子宮頸癌診斷及治療的新契機

馬偕紀念醫院

婦產部 婦癌科主任

陳楨瑞

Disclosure

- I have nothing to be disclosed.

- Abbreviations of this presentation:
  - Cx Ca: cervical cancer
  - ESCC: Early stage cervical cancer
  - LACC: Locally advanced cervical cancer
  - CCRT: Concurrent chemo-radiation therapy
  - ICI: Immune check-point inhibitor
  - ADC: Antibody drug conjugate

111 年台灣男女性 10 大癌症標準化發生率

男性			女性	
(9,989人)大腸	49.8/10^5		92.0/10^5	乳房(17,366人)
(9,417人)肺、支氣管及氣管	45.9/10^5		38.5/10^5	肺、支氣管及氣管(8,565人)
(9,062人)攝護腺	41.6/10^5		33.5/10^5	大腸(7,654人)
(7,472人)口腔	40.0/10^5		26.9/10^5	甲狀腺(4,209人)
(7,244人)肝及肝內膽管	35.8/10^5		18.8/10^5	子宮體(3,541人)
(2,600人)食道	13.4/10^5		12.7/10^5	肝及肝內膽管(3,189人)
(2,625人)胃	12.6/10^5		10.6/10^5	卵巢、輸卵管及寬韌帶(1,859人)
(2,246人)皮膚	10.6/10^5		7.8/10^5	皮膚(1,960人)
(1,616人)白血症	9.7/10^5		7.6/10^5	子宮頸(1,384人)
(1,778人)非何杰金氏淋巴瘤	9.6/10^5		7.4/10^5	胃(1,752人)
(13,250人)其他癌症				其他癌症(11,515人)
(67,299人) 總計 342.3/10^5			311.2/10^5 總計 (62,994人)	

子宮頸癌為第九大女性癌症

https://www.hpa.gov.tw/Pages/Detail.aspx?nodeid=4809&pid=18699

Outline

- Primary therapy
  - ESCC: Surgical intervention
  - LACC: Additional modalities in combination with traditional CCRT
- Recurrent/Metastatic therapy
  - Immunotherapy (ICI)
  - ADC
  - Radiation therapy
- Summary of ongoing trials
- Conclusion

Part-I

- Primary therapy
  - ESCC: Surgical intervention
  - LACC: Additional modalities in combination with traditional CCRT
- Recurrent/Metastatic therapy
  - Immunotherapy (ICI)
  - ADC
  - Radiation therapy
- Summary of ongoing trials
- Conclusion

ESCC: Surgical intervention-LACC trial

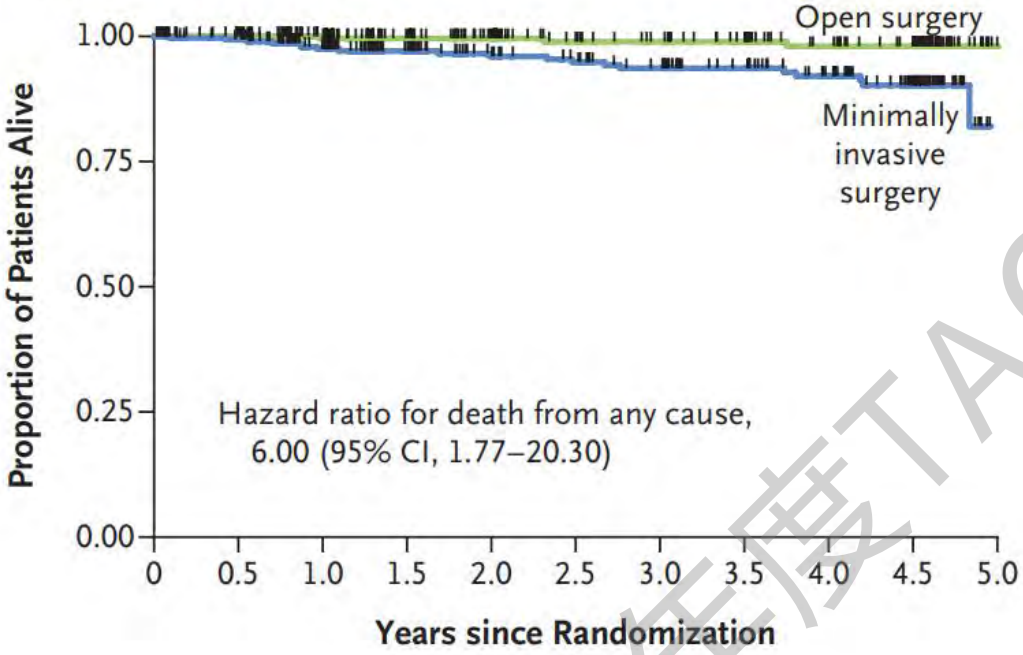
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 15, 2018 VOL. 379 NO. 20

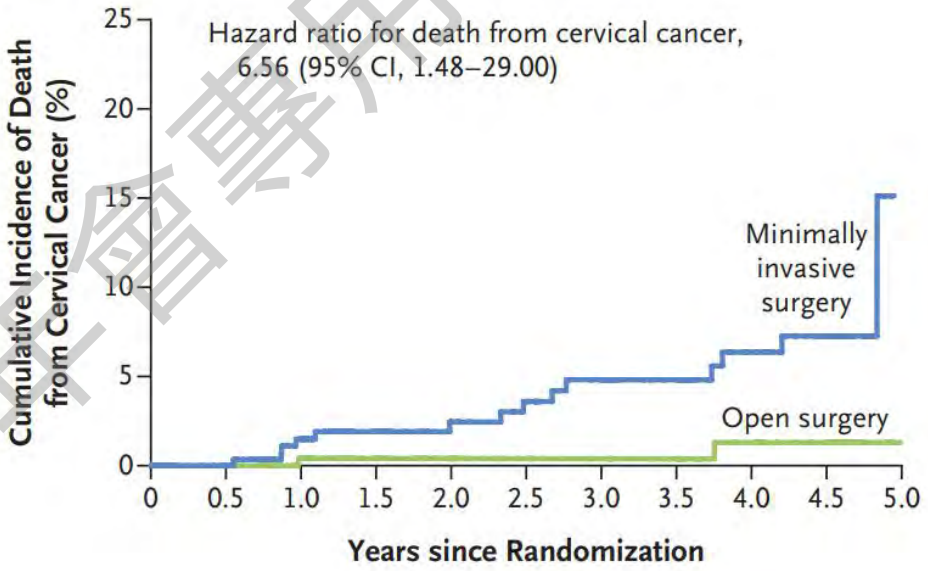
Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer

Pedro T. Ramirez, M.D., Michael Frumovitz, M.D., Rene Pareja, M.D., Aldo Lopez, M.D., Marcelo Vieira, M.D., Reitan Ribeiro, M.D., Alessandro Buda, M.D., Xiaojian Yan, M.D., Yao Shuzhong, M.D., Naven Chetty, M.D., David Isla, M.D., Mariano Tamura, M.D., Tao Zhu, M.D., Kristy P. Robledo, Ph.D., Val Gebski, M.Stat., Rebecca Asher, M.Sc., Vanessa Behan, B.S.N., James L. Nicklin, M.D., Robert L. Coleman, M.D., and Andreas Obermair, M.D.

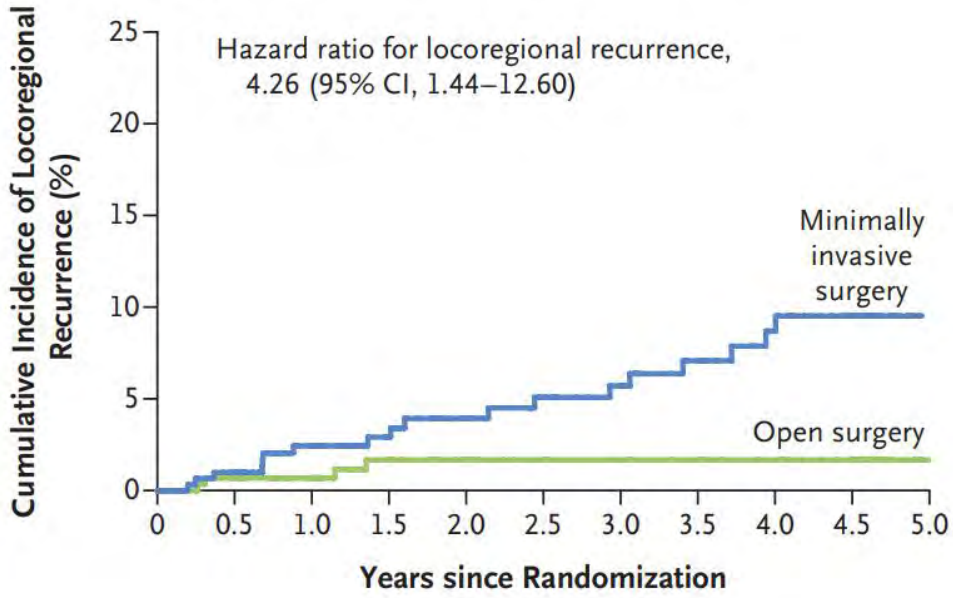
A Overall Survival



B Disease-Specific Survival



C Locoregional Recurrence



ESCC: Surgical intervention-SEER data

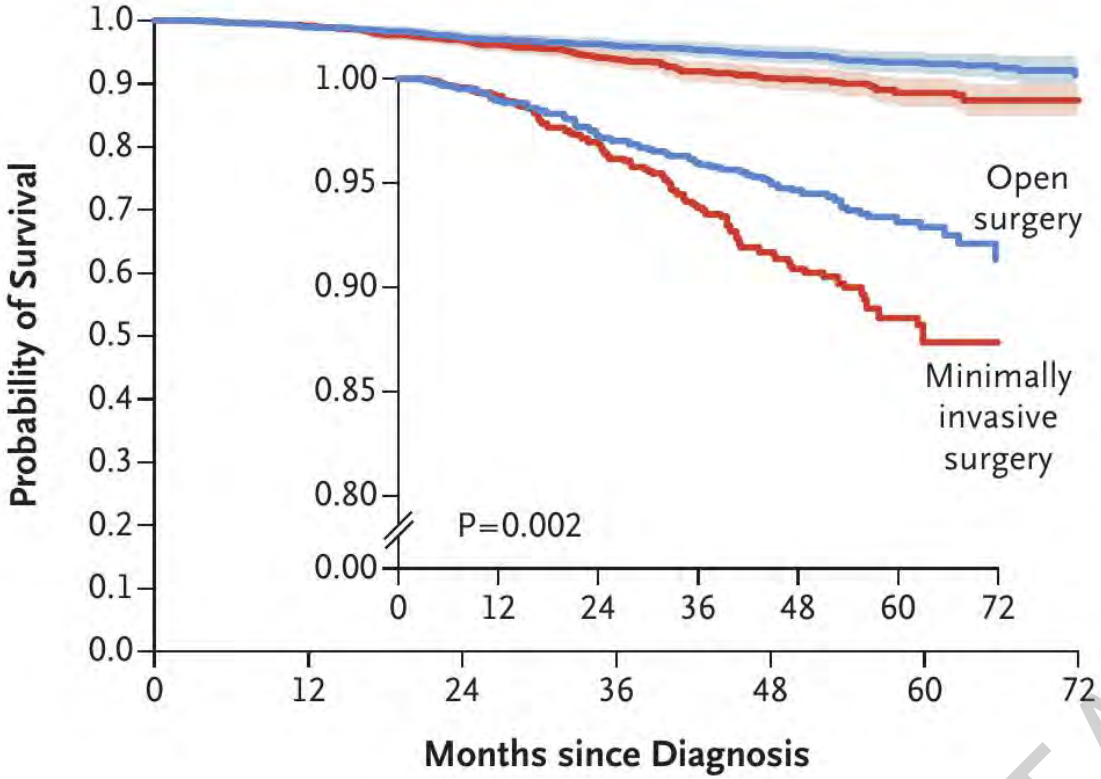
The NEW ENGLAND JOURNAL of MEDICINE

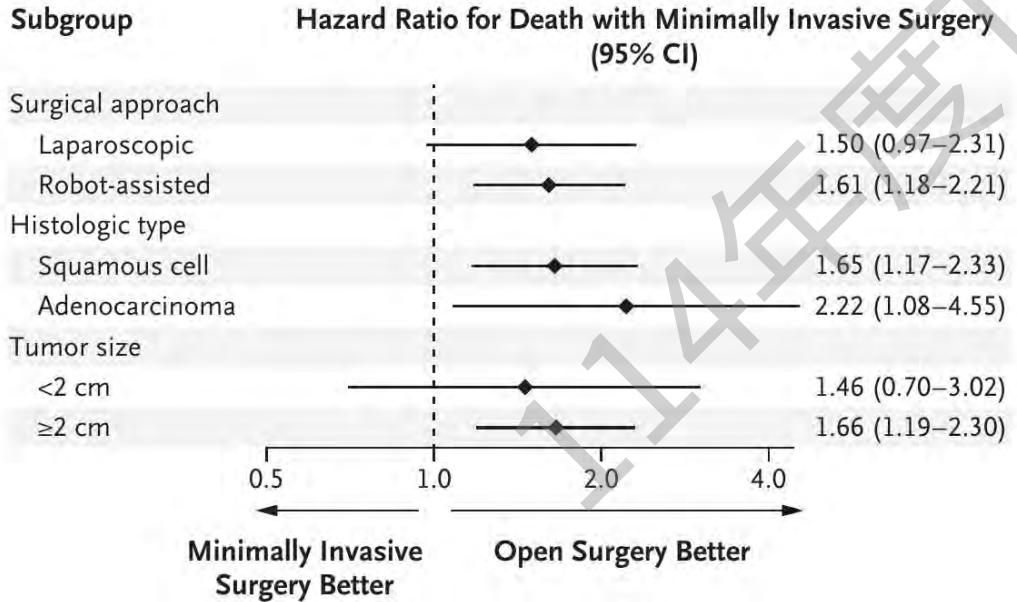
ORIGINAL ARTICLE

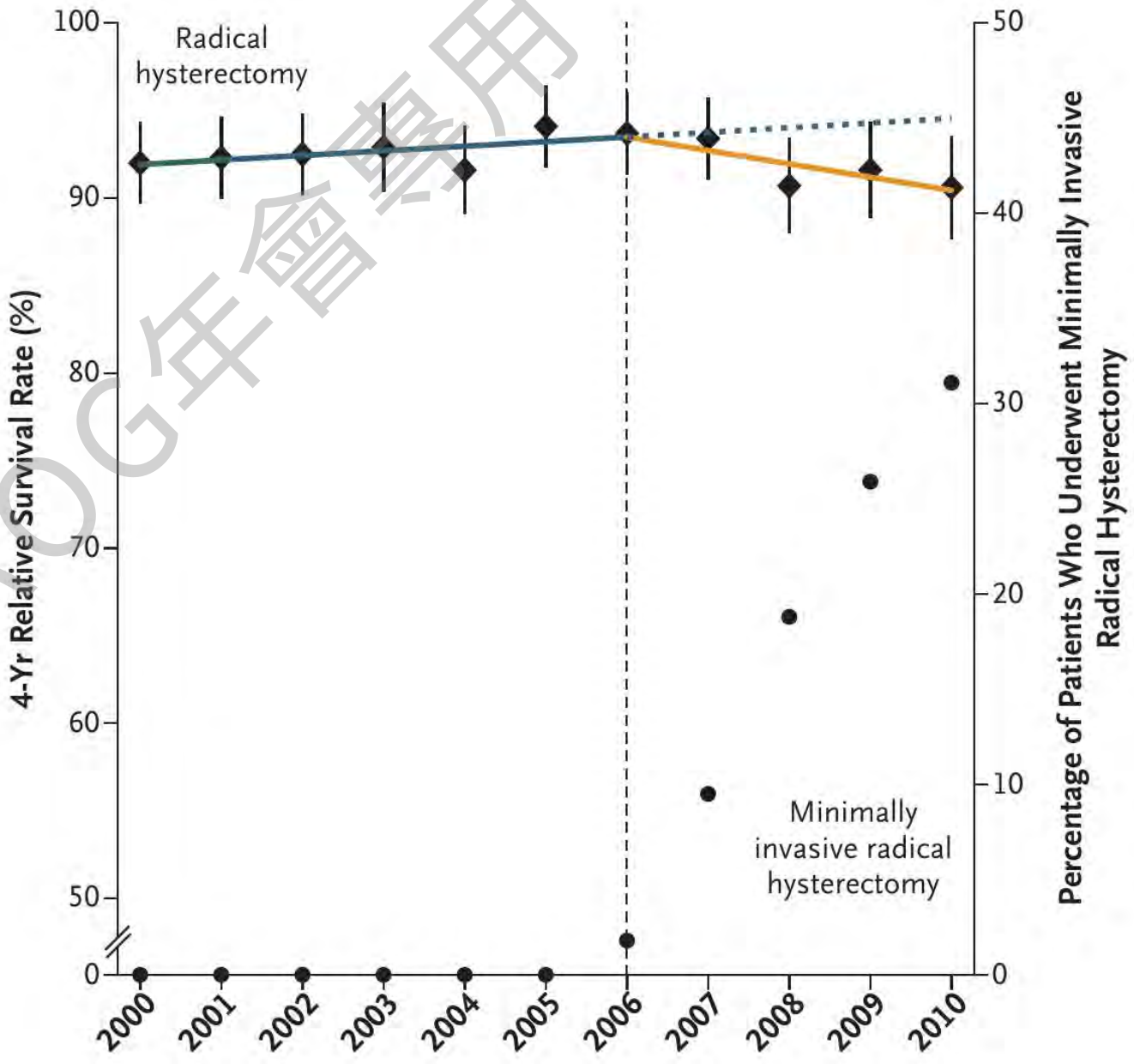
Survival after Minimally Invasive Radical Hysterectomy for Early-Stage Cervical Cancer

Alexander Melamed, M.D., M.P.H., Daniel J. Margul, M.D., Ph.D.,
Ling Chen, M.D., M.P.H., Nancy L. Keating, M.D., M.P.H.,
Marcela G. del Carmen, M.D., M.P.H., Junhua Yang, M.S.,
Brandon-Luke L. Seagle, M.D., Amy Alexander, M.D., Emma L. Barber, M.D.,
Laurel W. Rice, M.D., Jason D. Wright, M.D., Masha Kocherginsky, Ph.D.,
Shohreh Shahabi, M.D., E.M.H.A., and J. Alejandro Rauh-Hain, M.D., M.P.H.

N Engl J Med 2018;379:1905-14.



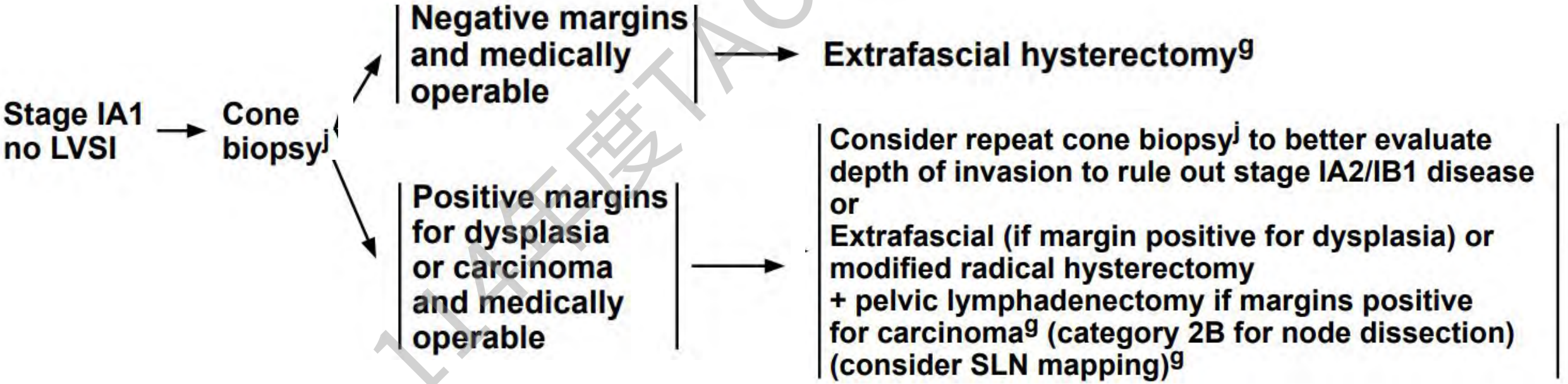




ESCC: Surgical intervention- IA1,LVSI(-)

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Cervical Cancer



ESCC: Surgical intervention-IA2/IB1 LVSI(-)

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Cervical Cancer

Stage IA2–IB1 cervical carcinoma (Based on cone biopsy and all conservative surgery criteria must be met):
- **No LVSI**
- **Negative cone margins**
- **Squamous cell (any grade) or usual type adenocarcinoma (grade 1 or 2 only)**
- **Tumor size ≤2 cm**
- **Depth of invasion ≤10 mm**
- **Negative imaging for metastatic disease**

→ **Extrafascial hysterectomy + pelvic lymphadenectomy[g] (or SLN mapping)** —

Ultra-conservative selective criteria for IB1 ESCC

Stage IA1–IA2 with LVSI → **Modified radical hysterectomy + pelvic lymphadenectomy[g] (consider SLN mapping)[g]**

ESCC: Surgical intervention-ConCerv trial

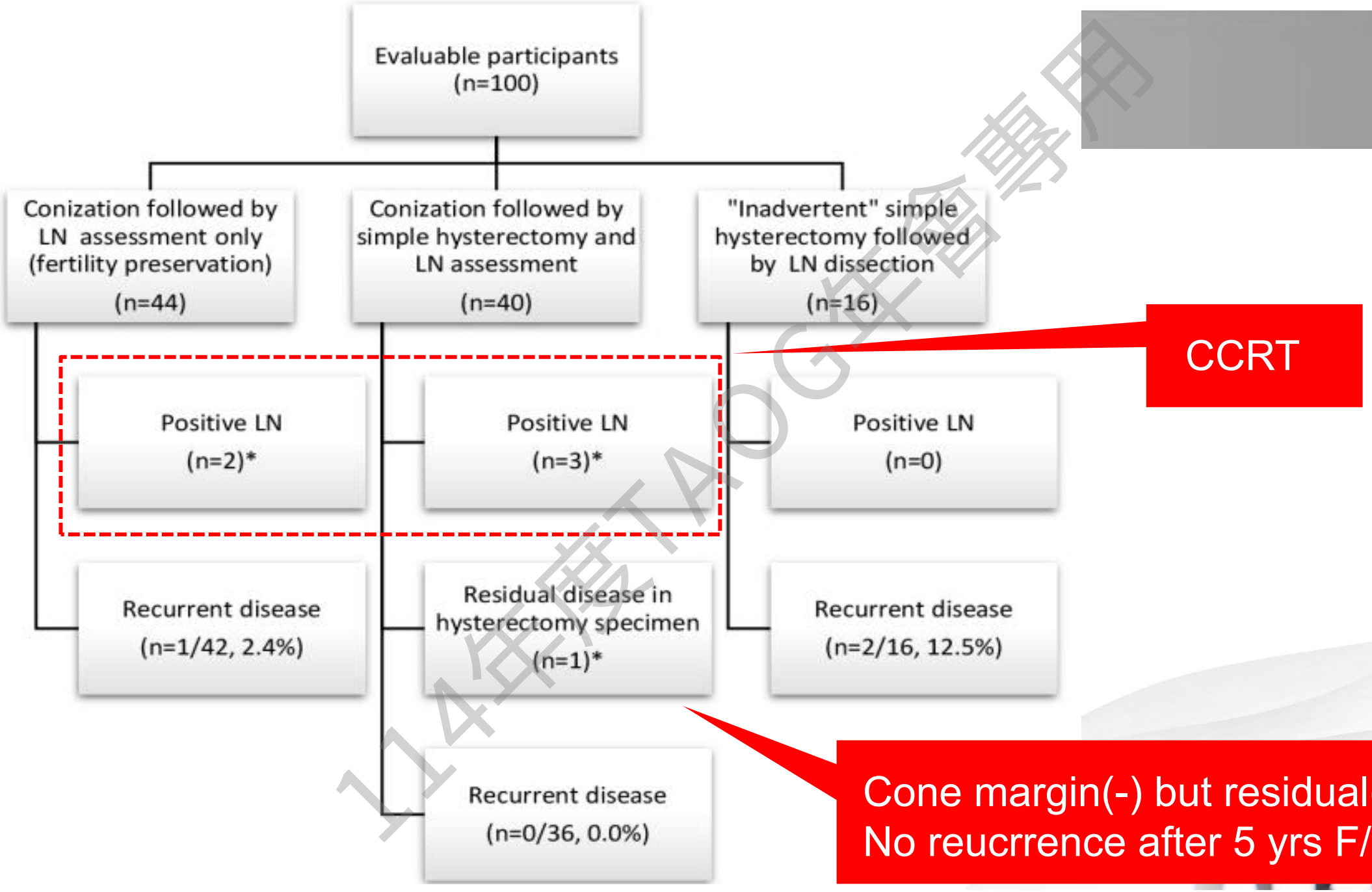
ConCerv: a prospective trial of conservative surgery for low-risk early-stage cervical cancer

Kathleen M Schmeler,[1] Rene Pareja,[2] Aldo Lopez Blanco,[3] Jose Humberto Fregnani,[4] Andre Lopes,[5] Myriam Perrotta,[6] Audrey T Tsunoda,[7] David F Cantú-de-León,[8] Lois M Ramondetta,[1] Tarinee Manchana,[9] David R Crotzer,[10] Orla M McNally,[11] Martin Riege,[12] Giovanni Scambia,[13] Juan Manuel Carvajal,[14] Julian Di Guilmi,[15] Gabriel J Rendon,[16] Preetha Ramalingam,[17] Bryan M Fellman,[18] Robert L Coleman,[19] Michael Frumovitz,[1] Pedro T Ramirez[1]

Int J Gynecol Cancer. 2021 Oct;31(10):1317-1325.

ESCC: Surgical intervention-ConCerv trial

Eligible Criteria	
FIGO Stage (2009)	IA2-IB1
Histology	Squamous (any grade), Adenocarcinoma (grade 1/2 only)
Tumor size	≦ 2 cm (PE or image)
LVSI	No LVSI
Lymph nodes	No metastasis on CT, MRI, or PET
Depth	Depth of invasion ≦ 10mm
Margin	No malignancy or high grade dysplasia



ESCC: Surgical intervention-SHAPE trial

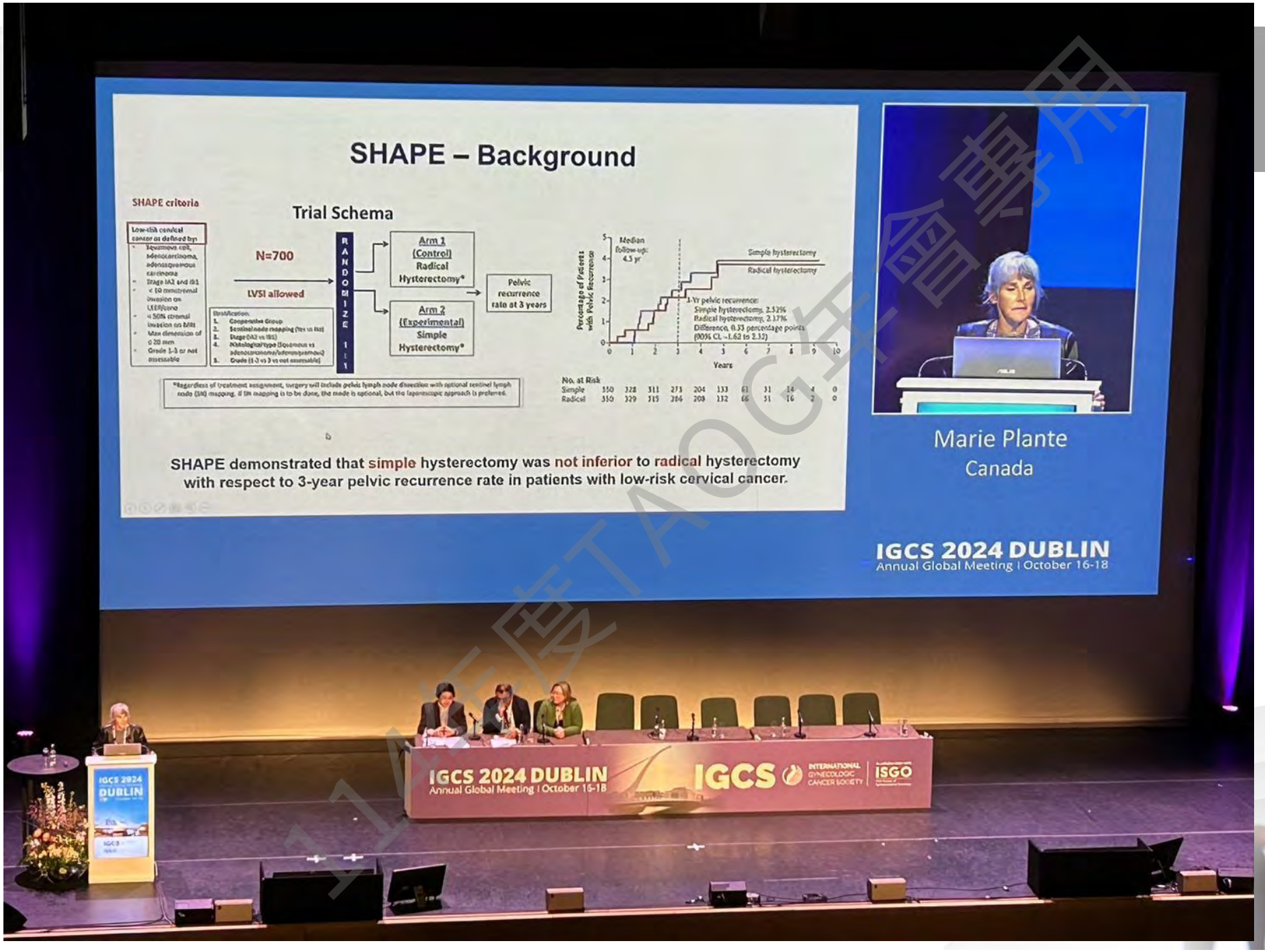
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

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

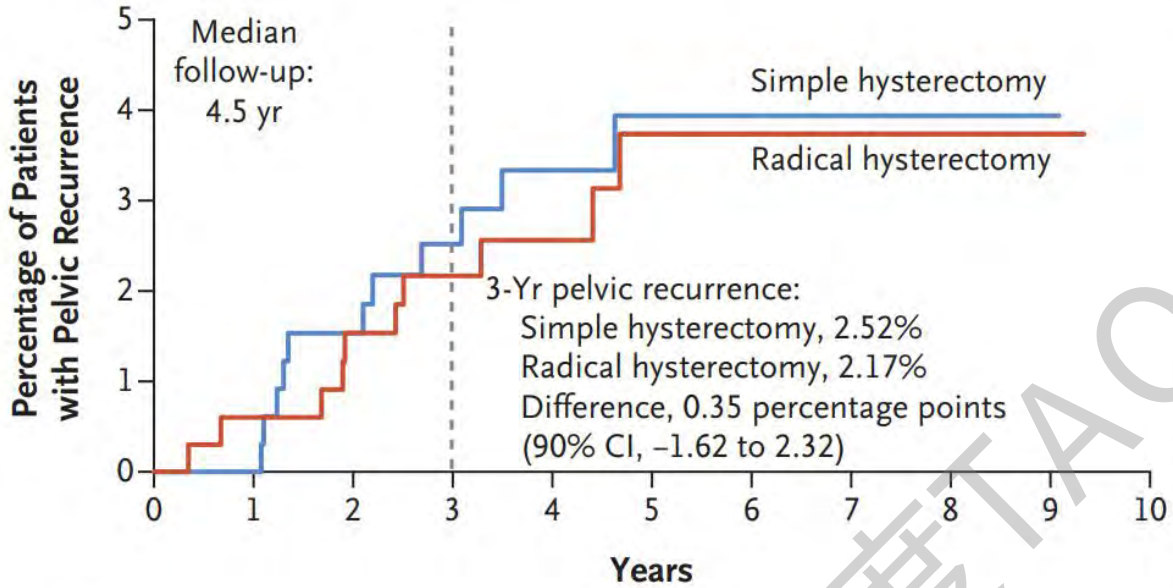
N Engl J Med. 2024 Feb 29;390(9):819-829.


SHAPE – Background
SHAPE criteria
Low-risk cervical cancer as defined by:
Squamous cell, adenocarcinoma, adenosquamous carcinoma
Stage IA2 and IB1
< 1/3 cervical invasion on LEEP/cone
< 50% stromal invasion on MRI
Max dimension of ≤ 20 mm
Grade 1-3 or not assessable
Trial Schema
N=700
LVSI allowed
Stratification:
1. Cooperative Group
2. Sentinel node mapping (Yes vs No)
3. Stage (IA2 vs IB1)
4. Histological type (Squamous vs adenocarcinoma/adenosquamous)
5. Grade (1-2 vs 3 vs not assessable)
RANDOMIZE 1:1
Arm 1 (Control) Radical Hysterectomy*
Arm 2 (Experimental) Simple Hysterectomy*
Pelvic recurrence rate at 3 years
*Regardless of treatment assignment, surgery will include pelvic lymph node dissection with optional sentinel lymph node (SN) mapping. If SN mapping is to be done, the node is optional, but the laparoscopic approach is preferred.
Median follow-up: 4.5 yr
Simple hysterectomy
Radical hysterectomy
Percentage of Patients with Pelvic Recurrence
Years
1-Yr pelvic recurrence:
Simple hysterectomy, 2.52%
Radical hysterectomy, 2.17%
Difference, 0.33 percentage points
(90% CI, −1.62 to 2.32)
No. at Risk
Simple 350 328 311 273 204 133 61 31 14 4 0
Radical 350 329 315 284 209 132 66 31 16 2 0
SHAPE demonstrated that simple hysterectomy was not inferior to radical hysterectomy with respect to 3-year pelvic recurrence rate in patients with low-risk cervical cancer.
Marie Plante
Canada
IGCS 2024 DUBLIN
Annual Global Meeting | October 16-18
IGCS 2024 DUBLIN
Annual Global Meeting | October 16-18
IGCS
INTERNATIONAL GYNECOLOGIC CANCER SOCIETY
ISGO

ESCC: Surgical intervention-SHAPE trial

Eligible Criteria	
FIGO Stage (2009)	IA2-IB1
Histology	Squamous, Adenocarcinoma, Adenosquamous carcinoma (any grade)
Tumor size	≦ 2 cm (Cone specimen or MRI if biopsy only)
LVSI	Invasion(+) was not an exclusion criterion.
Lymph nodes	No metastasis on CT, MRI, or PET
Depth	Depth of invasion ≦ 10mm or ≦50% stromal invasion (by cone specimen or MRI)
Pre-hysterectomy	Biopsy only (20%) or Conization (80%)

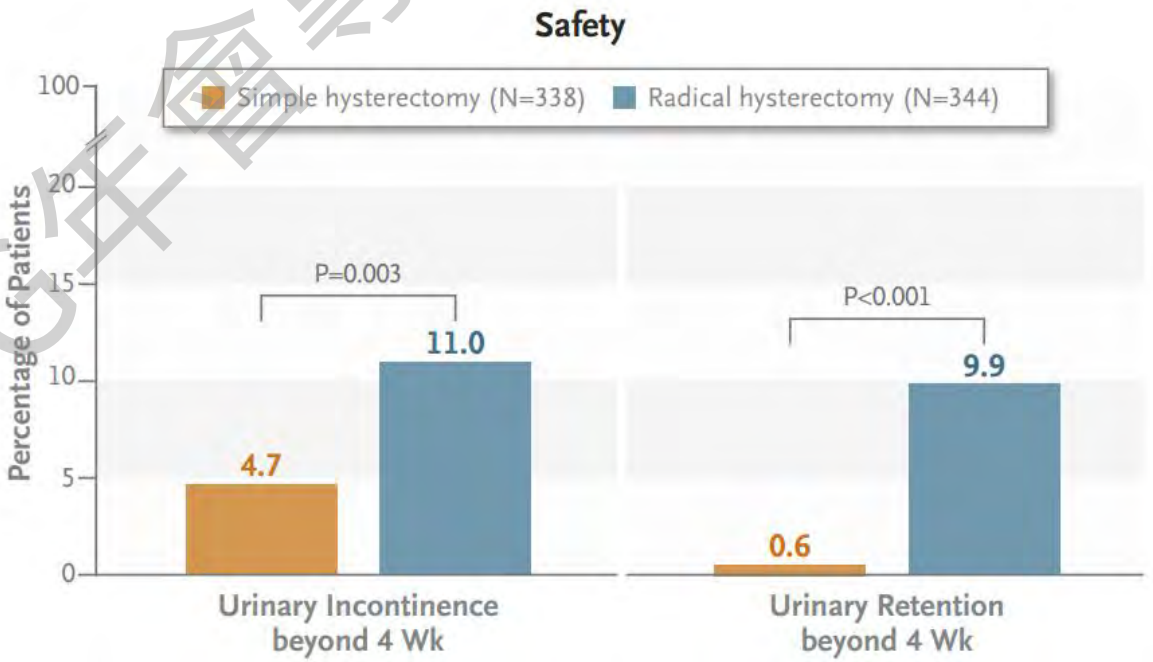
ESCC: Surgical intervention-SHAPE trial



No. at Risk

Simple	350	328	311	273	204	133	61	31	14	4	0
Radical	350	329	315	286	208	132	66	31	16	2	0

Figure 1. Kaplan–Meier Curves for Pelvic Recurrence.



CONCLUSIONS

In patients with low-risk, early-stage cervical cancer, simple hysterectomy was noninferior to radical hysterectomy with respect to pelvic recurrence at 3 years and was associated with fewer urologic complications.

No difference after 3 yrs F/U

ESCC: Surgical intervention- Cohort study

OBSTETRICS & GYNECOLOGY

Original Research

Survival After Simple Compared With Radical Hysterectomy for Patients With Early-Stage Cervical Cancer

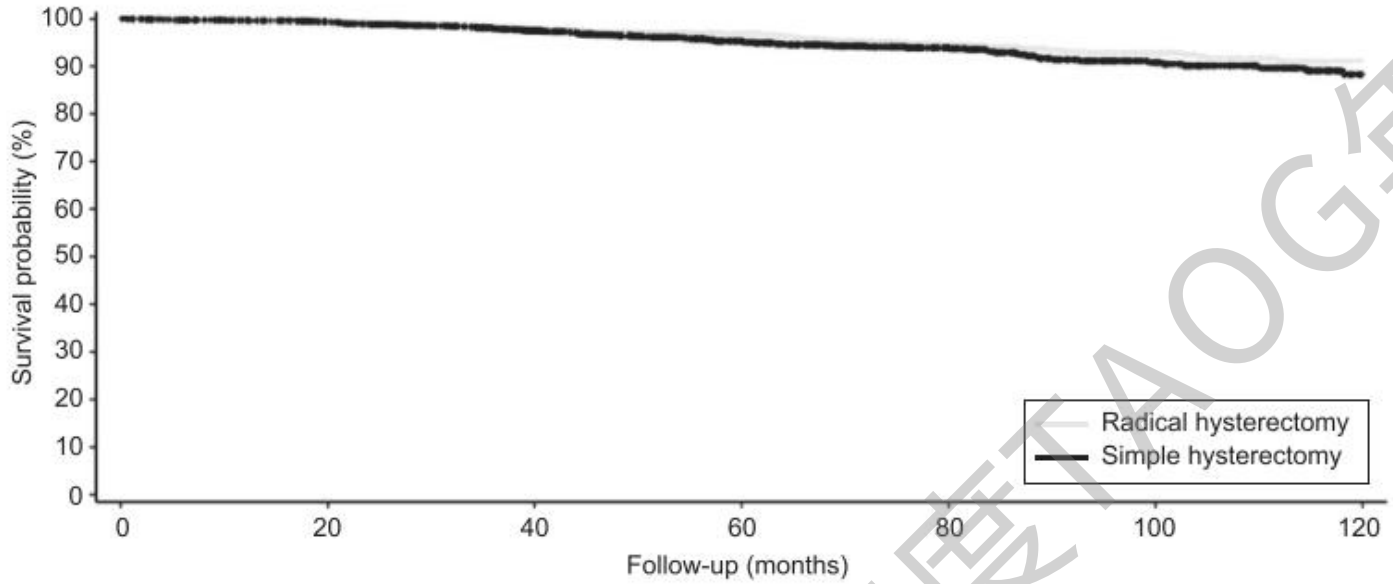
David Viveros-Carreño, MD, Nuria Agusti, MD, Chi-Fang Wu, PhD, Alexander Melamed, MD, MPH, Roni Nitecki Wilke, MD, MPH, Alexa Kanbergs, MD, ScM, MS, René Pareja, MD, Abigail S. Zamorano, MD, MPHS, and J. Alejandro Rauh-Hain, MD, MPH

Obstetrics & Gynecology 145(1):p 99-107, January 2025.

ESCC: Surgical intervention-Cohort study

Eligible Criteria	
FIGO Stage (2009)	IA1-IB1
Histology	Squamous, Adenocarcinoma, Adenosquamous carcinoma (any grade)
Tumor size	≦ 2 cm
LVSI	Invasion(+) in IA1, others not limited
Lymph nodes	Dissection is required (negative in pathology)
Surgery	Hysterectomy is needed (simple or radical)

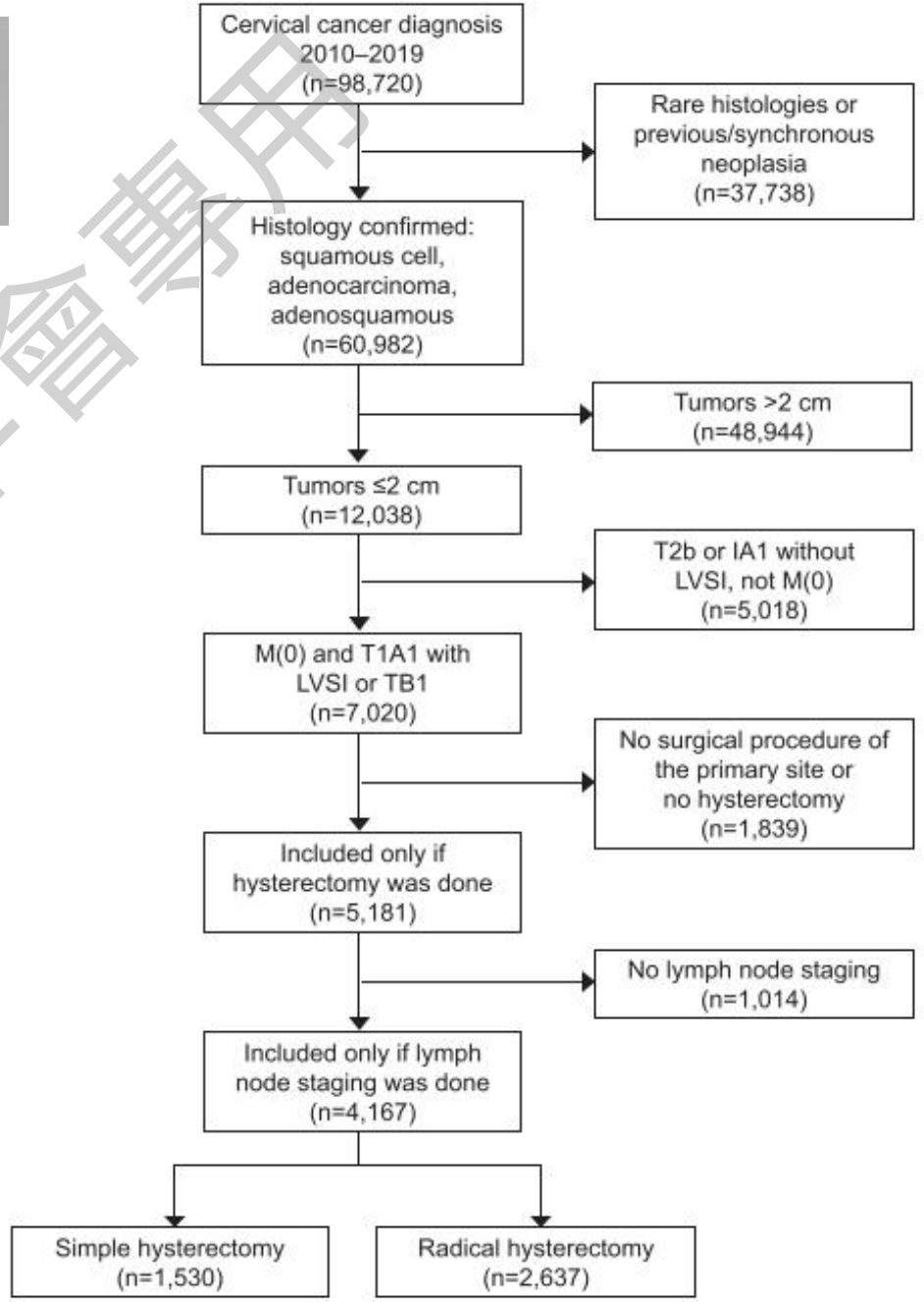
ESCC: Surgical intervention-Cohort study



Overall survival did not significantly differ.

5 yr survival probability: 95% vs 97% (SH vs RH)

10 yr survival probability: 88% vs 91% (SH vs RH)



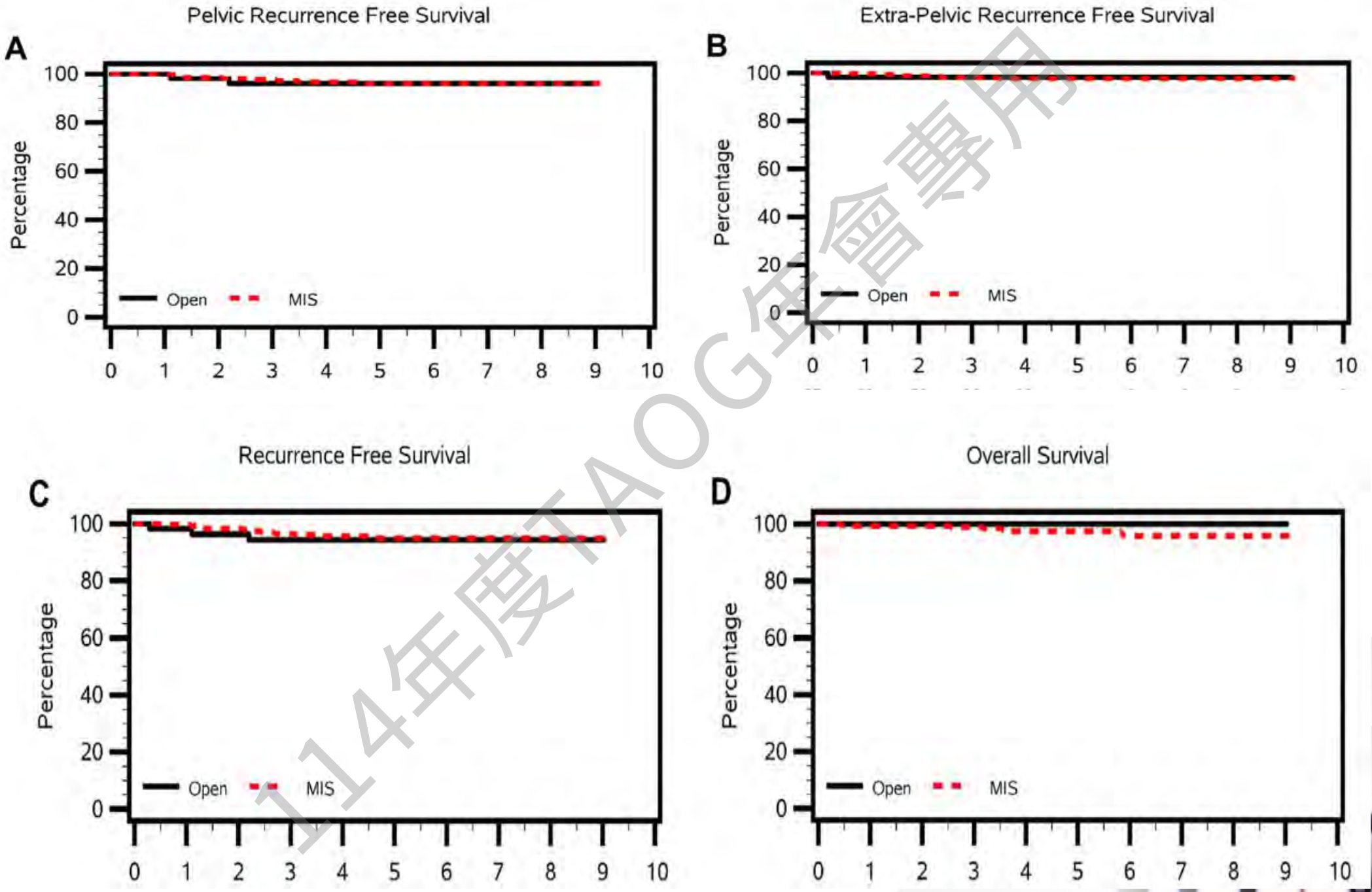
ESCC: Surgical intervention- Simple hysterectomy, Open vs. MIS?

ORIGINAL RESEARCH

Minimally invasive compared to open surgery in patients with low-risk cervical cancer following simple hysterectomy: An exploratory analysis from the Gynegologic Cancer Intergroup/Canadian Cancer Trials Group CX.5/SHAPE trial

Marie Plante[a,*], Sven Mahner[b], Alexandra Sebastianelli[c], Paul Bessette[d], Eric Lambaudie[e], Frederic Guyon[f], Jurgen Piek[g], Ramon Smolders[h], John Tidy[i], Karin Williamson[j], Lars Hanker[k], Frederic Goffin[l], Irina Tsibulak[m], Brynhildur Eyjolfsdottir[n], Noreen Gleeson[o], Jung-Yun Lee[p], Yuwei Ke[q], Janice S. Kwon[r], Sarah E. Ferguson[s], Lois Shepherd[q], Dongsheng Tu[q]

Int J Gynecol Cancer. 2025 Jan;35(1):100001.



ESCC: Surgical intervention-MIS, future?

National Library of Medicine
National Center for Biotechnology Information

ClinicalTrials.gov

Recruiting

Minimally Invasive Simple Hysterectomy in Low Risk Cervical Cancer (LASH)

ClinicalTrials.gov ID NCT06416748

Sponsor Fondazione Policlinico Universitario Agostino Gemelli IRCCS

Information provided by Bizzarri Nicolò, Fondazione Policlinico Universitario Agostino Gemelli IRCCS (Responsible Party)

Last Update Posted 2024-10-29

ESCC: Surgical intervention- MIS-Stapler

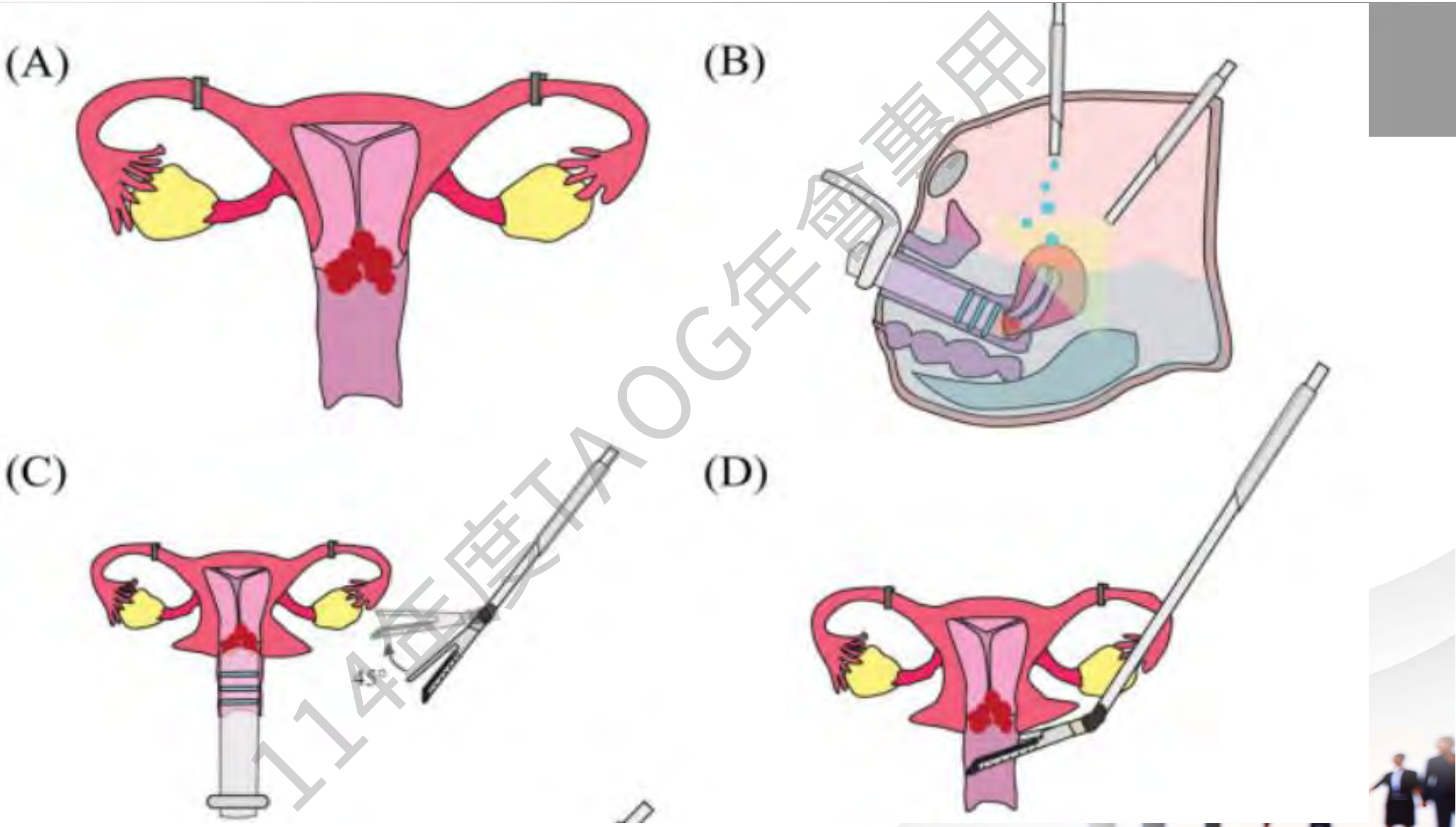
Park *et al. BMC Cancer* (2022) 22:331
https://doi.org/10.1186/s12885-022-09429-z

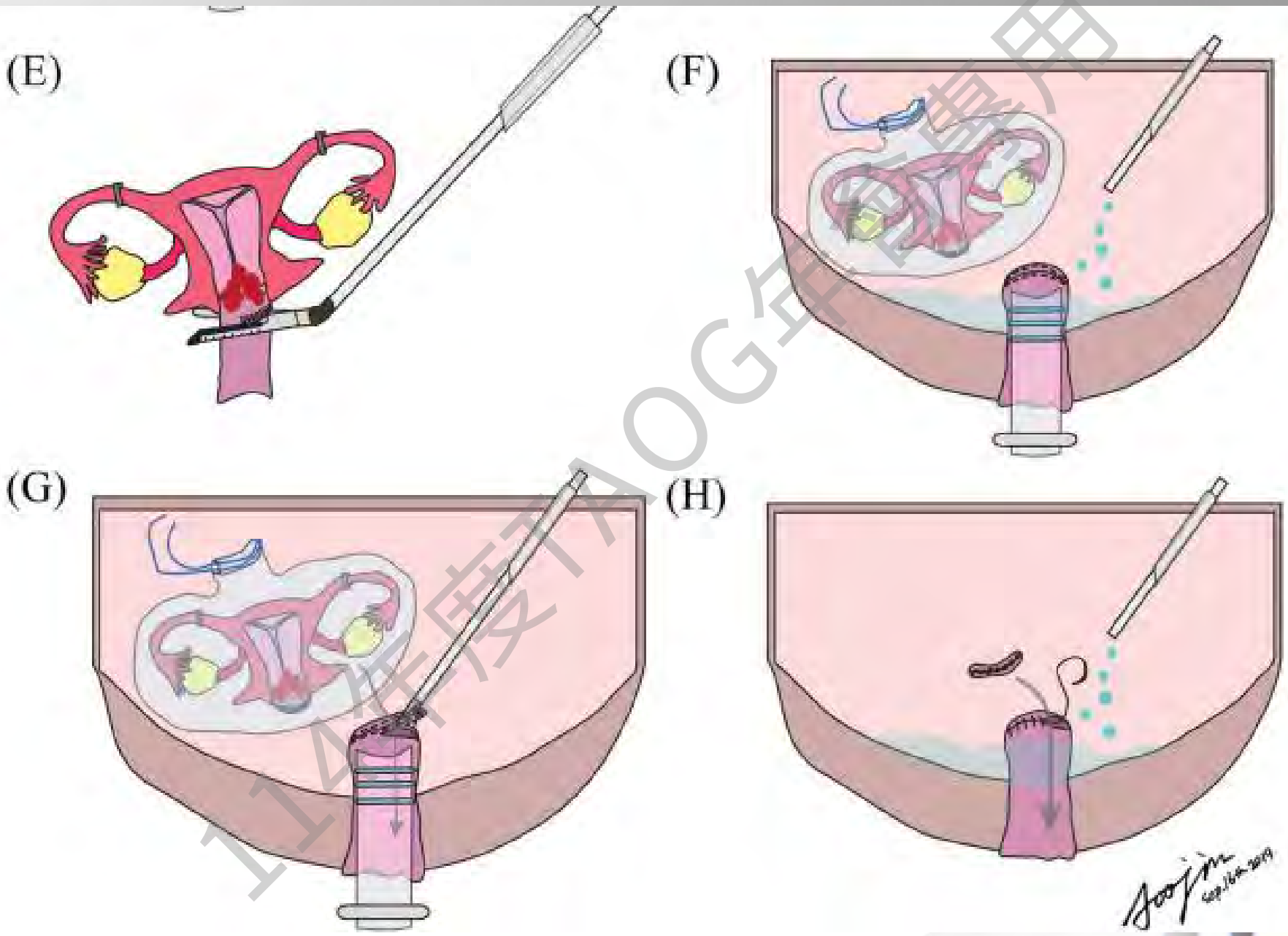
BMC Cancer

STUDY PROTOCOL Open Access

Safety and efficacy study of laparoscopic or robotic radical surgery using an endoscopic stapler for inhibiting tumour spillage of cervical malignant neoplasms evaluating survival (SOLUTION): a multi-centre, open-label, single-arm, phase II trial protocol

Soo Jin Park[1], Tae Wook Kong[2], Taehun Kim[3], Maria Lee[1], Chel Hun Choi[4], Seung-Hyuk Shim[5], Ga Won Yim[6], Seungmee Lee[7], Eun Ji Lee[1], Myong Cheol Lim[8], Suk-Joon Chang[2], Sung Jong Lee[9], San Hui Lee[10], Taejong Song[11], Yoo-Young Lee[4], Hee Seung Kim[1*] and Eun Ji Nam[12*]




(E)
(F)
(G)
(H)

LACC: In combination with CCRT KEYNOTE-A18

Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): a randomised, double-blind, phase 3 clinical trial

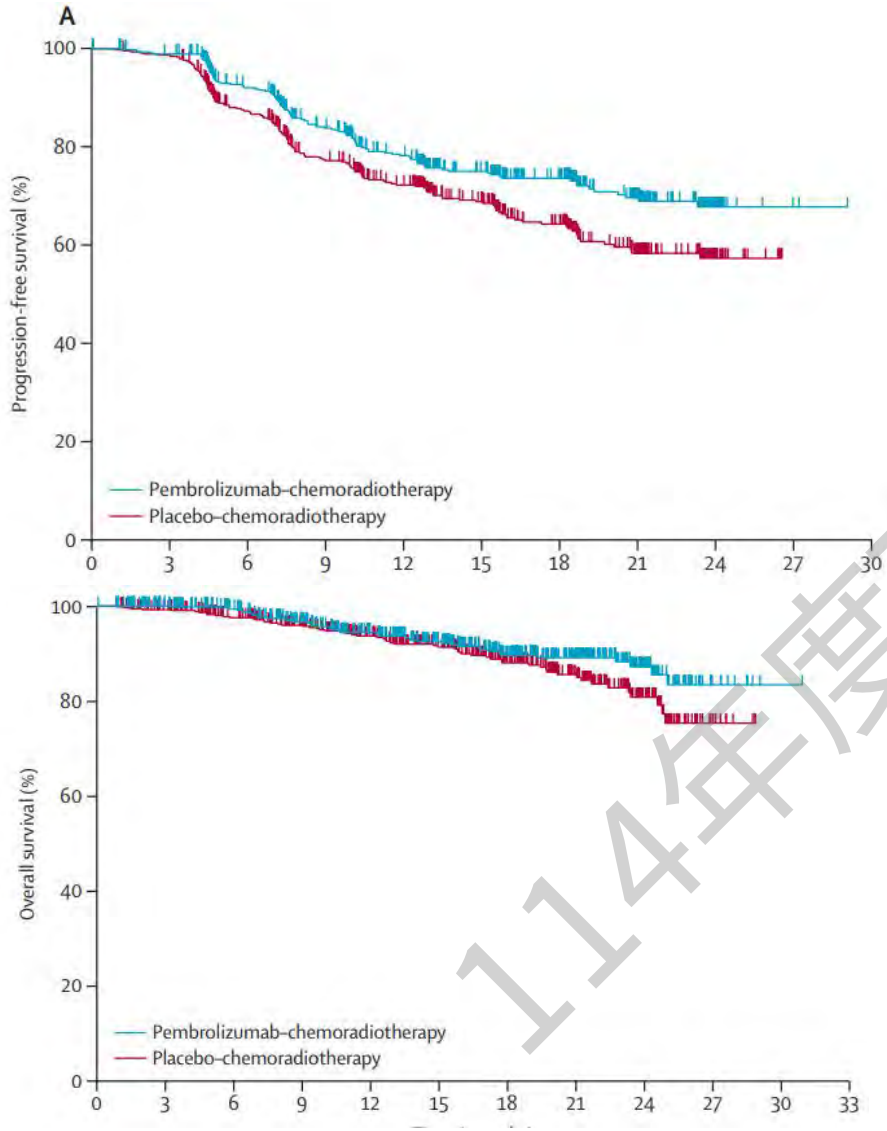
Domenica Lorusso, Yang Xiang, Kosei Hasegawa, Giovanni Scambia, Manuel Leiva, Pier Ramos-Elias, Alejandro Acevedo, Vladyslav Sukhin, Noelle Cloven, Andrea J Pereira de Santana Gomes, Fernando Contreras Mejía, Ari Reiss, Ali Ayhan, Jung-Yun Lee, Valeriya Saevets, Flora Zagouri, Lucy Gilbert, Jalid Sehouli, Ekkasit Tharavichitkul, Kristina Lindemann, Roberta Lazzari, Chih-Long Chang, Rudolf Lampé, Hong Zhu, Ana Oaknin, Melissa Christiaens, Stephan Polterauer, Tomoka Usami, Kan Li, Karin Yamada, Sarper Toker, Stephen M Keefe, Sandro Pignata, Linda R Duska*, on behalf of the ENGOT-cx11/GOG-3047/KEYNOTE-A18 investigators†*

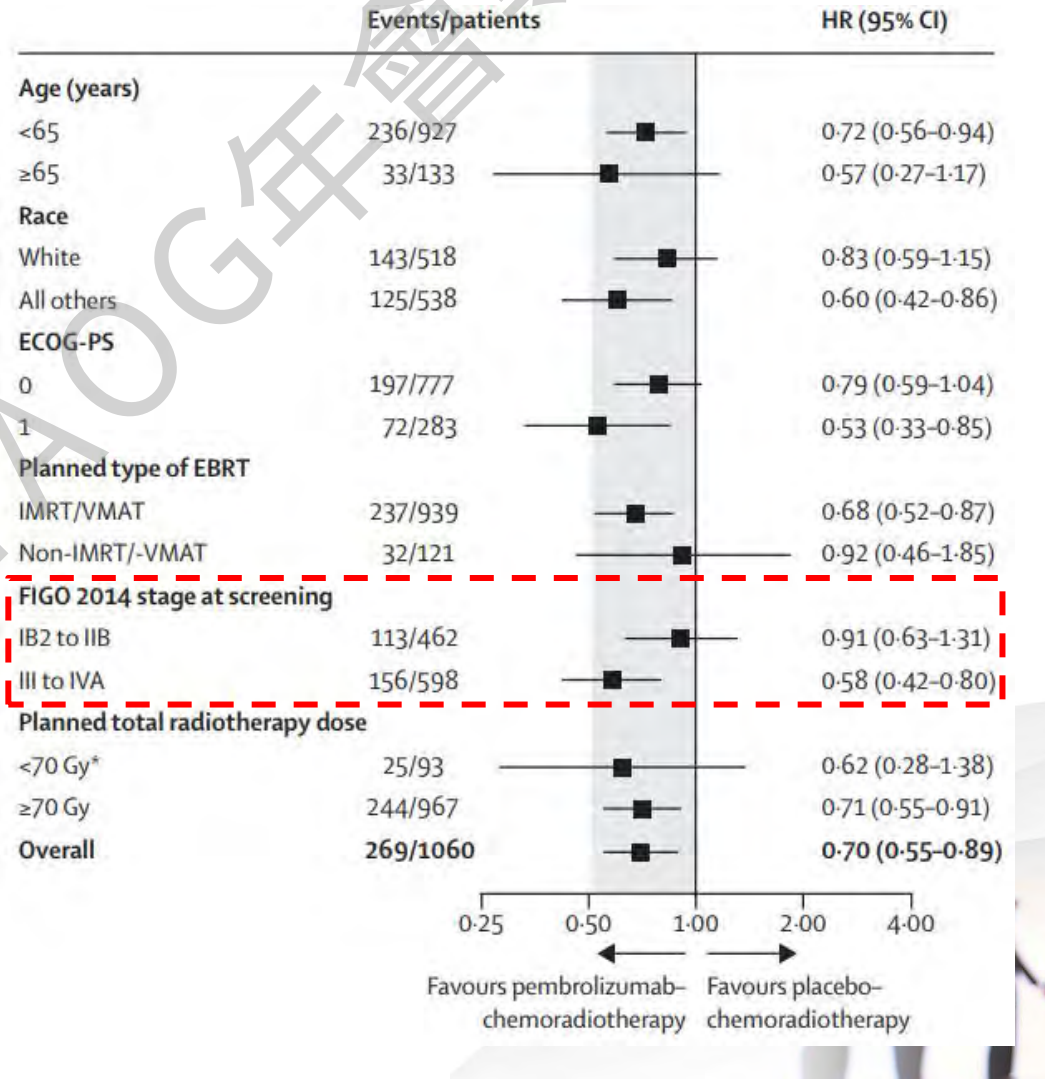
Summary

Background Pembrolizumab has shown efficacy in persistent, recurrent, or metastatic cervical cancer. The effect of

Lancet 2024; 403: 1341–50

LACC: In combination with CCRT
KEYNOTE-A18





U.S. FOOD & DRUG ADMINISTRATION

KEYNOTE-A18

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

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

Full prescribing information for Keytruda will be posted here (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm).

Efficacy was evaluated in KEYNOTE-A18 (NCT04221945), a multicenter, randomized, double-blind, placebo-controlled trial enrolling 1060 patients with cervical cancer who had not previously received definitive surgery, radiation, or systemic therapy. The trial included 596 patients with FIGO 2014 Stage III-IVA disease and 462 patients with FIGO 2014 Stage IB2-IIB, node-positive disease.

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-chemoradiotherapy-figo-2014-stage-iii-iva-cervical-cancer

LACC: In combination with CCRT
CALLA

Durvalumab versus placebo with chemoradiotherapy for locally advanced cervical cancer (CALLA): a randomised, double-blind, phase 3 trial

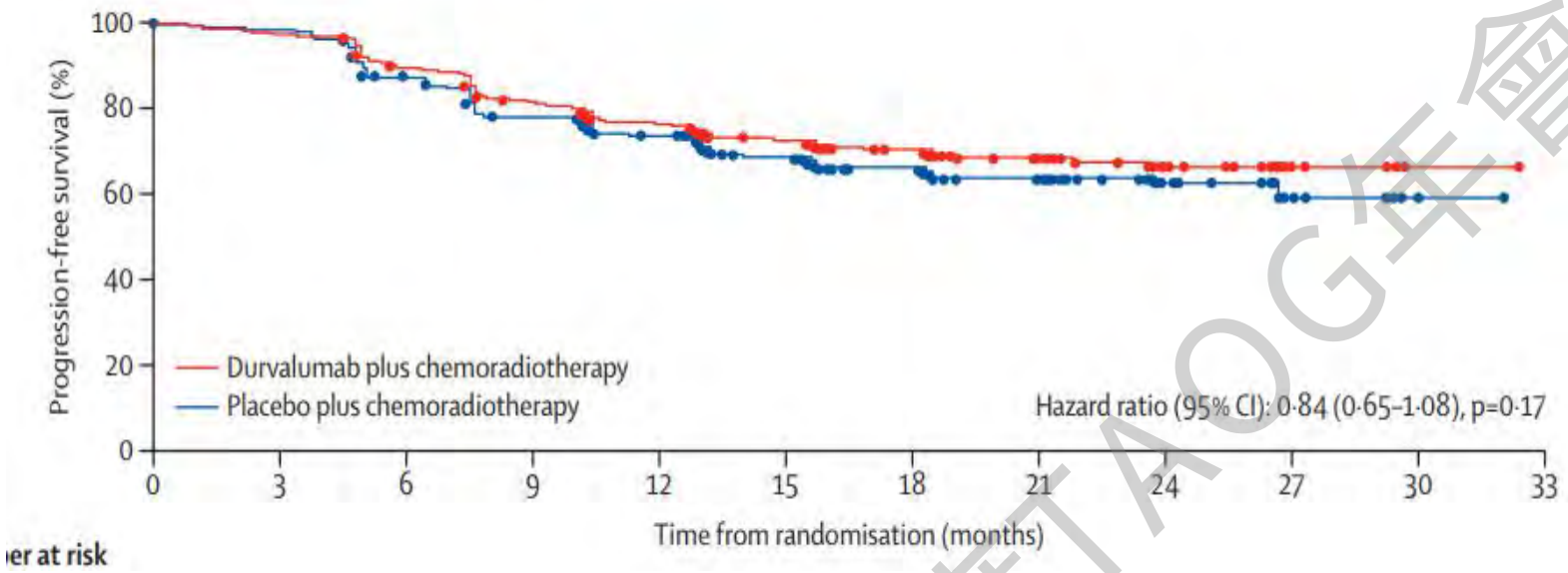
Bradley J Monk, Takafumi Toita, Xiaohua Wu, Juan C Vázquez Limón, Rafal Tarnawski, Masaki Mandai, Ronnie Shapira-Frommer, Umesh Mahantshetty, Maria del Pilar Estevez-Diz, Qi Zhou, Sewanti Limaye, Francisco J Ramirez Godinez, Christina Oppermann Kussler, Szilvia Varga, Natalia Valdiviezo, Daisuke Aoki, Manuel Leiva, Jung-Yun Lee, Raymond Sulay, Yulia Kreynina, Wen-Fang Cheng, Felipe Rey, Yi Rong, Guihao Ke, Sophie Wildsmith, Andrew Lloyd, Hannah Dry, Ana Tablante Nunes, Jyoti Mayadev

Lancet Oncol 2023; 24: 1334–48

Summary

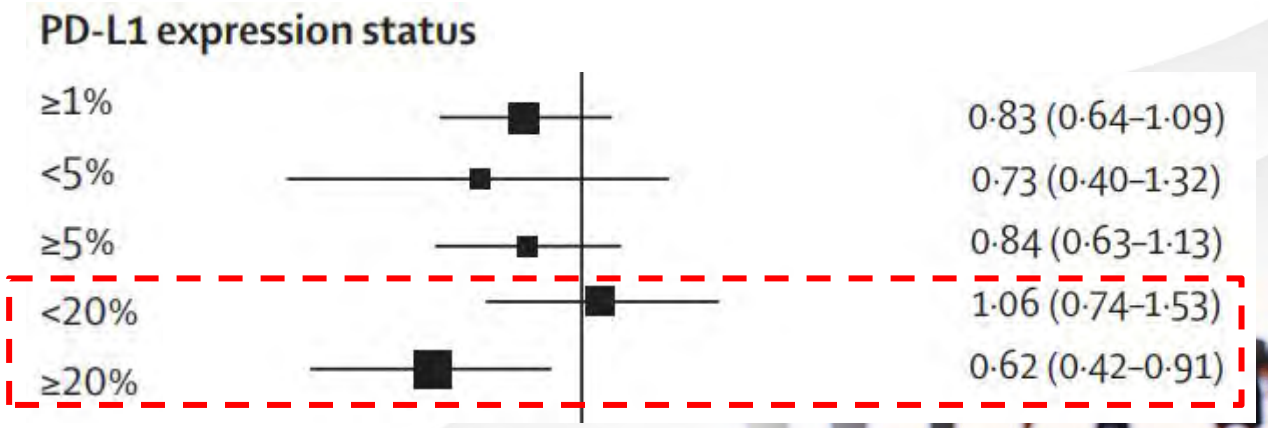
Background Concurrent chemoradiotherapy has been the standard of care for locally advanced cervical cancer for over

LACC: In combination with CCRT CALLA



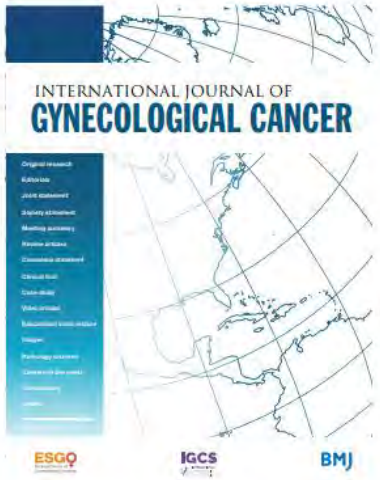
FIGO 2009 stage*		
IB2	19 (5%)	20 (5%)
IIA	21 (6%)	13 (3%)
IIB	95 (25%)	97 (25%)
IIIA	54 (14%)	64 (17%)
IIIB	171 (44%)	172 (45%)
IVA	25 (7%)	19 (5%)
Nodal involvement		
N0	106 (28%)	94 (24%)
N1	279 (73%)	291 (76%)

Within the PD-L1 TAP 20% or greater population, the progression-free survival benefit was evident regardless of LN involvement.



LACC: In combination with CCRT Hyperthermia

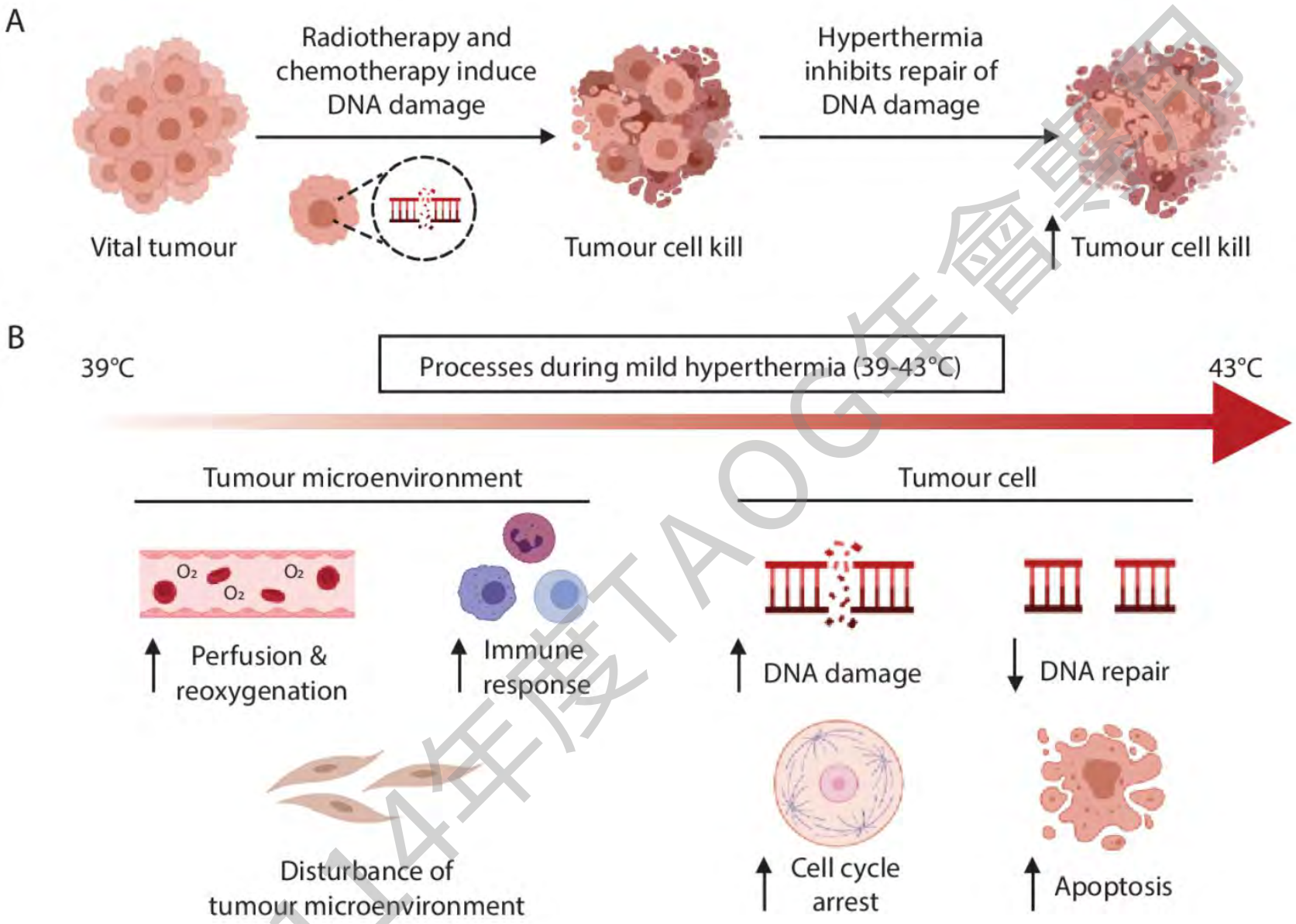
Review



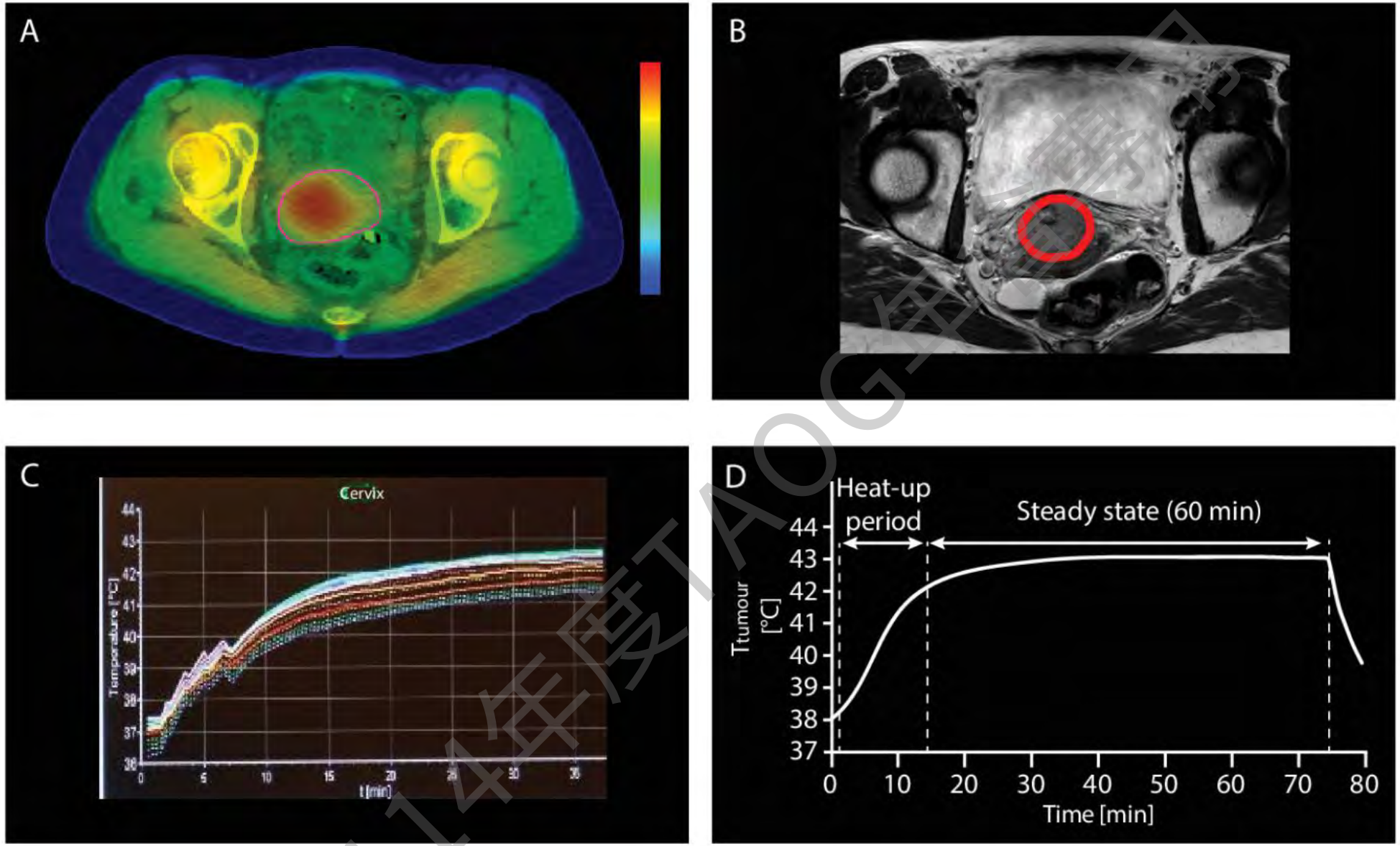
The role of hyperthermia in the treatment of locally advanced cervical cancer: a comprehensive review

Marloes IJff [1,2] Johannes Crezee,[1] Arlene L Oei,[1,2] Lukas J A Stalpers,[1,2] Henrike Westerveld[1]

IJff M, et al. Int J Gynecol Cancer 2022;32:288–296.



IJff M, et al. Int J Gynecol Cancer 2022;32:288–296.

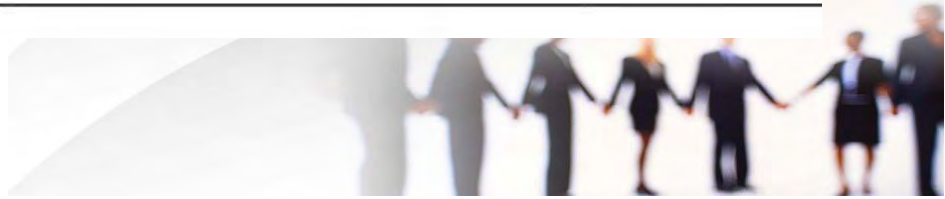


IJff M, et al. Int J Gynecol Cancer 2022;32:288–296.

LACC: In combination with CCRT Hyperthermia

Author (year of publication)	Years of inclusion	No of patients	Mono/ multi center	Treatment arms	HT temp (median °C)	Outcome		
						LC/PC	DFS	OS
Harima (2001)[42]	1994–1999	40	Mono	RT vs RHT	40.6	**10 vs 16***	**10 vs 16***	48 vs 58*
Van der Zee (2002)[35]	1990–1996	114	Multi	RT vs RHT	NA	**41 vs 61***	NA	**27 vs 51***
Vasanathan (2005)	1998–2002	110	Multi	RT vs RHT	41.6	69*	NA	73*
Lutgens (2016)[37]	2003–2009	84	Multi	CRT vs RHT	NA	NA	1.15†	1.04†
Harima (2016)[38]	2001–2015	101	Multi	CRT vs RCHT	41.1	71 vs 80	61 vs 71	65 vs 78
Minnaar (2019)[34]	2014–2017	202	Mono	CRT vs RCHT	NA	20 vs 39‡	**20 vs 39‡**	82 vs 87‡
Wang (2020)[39]	2009–2013	373	Mono	CRT vs RCHT	40.5	NA	83 vs 87	**72 vs 82**

IJff M, et al. Int J Gynecol Cancer 2022;32:288–296.



Radiofrequency (75-120 MHz)
60-90 minutes weekly (4-5 times)
Deep regional HT 40-43°C
Constant temperature monitor

LACC: In combination with CCRT
GCIC-INTERLACE

Induction chemotherapy followed by standard chemoradiotherapy versus standard chemoradiotherapy alone in patients with locally advanced cervical cancer (GCIG INTERLACE): an international, multicentre, randomised phase 3 trial

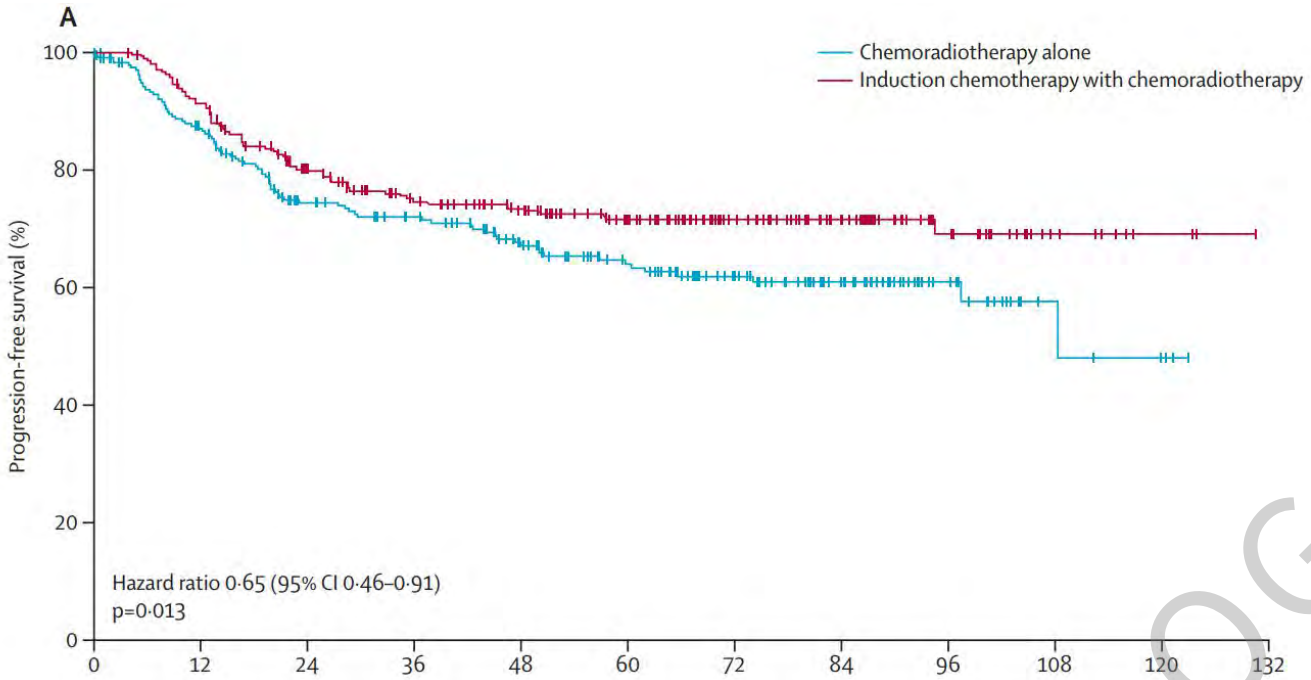
*Mary McCormack, Gemma Eminowicz, Dolores Gallardo, Patricia Diez, Laura Farrelly, Christopher Kent, Emma Hudson, Miguel Panades, Tony Mathew, Anjana Anand, Mojca Persic, Jennifer Forrest, Rajanee Bhana, Nicholas Reed, Anne Drake, Madhavi Adusumalli, Asima Mukhopadhyay, Margaret King, Karen Whitmarsh, John McGrane, Nicoletta Colombo, Choi Mak, Ranajit Mandal, Rahul Roy Chowdhury, Gabriela Alamilla-Garcia, Adriana Chávez-Blanco, Hilary Stobart, Amanda Feeney, Simran Vaja, Anne-Marie Hacker, Allan Hackshaw, Jonathan Andrew Ledermann, on behalf of the INTERLACE investigators**

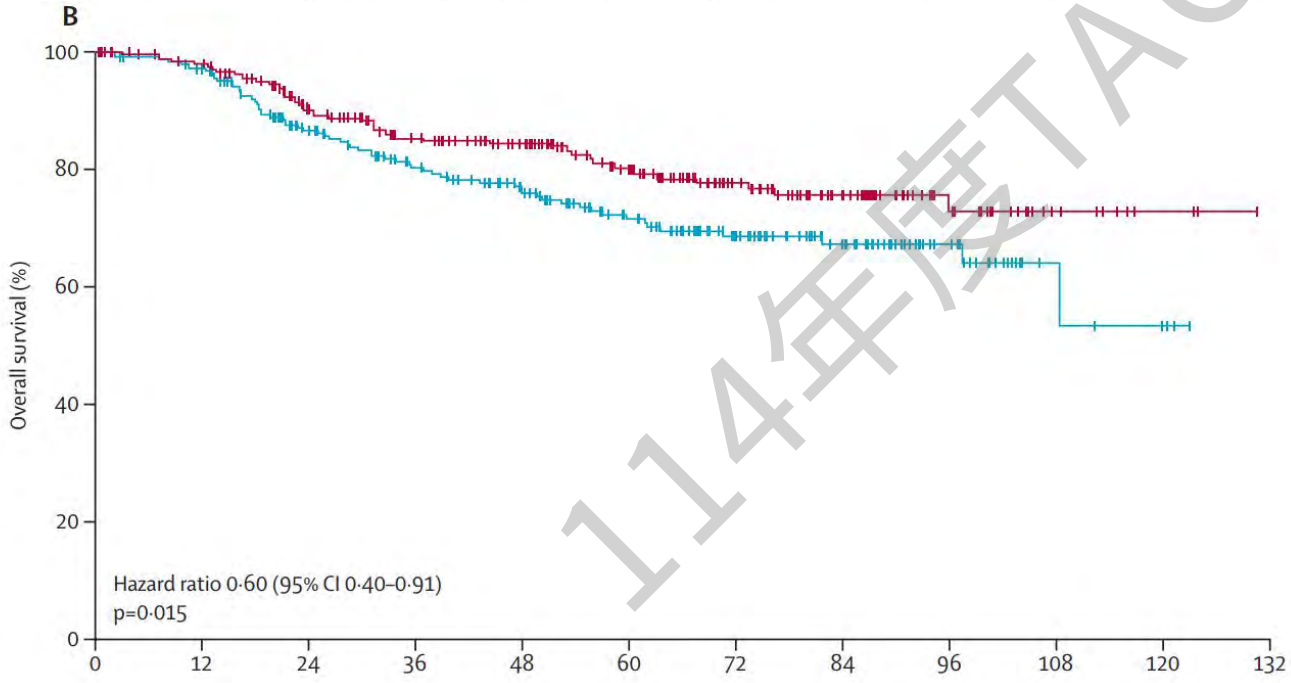
Summary

Background Locally advanced cervical cancer is treated with chemoradiotherapy (standard of care), but many patients

Lancet 2024; 404: 1525–35

GCIC-INTERLACE





	Induction chemotherapy with chemoradiotherapy (n=250)	Chemoradiotherapy alone (n=250)
FIGO stage (2008)		
IB1	2 (1%)	2 (1%)
IB2	19 (8%)	23 (9%)
IIA	17 (7%)	14 (6%)
IIB	178 (71%)	176 (70%)
IIIB	26 (10%)	30 (12%)
IVA	8 (3%)	5 (2%)
FIGO stage (2018)		
I and II	128 (51%)	126 (50%)
IIIB and IVA	22 (9%)	16 (6%)
IIIC	100 (40%)	108 (43%)

GCIC-INTERLACE

	Induction chemotherapy with chemoradiotherapy (n=250)		Chemoradiotherapy alone (n=250)
	Occurred at any time	Occurred after induction chemotherapy	
Any grade 3–4 event during induction chemotherapy	54 (22%)	NA	NA
Any adverse event	247 (99%)	243 (97%)	237 (95%)
Any grade 3–4 event	147 (59%)	131 (52%)	120 (48%)
Any haematological grade 3–4 event	74 (30%)	60 (24%)	32 (13%)
Neutropenia	48 (19%)	37 (15%)	13 (5%)
Anaemia	13 (5%)	9 (4%)	9 (4%)
Thrombocytopenia	13 (5%)	13 (5%)	5 (2%)
Any non-haematological grade 3–4 event	109 (44%)	98 (39%)	107 (43%)
Abdominal or pelvic pain	13 (5%)	11 (4%)	18 (7%)
Diarrhoea	20 (8%)	19 (8%)	31 (12%)
Fatigue, muscle weakness, or joint pain	28 (11%)	25 (10%)	14 (6%)
Infection	14 (6%)	12 (5%)	13 (5%)

There were three deaths within 30 days of completing treatment, one (respiratory failure) in the induction chemotherapy with chemoradiotherapy group, and two in the chemoradiotherapy alone group (sepsis and pulmonary embolism); none were considered treatment-related. NA=not applicable.

Table 4: **Adverse events**

More patients had grade 3–4 haematological adverse events in the induction chemotherapy with chemoradiotherapy group (30% vs 13%), largely neutropenia (19% of 5%).

LACC: In combination with CCRT
OUTBACK

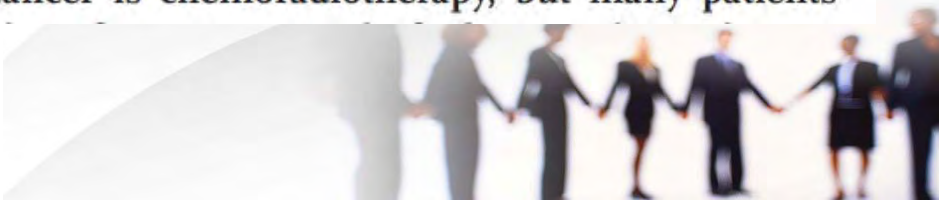
Adjuvant chemotherapy following chemoradiotherapy as primary treatment for locally advanced cervical cancer versus chemoradiotherapy alone (OUTBACK): an international, open-label, randomised, phase 3 trial

Linda R Mileshkin, Kathleen N Moore*, Elizabeth H Barnes, Val Gebski, Kailash Narayan, Madeleine T King, Nathan Bradshaw, Yeh Chen Lee, Katrina Diamante, Anthony W Fyles, William Small Jr, David K Gaffney, Pearly Khaw, Susan Brooks, J Spencer Thompson, Warner K Huh, Cara A Mathews, Martin Buck, Aneta Suder, Thomas E Lad, Igor J Barani, Christine H Holschneider, Sylvia Van Dyk, Michael Quinn, Danny Rischin, Bradley J Monk†, Martin R Stockler†*

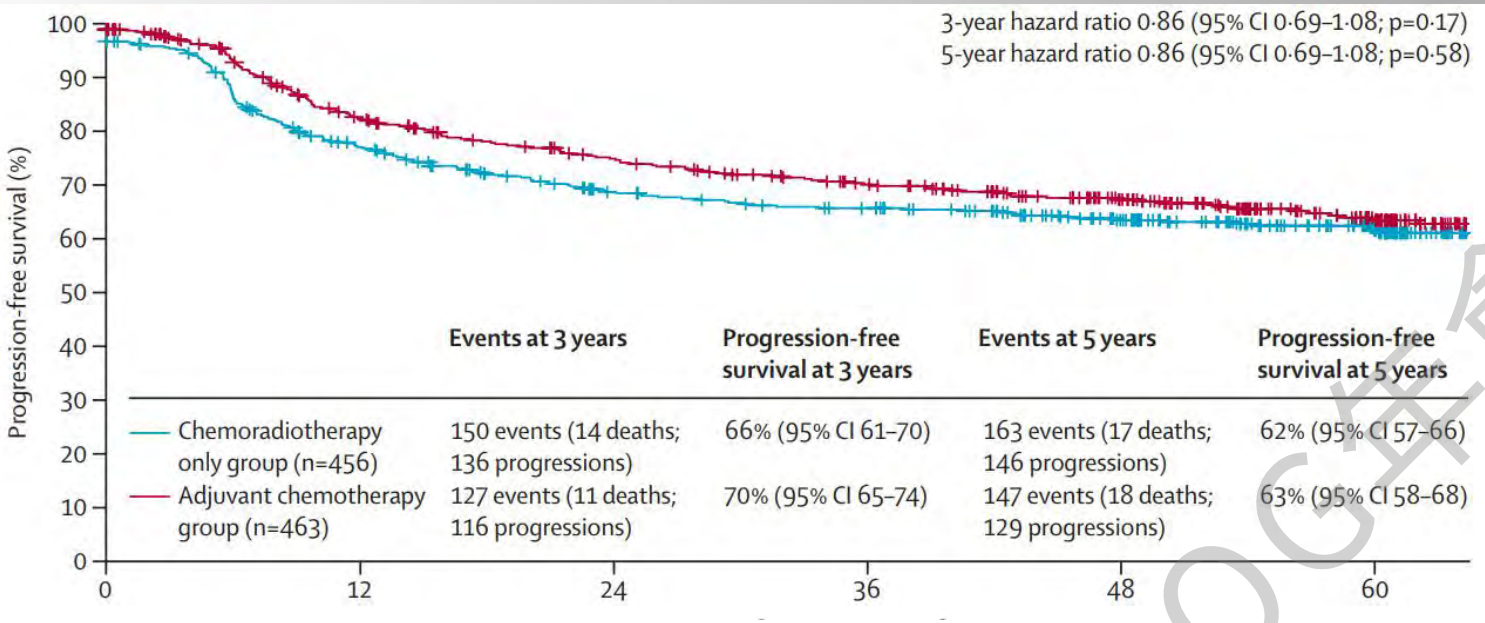
Lancet Oncol 2023; 24: 468–82

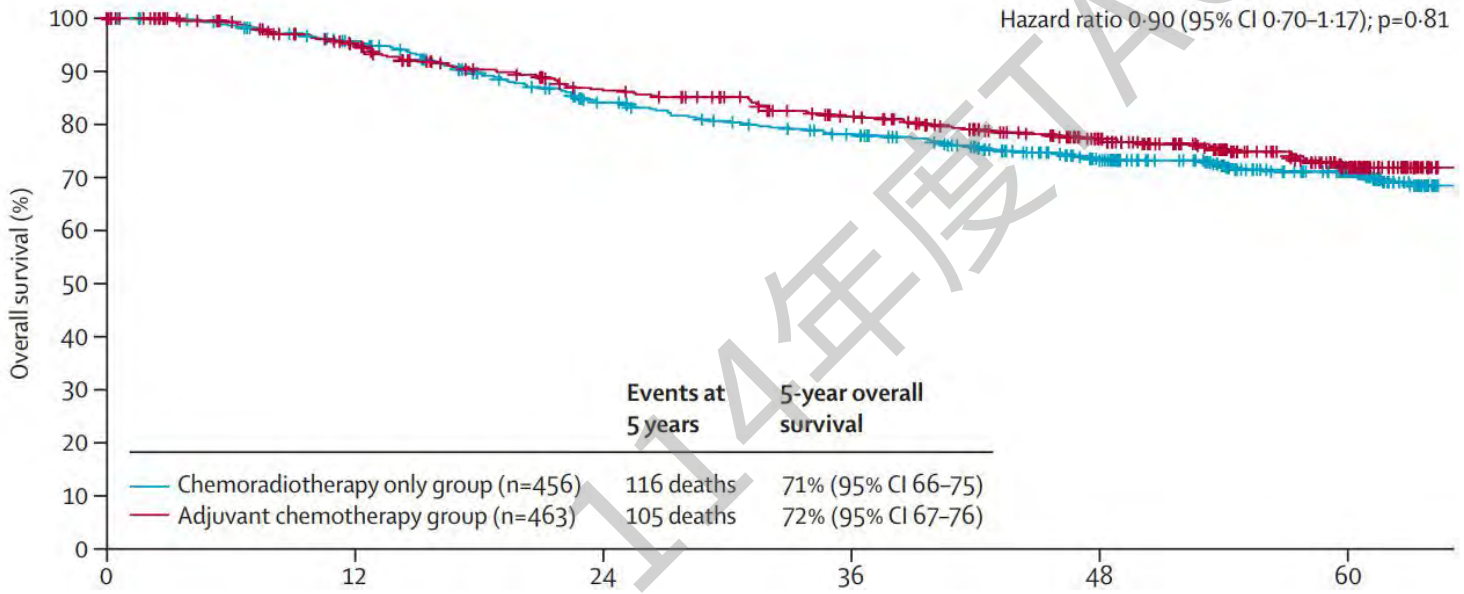
Summary

Background Standard treatment for locally advanced cervical cancer is chemoradiotherapy, but many patients



OUTBACK





Grade 3 or worse adverse events were reported in 292 (81%) patients in the adjuvant chemotherapy group versus 280 (62%) patients in the chemoradiotherapy only group ($p<0·0001$).

LACC: In combination with CCRT Maintenance ICIs

AstraZeneca

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Study of Volrustomig in Women With High Risk Locally Advanced Cervical Cancer (eVOLVE-Cervical) - eVOLVECervical

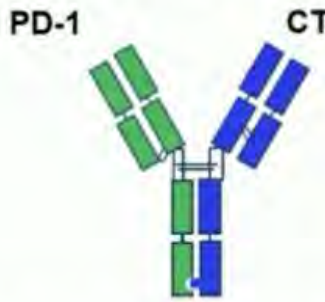
Study identifier:
D7984C00002

ClinicalTrials.gov identifier:
NCT06079671

EudraCT identifier:
N/A

CTIS identifier:
2023-504374-38-00

MEDI5752: A monovalent bispecific antibody



- Affinity to human CTLA-4: 0.42 nM
- Affinity to human PD-1: 0.81 nM
- Fc isotype: human IgG1-TM (reduced antibody-dependent cellular cytotoxicity)
- CTLA-4 arm = Tremelimumab arm

Tran AACR2022, Albiges ASCO2023

J Gynecol Oncol. 2024 Jul;35(4):e82
https://doi.org/10.3802/jgo.2024.35.e82
pISSN 2005-0380·eISSN 2005-0399

JGO JOURNAL OF GYNECOLOGIC ONCOLOGY

Review Article

Bispecific immunotherapy MEDI5752 or volrustomig and cervical cancer

歡迎閱讀最新的 eVOLVE-Cervical 全球的Investigator Newsletter，本次重點摘要如下，細節部分還請您參閱附件：

首先，代表全球和臺灣團隊，非常感謝您對 eVOLVE-Cervical試驗的支持、參與及提供非常寶貴的意見

台灣試驗機構與收案狀況如下 (as of 24Dec): **(括號內數字表示13 Nov後增加的人數)**

Site Number	Site's Name	PI's Name	Total Part 1 Screened	In Screen Part 1	Total Part 2 Screened	In Screen Part 2	Screen Failed	Randomized Patients
7401	TPVGH	Peng-Hui Wang	6	0	6	0	3 (+1)	3
7402	TCVGH	Chien-Hsing Lu	5	1	2	0	4	1
7403	MMH	Chih-Long Chang	4	0	2	0	3 (+1)	1
7404	NCKUH	Yu-Fang Huang	10 (+2)	3	5	0	4	3
7405	CGMF-LK	Yun-Hsin Tang	7	0	5	0	3	4
7406	FEMH	Sheng Mou Hsiao	4	0	3	0	1	3
7407	KSVGH	Wen Shiung Liou	5	0	3	0	2	3
7408	CGMF-KS	Chen-Hsuan Wu	1	0	1	0	1	0
		Total	43 (+2)	4	27	0	21 (+2)	18

Part-II

- Primary therapy
  - ESCC: Surgical intervention
  - LACC: Additional modalities in combination with traditional CCRT
- Recurrent/Metastatic therapy
  - Immunotherapy (ICI)
  - ADC
  - Radiation therapy
- Summary of ongoing trials
- Conclusion

Anti-VEGF Target Therapy- GOG-240

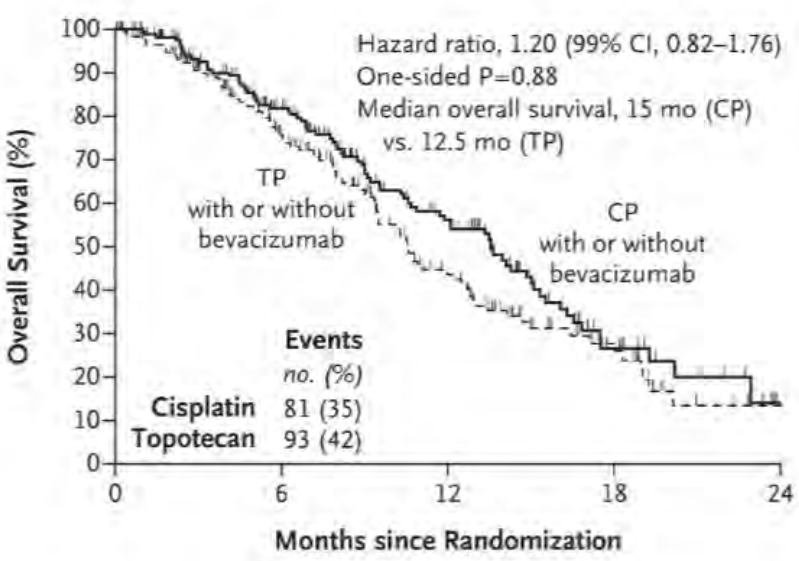
ORIGINAL ARTICLE

Improved Survival with Bevacizumab in Advanced Cervical Cancer

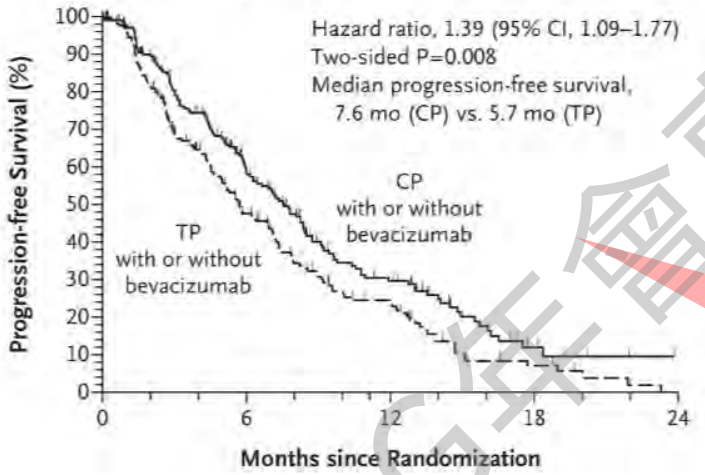
Krishnansu S. Tewari, M.D., Michael W. Sill, Ph.D., Harry J. Long III, M.D., Richard T. Penson, M.D., Helen Huang, M.S., Lois M. Ramondetta, M.D., Lisa M. Landrum, M.D., Ana Oaknin, M.D., Thomas J. Reid, M.D., Mario M. Leitao, M.D., Helen E. Michael, M.D., and Bradley J. Monk, M.D.

N Engl J Med. 2014 Feb 20;370(8):734-43.

GOG-240



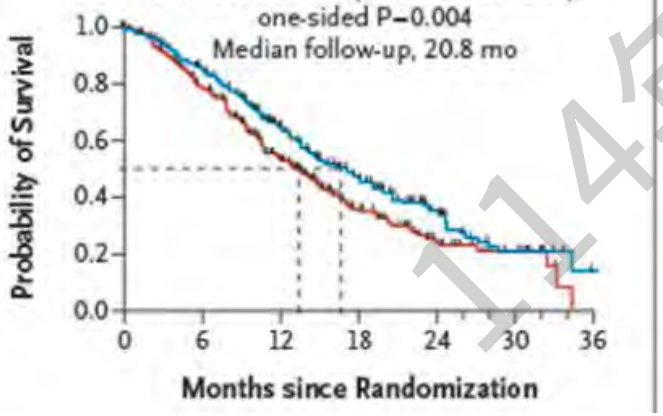
	No Disease Progression	Disease Progression	Total
Cisplatin	97	132	229
Topotecan	73	150	223



Platinum-based chemotherapy is better than non-platinum based regimen.

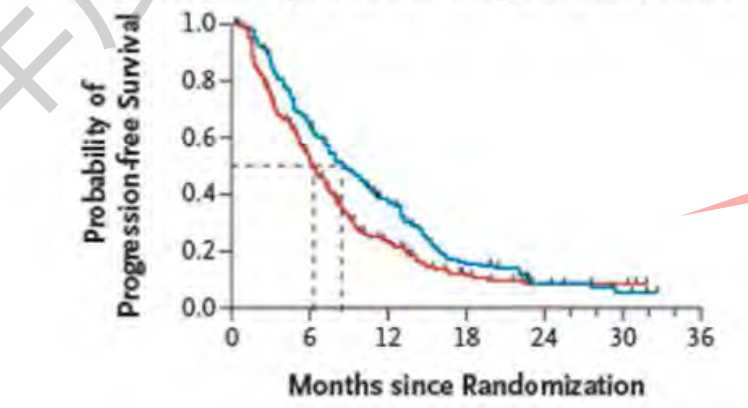
A

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



B

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



Chemotherapy plus bevacizumab is better than non-bevacizumab regimen.

ICI- KEYNOTE 826

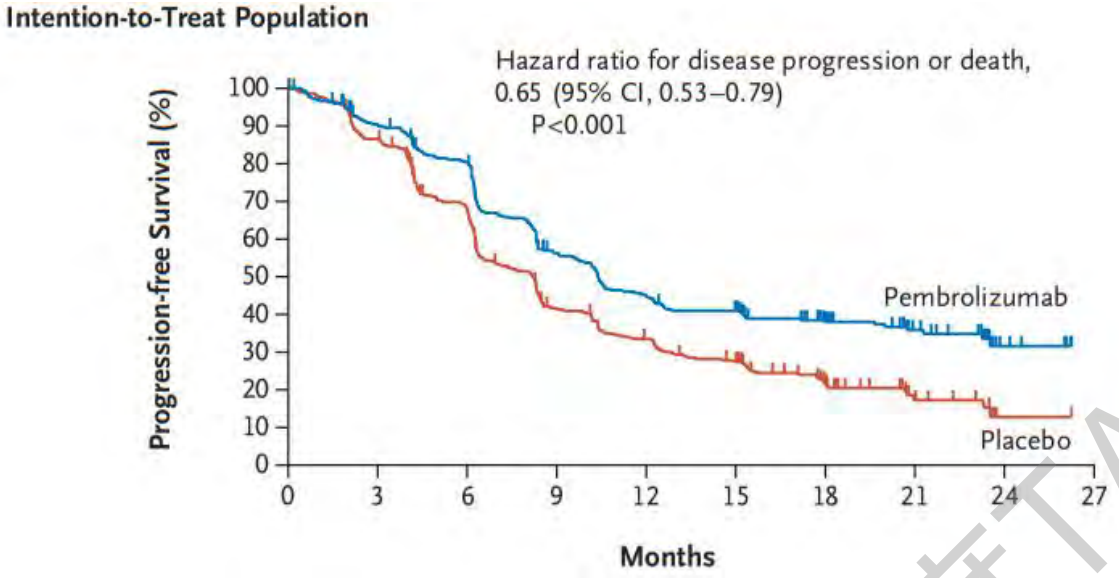
ORIGINAL ARTICLE

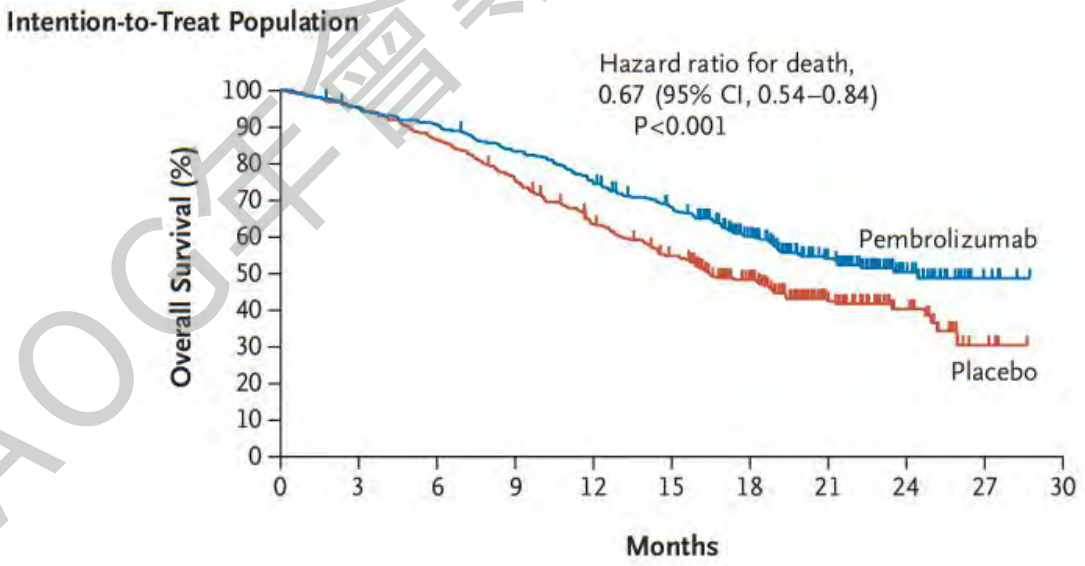
Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer

N. Colombo, C. Dubot, D. Lorusso, M.V. Caceres, K. Hasegawa, R. Shapira-Frommer, K.S. Tewari, P. Salman, E. Hoyos Usta, E. Yañez, M. Gümüş, M. Olivera Hurtado de Mendoza, V. Samouëlian, V. Castonguay, A. Arkhipov, S. Toker, K. Li, S.M. Keefe, and B.J. Monk, for the KEYNOTE-826 Investigators*

N Engl J Med. 2021 Nov 11;385(20):1856-1867.

ICI- KEYNOTE 826





PD-L1 combined positive score		
<1	51/69	0.94 (0.52–1.70)
1 to <10	152/231	0.68 (0.49–0.94)
≥10	203/317	0.58 (0.44–0.77)
Concomitant bevacizumab		
Yes	234/389	0.61 (0.47–0.79)
No	172/228	0.74 (0.54–1.01)

CPS≥1 showed better outcome. Bevacizumab adding is not matter.

ICI- KEYNOTE 826

FDA approves pembrolizumab combination for the first-line treatment of cervical cancer

On October 13,2021, the Food and Drug Administration approved pembrolizumab (Keytruda, Merck) in combination with chemotherapy, with or without bevacizumab, for patients with persistent, recurrent or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1), as determined by an FDA-approved test.

FDA also granted regular approval to pembrolizumab as a single agent 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. In June 2018, FDA had granted accelerated approval to this indication with the companion diagnostic, PD-L1 IHC 22C3 pharmDx (Dako North America Inc.).

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-combination-first-line-treatment-cervical-cancer

ICI- BEATcc

Atezolizumab plus bevacizumab and chemotherapy for metastatic, persistent, or recurrent cervical cancer (BEATcc): a randomised, open-label, phase 3 trial

*Ana Oaknin, Laurence Gladieff, Jerónimo Martínez-García, Guillermo Villacampa, Munetaka Takekuma, Ugo De Giorgi, Kristina Lindemann, Linn Woelber, Nicoletta Colombo, Linda Duska, Alexandra Leary, Ana Godoy-Ortiz, Shin Nishio, Antoine Angelergues, Maria Jesús Rubio, Lorena Fariñas-Madrid, Satoshi Yamaguchi, Domenica Lorusso, Isabelle Ray-Coquard, Luis Manso, Florence Joly, Jesús Alarcón, Philippe Follana, Ignacio Romero, Coriolan Lebreton, J Alejandro Pérez-Fidalgo, Mayu Yunokawa, Hanna Dahlstrand, Véronique D'Hondt, Leslie M Randall for the ENGOT-Cx10–GEICO 68-C–JGOG1084–GOG-3030 Investigators**

Summary

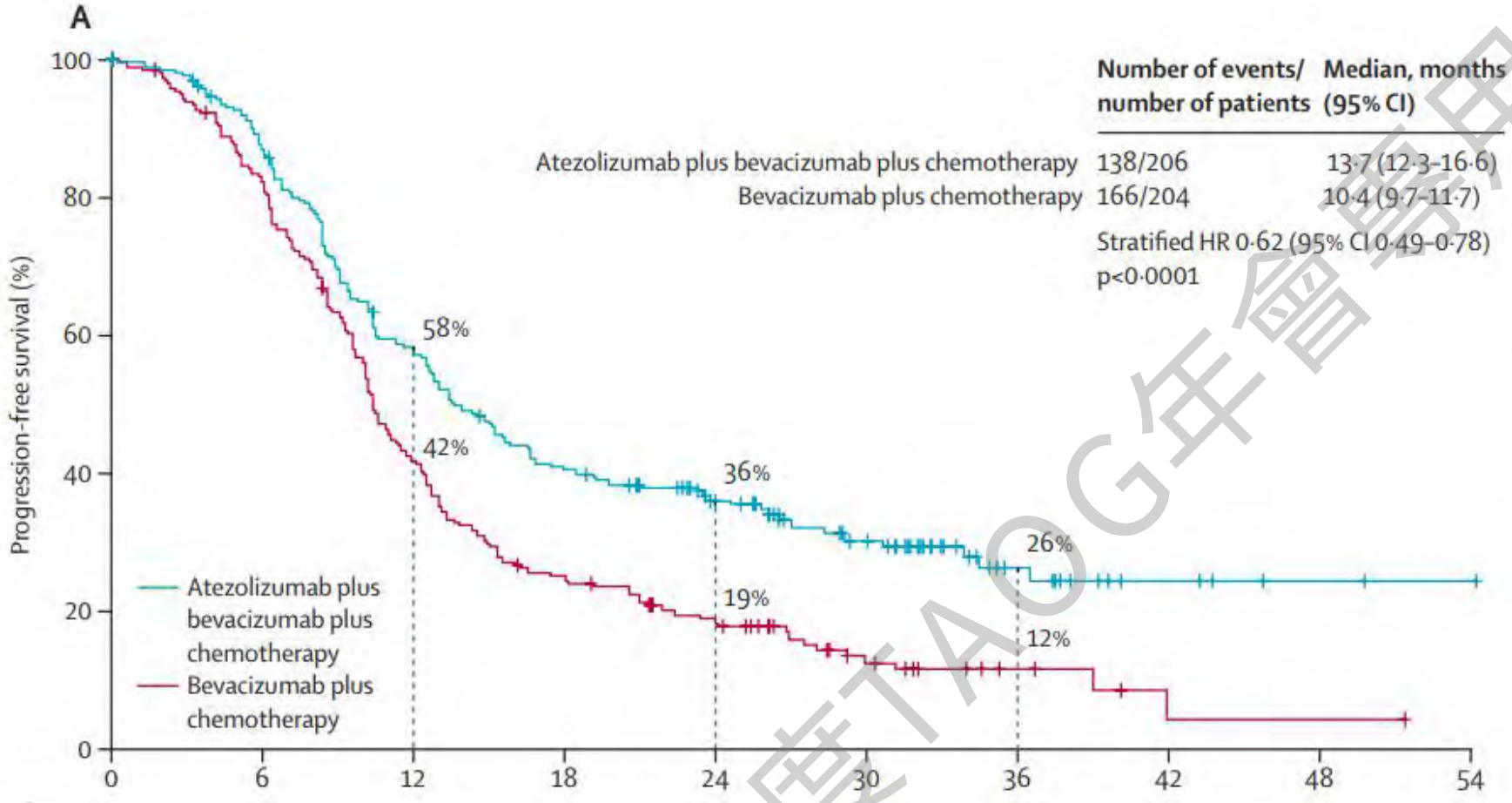
Background The GOG240 trial established bevacizumab with chemotherapy as standard first-line therapy for

Lancet 2024; 403: 31–43

	Atezolizumab plus bevacizumab plus chemotherapy (experimental group; n=206)	Bevacizumab plus chemotherapy (standard group; n=204)
(Continued from previous page)		
Histological subtype		
Squamous cell carcinoma	164 (80%)	157 (77%)
Adenocarcinoma	36 (17%)	43 (21%)
Adenosquamous cell carcinoma	6 (3%)	4 (2%)

The BEATcc trial enrolled an all-comer population with no biomarker selection. These and previously reported results for other agents raise the question of whether PD-L1 is necessary to select patients deriving greatest benefit from immunotherapy for cervical cancer, or whether the relationship between PD-L1 and HPV infection makes it a less discerning biomarker.

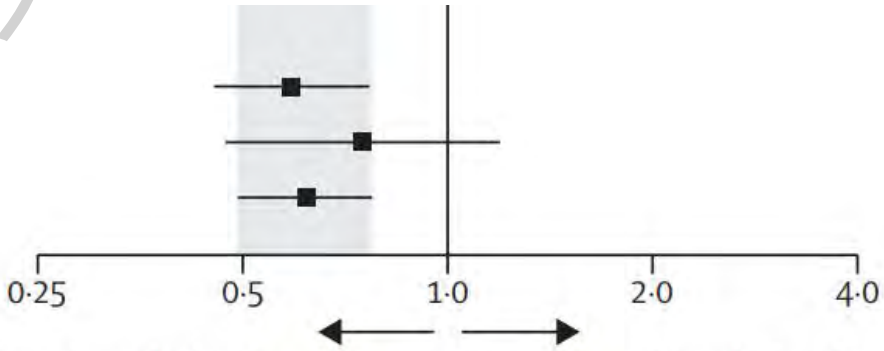
BEATcc



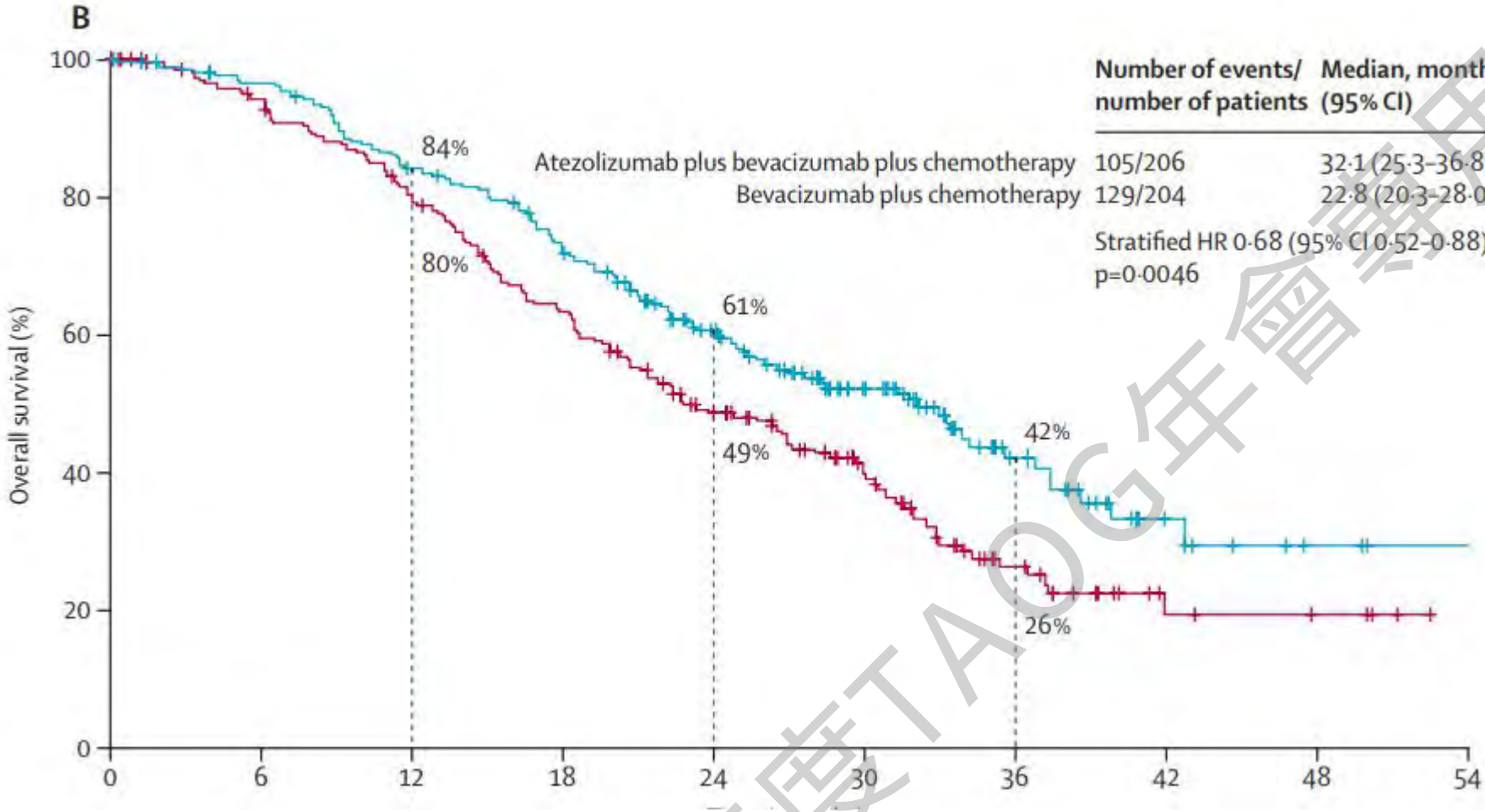
	Number of events/ number of patients	Median, months (95% CI)
Atezolizumab plus bevacizumab plus chemotherapy	138/206	13·7 (12·3–16·6)
Bevacizumab plus chemotherapy	166/204	10·4 (9·7–11·7)

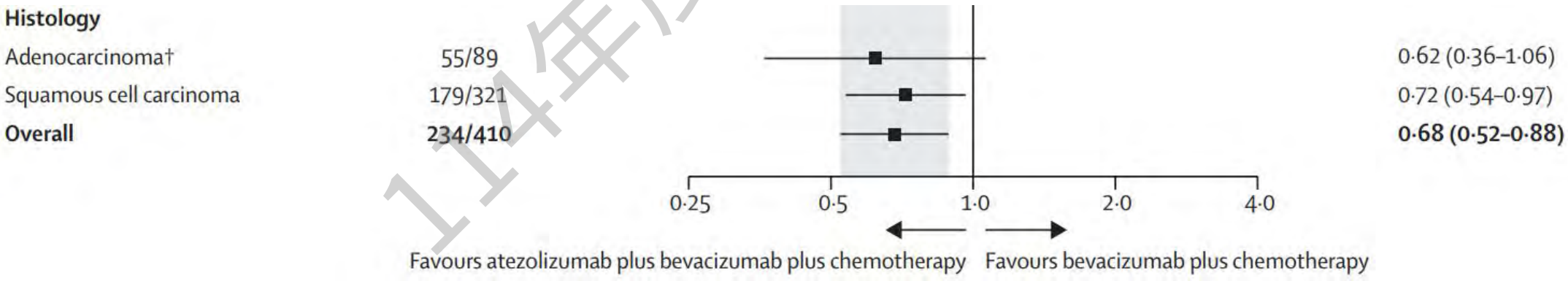
Stratified HR 0·62 (95% CI 0·49–0·78)
p<0·0001

Histology		
Adenocarcinoma†	73/89	0·59 (0·45–0·76)
Squamous cell carcinoma	231/321	0·75 (0·47–1·19)
Overall	**304/410**	**0·62 (0·49–0·78)**



BEATcc





ICI- CMPASSION-16

Cadonilimab plus platinum-based chemotherapy with or without bevacizumab as first-line treatment for persistent, recurrent, or metastatic cervical cancer (COMPASSION-16): a randomised, double-blind, placebo-controlled phase 3 trial in China

Xiaohua Wu, Yang Sun, Hongying Yang, Jing Wang, Hanmei Lou, Dan Li, Ke Wang, Hui Zhang, Tao Wu, Yuzhi Li, Chunyan Wang, Guiling Li, Yifeng Wang, Dapeng Li, Ying Tang, Mei Pan, Hongyi Cai, Weihu Wang, Bing Yang, Hua Qian, Qiuhong Tian, Desheng Yao, Ying Cheng, Bing Wei, Xiumin Li, Tao Wang, Min Hao, Xiaohong Wang, Tiejun Wang, Juntao Ran, Hong Zhu, Lijing Zhu, Xianling Liu, Yunxia Li, Lihong Chen, Qingshan Li, Xiaojian Yan, Fei Wang, Hongbing Cai, Yunyan Zhang, Zhiqing Liang, Funan Liu, Yi Huang, Bairong Xia, Pengpeng Qu, Genhai Zhu, Youguo Chen, Kun Song, Meili Sun, Zhengzheng Chen, Qiang Zhou, Lina Hu, Guzhalinuer Abulizi, Hongyan Guo, Sihai Liao, Yijing Ye, Ping Yan, Qiu Tang, Guoping Sun, Ting Liu, Dongmei Lu, Mingxiu Hu, Zhongmin M Wang, Baiyong Li, Michelle Xia

Lancet 2024; 404: 1668–76

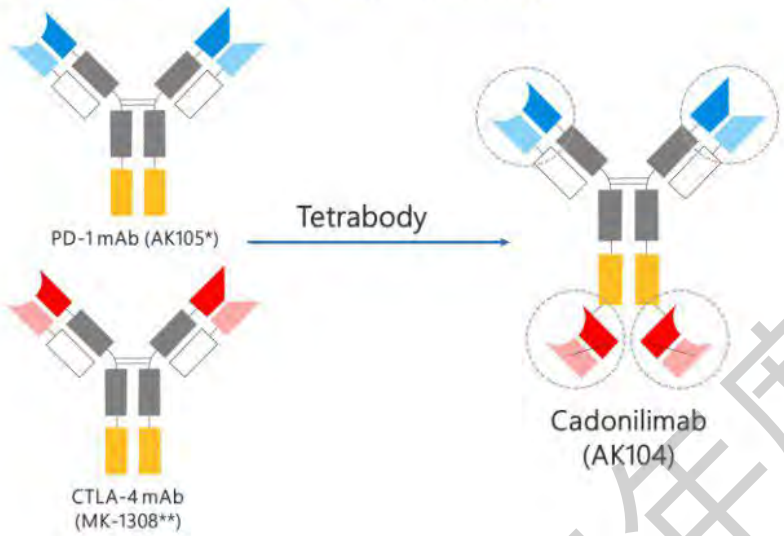
Summary

Background Cadonilimab is a bispecific antibody targeting PD-1 and CTLA-4, which has shown substantial clinical

AK104 (CADONILIMAB)

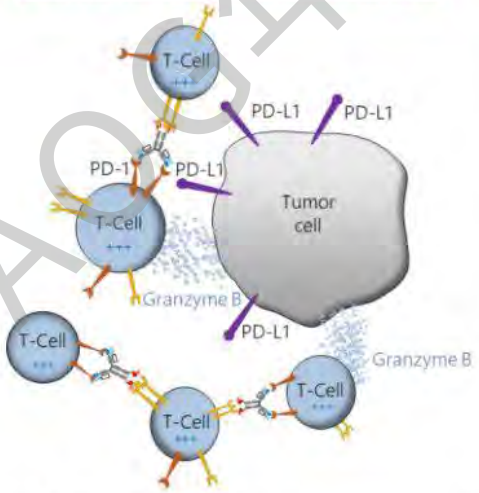
- AK104 is a next-generation, potential first-in-class humanized bi-specific antibody drug candidate targeting PD-1 and CTLA-4 simultaneously
- AK104 is designed as a novel tetrameric form, which can bind tetravalently to TILs co-expressing PD-1 & CTLA-4 with higher avidity
- Therefore, AK104 is designed to retain the efficacy of dual blockade of PD-1 and CTLA-4 and improve the safety profile of this combination therapy

First-in-class bi-specific antibody

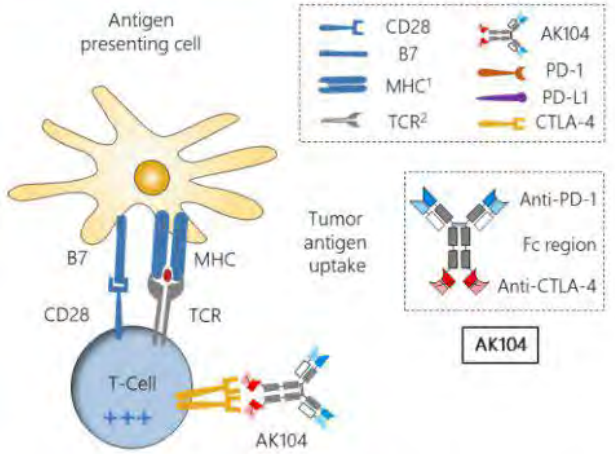


*: Penpulimab **: CTLA-4 mAb out-licensed to MSD

Tumour Microenvironment

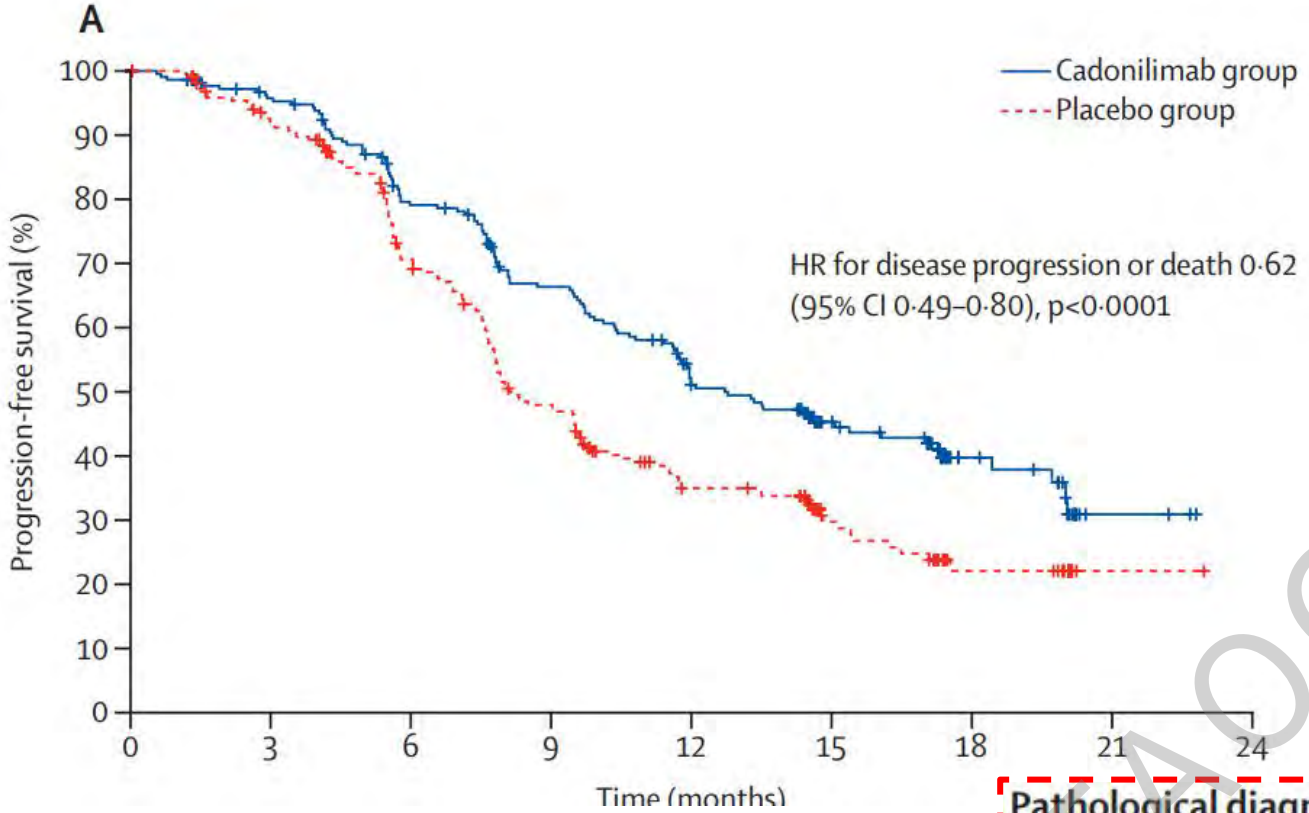


Peripheral Sites



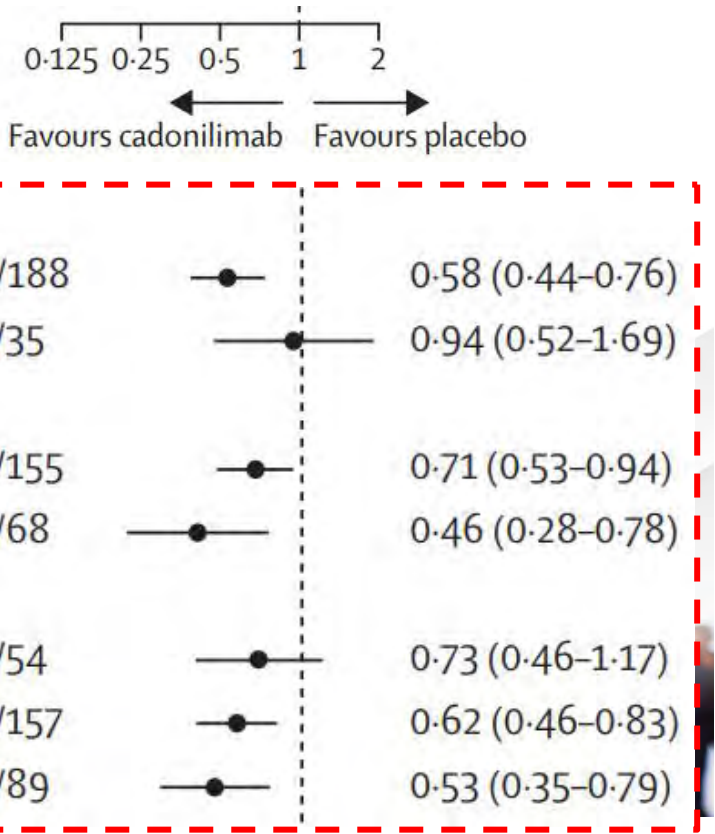
- PD-1 and CTLA-4 are co-expressed in tumor infiltrating lymphocytes (TILs), but not in normal peripheral tissue lymphocytes
- Anti-PD-1/CTLA-4 bi-specific may display higher avidity for lymphocytes in the tumor microenvironment versus peripheral sites

CMPASSION-16

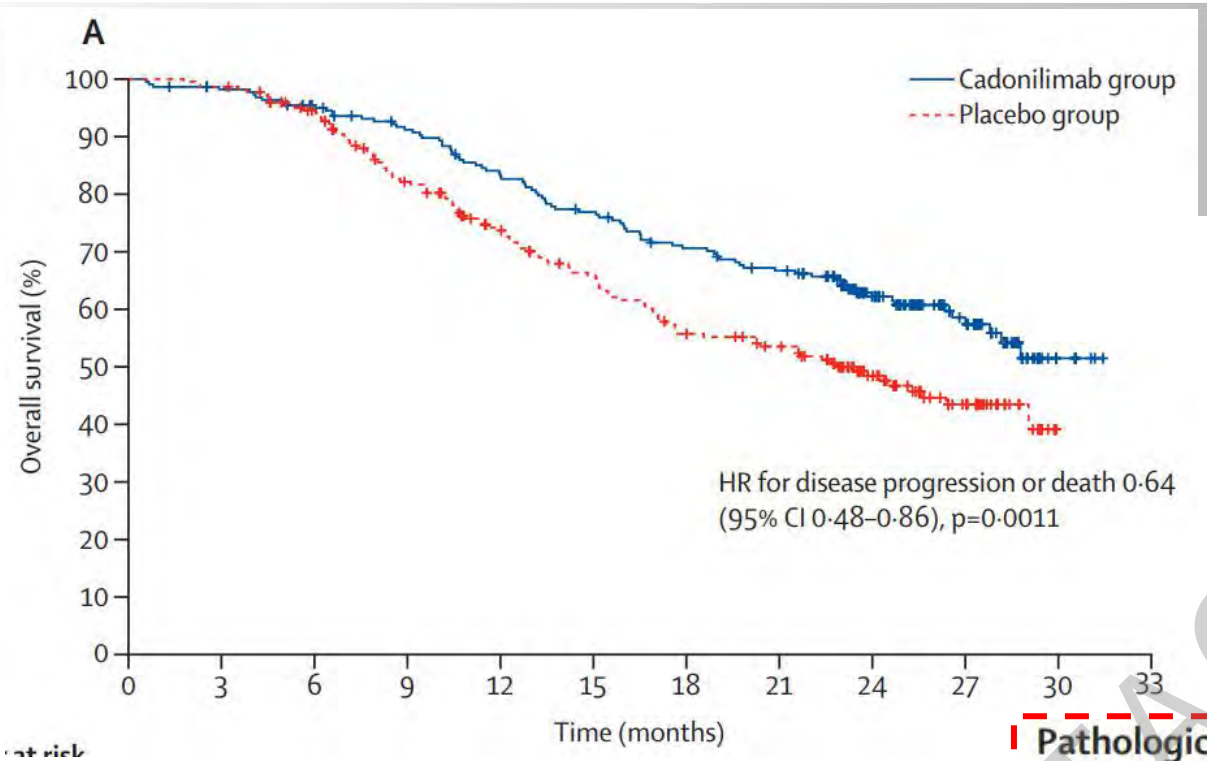


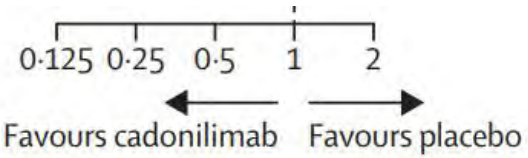
PFS survival curves.

SCC, PD-L1≥1 showed better in PFS while adding cadolinimab to standard chemotherapy.



CMPASSION-16





Pathological diagnosis			
Squamous cell carcinoma	67/182	88/188	0·64 (0·47–0·88)
Non-squamous cell carcinoma	19/40	19/35	0·63 (0·33–1·22)
Metastatic			
Yes	68/168	70/155	0·73 (0·52–1·02)
No	18/54	37/68	0·48 (0·27–0·86)
PD-L1 combined positive score			
<1	25/62	24/54	0·77 (0·44–1·34)
≥1	61/155	74/157	0·69 (0·49–0·97)
≥10	33/91	37/89	0·68 (0·42–1·08)

OS survival curves.

SCC, PD-L1≥1 showed better in OS while adding cadolinimab to standard chemotherapy.

ICI- CMPASSION-16

New Drug Application for Cadonilimab (PD-1/CTLA-4 Bi-Specific Antibody) for the Treatment of Relapsed or Metastatic Cervical Cancer Accepted by NMPA

2021-09-24

(HONG KONG, 24 Sept 2021) Akeso, Inc. (the Company, 9926.HK) announces that the National Medical Products Administration (the NMPA) of China has officially accepted the new drug application for the world's first-in-class Cadonilimab (PD-1/CTLA-4 bi-specific antibody, research and development code: AK104) for the treatment of relapsed or metastatic cervical cancer, which has received priority review. Cadonilimab, independently developed and manufactured by the Company, is the first PD-1 based bi- specific antibody drug in the world to submit new drug application.

Milestones of Cadonilimab for treatment of cervical cancer:

July 2021, the phase III clinical trial of Cadonilimab in combination with chemotherapy for treatment of advanced cervical cancer officially initiated.

Feb 2021, the Food and Drug Administration of the United States (the FDA) granted orphan drug designation to Cadonilimab for treatment of cervical cancer.

Oct 2020, Cadonilimab for treatment of relapsed or metastatic cervical cancer patients after the failure of platinum-based chemotherapy was included in the list of "Breakthrough Therapy Designation" by the Center for Drug Evaluation (the CDE) under the NMPA.

July 2020, the FDA granted fast track designation to Cadonilimab for treatment of relapsed or metastatic cervical cancer patients after the failure of platinum-based chemotherapy.

Currently major indications of Cadonilimab include gastric cancer, lung cancer, liver cancer, esophageal squamous cancer, nasopharyngeal cancer, etc. Among which the phase III clinical trial for first-line treatment of gastric cancer has officially initiated.

Brief Summary-1st Line

	KEYNOTE-826	BEATcc	COMPASSION-16
Enrolled cases	All comer: SCC, AdenoCa, Adenosaquamous, naive for systemic/curative therapy	All comer: SCC(80%), AdenoCa(including Adenosaquamous 20%) Anti-VEGF/anti-PD(L)-1 naive	All Chinese, SCC(80%), AdenoCa(including Adenosaquamous 20%)
Experimental arm	Paclitaxel+Cisapltin/Carboplatin +/- Bevacizumab+ Pemrolizumab	Paclitaxel+Cisapltin/Carboplatin+Bevacizumab+ Atezolizumab	Paclitaxel+Cisapltin/Carboplatin +/-Bevacizumab+ Cadonilimab
Control arm	Paclitaxel+Cisapltin/Carboplatin +/-Bevacizumab	Paclitaxel+Cisapltin/Carboplatin+Bevacizumab	Paclitaxel+Cisapltin/Carboplatin +/-Bevacizumab
PDL1 expression	(22C3 pharmDx assay (Agilent)) <1: 11.4%, ≥1: 88.6%	(not provided)	(22C3 pharmDx assay (Agilent)) <1: 25-28%, ≥1: 70%
Approval for Cx Ca	US FDA (2021-10)	?	EU (2022-11)

ICI- EMPOWER Cervical 1

(progressed after platinum-containing therapy)

The NEW ENGLAND JOURNAL of MEDICINE

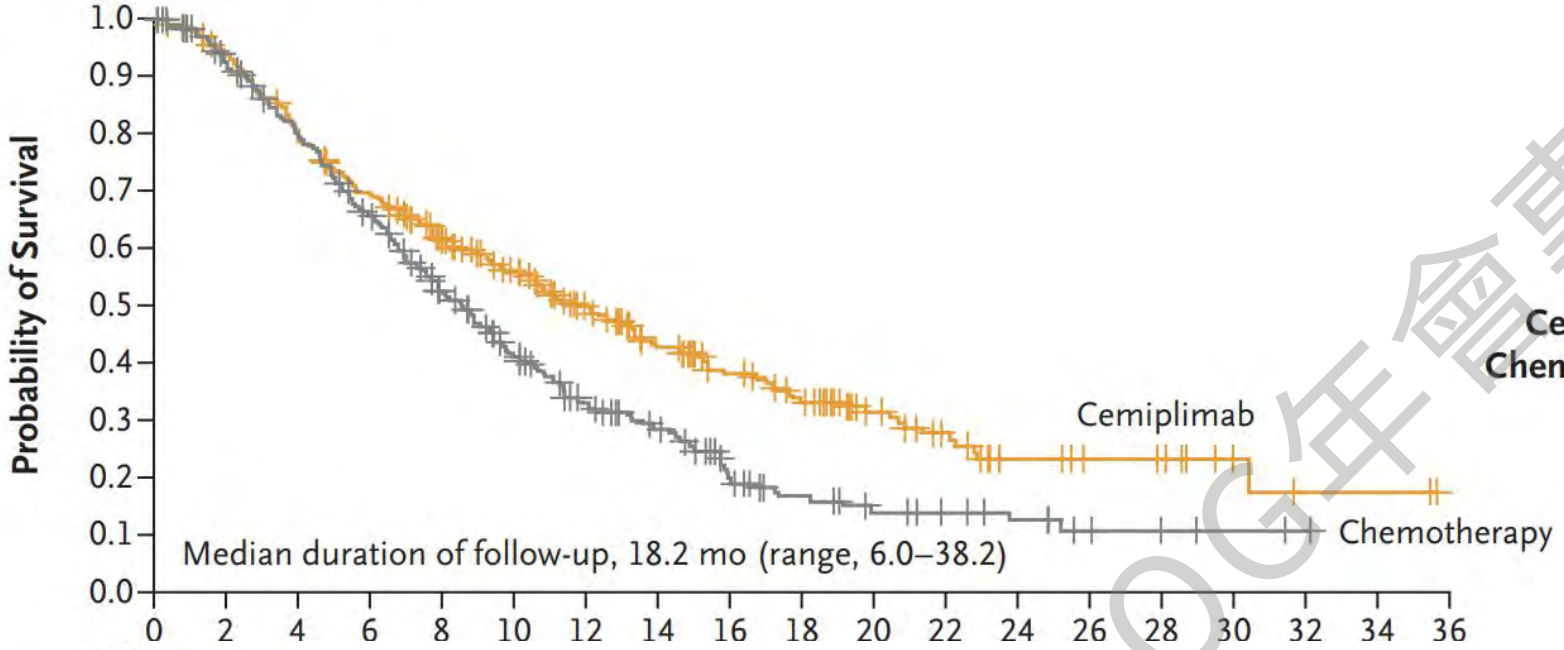
ORIGINAL ARTICLE

Survival with Cemiplimab in Recurrent Cervical Cancer

K.S. Tewari, B.J. Monk, I. Vergote, A. Miller, A.C. de Melo, H.-S. Kim, Y.M. Kim, A. Lisyanskaya, V. Samouëlian, D. Lorusso, F. Damian, C.-L. Chang, E.A. Gotovkin, S. Takahashi, D. Ramone, J. Pikiel, B. Maćkowiak-Matejczyk, E.M. Guerra Alía, N. Colombo, Y. Makarova, D. Rischin, S. Lheureux, K. Hasegawa, K. Fujiwara, J. Li, S. Jamil, V. Jankovic, C.-I Chen, F. Seebach, D.M. Weinreich, G.D. Yancopoulos, I. Lowy, M. Mathias, M.G. Fury, and A. Oaknin, for the Investigators for GOG Protocol 3016 and ENGOT Protocol En-Cx9*

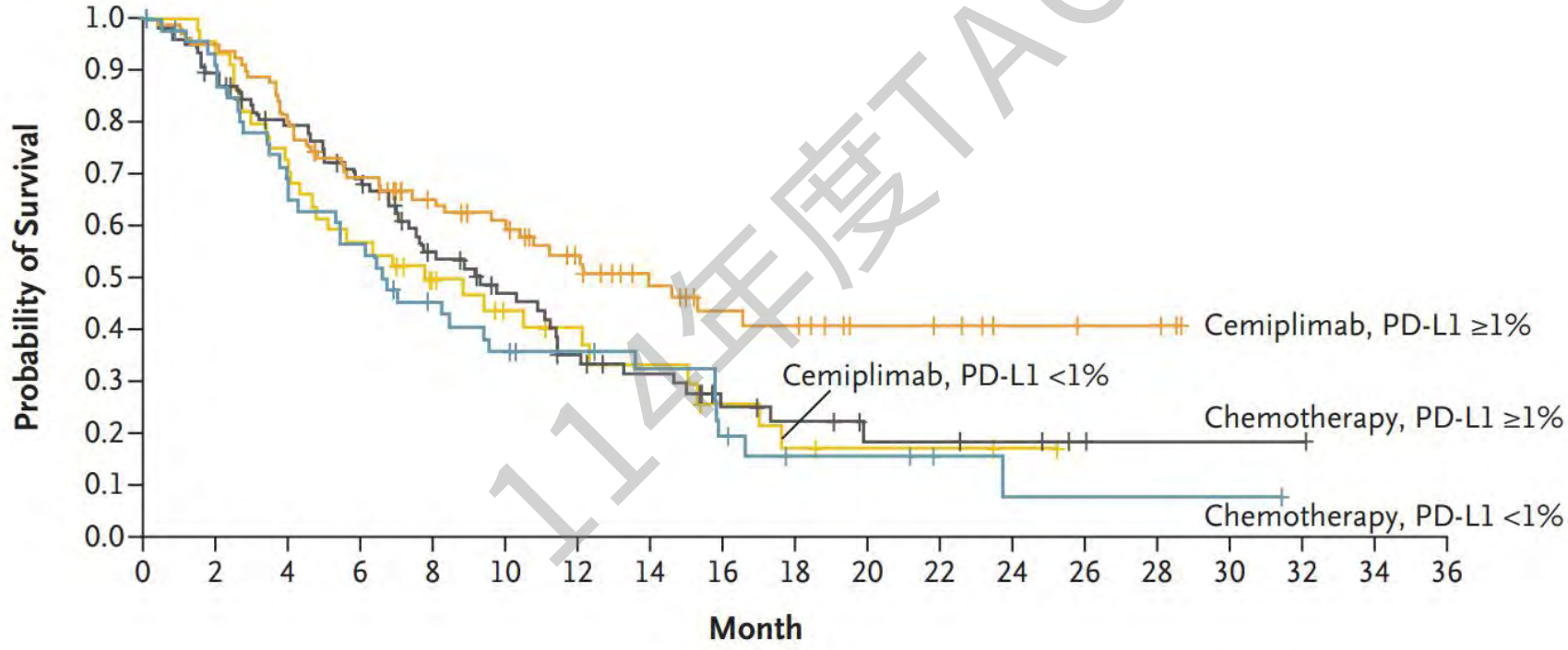
N Engl J Med. 2022 Feb 10;386(6):544-555.

Overall Survival, All Patients



	No. of Patients	Median Overall Survival (95% CI)
		mo
Cemiplimab	304	12.0 (10.3–13.5)
Chemotherapy	304	8.5 (7.5–9.6)

Hazard ratio for death, 0.69 (95% CI, 0.56–0.84)
Two-sided P<0.001



Patients with PD-L1 expression of less than 1% generally had an overall survival benefit as good as or slightly better than that of patients who received chemotherapy (7.7 vs 6.7M).

REGENERON

Libtayo® (cemiplimab) Approved by the European Commission as the First Immunotherapy in Second Line Recurrent or Metastatic Cervical Cancer Irrespective of PD-L1 Expression Level or Tumor Histology

November 22, 2022

Approval based on a Phase 3 trial that demonstrated significant survival benefit in patients with recurrent or metastatic cervical cancer, with Libtayo reducing the risk of death by 31% compared to chemotherapy during the study

Libtayo now approved to treat four cancer types in the European Union

Cemiplimab FDA Approval Application for Recurrent or Metastatic Cervical Cancer Withdrawn

January 28, 2022
By Nichole Tucker

The supplemental biologics license application (sBLA) for the PD-1 inhibitor cemiplimab-wlc (Libatyo) to treat patients with recurrent or metastatic cervical cancer whose disease progressed on or after chemotherapy, has been voluntarily withdrawn by Regeneron Pharmaceutical, Inc and Sanofi, according to a press release by Regeneron.
The company and the FDA were reportedly unable to agree on key post-marketing studies.

ADC- Innova TV-301

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tisotumab Vedotin as Second- or Third-Line Therapy for Recurrent Cervical Cancer

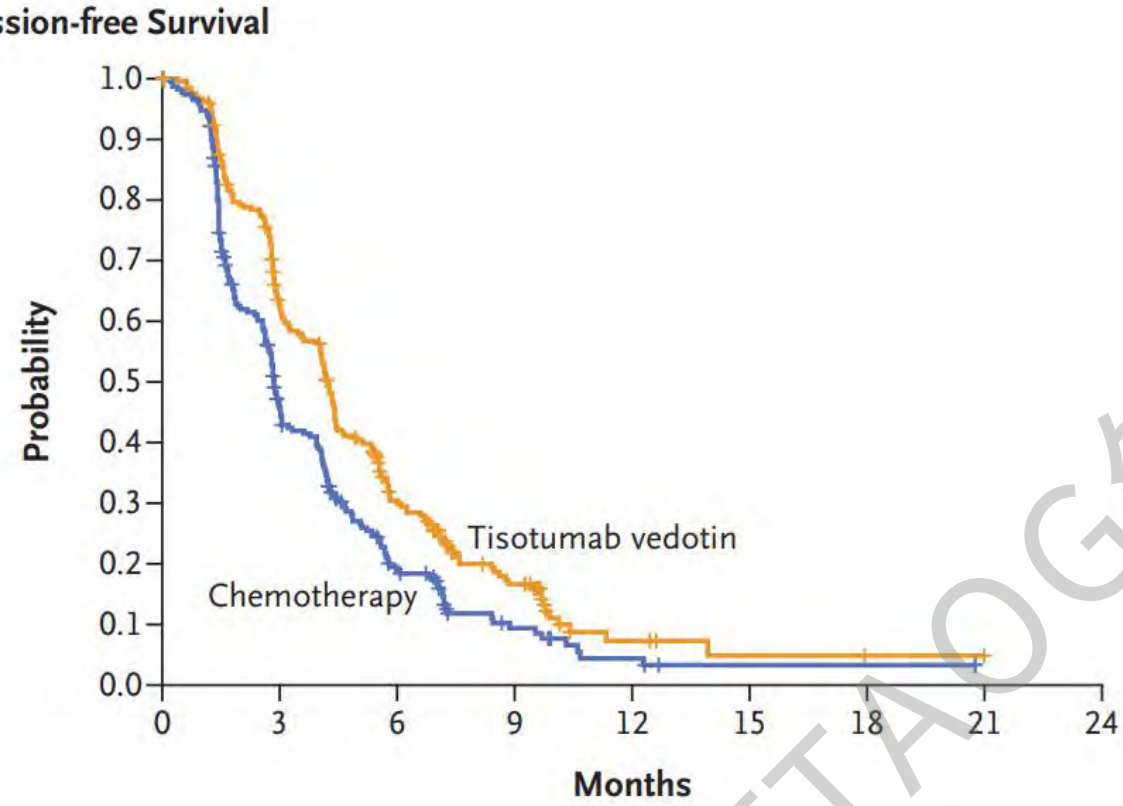
I. Vergote, A. González-Martín, K. Fujiwara, E. Kalbacher, A. Bagaméri, S. Ghamande, J.-Y. Lee, S. Banerjee, F.C. Maluf, D. Lorusso, K. Yonemori, E. Van Nieuwenhuysen, L. Manso, L. Woelber, A. Westermann, A. Covens, K. Hasegawa, B.-G. Kim, M. Raimondo, M. Bjurberg, F.M. Cruz, A. Angelergues, D. Cibula, L. Barraclough, A. Oaknin, C. Gennigens, L. Nicacio, M.S.L. Teng, E. Whalley, I. Soumaoro, and B.M. Slomovitz, for the innovaTV 301/ENGOT-cx12/GOG-3057 Collaborators*

N Engl J Med. 2024 Jul 4;391(1):44-55.

ADC- Innova TV-301

https://youtu.be/MKG5Gt1ji7Y

Innova TV-301

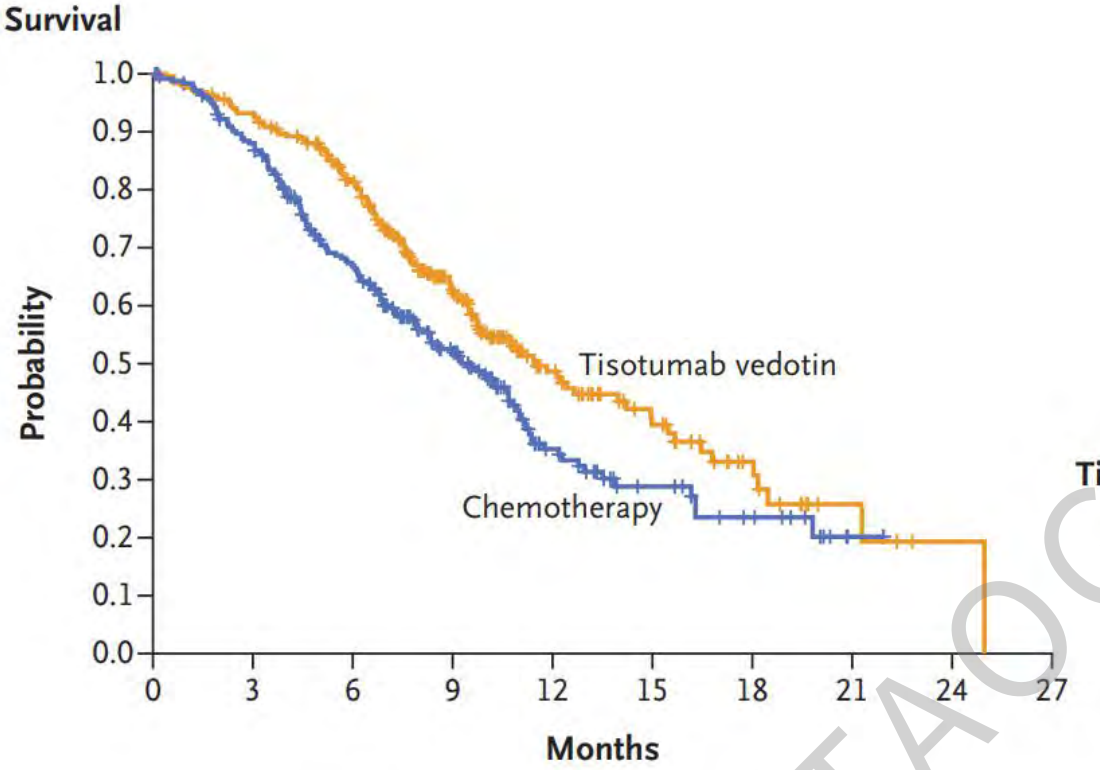


	No. of Events/ Total No. of Patients	Median Progression-free Survival (95% CI)
		mo
Tisotumab Vedotin	198/253	4.2 (4.0–4.4)
Chemotherapy	194/249	2.9 (2.6–3.1)

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

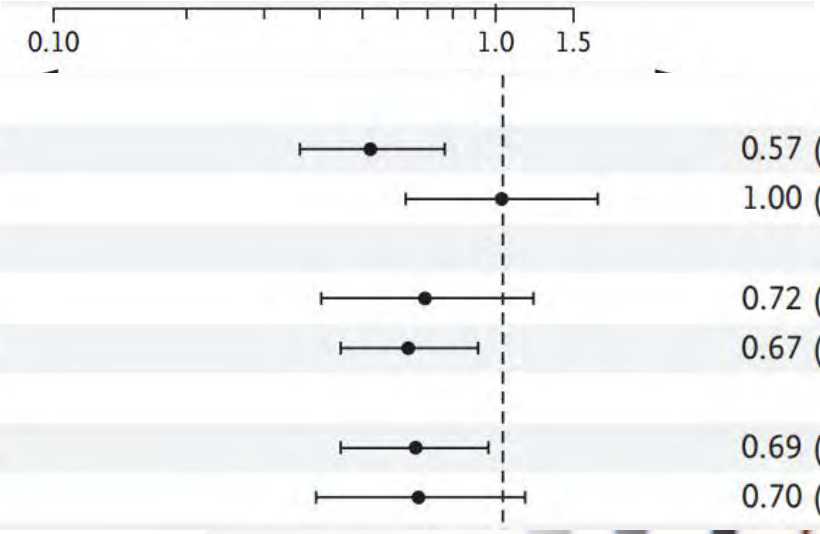
Previous bevacizumab administration			
Yes	130/164	122/157	0.59 (0.46–0.76)
No	68/89	72/92	0.83 (0.59–1.16)
Previous anti–PD-1 or anti–PD-L1 therapy administration			
Yes	53/71	50/67	0.66 (0.44–0.99)
No	145/182	144/182	0.67 (0.53–0.85)
Histologic features			
Squamous-cell carcinoma	124/160	122/157	0.71 (0.55–0.93)
Adenocarcinoma and adenosquamous carcinoma	74/93	72/92	0.63 (0.44–0.89)

Innova TV-301



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

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



Previous bevacizumab administration			
Yes	77/164	92/157	0.57 (0.42–0.78)
No	46/89	48/92	1.00 (0.66–1.50)
Previous anti–PD-1 or anti–PD-L1 therapy administration			
Yes	42/71	42/67	0.72 (0.46–1.14)
No	81/182	98/182	0.67 (0.50–0.90)
Histologic features			
Squamous-cell carcinoma	81/160	92/157	0.69 (0.50–0.94)
Adenocarcinoma and adenosquamous carcinoma	42/93	48/92	0.70 (0.45–1.10)

ADC- Innova TV-301

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

On April 29, 2024, the Food and Drug Administration granted traditional approval to tisotumab vedotin-tftv (Tivdak, Seagen Inc. [now a part of Pfizer Inc.]) for recurrent or metastatic cervical cancer with disease progression on or after chemotherapy. Tisotumab vedotin-tftv previously received (/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-tisotumab-vedotin-tftv-recurrent-or-metastatic-cervical-cancer) accelerated approval for this indication.

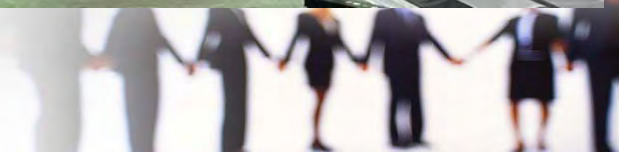
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tisotumab-vedotin-tftv-recurrent-or-metastatic-cervical-cancer

Brief Summary- above 2nd Line

	EMPOWER Cervical 1	Innova TV-301
Enrolled cases	All comer fail prior platinum-based chemotherapy (>90% with paclitaxel, >50% with bevacizumab), anti-PD(L)-1 naive	All comer: SCC(63.1%), AdenoCa(31.9%), Adenosaquamous (5%) Anti-VEGF/anti-PD(L)-1 acceptable (prior bevacizumab 63.9%, anti-PD(L)-1: 27.5%)
Experimental arm	Cemiplimab	tisotumab vedotin
Control arm	pemetrexed, topotecan/irrinotecan, gemicitabine, or vinorebine	topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed
PDL1 expression	(SP263 mab (Ventana)) ≥1: 70.7%(SCC), 32.6 (non-SCC)	(not provided)
Approval for Cx Ca	EU (2022-11), withdrawn from US FDA	US FDA (2024-9)

Radiation therapy- **Proton** therapy

for recurrence in prior irradiated field

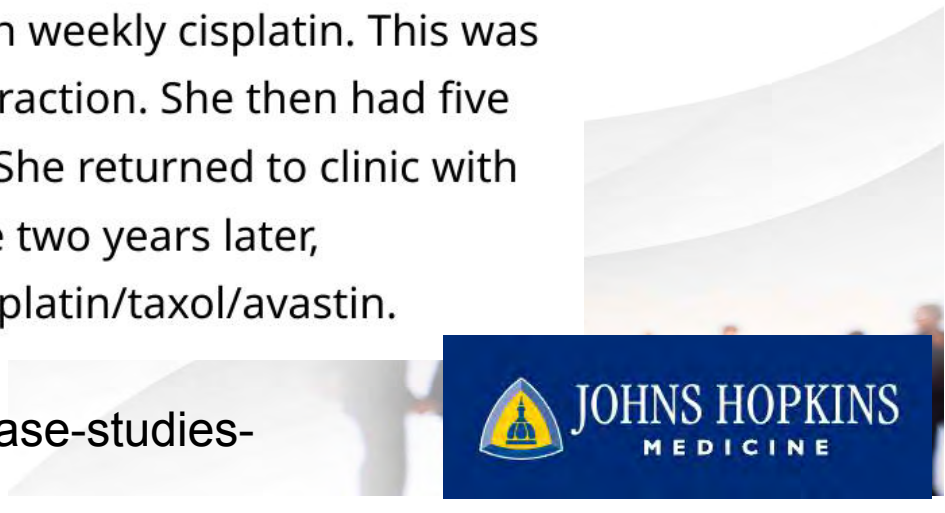


JOHNS HOPKINS KIMMEL CANCER CENTER IN THE D.C. REGION

Johns Hopkins Proton Therapy Center

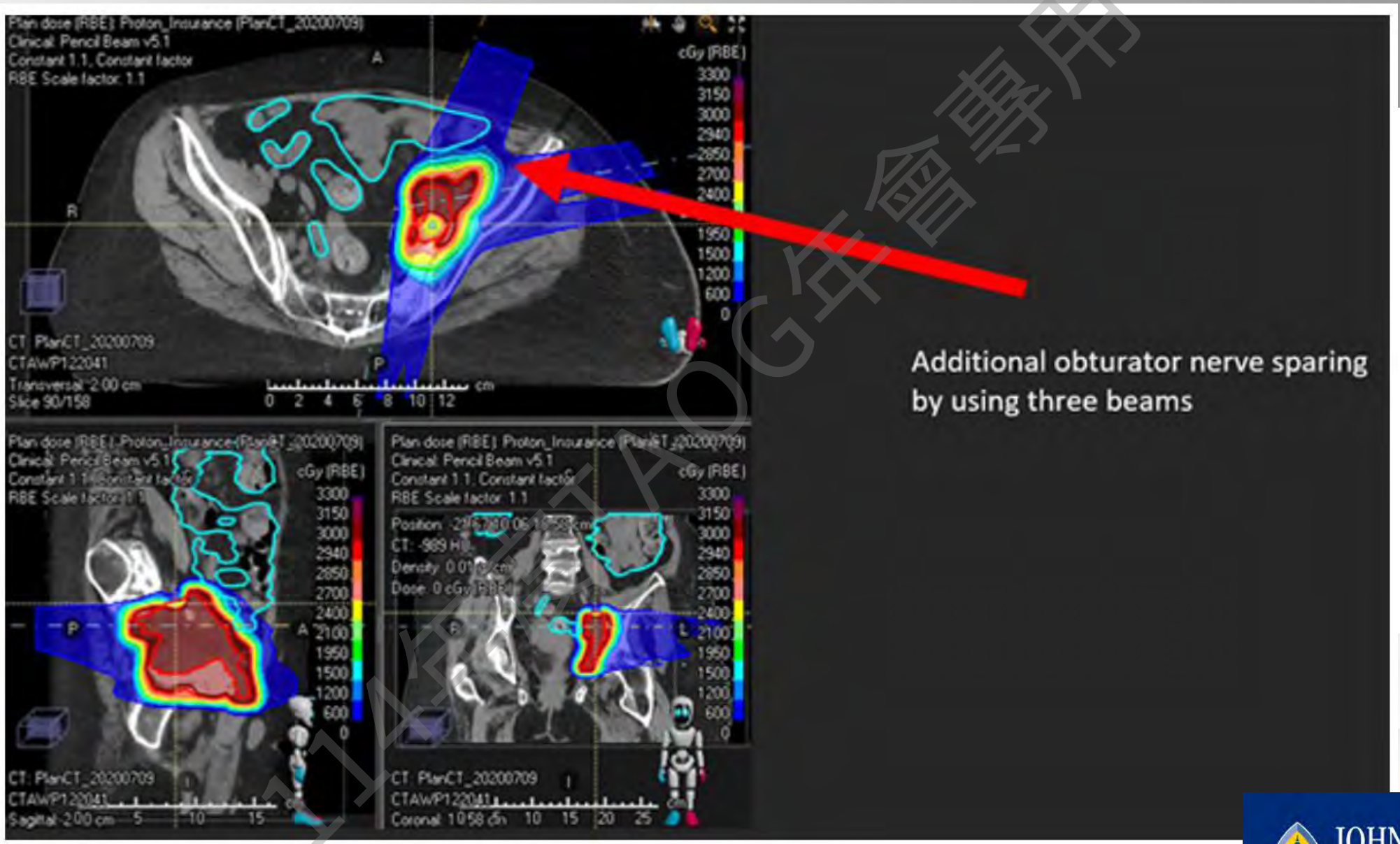
Case 3: Re-Irradiation in the Setting of Metastatic Cervical Cancer to Enlarging Lymph Node

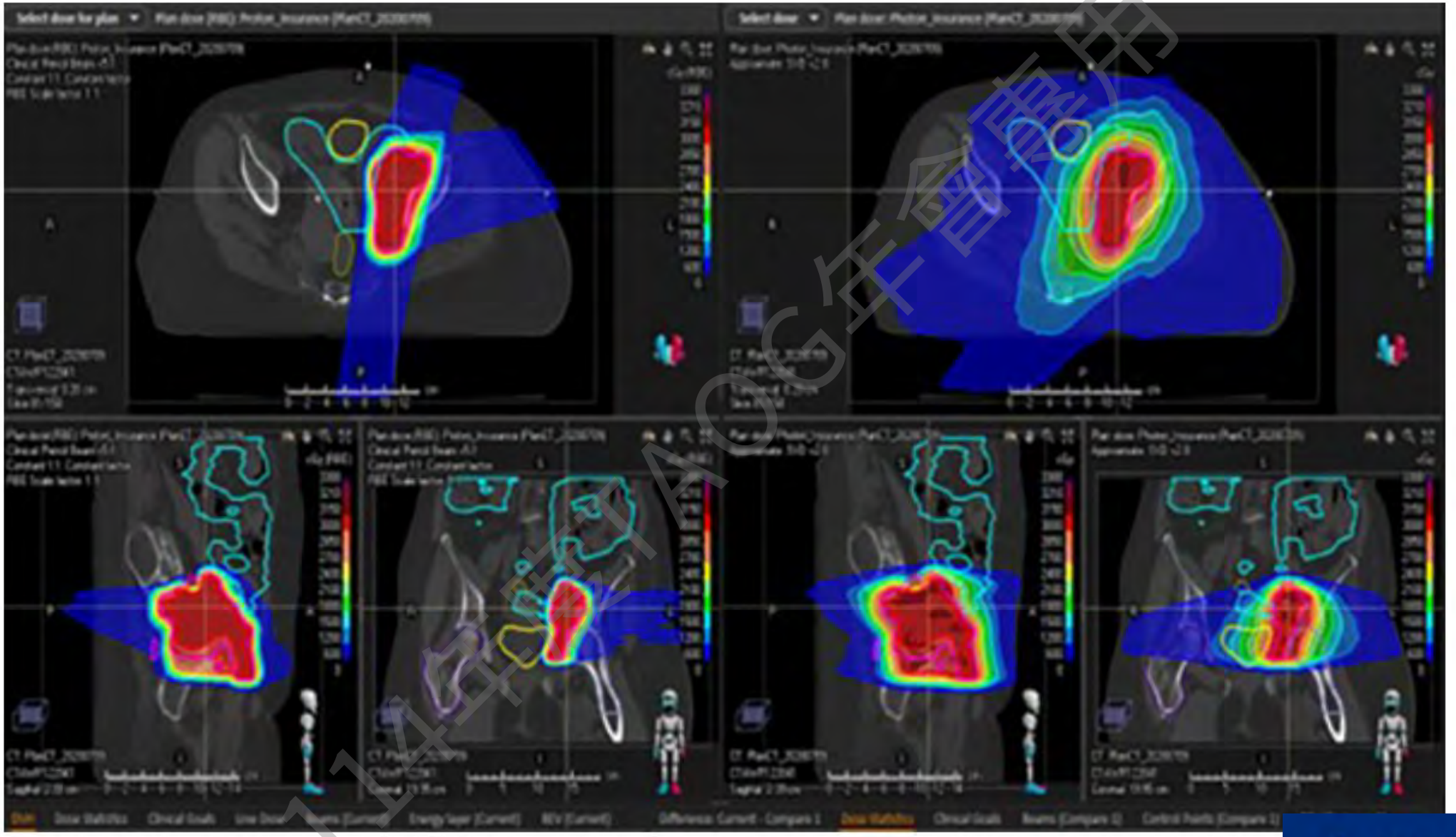
A 63 year old woman presented with squamous cell carcinoma of the cervix that was metastatic to the para-aortic and pelvic lymph nodes. She completed chemoradiation with external beam to 45 Gy with a pelvic boost to 65 Gy along with weekly cisplatin. This was followed by a brachytherapy boost to the cervix, 700cGy in 1 fraction. She then had five cycles of adjuvant chemotherapy with carboplatin/paclitaxel. She returned to clinic with biopsy proven recurrent disease in an enlarging left iliac node two years later, compressing the obturator nerve. She was started with carboplatin/taxol/avastin.



JOHNS HOPKINS MEDICINE

https://www.hopkinsmedicine.org/news/articles/2022/11/proton-therapy-case-studies-gynecologic-cancers





Proton vs Photon Plan Comparison

JOHNS HOPKINS MEDICINE

Part-III

- Primary therapy
  - ESCC: Surgical intervention
  - LACC: Additional modalities in combination with traditional CCRT
- Recurrent/Metastatic therapy
  - Immunotherapy (ICI)
  - ADC
  - Radiation therapy
- Summary of ongoing trials
- Conclusion

Phase-III:
Prolgolimab + chemotherapy

- Prolgolimab (BCD-100) is an anti-PD-1 antibody with an Fc-silencing LALA (L234A/L235A) mutation.
- FERMATA trial (phase III):
  - chemotherapy (cisplatin or carboplatin + paclitaxel) ± bevacizumab with/without Prolgolimab (3mg/kg Q3wk) in untreated (first line) recurrent/metastatic Cx Ca.

Phase-II
Tisotumab vedotin + Pembrolizumab

- InnovaTV 205/ ENGOT-cx8/GOG-3024 (phase II study):
  - TV combined with pembrolizumab for previously-treated recurrent/metastatic Cx Ca):
  - After median follow-up of 13 months, confirmed response rate was 38% and median DoR was 13.8 months.

Phase-II: Geptanolimab

- Geptanolimab (GB226) is an anti-PD-1 monoclonal antibody.
- Gxplore-008 (ongoing phase II pivotal trial in China):
  - for second-line or later treatment of patients with PD-L1-positive recurrent/metastatic Cx Ca.
  - ASGO 2023 abstract:
    - The ORR was 18.0% (CR (5.0%) and PR (13.0%))
    - Median PFS was 1.91 months (95%CI: 1.87, 3.55), and median OS was 16.69 months (95%CI: 11.07, NR).

Phase-II: Zimberelimab

- Zimberelimab (GLS-010) is a novel, fully-human anti-PD-1 monoclonal antibody.
- The phase II registrational trial (in China):
  - for PDL-1(+) (combined positive score [CPS] ≥ 1) recurrent/metastatic cx ca, failed ≥ 1 line prior chemotherapy regimen.
  - investigator-assessed ORR was 27%, Median OS (not reached, 12-month OS rates were 54%), Median PFS was 3.7 months.

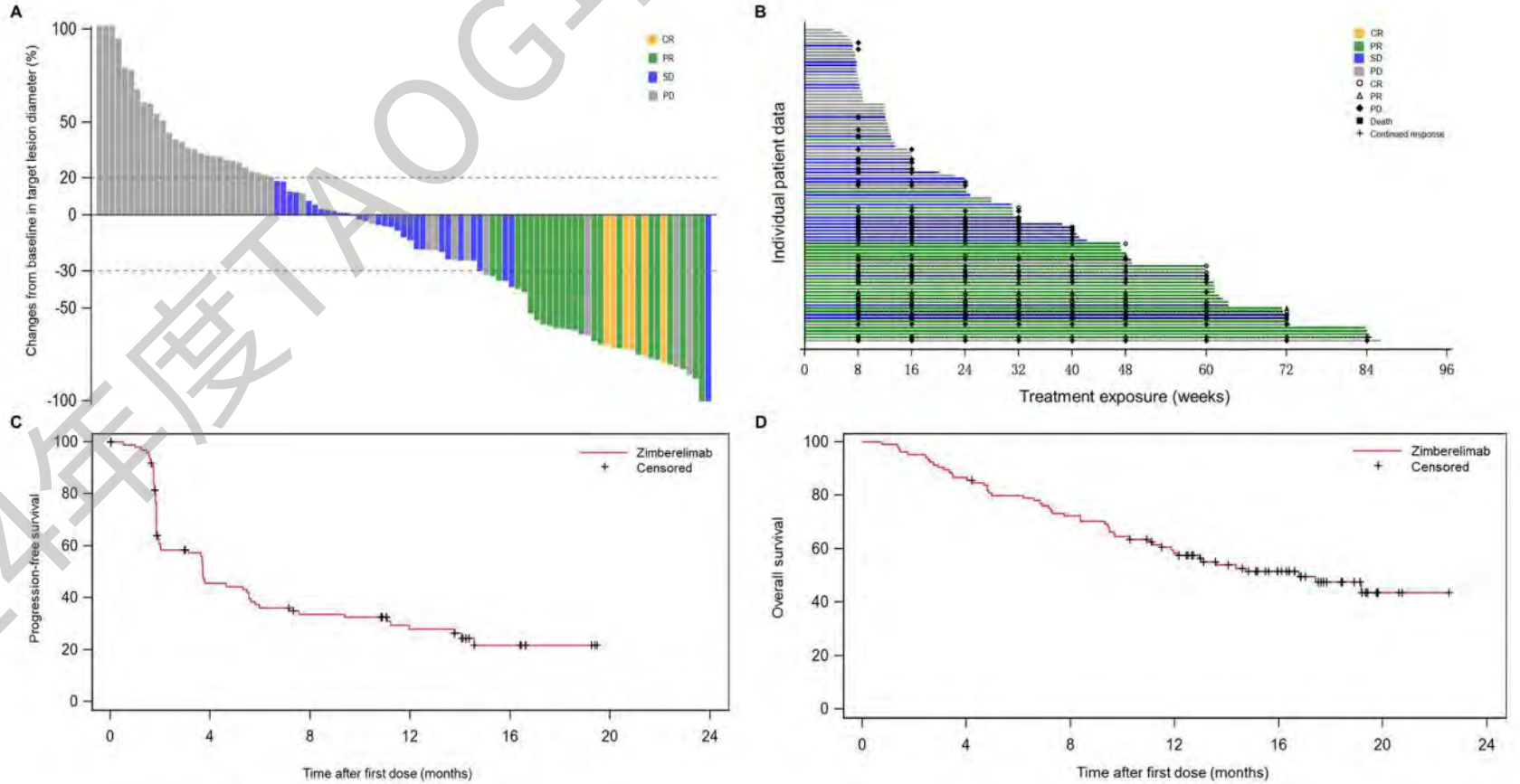
GLS-010

INTERNATIONAL JOURNAL OF GYNECOLOGICAL CANCER

Efficacy and safety of zimberelimab (GLS-010) monotherapy in patients with recurrent or metastatic cervical cancer: a multicenter, single-arm, phase II study

Lingfang Xia,[1] Jing Wang,[2,3] Chunyan Wang,[4] Qingming Zhang,[5,6] Jianqing Zhu,[7] Qunxian Rao,[8] Huijun Cheng,[9] Zheng Liu,[10] Yongmei Yin,[11] Xiaohong Ai,[12] Kurban Gulina,[13] Hong Zheng,[14] Xiaoyong Luo,[15] Baoping Chang,[16] Li Li,[17] Haiyan Liu,[18] Yunxia Li,[19] Ge Lou,[20] Qi Zhou,[21] Yanling Zhu,[22] Zemin Xiao,[23] Jiandong Tong,[24] Ke Wang,[25] Jie Chen,[25] Xia Wang,[26] Lijie Song,[27] Zhixia Wei,[28] Yijing Ye,[29] Jiman Zhu,[30] Xiaohua Wu[1]

OPEN ACCESS



Xia L, et al. Int J Gynecol Cancer 2023;33:1861–1868. doi:10.1136/ijgc-2023-004705

Gloria Biosciences Announces Zimberelimab Approved in China for the Treatment of Recurrent or Metastatic Cervical Cancer

NEWS PROVIDED BY
Guangzhou Gloria Biosciences →
Sep 06, 2023, 07:00 ET

BEIJING and SHANGHAI, Sept. 6, 2023 /PRNewswire/ -- Guangzhou Gloria Biosciences ("GloriaBio"), a commercial stage biopharmaceutical company focusing on the discovery, development and commercialization of biologics in immuno-oncology, today announced that its fully human anti-PD-1 monoclonal antibody, Zimberelimab injection (YuTuo®, GLS-010) has received marketing approval from the China National Medical Products Administration (NMPA), as monotherapy for the treatment of recurrent or metastatic cervical cancer (R/M CC) patients with positive PD-L1 expression (CPS≥1) who progressed on or after platinum-based chemotherapy. Zimberelimab is the first and only immune checkpoint inhibitor (ICI) antibody approved in China for cervical cancer, and third one globally.

Phase-II:
Balstilimab + zalifrelimab

- Balstilimab (bal) is a fully-human anti-PD-1 antibody.
- Zalifrelimab (zal) is a fully-human anti-CTLA-4 antibody.
- C-550–01 (phase II study):
  - for recurrent/metastatic Cx Ca:
  - the ORR: 25.6% and median DoR (NR), median PFS:2.7 months and median OS: 12.8 months.
- RaPiDS (ongoing pivotal, phase II randomized trial):
  - second-line bal monotherapy vs. bal + zal in patients with previously treated recurrent/metastatic Cx Ca.

Phase-II: Nivolumab + ipilimumab

- Nivolumab is an anti-PD-1 antibody
- Ipilimumab is an anti-CTLA-4 antibody
- Checkmate 358 study (phase-II):
  - for recurrent/metastatic Cx Ca (treated but fail or untreated)
    - combo A: nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W
    - combo B: nivolumab 1 mg/kg +ipilimumab 3 mg/kg Q3W (four doses), then nivolumab 240 mg Q2W) :

CheckMate 358

Nivolumab with or without ipilimumab in patients with recurrent or metastatic cervical cancer (CheckMate 358): a phase 1–2, open-label, multicohort trial

Ana Oaknin, Kathleen Moore, Tim Meyer, José López-Picazo González, Lot A Devriese, Asim Amin, Christopher D Lao, Valentina Boni, William H Sharfman, Jong Chul Park, Makoto Tahara, Suzanne L Topalian, Manuel Magallanes, Alejandro Molina Alavez, Tariq Aziz Khan, Catherine Copigneaux, Michelle Lee, Charlie Garnett-Benson, Xuya Wang, R Wendel Naumann

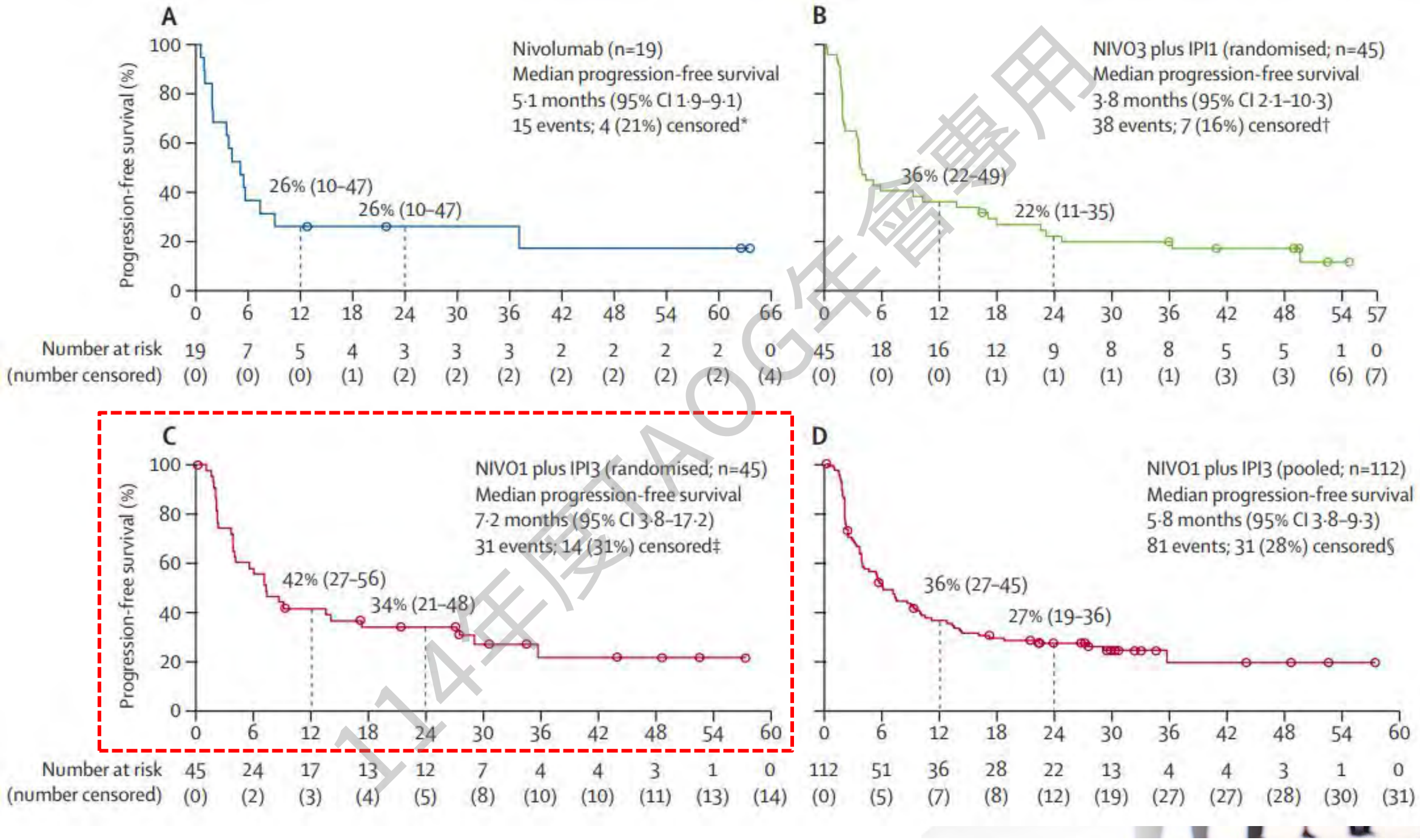
Lancet Oncol 2024; 25: 588–602

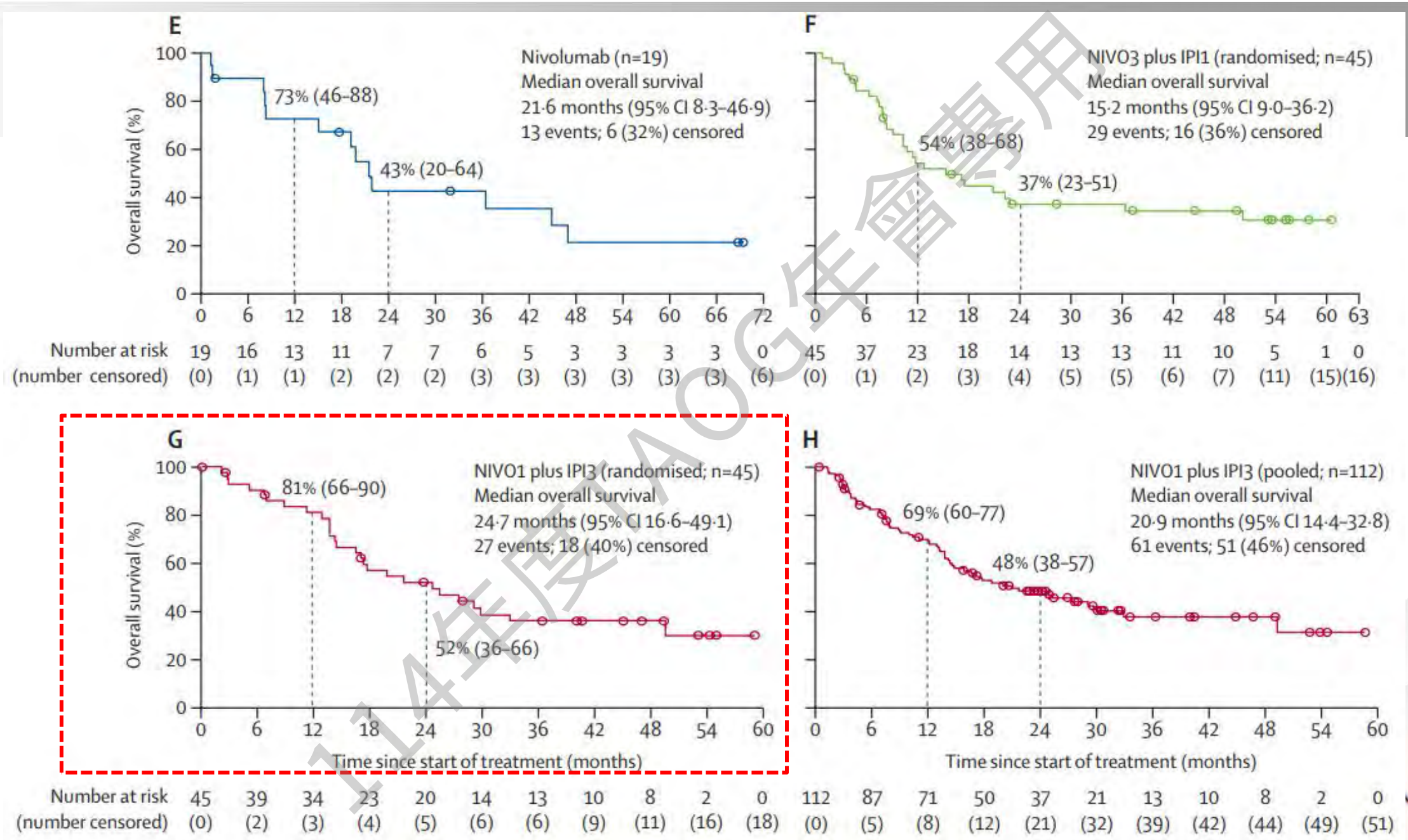
Summary

Background In preliminary findings from the recurrent or metastatic cervical cancer cohort of CheckMate 358,

A histologically confirmed diagnosis of squamous cell carcinoma of the cervix with recurrent or metastatic disease, had received up to two previous systemic therapies.

Patients who had previously undergone experimental antitumour vaccine treatment or immune checkpoint inhibitor treatment were not eligible




E
Nivolumab (n=19)
Median overall survival
21·6 months (95% CI 8·3–46·9)
13 events; 6 (32%) censored
73% (46–88)
43% (20–64)
Overall survival (%)
Number at risk (number censored)
19 (0) 16 (1) 13 (1) 11 (2) 7 (2) 7 (2) 6 (3) 5 (3) 3 (3) 3 (3) 3 (3) 3 (3) 0 (6)
F
NIVO3 plus IPI1 (randomised; n=45)
Median overall survival
15·2 months (95% CI 9·0–36·2)
29 events; 16 (36%) censored
54% (38–68)
37% (23–51)
45 (0) 37 (1) 23 (2) 18 (3) 14 (4) 13 (5) 13 (5) 11 (6) 10 (7) 5 (11) 1 (15) 0 (16)
G
NIVO1 plus IPI3 (randomised; n=45)
Median overall survival
24·7 months (95% CI 16·6–49·1)
27 events; 18 (40%) censored
81% (66–90)
52% (36–66)
Time since start of treatment (months)
45 (0) 39 (2) 34 (3) 23 (4) 20 (5) 14 (6) 13 (6) 10 (9) 8 (11) 2 (16) 0 (18)
H
NIVO1 plus IPI3 (pooled; n=112)
Median overall survival
20·9 months (95% CI 14·4–32·8)
61 events; 51 (46%) censored
69% (60–77)
48% (38–57)
Time since start of treatment (months)
112 (0) 87 (5) 71 (8) 50 (12) 37 (21) 21 (32) 13 (39) 10 (42) 8 (44) 2 (49) 0 (51)

Phase-II
Sintilimab + IBI-310

- Sintilimab is a dual anti-PD-1/PD-L1 IgG4 monoclonal antibody
- IBI-310 is a biosimilar of ipilimumab.
- In this randomized, double-blind, placebo-controlled, phase 2 study (ClinicalTrials.gov: NCT04590599)
  - in recurrent/metastatic Cx Ca failed prior platinum-based chemotherapy: double-blind trial is evaluating efficacy and safety of sintilimab + IBI-310 versus sintilimab + placebo

Med

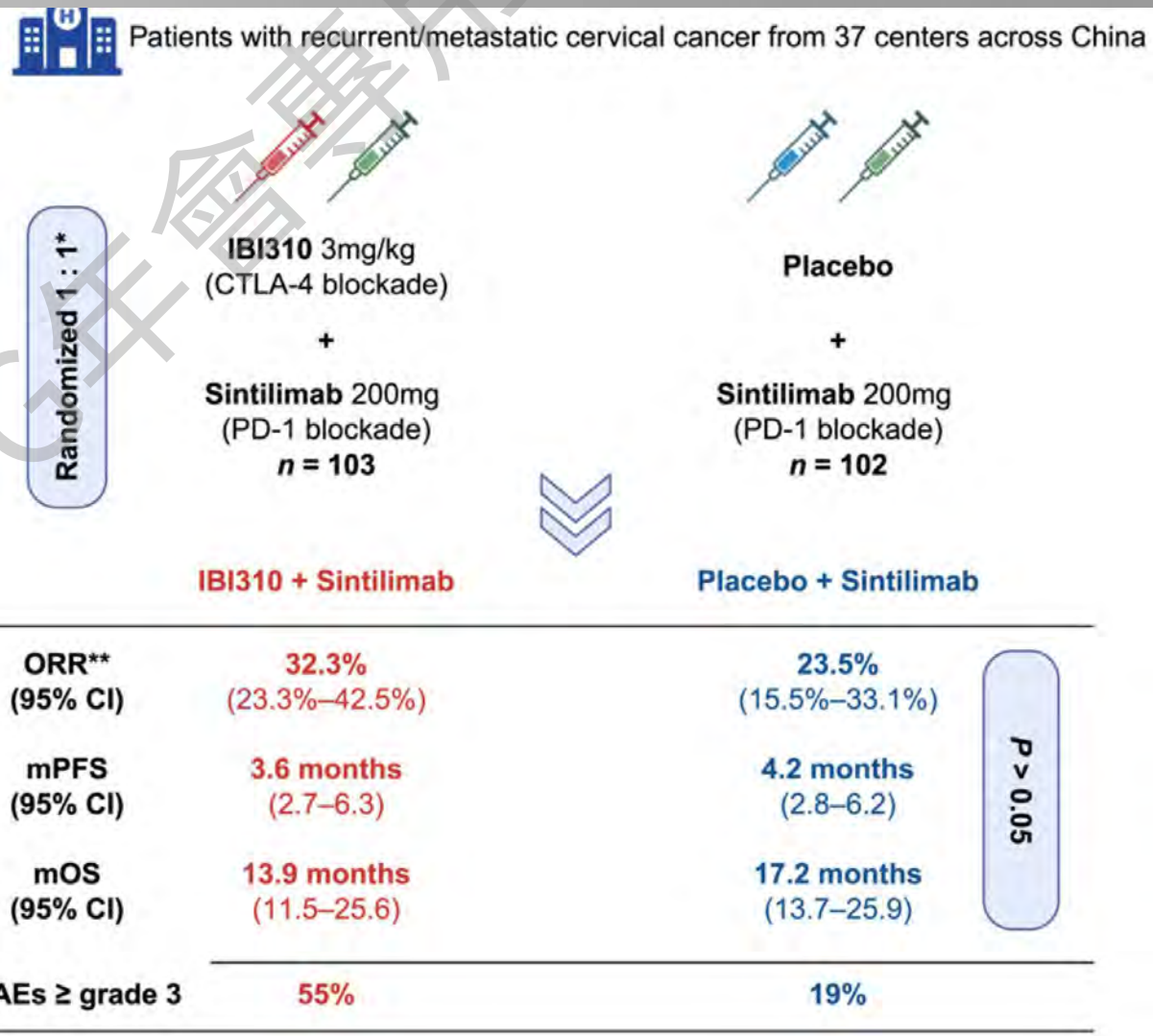
Available online 18 January 2025, 100573

In Press, Corrected Proof ? What's this?

Article

IBI310 plus sintilimab vs. placebo plus sintilimab in recurrent/metastatic cervical cancer: A double-blind, randomized controlled trial

Huayi Li [1 2 41], Yu Xu [1 2 41], Xiaofei Jiao [1 2 41], Qin Xu [3 41], Zikun Peng [1 2 41], Ying Tang [4 41], Jieqing Zhang [5 41], Bowen Huang [1 2], Yiyang Shen [1 2], Baoping Chang [6], Bairong Xia [7], Wei Duan [8], Danbo Wang [9], Lijing Zhu [10], Ruifang An [11], Guonan Zhang [12], Yaling Tang [13], Jianli Huang [14], Hui Qiu [15], Li Wang [16]...Qinglei Gao [1 2 42]



Phase-II: Camrelizumab + famitinib

- Camrelizumab is a humanized anti-PD-1 IgG4 monoclonal antibody
- Famitinib is a receptor tyrosine kinase inhibitor targeting c-Kit, vascular endothelial growth factor receptor-2 and -3, platelet-derived growth factor receptor, FMS-like tyrosine kinase-3 receptor, and Ret.
- SHR-1210- II-217 (Phase II, pivotal, randomized trial)
  - in recurrent/metastatic SCC who failed prior platinum-based chemotherapy

nature communications

Article

https://doi.org/10.1038/s41467-022-35133-4

A multicenter phase 2 trial of camrelizumab plus famitinib for women with recurrent or metastatic cervical squamous cell carcinoma

Received: 24 June 2022

Accepted: 17 November 2022

Published online: 08 December 2022

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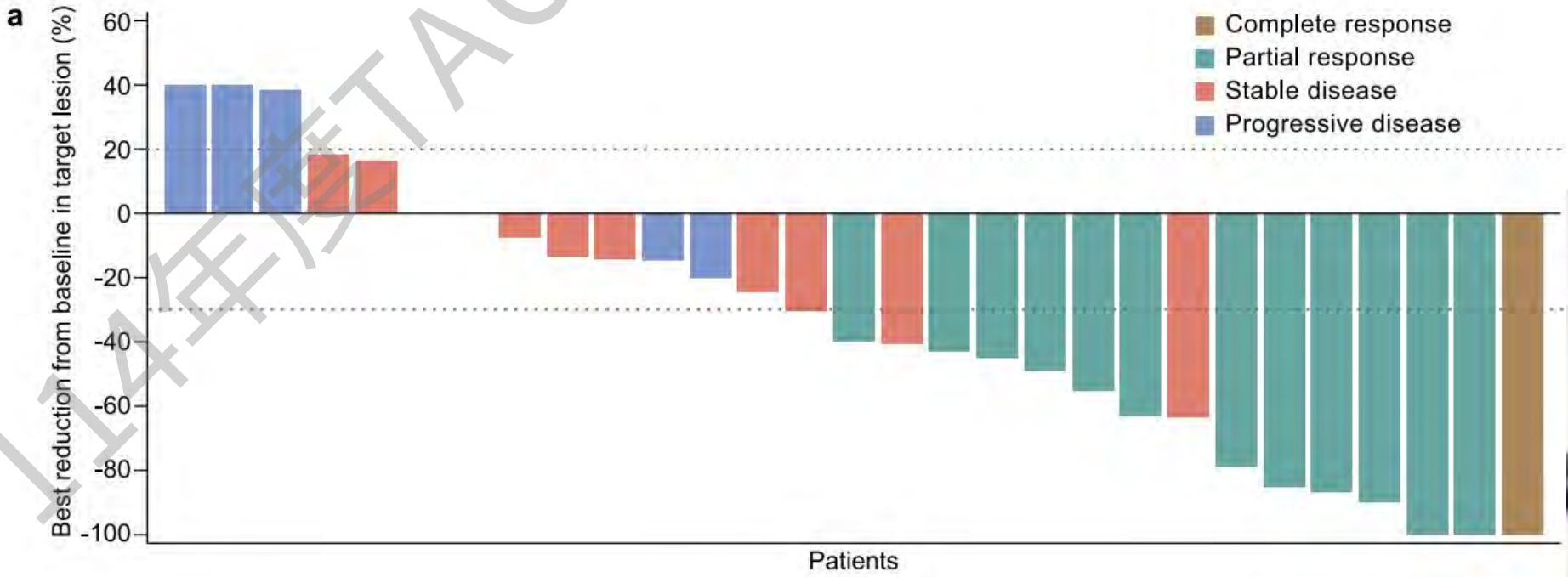

Phase-II:
Tiragolumab + atezolizumab

- Tiragolumab is anti-TIGIT (T-cell immunoreceptor with immunoglobulin and ITIM domains) antibody and Atezolizumab is anti-PD-L1 antibody.
- SKYSCRAPER-04 study (ongoing phase II, international):
  - PD-L1-positive recurrent/metastatic Cx Ca that progressed after ≥ 1 chemotherapy regimen.

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EFFICACY AND SAFETY RESULTS FROM SKYSCRAPER-04: AN OPEN-LABEL RANDOMIZED PHASE 2 TRIAL OF TIRAGOLUMAB PLUS ATEZOLIZUMAB FOR PD-L1-POSITIVE RECURRENT CERVICAL CANCER

PD-L1>10% (high expression) has better response than 5-10% (Low expression)

Endpoint	Tira+atezo (n=126)	Atezo (n=45)
Primary analysis (data cutoff Dec 8, 2021; median follow-up 8.5 months)		
IRC-assessed ORR, % (95% CI)	19.0 (12.6–27.0)	15.6 (6.5–29.5)
PD-L1$_{high}$ subgroup (n=105)	25.0 (15.8–36.3)	20.7 (8.0–39.7)
PD-L1$_{low}$ subgroup (n=66)	10.0 (3.3–21.8)	6.3 (0.2–30.2)
IRC-determined measurable disease subgroup (n=149)*	21.6 (14.4–30.4)	15.8 (6.0–31.3)
Median IRC-assessed PFS, months (95% CI)	2.8 (1.7–4.1)	1.9 (1.5–3.0)
Grade 3/4 adverse events, %	44	31
Grade ≥3 adverse events of special interest, %	8	11
Updated OS analysis (data cutoff Jun 30, 2022; median follow-up 10.4 months)		
Median OS, months (95% CI)	11.1 (9.6–14.5)	10.6 (6.9–13.8)

CI = confidence interval; OS = overall survival; PD-L1$_{high}$ = TAP ≥10%; PD-L1$_{low}$ = TAP 5–<10%; PFS = progression-free survival; TAP = PD-L1 tumor area positivity by SP263.

*Post hoc exploratory analysis.

Part-IV

- Primary therapy
  - ESCC: Surgical intervention
  - LACC: Additional modalities in combination with traditional CCRT
- Recurrent/Metastatic therapy
  - Immunotherapy (ICI)
  - ADC
- Summary of ongoing trials
- Conclusion

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REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Cervical Cancer

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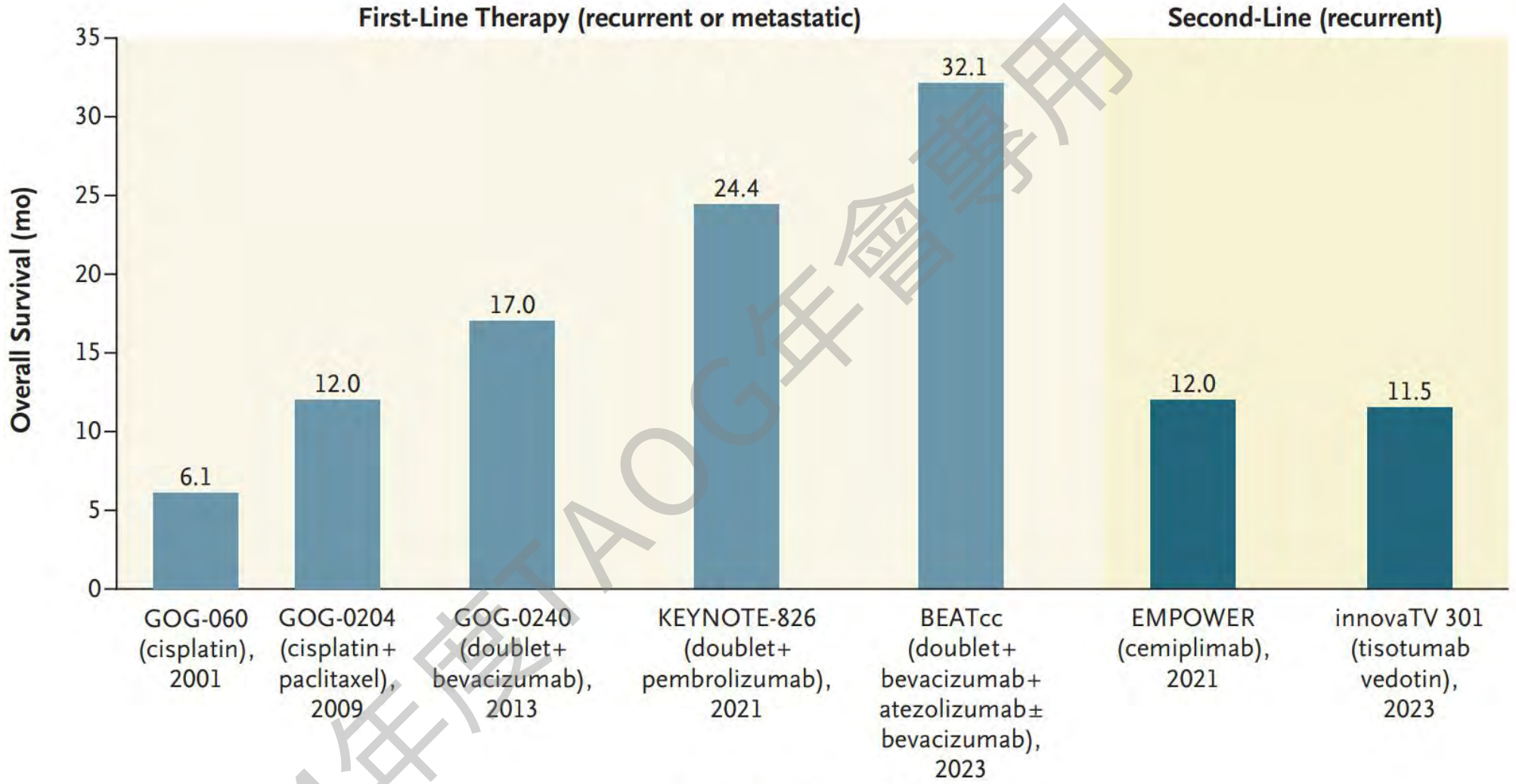
N Engl J Med 2025;392:56-71.
DOI: 10.1056/NEJMra2404457



Phase 3 Randomized Trial

Hazard Ratio for Death			0.71 (98% CI, 0.54–0.95)	0.64 (95% CI, 0.50–0.81)	0.68 (95% CI, 0.52–0.88)	0.69 (95% CI, 0.56–0.84)	0.70 (95% CI, 0.54–0.89)
Objective Response Rate — %	31.4	29.1	48.0	68.1 in PD-L1+	84.0	18.0 in PD-L1+	17.8

Tewari KS. N Engl J Med 2025;392:56-71.

Conclusions

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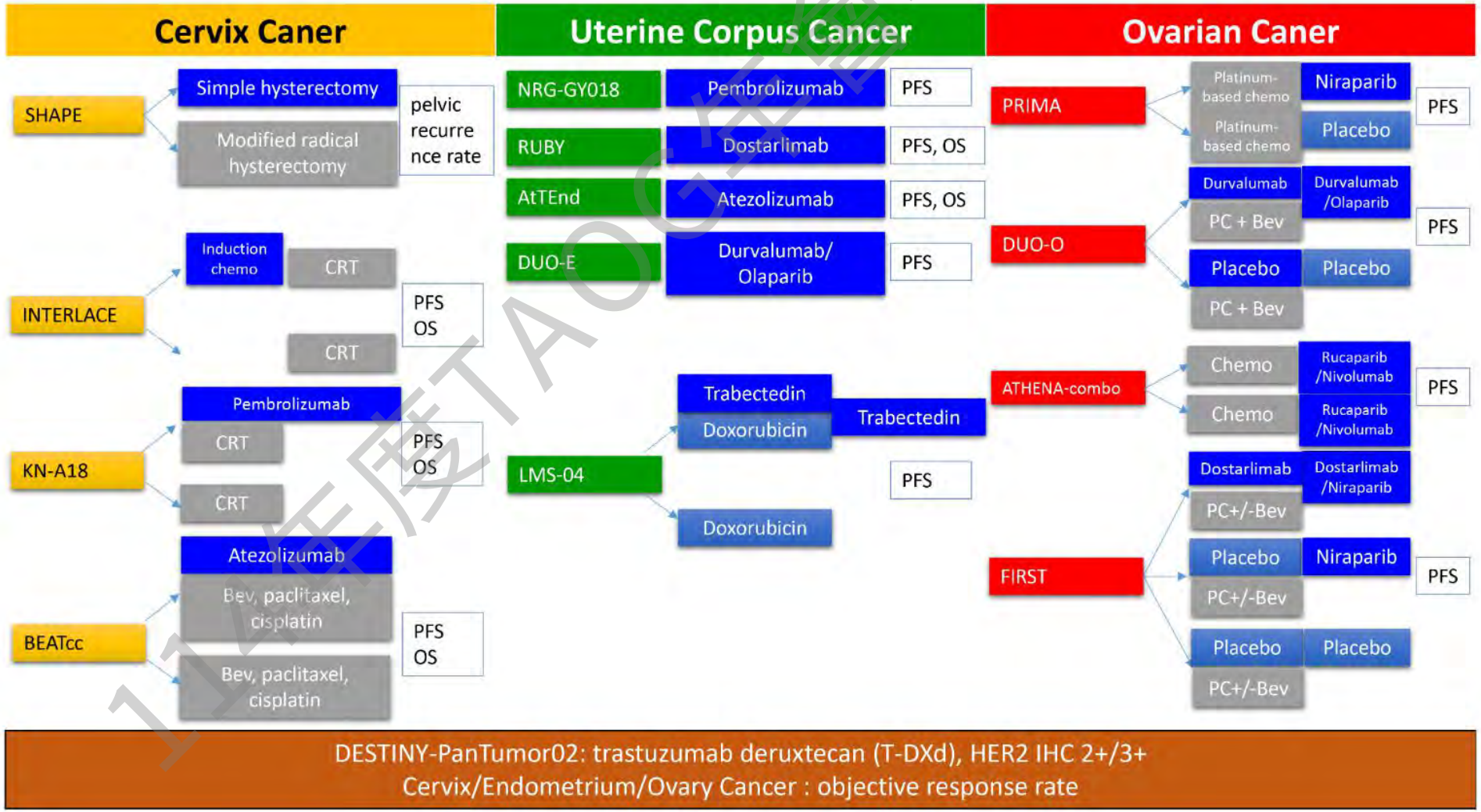
Graphical Abstract



J Gynecol Oncol. 2025 Jan;36(1):e72.

Thanks for listening