免疫療法在子宮頸癌與子宮內膜癌的應用

張廷彰 廖敏絜
林口長庚婦產部

癌症的形成

Evolution among somatic cells

- A cancer is a dynamic population of abnormal somatic cells evolving through natural selection
- Neoplastic cells produce complex and novel adaptations, often by removing or activating cell functions that are already in the human genome, but also sometimes through genetic novelties.

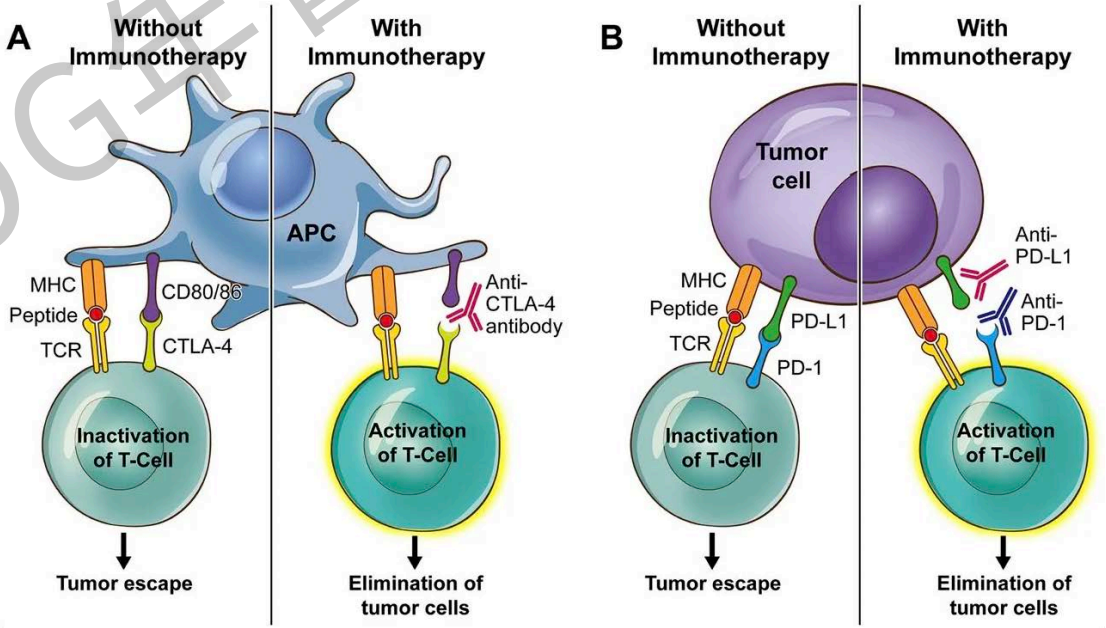
演化是生物發展的基石 Evolution by natural selection is the foundation for nea

細胞的演化速率遠高於生物的演化速率

細胞演化來自於突變的累積，而能避開免疫系統攻擊的，無生長極限的細胞成為癌症

免疫療法最大的優勢，是將治療癌症的概念，由只關注腫瘤本身，提升到了解整個免疫系統層次，而更能適應腫瘤的動態性變化，為治療帶來更持續性的效果。

INVESTIGATOR
BIOSCIENCES HONOR SOCIETY TAIWAN



免疫檢查點抑制劑療法。利用 anti-CTLA-4 和 anti-PD-1 抗體進行治療，可使 T 細胞維持活化狀態，進而消滅腫瘤細胞。 圖片來源：Gut 2018;67:2056-2067. doi: 10.1136/gutjnl-2018-316948.

1. Sambi, M., Bagheri, L., & Szewczuk, M. R. (2019). Current Challenges in Cancer Immunotherapy: Multimodal Approaches to Improve Efficacy and Patient Response Rates. *Journal of Oncology, 2019*, 1-12. doi:10.1155/2019/4508794

撰文｜李亞芸
修訂｜蔡京庭

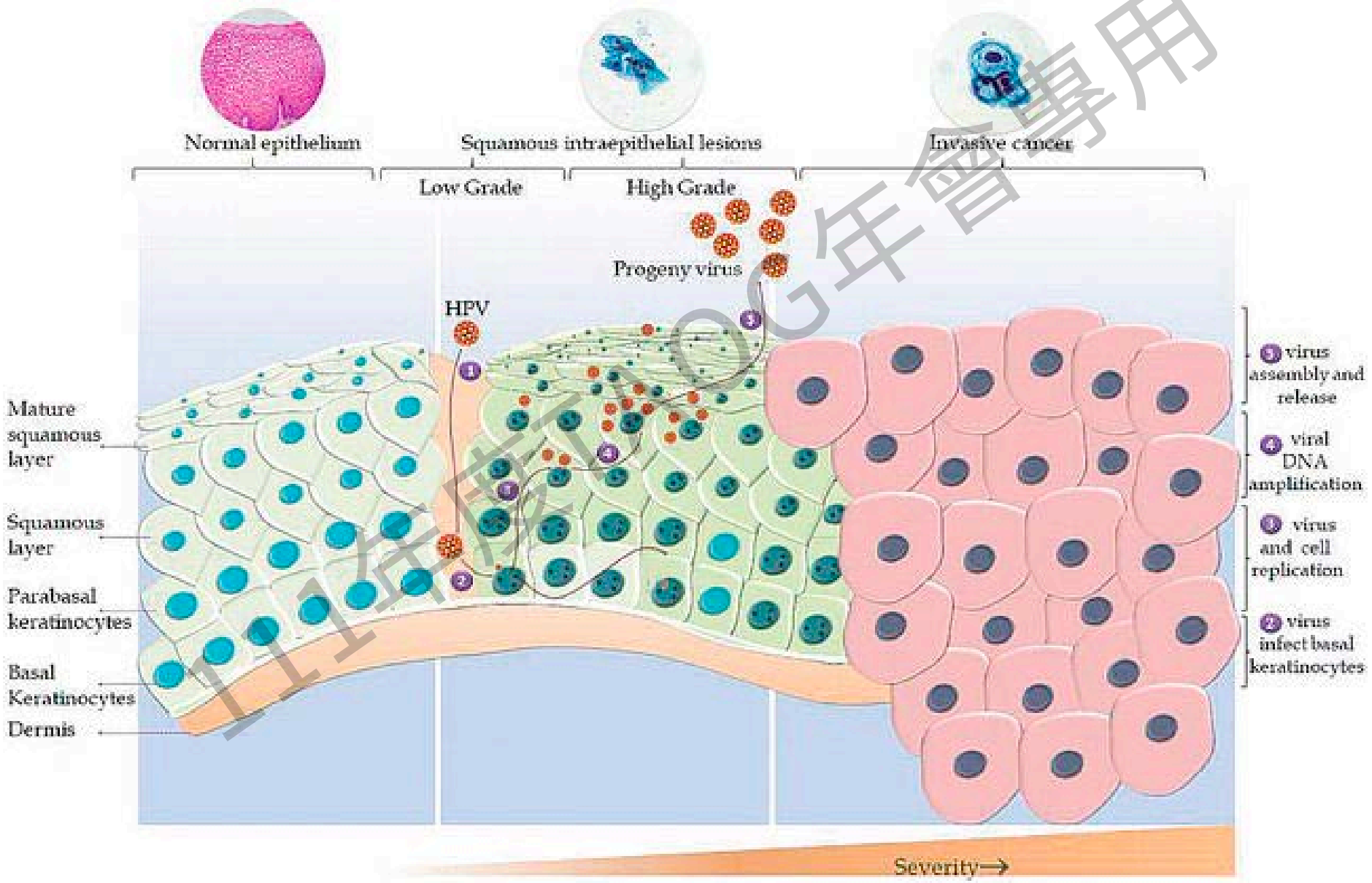
Activate immune system in cancer patients

- ✓Immune checkpoint inhibitors
- Therapeutic vaccines
- Engineered T cells
- Antibody-drug conjugates

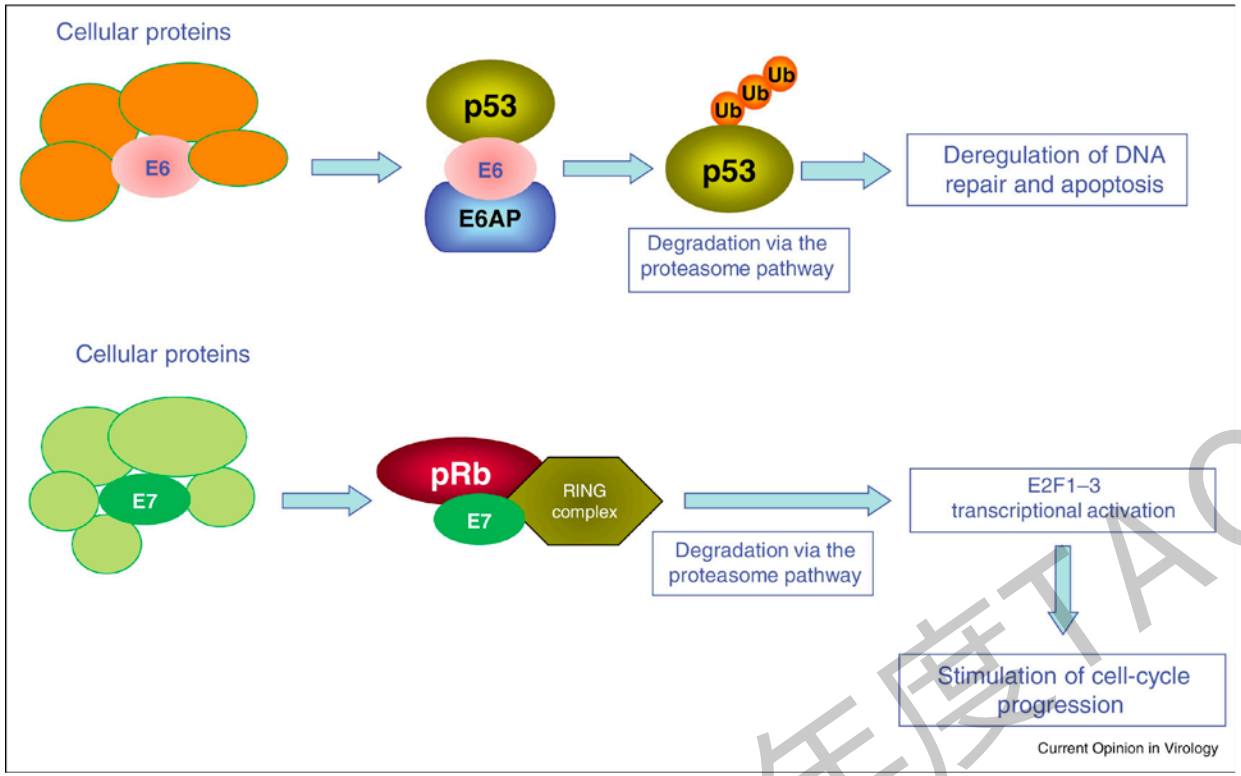
- ✓ New standard of care for patients with recurrent or metastatic diseases
- ✓ Combination of conventional chemotherapy or radiotherapy, or multiple immunomodulatory agents may provide further benefit

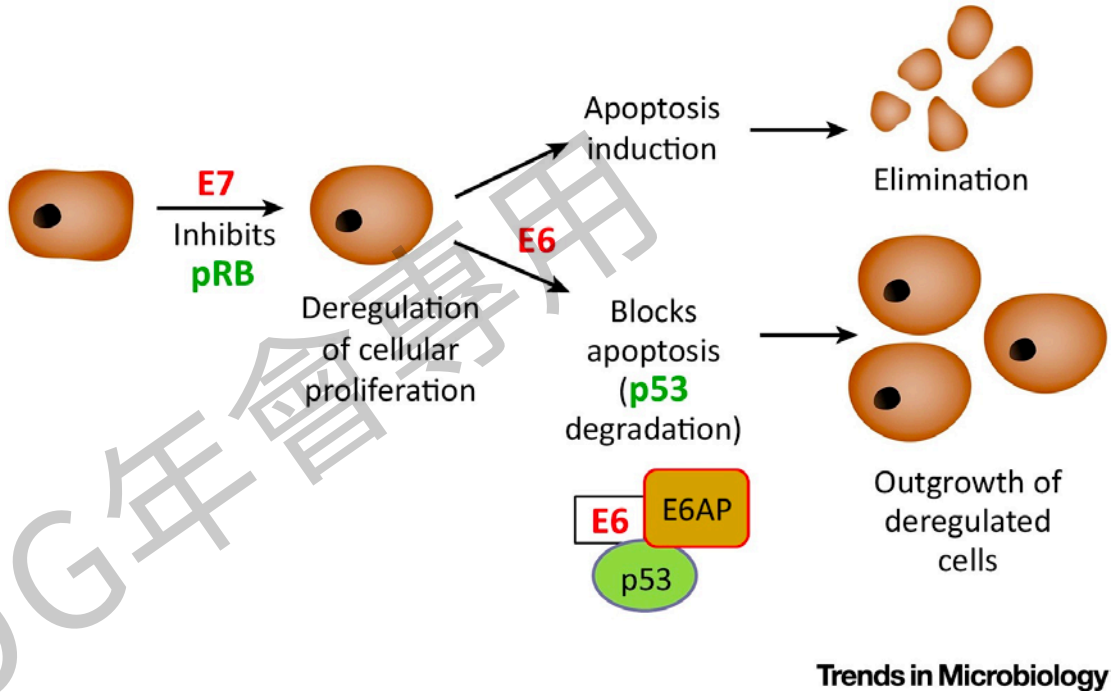
http://dx.doi.org/10.1136/ijgc-2021-002492

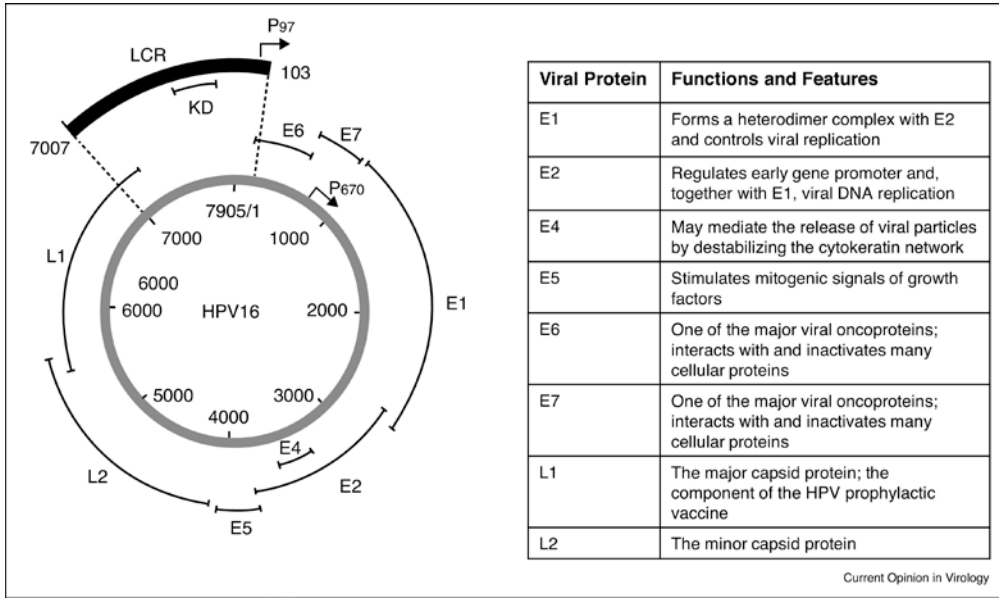
子宮頸癌的成因



子宮頸癌的成因







Viral Protein	Functions and Features
E1	Forms a heterodimer complex with E2 and controls viral replication
E2	Regulates early gene promoter and, together with E1, viral DNA replication
E4	May mediate the release of viral particles by destabilizing the cytokeratin network
E5	Stimulates mitogenic signals of growth factors
E6	One of the major viral oncoproteins; interacts with and inactivates many cellular proteins
E7	One of the major viral oncoproteins; interacts with and inactivates many cellular proteins
L1	The major capsid protein; the component of the HPV prophylactic vaccine
L2	The minor capsid protein

https://doi.org/10.1016/j.coviro.2017.07.014

Cervical Cancer

Pembrolizumab and chemotherapy in patients with persistent, recurrent, or metastatic cervical cancer: Subgroup analysis of KEYNOTE-826

Krishnansu Sujata Tewari, Nicoletta Colombo, Bradley J. Monk, Coraline Dubot, M. Valeria Caceres, Kosei Hasegawa, Ronnie Shapira-Frommer, Pamela Salman, Eduardo Ya~nez, Mahmut Gumus, Mivael Olivera Hurtado de Mendoza, Vanessa Samou€elian, Vincent Castonguay, Alexander Arkhipov, Cumhur Tekin, Kan Li, Sarper Toker, Stephen Michael Keefe, Domenica Lorusso

Oral Abstract Session
Gynecologic cancer

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

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

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

R 1:1

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

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

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

[a]Paclitaxel: 175 mg/m². Cisplatin: cisplatin 50 mg/m². Carboplatin: AUC 5 mg/mL/min. The 6-cycle limit was introduced with protocol amendment 2, although participants with ongoing clinical benefit who were tolerating chemotherapy could continue beyond 6 cycles after sponsor consultation.
CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100); PROs, patient-reported outcomes; VAS, visual analog scale. KEYNOTE-826 ClinicalTrials.gov identifier, NCT03635567.

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

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

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

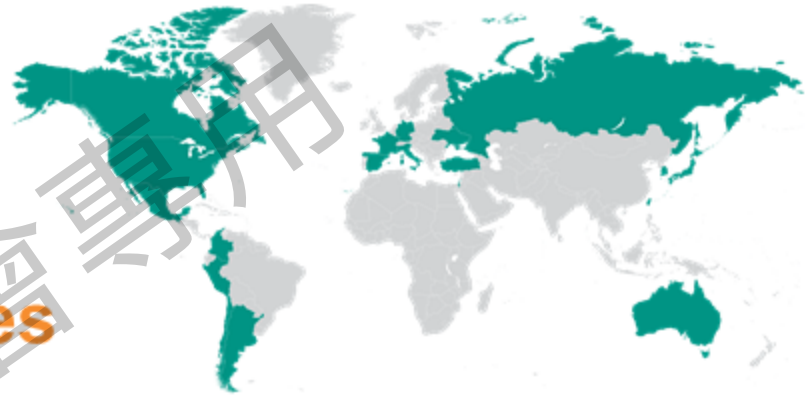
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer

Nicoletta Colombo, M.D., Ph.D., Coraline Dubot, M.D., Domenica Lorusso, M.D., Ph.D., Valeria Caceres, M.D., Ph.D., Kosei Hasegawa, M.D., Ph.D., Ronnie Shapira-Frommer, M.D., Krishnansu S. Tewari, M.D., Pamela Salman, M.D., Edwin Hoyos Usta, M.D., Eduardo Yañez, M.D., Mahmut Gümüş, M.D., Mivael Olivera Hurtado de Mendoza, M.D., Vanessa Samouëlian, M.D., Ph.D., Vincent Castonguay, M.D., Alexander Arkhipov, M.D., Ph.D., Sarper Toker, M.D., M.B.A., Kan Li, Ph.D., Stephen M. Keefe, M.D., and Bradley J. Monk, M.D., for the KEYNOTE-826 Investigators*

Acknowledgments



PARTICIPANTS AND THEIR FAMILIES

Investigators and site personnel from 151 sites in 19 countries who participated in this study

All personnel of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA who supported the study, particularly Gursel Aktan, Amy Blum, Susan Galligan, Matthew Monberg, Karyn O'Flaherty, Cumhur Tekin, Ying Zhang, and Jing Zhao

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Treatment Disposition, All-Comer Population

617 participants randomly allocated
from November 20, 2018, to January 31, 2020

Pembro + Chemo ± Bev Arm

- 308 allocated
- 307 treated

- 33.9% continuing ≥1 component
- 2.3% completed all components[b]
- 63.8% discontinued all components
  - 12.4% AE
  - 3.9% clinical PD
  - 0.7% CR
  - 0.3% excluded medication
  - 1.3% physician decision
  - 40.4% radiologic PD
  - 4.9% withdrawal of consent

Median (range) Follow-up[a]:
22.0 mo (15.1-29.4)

Placebo + Chemo ± Bev Arm

- 309 allocated
- 309 treated

- 17.5% continuing ≥1 component
- 0% completed all components[b]
- 82.5% discontinued all components
  - 7.8% AE
  - 7.1% clinical PD
  - 0.3% CR
  - 1.3% physician decision
  - 0.3% protocol violation
  - 58.6% radiologic PD
  - 7.1% withdrawal of consent

[a]Defined as the time from randomization to the data cutoff date of May 3, 2021.
[a]Includes participants who received bevacizumab and discontinued at cycle 35 or earlier.

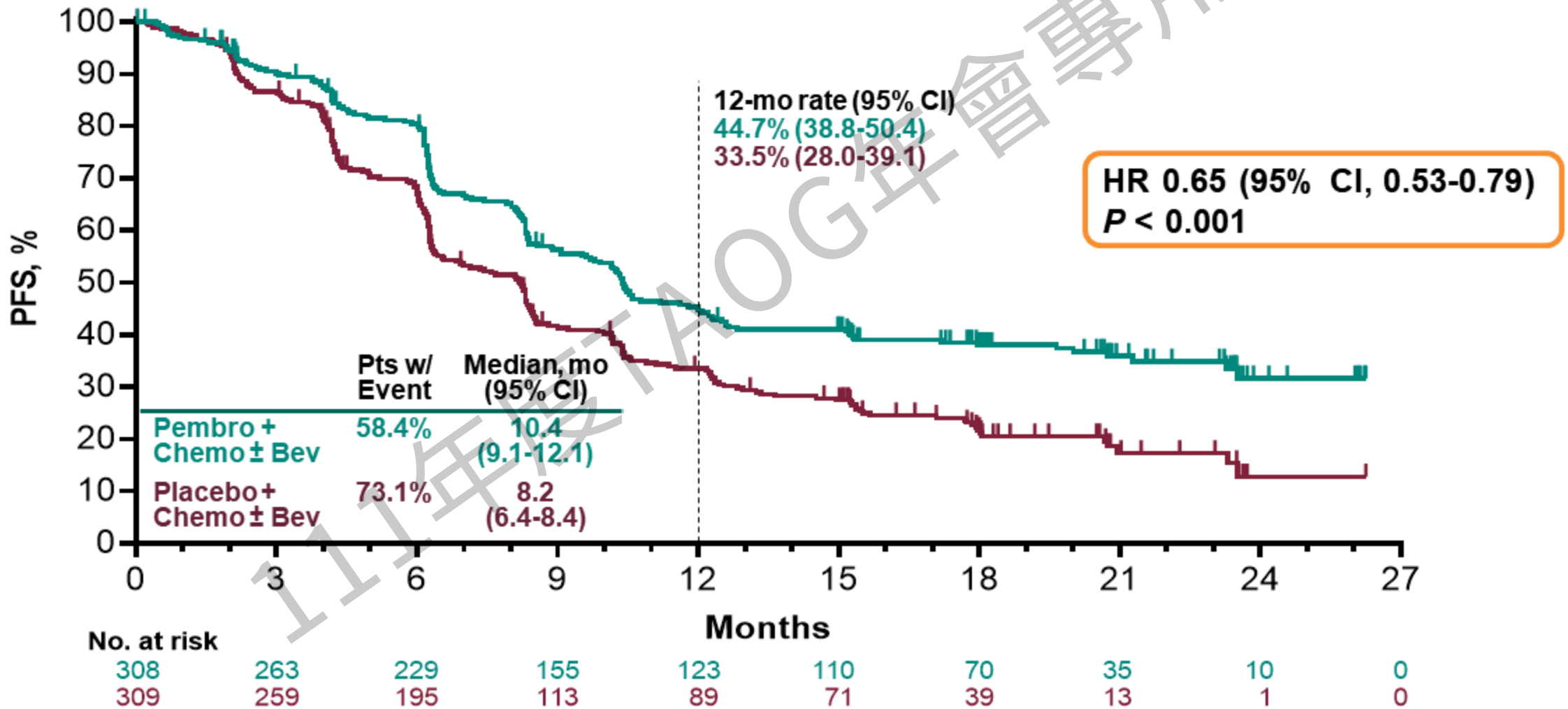
Baseline Characteristics, All-Comer Population

	Pembro Arm[a] (N = 308)	Placebo Arm[a] (N = 309)
Age, median (range)	51 y (25-82)	50 y (22-79)
ECOG PS 1	128 (41.6%)	139 (45.0%)
Squamous cell carcinoma	235 (76.3%)	211 (68.3%)
PD-L1 CPS		
<1	35 (11.4%)	34 (11.0%)
1 to <10	115 (37.3%)	116 (37.5%)
≥10	158 (51.3%)	159 (51.5%)
Prior therapy		
Chemoradiation or radiation with surgery	71 (23.1%)	79 (25.6%)
Chemoradiation or radiation only	156 (50.6%)	142 (46.0%)
Surgery only	23 (7.5%)	24 (7.8%)
None	58 (18.8%)	64 (20.7%)

	Pembro Arm[a] (N = 308)	Placebo Arm[a] (N = 309)
Stage at initial diagnosis (FIGO 2009/NCCN 2017 criteria)		
I	67 (21.8%)	58 (18.8%)
II	85 (27.6%)	93 (30.1%)
III	5 (1.6%)	8 (2.6%)
IIIA	4 (1.3%)	8 (2.6%)
IIIB	46 (14.9%)	42 (13.6%)
IVA	7 (2.3%)	4 (1.3%)
IVB	94 (30.5%)	96 (31.1%)
Disease status at study entry		
Metastatic[b]	58 (18.8%)	64 (20.7%)
Persistent or recurrent with distant metastases	199 (64.6%)	179 (57.9%)
Persistent or recurrent without distant metastases	51 (16.6%)	66 (21.4%)
Bevacizumab use during the study	196 (63.6%)	193 (62.5%)

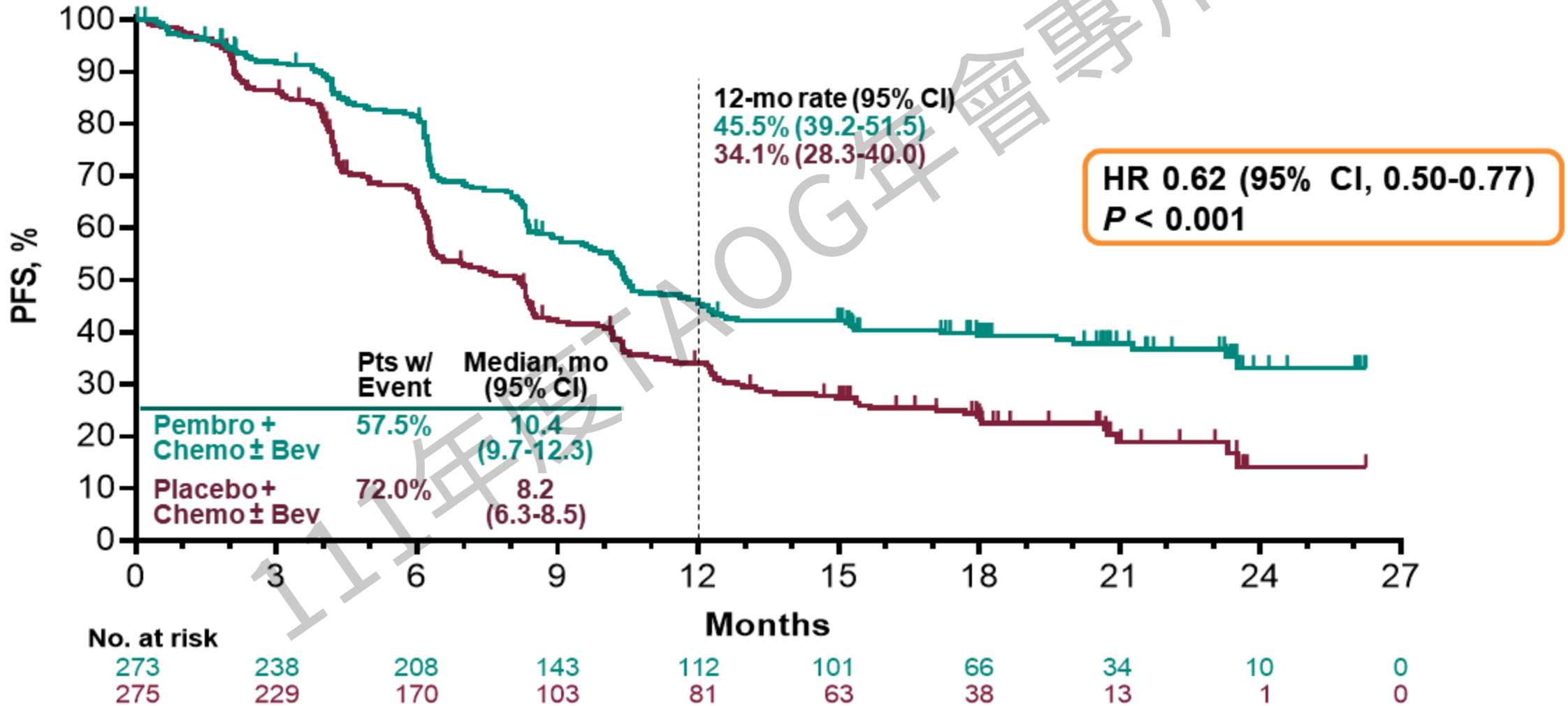
[a]The treatment regimen in both arms included chemo ± bev.
[b]Includes participants with para-aortic lymph node involvement. These participants were diagnosed with stage IVB disease and entered the study with no prior treatment for cervical cancer.
Data cutoff date: May 3, 2021.

PFS: All-Comer Population



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

PFS: PD-L1 CPS ≥1 Population



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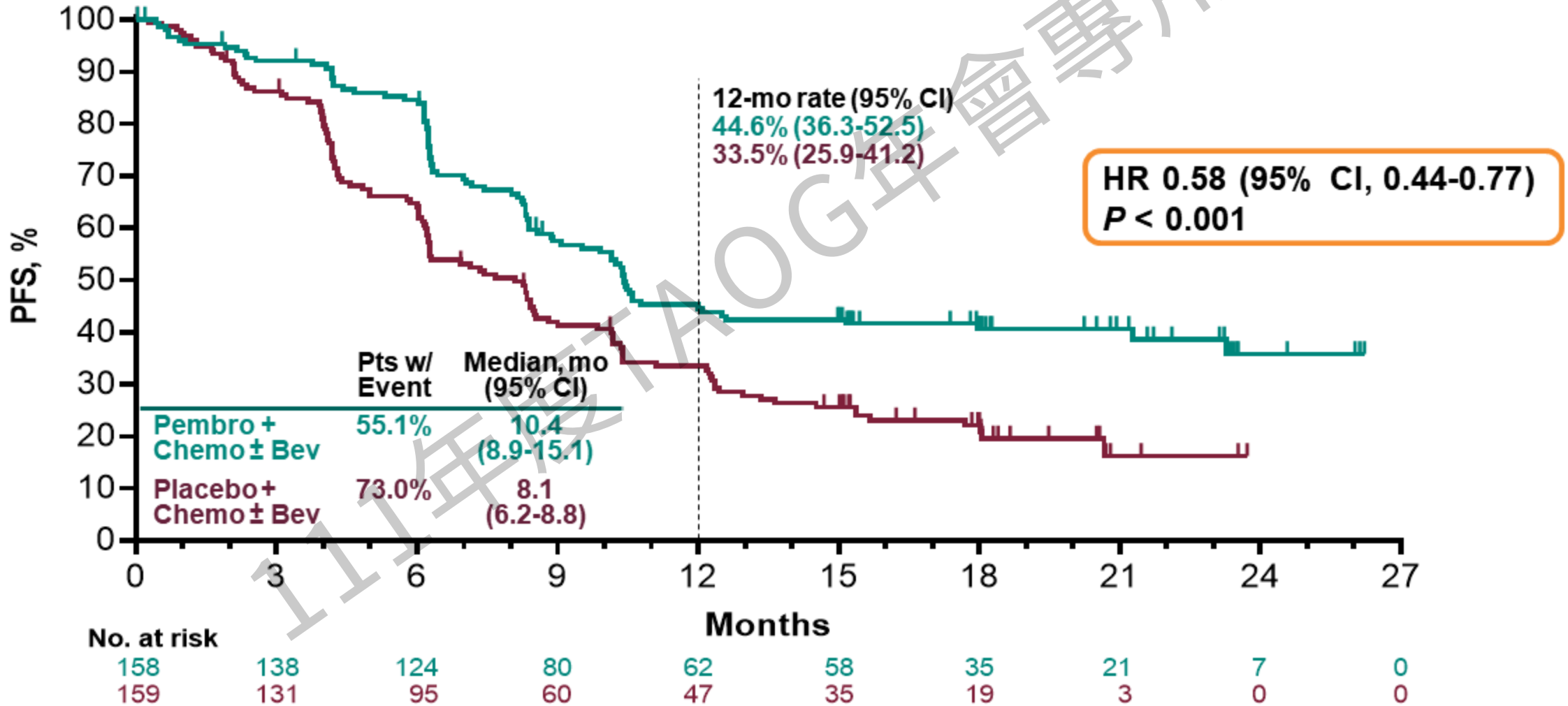
PFS: PD-L1 CPS ≥10 Population



Response assessed per RECIST v1.1 by investigator review.
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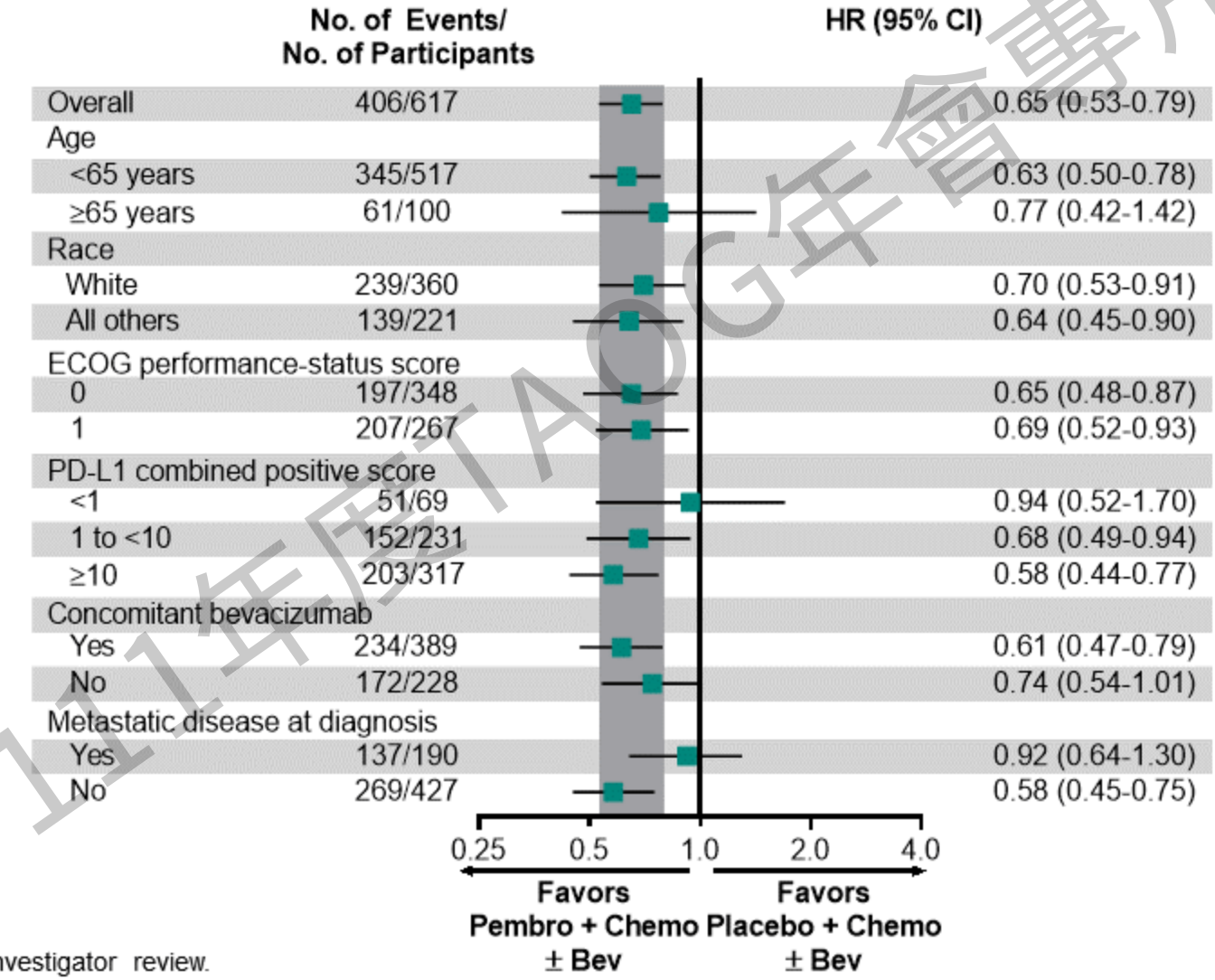
PFS: Protocol-Specified Subgroups, All-Comer Population



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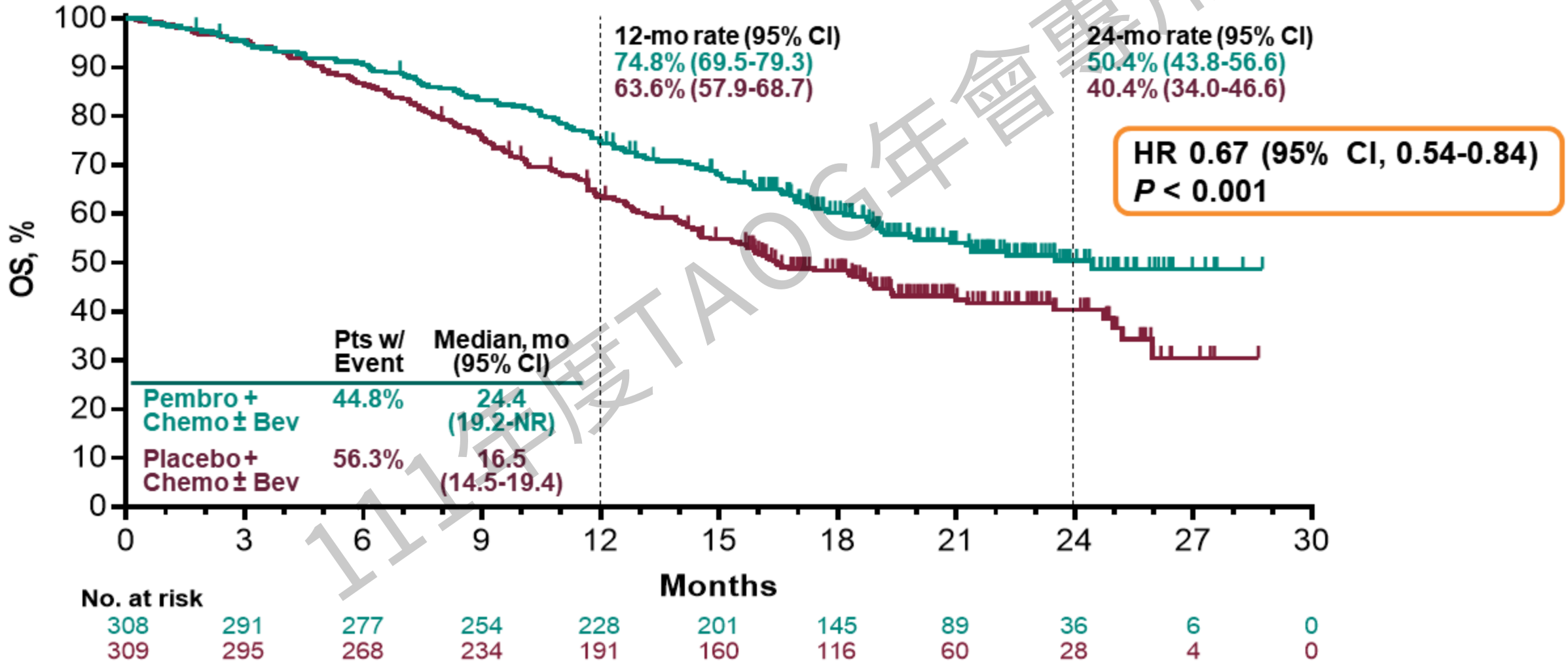
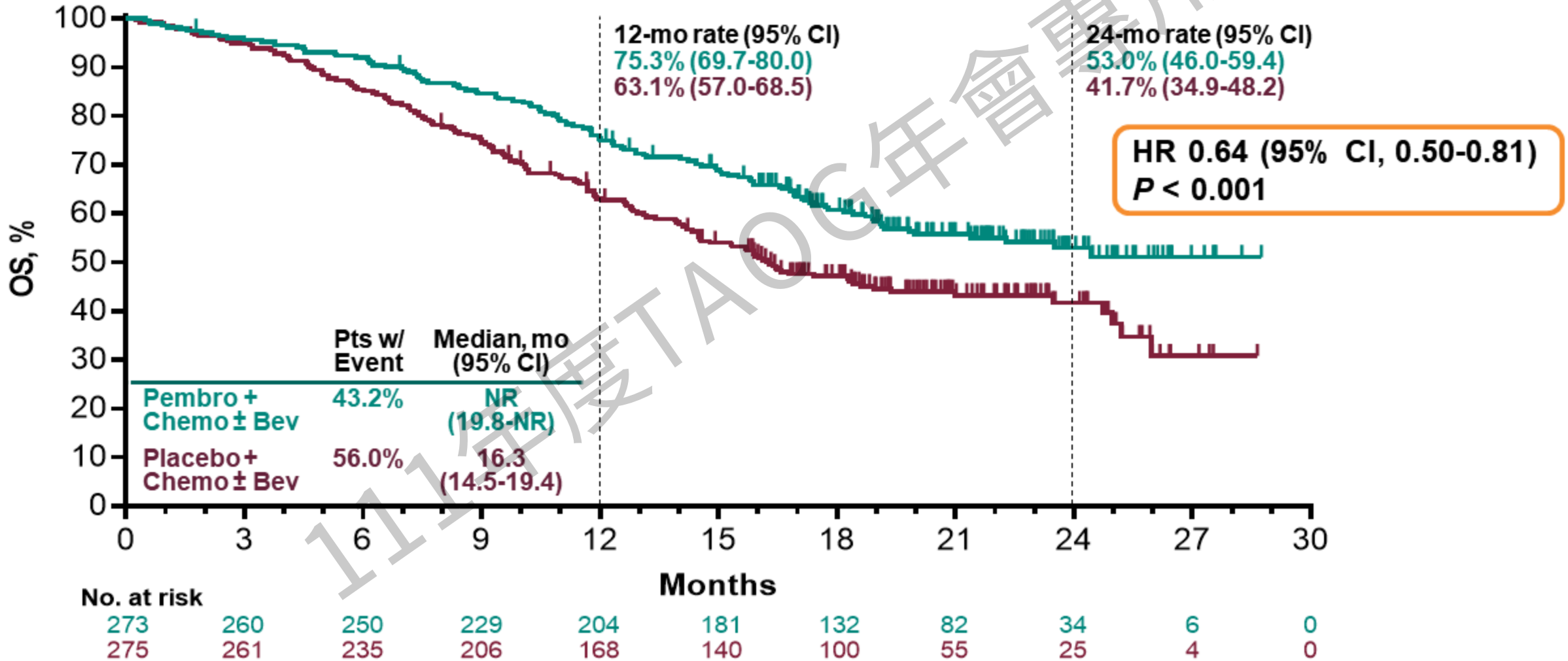
Data cutoff date: May 3, 2021.

OS: All-Comer Population



Data cutoff date: May 3, 2021.

OS: PD-L1 CPS ≥1 Population



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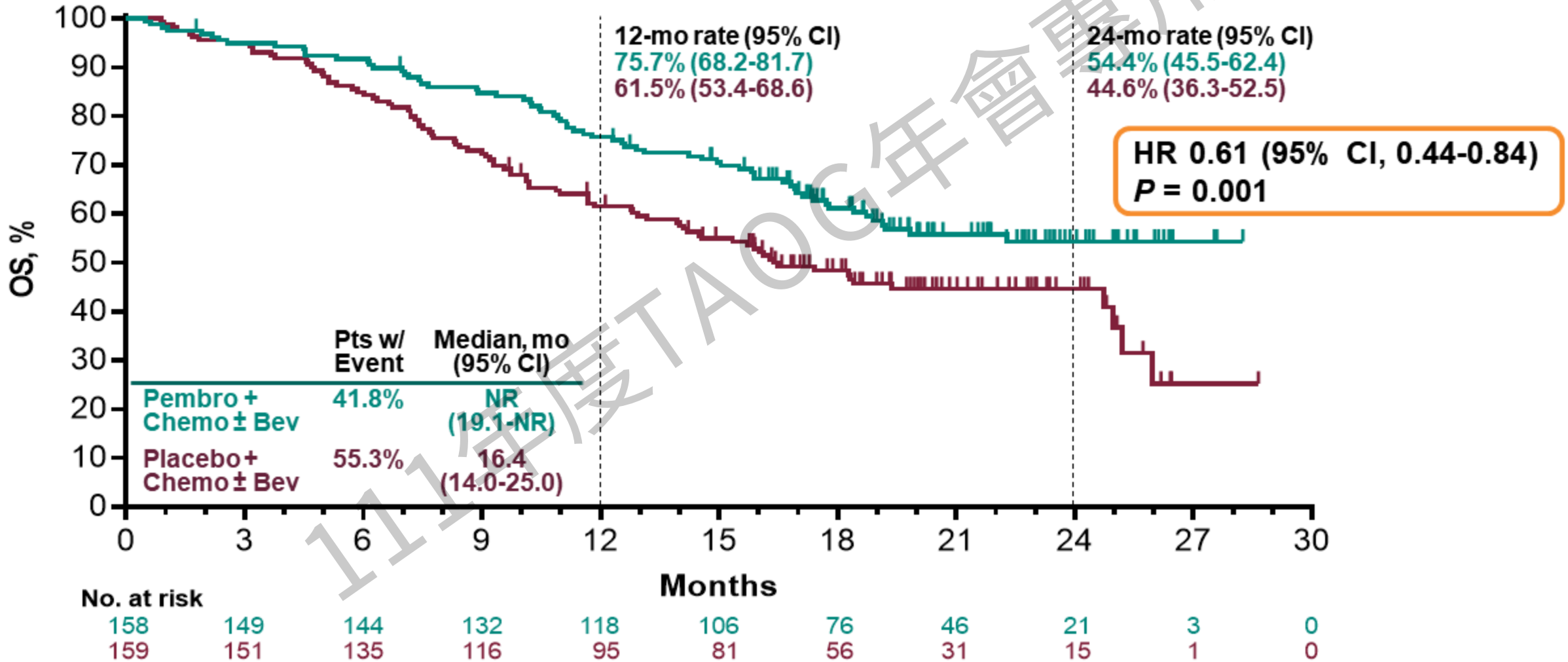
OS: PD-L1 CPS ≥10 Population



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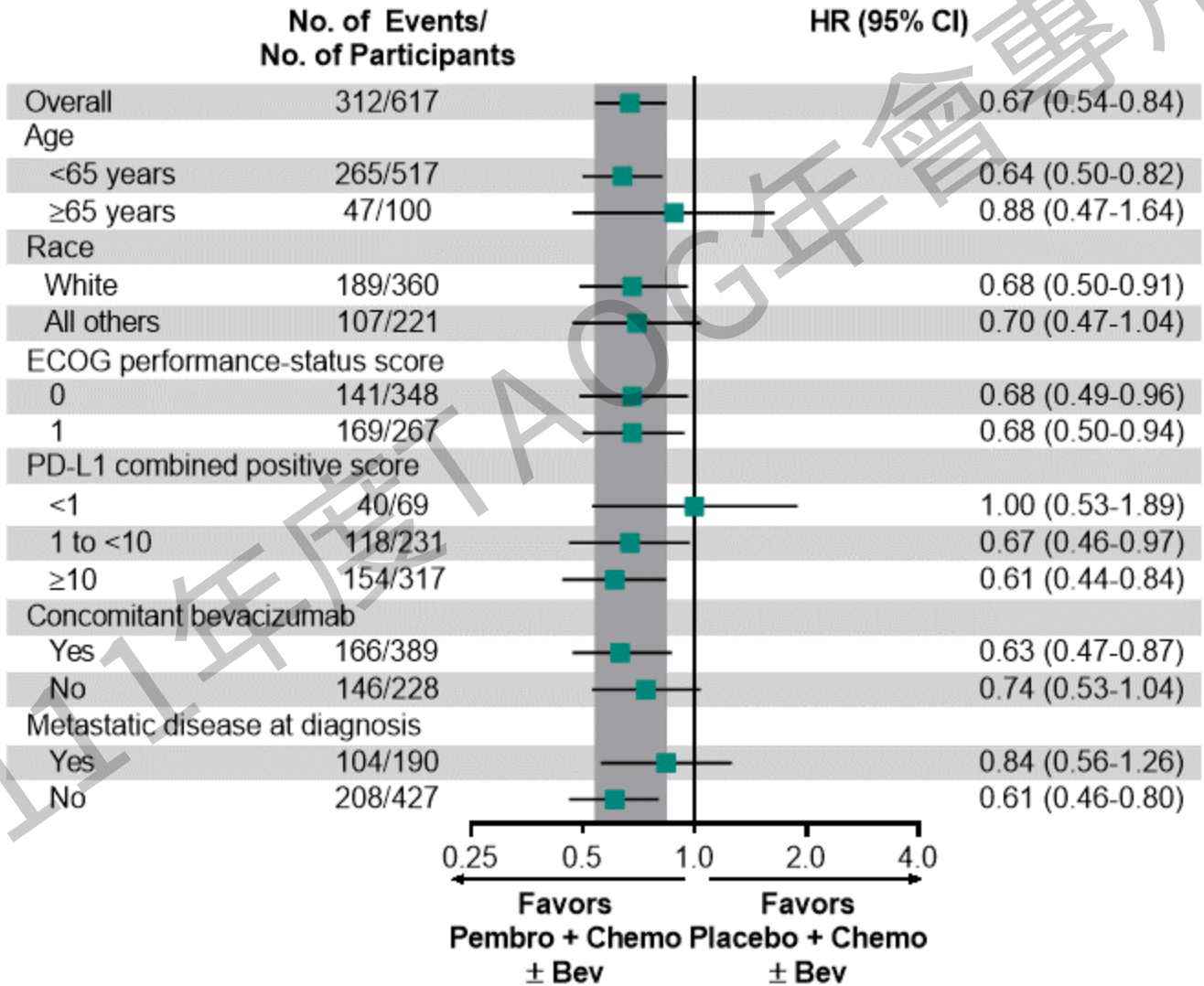
OS: Protocol-Specified Subgroups, All-Comer Population



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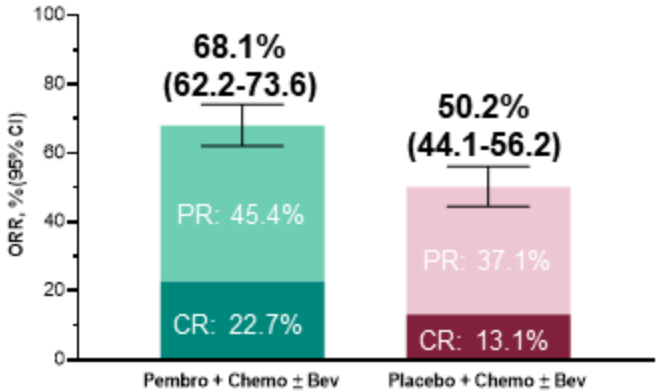
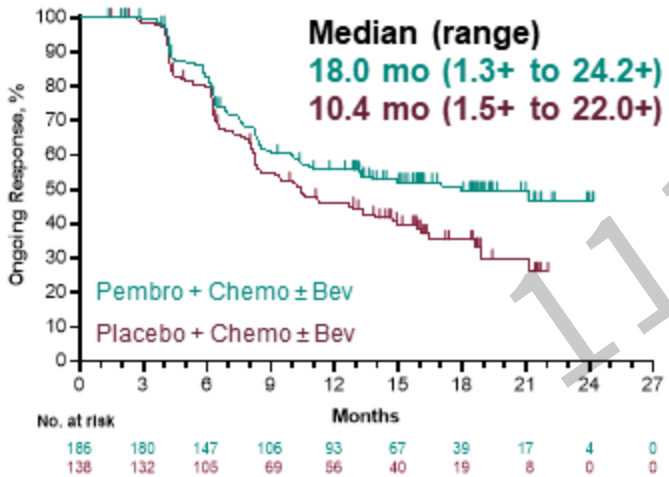
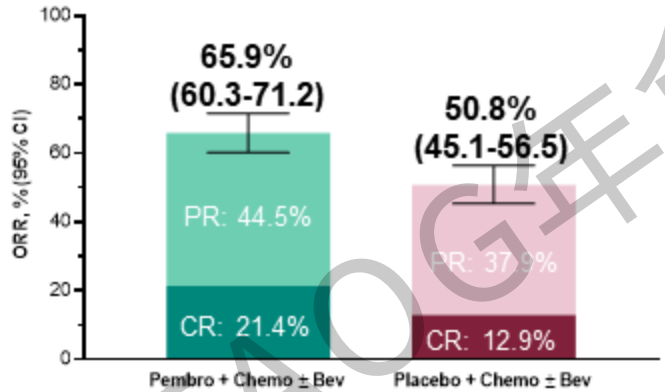
ORR and DOR: All Analysis Populations

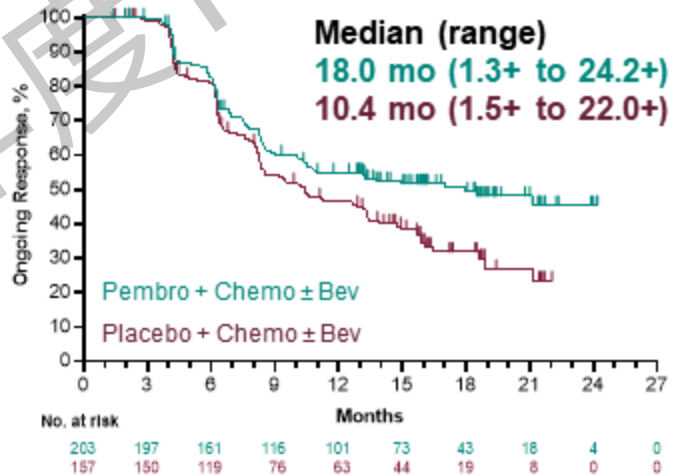
PD-L1 CPS ≥1



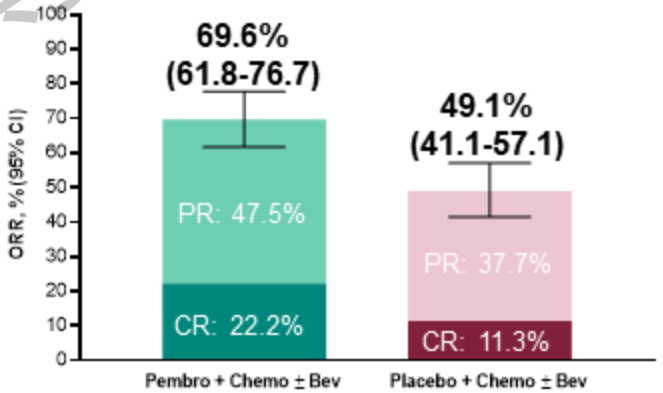


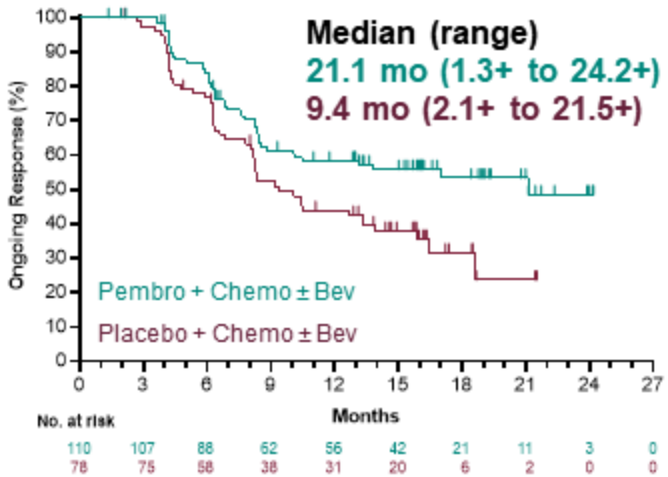
All-Comer





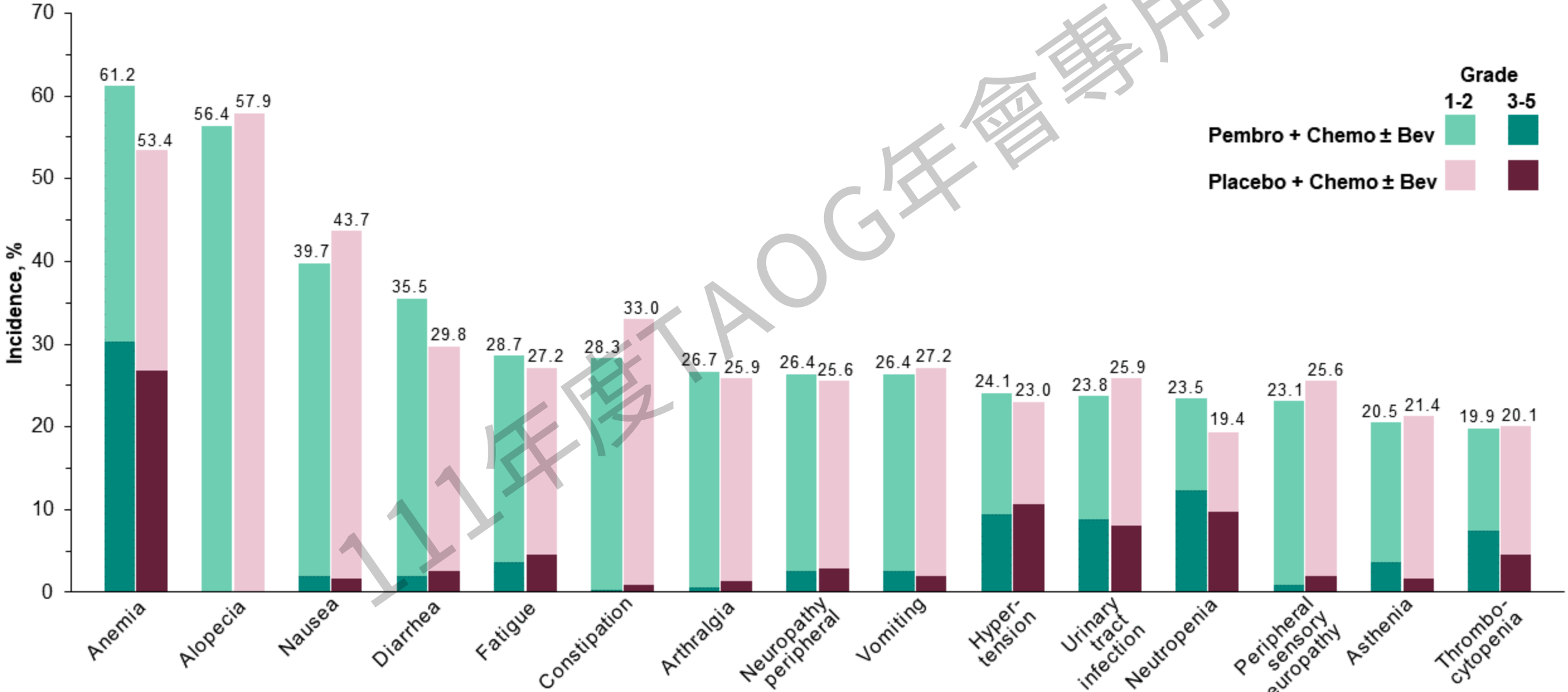
PD-L1 CPS ≥10





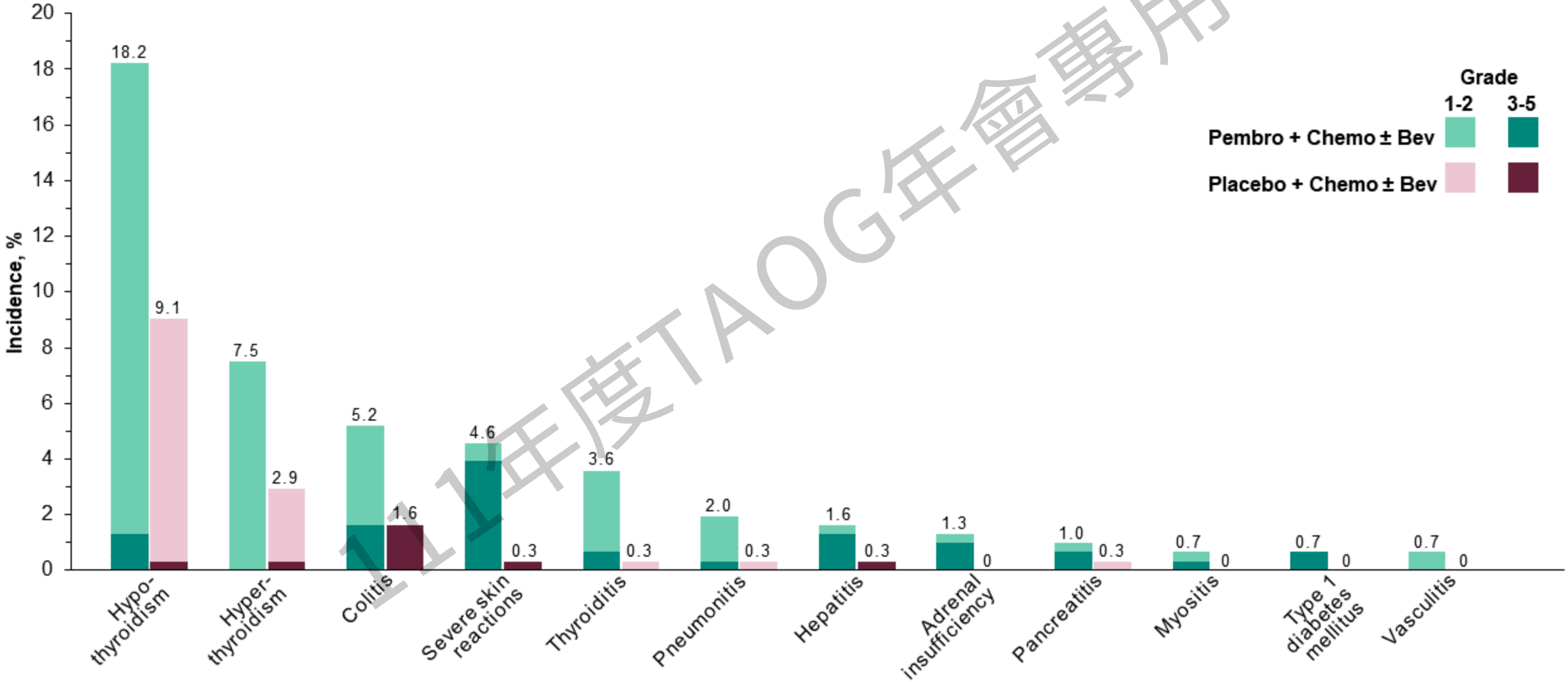
Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: May 3, 2021.

All-Cause AEs, Incidence ≥20% in Either Arm



Data cutoff date: May 3, 2021.

Immune-Mediated AEs, Incidence ≥2 Patients in Either Arm



[a]Events were considered regardless of attribution to treatment by the investigator. Related terms were included in addition to the specific terms listed.
Data cutoff date: May 3, 2021.

Neuroendocrine cervical cancer cT3aN1M1

- 70 y/o, G2P2
- Cervical cancer
- cT3aN1M1

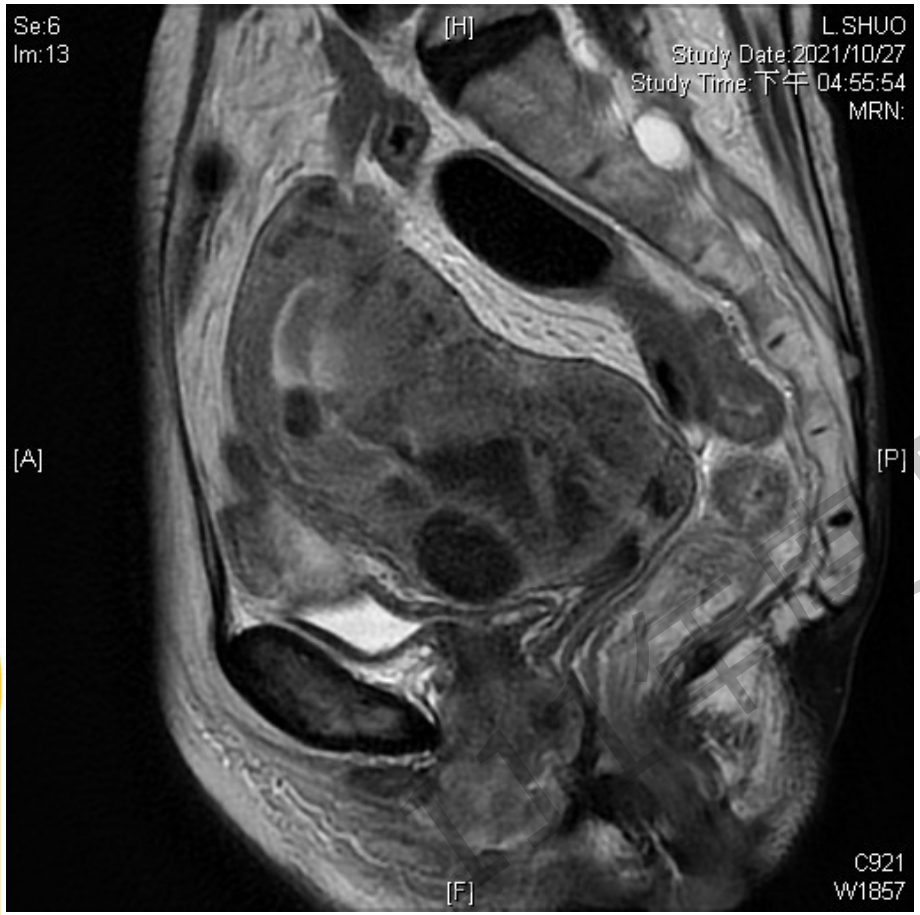
2021/11/04

cT3aN1M1

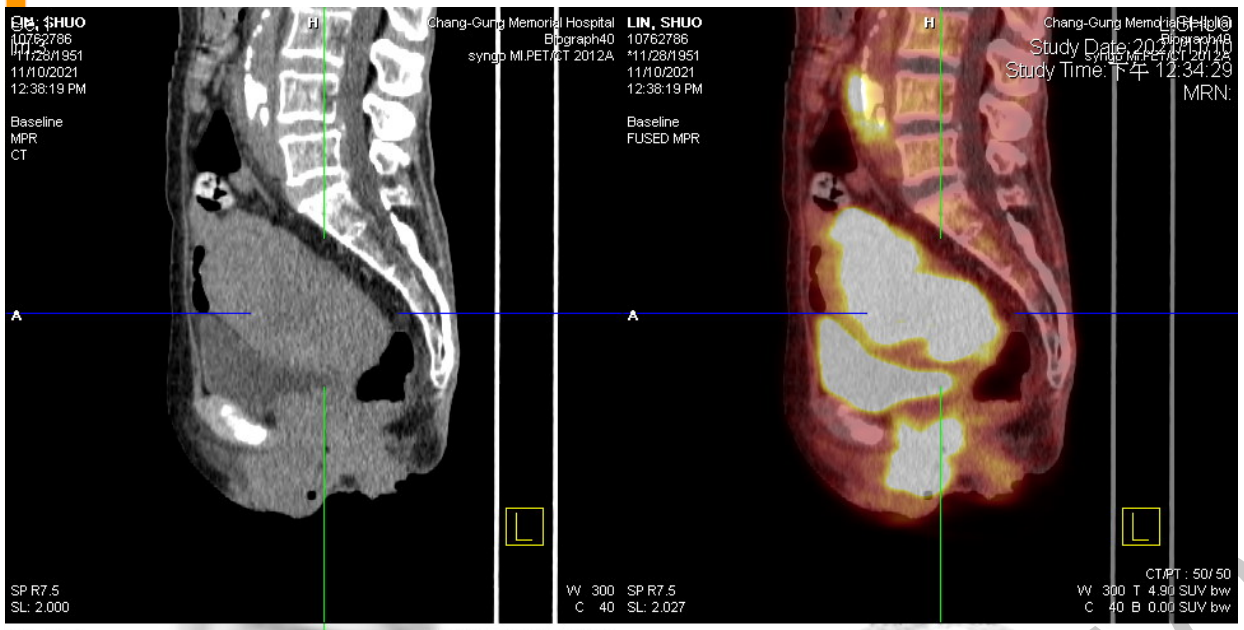
	20211104
SCC	6.7
CEA	32.2
CA153	WNL
CA125	WNL
CA199	WNL

- CC: **post menopausal bleeding** for one-year. Previous smear (2021/5) at neighboring clinic showed reactive and HPV (-)
  - Continuous bleeding and a vaginal tumor bx at a regional hospital : **poorly differentiated carcinoma** with **focal neuroendocrine differentiation**
  - General weakness and abdominal pain
    - PV: large, denuded suburethral tumor and narrow vaginal canal due to tumor infiltration into vaginal wall.
    - PR: 6cm tumor with bil. parametrial involvement, FIGO IIIA
    - HPV test : negative

2021/11/04



- MRI: bulky tumor with multiple enlarge pelvic LNs
- PET: cervical cancer with bil iliac , right common iliac, right common iliac and para aortic LNs involvements and supseced **left lower lung metastasis**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Chang-Gung Memorial Hospital
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syngo MI.PET/CT 2012A
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C 40
SP R7.5
SL: 2.027
CT/PT : 50/ 50
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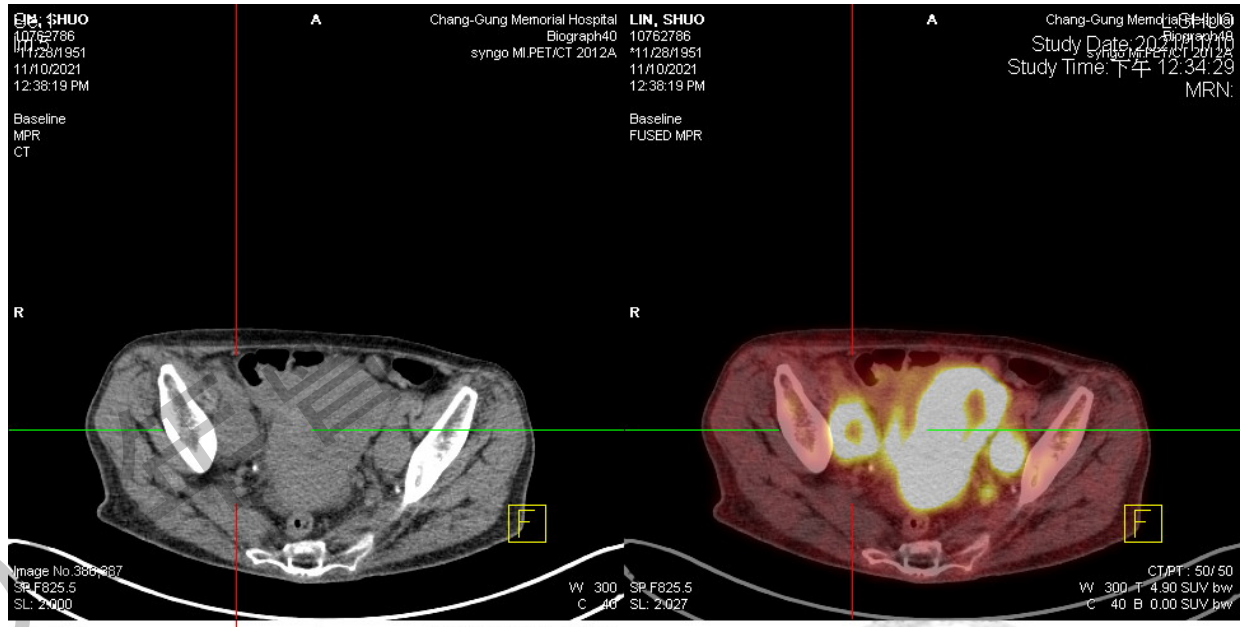
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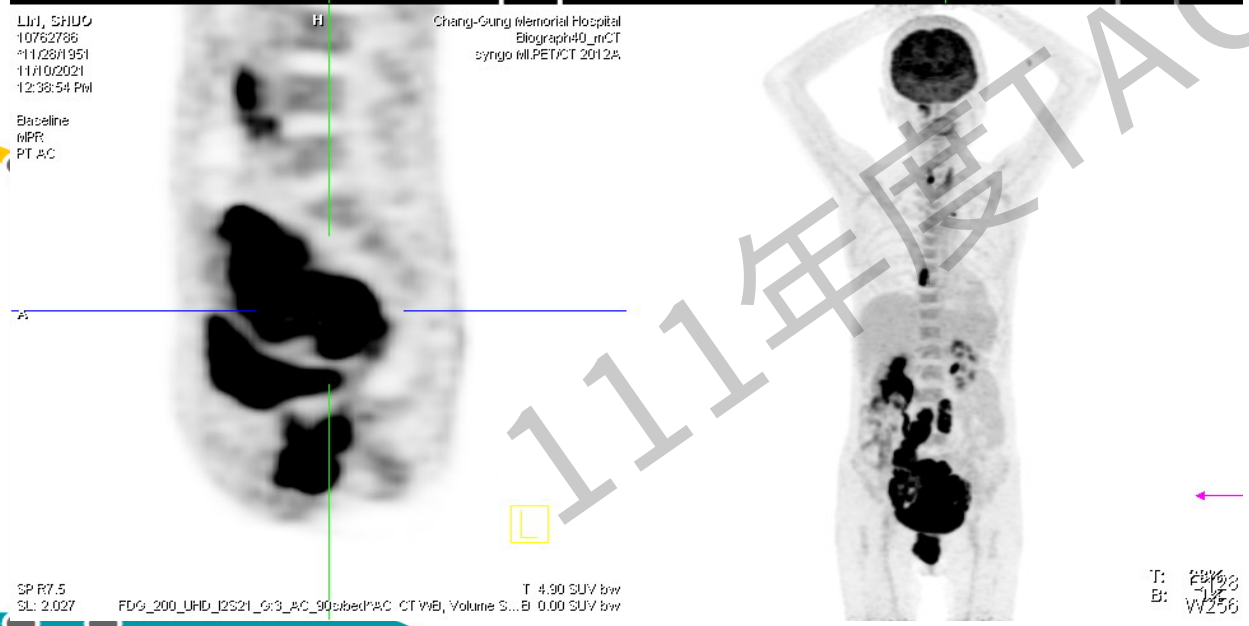
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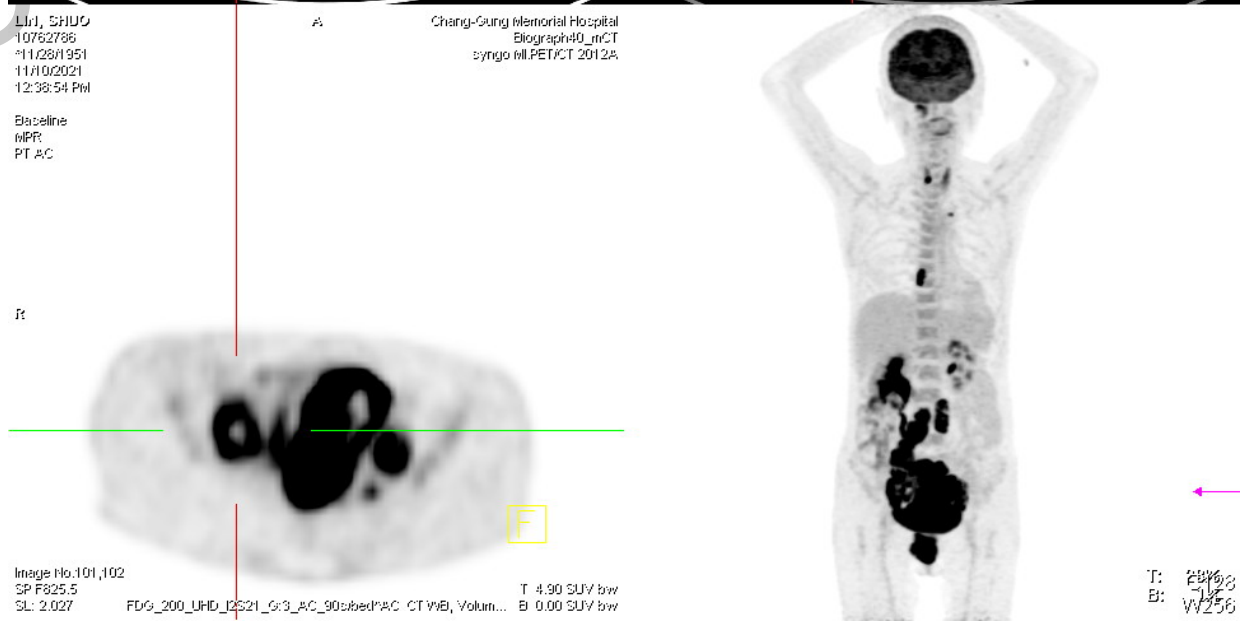
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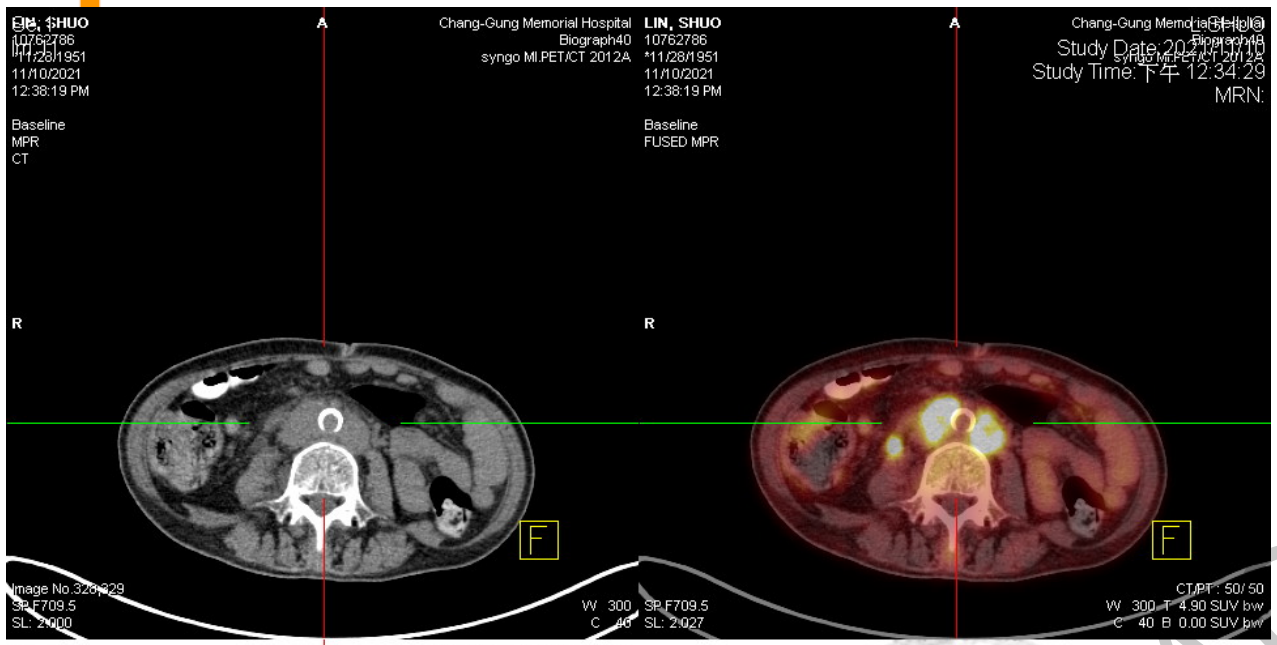
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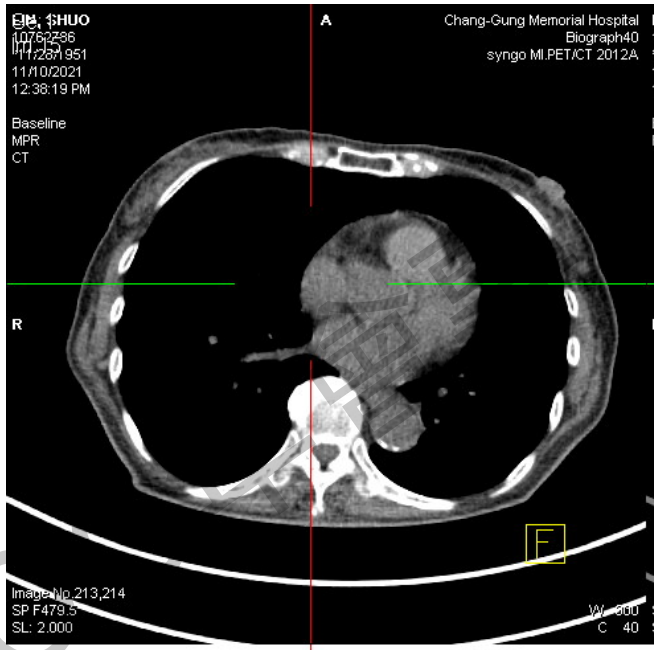
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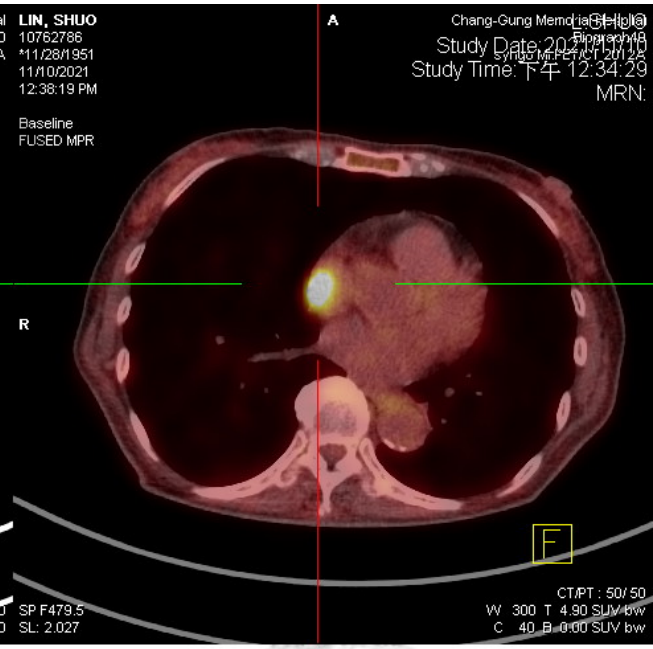
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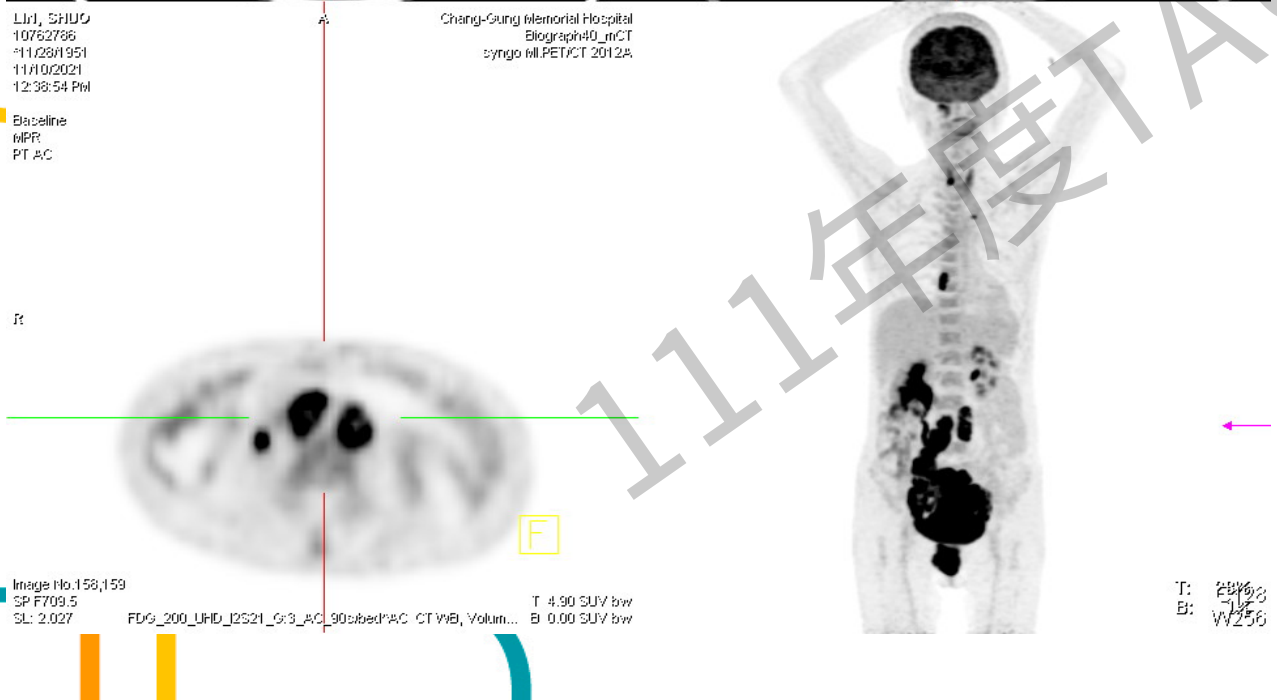
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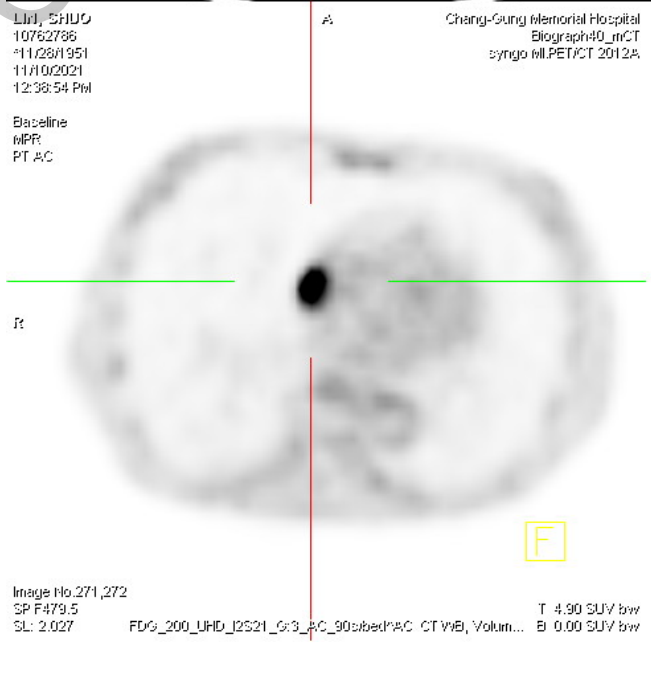
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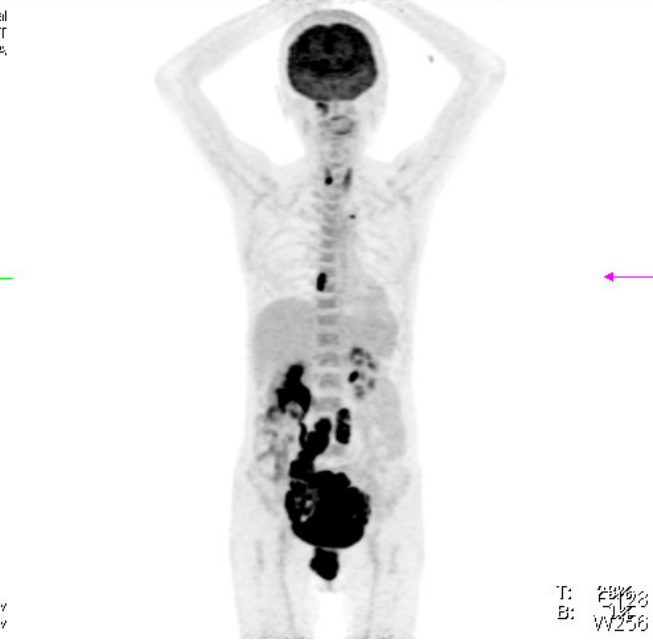

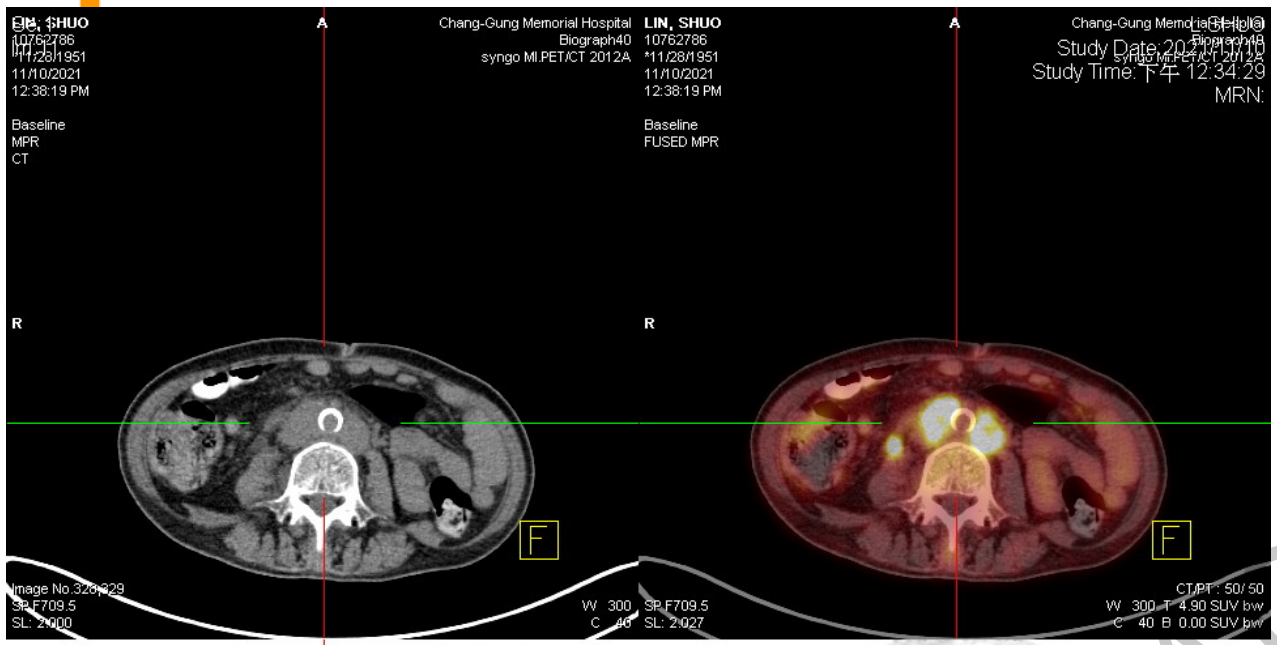
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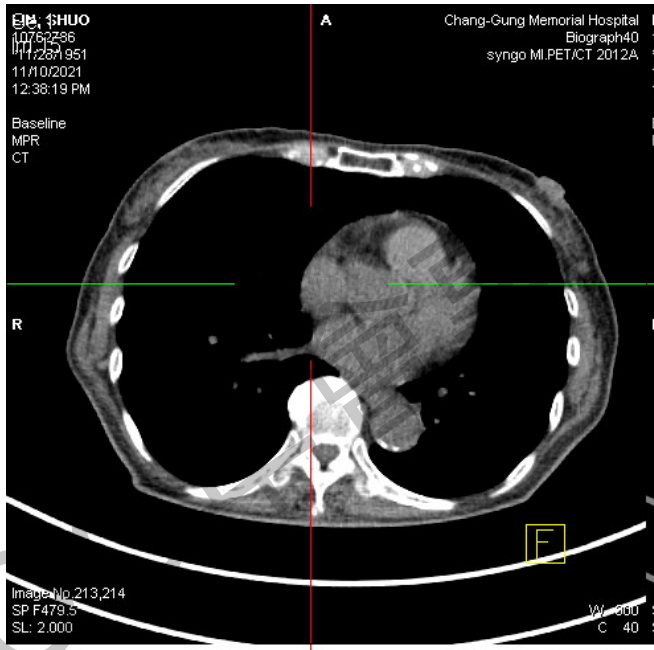
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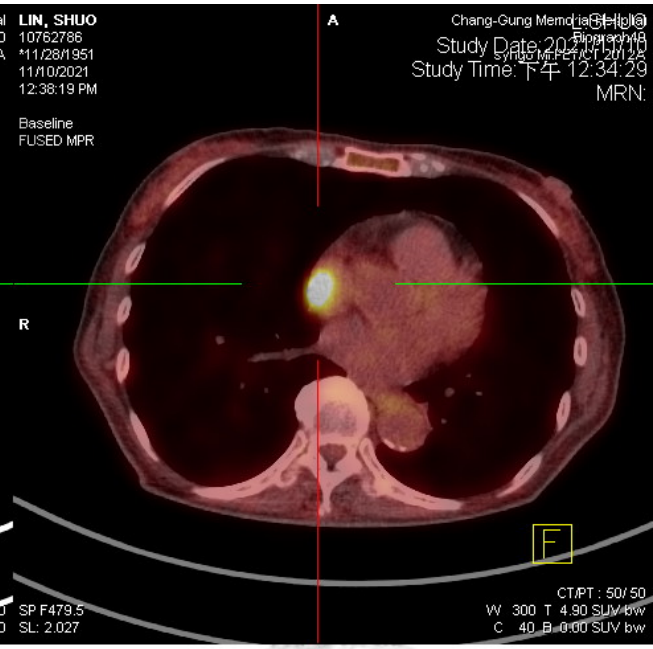
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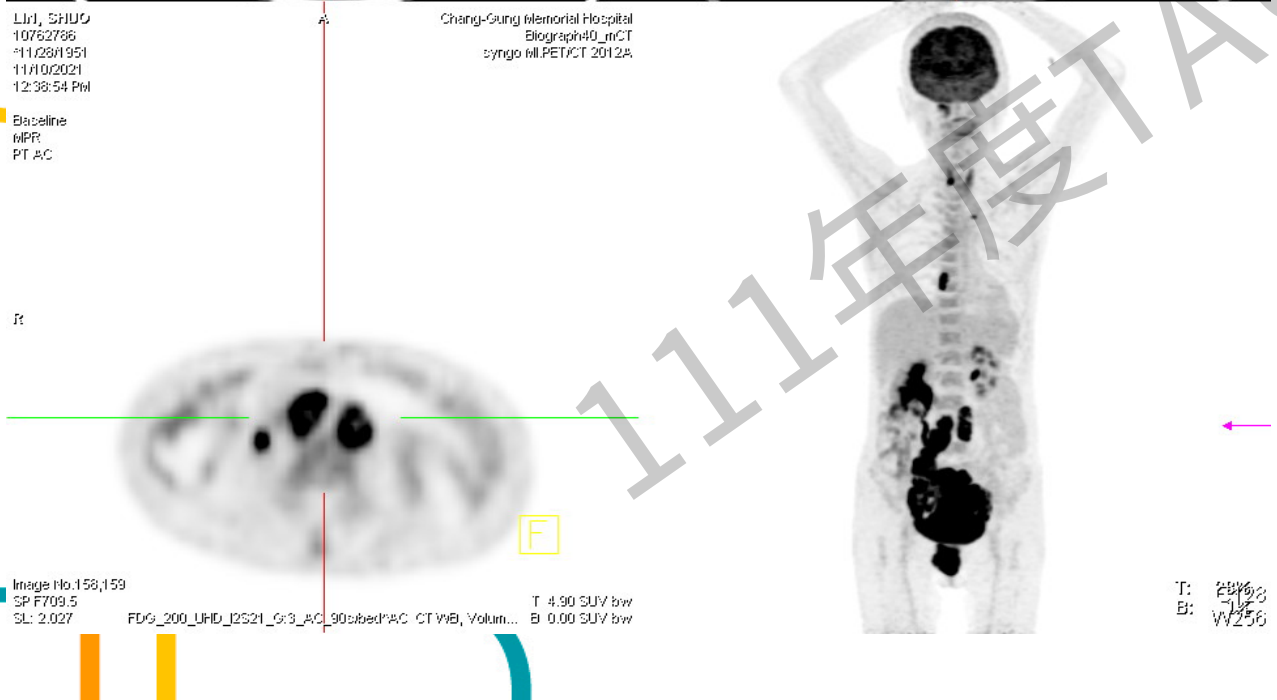
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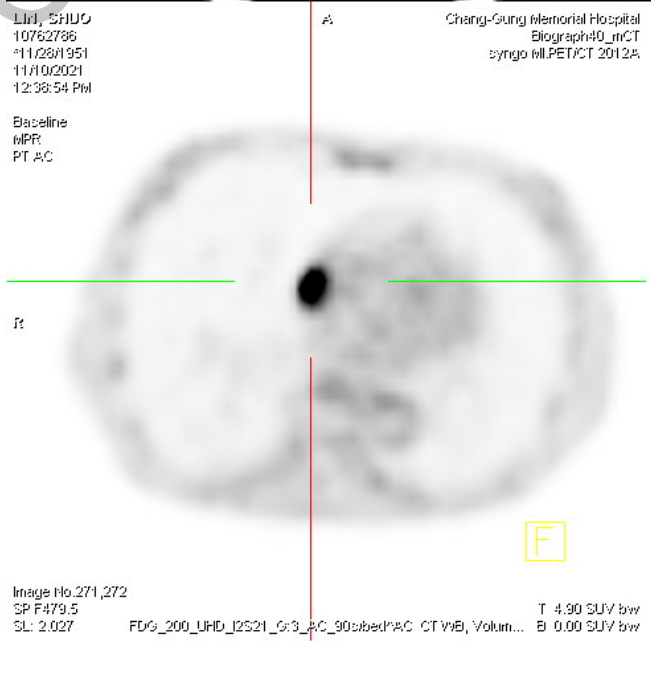
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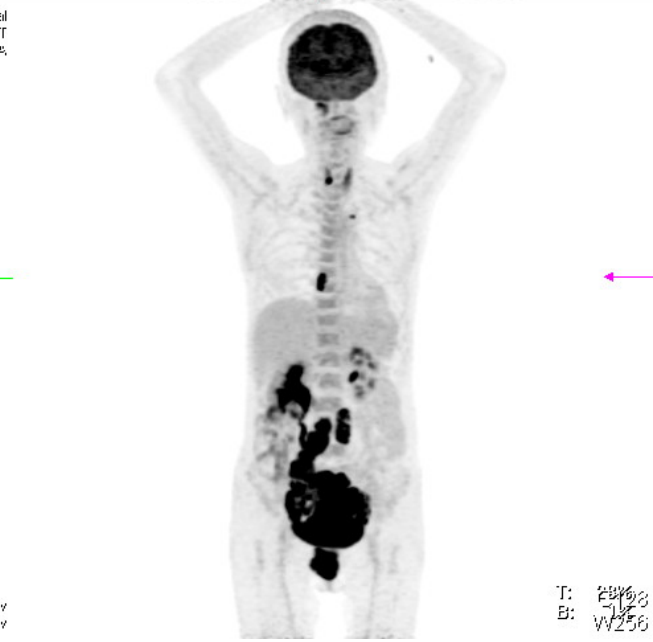
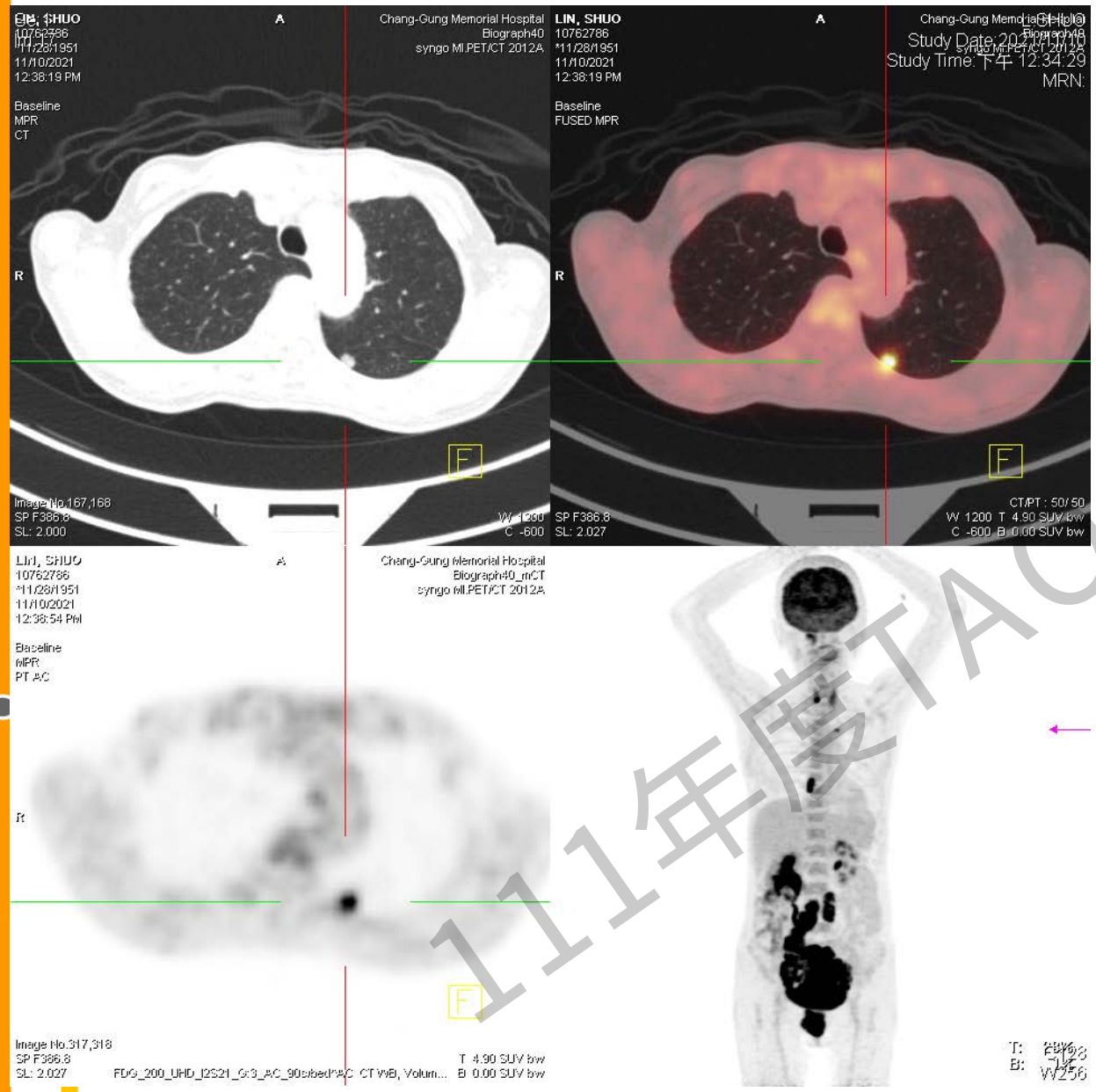




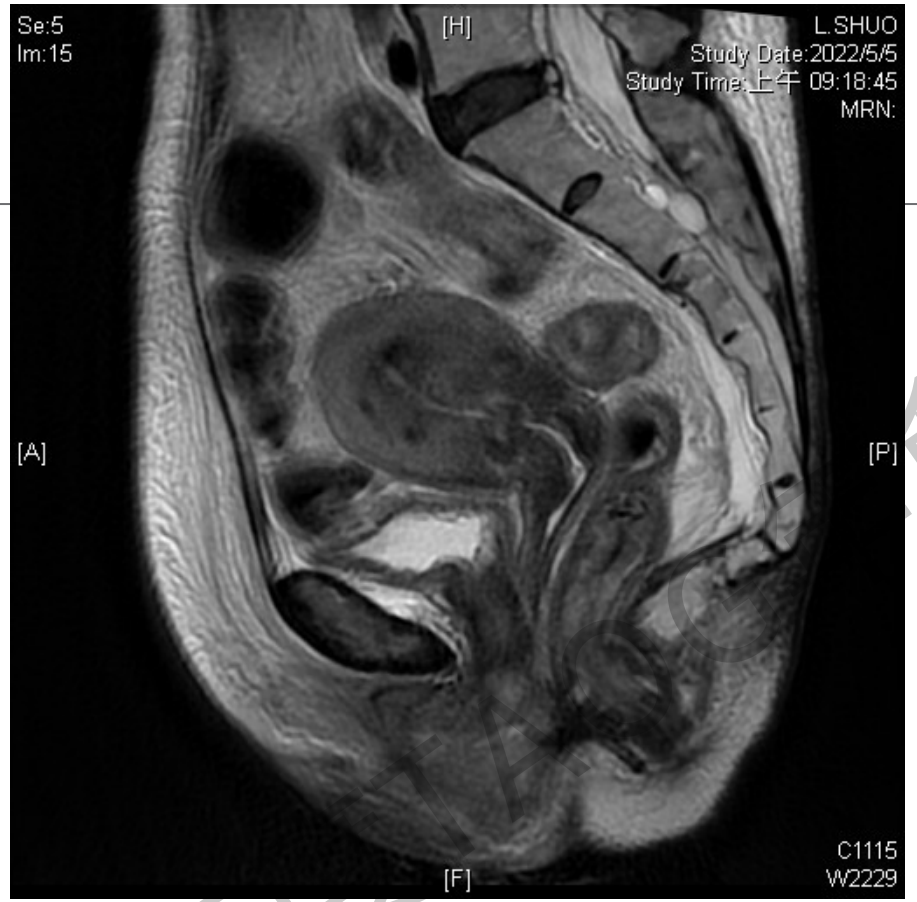
- Thoracoscopic wedge resection of LUL lesion
- Patho: **poorly differentiated carcinoma with focal squamous and focal neuroendocrine differentiation**

Case-Cx Ca

2021/11/06
2022/01/24

- **CCRT + immunotherapy**
  - Etoposide(100mg/m2) + cisplatin (100mg/m2)+ pembrolizumab 200mg X4 times
  - Radiotherapy for gross tumor

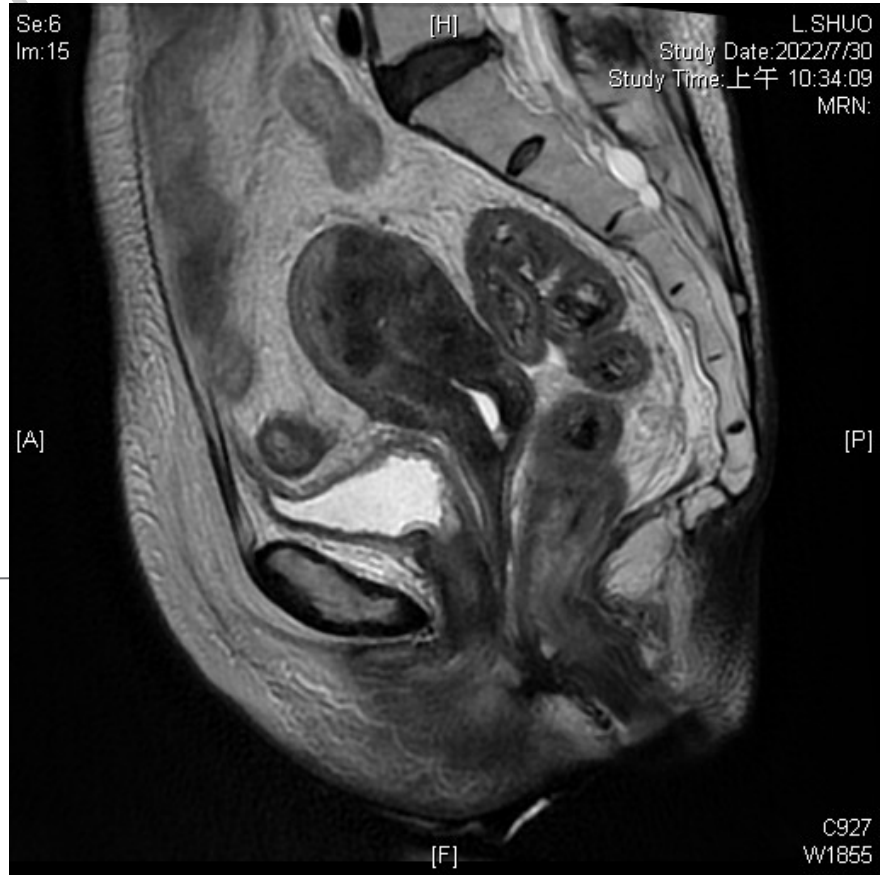
2022/5/5



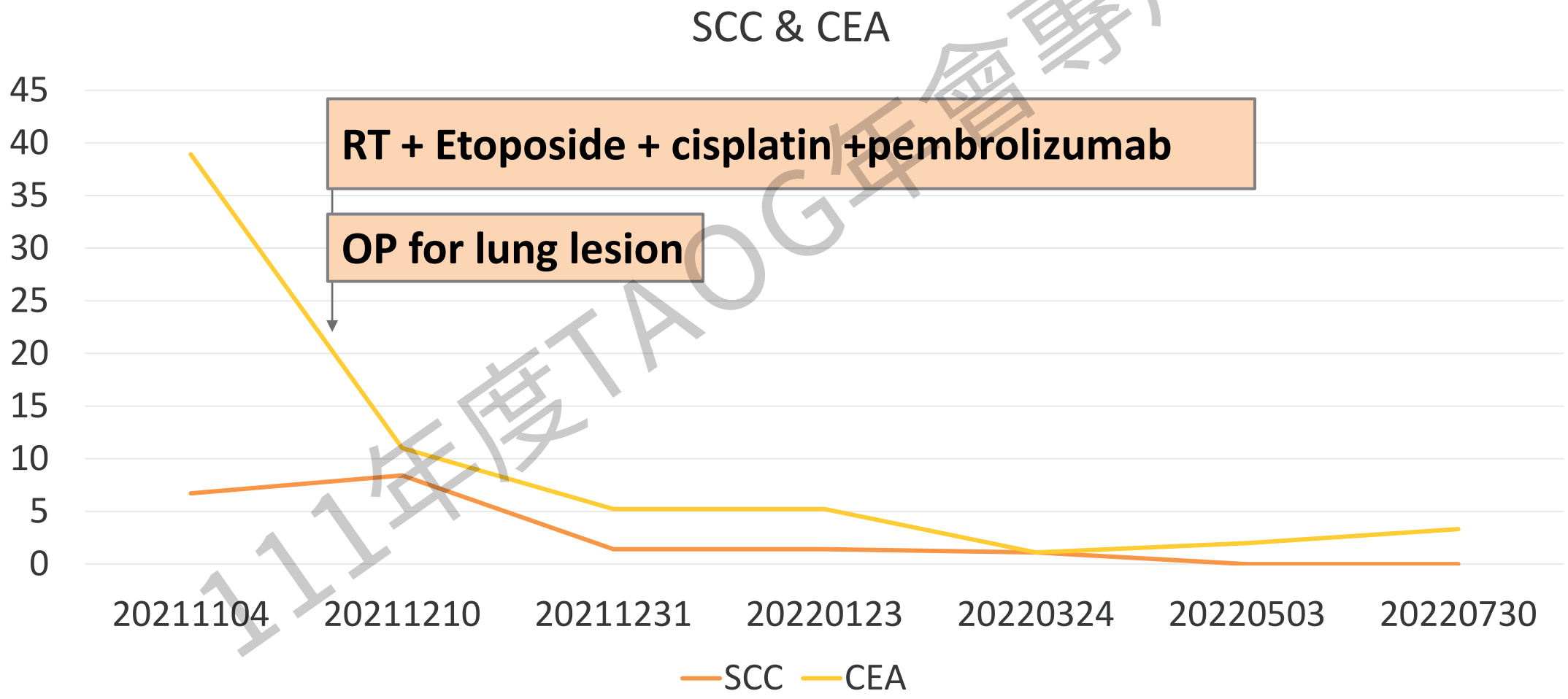
MRI: radiological remission

2022/07/30

MRI: stationary residual lesion at right vaginal opening and vulva region



Treatment and tumor markers



Recurrent cervical cancer

2017/5, Papillary squamous cervical cancer cT2bN0M0

SCC-Ag 3.0, HPV 16 (+)

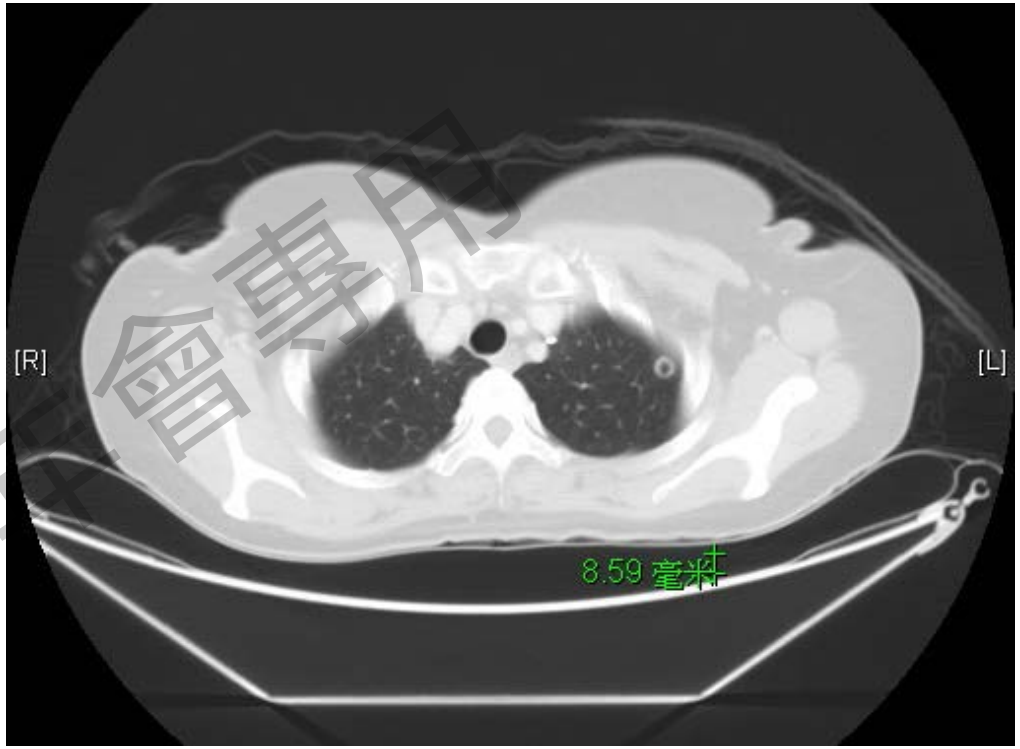
Primary CCRT, cisplatin 40 mg/m2/wk x 6

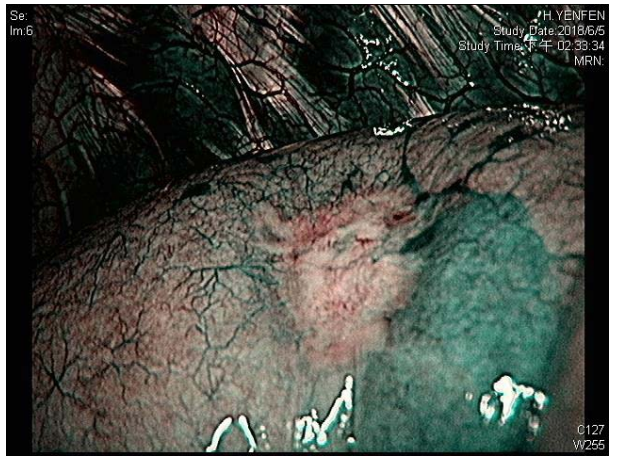
2017/8, Complete CCRT, SCC 1.1

2017/11, CT, NED, Pap, reactive, SCC, 1.0, HPV 16 (+)

2018/4/17, SCC, 1.4, CT, two lung nodules with central cavity, left apical (8.5 mm) and left lower lung (3.5 mm), Pap, CIN3

2018/6, resection of left apical tumor, histology: metastatic squamous carcinoma





2018/7, Cisplatin 60 mg/m2 + pembrolizumab 100 mg every 3 wks for 3 cycles

2018/10, PET showed NED

She declined further therapy

2019/3, SCC, 2.4; 2019/5, SCC, 2.7; 2019/8, SCC, 3.0, 2020/10, SCC, 4.5

2020/11, slightly indurated erythematous plaques, bilateral medial vulvae, reached periurethral region and very close to anus

Radiation oncologist suggested immunochemotherapy

2020/12, cisplatin 60mg/m2 + pembrolizumab 100 mg

partial resolved vulvar lesion, SCC 2.1 after

2021/3, cisplatin 60 mg/m2 + pembrolizumab 100 mg, due to reappeared vulvar tumor

Flat, injected vulvar lesion, PR; chest CT: tiny RLL nodule; declined further tx

2022/3, Stationary mentioned by her husband, SCC, 2.5

Continuing her professional work

Endometrial Cancer

KEYNOTE-775/Study 309

A multicenter, open-label, randomized, active-controlled trial of KEYTRUDA in combination with lenvatinib vs doxorubicin or paclitaxel (N=827) in patients with advanced endometrial carcinoma

- Advanced, metastatic, or recurrent endometrial cancer
- Previously treated with at least 1 prior platinum-based chemotherapy regimen (including adjuvant and neoadjuvant settings)

Exclusion Criteria

- Endometrial sarcoma, including carcinosarcoma
- Active autoimmune disease
- A medical condition that requires immunosuppression

Randomized 1:1
N=827

n=411

pembrolizumab
200 mg IV every 3 weeks
+
lenvatinib
20 mg orally once daily

n=416

Doxorubicin
60 mg/m^2 IV every 3 weeks
OR
Paclitaxel
80 mg/m^2 IV weekly (3 weeks on/1 week off)

- Treatment with pembro + lenvatinib continued until RECIST v1.1-defined progression of disease as verified by BICR,[a] unacceptable toxicity, or for pembro, a maximum of 24 months

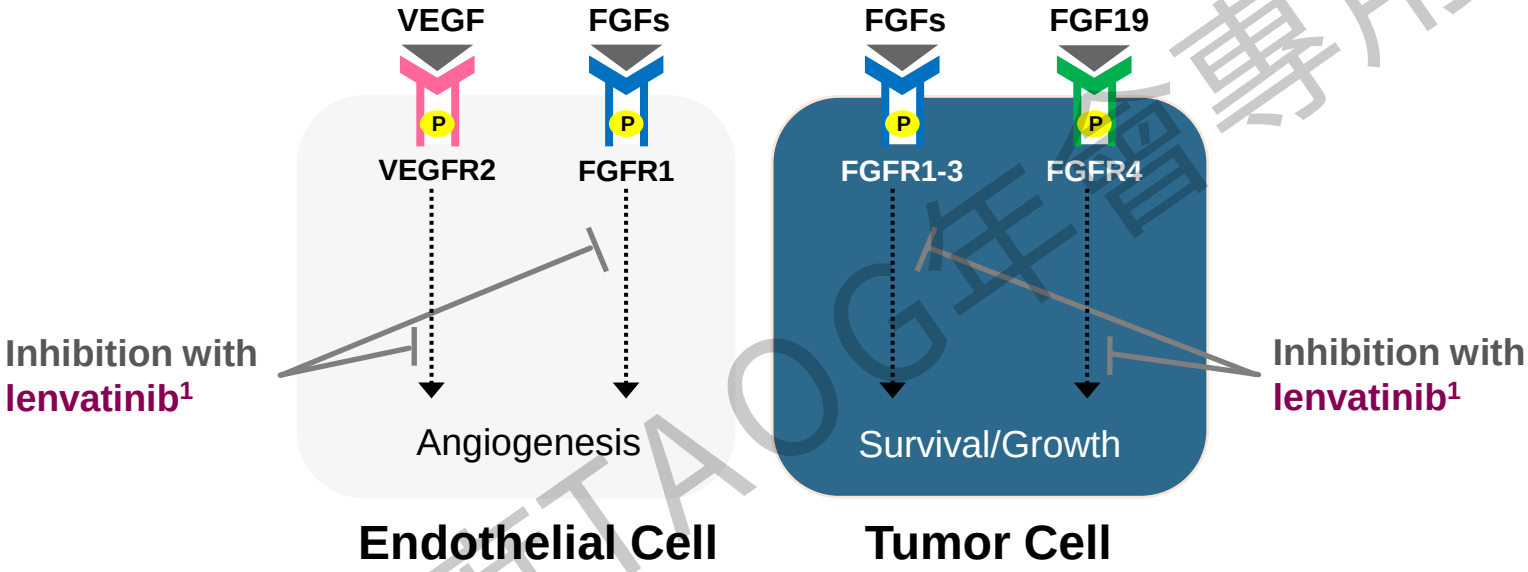
Primary end points:
- Overall survival[b]
- Progression-free survival[b]

Secondary end points:
- Objective response rate[c]
- Duration of response[c]

- Median follow-up: 11.4 months (range: 0.3-26.9 months)
- Assessment of tumor status was performed every 8 weeks

[a]Treatment was permitted beyond RECIST v1.1-defined disease progression if the treating investigator considered the patient to be deriving clinical benefit and the treatment was tolerated. [b]As assessed by BICR according to RECIST v1.1,. [c]As assessed by BICR according to RECIST v1.1, and safety
BICR = blinded independent central review; IV = intravenous; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors v1.1.
Reference: 1. Makker V, Colombo N, Herráez AC, et al. A multicenter, open-label, randomized, phase 3 study to compare the efficacy and safety of lenvatinib in combination with pembrolizumab vs treatment of physician's choice in patients with advanced endometrial cancer: Study 309/KEYNOTE-775. Virtual Annual Meeting on Women's Cancer, 2021.

Lenvatinib is Thought to Block Receptors Required for Tumor Growth and Blood Vessel Development



- lenvatinib is a kinase inhibitor that inhibits the kinase activities of vascular endothelial growth factor receptors (VEGFR): VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4).
- lenvatinib inhibits other kinases (including FGFR 1, 2, 3, and 4; PDGFRα, KIT, and RET) that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression, in addition to their normal cellular functions.

FGF = fibroblast growth factor; FGFR = fibroblast growth factor receptor; FLT = Fms-related tyrosine kinase 1; KDR = kinase insert domain receptor; PDGFR = platelet-derived growth factor receptor.

Reference: 1. Kudo M et al. *Liver Cancer*. 2018;7(1):1–19.

KEYNOTE-775/Study 309: Baseline Characteristics of Patients With Advanced Endometrial Carcinoma

Baseline characteristics of patients enrolled in KEYNOTE-775/Study 309 (N=827)

Characteristic	Population (N=827)
Median age, years (range)	65 years (30-86)
Age ≥65 years, %	50%
Race	
White	61%
Asian	21%
Black	4%
ECOG PS	
0	59%
1	41%
Histological subtypes	
Endometrioid carcinoma	60%
Serous carcinoma	26%
Clear cell carcinoma	6%
Mixed	5%
Other	3%
Received prior systemic therapies	
1	69%
2	28%
≥3	3%
Prior neoadjuvant or adjuvant therapy only	37%

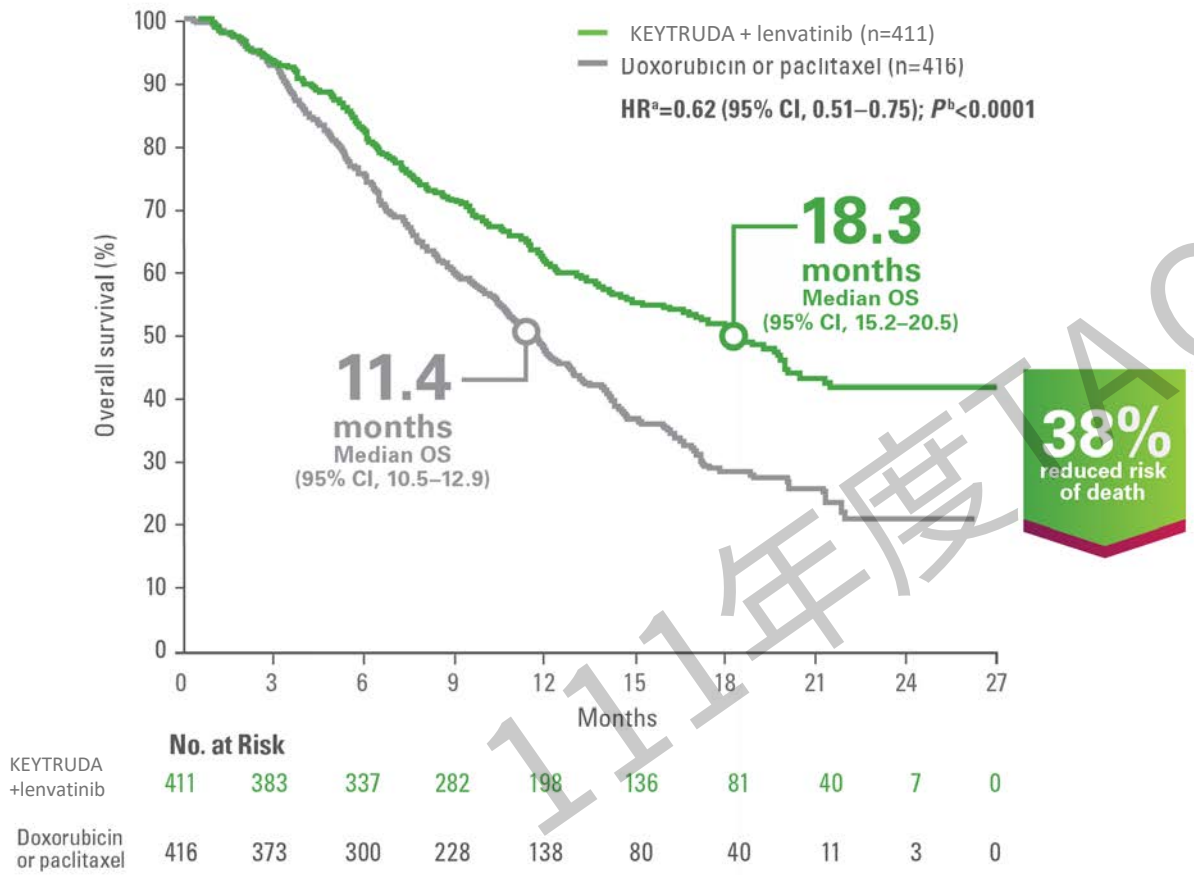
ECOG PS = Eastern Cooperative Oncology Group performance status.

Reference: 1. Makker V, Colombo N, Herráez AC, et al. A multicenter, open-label, randomized, phase 3 study to compare the efficacy and safety of lenvatinib in combination with pembrolizumab vs treatment of physician's choice in patients with advanced endometrial cancer: Study 309/KEYNOTE-775. Virtual Annual Meeting on Women's Cancer, 2021.

PATIENTS WITH ADVANCED ENDOMETRIAL CARCINOMA (N=827)

KEYNOTE-775/Study 309: Superior OS vs Doxorubicin or Paclitaxel[1]

Kaplan-Meier Estimates of OS in KEYNOTE-775/Study 309[c]



38% Reduction in risk of death with pembrolizumab + lenvatinib vs doxorubicin or paclitaxel (HR[a] [95% CI]=0.62 [0.51–0.75]; *P*[b]<0.0001)

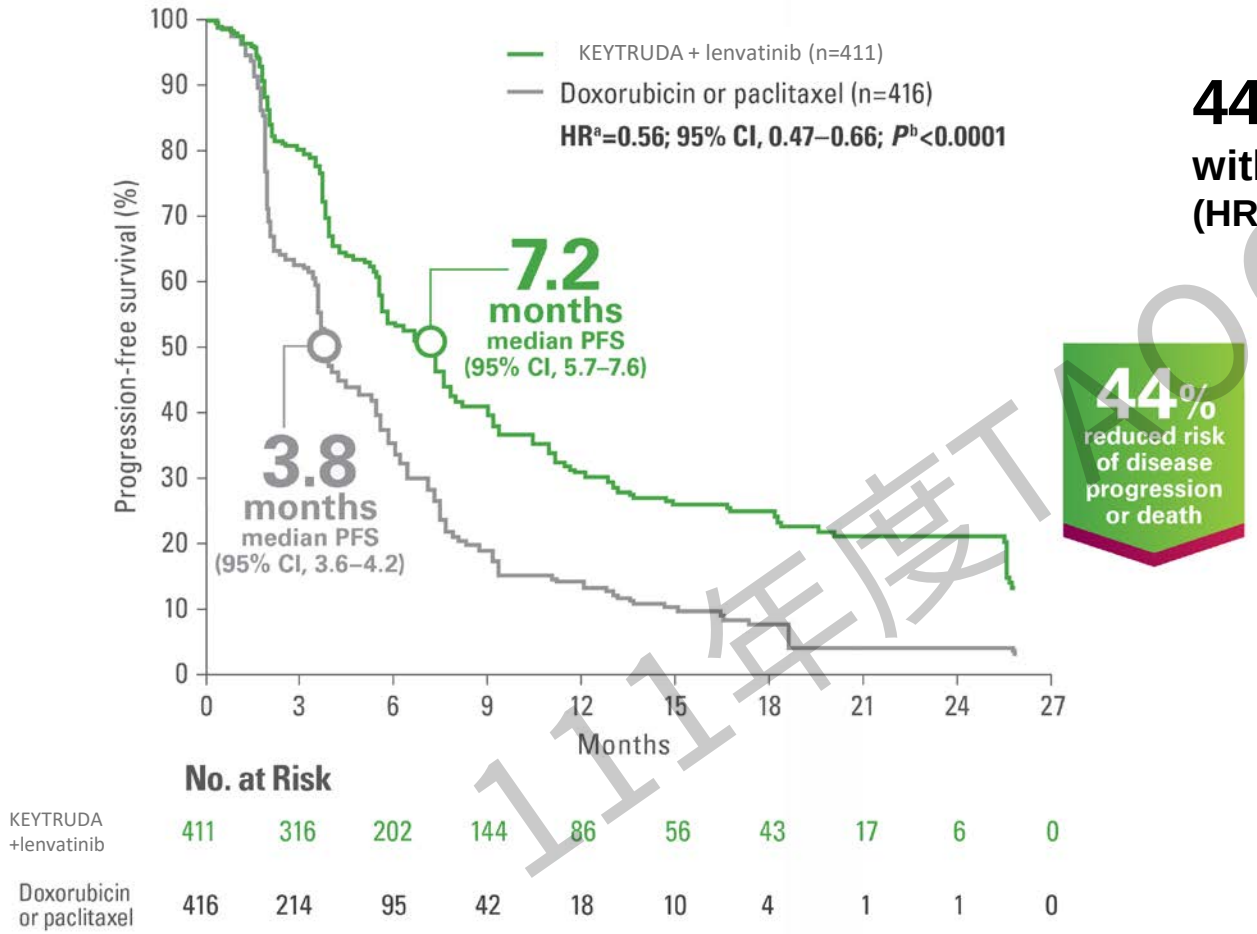
- The **number of patients with an event** was 188/411 (46%) with pembro + lenvatinib vs 245/416 (59%) with doxorubicin or paclitaxel
- **Median OS** was 18.3 months (95% CI, 15.2–20.5) with pembro + lenvatinib vs 11.4 months (95% CI, 10.5–12.9) with doxorubicin or paclitaxel

[a]Based on the stratified Cox regression model. [b]Based on stratified log-rank test. [c]Assessed by BICR according to RECIST v1.1.
CI = confidence interval; HR = hazard ratio; OS = overall survival. BICR = blinded independent central review. RECIST v1.1 = Response Evaluation Criteria In Solid Tumors v1.1.
Reference: 1. Makker V, Colombo N, Herráez AC, et al. A multicenter, open-label, randomized, phase 3 study to compare the efficacy and safety of lenvatinib in combination with pembrolizumab vs treatment of physician's choice in patients with advanced endometrial cancer: Study 309/KEYNOTE-775. Virtual Annual Meeting on Women's Cancer, 2021.

PATIENTS WITH ADVANCED ENDOMETRIAL CARCINOMA (N=827)

KEYNOTE-775/Study 309: Superior PFS vs Doxorubicin or Paclitaxel[1]

Kaplan-Meier Estimates of PFS in KEYNOTE-775/Study 309[c]



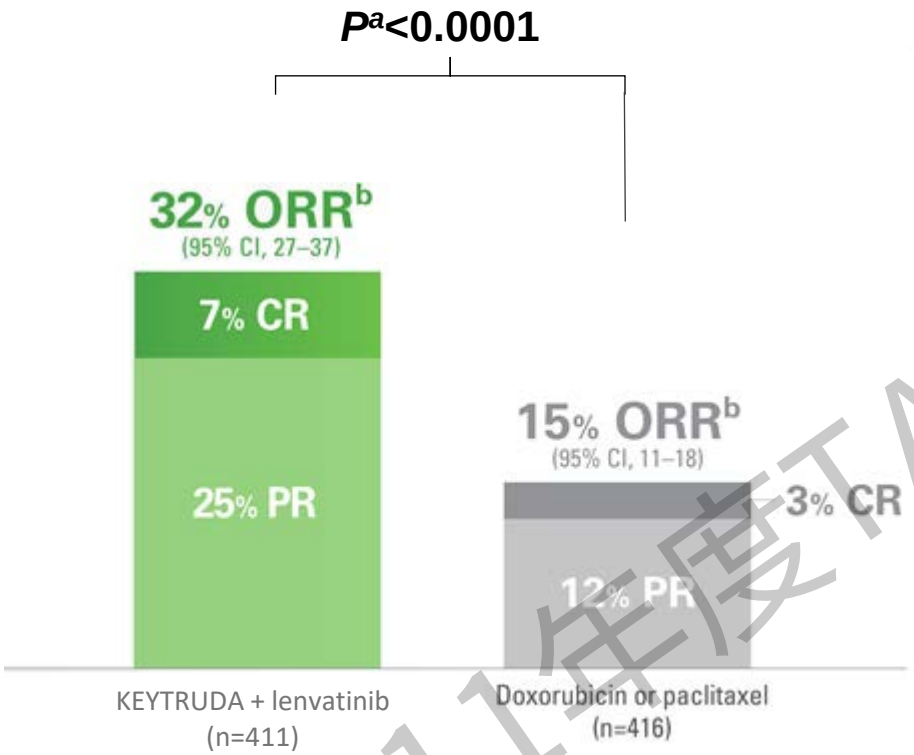
44% Reduction in the risk of disease progression or death with pembro + lenvatinib vs doxorubicin or paclitaxel (HR[a] [95% CI]=0.56 [0.47–0.66]; *P*[b]<0.0001)

- The **number of patients with an event** was 281/411 (68%) with KEYTRUDA + lenvatinib vs 286/416 (69%) with doxorubicin or paclitaxel
- **Median PFS** was 7.2 months (95% CI, 5.7–7.6) with KEYTRUDA + lenvatinib and 3.8 months (95% CI, 3.6–4.2) with doxorubicin or paclitaxel

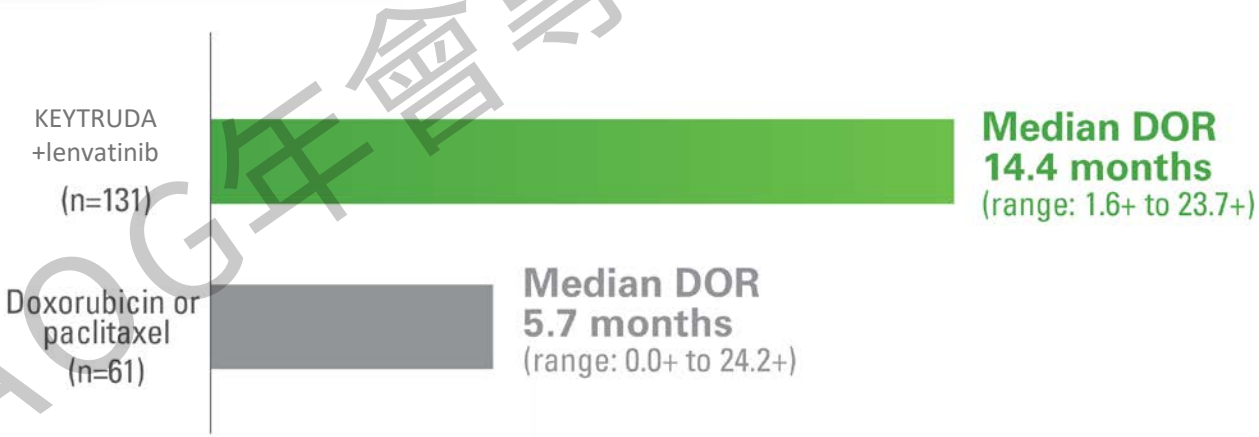
[a]Based on the stratified Cox regression model. [b]Based on stratified log-rank test. [c]Assessed by BICR according to RECIST v1.1.
CI = confidence interval; HR = hazard ratio; PFS = progression-free survival. BICR = blinded independent central review. RECIST v1.1 = Response Evaluation Criteria In Solid Tumors v1.1.

Reference: 1. Makker V, Colombo N, Herráez AC, et al. A multicenter, open-label, randomized, phase 3 study to compare the efficacy and safety of lenvatinib in combination with pembrolizumab vs treatment of physician's choice in patients with advanced endometrial cancer: Study 309/KEYNOTE-775. Virtual Annual Meeting on Women's Cancer, 2021.

Objective Response Rate



Median Duration of Response[c]



[a]Based on Miettinen and Nurminen method stratified by MMR status, ECOG performance status, geographic region, and history of pelvic radiation.
[b]Best Objective response as confirmed CR or PR. [c]Response duration was based on Kaplan-Meier estimation.
CI = confidence interval; CR = complete response; DOR = duration of response; ORR = objective response rate; PR = partial response. ECOG = Eastern Cooperative Oncology Group.
MMR = mismatch repair.

Among the 827 patients enrolled:

- **697** patients had tumors that were not MSI-H or dMMR
  - Of these patients, **37%** had received only prior neoadjuvant or adjuvant therapy

Baseline characteristics of patients enrolled in KEYNOTE-775/Study 309 (N=697)

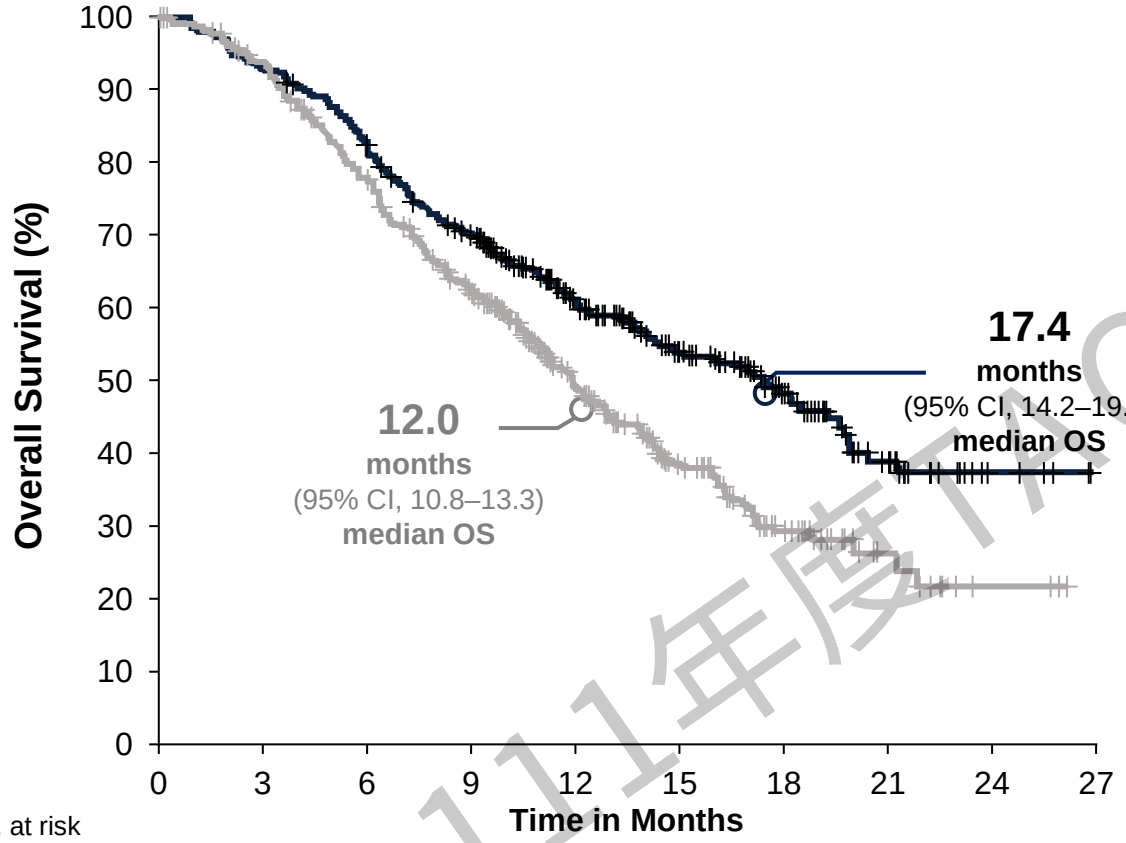
Characteristic	Not MSI-H or dMMR Population
Median age, years (range)	65 years (30-86)
Age ≥65 years, %	52%
Race	
White	62%
Asian	22%
Black	3%
ECOG PS	
0	60%
1	40%
Histological subtypes	
Endometrioid carcinoma	55%
Serous carcinoma	30%
Clear cell carcinoma	7%
Mixed	4%
Other	3%
Received prior systemic therapies	
1	67%
2	30%
≥3	3%

ECOG PS = Eastern Cooperative Oncology Group performance status; dMMR = mismatch repair deficient; MSI-H = microsatellite instability-high.

PATIENTS WITH ADVANCED ENDOMETRIAL CARCINOMA THAT WAS NOT MSI-H OR dMMR (N=697)

KEYNOTE-775/Study 309: Superior OS vs Doxorubicin or Paclitaxel

Kaplan-Meier Estimates of OS in KEYNOTE-775/Study 309 (Not MSI-H/dMMR)



(HR[a] [95% CI]=0.68 [0.56–0.84]; *P*[b]=0.0001)

No. at risk

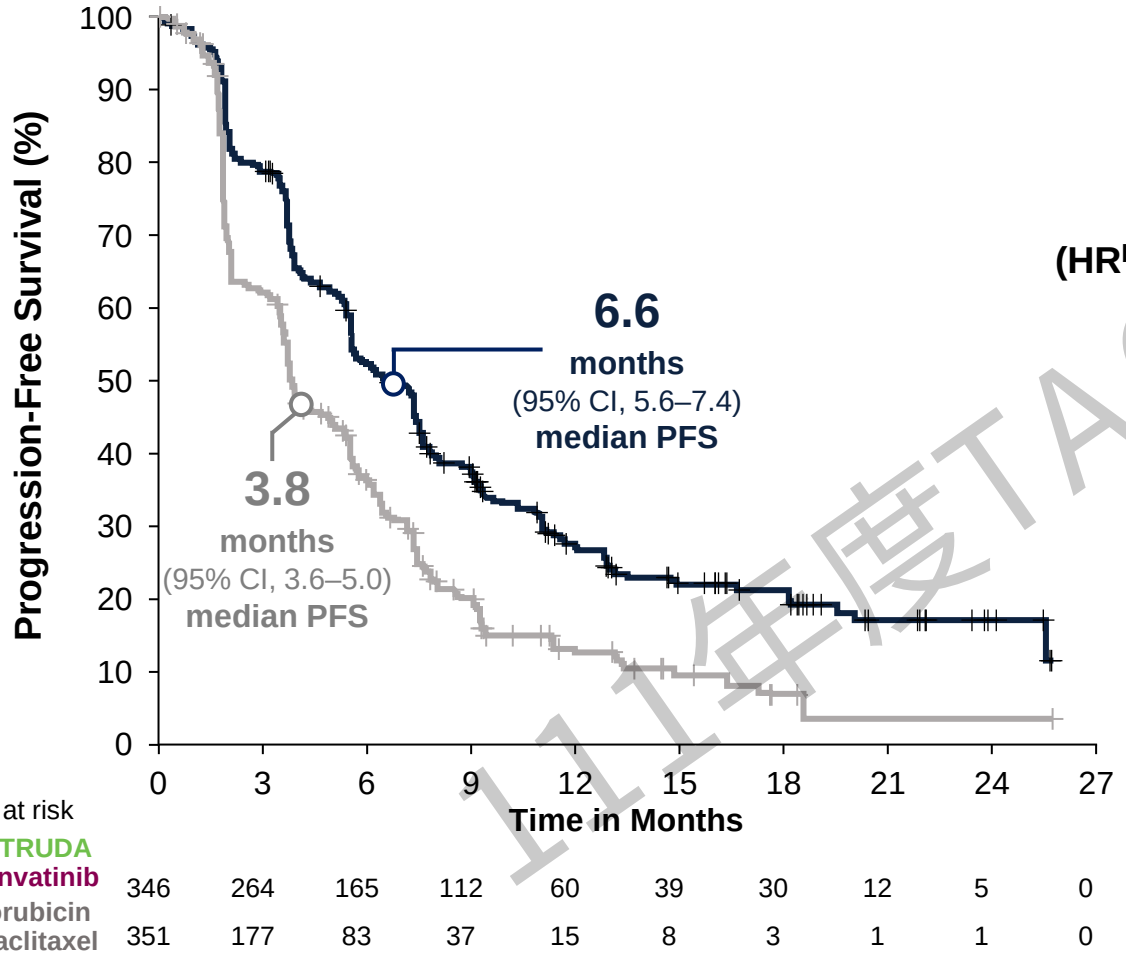
KEYTRUDA + lenvatinib	346	322	285	232	160	109	62	28	5	0
Doxorubicin or paclitaxel	351	319	262	201	120	70	33	11	3	0

[a]Based on the stratified Cox regression model. [b]Based on stratified log-rank test.
CI = confidence interval; dMMR = mismatch repair deficient; HR = hazard ratio; OS = overall survival; MSI-H = microsatellite instability-high.

PATIENTS WITH ADVANCED ENDOMETRIAL CARCINOMA THAT WAS NOT MSI-H OR dMMR (N=697)

KEYNOTE-775/Study 309: Superior PFS vs Doxorubicin or Paclitaxel

Kaplan-Meier Estimates of PFS[a] in KEYNOTE-775/Study 309 (Not MSI-H/dMMR)

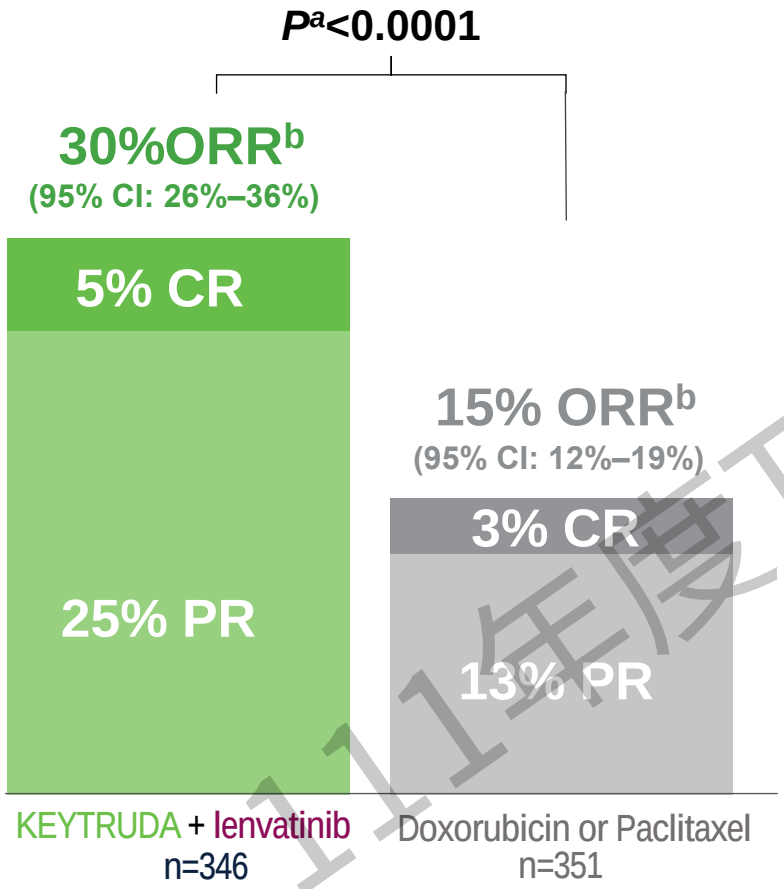


(HR[b] [95% CI]=0.60 [0.50–0.72]; *P*[c]<0.0001)

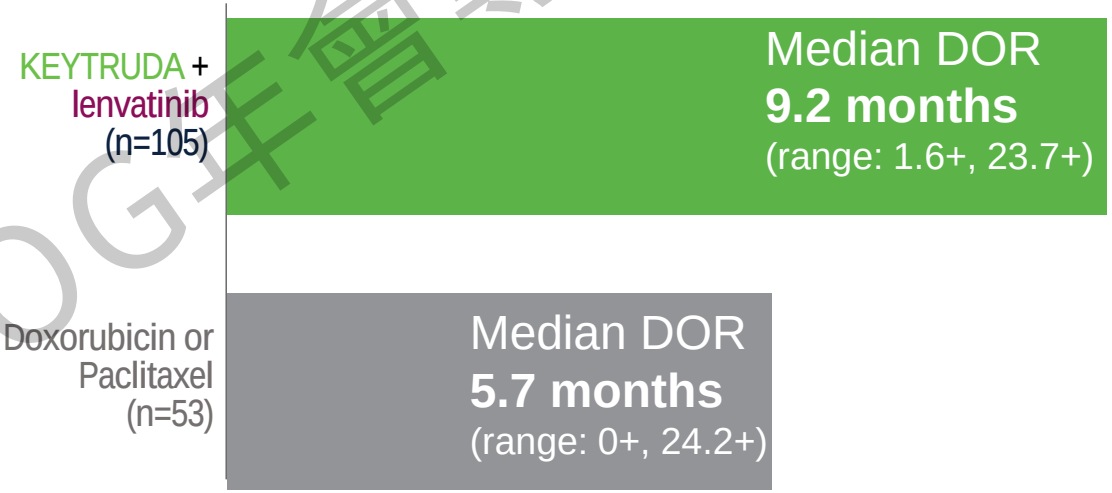
[a]Per independent radiology review. [b]Based on the stratified Cox regression model. [c]Based on stratified log-rank test.
CI = confidence interval; dMMR = mismatch repair deficient; HR = hazard ratio; PFS = progression-free survival; MSI-H = microsatellite instability-high.

PATIENTS WITH ADVANCED ENDOMETRIAL CARCINOMA THAT WAS NOT MSI-H OR dMMR (N=697)

Objective Response Rate



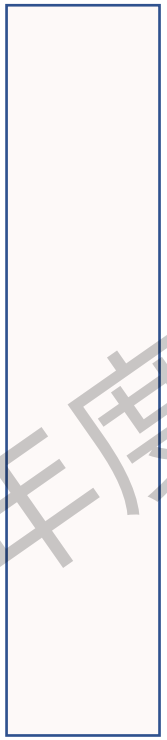
Median Duration of Response



[a]Based on Miettinen and Nurminen method stratified by MMR status, ECOG performance status, geographic region, and history of pelvic radiation.
[b]Per independent radiology review.
CI = confidence interval; CR = complete response; dMMR = mismatch repair deficient; DOR = duration of response; MSI-H = microsatellite instability-high; ORR = objective response rate; PR = partial response.

PATIENTS WITH ADVANCED ENDOMETRIAL CARCINOMA RECEIVING *KEYTRUDA + lenvatinib* (n=406)

KEYNOTE-775/Study 309: Adverse Events Occurring in ≥20% of Patients[a]



[a]The median duration of study treatment was 7.6 months (range: 1 day–26.8 months). The median duration of exposure to KEYTRUDA was 6.9 months (range: 1 day–25.8 months), and the median duration of exposure to LENVIMA was 6.9 months (range: 1 day–26.8 months), compared to 3.4 months (range: 1 day–25.8 months) for doxorubicin or paclitaxel.
[b]Graded per NCI-CTCAE v4.03.
[c]There was one Grade 5 (0.2%) reported.

ALT = alanine aminotransferase; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events.

PATIENTS WITH ADVANCED ENDOMETRIAL CARCINOMA RECEIVING *KEYTRUDA + lenvatinib* (n=406)

KEYNOTE-775/Study 309: Patients who reduced dose with lenvatinib, interrupted treatment, or discontinued treatment with KEYTRUDA + lenvatinib (n=406) due to an adverse reaction (Grades 1–4)

	Discontinuation	Dose interruption	Dose reduction
KEYTRUDA +lenvatinib	11.0%	31.0%	–
KEYTRUDA, lenvatinib, or both	30.0%	69.0%	–
KEYTRUDA	15.0%	50.0%	–
lenvatinib	30.8%	58.6%	66.5%

Reference: 1. Makker V, Colombo N, Herráez AC, et al. A multicenter, open-label, randomized, phase 3 study to compare the efficacy and safety of lenvatinib in combination with pembrolizumab vs treatment of physician's choice in patients with advanced endometrial cancer: Study 309/KEYNOTE-775. Virtual Annual Meeting on Women's Cancer, 2021.

NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms (Version 1.22)Systemic Therapy for Endometrial Carcinoma

Recurrent, Metastatic, or High-Risk Disease[a,b]

Systematic Therapies[a,b]

Preferred Regimens

- Carboplatin/paclitaxel (Category 1 for carcinosarcoma)
- Carboplatin/paclitaxel/trastuzumab[c] (for stage III/IV or recurrent HER-2 positive uterine serous carcinoma

Other Recommended Regimens

- Carboplatin/docetaxel[d]
- Cisplatin/doxorubicin
- Cisplatin/doxorubicin/ paclitaxel[e,f]
- Carboplatin/paclitaxel/ bevacizumab[e,g]
- Cisplatin
- Carboplatin
- Doxorubicin
- Liposomal doxorubicin
- Paclitaxel
- Albumin-bound paclitaxel[h]
- Topotecan
- Bevacizumab[g,i]
- Temsirolimus
- Docetaxel[d] (category 2B)
- Ifosfamide (for carcinosarcoma)
- Ifosfamide/paclitaxel (for carcinosarcoma)
- Cisplatin/Ifosfamide (for carcinosarcoma)

Biomarker-directed systematic treatment for second-line treatment

Preferred Regimens

- **Lenvatinib/pembrolizumab (category 1) for non–MSI-high [MSI-H]/non–MMR-deficient[dMMR] tumors[j]**
- **Pembrolizumab[k] for TMB-H or MSI-H/dMMR tumors[l]**

Other Recommended Regimens

- Nivolumab for dMMR/MSI-H tumors
- Dostarlimab-gxly for dMMR/MSI-H tumors[m]
- Larotrectinib or entrectinib for NTRK gene fusion-positive tumors (category 2B)[e]
- Avelumab for dMMR/MSI-H tumors
- Cabozantinib

[o]Hormonal therapy is typically used for lower-grade endometrioid histologies, preferably in patients with small tumor volume or an indolent growth pace. Referenced: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Uterine Neoplasms V.1.2022.

Case – EM Ca

- 56 y/o, G2P2
- Menopause at 48 y/o

2018/01/09

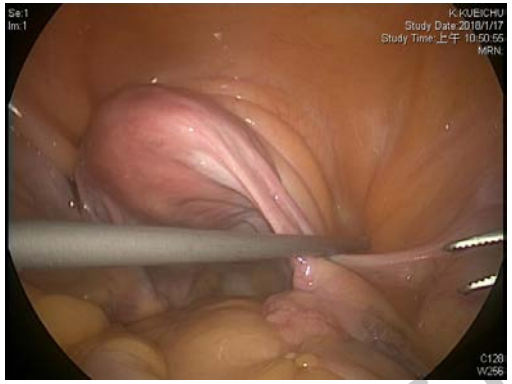
- CC : CA-199 elevation at health check
  Vaginal bleeding (-) , abdominal pain (-)
  - Endometrial curettage: in LMD endometrioid carcinoma
  - Cervical biopsy at OPD: endometrioid carcinoma
  - MRI: bulky tumor 4cm crossed EM and cervix , possible anterior upper vaginal involvement, lymph node(-)

	20180109
SCC	0.8
CEA	2.5
CA199	445.6

Case – EM Ca

2018/01/17

pT3bN0M0



- Operation: laproscopic radical hysterecdtomy + bilateral salpingo-oopherectomy + biopsy of sentinel lymph node dissection
- Patho: **endometrioid carcinoma, pT3bN0M0**
  - cervix(+, 100%invasion), vagina (+) , right parametrium (+), bil ov (-), bil tube (-), left parametrium(-), bil pelvic sentinel LNs(-)
  - ER: 70%, PR:50%

Case – EM Ca

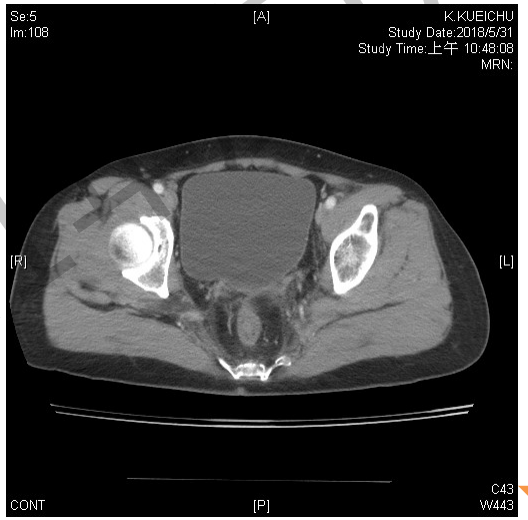
2018/02/01
2018/04/12

- **CCRT**

	20180201
CA199	67.02

2018/05/31

- CT:NED



	20180531
CA199	31.10

Case – EM Ca

2018/09/13

rT0N0M1

- Tumor scan: right lower sternal body lesion , score 3.

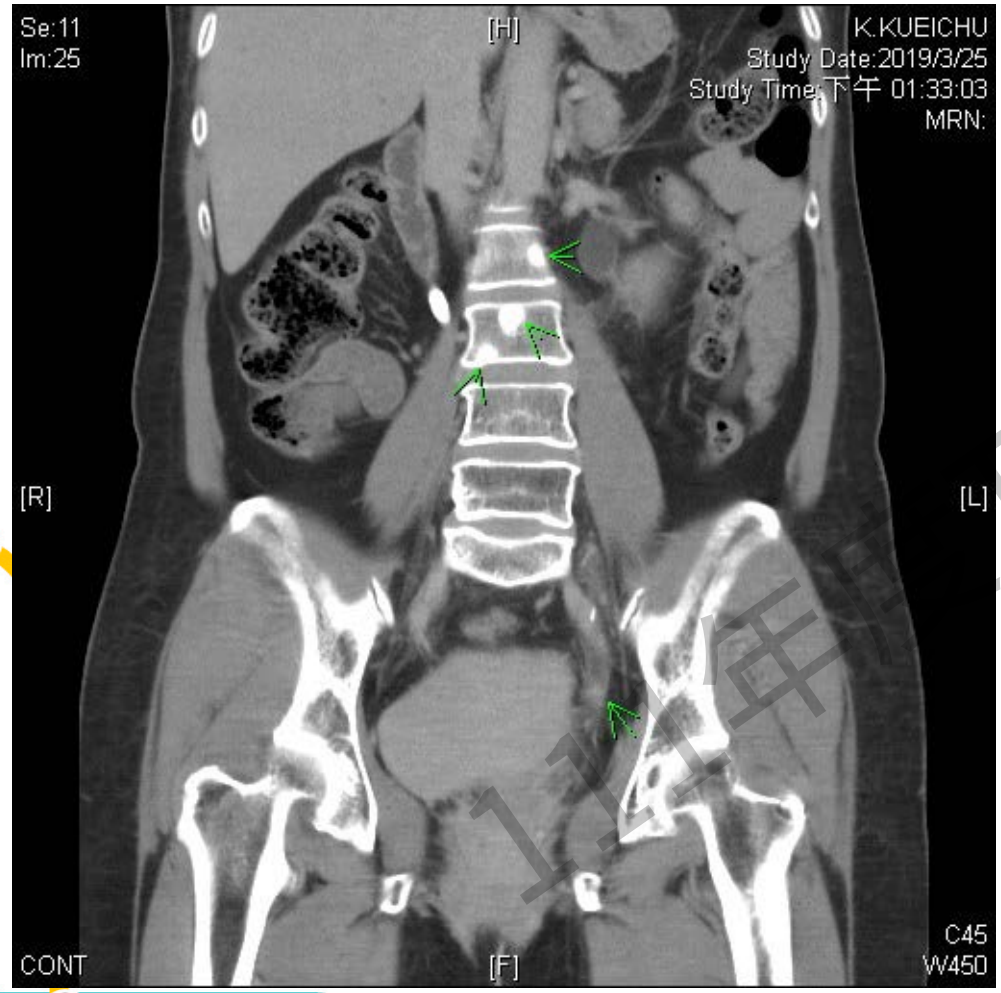
	20180901
CA199	61.49

2018/10/02

- External beam therapy of radiotherapy for single bone metastasis

Case – EM Ca

2019/03/25



- CTU
  - Stationary infiltrative soft tissue at left lower ureter causing hydronephrosis, fevor paritoneal metastasis
  - Interval enalrgement of L2/L3 osteoclerotic nodule , r/o bony metastasis

	20190325
CA199	136

Case – EM Ca

2019/04/02

- Start **Letrozole** 2.5mg 1pc QD
- Arrange IHC study
  - MLH1 and PMS2: loss of expression
  - MSH2 and MSH6: retained expression

2019/04/03

- Bone scan :multiple active bone lesion, compatible with malignancy bony metastasis

Case – EM Ca

2019/05/06
2019/08/25

- **<u>Cisplatin 40mg/m2 + pembrolizumab(2mg/kg)</u>** for 6 cycles
- Pallative RT for L2-4 bone metastasis

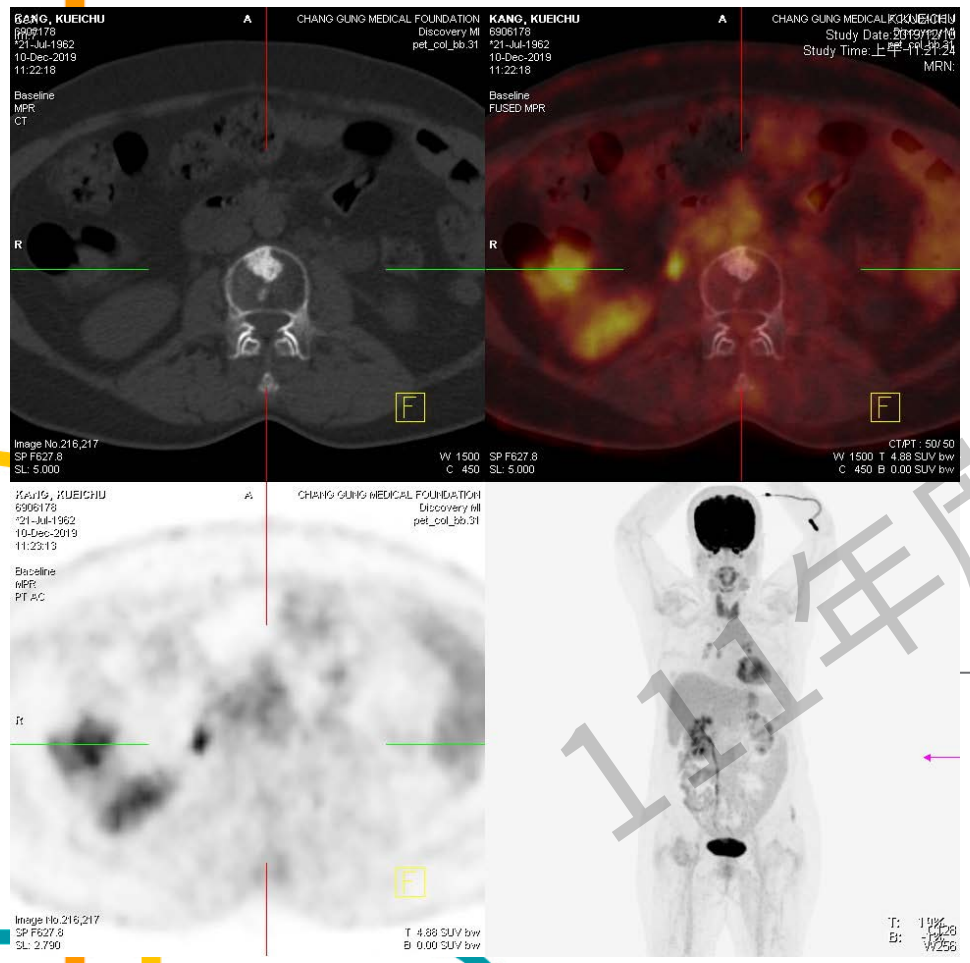
	CA199
20190506	223
20190617	153

2019/07/10

- Tumor scan:
  - multiple sclerotic bone lesion, probably bony metastasis

	CA199
20190825	113

Case – EM Ca



2019/08/27

- Refer to Meta OPD due to goiter
  - TSH 0.139
  - Anti-TPO 1.12
  - Anti-THYG 45.40
  - Anti-TSHR <0.8
  - Free T4 1.37
  - T3 8.91
- → start Tx of hypothyroidsm with tyroxine

2019/12/10

- Tumor scan:
  - right L3 vertebra sclerotic lesion with mild FDG activity

Case – EM Ca

2020/02/12

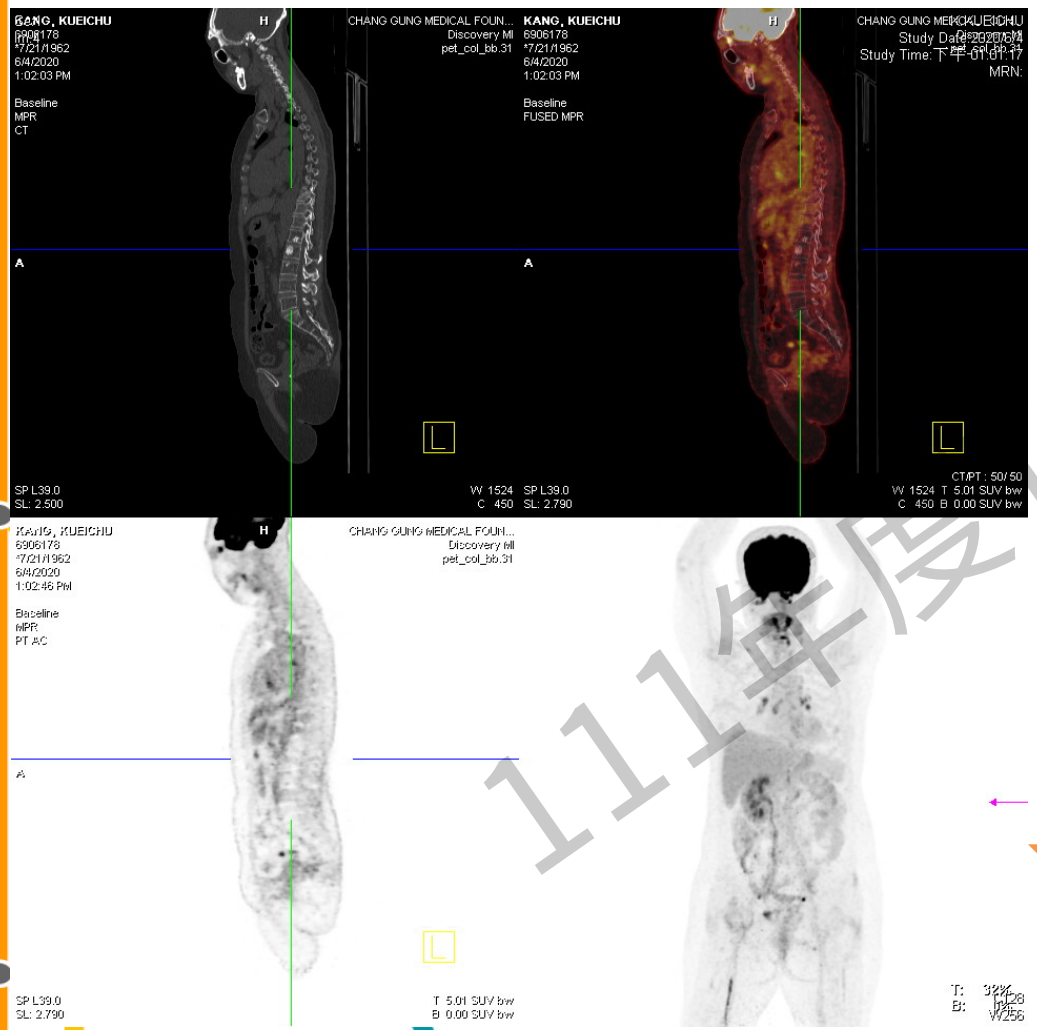
2020/08/21

- CA 199 412, and no more RT for bone metastasis
- Start carboplatin +Paclitaxel +Pembrolizumab + Avastin

	CA199
20200201	412
20200305	407
20200326	347
20200502	282
20200604	234
20200710	245

Case – EM Ca

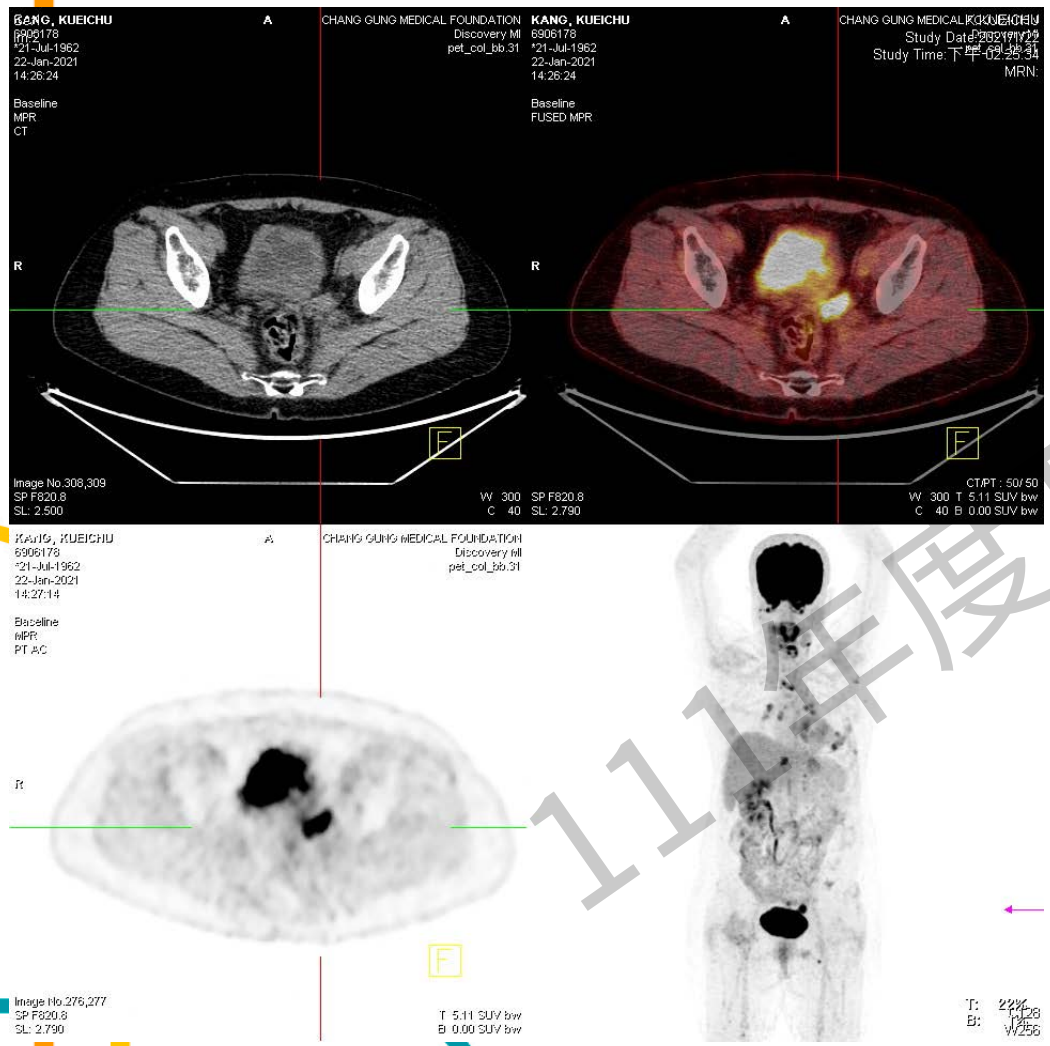
2020/06/04



- Tumor scan:
  - no abnormal uptake regarding these osteoblastic lesions ,
  - **good response to treatment** or partially due to its osteoblastic nature, stationary mediastinal / hilar nodes

Case – EM Ca

20210122



- Tumor scan : probably recurrent tumor over left CDS mass , and multiple bones , multiple lymph node lesions , reactive adenopathy was more likely. Mild left adrenal uptake

Case – EM Ca

2021/02/26
2021/04/09

- Carboplatin +Paclitaxel +Pembrolizumab
- Added prtoton therapy

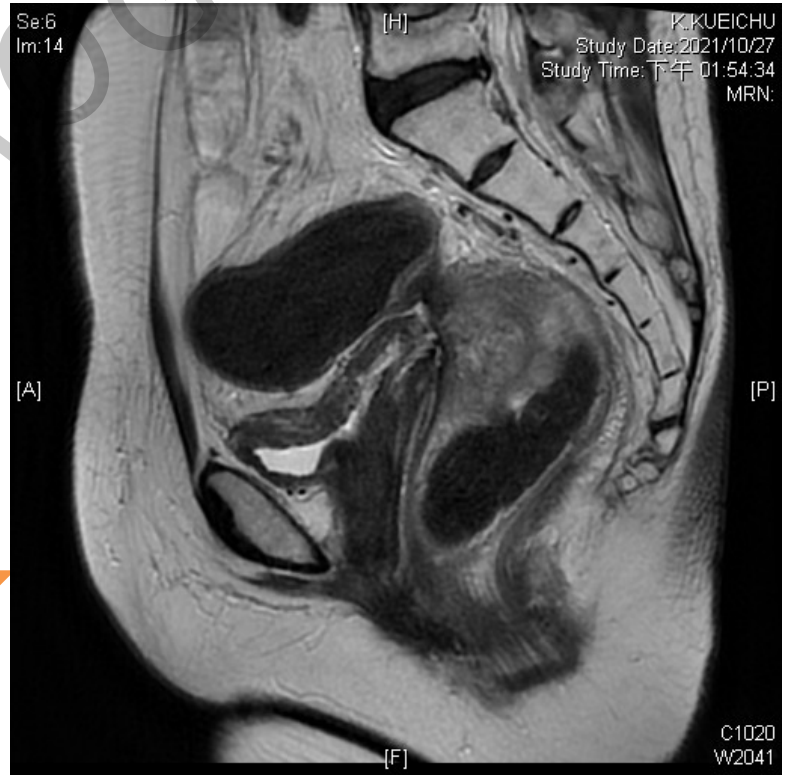
	CA199
20201205	350
20210422	393

Case – EM Ca

2021/10/27

- MRI: recurrent endometrial cancer with wide local extension invasion of ajacent organs , regional and non regional lymphnode mestastasis as resultant left obstructive uropathy

	CA199
20211016	1662
20211108	1429
20211115	1709
20211202	1608



Case – EM Ca

2021/11/01

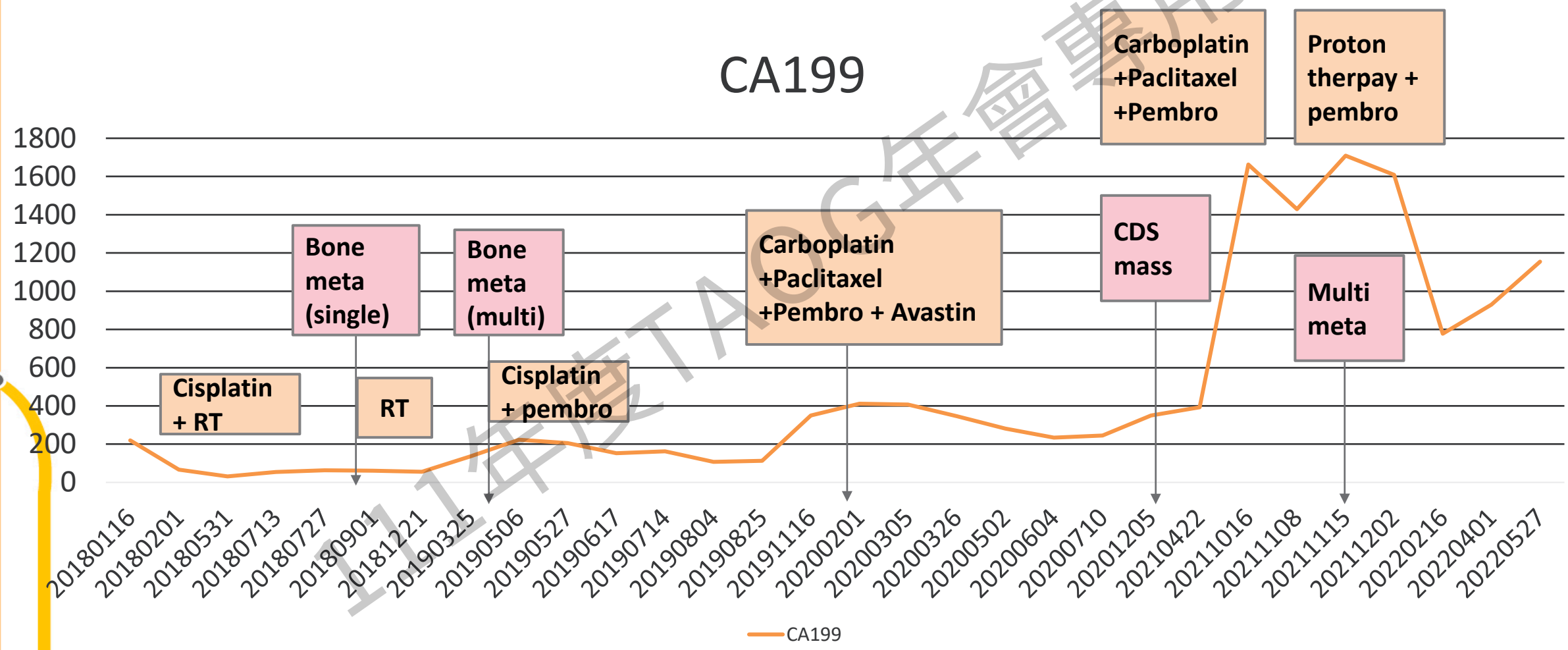
- CTA
  - Left lower leg DVT
  - A large recurrent tumor , 7cm , at left stump
    - invasion of rectal wall and left distal ureter and external intranal iliac veins and urinary bladder
  - Lymph node metastasis at left external and internal iliac area

2021/11/10
2022/12/20

- Keep pembrolizumab
- Added prtoton therapy

	CA199
20211202	1608
20220216	777

Case – EM Ca -Summary



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