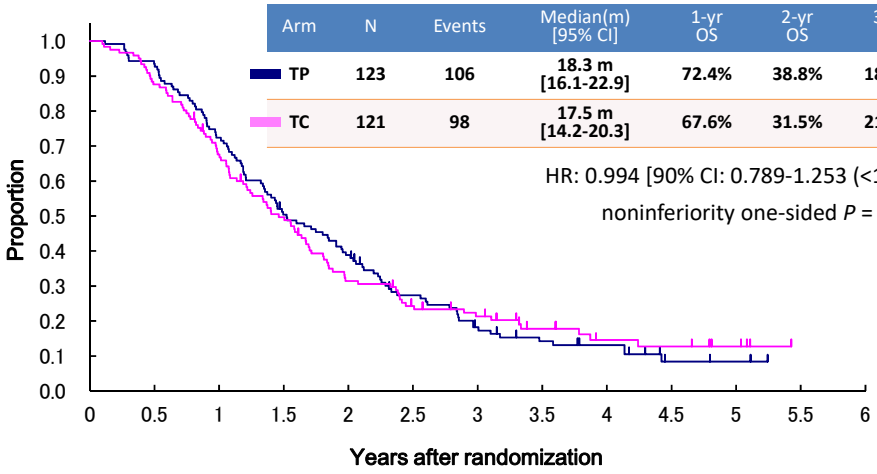
Overall Survival

JCOG Japan Clinical Oncology Group

Arm	N	Events	Median(m) [95% CI]	1-yr OS	2-yr OS	3-yr OS
TP	123	106	18.3 m [16.1-22.9]	72.4%	38.8%	18.3%
TC	121	98	17.5 m [14.2-20.3]	67.6%	31.5%	21.3%

HR: 0.994 [90% CI: 0.789-1.253 (<1.29)]

noninferiority one-sided *P* = .032#



Kitagawa R, et al. *J Clin Oncol.* 2012;30(Suppl): Abstract 5006.
J Clin Oncol. 2015 Jul 1;33(19):2129-35.

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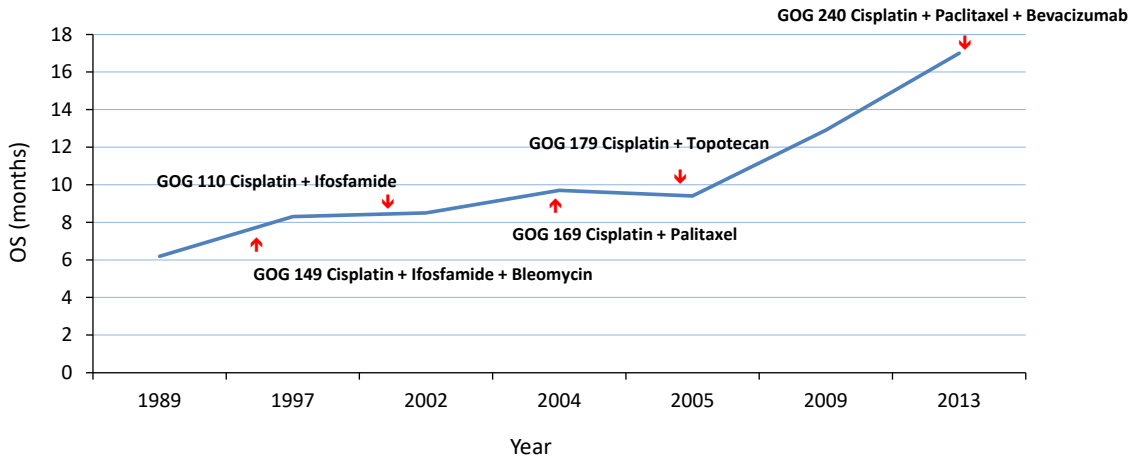
Improving OS in Recurrent or Metastatic Cervical Cancer



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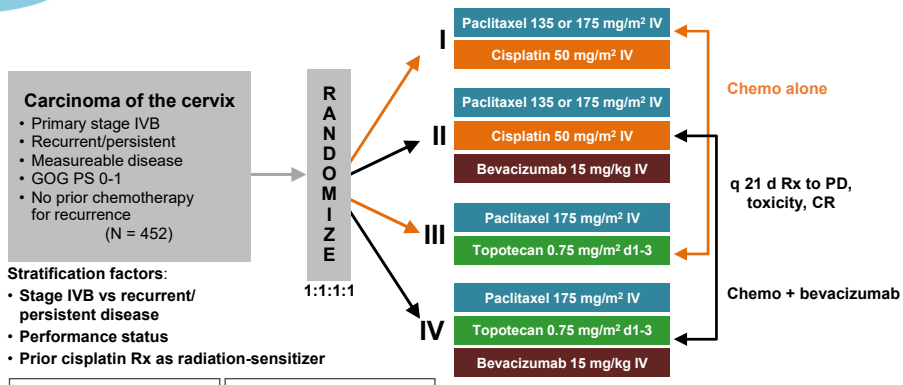
GOG 240 Schema



National Institutes of Health. http://clinicaltrials.gov/ct2/show/NCT00803062. Accessed 15 January 2018.

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New England Journal of Medicine and *THE LANCET*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Bevacizumab in Advanced Cervical Cancer

Krishnansu S. Tewari, M.D., Michael W. Sill, Ph.D., Harry J. Long III, M.D., Richard T. Penson, M.D., Helen Huang, M.S., Lois M. Ramondetta, M.D., Lisa M. Landrum, M.D., Ana Oaknin, M.D., Thomas J. Reid, M.D., Mario M. Leitao, M.D., Helen E. Michael, M.D., and Bradley J. Monk, M.D.

ABSTRACT

Tewari KS, et al. *N Engl J Med*. 2014;370(8):734-743.

THE LANCET

Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240)

Krishnansu S Tewari, Michael W Sill, Richard T Penson, Helen Huang, Lois M Ramondetta, Lisa M Landrum, Ana Oaknin, Thomas J Reid, Mario M Leitao, Helen E Michael, Philip J DiSaia, Larry J Copeland, William T Creasman, Frederick B Stehman, Mark F Brady, Robert A Burger, J Tate Thigpen, Michael J Birrer, Steven E Waggoner, David H Moore, Katherine Y Look, Wui-Jin Koh, Bradley J Monk

Tewari KS, et al. *Lancet*. 2017;390(10103):1654-1663.

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GOG 240 – Demographics & Baseline Characteristics

Characteristic		Chemotherapy (n=225)	Chemotherapy + Bevacizumab (n=227)
Median age, years (range)		46 (20-83)	48 (22-85)
Histology	Squamous	68	70
	Adenocarcinoma, unspecified	20	19
Race	White	80	75
	African American	11	16
	Asian	3	5
	Pacific Islander	0	0
Disease Stage	Recurrent	73	70
	Persistent	10	12
	Advanced	16	17
Performance status	0	58	58
	1	42	42
Prior platinum, %		74	75
Pelvic disease, %		53	54

Bev, bevacizumab; chemo, chemotherapy; GOG, Gynecologic Oncology Group; unspec., unspecified.
Tewari KS, et al. *N. Engl J Med* 2014;370:734-43.

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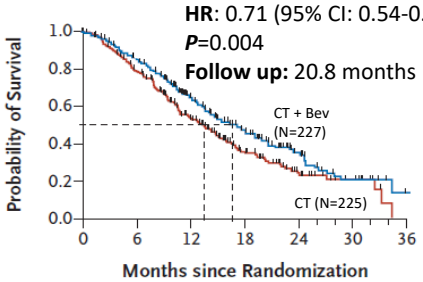
GOG-0240: Final OS/PFS

A

	Events no. (%)	Median Overall Survival mo
Chemotherapy (N=225)	140 (62)	13.3
Chemotherapy+Bev (N=227)	131 (58)	17.0

HR: 0.71 (95% CI: 0.54-0.95)
P=0.004
Follow up: 20.8 months



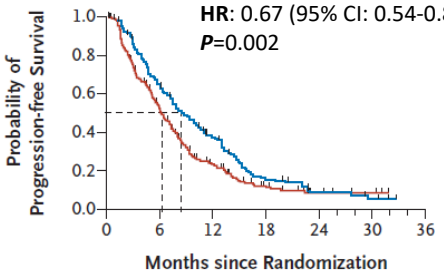
No. at Risk

Chemotherapy	225	167	94	45	17	8
Chemotherapy +bev	227	184	121	69	30	10

B

	Events no. (%)	Median Progression-free Survival mo
Chemotherapy (N=225)	184 (82)	5.9
Chemotherapy+Bev (N=227)	183 (81)	8.2

HR: 0.67 (95% CI: 0.54-0.82)
P=0.002



No. at Risk

Chemotherapy	225	103	40	14	6	3
Chemotherapy +bev	227	132	70	22	6	3

Tewari KS, et al. *N. Engl J Med* 2014;370:734-43.

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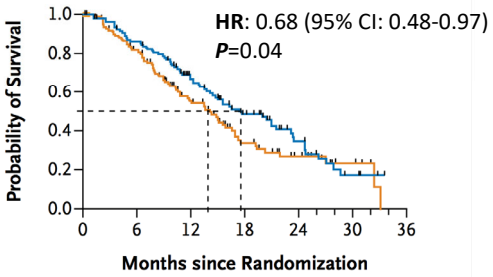
GOG-0240: Individual Arms ± Bev

C

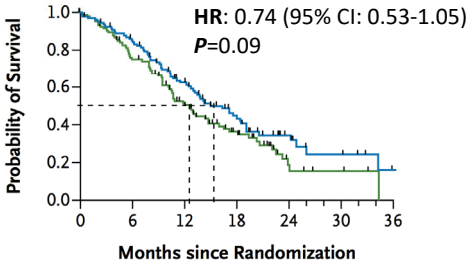
	Events no. (%)	Median Overall Survival mo
CP (N=114)	69 (61)	14.3
CP+Bev (N=115)	66 (58)	17.5



No. at Risk						
CP	114	89	50	22	12	5
CP+bev	115	94	63	37	17	5

D

	Events no. (%)	Median Overall Survival mo
TP (N=111)	71 (64)	12.7
TP+Bev (N=112)	65 (58)	16.2



No. at Risk						
TP	111	78	44	23	5	3
TP+bev	115	90	58	32	13	5

Tewari KS, et al. *N. Engl J Med* 2014;370:734-43.

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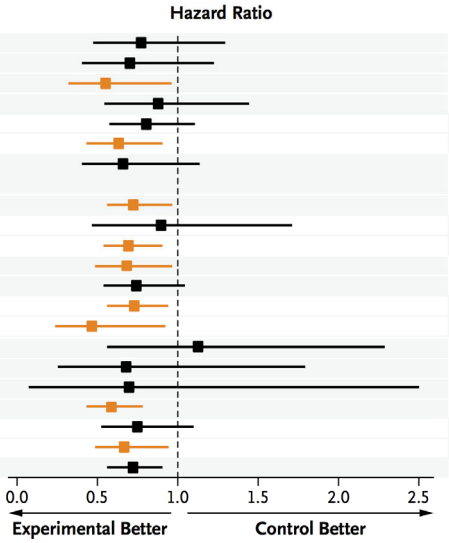
GOG-0240: Subgroup Analysis

Subgroup		No. of Patients
Age	≤40 yr	112
	40 to ≤48 yr	111
	48 to ≤56 yr	108
	>56 yr	121
Performance status	0	263
	1	189
Previous platinum radiation therapy	No	115
	Yes	337
Disease status	Advanced	76
	Recurrent or persistent	376
Topotecan treatment	No	229
	Yes	223
Race	Not black	392
	Black	60
Histologic type	Adenocarcinoma	86
	Adenosquamous	44
	Other	12
	Squamous	310
Pelvic disease	No	210
	Yes	242
Overall		452



Tewari KS, et al. *N. Engl J Med* 2014;370:734-43.

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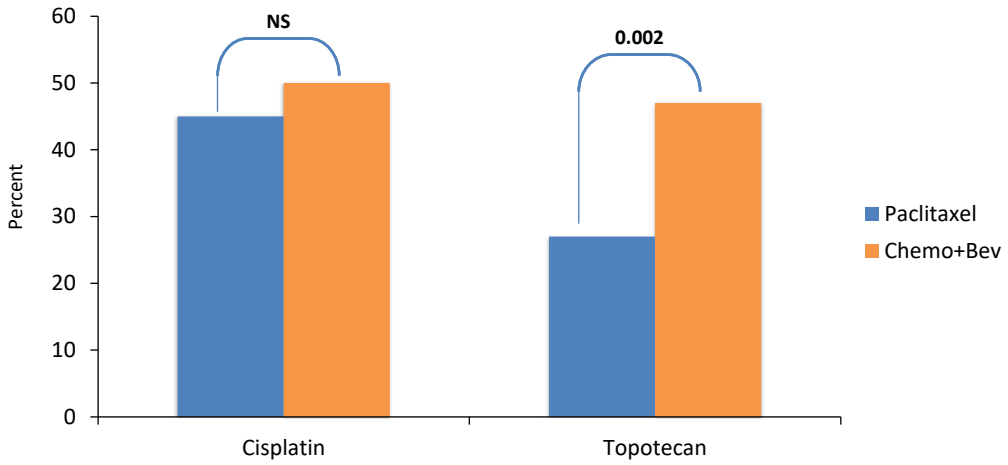
GOG 240 Objective Response



Tewari KS, et al. *N. Engl J Med* 2014;370:734-43.

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GOG 240: Toxicity

Event, n (%)		Chemotherapy (n=219)	Chemotherapy + Bevacizumab (n=220)
GI events (grade ≥2)[a]		96 (44)	114 (52)
Fistula	GI	0	7 (3)
	GU	1 (<1)	6 (3)
	Total[b]	1 (<1)	13 (6)
Hypertension (grade ≥2)[c]		4 (2)	54 (25)
Proteinuria (grade ≥3)		62 (28)	71 (32)
Neutropenia (grade ≥4)		57 (26)	78 (35)
Febrile neutropenia (grade ≥3)		12 (5)	12 (5)
Thromboembolism (grade ≥3)		3 (1)	18 (8)
CNS bleeding (grade ≥3)		0	0
GI bleeding (grade ≥3)		1 (<1)	4 (2)
GU bleeding (grade ≥3)		1 (<1)	6 (3)

[a]Excluding fistulas. [b]Fistulas were mainly managed supportively; one patient underwent colostomy, and another received nephrostomy tubes. [c]Hypertension of grade 2 or higher was defined as recurrent or continuous hypertension for a period of more than 254 hours or a symptomatic increase in blood pressure by more than 20 mm Hg diastolic or to <150/100 mm HG if the blood pressure was previously normal. [d]Bleeding was primarily managed with supportive therapy and transfusions of packed RBCs, most commonly in the outpatient setting.
CNS, central nervous system; GI, gastrointestinal; GU, genitourinary; RBC, red blood cells.
Tewari KS, et al. *N. Engl J Med* 2014;370:734-43.

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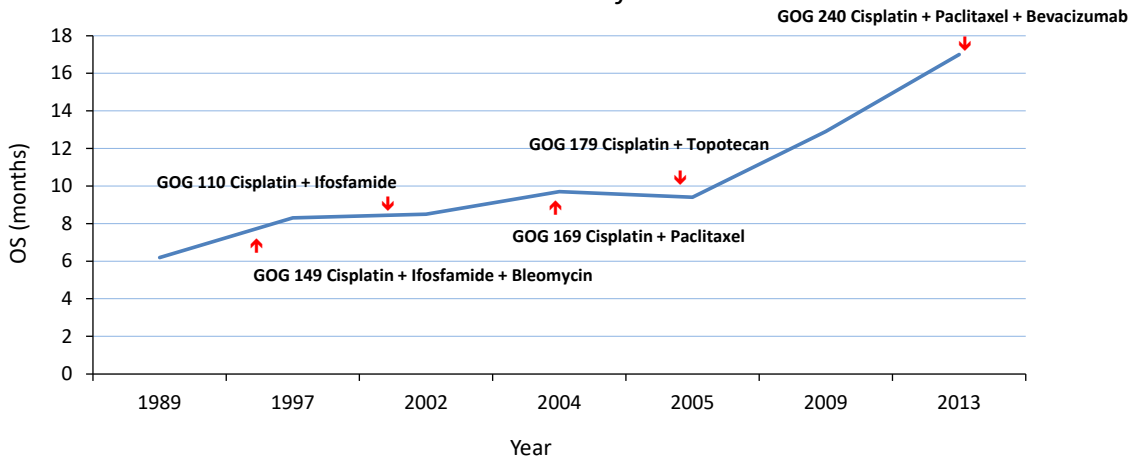
Improving OS in Recurrent or Metastatic Cervical Cancer

How do we move forward?



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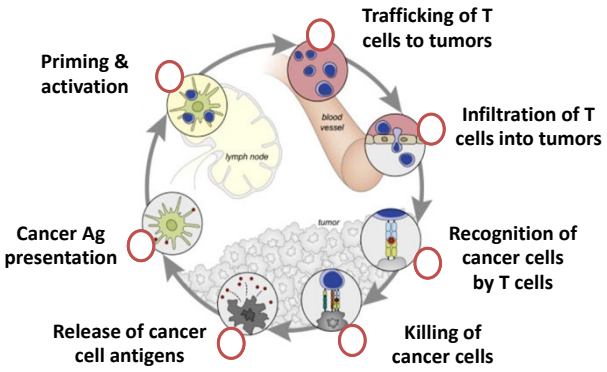
Rationale for Immunotherapy

- TCGA data
  - Amplifications in PD-L1/L2
    - Correlates with key immune cytolytic effectors
    - Can limit protective immunity
- Immunotherapy
  - PD-1/L1 inhibition
    - Promote T-cell activation against tumors
  - CTLA-4 inhibition
    - Enhances tumor-specific CD8+ T-cell responses



TCGA, Nature 2017. Chen DS, Immunity 2013.

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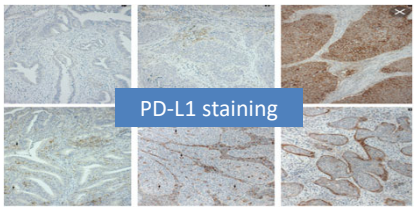
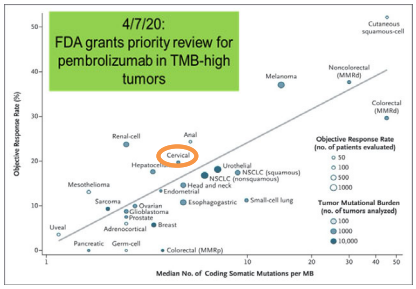
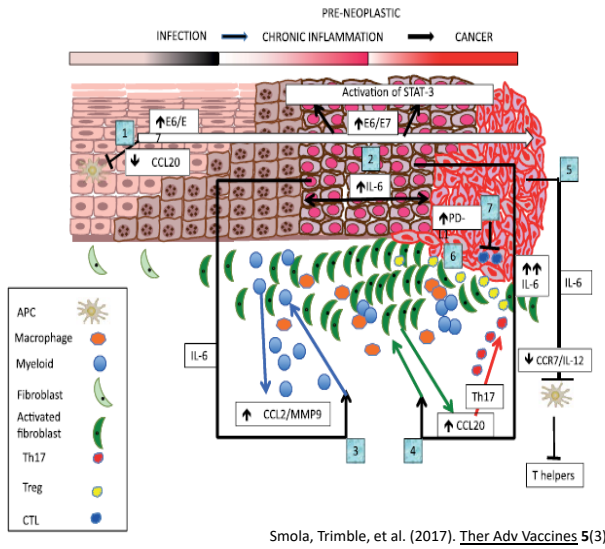
Immunotherapy Biomarkers

- PD-L1 expression
  - ~60% in cervical cancer
- Combined positive score (CPS)
  - Ratio of the number of PD-L1+ cells (tumor cells, lymphocytes, macrophages) to all tumor cells
  - CPS ≥1% used for cervical cancer
- Tumor mutational burden (TMB) high status = ~6%
- Microsatellite Instability (MSI)
  - Ranges from 2.6% to 14%





Meng Y. J Cancer 2018. Enwere E. Mod Pathol 2017. Zhang L. N Engl J Med 2003. Yarchoan M. N Engl J Med 2017.
Kulangara K. Arch Pathol Lab Med 2019. Chung TK. Gynecol Obstet Invest 2001. Bonneville R. JCO Precis Oncol 2017.

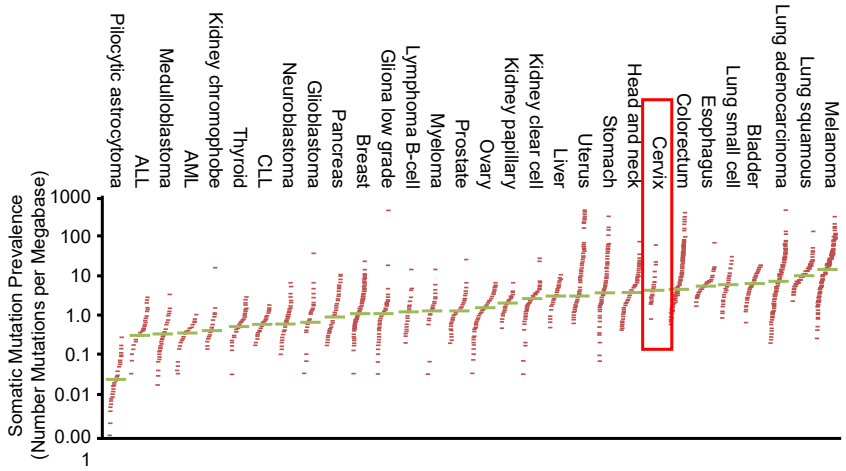


Smola, Trimble, et al. (2017). Ther Adv Vaccines **5**(3): 69-82.

Immunosuppression↔Invasion

- HPV E6 and E7 induce cascade of cytokines and Tcell signaling (1,2)
- ↑IL-6
  - Myelo-,monocyte infiltration (3)
  - Activated fibroblast inflammation (4)
  - Disables antigen presentation (5)
- Tregs and MDSC infiltration (6)
- PDL1 upregulation (7)
- All worse with hypoxia, TGFb, ROS

Mutational Burden Compared With Other Tumors



Alexandrov LB, et al. *Nature.* 2013;500(7463):415-421.

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KEYNOTE 158: Study Design and Baseline Characteristics

Patients
- Age ≥18 years
- Histologically or cytologically confirmed advanced cervical cancer
- Progression on/intolerance to ≥1 line of standard therapy
- ECOG PS 0 or 1
- Tumor sample for biomarker analysis

→ Pembrolizumab 200 mg Q3W → Treat for 2 years[a] or until progression[b], intolerable toxicity, or study withdrawal → Survival follow-up

Endpoints
- **Primary:** ORR
- **Secondary:** DOR, PFS, OS

Median follow-up: 36.9 months
Range: 34.3-41.0 months

Baseline characteristic, n (%)		N=98
Median age (range)		46.0 (24-75)
ECOG PS 1		64 (65)
PD-L1+ tumor[a]		82 (84)
Number of prior therapies	1	44 (45)
	2	31 (32)
	3	13 (13)
	≥4	8 (8)

[a]CPS ≥1
Chung HC. Abstract 41. SGO Annual Meeting 2021.

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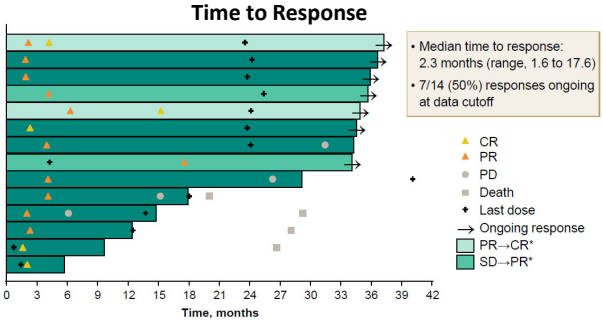
KEYNOTE-158: Safety and Efficacy

Outcome	Overall[a] N=98
ORR[d], % (95% CI)	14.3 (8.0-22.8)
Best overall response, n (%)	
CR	5 (5.1)
PR	9 (9.2)
SD	16 (16.3)
PD	55 (56.1)
Non-evaluable[e]	4 (4.1)
No assessment[f]	9 (9.2)

Time to Response



Safety Summary
- 65% of patients experienced any TRAE
- 12% had grade ≥3 TRAEs
- 4% had TRAEs leading to discontinuation
- ~25% of patients had any irAE; ~4% were grade ≥3, ~50% resolved
- 2% of patients discontinued pembrolizumab due to irAEs (hepatitis, n=2)

Pembrolizumab received FDA approval for the treatment of PD-L1+ r/m cervical cancer; q6w dosing approved in April 2020

[a]Includes 1 patient with unknown PD-L1 expression level. [b]CPS ≥1. [c]CPS <1. [d]At the time of analysis, all responses were confirmed. [e]Target lesions not captured on ≥1 post-baseline imaging assessment. [f]Post-baseline tumor assessment not performed. [g]TRAEs leading to discontinuation included hepatitis (n=2), diarrhea (n=1), and stomatitis (n=1)

Chung HC. Abstract 41. SGO Annual Meeting 2021.

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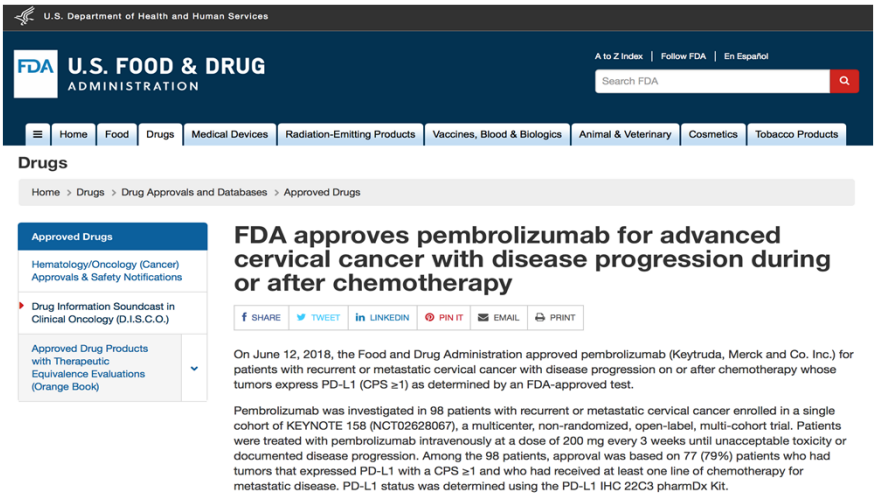
US FDA Accelerated Approval of Pembrolizumab (June 12, 2018)



Companion Diagnostic
PD-L1 IHC 22C3
CPS≥1

U.S. FDA Press Release. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm610572.htm. Accessed March 13, 2019.

54

2021 ESMO congress

16-21 SEPTEMBER 2021

ESMO 2021 LBA2

Pembrolizumab plus Chemotherapy versus Placebo plus Chemotherapy for Persistent, Recurrent, or Metastatic Cervical Cancer: Randomized, Double-Blind, Phase 3 KEYNOTE-826 Study

Nicoletta Colombo,[1] Coraline Dubot,[2] Domenica Lorusso,[3] Valeria Caceres,[4] Kosei Hasegawa,[5] Ronnie Shapira-Frommer,[6] Krishnansu S. Tewari,[7] Pamela Salman,[8] Edwin Hoyos Usta,[9] Eduardo Yañez,[10] Mahmut Gümüş,[11] Mivael Olivera Hurtado de Mendoza,[12] Vanessa Samouëlian,[13] Vincent Castonguay,[14] Alexander Arkhipov,[15] Sarper Toker,[16] Kan Li,[16] Stephen M. Keefe,[16] Bradley J. Monk,[17] on behalf of the KEYNOTE-826 Investigators

[1]University of Milan-Bicocca and European Institute of Oncology (IEO) IRCCS, Milan, Italy; [2]Institut Curie Saint-Cloud, Saint-Cloud, France, Group d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO); [3]Fondazione Policlinico Universitario A Gemelli IRCCS and Catholic University of Sacred Heart, Rome, Italy; [4]Instituto de Oncología Ángel H. Roffo, Buenos Aires, Argentina; [5]Saitama Medical University International Medical Center, Hidaka, Saitama, Japan; [6]Ella Lemelbaum Institute for Immuno-Oncology, Sheba Medical Center, Ramat Gan, Israel; [7]University of California, Irvine, Orange, CA, USA; [8]Oncovida Cancer Center, Providencia, Chile; [9]IMAT Oncomedica S.A., Monteria, Colombia; [10]Universidad de la Frontera, Temuco, Chile; [11]Istanbul Medeniyet University Hospital, Istanbul, Turkey; [12]Instituto Nacional de Enfermedades Neoplásicas, INEN, Lima, Perú; [13]Centre Hospitalier de l'Université de Montréal (CHUM), Centre de Recherche de l'Université de Montréal (CRCHUM), Université de Montréal, Montréal, QC, Canada; [14]Centre Hospitalier Universitaire de Québec, Université Laval, Québec City, QC, Canada; [15]Medical Rehabilitation Center under the Ministry of Health of Russian Federation, Moscow, Russia; [16]Merck & Co., Inc., Kenilworth, NJ, USA; [17]Arizona Oncology (US Oncology Network), University of Arizona College of Medicine, Creighton University School of Medicine, Phoenix, AZ, USA

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KEYNOTE-826: Randomized, Double-Blind, Phase 3 Study

Key Eligibility Criteria

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

Stratification Factors

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

R 1:1

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

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

End Points

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

[a]Paclitaxel: 175 mg/m^2. Cisplatin: cisplatin 50 mg/m^2. Carboplatin: AUC 5 mg/mL/min. The 6-cycle limit was introduced with protocol amendment 2, although participants with ongoing clinical benefit who were tolerating chemotherapy could continue beyond 6 cycles after sponsor consultation.
CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100); PROs, patient-reported outcomes; VAS, visual analog scale. KEYNOTE-826 ClinicalTrials.gov identifier, NCT03635567.

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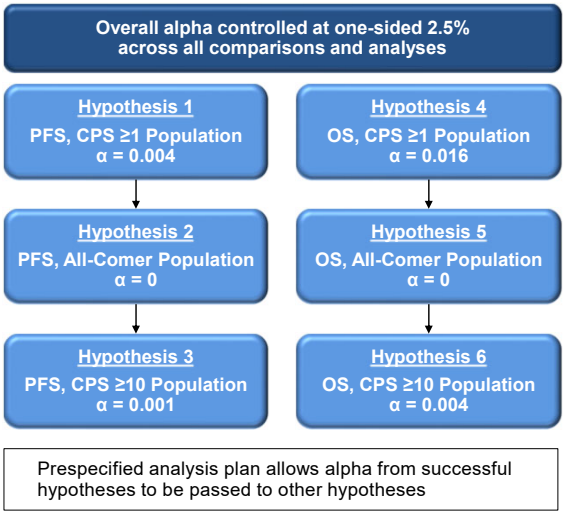
Statistical Considerations



Protocol-specified first interim analysis (IA1)

- Timing: when ~370 events of PD or death occurred in the CPS ≥1 population
- Objective: to assess whether adding pembrolizumab to chemotherapy ± bevacizumab significantly improves PFS and OS in the CPS ≥1, all-comer, and CPS ≥10 populations
- Data cutoff date: May 3, 2021

Analysis populations

- Efficacy: all randomized participants
- Safety: all randomized participants who received ≥1 dose of study drug

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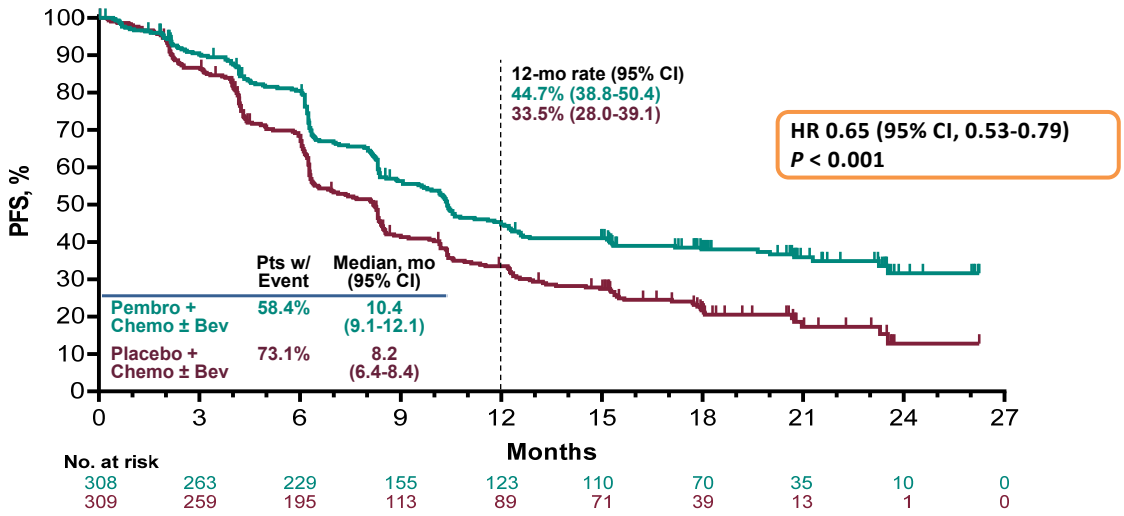
PFS: All-Comer Population



Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: May 3, 2021.

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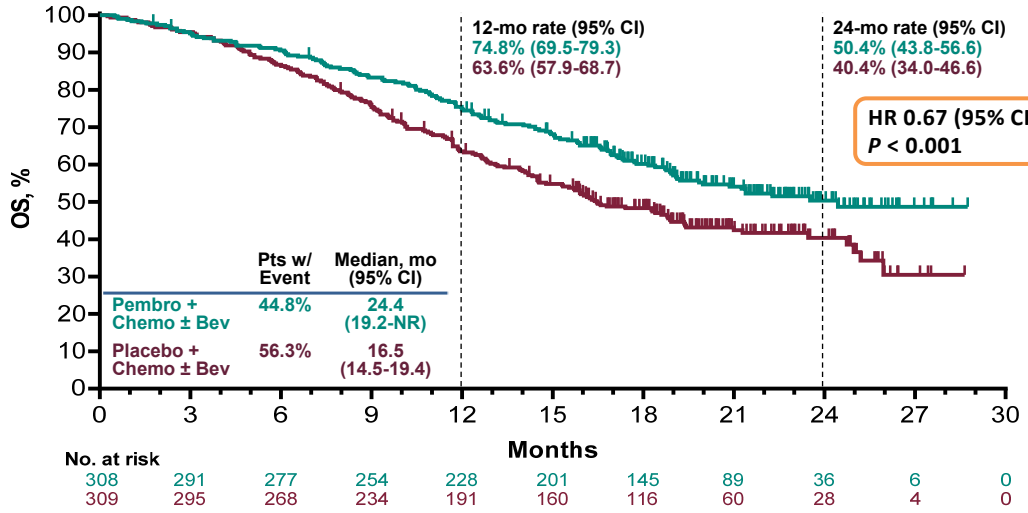
OS: All-Comer Population



Data cutoff date: May 3, 2021.

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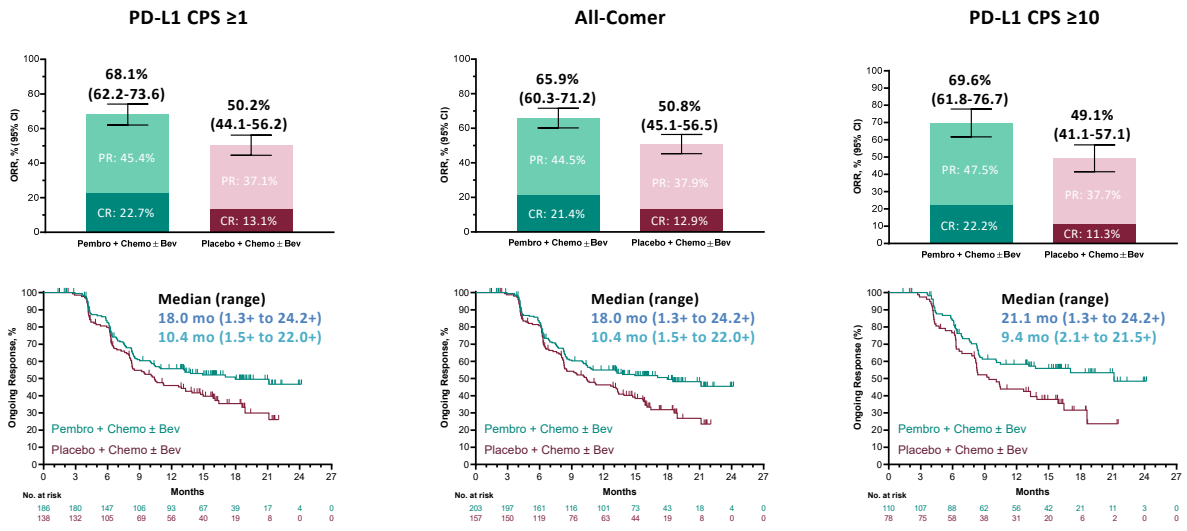
ORR and DOR: All Analysis Populations



Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: May 3, 2021.

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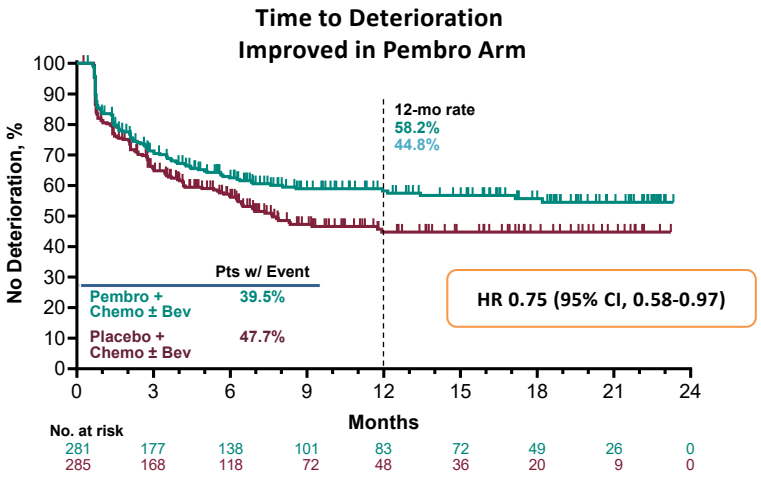
EuroQol EQ-5D-5L VAS, All-Comer Population

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



[a]Compliance was defined as the proportion of participants who completed the patient-reported outcome questionnaire among those who were expected to complete the questionnaire at the time point, excluding those missing by design; missing by design includes adverse event, death, discontinuation, translations not available, and no visit scheduled.
Data cutoff date: May 3, 2021.

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NCCN Guidelines: Systemic Therapy for Cervical Cancer

	Preferred regimens	Other recommended regimens
Chemoradiation	Cisplatin, carboplatin if cisplatin intolerant	N/A
First-line combinations	Cisplatin/paclitaxel/bevacizumab Carboplatin/paclitaxel/bevacizumab	Cisplatin/paclitaxel Carboplatin/paclitaxel Topotecan/paclitaxel ± bevacizumab Cisplatin/topotecan
Possible first-line monotherapy	Cisplatin	Carboplatin or paclitaxel
Second-line therapy	Pembrolizumab (for PD-L1+ or MSI-H/dMMR tumors)	Bevacizumab, albumin-bound paclitaxel, docetaxel, fluorouracil, gemcitabine, ifosfamide, irinotecan, mitomycin, pemetrexed, topotecan, vinorelbine Pembrolizumab for TMB-H tumors Larotrectinib or entrectinib for *NTRK+* gene fusion positive tumors

1. NCCN. NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer. Version 2.2020. https://www.nccn.org/professionals/physician_gls/PDF/cervical.pdf. Accessed 19 September 2020.

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Randomized phase III ICI trials in metastatic/recurrent setting

Frontline ICI trial	Agent (n)	Design	Stratification factors	Primary endpoint(s)
Keynote-826 (NCT03635567)	Pembro (600)	2 arm 1:1 GOG 240 control MD choice bev	• Stage • +/- Bev • PD-L1 status	• PFS BICR • OS
BEATcc (NCT03556839)	Atezo (404)	2 arm 1:1 GOG 240 control Mandatory bev	• Prior CRT • Histology • Chemotherapy Backbone: • Cis v Carbo	• OS
FERMATA (NCT03912415)	BCD-100 (316)	2 arm 1:1 GOG 240 control MD choice bev	• Stage • +/- Bev • PDL1 status • Ethnicity	• OS

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ESMO VIRTUAL PLENARY

EMPOWER GOG FOUNDATION ENGOT European Network of Gynaecological Oncological Trial groups

EMPOWER-CERVICAL 1/GOG-3016/ENGOT-CX9: RESULTS OF PHASE 3 TRIAL OF CEMIPLIMAB VS INVESTIGATOR'S CHOICE (IC) CHEMOTHERAPY (CHEMO) IN RECURRENT/METASTATIC (R/M) CERVICAL CARCINOMA

Krishnansu S Tewari,* Bradley J Monk,* Ignace Vergote, Austin Miller, Andreia Cristina de Melo, Hee Seung Kim, Yong Man Kim, Alla Lisyanskaya, Vanessa Samouëlian, Domenica Lorusso, Fernanda Damian, Chih-Long Chang, Evgeniy A Gotovkin, Shunji Takahashi, Daniella Ramone, Joanna Pikiel, Beata Maćkowiak-Matejczyk, Eva Maria Guerra, Nicoletta Colombo, Yulia Makarova,
Jingjin Li, Shaheda Jamil, Vladimir Jankovic, Chieh-I Chen, Frank Seebach, David M Weinreich, George D Yancopoulos, Israel Lowy, Melissa Mathias, Matthew G Fury, and Ana Oaknin

12 May 2021

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

*Contributed equally to this presentation.

This study (NCT03257267) was sponsored by Regeneron Pharmaceuticals, Inc. and Sanofi.

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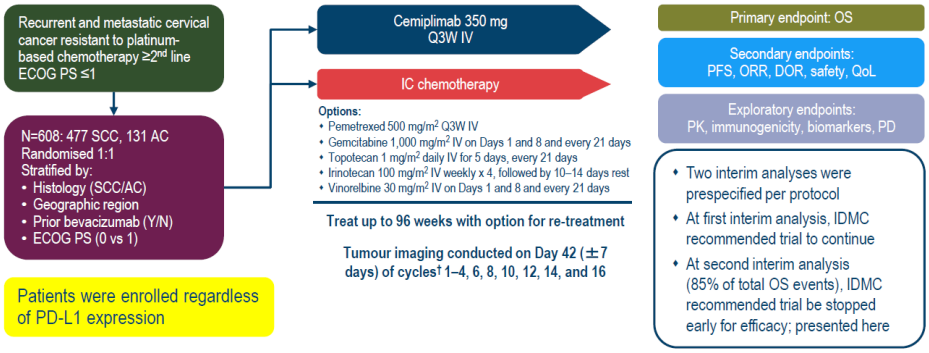
EMPOWER: Interim Analysis of a Phase 3 trial of Cemiplimab versus Investigator's Choice Chemotherapy in R/M Cervical Carcinoma



*Performed according to ENGOT Model C.†To account for differences in drug administration schedules, one cycle is defined as 6 weeks.
AC, adenocarcinoma or adenosquamous carcinoma; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, investigator's choice; IDMC, Independent Data Monitoring Committee; IV, intravenously; ORR, objective response rate; OS, overall survival; PD, pharmacodynamics; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; QoL, quality of life; SCC, squamous cell carcinoma.
1. Vergote I et al. *Int J Gynecol Cancer.* 2019;0:1–4.

- Opened: Sept 2017
- Closed: June 2020
- N = 590
- Sites = 105

Tewari KS, et al. Presented at ESMO Virtual Plenary. 12–13 May 2021.

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Statistical Assumptions and Analysis

Statistical considerations	
Sample size	608 (SCC + non-SCC)
Randomisation	1:1 assignment (cemiplimab vs IC chemotherapy)
Primary endpoint	OS
Power	90%*
Alpha	1-sided type 1 error rate limited to 0.025
HR assumption	0.70 (median OS: 7 months vs 10 months)
Assumed dropout rate	10% per year
Events needed	340 OS events planned in SCC patients

Hierarchical testing†

Primary endpoint

1. OS in SCC patients
2. OS in overall population

Secondary endpoints

3. PFS in SCC patients
4. Overall mean change from baseline in GHS/QoL scale in SCC patients
5. Overall mean change from baseline in physical functioning scale in SCC patients
6. ORR in SCC patients
7. PFS in overall population
8. ORR in overall population

*For SCC. The power for testing OS in the overall population will be >90%. †Hierarchical testing included six additional secondary endpoints not included in this presentation.
GHS, Global Health Status; HR, hazard ratio; IC, investigator's choice; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; SCC, squamous cell carcinoma.

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Patient Demographics And Baseline Characteristics

	Cemiplimab (n=304)	Chemotherapy (n=304)	Total (N=608)
Age (years)			
n	304	304	608
Mean (SD)	51.1 (11.6)	51.2 (11.8)	51.1 (11.7)
Median	51.0	50.0	51.0
Q1 : Q3	42.0 : 60.0	43.0 : 59.0	43.0 : 59.0
Min : Max	22 : 81	24 : 87	22 : 87
Age groups (years), n (%)			
<65	269 (88.5)	264 (86.8)	533 (87.7)
≥65 and <75	30 (9.9)	29 (9.5)	59 (9.7)
≥75	5 (1.6)	11 (3.6)	16 (2.6)
Geographic region, n (%)			
North America	32 (10.5)	34 (11.2)	66 (10.9)
Asia	83 (27.3)	83 (27.3)	166 (27.3)
Rest of World	189 (62.2)	187 (61.5)	376 (61.8)
ECOG performance status, n (%)			
0	142 (46.7)	141 (46.4)	283 (46.5)
1	162 (53.3)	163 (53.6)	325 (53.5)

	Cemiplimab (n=304)	Chemotherapy (n=304)	Total (N=608)
Histology/cytology, n (%)			
SCC	240 (78.9)	233 (76.6)	473 (77.8)
Adenocarcinoma	54 (17.8)	62 (20.4)	116 (19.1)
Adenosquamous carcinoma	10 (3.3)	9 (3.0)	19 (3.1)
Extent of disease, n (%)			
Metastatic	284 (93.4)	290 (95.4)	574 (94.4)
Recurrent/persistent	20 (6.6)	14 (4.6)	34 (5.6)
Prior lines of therapy for R/M disease			
1	177 (58.2)	169 (55.6)	346 (56.9)
>1	124 (40.8)	135 (44.4)	259 (42.6)
Prior bevacizumab use, n (%)*			
Yes	149 (49.0)	147 (48.4)	296 (48.7)
No	155 (51.0)	157 (51.6)	312 (51.3)

- 608 patients were randomised
  - 477 with SCC*
  - 131 with AC*

*Based on interactive web response system data. AC, adenocarcinoma or adenosquamous carcinoma; ECOG, Eastern Cooperative Oncology Group; Q, quarter; R/M, recurrent or metastatic; SCC, squamous cell carcinoma; SD, standard deviation.

Data cutoff date: 4 Jan 2021

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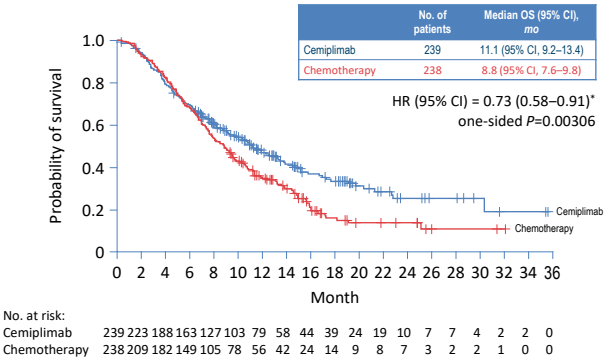
Overall Survival

SCC Population

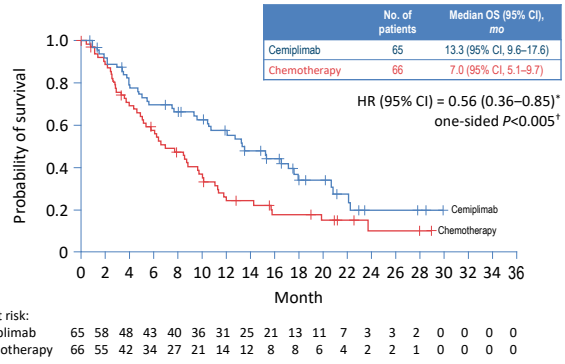


No. at risk:

Cemiplimab	239	223	188	163	127	103	79	58	44	39	24	19	10	7	7	4	2	2	0
Chemotherapy	238	209	182	149	105	78	56	42	24	14	9	8	7	3	2	2	1	0	0

Median duration of follow-up‡: 16.8 months (range: 6.0–38.2)

AC Population



No. at risk:

Cemiplimab	65	58	48	43	40	36	31	25	21	13	11	7	3	3	2	0	0	0	0
Chemotherapy	66	55	42	34	27	21	14	12	8	8	6	4	2	2	1	0	0	0	0

Median duration of follow-up‡: 21.9 months (range: 6.9–36.6)

*Stratified by geographic region (North America vs Asia vs ROW) according to interactive web response system. †One-sided nominal *P* value, not adjusted for multiplicity.
‡From randomisation to data cutoff date.
AC, adenocarcinoma or adenosquamous carcinoma; CI, confidence interval; HR, hazard ratio; mo, month; OS, overall survival; ROW, rest of world; SCC, squamous cell carcinoma.

Data cutoff date: 4 Jan 2021

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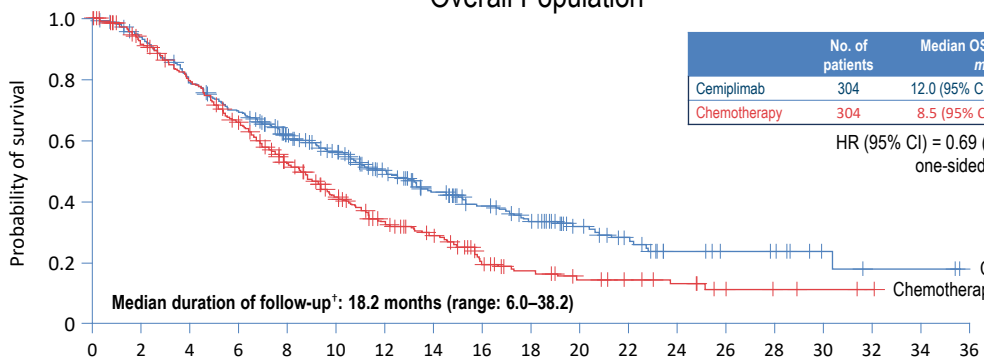
Overall Survival

- At second interim analysis (85% of total OS events), IDMC recommended trial be stopped early for efficacy

Overall Population



	No. of patients	Median OS (95% CI), *mo*
Cemiplimab	304	12.0 (95% CI, 10.3–13.5)
Chemotherapy	304	8.5 (95% CI, 7.5–9.6)

HR (95% CI) = 0.69 (0.56–0.84)*
one-sided *P*=0.00011

No. at risk:																			
Cemiplimab	304	281	236	206	167	139	110	83	65	52	35	26	13	10	9	4	2	2	0
Chemotherapy	304	264	224	183	132	99	70	54	32	22	15	12	9	5	3	2	1	0	0

*Stratified by geographic region (North America vs Asia vs ROW) and Histology (SCC vs AC) according to interactive web response system. †From randomisation to data cutoff date.
AC, adenocarcinoma or adenosquamous carcinoma; CI, confidence interval; HR, hazard ratio; IDMC, Independent Data Monitoring Committee; mo, month; ROW, rest of world; OS, overall survival.

Data cutoff date: 4 Jan 2021

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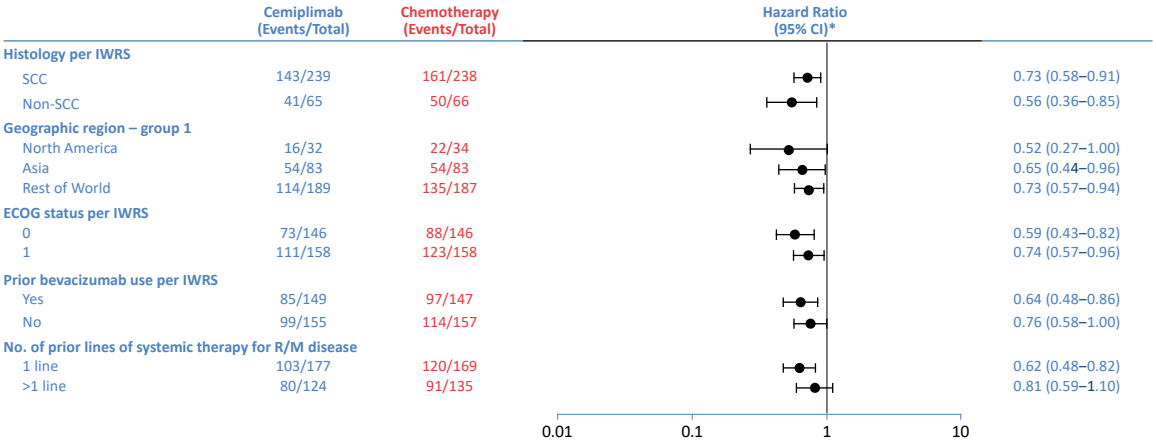
Overall Survival

Prespecified Subgroup Analyses in Overall Population



*Stratified by geographic region (North America vs Asia vs ROW per IWRS) and histology (SCC vs AC per IWRS) except for geographic region, histology subgroups (cemiplimab vs chemotherapy). Geographic region is stratified by histology (SCC vs AC per IWRS). Histology is stratified by geographic region (North America vs Asia vs ROW per IWRS) (cemiplimab vs chemotherapy).
AC, adenocarcinoma or adenosquamous carcinoma; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; IWRS, interactive web response system; ROW, rest of world; R/M, recurrent or metastatic; SCC, squamous cell carcinoma.

Data cutoff date: 4 Jan 2021

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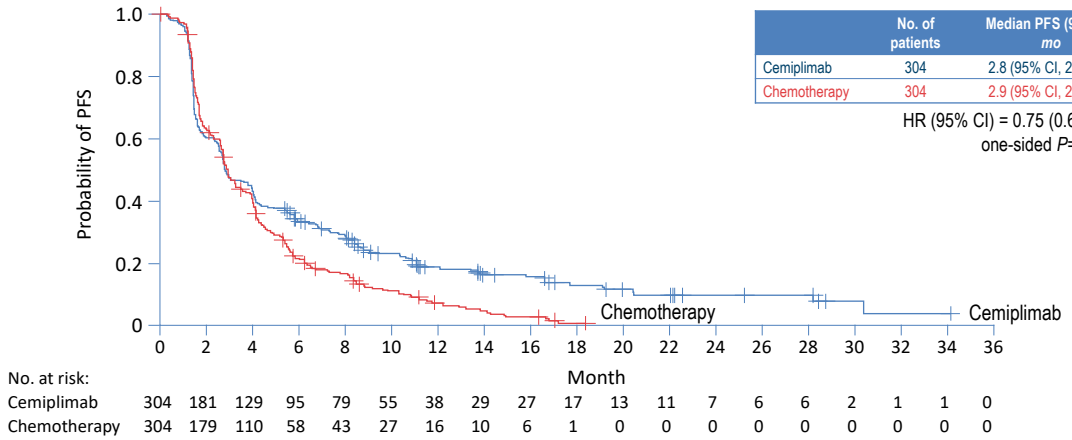
Progression-free Survival

Overall Population



	No. of patients	Median PFS (95% CI) *mo*
Cemiplimab	304	2.8 (95% CI, 2.6–3.9)
Chemotherapy	304	2.9 (95% CI, 2.7–3.4)

HR (95% CI) = 0.75 (0.63–0.89)*
one-sided *P*=0.00048

No. at risk:																		
Cemiplimab	304	181	129	95	79	55	38	29	27	17	13	11	7	6	6	2	1	1	0
Chemotherapy	304	179	110	58	43	27	16	10	6	1	0	0	0	0	0	0	0	0	0

*Stratified by geographic region (North America vs Asia vs ROW) and Histology (SCC vs AC) according to interactive web response system.
AC, adenocarcinoma or adenosquamous carcinoma; CI, confidence interval; HR, hazard ratio; mo, month; PFS, progression-free survival; ROW; rest of world; SCC, squamous cell carcinoma.

Data cutoff date: 4 Jan 2021

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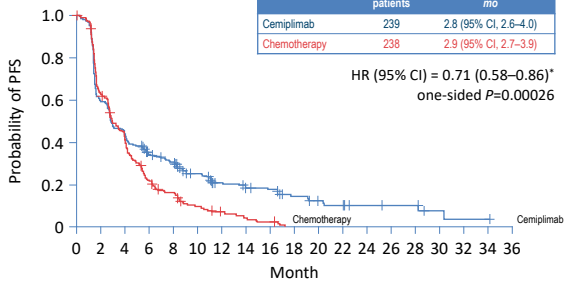
Progression-free Survival

SCC Population

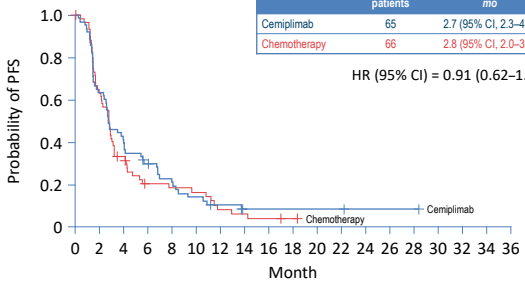


	No. of patients	Median PFS (95% CI), *mo*
Cemiplimab	239	2.8 (95% CI, 2.6–4.0)
Chemotherapy	238	2.9 (95% CI, 2.7–3.9)

HR (95% CI) = 0.71 (0.58–0.86)*
one-sided *P*=0.00026

No. at risk:																		
Cemiplimab	239	141	104	77	67	47	33	27	25	15	11	9	6	5	5	2	1	1	0
Chemotherapy	238	141	91	48	34	19	12	7	4	0	0	0	0	0	0	0	0	0	0

AC Population



	No. of patients	Median PFS (95% CI), *mo*
Cemiplimab	65	2.7 (95% CI, 2.3–4.0)
Chemotherapy	66	2.8 (95% CI, 2.0–3.2)

HR (95% CI) = 0.91 (0.62–1.34)*

No. at risk:																		
Cemiplimab	65	40	25	18	12	8	5	2	2	2	2	2	1	1	1	0	0	0	0
Chemotherapy	66	38	19	10	9	8	4	3	2	1	0	0	0	0	0	0	0	0	0

*Stratified by geographic region (North America vs Asia vs ROW) according to interactive web response system.
AC, adenocarcinoma or adenosquamous carcinoma; CI, confidence interval; HR, hazard ratio; mo, month; PFS, progression-free survival; ROW, rest of world; SCC, squamous cell carcinoma.

Data cutoff date: 4 Jan 2021

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Objective Response Rate

By investigator assessment	Overall population	
	Cemiplimab (n=304)	Chemotherapy (n=304)
Response		
Objective response rate (ORR:CR+PR)	50 (16.4)	19 (6.3)
95% CI for ORR[a]	(12.5, 21.1)	(3.8, 9.6)
Best overall tumour response, n (%)		
Complete response (CR)[b]	10 (3.3)	3 (1.0)
Partial response (PR)[b]	40 (13.2)	16 (5.3)
Stable disease (SD)[c]	125 (41.1)	148 (48.7)
Progressive disease (PD)	105 (34.5)	88 (28.9)
Not evaluable (NE)	24 (7.9)	49 (16.1)
Stratified CMH test one-sided *P*-value[d]	0.00004	
Odds ratio (95% CI)[d]	2.984 (1.707, 5.215)	
KM estimated median DOR, months (95% CI)[e]	16.4 (12.4, NE)	6.9 (5.1, 7.7)
Median observed time to response, months (range)	2.7 (1.2–11.4)	1.6 (1.2–9.0)

- ORR of SCC population
  - Cemiplimab: 17.6% (95% CI: 13.0–23.0)
  - Chemotherapy: 6.7% (95% CI: 3.9–10.7)
- ORR of AC population
  - Cemiplimab: 12.3% (95% CI: 5.5–22.8)
  - Chemotherapy: 4.5% (95% CI: 0.9–12.7)

[a]Clopper-Person exact confidence interval (CI); [b]CR/PR must be confirmed by repeated assessments no less than 4 weeks apart; [c]SD criteria must be met at least once for a minimum duration of 4 weeks after first dose date; [d]One-sided *P*-value and odds ratio using geographic region and histology stratified Cochran-Mantel-Haenszel (CMH) test. Due to the low response rate in the chemotherapy arm, the results from CMH test should be interpreted with caution; [e]Based on patients with confirmed CR or PR.
AC, adenocarcinoma or adenosquamous carcinoma; DOR, duration of response; KM, Kaplan-Meier; SCC, squamous cell carcinoma.

Data cutoff date: 4 Jan 2021

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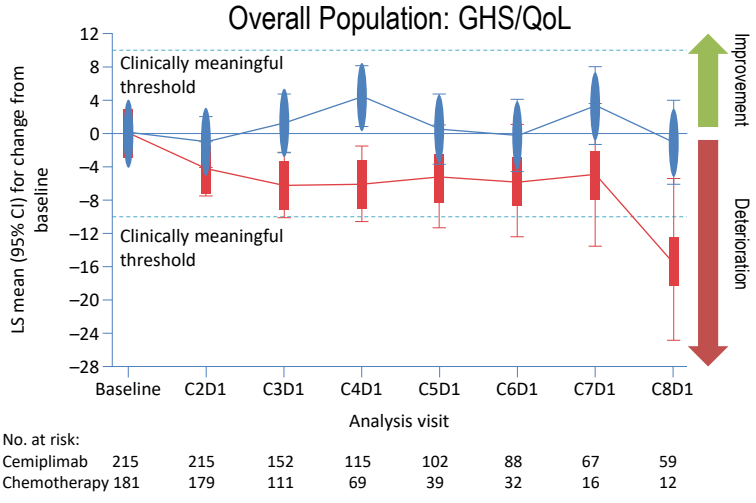
Mean Change From Baseline In GHS/QoL Scale

MMRM Estimates



Overall (SE)
Cemiplimab: 1.01 (1.54)
Chemotherapy: −6.81 (2.12)
Difference: 7.81, one-sided nominal *P*=0.00040

- Overall population: nominally significant difference in favour of cemiplimab over IC chemotherapy
- Patients receiving cemiplimab improved or maintained GHS/QoL from baseline
- Patients receiving chemotherapy generally showed deterioration in these scores

C, cycle; CI, confidence interval; D, day; GHS, Global Heath Status; IC, investigator's choice; LS, least squares; MMRM, mixed-model repeated measure; QoL, quality of life; SE, standard error.

Data cutoff date: 4 Jan 2021

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Safety Summary

n (%), unless stated	Cemiplimab (n=300)		Chemotherapy (n=290)	
Median duration of exposure (range), weeks	**15.2 (1.4–100.7)**		**10.1 (1.0–81.9)**	
Treatment-emergent AEs, regardless of attribution	**Any grade**	**Grade 3–5**	**Any grade**	**Grade 3–5**
Overall	265 (88.3)	135 (45.0)	265 (91.4)	155 (53.4)
Led to discontinuation	26 (8.7)	20 (6.7)	15 (5.2)	11 (3.8)
Led to death	5 (1.7)	5 (1.7)	2 (0.7)	2 (0.7)
Treatment-related AEs				
Overall	170 (56.7)	44 (14.7)	236 (81.4)	117 (40.3)
Led to discontinuation	17 (5.7)	12 (4.0)	10 (3.4)	8 (2.8)
Led to death	0	0	2 (0.7)	2 (0.7)
Sponsor-identified immune-related AEs				
Overall	48 (16.0)	18 (6.0)	2 (0.7)	2 (0.7)
Led to discontinuation	15 (5.0)	11 (3.7)	2 (0.7)	2 (0.7)
Led to death	0	0	0	0

Safety was analysed in all randomised patients who received any study treatment.
AE, adverse events; PD-1, programmed cell death-1; PD-L1, PD-ligand 1.

Treatment-emergent AEs in ≥15% of patients in either arm, n (%)	Cemiplimab (n=300)		Chemotherapy (n=290)	
	Any grade	**Grade 3–5**	**Any grade**	**Grade 3–5**
Overall	265 (88.3)	135 (45.0)	265 (91.4)	155 (53.4)
Anaemia	75 (25.0)	36 (12.0)	129 (44.5)	78 (26.9)
Nausea	55 (18.3)	1 (0.3)	97 (33.4)	6 (2.1)
Fatigue	50 (16.7)	4 (1.3)	45 (15.5)	4 (1.4)
Vomiting	48 (16.0)	2 (0.7)	68 (23.4)	7 (2.4)
Decreased appetite	45 (15.0)	1 (0.3)	46 (15.9)	2 (0.7)
Constipation	45 (15.0)	0	59 (20.3)	1 (0.3)
Pyrexia	35 (11.7)	1 (0.3)	61 (21.0)	0
Asthenia	33 (11.0)	7 (2.3)	44 (15.2)	3 (1.0)
Neutropenia	6 (2.0)	3 (1.0)	44 (15.2)	26 (9.0)

- There were no new immune-related AEs that are not well described for the PD-1/PD-L1 inhibitor class

Data cutoff date: 4 Jan 2021

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VIRTUAL 2020 ESMO congress

#5401

Balstilimab (anti-PD-1) Alone and in Combination with Zalifrelimab (anti-CTLA-4)

for Recurrent/Metastatic (R/M) Cervical Cancer (CC) Preliminary Results of Two Independent Ph2 Trials

(NCT03104699 and NCT03495882)

O'Malley DM[1]; Oaknin A[2]; Monk B[3]; Leary A[4]; Selle F[5]; Alexandre J[6]; Randall L[6]; Rojas C[7]; Neffa M[8]; Kryzhanivska A[9]; Gladieff L[10]; Berton D[11]; Meniawy T[12]; Lugowska I[13]; Bondarenko I[14]; Moore K[15]; Ortuzar Feliu W[16]; Ancukiewicz M[16]; Shapiro I[16]; Ray-Coquard I[17]

[1]The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA; [2]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [3]University of Arizona College of Medicine, Creighton University School of Medicine at St. Joseph's Hospital Phoenix, AZ, USA; [4]Institut de Cancérologie Gustave Roussy, Villejuif, France; [5]APHP Centre - Université de Paris, Hôpital Cochin, Paris, France; [6]Massey Cancer Center, Virginia Commonwealth University, Richmond, VA, USA; [7]Centro de Investigaciones Clinicas, Bradford Hill, Chile; [8]CI of Healthcare Regional Clinical Specialized Dispensary of the Radiation Protection, Department of Surgery, Kharkiv, Ukraine; [9]CI Transcarpathian CI Onc Center Dep of Surgery#1 SHEI Ivano-Frankivsk NMU, Ivano-Frankivsk, Ukraine; [10]Le Centre René Gauducheau, Saint-Herblain, France; [11]Institut Claudius Regaud, IUCT Oncopole, Toulouse, France; [12]Linear Clinical Research, Perth, Australia; [13]Centrum Onkologii-Instytut im.M.Sklodowskiej Curie, Warsaw, Poland; [14]CI Dnipropetrovsk CMCH #4 of Dnipropetrovsk RC Dept of Chemotherapy SI Dnipropetrovsk MA of MOHU, Dniepro, Ukraine; [15]Stephenson Cancer Center at the University of Oklahoma, Oklahoma City, OK, USA ; [16]Agenus Inc., Lexington, MA, USA; [17]Centre Léon Bérard, Lyon, France

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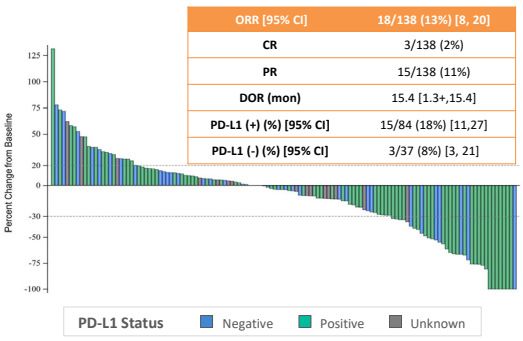
Maximal Change in Target Lesions and Tumor Response

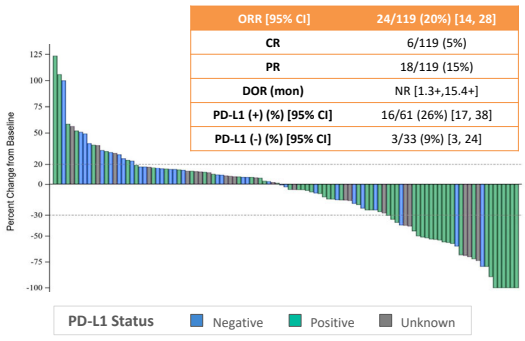
Balstilimab Monotherapy

- Patients with ≥1 prior chemotherapy (n=138)



Balstilimab + Zalifrelimab

- Patients with ≥1 prior chemotherapy (n=119)



O'Malley DM, LBA34. ESMO 2020.

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FDA Approval Sought for Balstilimab (anti–PD-1) for Recurrent Cervical Cancer

BLA Filing: April 19, 2021
PDUFA Date: Dec 16, 2021

202O ESMO Virtual Congress

- Overall response rate = 14% (n = 23/138; 95% CI, 10%-21%) in patients who receive 1 or more prior lines of chemotherapy
- Duration of response = was 15.4 months.

O'Malley DM, Oaknin A, Monk B, et al. Single-agent anti-PD-1 balstilimab or in combination with anti-CTLA-4 zalifrelimab for recurrent/metastatic (R/M) cervical cancer (CC): preliminary results of two independent phase II trials. *Ann Oncol*. 2020;31(suppl 4):S1164-S1165. doi:10.1016/j.annonc.2020.08.2264

Agenus submits balstilimab biologics license application to the US FDA for patietns with recurrent or metastatic cervical cancer. News release. Agenus Inc. April 19, 2021. Accessed April 19, 2021. https://bit.ly/2P103PA

https://investor.agenusbio.com/news-releases/news-release-details/agenus-announces-us-fda-acceptance-and-priority-review

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GOG-3028/RaPiDS - A Two Arm, Randomized, Non Comparative Blinded Phase 2 Trial of Balstilmab in Combination Therapy Zalfrelimab or Placebo for Second Line Cervical Cancer

Patient Eligibility

- Cervical cancer that has relapsed after a platinum-based treatment (first line) regimen for advanced (recurrent, unresectable, or metastatic) disease
- Measurable disease on imaging based on RECIST version 1.1
- ECOG PS ≤1
- sufficient and adequate formalin-fixed paraffin embedded (FFPE)

Randomization 1:1

Treatment up to 24 months

- AGEN2034 (300 mg) every 3 weeks Placebo every 6 weeks
- AGEN2034 (300 mg) every 3 weeks AGEN1884 (1 mg/kg) every 6 weeks

Primary Endpoint

- ORR according to RECIST 1.1

NCT03894215
US PI Dave O'Malley
Co-PI Camille Gunderson

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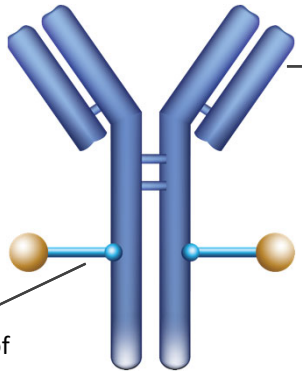
Anatomy of an Antibody-Drug Conjugate



Antibody – specific to a tumor antigen

Payload – highly potent cytotoxic agent

Linker – Efficient release of payload at tumor site; Stable in circulation

Panowski S, et al. mAbs. 2014;6:34-45.

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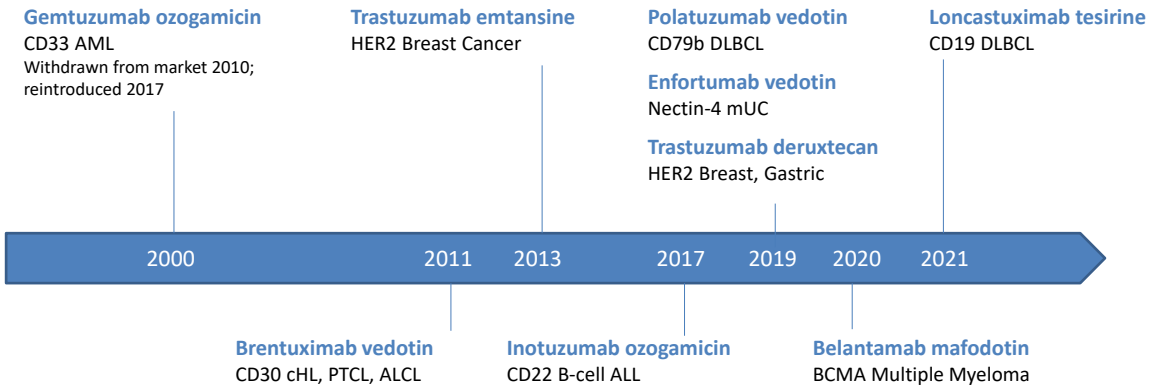
Antibody Drug Conjugates Currently Approved for Cancer Therapy in the US



Six different platforms represented by approved agents

ALCL, Anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; cHL, classical Hodgkins lymphoma; DLBCL, diffuse large B-cell lymphoma; mUC, metastatic urothelial cancer; PTCL, peripheral T-cell lymphoma; TNBC, triple negative breast cancer.

FDA website. Drugs@FDA. https://www.accessdata.fda.gov/scripts/cder/daf/ Accessed July 13, 2021.

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Target: Tissue Factor (TF)

= transmembrane receptor for coagulation factor VII/VIIa
expressed on subendothelial vessel wall cells

Normal physiological conditions:
central role in initiation of the extrinsic pathway of the coagulation cascade

In oncogenesis: role in tumour angiogenesis, proliferation, metastases, thrombotic events

Antigen	Gynaecologic malignancy	Expression frequency
Tissue factor	Ovarian cancer	23.8%-100%
	Uterine cancer	100%
	Cervical cancer	**94-100%**

highly expressed in squamous AND adenocarcinomas of the uterine cervix

Lee et Lui, *Gynecol Oncol 2019;* Cocco et al, *BMC Cancer 2011;* Förster Y, et al. *Clin Chim Acta 2006*

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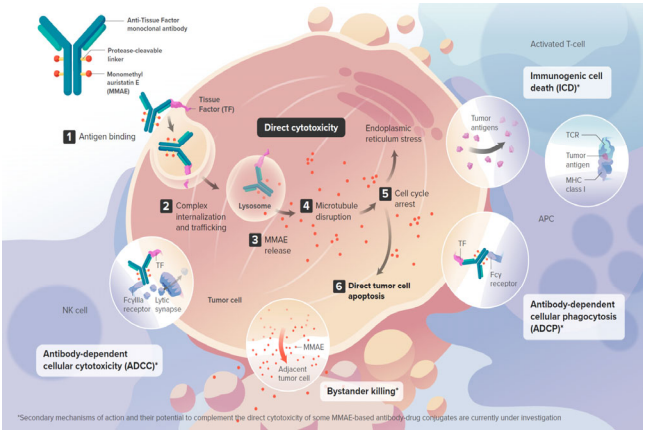
Proposed MOA of Tisotumab Vedotin

- Tisotumab vedotin is an **investigational antibody-drug conjugate directed to tissue factor** (TF) and covalently linked to the microtubule-disrupting agent MMAE via a protease-cleavable linker[1,2]
- **TF (thromboplastin) is highly prevalent in cervical cancer** and other solid tumors and is associated with cancer pathophysiology and poor prognosis[3-5]
  - TF is co-opted by tumor cells to promote tumor growth, angiogenesis, and metastasis[6]
  - In normal physiology, TF's primary role is to initiate the coagulation cascade after vascular injury[6]
- Tisotumab vedotin has **multiple** anti-tumor effects[1,2,7]



Tisotumab vedotin is an investigational agent, and its safety and efficacy have not been established.

1. Breij EC et al. Cancer Res. 2014;74(4):1214-1226. 2. De Goeij BE et al. Mol Cancer Ther. 2015;14(5):1130-1140. 3. Pan L et al. Mol Med Rep. 2019;19:2077-2086. 4. Cocco E et al. BMC Cancer. 2011;11:263. 5. Zhao X et al. Exp Ther Med. 2018;16:4075-4081. 6. Forster Y et al. Clin Chim Acta. 2006;364:12-21 7. Alley SC et al. American Association for Cancer Research Annual Meeting; March 29 – April 3, 2019; Atlanta, GA, USA; Abstract #221.

ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; MMAE, monomethyl auristatin E; MOA, mechanism of action; TF, tissue factor.

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Tisotumab Vedotin: Cervical Cancer Expansion cohort (n=55)

Phase I /II innovaTV 201 Study (NCT02001623)

ENGOT European Network of Gynaecological Oncological Trial groups

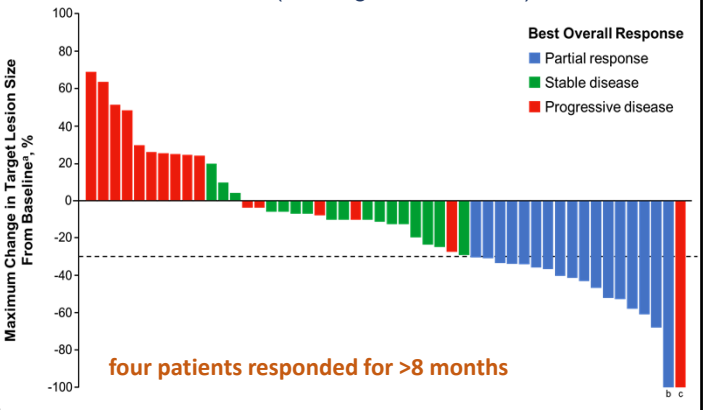
BGOG

Investigator- / independent review committee-assessed antitumor activity of tisotumab vedotin

	Cervical Cancer Cohort *N* = 55	
Antitumor Activity	**Investigator-assessed**	**IRC-assessed**
ORR (95% CI), %[a]	24 (13–37)	22 (12–35)
CR, *n* (%)	0	1 (2)
PR, *n* (%)	13 (24)	11 (20)
SD, *n* (%)	21 (38)	19 (35)
Non-CR/Non-PD, *n* (%)	0	2 (4)
PD, *n* (%)	17 (31)	17 (31)
Not evaluable, *n* (%)	4 (7)	5 (9)
Median TTR (range), months	2.6 (1.1–3.9)	2.1 (1.1–4.6)
Median DOR (range), months	4.2 (1.0*–9.7)	6.0 (1.0*–9.7)
Median PFS (95% CI), months	4.2 (2.1–5.3)	4.1 (1.7–6.7)
6-month PFS rate, % (95% CI)	29 (17–43)	40 (24–55)

CI, confidence interval; CR, complete response; DOR, duration of response; IRC, independent review committee; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TTR, time to response. *Indicates censored value due to ongoing response.
[a]Confirmed ORR by Response Evaluation Criteria In Solid Tumors v1.1 criteria.

Maximum changes in target lesion size from baseline (investigator-assessed)



Vergote I et al. ESMO 2017. Abstract 1067.
Hong D & Concin N et al, *Clincial Cancer Research 2020*

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GOG-3023/ENGOT-cx6/innovaTV 204 Study Design

innovaTV 204 (NCT03438396) is a pivotal phase 2 single-arm, multicenter (United States and Europe) study evaluating tisotumab vedotin in patients with previously treated recurrent and/or metastatic cervical cancer

Key Eligibility Criteria

- Recurrent or extrapelvic metastatic cervical cancer
- Progressed during or after doublet chemotherapy[a] with bevacizumab (if eligible)
- Received ≤2 prior systemic regimens[b]
- ECOG PS 0-1

Enrolled: 102[c]
Treated: 101*

Tisotumab vedotin 2.0 mg/kg IV Q3W

Until PD or unacceptable toxicity

Tumor responses assessed using CT or MRI at baseline, every 6 weeks for the first 30 weeks, and every 12 weeks thereafter

Primary Endpoint
- ORR[d] per RECIST v1.1, by independent imaging review committee (IRC)

Secondary Endpoints
- ORR[d] per RECIST v1.1, by investigator
- DOR, TTR, and PFS by IRC and investigator
- OS
- Safety

Exploratory Endpoints
- Biomarkers
- HRQoL

*Study sample size calculated assuming a confirmed ORR of 21% to 25% with tisotumab vedotin and to provide ≥80% power to exclude an ORR of ≤11%[e]

Study was performed according to ENGOT-GOG Model C

[a]Paclitaxel plus platinum (cisplatin or carboplatin) or paclitaxel plus topotecan. [b]Adjuvant or neoadjuvant chemotherapy or if administered with radiation therapy, was not counted as a prior systemic regimen. [c]June 2018 to April 2019. [d]Responses were confirmed by subsequent repeat imaging performed ≥4 weeks after initial response assessment. [e]Using one-sided exact binomial test at 0.025 significance level.
CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IRC, independent review committee; IV, intravenous; MRI, magnetic resonance imaging; OS, overall survival; PD, progressive disease; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; TTR, time to response.

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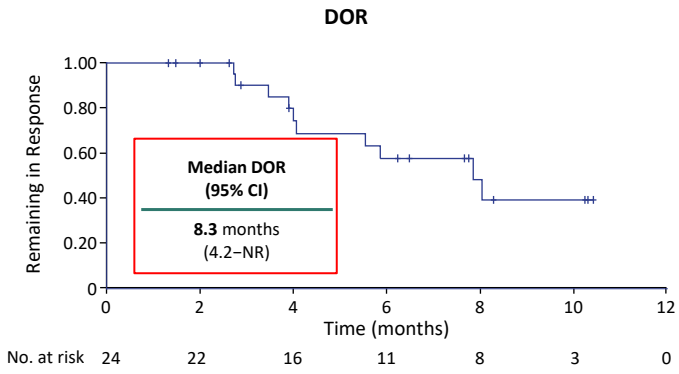
Antitumor Activity by IRC Assessment

	N=101
Confirmed ORR (95% CI),[a] %	**24 (15.9–33.3)**
CR, n (%)	7 (7)
PR, n (%)	17 (17)
SD, n (%)	49 (49)
PD, n (%)	24 (24)
Not evaluable, n (%)	4 (4)



Clinically meaningful and durable responses were observed

Data cutoff: February 06, 2020. Median duration of follow-up: 10.0 months.
[a]Based on the Clopper-Pearson method.
CI, confidence interval; CR, complete response; DOR, duration of response; IRC, independent review committee; NR, not reached; ORR, objective response rate; PD, disease progression; PR, partial response; SD, stable disease.

Coleman RL et al. ESMO 2020. Abstract LBA32.
Coleman RL. *Lancet Oncol.* 2021:S1470-2045(21)00056-5.

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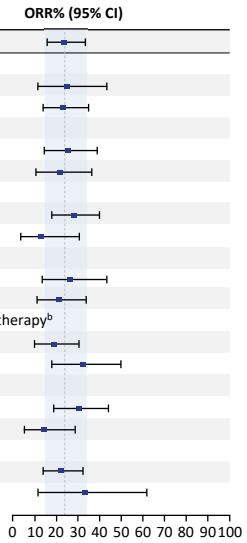
ORR Subgroup Analysis

Subgroup	n/N	% (95% CI)
Overall	24/101	24 (15.9–33.3)
Histology		
Nonsquamous	8/32	25 (11.5–43.4)
Squamous	16/69	23 (13.9–34.9)
Prior cisplatin + radiation		
Yes	14/55	26 (14.7–39.0)
No	10/46	22 (10.9–36.4)
Prior lines of systemic regimen		
1 line	20/71	28 (18.1–40.1)
2 lines	4/30	13 (3.8–30.7)
Response to last systemic regimen[a]		
Yes	10/38	26 (13.4–43.1)
No	12/57	21 (11.4–33.9)
Bevacizumab in combination with chemotherapy doublet as 1L therapy[b]		
Yes	12/64	19 (10.1–30.5)
No	12/37	32 (18.0–49.8)
ECOG performance status		
0	18/59	31 (19.2–43.9)
1	6/42	14 (5.4–28.5)
Region		
European Union	19/86	22 (13.9–32.3)
United States	5/15	33 (11.8–61.6)



Responses generally consistent across subgroups regardless of:

- **Tumor histology**
- **Responses to prior systemic regimen**
- **Doublet chemotherapy with bevacizumab as 1L treatment**

Coleman RL et al. ESMO 2020. Abstract LBA32.
Coleman RL. *Lancet Oncol.* 2021:S1470-2045(21)00056-5.

Data cutoff: February 06, 2020. Median duration of follow-up: 10.0 months. The vertical line indicates 24%, which was the ORR of the entire study cohort.
[a]Response to last systemic regimen was not available for 6 subjects. [b]The term chemotherapy doublet includes either paclitaxel plus cisplatin or carboplatin or paclitaxel plus topotecan.
1L, first-line; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate.

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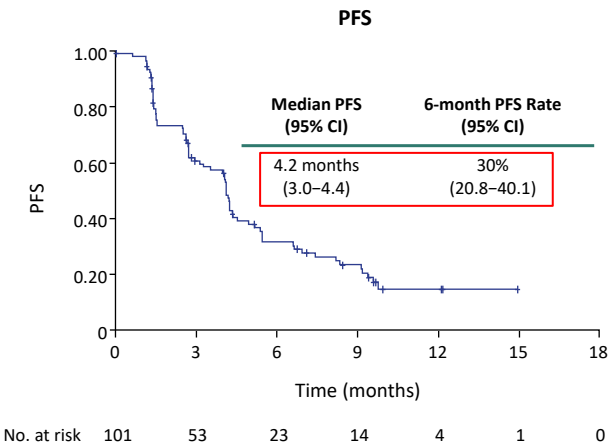
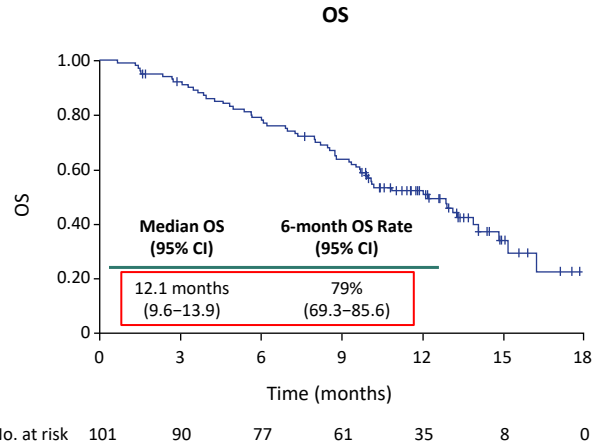
PFS by IRC Assessment and OS





Data cutoff: February 06, 2020. Median duration of follow-up: 10.0 months.
CI, confidence interval; OS, overall survival; PFS, progression-free survival.

Coleman RL et al. ESMO 2020. Abstract LBA32.
Coleman RL. *Lancet Oncol.* 2021:S1470-2045(21)00056-5.

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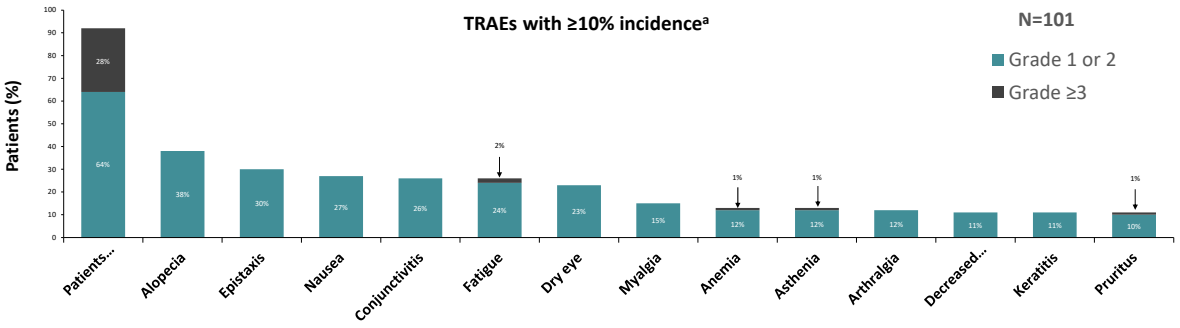
Most Common TRAEs with Tisotumab Vedotin



- **Most TRAEs were grade 1 or 2 and no new safety signals were reported**
- **One death due to septic shock was considered by the investigator to be related to therapy[b]**

Data cutoff: February 06, 2020. Median duration of follow-up: 10.0 months. Median duration of treatment: 4.2 months (range, 1–16).
[a]Any-grade AEs included if ≥10%. [b]Three treatment-emergent deaths unrelated to therapy included one case of ileus and two with unknown causes.
TRAE, treatment-related adverse event.

Coleman RL et al. ESMO 2020. Abstract LBA32.
Coleman RL. *Lancet Oncol.* 2021:S1470-2045(21)00056-5.

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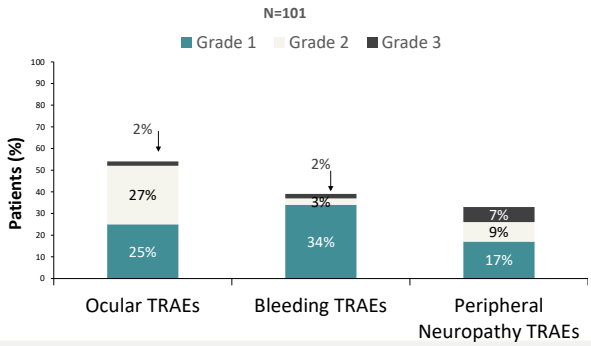
Prespecified AEs of Interest of Tisotumab Vedotin

Ocular,[a] bleeding,[b] and peripheral neuropathy[c] TRAEs



	Ocular	Bleeding	Peripheral Neuropathy
Time to onset (median, months)	1.4	0.3	3.1
Events resolved, %	86	90	21
Time to resolution[d] (median, months)	0.7	0.5	0.6

- **Ocular AEs were mostly mild to moderate, resolved, and were manageable with an eye care plan**
- **Most bleeding events were grade 1 epistaxis (28%) of which majority resolved**
- **Most peripheral neuropathy events (known MMAE-related toxicity) were grade 1 and manageable with dose modifications; resolution was limited by follow-up period**

Data cutoff: February 06, 2020. Median duration of follow-up: 10.0 months.
[a]Any ocular SMQ (conjunctival disorders SMQ, corneal disorders SMQ, scleral disorders SMQ, retinal disorders SMQ, periorbital and eyelid disorders SMQ, ocular infections SMQ, optic nerve disorders SMQ, glaucoma SMQ, lacrimal disorders SMQ, and eye disorders SMQ). [b]Hemorrhage SMQ. [c]Peripheral neuropathy SMQ. [d]Assessment limited by the protocol-defined follow-up period for AE of only 30 days after the last dose.
AE, adverse event; MMAE, monomethyl auristatin E; SMQ, standardized MedDRA queries; TRAE, treatment-related adverse events.

Coleman RL et al. ESMO 2020. Abstract LBA32.
Coleman RL. *Lancet Oncol.* 2021:S1470-2045(21)00056-5.

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Bringing TV to the Clinic

- FDA filing of the tisotumab vedotin BLA (Biologics License Application) for accelerated approval announced in April 21
- Under the PDUFA (Prescription Drug User Fee Act), the FDA has set a target action date 10 October 21 (priority review)

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ENGOT cx12/GOG-3057/innovaTV 301: Schema

Phase 3, randomized trial of Tisotumab Vedotin vs Investigator's choice chemotherapy in 2nd or 3rd line recurrent cervical cancer

BGOG ENGOT European Network of Gynaecological Oncological Trial groups GOG Gynecologic Oncology Group

Primary endpoints: Overall survival
Secondary endpoints: PFS (Inv), Confirmed ORR (Inv), Safety, PRO, TTR, DOR
Exploratory endpoints: PK, biomarkers

- **Progressed during or after 1L chemo of taxane/platin or tax/topo w/wo Bev for metastatic/ recurrent cxca**
- **1 or 2 prior lines for metastatic or recurrent disease**
- **Measurable disease**

1:1
R
N= 482

Tisotumab Vedotin 2 mg/kg Q3W

Investigator's choice chemo

Options (provided by Sponsor, if needed):
- Topotecan 1,5 mg/m² d1-5 q3wks*
- Irinotecan 100 or 125 mg/m² d1,8,15,22 q6wks*
- Gemcitabine 1000 mg/m² d1,8 q3wks*
- Vinorelbine 30 mg/m² d1,8 q3wks*
- Pemetrexed 500 mg/m² d1 q3wks*

Imaging: q 6 wks for 30 wks, then q 12 wks until radiographic PD

OS

Stratification:
- ECOG (0 vs 1)
- Region
- Prior PD-1 or PD-L1 therapy Y/N
- Prior Bev Y/N

Planned No. of patients: 482

https://www.clinicaltrials.gov/ct2/show/NCT04697628

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Tisotumab Vedotin + Bevacizumab or Pembrolizumab or Carboplatin in Recurrent/Metastatic Cervical Cancer: Phase 1b/2 ENGOT-Cx8/GOG-3024/innovaTV 205 Study Dose-Escalation Results

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Phase 1b/2 ENGOT-Cx8/GOG-3024/innovaTV 205: Design of Dose-Escalation (Part 1b) and Objectives

- ≥18 years of age with recurrent or metastatic cervical cancer
- Measurable disease at baseline per RECIST v1.1
- Progressed on/after or were ineligible/intolerant to standard-of-care
- ECOG performance status of 0 or 1 and life expectancy ≥3 months

Arm A TV + Bevacizumab	Arm B TV + Pembrolizumab	Arm C TV + Carboplatin
DL1 (n = 3): TV 1.3 mg/kg + Bevacizumab 7.5 mg/kg	DL1 (n = 6): TV 1.3 mg/kg + Pembrolizumab 200 mg	DL1 (n = 6): TV 1.3 mg/kg + Carboplatin AUC 5
DL2 (n = 3): TV 1.3 mg/kg + Bevacizumab 15 mg/kg	DL2 (n = 7): TV 2.0 mg/kg + Pembrolizumab 200 mg	DL2 (n = 7): TV 2.0 mg/kg + Carboplatin AUC 5
DL3 (n = 9): TV 2.0 mg/kg + Bevacizumab 15 mg/kg		

Primary Objective: To establish the maximum tolerated dose (MTD) and recommended phase 2 dosing (RP2D) of TV + bevacizumab (Arm A) or pembrolizumab (Arm B) or carboplatin (Arm C) all given Q3W

Secondary Objectives: Evaluation of safety and tolerability, antitumor activity, durability of tumor response, clinical efficacy including survival outcomes, and the pharmacokinetics and immunogenicity of TV combinations

AUC, area under the curve; DL, dose level; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; Q3W, every 3 weeks; TV, tisotumab vedotin.
Drugs administered IV on day 1 of 21-day cycle. Patients were treated for at least 2 cycles to evaluate DLTs.

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Baseline Demographics and Clinical Characteristics

	Arm A: TV/Bev (N=15)	Arm B: TV/Pembro (N=13)	Arm C: TV/Carbo (N=13)
Age, median (range), years	46.0 (30–62)	45.0 (32–75)	52.0 (35–65)
ECOG performance status, n (%)			
0	13 (86.7)	8 (61.5)	9 (69.2)
1	2 (13.3)	5 (38.5)	4 (30.8)
Histology, n (%)			
Squamous	8 (53.3)	7 (53.8)	6 (46.2)
Adenocarcinoma	7 (46.7)	6 (46.2)	6 (46.2)
Adenosquamous	0	0	1 (7.7)
Prior lines of systemic treatment*, n (%)			
0	1 (6.7)	0	0
1	6 (40.0)	5 (38.5)	5 (38.5)
2	6 (40.0)	4 (30.8)	4 (30.8)
3	1 (6.7)	3 (23.1)	2 (15.4)
4	1 (6.7)	1 (7.7)	2 (15.4)
Bevacizumab plus chemotherapy doublet as first-line therapy#, n (%)			
Yes	6 (40.0)	6 (46.2)	4 (30.8)
No	9 (60.0)	7 (53.8)	9 (69.2)

*In the metastatic or recurrent setting;
paclitaxel + cisplatin/carboplatin or paclitaxel + topotecan
Bev, bevacizumab; Carbo, carboplatin; ECOG, Eastern Cooperative Oncology Group; pembro, pembrolizumab; TV, tisotumab vedotin

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Patient Disposition

- At the time of data cutoff (March 1, 2021) the median duration of followup was 8.6 (5 – 20) months in Arm A, 16.0 (0 – 22) months in Arm B, and 12.5 (0 – 20) months in Arm C
- No patients discontinued from the study due to pregnancy, loss to follow-up, poor/non-compliance, sponsor decision, patient request, COVID-19 or other reasons
  - The most common reason for discontinuation of study treatment was disease progression

	Arm A: TV/Bev (N=15)	Arm B: TV/Pembro (N=13)	Arm C: TV/Carbo (N=13)
Patients with ongoing treatment	9 (60.0)	1 (7.7)	2 (15.4)
Patients who discontinued treatment	6 (40.0)	12 (92.3)	11 (84.6)
Radiographical PD	6 (40.0)	7 (53.8)	8 (61.5)
Death	0	1 (7.7)	1 (7.7)
AEs	0	2 (15.4)	2 (15.4)
Withdrawal of consent	0	1 (7.7)	0
Clinical PD	0	1 (7.7)	0

AE, adverse event; Bev, bevacizumab; Carbo, carboplatin; PD, progressive disease; Pembro, pembrolizumab; TV, tisotumab vedotin.

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Safety Summary

- AEs of special interest with TV included ocular adverse events, peripheral neuropathy, and bleeding and were mostly grade 1 or 2
- Serious AEs related to TV occurred in 3 patients each in Arms B and C
- No patients in Arms A and B had grade 4 events related to TV; 3 patients in Arm C had grade 4 events related to TV
- No fatal AEs were reported

	Arm A: TV/Bev (N=15)	Arm B: TV/Pembro (N=13)	Arm C: TV/Carbo (N=13)
Patients with at least one TEAE, n (%)			
AE	15 (100.0)	13 (100.0)	13 (100.0)
AE related to TV	15 (100.0)	12 (92.3)	12 (92.3)
AESI for TV, n (%)			
Ocular AE	12 (80.0)	7 (53.8)	8 (61.5)
Peripheral neuropathy	9 (60.0)	7 (53.8)	3 (23.1)
Bleeding AE	11 (73.3)	6 (46.2)	7 (53.8)
Grade ≥3 AE, n (%)	5 (33.3)	12 (92.3)	8 (61.5)
Grade ≥3 AE related to TV	2 (13.3)	8 (61.5)	7 (53.8)
SAE, n (%)	3 (20.0)	8 (61.5)	5 (38.5)
SAE related to TV	0	3 (23.1)	3 (23.1)
Fatal AE, n (%)	0	1 (7.7)	1 (7.7)
Fatal AE related to TV	0	0	0

AE, adverse event; AESI, adverse event of special interest; Bev, bevacizumab; Carbo, carboplatin; pembro, pembrolizumab; PN, peripheral neuropathy; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TV, tisotumab vedotin.

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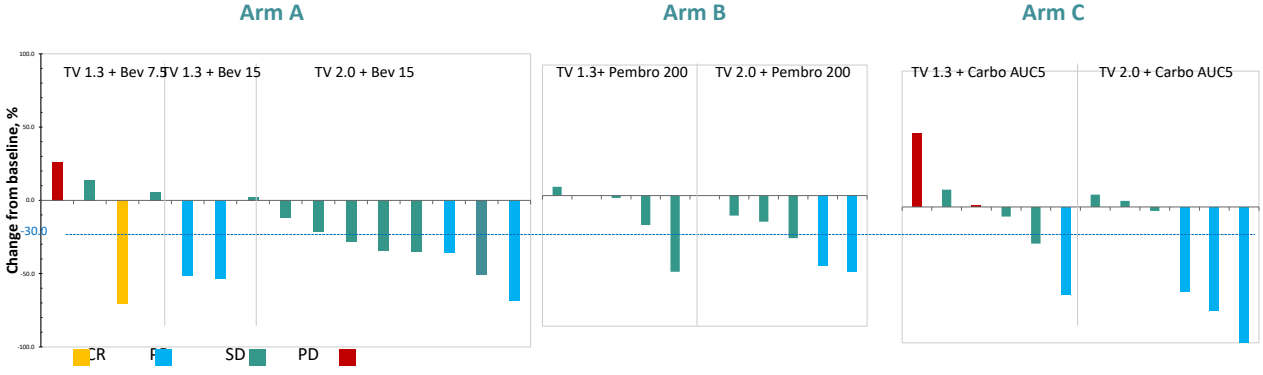
Tumor Response

- Compared to baseline, the tumors in most patients receiving TV plus bevacizumab, pembrolizumab, or carboplatin decreased in size, and many showed a decrease >30%
- The median time to response was 2.8, 2.1, and 1.5 months in Arms A, B, and C, respectively



AUC, area under the curve; Bev, bevacizumab; Carbo, carboplatin; CR, complete response; DL, dose level; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; PD, progressive disease; Pembro, pembrolizimab; PR, partial response; SD, stable disease; Q3W, every 3 weeks; TV, tisotumab vedotin.

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Efficacy Summary

- The confirmed ORR was 33.3%, 15.4%, and 30.8% of patients in Arms A, B, and C, respectively

	Arm A: TV/Bev (N=15)	Arm B: TV/Pembro (N=13)	Arm C: TV/Carbo (N=13)
Median follow-up time (months) (range)	8.6 (5–20)	16.0 (0–22)	12.5 (0–20)
Confirmed BOR, n (%)			
CR	1 (6.7)	0	0
PR	4 (26.7)	2 (15.4)	4 (30.8)
SD	9 (60.0)	9 (69.2)	6 (46.2)
PD	1 (6.7)	0	2 (15.4)
Not evaluable	0	2 (15.4)	1 (7.7)
ORR*, n (%) [95% CI#]	5 (33.3) [11.8–61.6]	2 (15.4) [1.9–45.4]	4 (30.8) [9.1–61.4]
DCR, n (%) [95% CI#]	14 (93.3) [68.1–99.8]	11 (84.6) [54.6–98.1]	10 (76.9) [46.2–95.0]
Time to response (months), median (range)	2.8 (1.5–9.8)	2.1 (1.2–2.9)	1.5 (1.2–2.8)
Median DOR (months)	NE	NE	6.5
Median PFS (months)	11.3	5.6	4.4
Median OS (months)	NE	17.1	12.5

*Objective Response Rate is the proportion of patients whose best overall response is either CR or PR according to RECIST v1.1. # Exact 95% two-sided confidence interval using the Clopper-Pearson method
Bev, bevacizumab; BOR, best overall response; Carbo, carboplatin; CI, confidence interval; CR, complete response; DCR, disease control rate [DCR=CR+PR+SD]; DOR, duration of response; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; pembro, pembrolizumab; PR, partial response; SD, stable disease; TV, tisotumab vedotin.

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Tisotumab Vedotin (TV) FDA Biologics License Application for Recurrent or Metastatic Cervical Cancer

- Phase 3 trial: TV vs Chemotherapy in 2-L or 3-L Recurrent Cervical Cancer (GOG 3057/ innovaTV 301)
  - Opened to enrollment Jan 22, 2021
  - N = 482
- Filed Feb 10, 2021
- PDUFA date Oct 10, 2021

https://investor.seagen.com/press-releases/news-details/2021/Seagen-and-Genmab-Announce-U.S.-FDA-Filing-Acceptance-for-Priority-Review-of-Tisotumab-Vedotin-Biologics-License-Application-for-Patients-with-Recurrent-or-Metastatic-Cervical-Cancer/default.aspx

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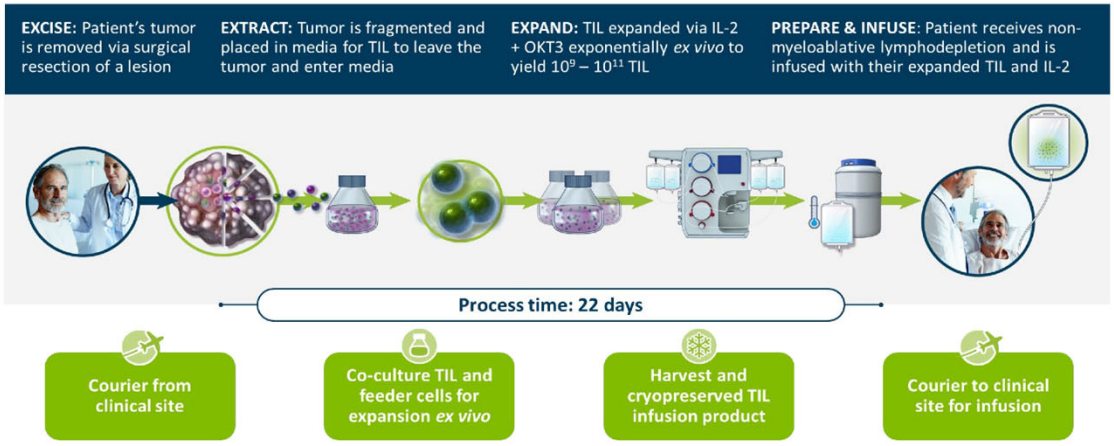
Cryopreserved Autologous TIL (LN-145)



https://www.iovance.com/

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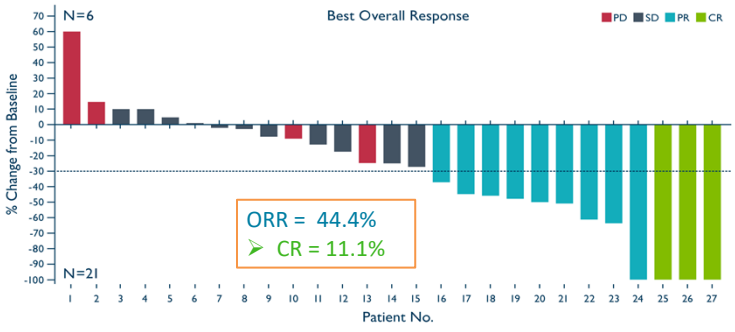
LN-145: Responses and Safety



- 78% of patients had a reduction in tumor burden
- Median follow up is 7.4 months
- Mean number of TLC cells infused: 28 × 10^9
- Median number of IL-2 doses administered was 6.0

Safety

- The AE profile was generally consistent with the underlying advanced disease and in line with lymphodepletion & IL-2 regimens
- Onset of AEs most commonly occurred in the first ~8 days following infusion
  - Frequency of AEs over time is reflective of potential benefit of one time treatment with LN-145

NCT03108495; Jazaeri AA et al. J Clin Onc. 2019;37(15)2538.

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Iovance Biotherapeutics Announces Breakthrough Therapy Designation for LN-145 for Treatment of Advanced Cervical Cancer Patients Who Have Progressed on or After Chemotherapy

- May 22, 2019
  - Announced that the FDA has granted Breakthrough Therapy designation to Iovance TIL therapy candidate LN-145 in recurrent, metastatic, or persistent cervical cancer with disease progression on or after chemotherapy
  - The FDA decision on BTD for LN-145 in advanced cervical cancer was based on clinical data from the ongoing innovaTIL-04 (C-145-04) trial. The company will present the data on June 1, 2019, at the American Society of Clinical Oncology (ASCO) Annual Meeting.
- Pivotal cohort 1 enrolled q4 2020

https://ir.iovance.com/node/10706/pdf
ClinicalTrials.gov Identifier: NCT03108495

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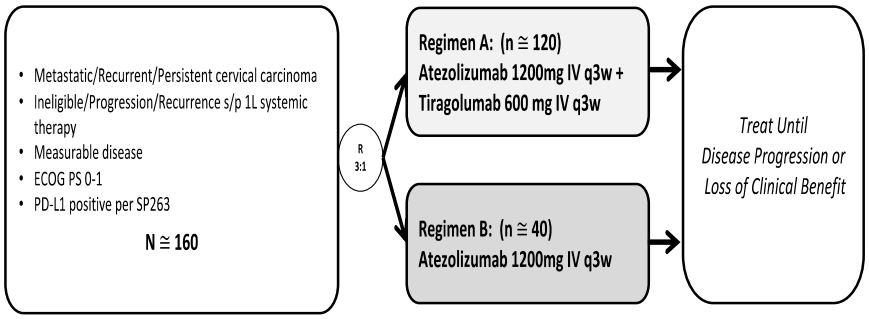
A Study of Tiragolumab (Anti-TGIT) Plus Atezolizumab and Atezolizumab Monotherapy in Participants With Metastatic and/or Recurrent PD-L1–Positive Cervical Cancer (SKYSCRAPER-04)



Stratification factors:
- Prior (cis)RT
- Prior systemic therapy (*de novo*/primary disease vs. persistent/recurrent disease)
- ECOG PS (0 vs. 1)

- Opened: June 2020
- Closed: March 2021
- N = 220
- Sites = 98

ClinicalTrials.gov Identifier: NCT04300647
Accessed March 9, 2021

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Evolving Cervical Cancer Treatment Paradigm

- Cisplatin with radiation (CCRT) 1999
- Platinum + paclitaxel +/- bevacizumab 1-L 2014
- Pembrolizumab 2-L 2018
  - Bastilimab 2021
  - Cemiplimab 2021
- Adding pembrolizumab to 1-L based on KN-826 2021
- Lifileucel (LN-144) cryopreserved TIL in2-L TBD
- Adding durvalumab to CCRT based on CALLA? TBD

Thank you for your attention!

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