Locally Advanced and Recurrent Cervical Cancer: Current Landscape

Brian M. Slomovitz, MD, MS, FACOG

Professor, Florida International University
Director, Gynecologic Oncology and Co-Chair, Cancer Research Committee
Mount Sinai Medical Center
Member, Board of Directors, GOG Foundation
Uterine Cancer Lead, GOG Partners

Thursday, September 9, 2021

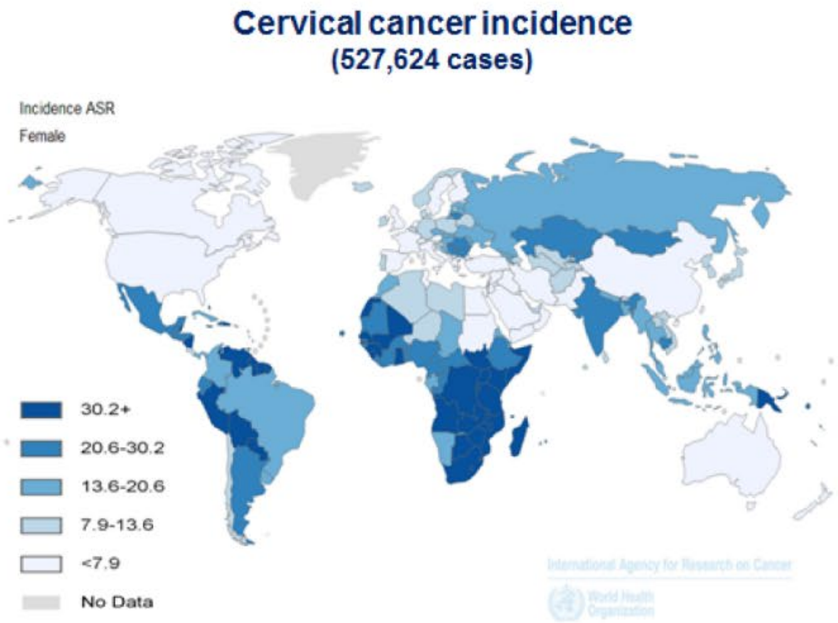
GOG FOUNDATION®
Transforming the standard of care™

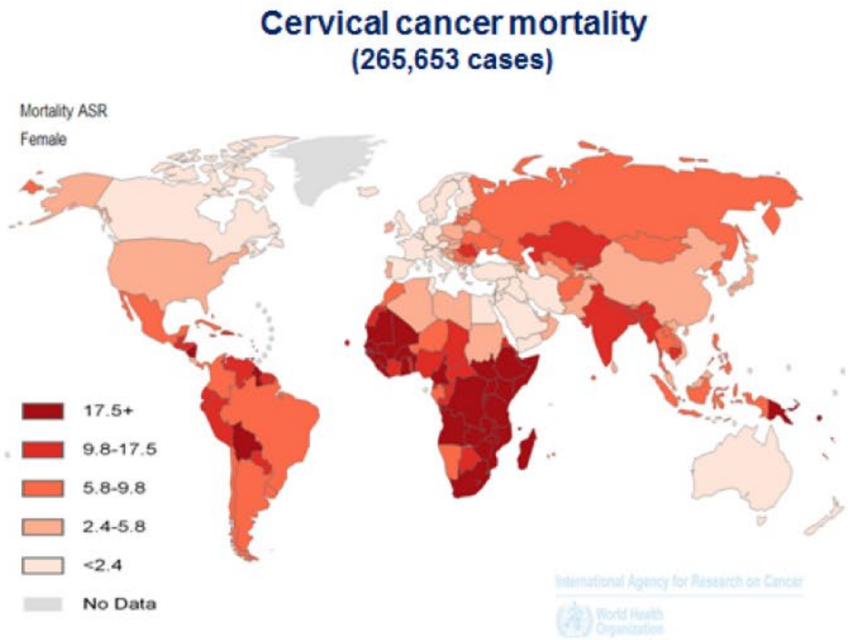
Faculty Disclosure

	No, nothing to disclose
x	Yes, please specify:

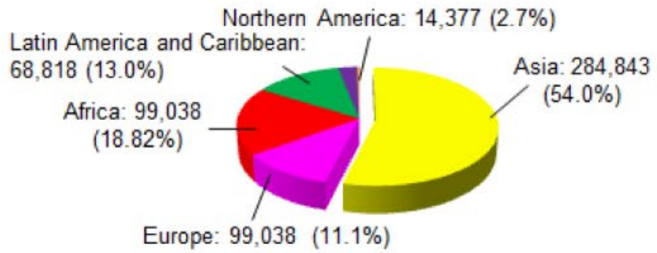
Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Merck		x						
GSK		x						
AstraZeneca		x						
Agenus		x						
GOG Foundation		x						
GNE/Roche		x						
Lill		x		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

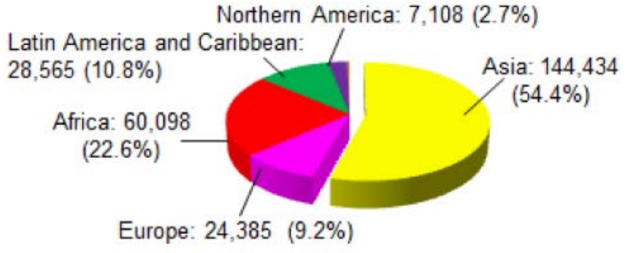
Cervical Cancer is an International Health Concern





Mortality: Incidence ratio: 50%

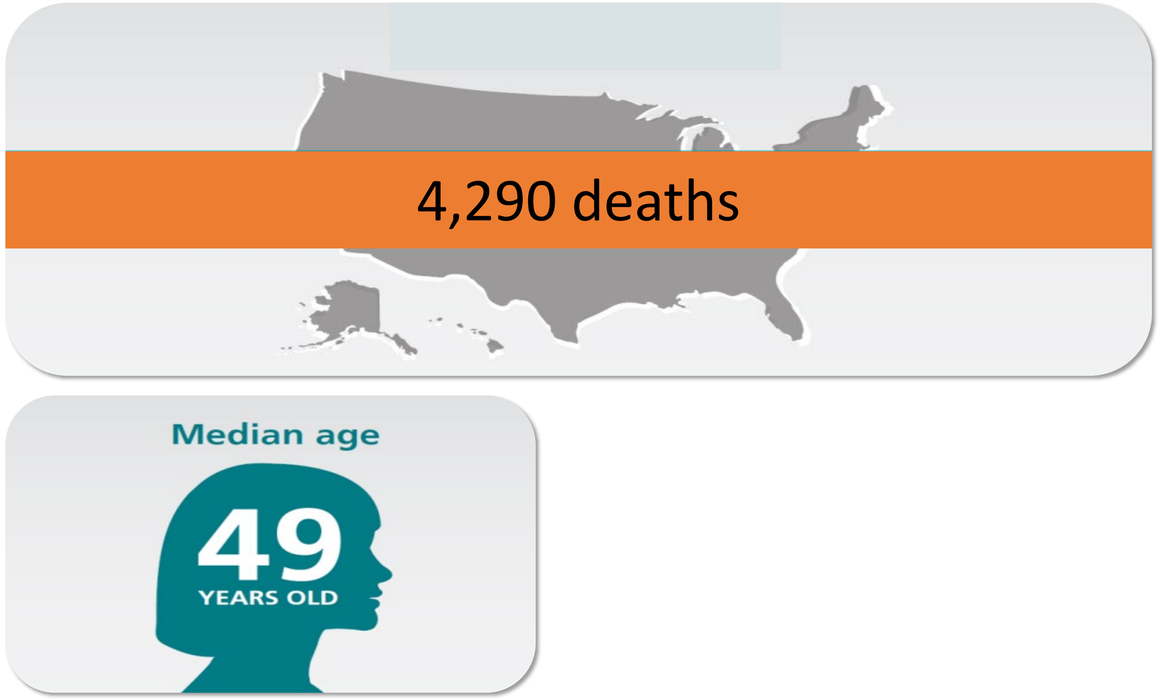




Jung HS et al. J Clin Med. 2015. 4(5): 1126

GOG FOUNDATION

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

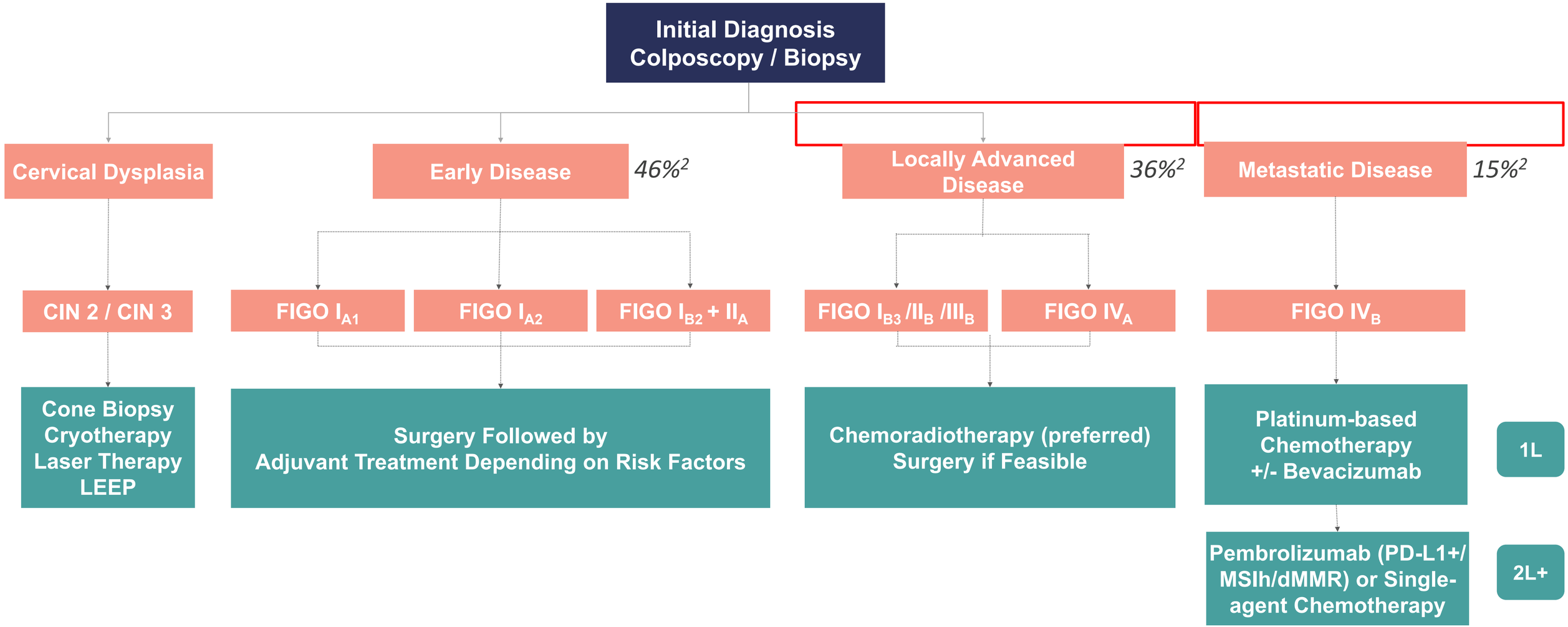
FIGO staging systems: differences between the 2009 and 2018 FIGO staging systems for cervical cancer

	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.

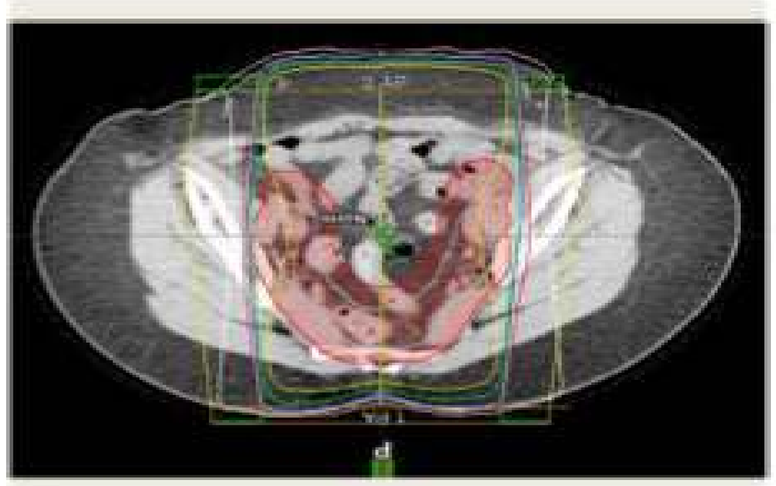
Cervical cancer: summary of treatment

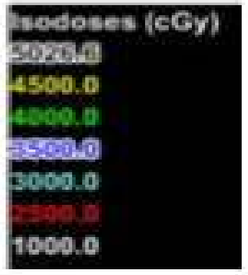


LEEP: Loop Electrosurgical Excision Procedure; PD-L1: Programmed Cell Death Ligand-1; MSIh: Microsatellite Instability High; dMMR: deficient Mismatch Repair

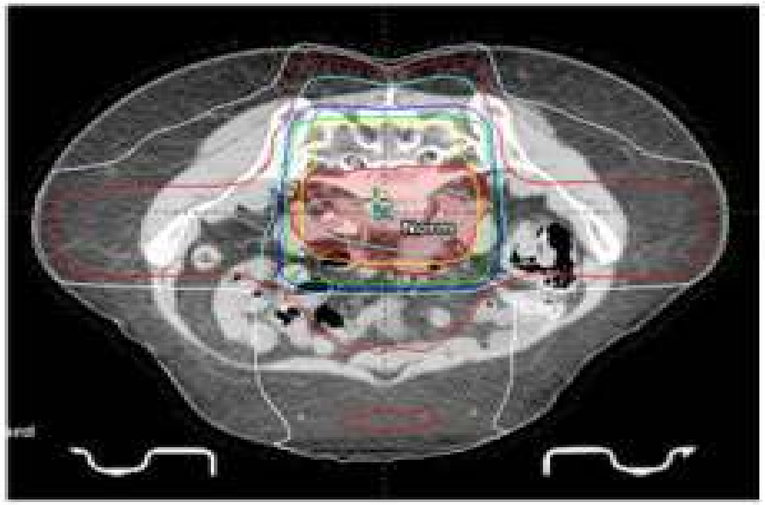
1. National Comprehensive Cancer Network. NCCN Cervical Cancer Guidelines version 1.2021. https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf. Accessed 10 June 2021; 2. National Cancer Institute. SEER Cancer Stat Facts: Cervical Cancer. https://seer.cancer.gov/statfacts/html/cervix.html.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

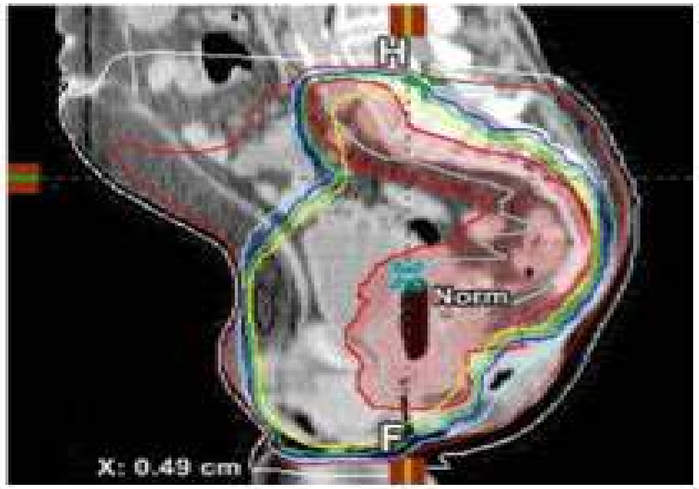
External Beam Radiation



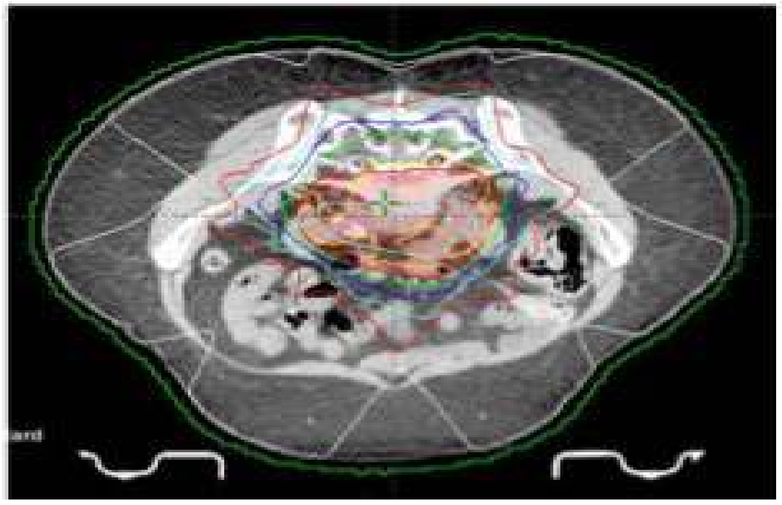


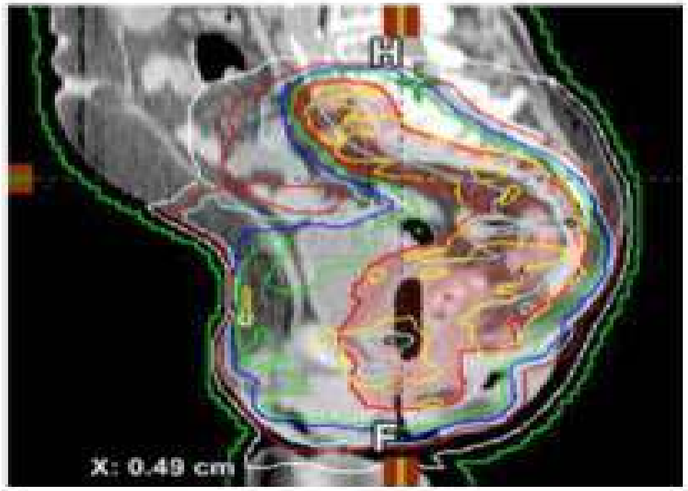
APP/PA Fields





3D Conformal



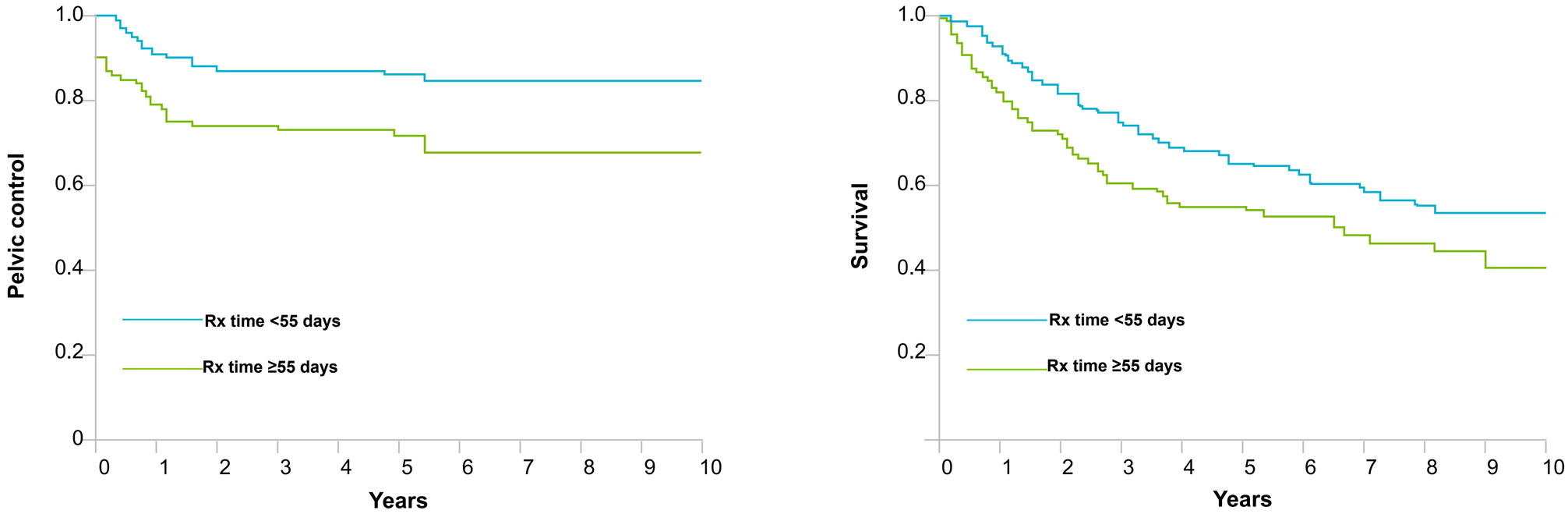


IMRT

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]

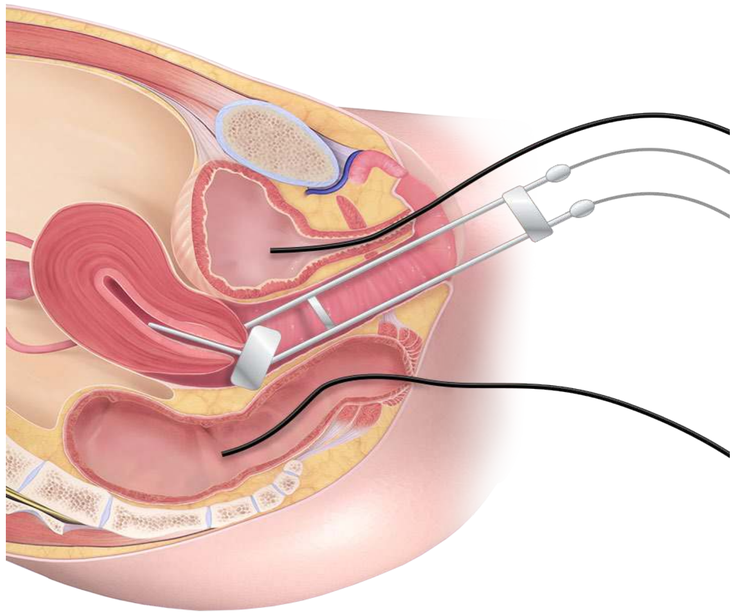
Effect of treatment time on pelvic control and survival[3]



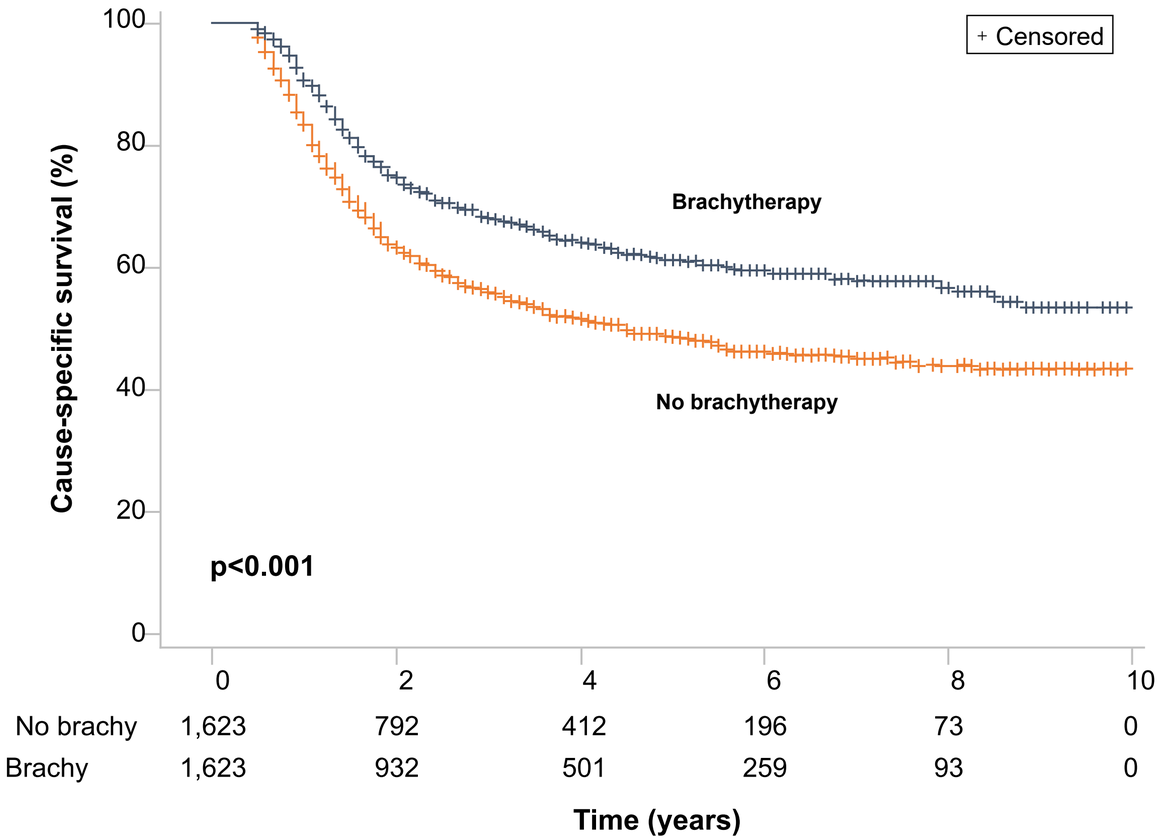
1. Bhatla N, et al. *Int J Gynaecol Obstet* 2018;143:22–36; 2. Song S, et al. *Cancer* 2013;119:325–331; 3. Petereit DG, et al. *Int J Radiat Oncol Biol Phys* 1995;32:1301–1307.

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]



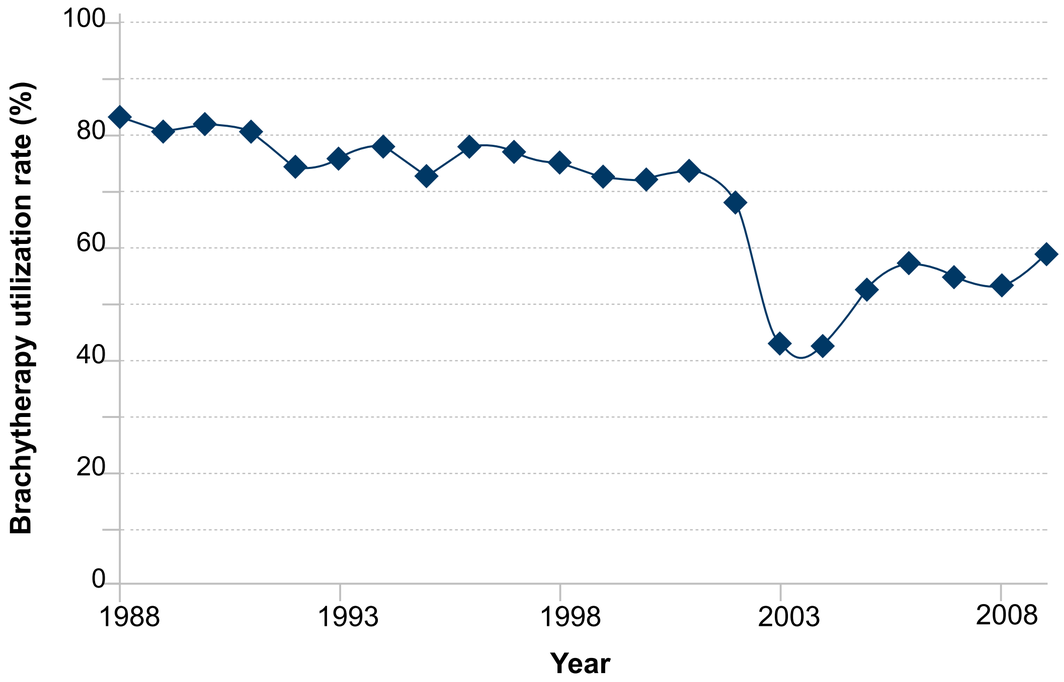
A radioactive source is placed in or near the tumor, which allows for the tumor to receive a concentrated dose while relatively sparing the surrounding normal tissue[1]



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.

Underutilization of Brachytherapy

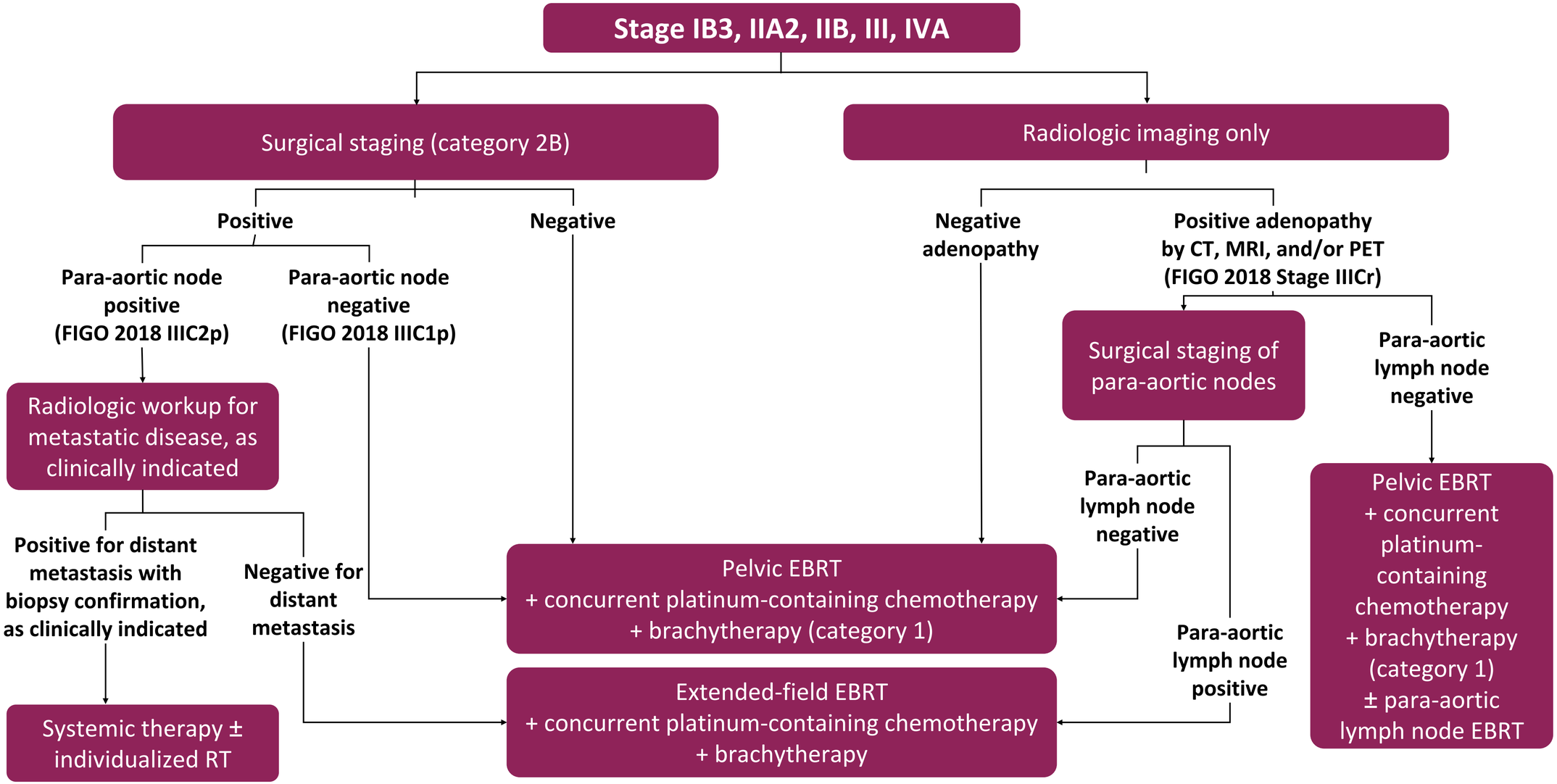
- SEER data shows brachytherapy **utilization decreased from 83% in 1988 to 58% in 2009** ($p<0.001$)[1]
- Brachytherapy treatment was associated with higher 4-year cause-specific survival (64.3% vs 51.5%, $p<0.001$) and overall survival (58.2% vs 46.2%, $p<0.001$)[1]



- 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.

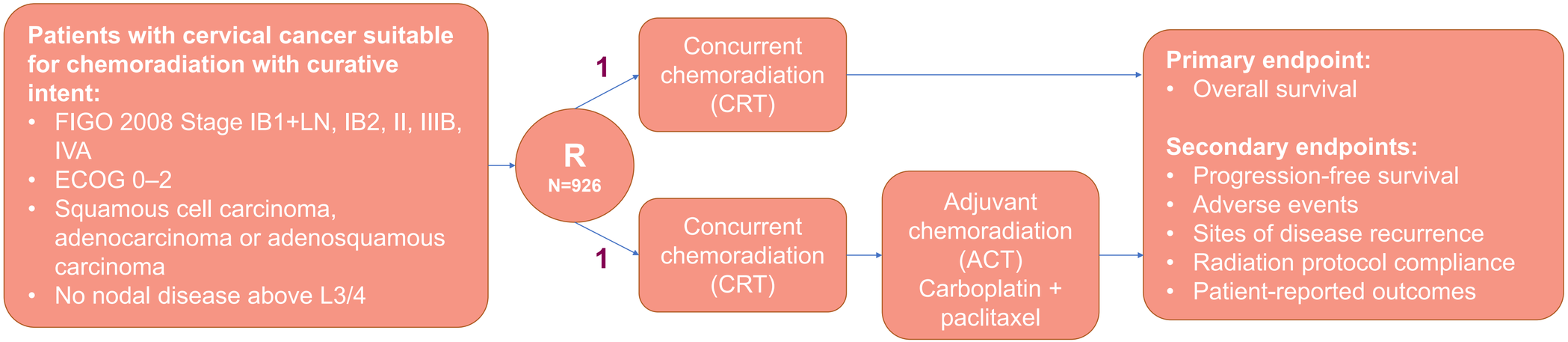
NCCN guidelines[1]



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.

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

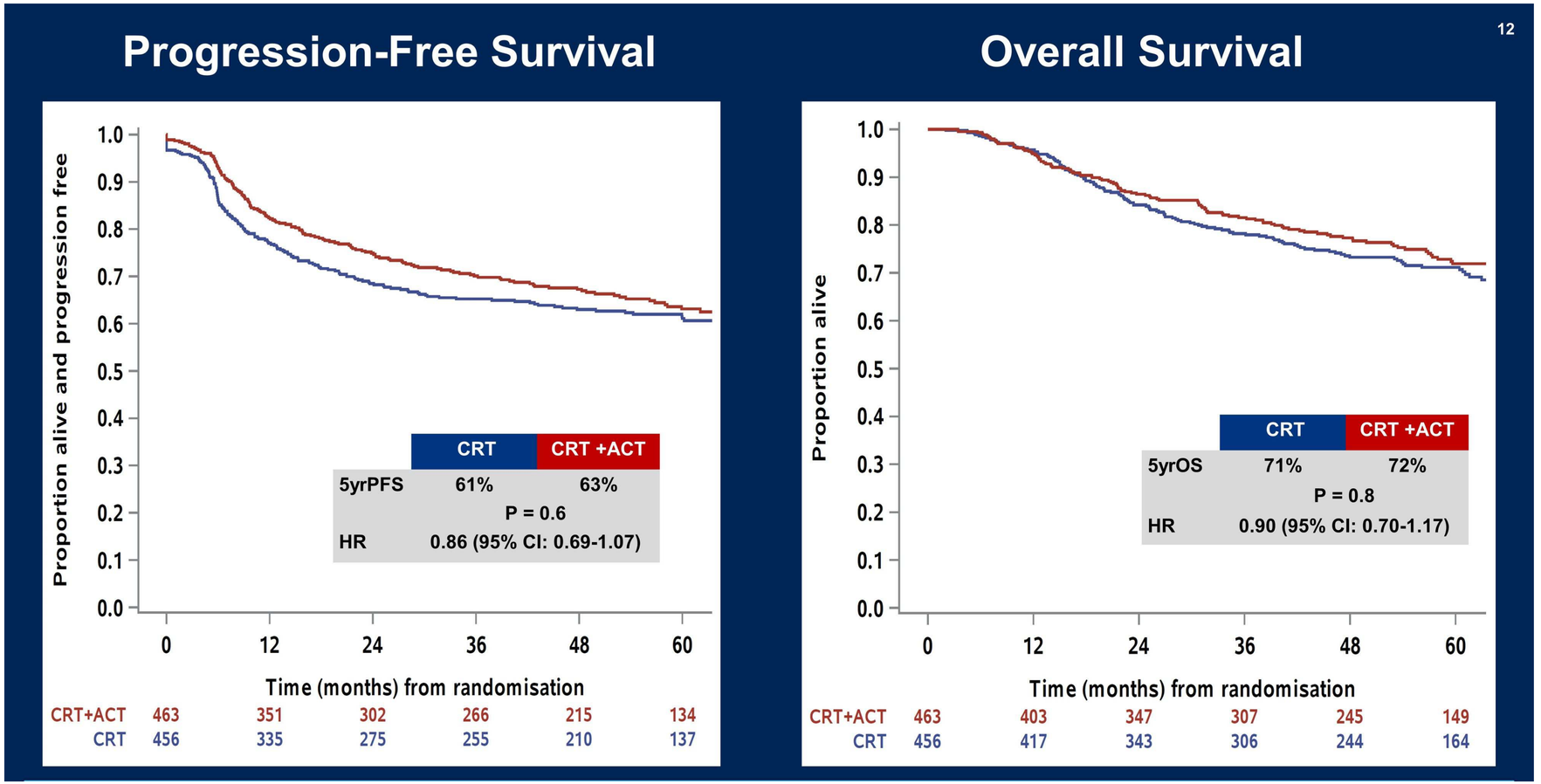
Study schema



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.

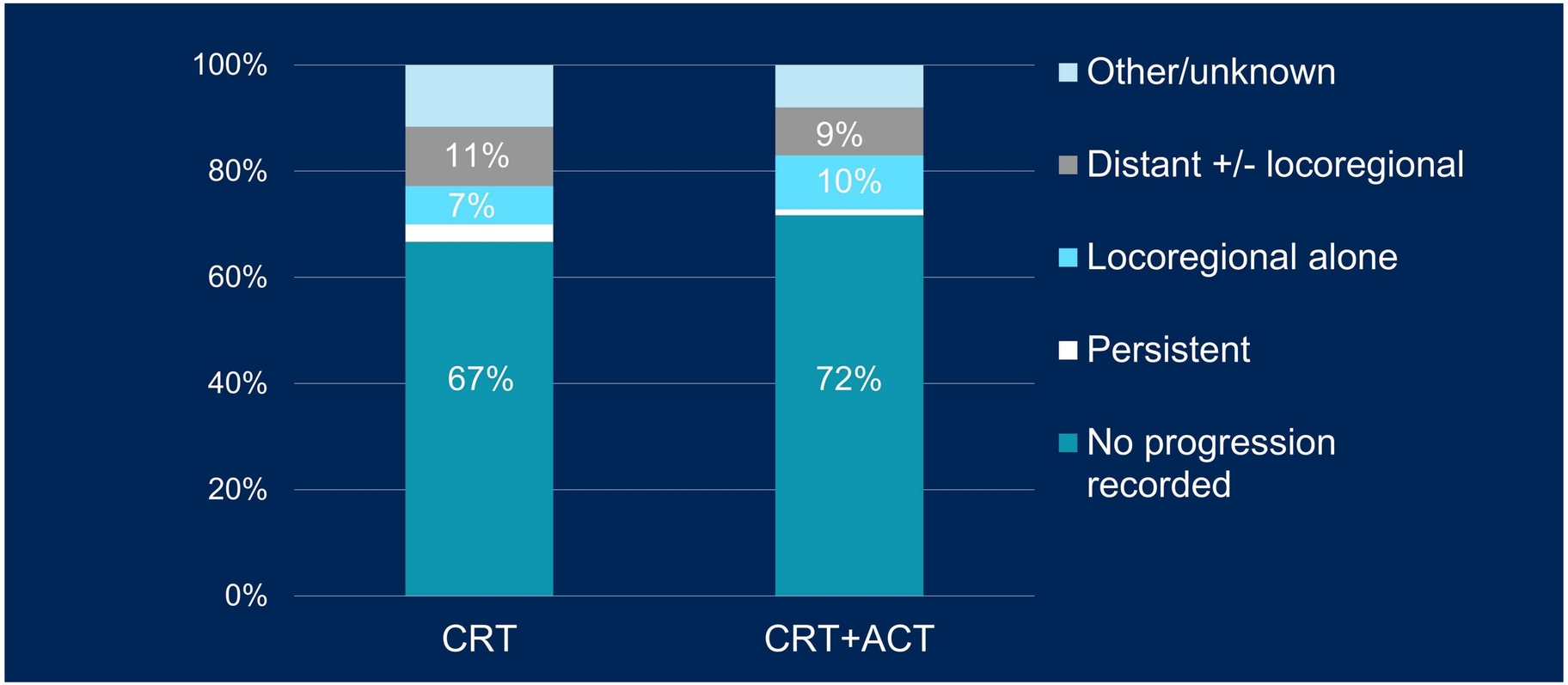
OUTBACK: Key Efficacy Outcomes



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

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

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.

OUTBACK: Sensitivity Analysis

	Survival Rates at 5 years (%)				Hazard ratios from Cox regressions		Interaction P
	CRT	CRT +ACT	Difference (95% CI)	P	(95% CI)	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	

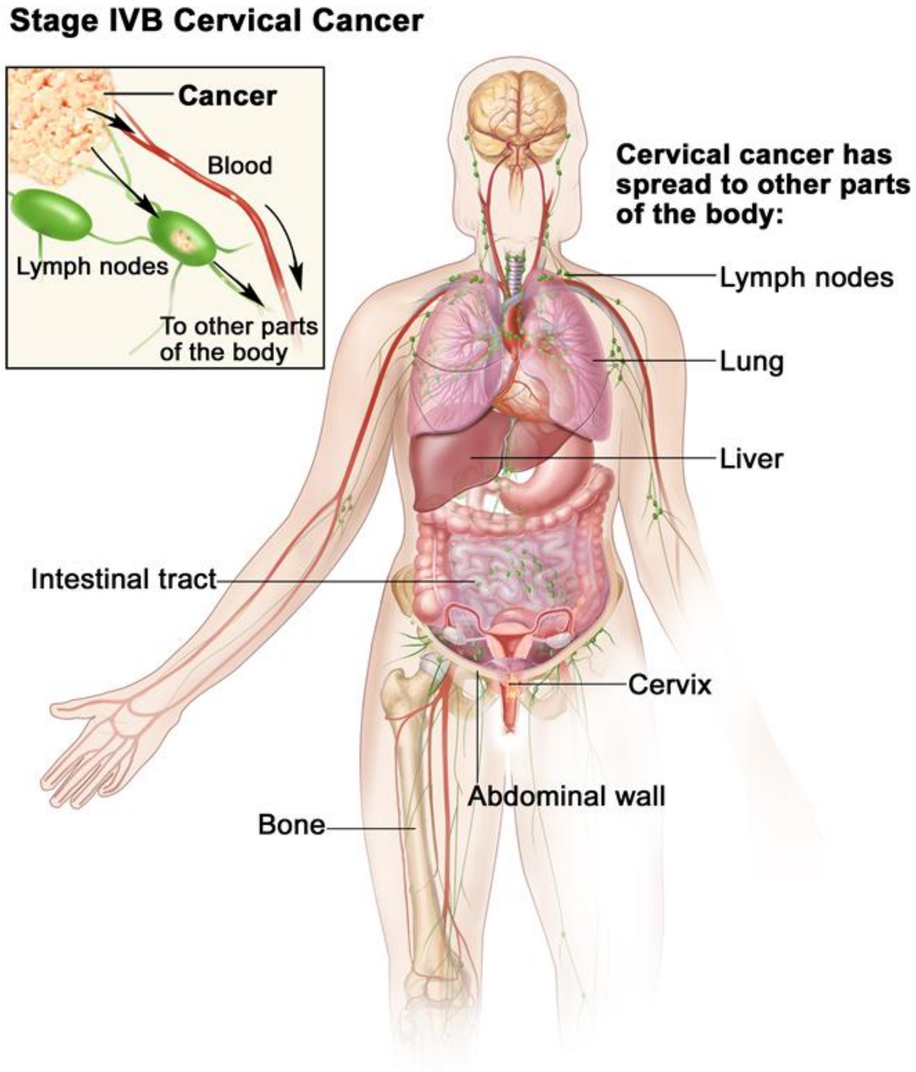
There was an **absolute difference of 3% for OS**, which was not greater than expected by chance alone

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

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

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.

GOG-204: Study Design

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

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

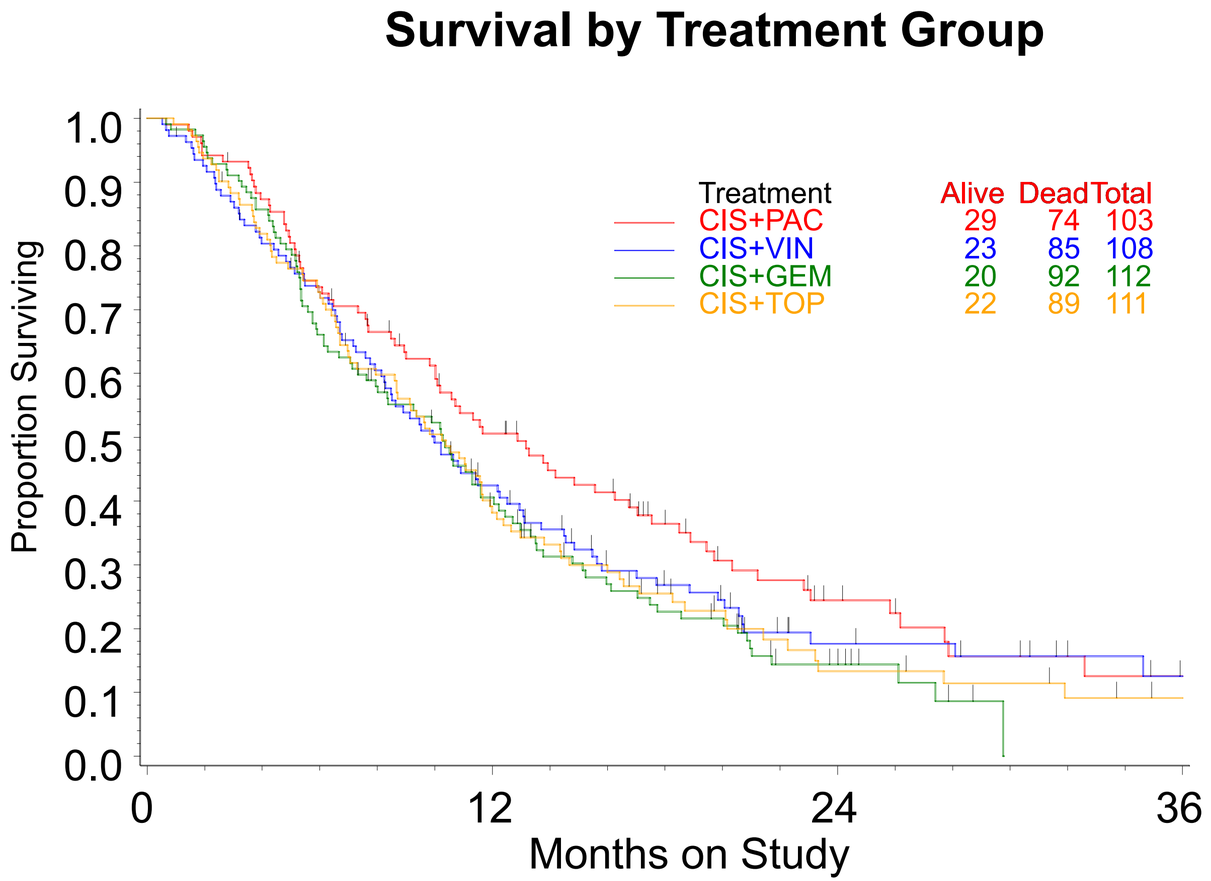
Regimen 4
Topotecan 0.75 mg/m^2 over 30 min days 1, 2, 3 CDDP 50 mg/m^2 IV day 1, q3w, 6 cycles

Quality of life was assessed for all regimens

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

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.

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

GOG FOUNDATION

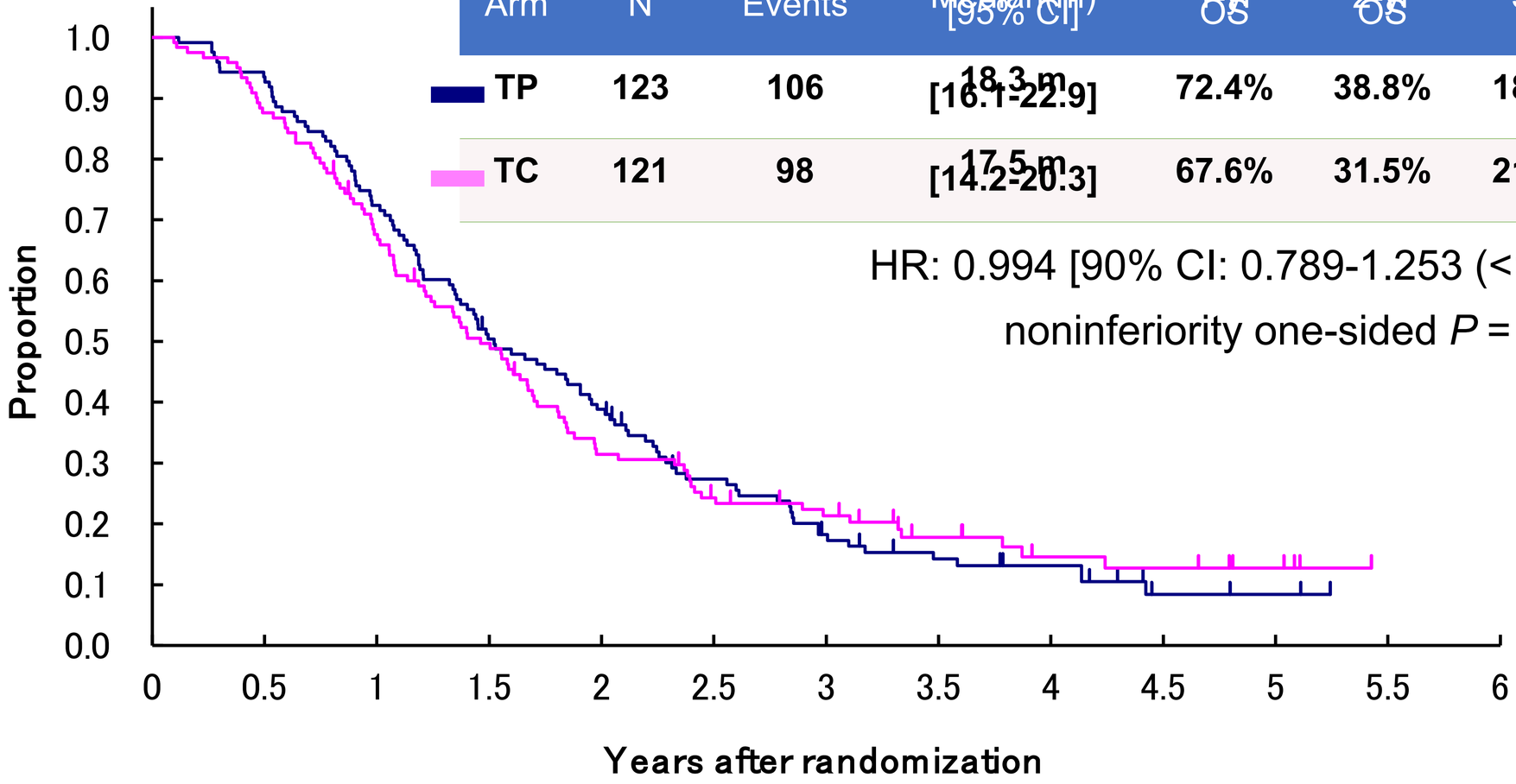
Overall Survival

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.

GOG FOUNDATION®

GOG 240 Schema

Carcinoma of the cervix
- Primary stage IVB
- Recurrent/persistent
- Measureable disease
- GOG PS 0-1
- No prior chemotherapy for recurrence

(N = 452)

Stratification factors:
- **Stage IVB vs recurrent/ persistent disease**
- **Performance status**
- **Prior cisplatin Rx as radiation-sensitizer**

RANDOMIZE

1:1:1:1

I	Paclitaxel 135 or 175 mg/m² IV	Cisplatin 50 mg/m² IV
II	Paclitaxel 135 or 175 mg/m² IV	Cisplatin 50 mg/m² IV + Bevacizumab 15 mg/kg IV
III	Paclitaxel 175 mg/m² IV	Topotecan 0.75 mg/m² d1-3
IV	Paclitaxel 175 mg/m² IV	Topotecan 0.75 mg/m² d1-3 + Bevacizumab 15 mg/kg IV

Chemo alone

q 21 d Rx to PD, toxicity, CR

Chemo + bevacizumab

Activated: 4/6/09 Closed to accrual: 1/3/12	United States, Canada & Spain

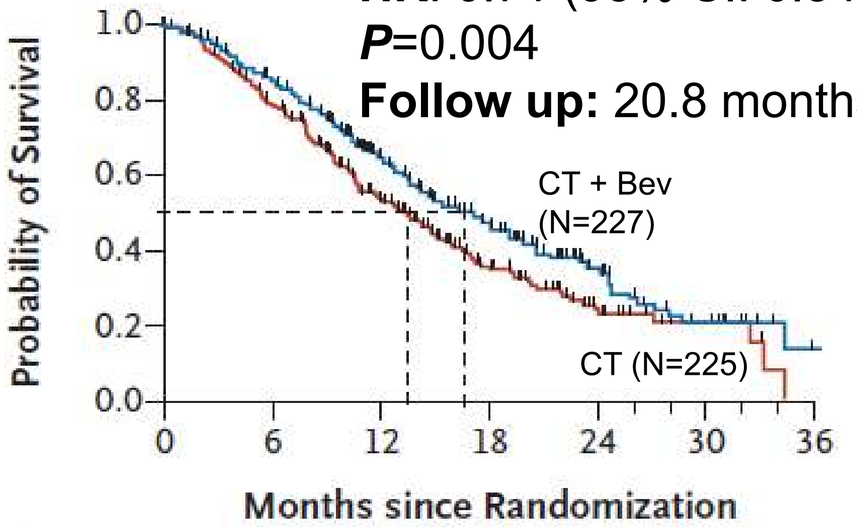
National Institutes of Health. http://clinicaltrials.gov/ct2/show/NCT00803062. Accessed 15 January 2018.

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

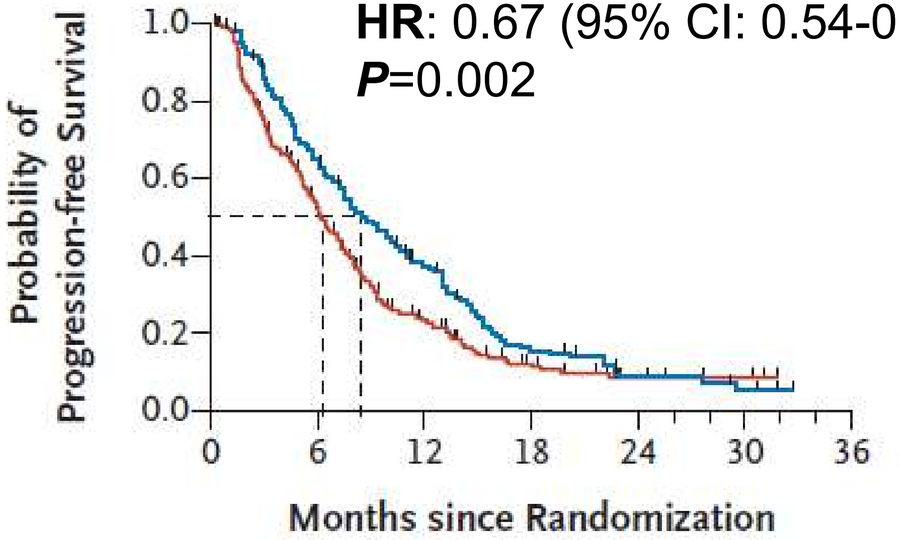


No. at Risk						
Chemotherapy	225	167	94	45	17	8
Chemotherapy +bev	227	184	121	69	30	10

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.

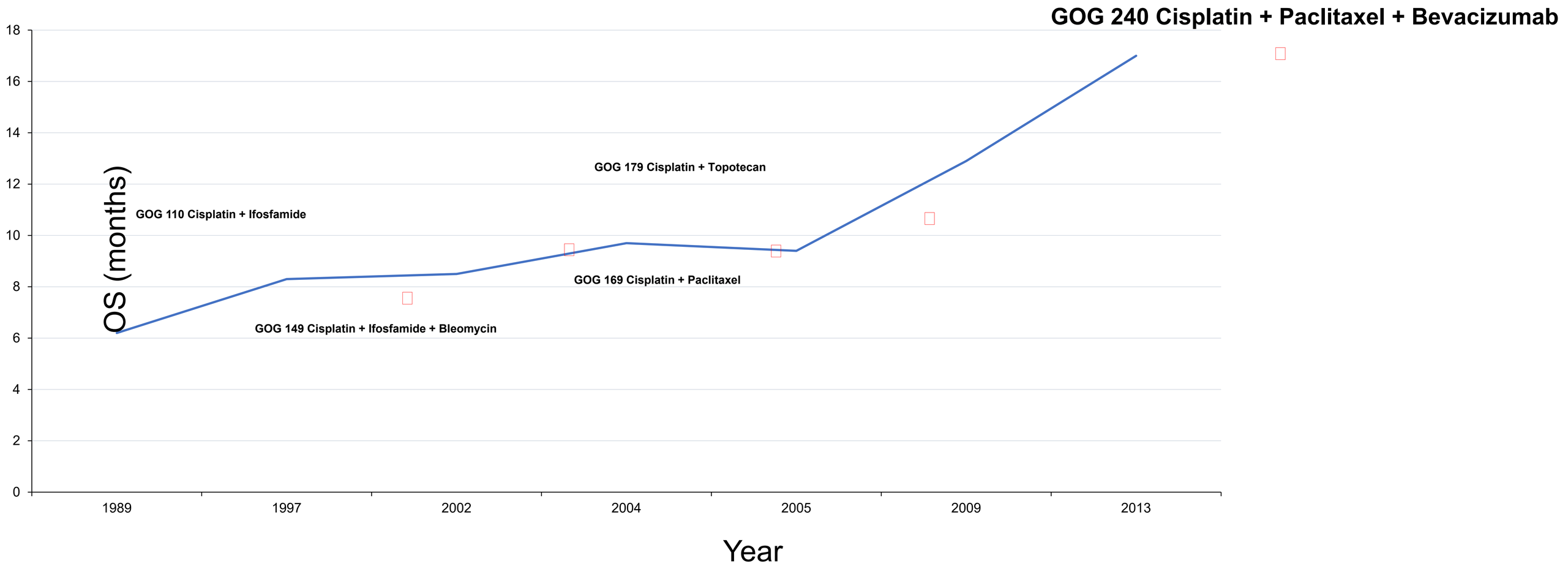
GOG FOUNDATION

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)

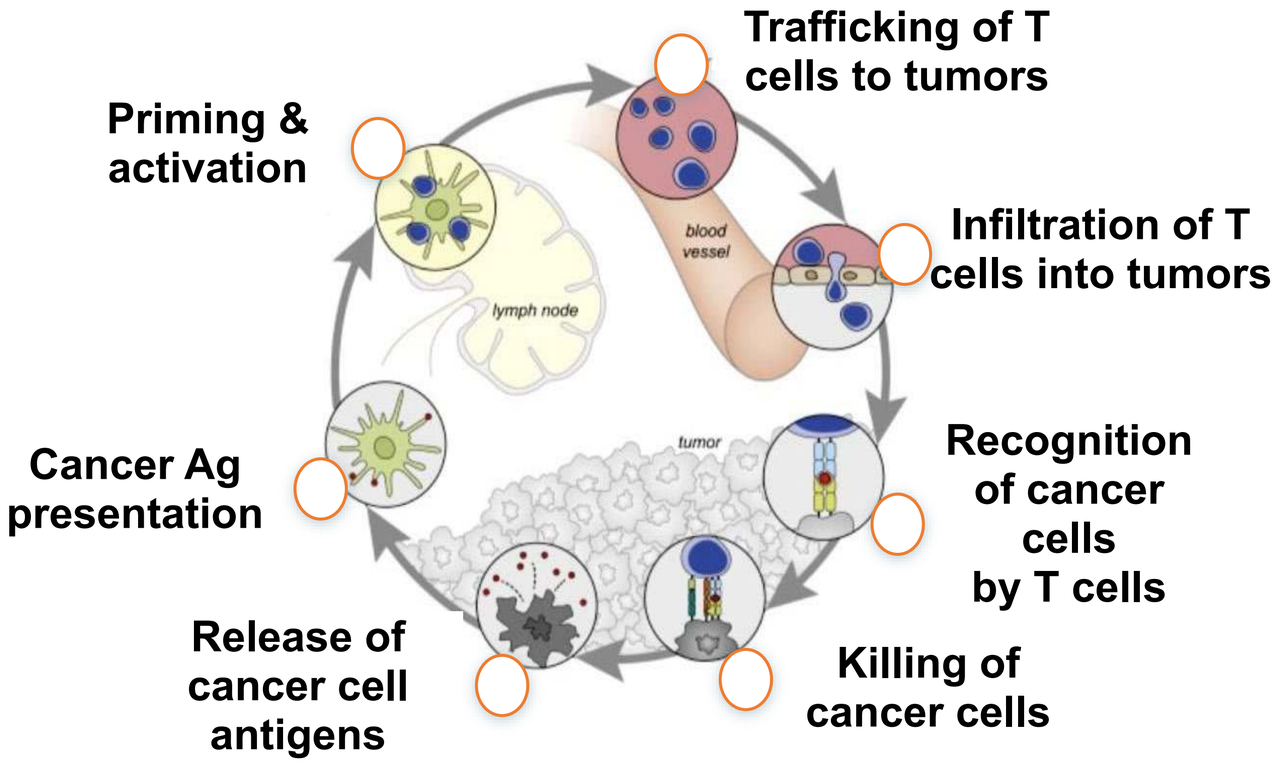
- [a]Excluding fistulas. [b]Fistulas were mainly managed supportively; one patient underwent colostomy, and another received nephrostomy tubes. [c]Hypertension of grade 2 or higher was defined as recurrent or continuous hypertension for a period of more than 254 hours or a symptomatic increase in blood 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.

Improving OS in Recurrent or Metastatic Cervical Cancer
How do we move forward?



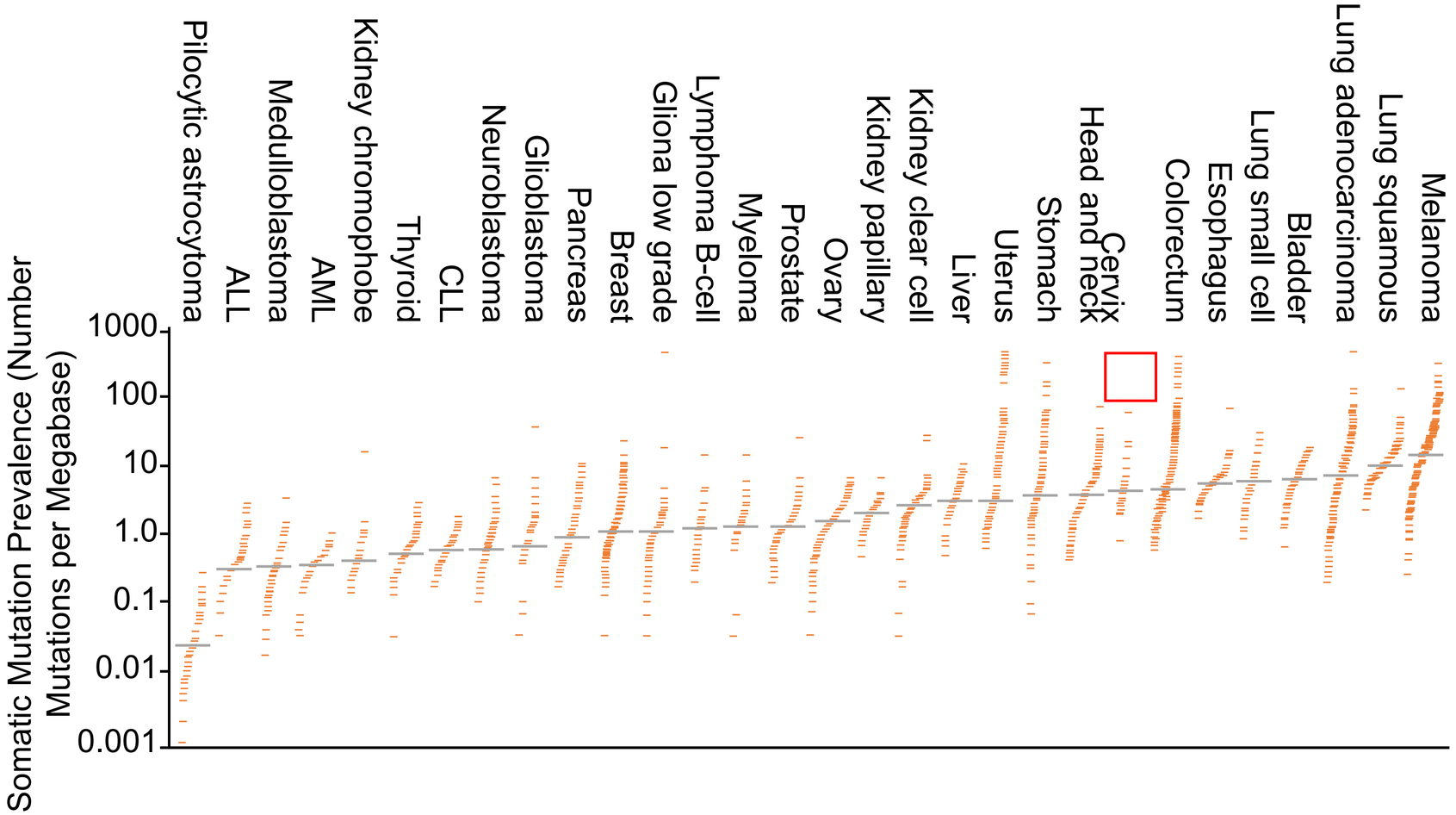
Rationale for Immunotherapy

- 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.

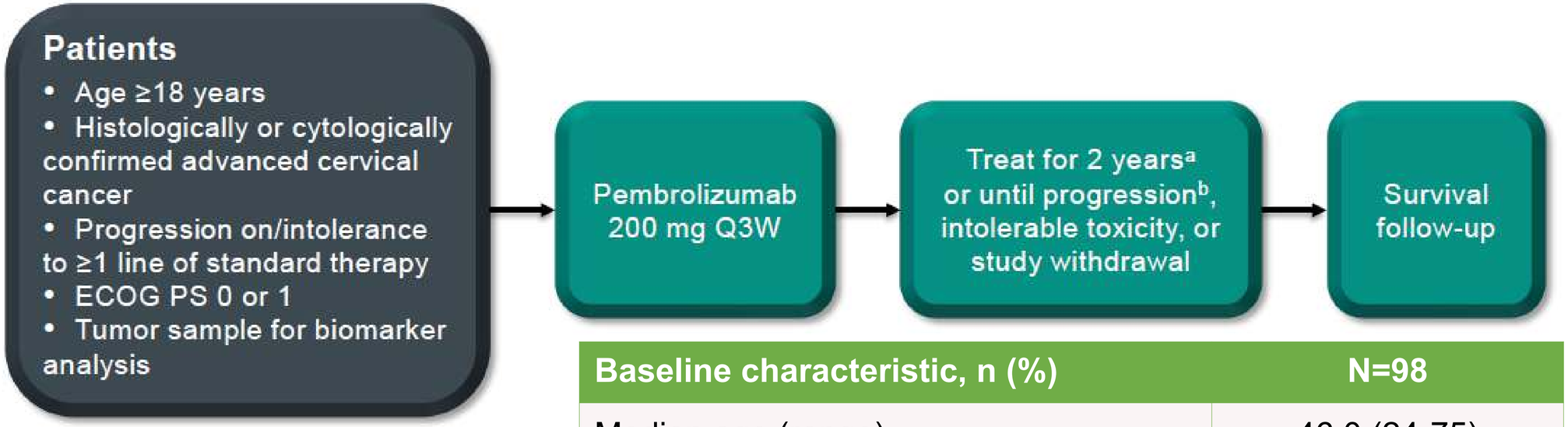
Mutational Burden Compared With Other Tumors



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

GOG FOUNDATION®

KEYNOTE 158: Study Design and Baseline Characteristics



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

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

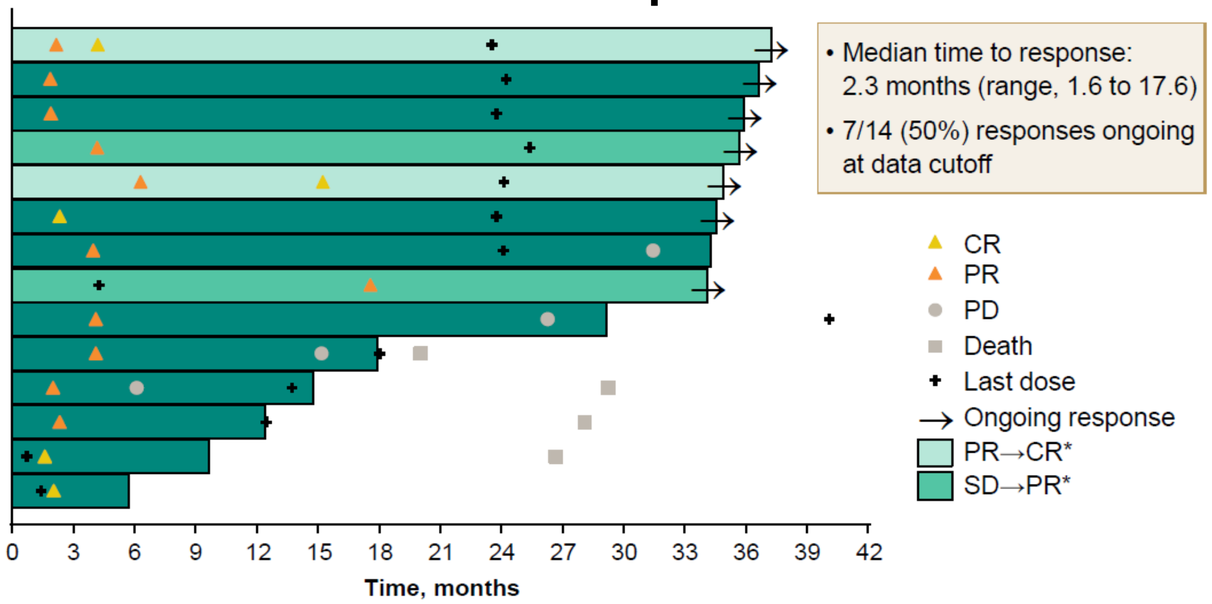
Baseline characteristic, n (%)		N=98
Median age (range)		46.0 (24-75)
ECOG PS 1		64 (65)
PD-L1+ tumor[a]		82 (84)
Number of prior therapies	1	44 (45)
	2	31 (32)
	3	13 (13)
	≥4	8 (8)

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

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



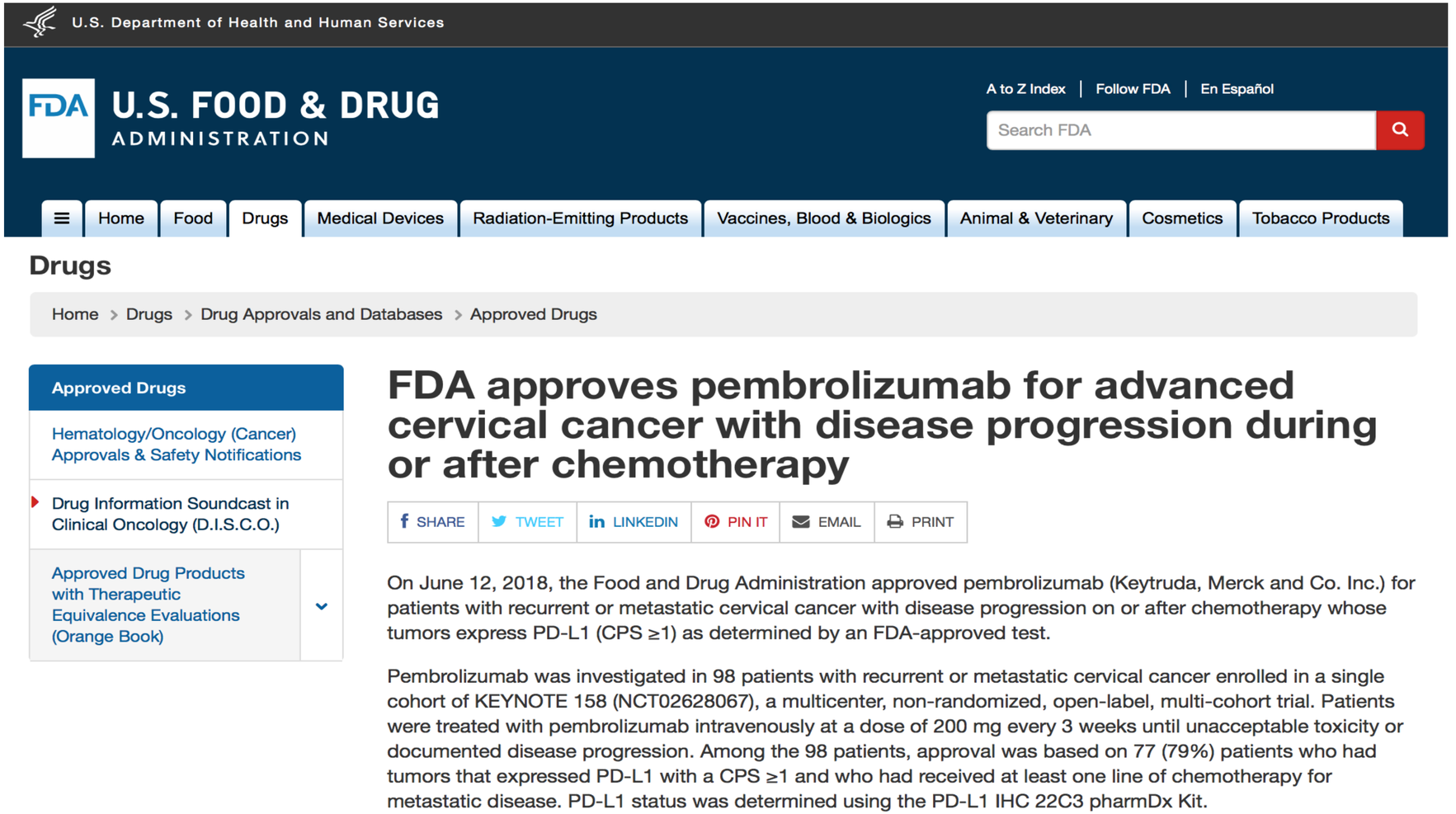
Safety Summary

- 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.

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



U.S. Department of Health and Human Services

FDA U.S. FOOD & DRUG ADMINISTRATION

A to Z Index | Follow FDA | En Español

Search FDA

Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Tobacco Products

Drugs

Home > Drugs > Drug Approvals and Databases > Approved Drugs

Approved Drugs

Hematology/Oncology (Cancer) Approvals & Safety Notifications

Drug Information Soundcast in Clinical Oncology (D.I.S.C.O.)

Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)

FDA approves pembrolizumab for advanced cervical cancer with disease progression during or after chemotherapy

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

On June 12, 2018, the Food and Drug Administration approved pembrolizumab (Keytruda, Merck and Co. Inc.) for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

Pembrolizumab was investigated in 98 patients with recurrent or metastatic cervical cancer enrolled in a single cohort of KEYNOTE 158 (NCT02628067), a multicenter, non-randomized, open-label, multi-cohort trial. Patients were treated with pembrolizumab intravenously at a dose of 200 mg every 3 weeks until unacceptable toxicity or documented disease progression. Among the 98 patients, approval was based on 77 (79%) patients who had tumors that expressed PD-L1 with a CPS ≥1 and who had received at least one line of chemotherapy for metastatic disease. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx Kit.

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.

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.

ESMO VIRTUAL PLENARY

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

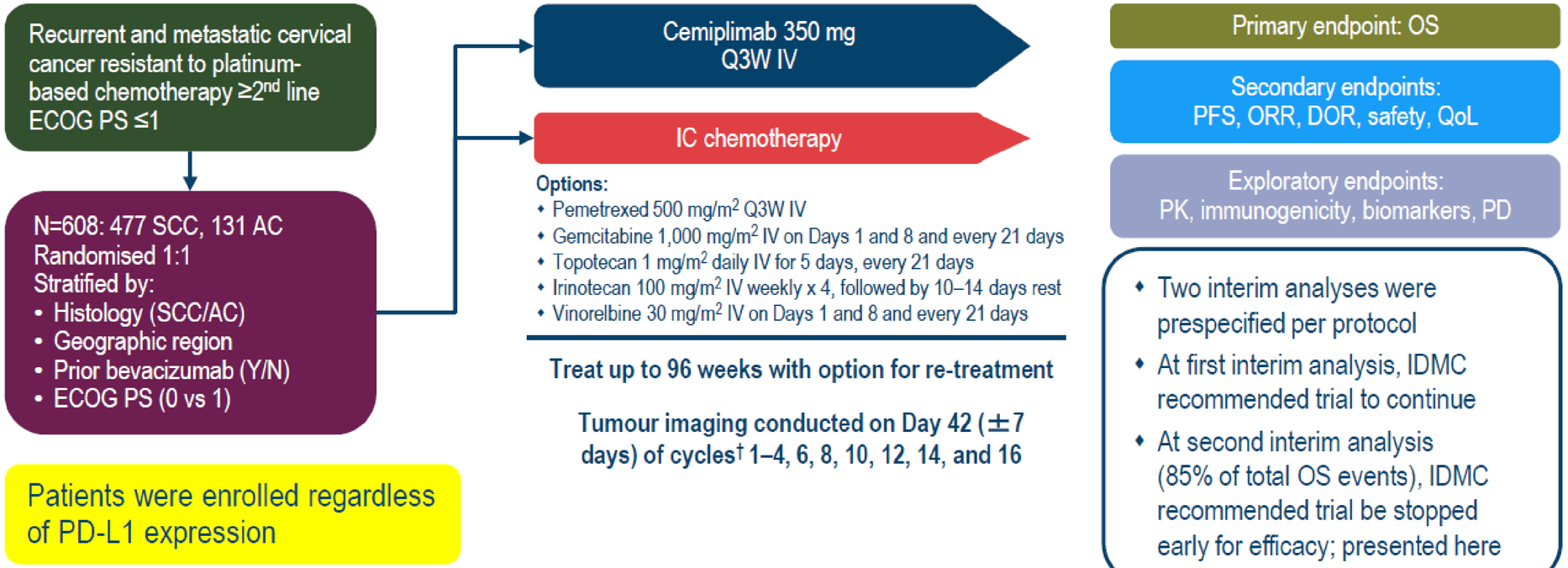
12 May 2021

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

*Contributed equally to this presentation.

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

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.[1] †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

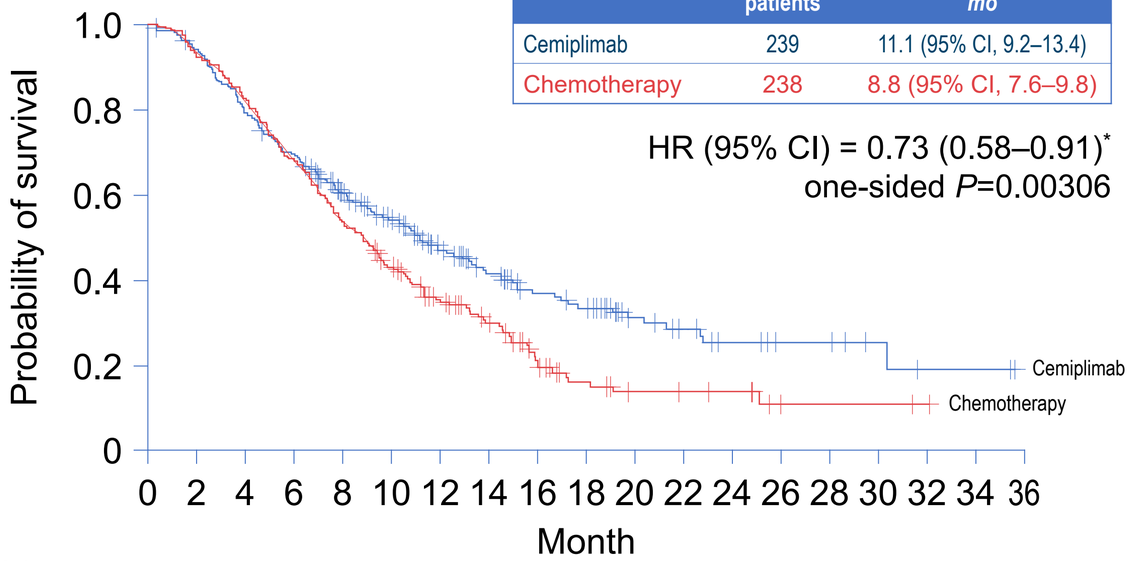
Tewari KS, et al. Presented at ESMO Virtual Plenary. 12–13 May 2021.

Overall Survival

SCC Population

	No. of patients	Median OS (95% CI), *mo*
Cemiplimab	239	11.1 (95% CI, 9.2–13.4)
Chemotherapy	238	8.8 (95% CI, 7.6–9.8)

HR (95% CI) = 0.73 (0.58–0.91)*
one-sided *P*=0.00306



No. at risk:

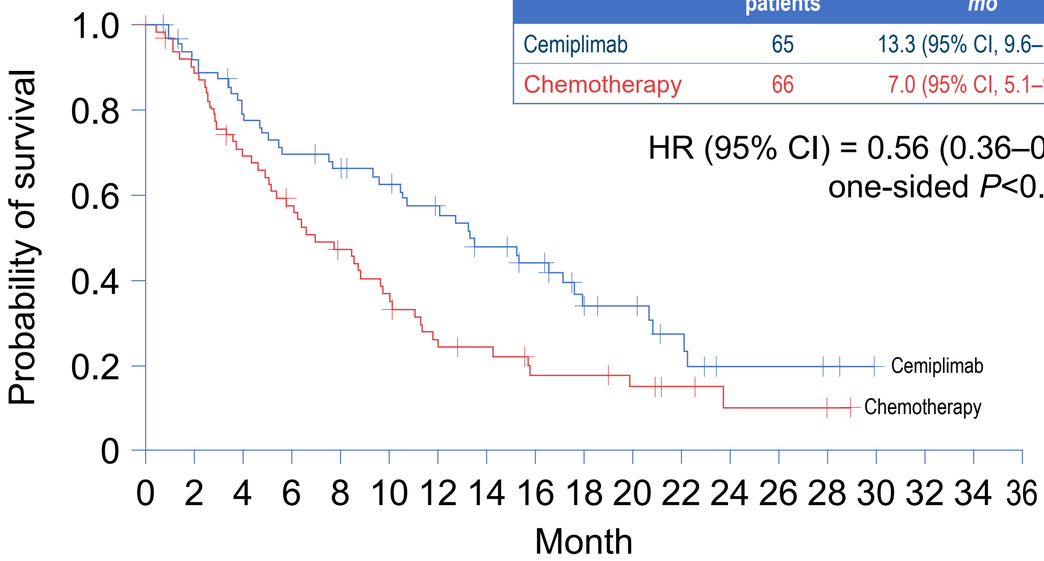
Cemiplimab	239	223	188	163	127	103	79	58	44	39	24	19	10	7	7	4	2	2	0
Chemotherapy	238	209	182	149	105	78	56	42	24	14	9	8	7	3	2	2	1	0	0

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

AC Population

	No. of patients	Median OS (95% CI), *mo*
Cemiplimab	65	13.3 (95% CI, 9.6–17.6)
Chemotherapy	66	7.0 (95% CI, 5.1–9.7)

HR (95% CI) = 0.56 (0.36–0.85)*
one-sided *P*<0.005†



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)

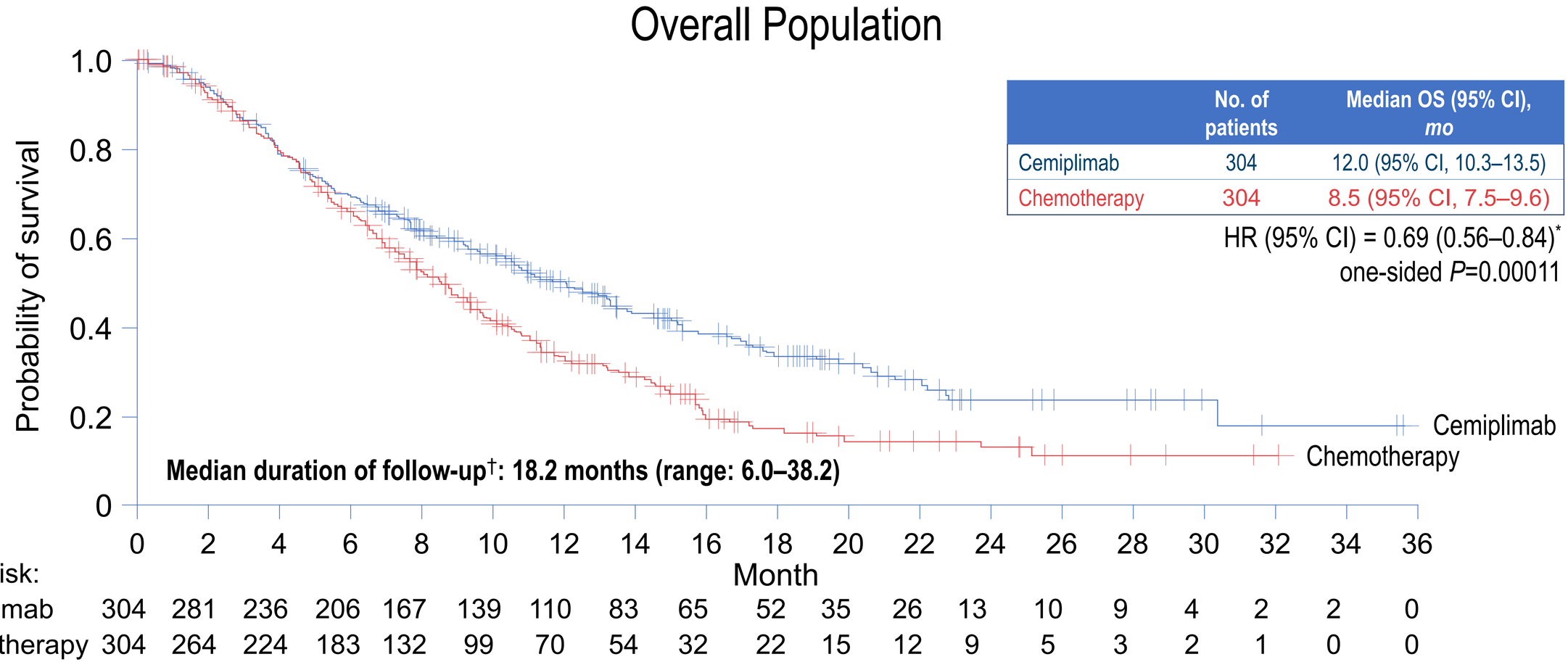
Data cutoff date: 4 Jan 2021

*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.

GOG FOUNDATION®

Overall Survival

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



	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

Data cutoff date: 4 Jan 2021

*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.

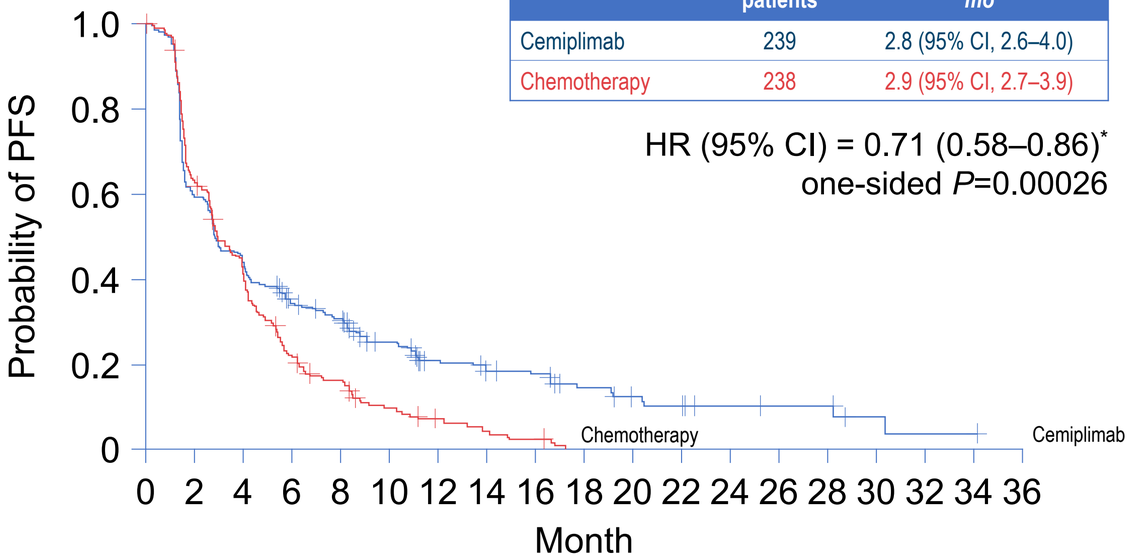
GOG FOUNDATION®

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



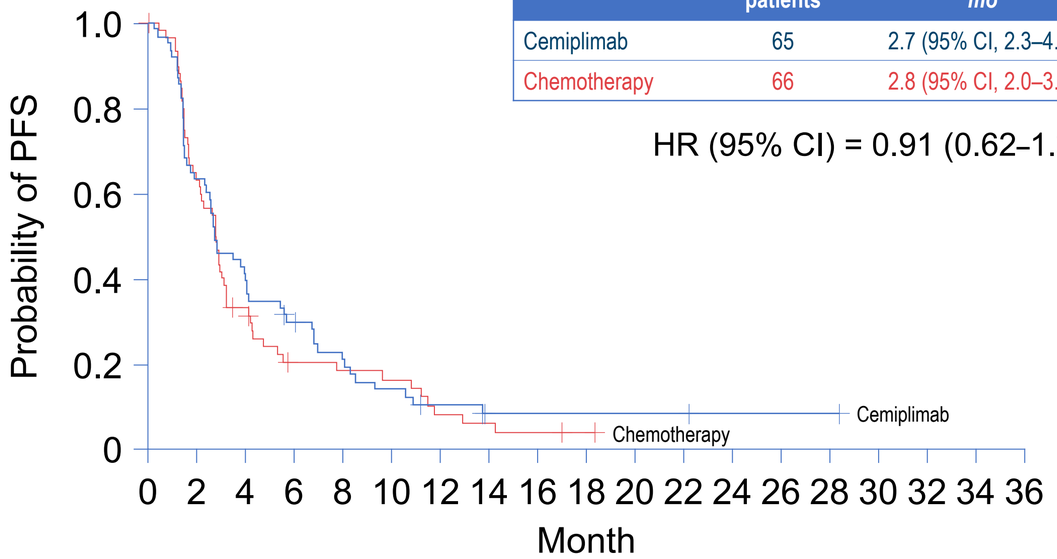
No. at risk:

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

Data cutoff date: 4 Jan 2021

*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.

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)

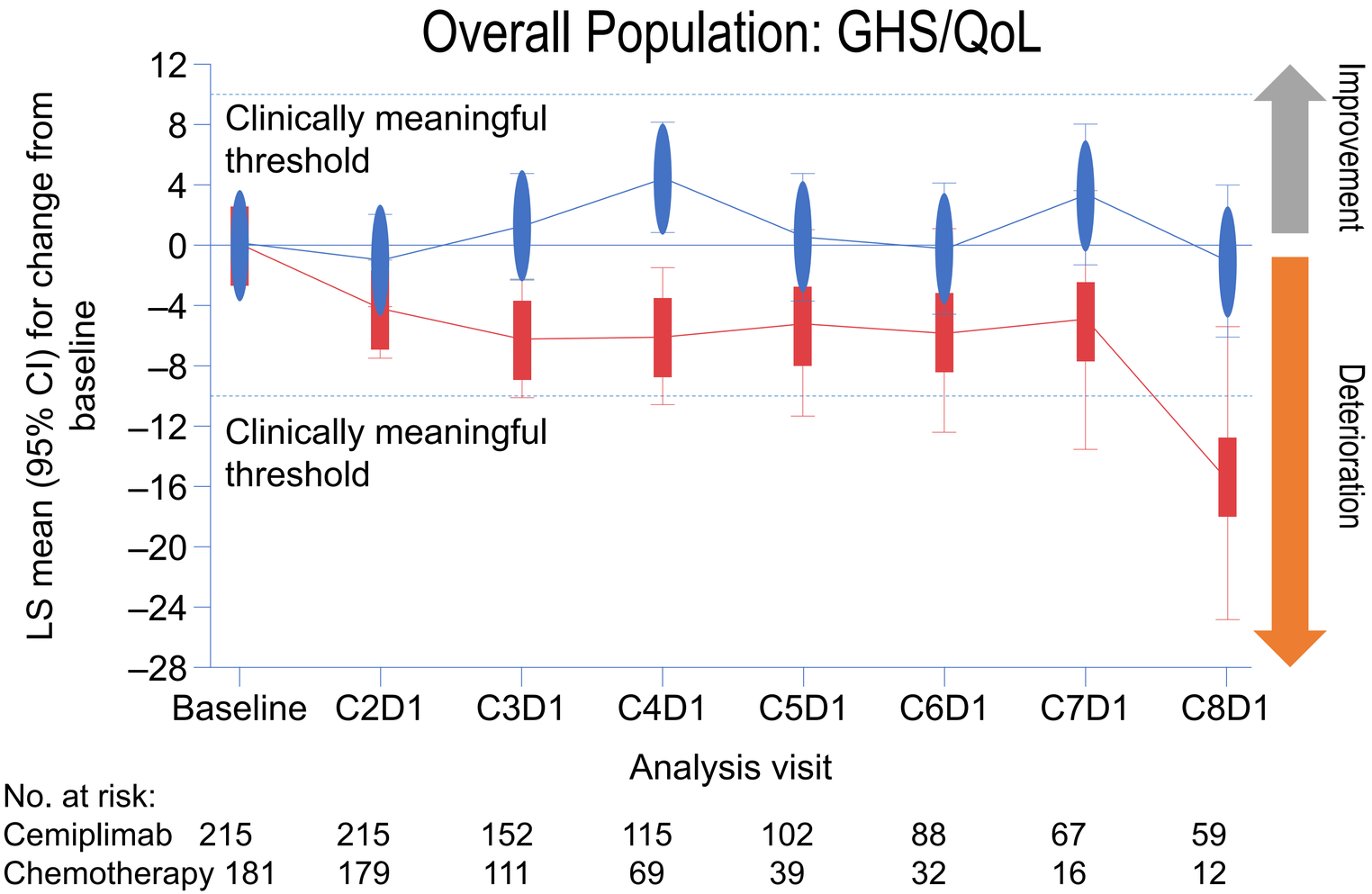
- ORR of SCC population
  - Cemiplimab: 17.6% (95% CI: 13.0–23.0)
  - Chemotherapy: 6.7% (95% CI: 3.9–10.7)
- ORR of AC population
  - Cemiplimab: 12.3% (95% CI: 5.5–22.8)
  - Chemotherapy: 4.5% (95% CI: 0.9–12.7)

[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

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

Data cutoff date: 4 Jan 2021

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.

The Future is Bright