子宮頸癌治療的新趨勢與展望

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Agenda

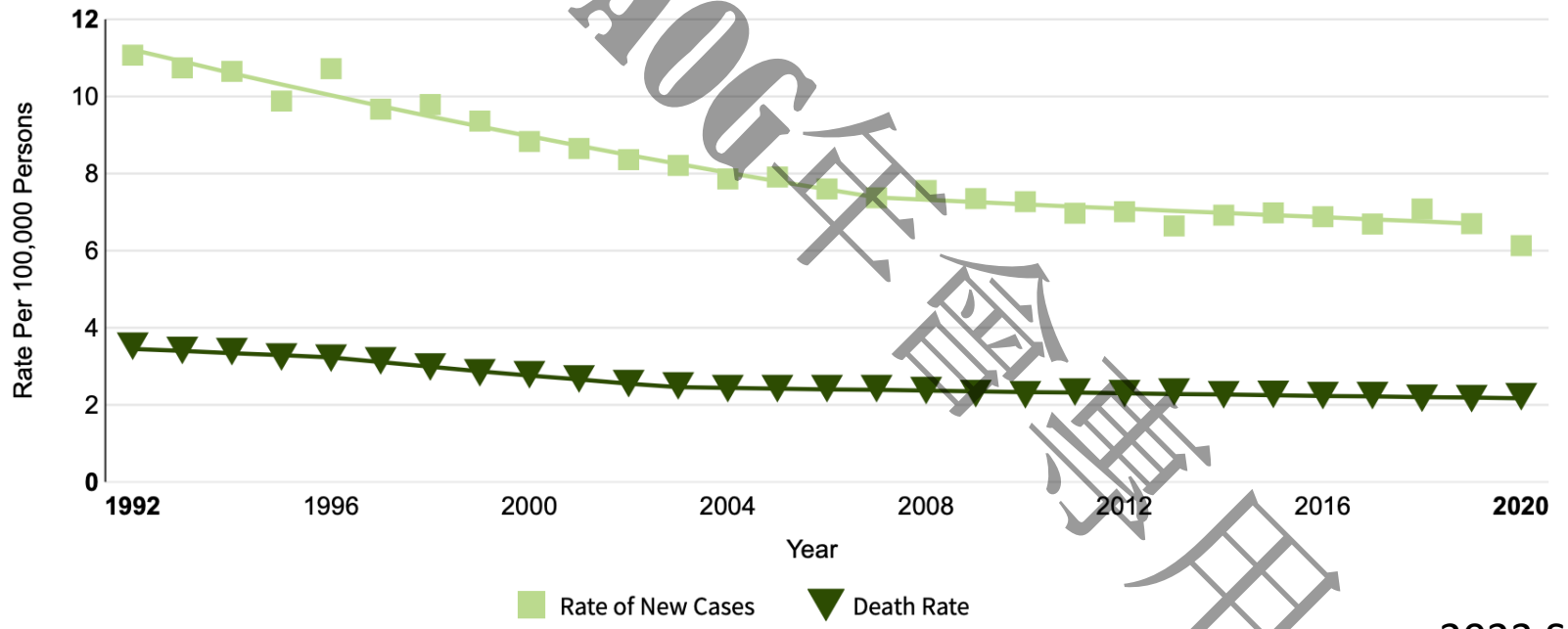
- Background
- Therapy by treatment setting
  - Early stage
  - Locally advanced disease
  - Metastatic/recurrent disease
  - Future directions
- Conclusions

Photo from https://www.trs.texas.gov

Estimated New Cases in 2023	13,960
% of All New Cancer Cases	0.7%

Estimated Deaths in 2023	4,310
% of All Cancer Deaths	0.7%

5-Year Relative Survival
67.2%
2013–2019



2023 SEER report, USA

發生率掉出10名外，死亡率仍在第8名

女性 **10** 大癌症（不含原位癌 [3]）發生率（每 **10** 萬人口），民國 **110** 年

順位	ICD-O-3	原發部位	個案數（人）	粗發生率	年齡標準化發生率 [2a]	年齡標準化發生率 [2b]
1	C50	女性乳房	15,448	130.95	76.15	82.51
2	C33-C34	肺、支氣管及氣管	7,919	67.13	32.32	35.96
3	C18-C21	結腸、直腸、乙狀結腸連結部及肛門	6,941	58.84	26.96	30.67
4	C73	甲狀腺	3,497	29.64	20.38	22.14
5	C54	子宮體	3,181	26.97	15.75	17.01
6	C22	肝及肝內膽管	3,327	28.20	11.63	13.60
7	C56, C57.0-C57.4	卵巢、輸卵管及寬韌帶	1,793	15.20	9.45	10.20
8	C44	皮膚	1,827	15.49	6.11	7.25
9	C16	胃	1,647	13.96	6.27	7.19
10	C82-C85	非何杰金氏淋巴瘤	1,438	12.19	6.41	7.09
	C00-C80	全癌症	58,039	492.00	261.05	288.36
11		子宮頸			6.32	7.04

女性 **10** 大癌症死亡率（每 **10** 萬人口），民國 **110** 年

順位	ICD-10	原發部位	個案數（人）	粗死亡率	年齡標準化死亡率 [2a]	年齡標準化死亡率 [2b]
1	C33-C34	肺、支氣管及氣管	3,705	31.41	12.68	14.86
2	C50	女性乳房	2,913	24.69	12.46	13.77
3	C18-C21	結腸、直腸、乙狀結腸連結部及肛門	2,841	24.08	9.45	11.21
4	C22	肝及肝內膽管	2,559	21.69	8.03	9.83
5	C25	胰	1,217	10.32	4.17	4.92
6	C16	胃	891	7.55	3.06	3.61
7	C56, C57.0-C57.4	卵巢、輸卵管及寬韌帶	696	5.90	3.03	3.33
8	C53	子宮頸	608	5.15	2.42	2.75
9	C82-C85	非何杰金氏淋巴瘤	594	5.04	2.04	2.44
10	C91-C95 [4]	白血病	472	4.00	2.03	2.28
	C00-C97	全癌症	20,535	174.08	74.30	86.30

The 2018 FIGO staging classification

FIGO Stage	Description
Stage I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm[a]
IA1	Measured stromal invasion <3 mm in depth
IA2	Measured stromal invasion ≥3 mm and <5 mm in depth
IB	Invasive carcinoma with measured deepest invasion ≥5 mm (greater than Stage IA), lesion limited to the cervix uteri[b]
IB1	Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension
IB2	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
IB3	Invasive carcinoma ≥4 cm in greatest dimension
Stage II	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement
IIA1	Invasive carcinoma <4 cm in greatest dimension
IIA2	Invasive carcinoma ≥4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
Stage III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent (with r and p notations)[c]
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum (a bullous edema, as such, does not permit a case to be assigned to Stage IV)
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

Width is no longer included

<4 cm has been subdivided into <2 cm and >2 cm. New stage assigned to >4 cm

Lymph node status included in staging

Gynecol Oncol 2023-11 SGO statement

Fertility Sparing Treatment

低風險條件(需全部符合)

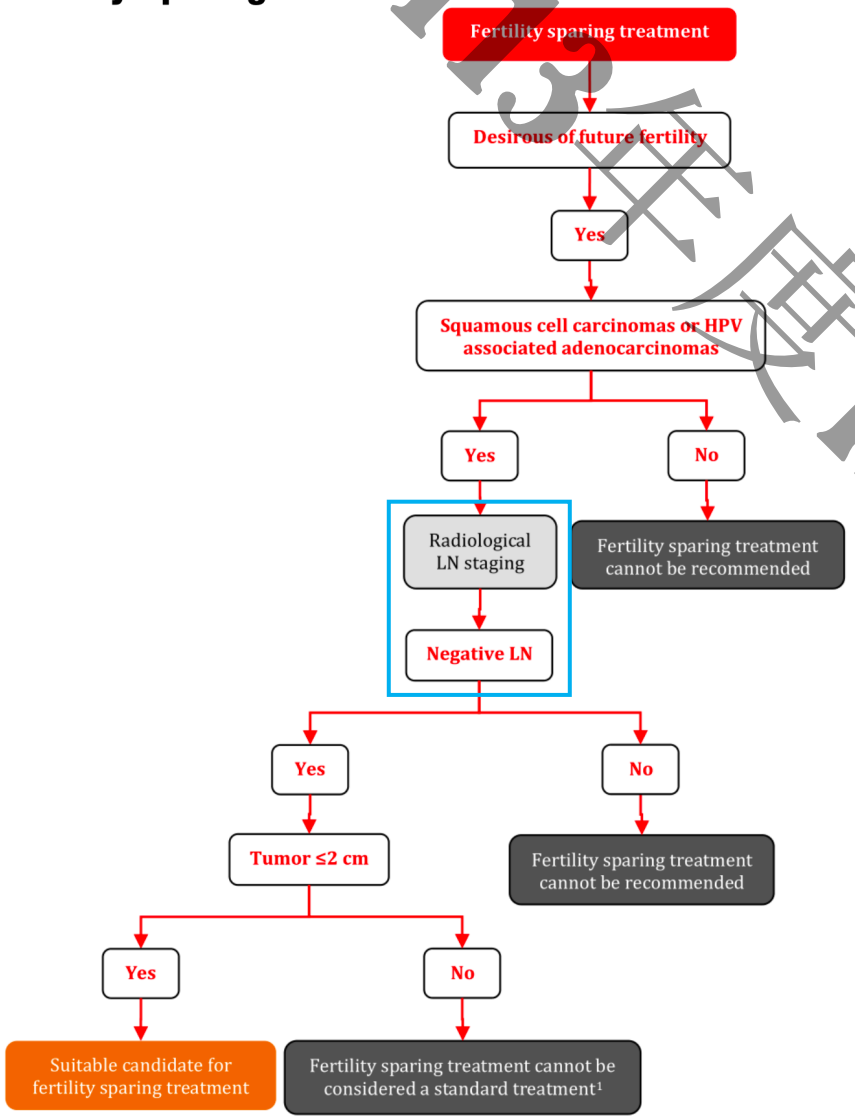
- 子宮頸基質之淋巴血管腔「無」腫瘤細胞侵入 (LVSI-)
- 切除邊緣已無病灶
- 鱗狀上皮癌(任何分化程度)或 常見型態腺癌(只限低度分化grade1/2)
- 腫瘤大小≤2cm
- 侵犯深度≤10mm
- 影像學上無遠端轉移

- <2cm (SCC and HPV-related adenocarcinoma) who want to preserve the option to have children
- Uncommon and rare histological types/subtypes of cervical cancer with aggressive behavior including neuroendocrine carcinomas, HPV-independent adenocarcinomas and carcinosarcomas: not candidate!

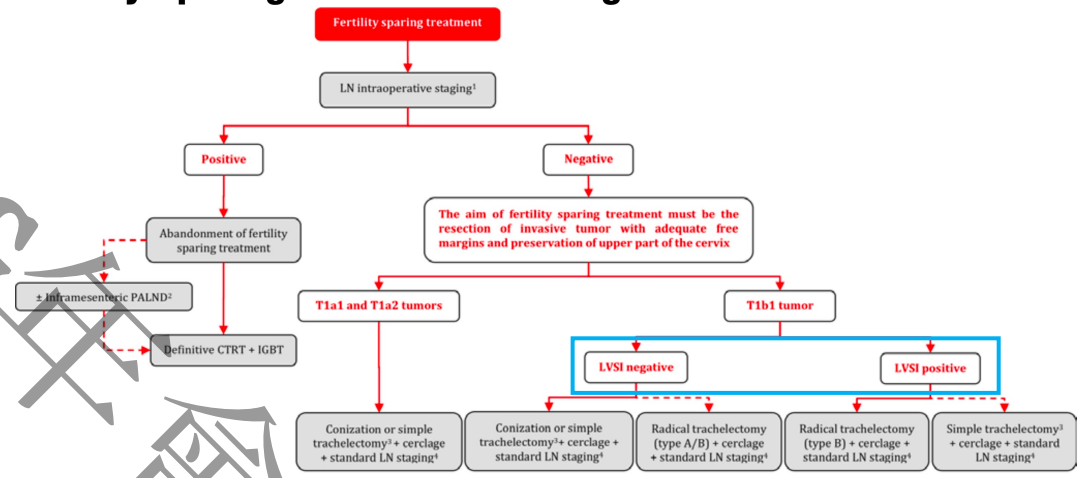
- IA1: cone, IA2/IB1 + low risk: cone + SLN mapping
- IA1/IA2 + LVSI: radical trachelectomy + PLND (consider cone + PLND)
- IB1: radical trachelectomy + PLND

NCCN 2024 Ver.2

Fertility Sparing Treatment - Selection of Candidates



Fertility Sparing Treatment - Management



2023 April ESGO/ESTRO/ESP Guidelines

SHAPE trial

Lesser is safer?

Patient selection is important!

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

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

Plante M et al. DOI: 10.1056/NEJMoa2308900

CLINICAL PROBLEM

Radical hysterectomy remains standard care for patients with early-stage cervical cancer. However, retrospective studies indicate that parametrial infiltration is unlikely in early-stage disease, which suggests that less-radical surgery could be a safe option. Randomized trials comparing simple hysterectomy with radical hysterectomy in patients with early-stage cervical cancer are needed.

CLINICAL TRIAL

Design: A phase 3, international, randomized, noninferiority trial assessed the efficacy and safety of simple hysterectomy as compared with radical hysterectomy in women with low-risk, early-stage cervical cancer.

Intervention: 700 patients with International Federation of Gynecology and Obstetrics (FIGO) 2009 stage IA_2 or IB_1 tumors measuring ≤2 cm, with limited depth of cervical stromal invasion, and with no evidence of lymph-node metastasis on preoperative imaging were assigned to undergo simple hysterectomy (removal of the uterus with the cervix, without adjacent parametria) or radical hysterectomy (removal en bloc of the uterus, cervix, medial one third of parametria, 2 cm of the uterosacral ligaments, and upper 1 to 2 cm of the vagina). The primary outcome was cancer recurrence in the pelvic area (pelvic recurrence) at 3 years.

RESULTS

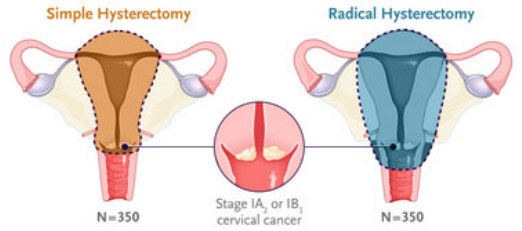
Efficacy: Simple hysterectomy was noninferior to radical hysterectomy with respect to the 3-year incidence of pelvic recurrence.

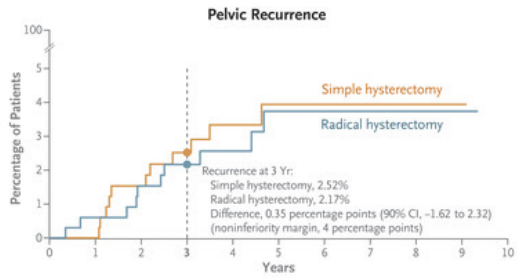
Safety: The incidence of surgery-related adverse events, urinary incontinence, and urinary retention was lower with simple hysterectomy than with radical hysterectomy.

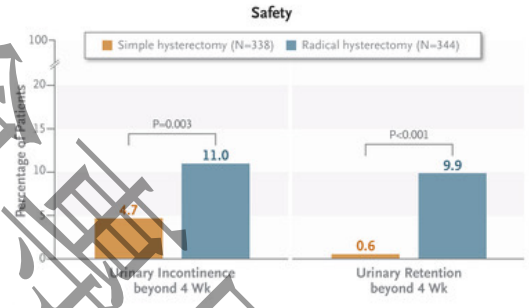
LIMITATIONS AND REMAINING QUESTIONS

- The small number of recurrences resulted in wide confidence intervals around hazard ratios for time-to-event outcomes.
- The median follow-up time was 4.5 years; later recurrences are possible.
- The surgical approach was chosen by trial surgeons after randomization and was not a stratification factor.

Links: Full Article | NEJM Quick Take | Editorial







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.

N Engl J Med. 2024 Feb 29

Agenda

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  - Early stage
  - **Locally advanced disease**
  - Metastatic/recurrent disease
  - Future directions
- Conclusions

Photo from https://www.trs.texas.gov

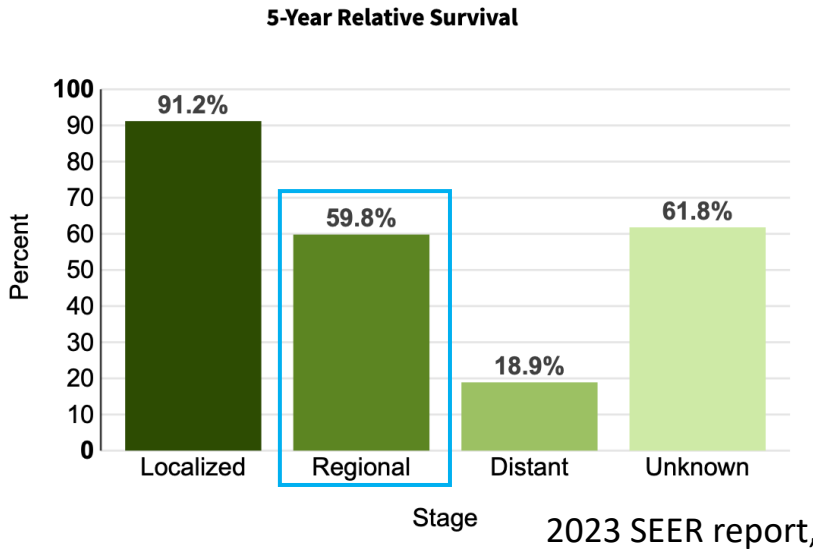
The 2018 FIGO staging classification --Locally advanced disease (LACC)

FIGO Stage	Description
IIB	With parametrial involvement but not up to the pelvic wall
Stage III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent (with r and p notations)[c]
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum (a bullous edema, as such, does not permit a case to be assigned to Stage IV)
IVA	Spread to adjacent pelvic organs

Lymph node status included in staging

Gynecol Oncol 2023-11 SGO statement

Challenge in locally advanced CC



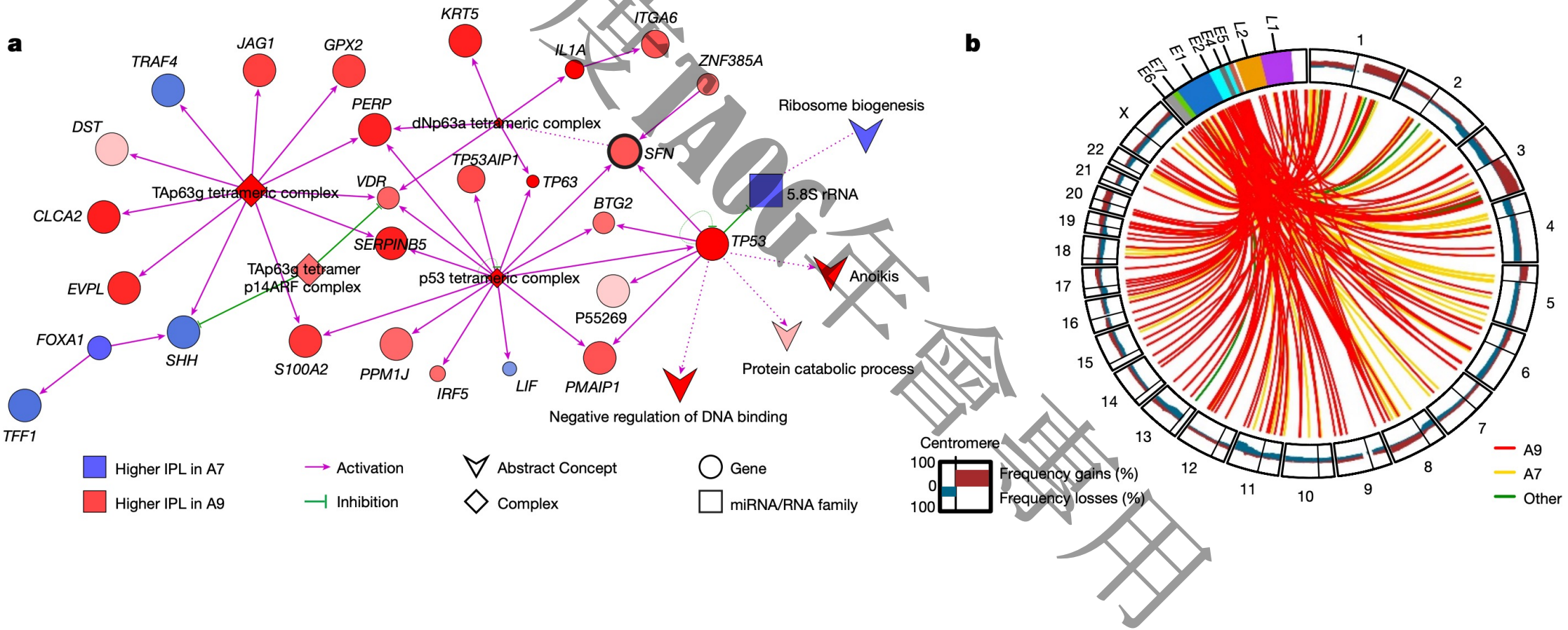
2023 SEER report, USA

- Many women not cured!
- Development of distant metastases from local lesion…
- 5-year disease free survival approximately 58-68%

FIGO 期別 [2]										
0 期	2229	66.02	-	-	2229	66.02	1189	61.61	1040	71.92
1 期	6	0.18	-	-	6	0.18	5	0.26	1	0.07
1A 期	8	0.24	-	-	8	0.24	3	0.16	5	0.35
1A1 期	73	2.16	-	-	73	2.16	53	2.75	20	1.38
1A2 期	13	0.39	-	-	13	0.39	6	0.31	7	0.48
1B 期	11	0.33	-	-	11	0.33	7	0.36	4	0.28
1B1 期	103	3.05	-	-	103	3.05	78	4.04	25	1.73
1B2 期	102	3.02	-	-	102	3.02	66	3.42	36	2.49
1B3 期	46	1.36	-	-	46	1.36	26	1.35	20	1.38
2 期	1	0.03	-	-	1	0.03	0	0.00	1	0.07
2A 期	8	0.24	-	-	8	0.24	0	0.00	8	0.55
2A1 期	22	0.65	-	-	22	0.65	16	0.83	6	0.41
2A2 期	19	0.56	-	-	19	0.56	10	0.52	9	0.62
2B 期	113	3.35	-	-	113	3.35	66	3.42	47	3.25
3 期	2	0.06	-	-	2	0.06	0	0.00	2	0.14
3A 期	21	0.62	-	-	21	0.62	13	0.67	8	0.55
3B 期	30	0.89	48.7% of CC			0.89	19	0.98	11	0.76
3C1 期	268	7.94				7.94	184	9.53	84	5.81
3C2 期	43	1.27	-	-	43	1.27	32	1.66	11	0.76
4 期	4	0.12	-	-	4	0.12	2	0.10	2	0.14
4A 期	49	1.45	-	-	49	1.45	23	1.19	26	1.80
4B 期	147	4.35	-	-	147	4.35	98	5.08	49	3.39
不詳	58	1.72	-	-	58	1.72	34	1.76	24	1.66

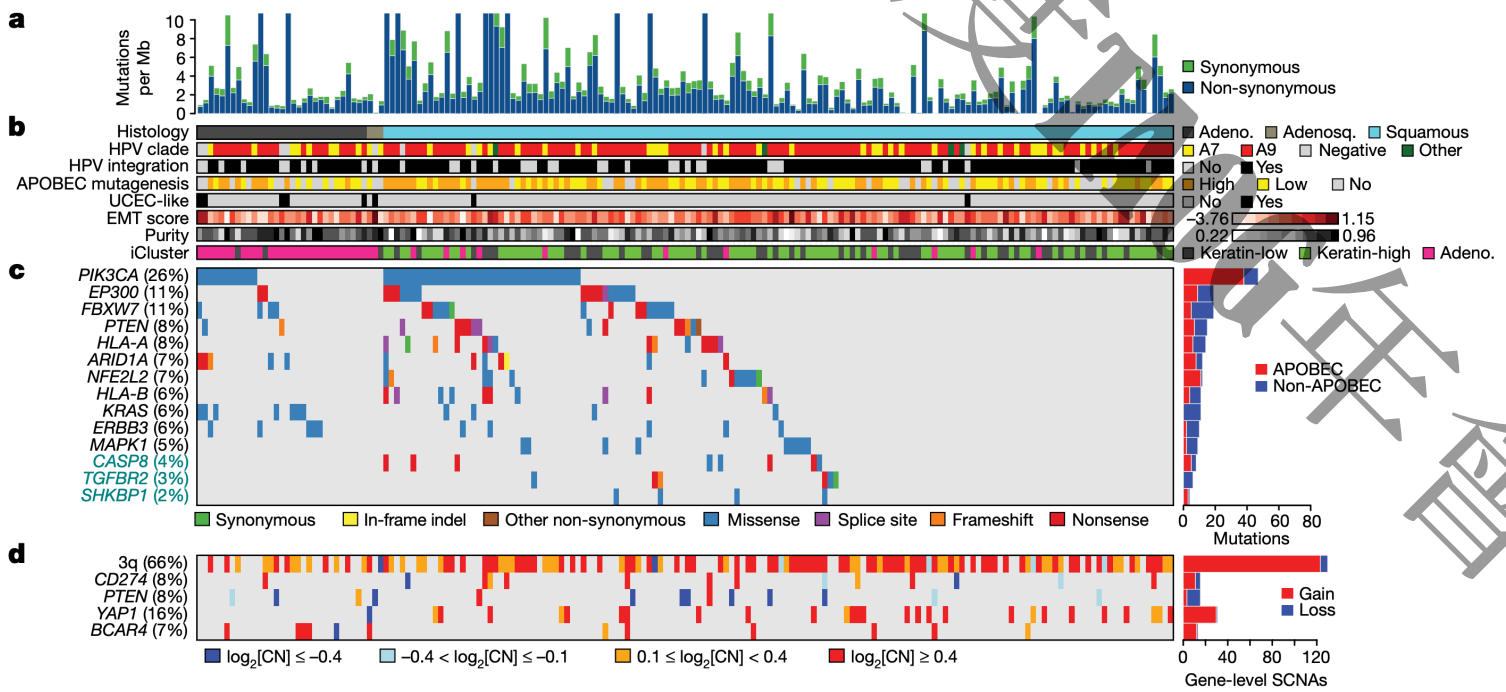
2023-11 國健署癌症年報

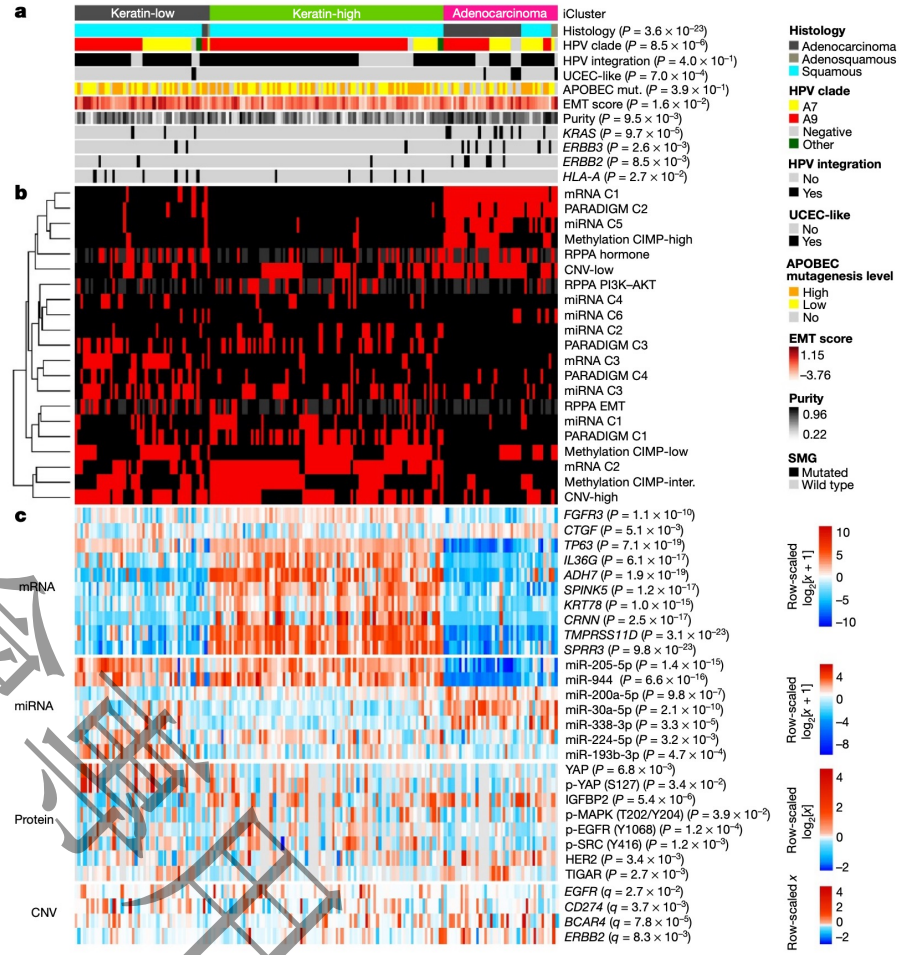
HPV integration and differential pathway activation between HPV subtypes



TCGA. Nature 2017 Mar 16;543(7645):378-384

Somatic alterations in CC and associations with molecular platform features & multiplatform integrative clustering of cervical cancers





TCGA. Nature 2017 Mar 16;543(7645):378-384

Further exploration about actionable biomarkers due to trials of MEK inhibitors to date have shown limited activity…

- Driver mutations: PIK3CA, KRAS, EGFR
- Amplification of PIK3CA: 36% CC, most commonly in SCC, higher rate of radiation resistance
- KRAS: more in adenocarcinoma, associated with HPV18, pathogenesis through RAS/RAF/MEK/ERK pathway

Locally Advanced Cervical Cancer

- CCRT with EBRT/Cisplatin as radiosensitizer (<=56 days)
- **EMBRACE-I study**[1]:

  >90% local control rate; lower OS in pts without brachy RT or >56days
- **OUTBACK trial**[2]: High-risk pts (pelvic lymph node-positive 2008 FIGO stage IB1, IB2, II, IIIB, and IVA patients with para-aortic nodal involvement above L3 or L4 were excluded)

[1]Lancet Oncol. 2021 Apr;22(4):538-547, [2]Lancet Oncol. 2023 May;24(5):468-482.

Locally Advanced Cervical Cancer

OUTBACK trial[1]

Stage IB_2-IVa Cervical cancer:

Stratify for

- FIGO stage
- Pelvic nodal involvement
- Uterine +ve on MRI

→ Standard chemoXRT → 4 cycles Carboplatin + Paclitaxel

→ Standard chemoXRT

N=926

Adjuvant chemotherapy:

- 22% did not initiate adj CT

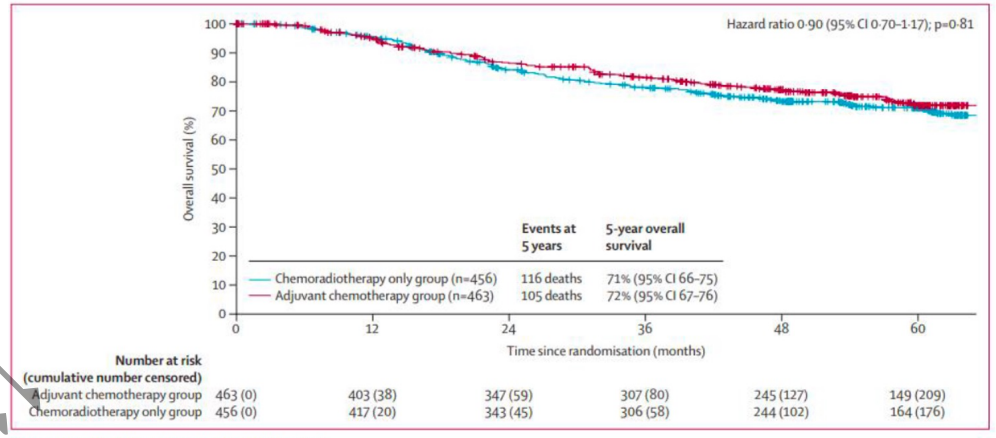
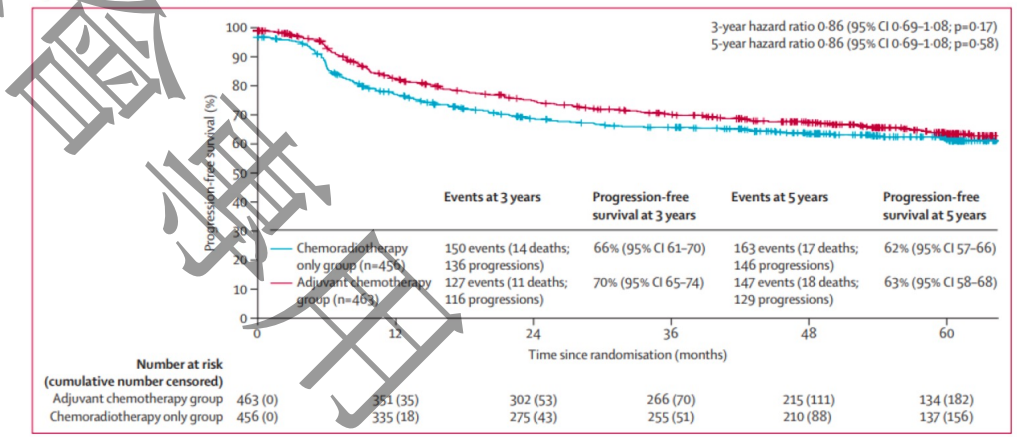


Figure 2: Kaplan-Meier estimates of overall survival



- **Addition of adjuvant chemotherapy didn't have overall survival benefit! But increased toxicity…**
- **A meta analysis[2] failed to demonstrate a clear improvement in OS with chemo but did show an association between outcome and short course chemo (OS improved by 7% at 5 years).**

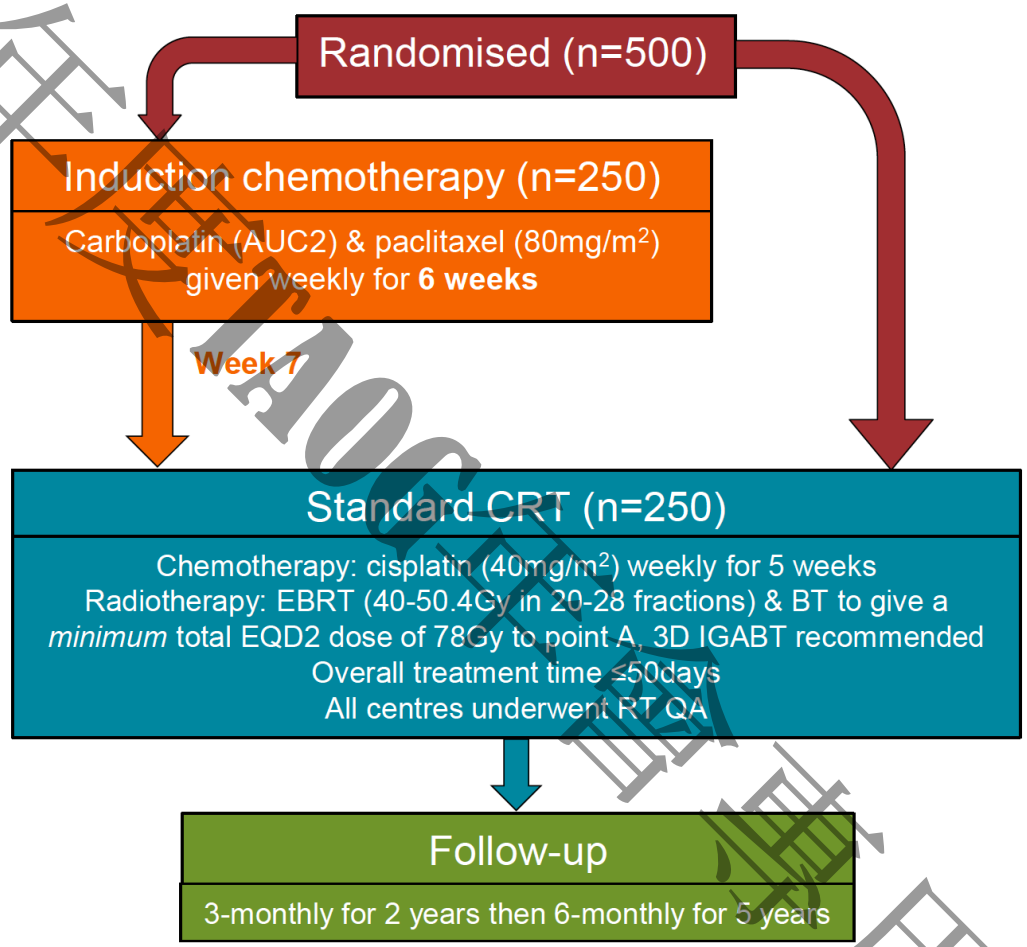
[1]Lancet Oncol. 2023 May;24(5):468-482; [2]Crit Rev Oncol Hematol. 2022 Apr:172:103638.

INTERLACE Trial Design

Key eligibility criteria

- Newly diagnosed histologically confirmed FIGO (2008) stages IB1 node+,IB2, II, IIIB, IVA squamous, adeno, adenosquamous cervical cancer
- No nodes above aortic bifurcation on imaging
- Adequate renal, liver & bone marrow function
- Fit for chemotherapy & radical RT
- No prior pelvic RT

RT = Radiotherapy
3D-Conformal = 3D conformal radiotherapy
IMRT = Intensity modulated radiotherapy
EBRT = External beam radiotherapy
BT = Brachytherapy
IGABT = Image-guided adaptive brachytherapy
RT QA = Radiotherapy quality assurance



Stratified by

- Site
- Stage
- Nodal status
- 3D-Conformal v IMRT EBRT
- 2D v 3D BT
- Tumour size
- SCC v other

Primary endpoints

- PFS
- OS

Secondary endpoints

- Adverse events
- Pattern of relapse
- QOL
- Time to subsequent treatment

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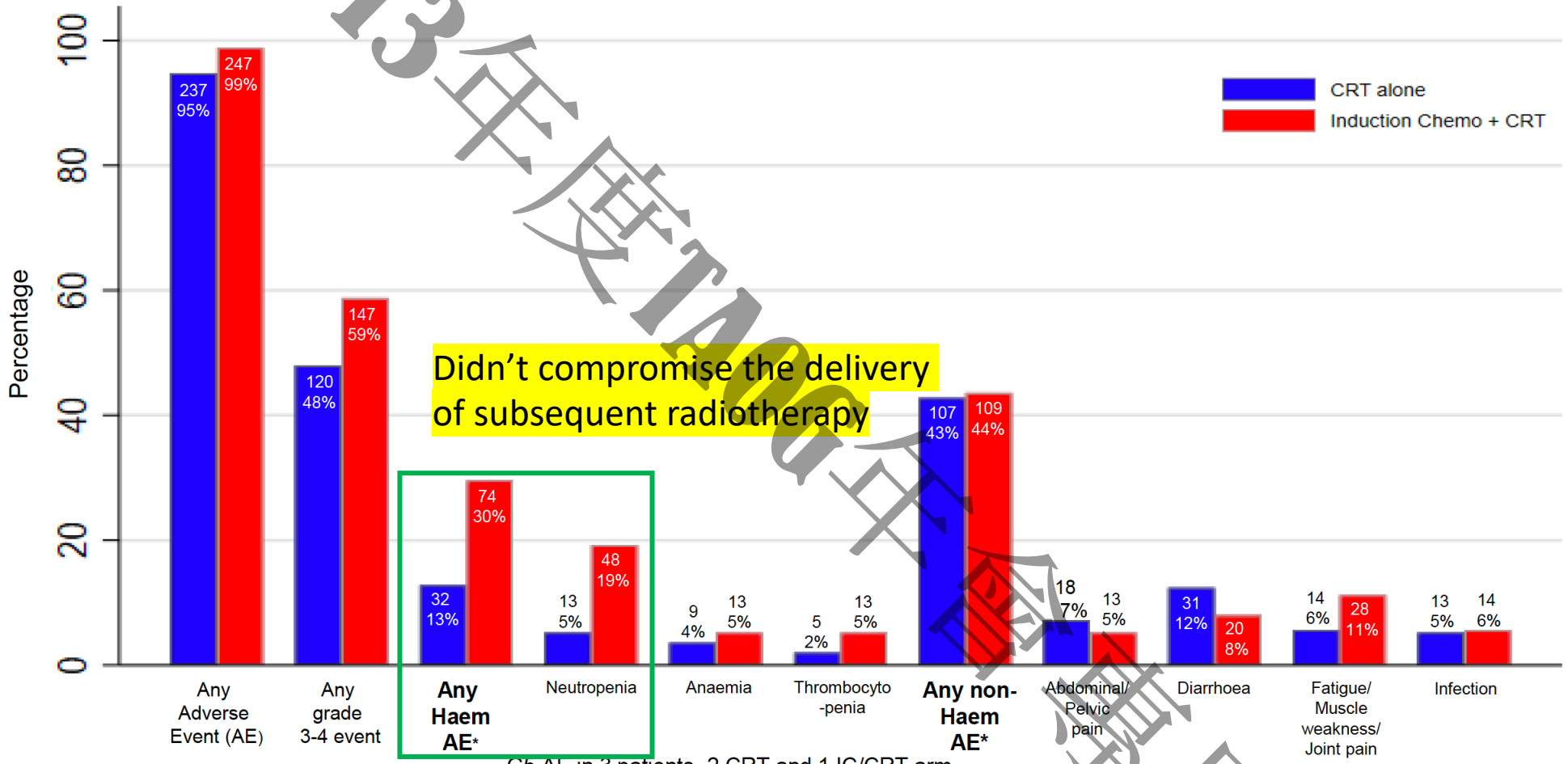
Adverse Events at any time



Didn't compromise the delivery of subsequent radiotherapy

G5 AE in 3 patients- 2 CRT and 1 IC/CRT arm

*Grade 3-4 only . *106 people (42%) reported grade 2 alopecia in the IC/CRT*

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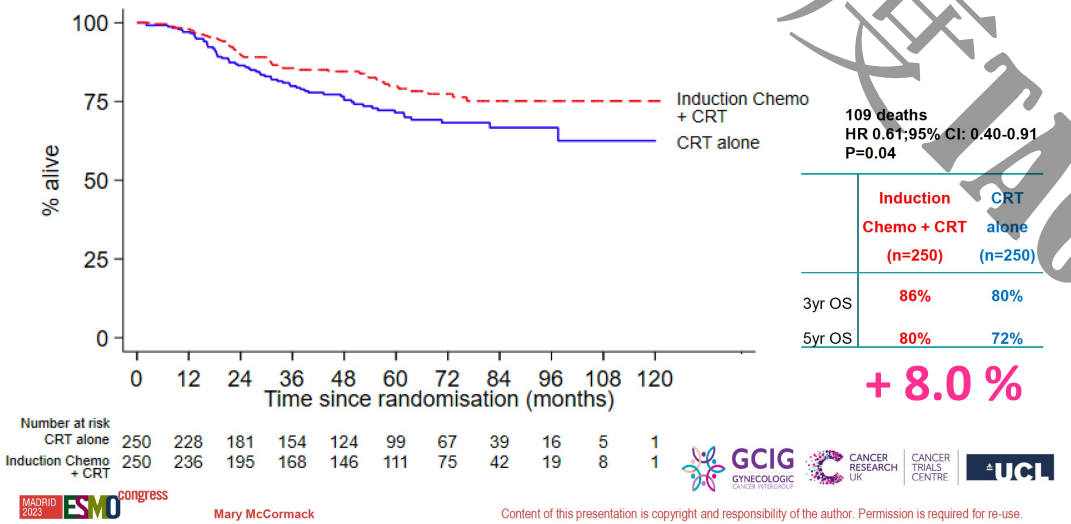
INTERLACE Overall Survival (median FU 64m)



109 deaths
HR 0.61;95% CI: 0.40-0.91
P=0.04

	Induction Chemo + CRT (n=250)	CRT alone (n=250)
3yr OS	86%	80%
5yr OS	80%	72%

+ 8.0 %

Number at risk											
CRT alone	250	228	181	154	124	99	67	39	16	5	1
Induction Chemo + CRT	250	236	195	168	146	111	75	42	19	8	1

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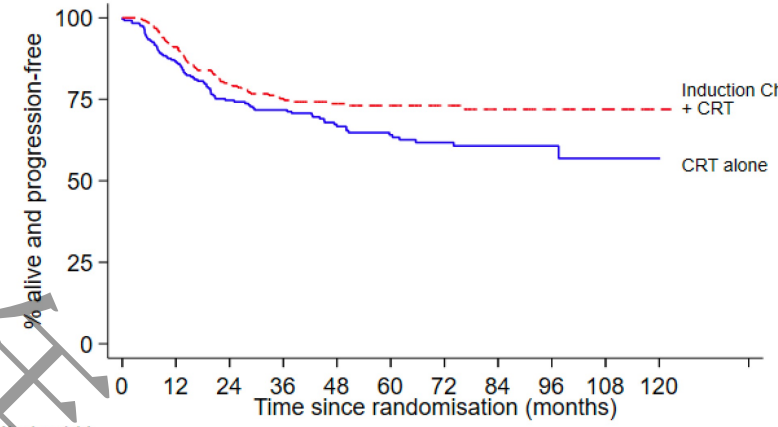
INTERLACE Progression-Free Survival (median FU 64m)



146 PFS events
HR 0.65;95% CI:0.46 -0.91
P=0.013

	Induction Chemo+ CRT (n=250)	CRT alone (n=250)
3yr PFS	75%	72%
5yr PFS	73%	64%

+ 9.0 %

Number at risk											
CRT alone	250	204	157	140	110	88	63	36	16	5	1
Induction Chemo + CRT	250	220	178	152	132	105	72	40	19	8	1

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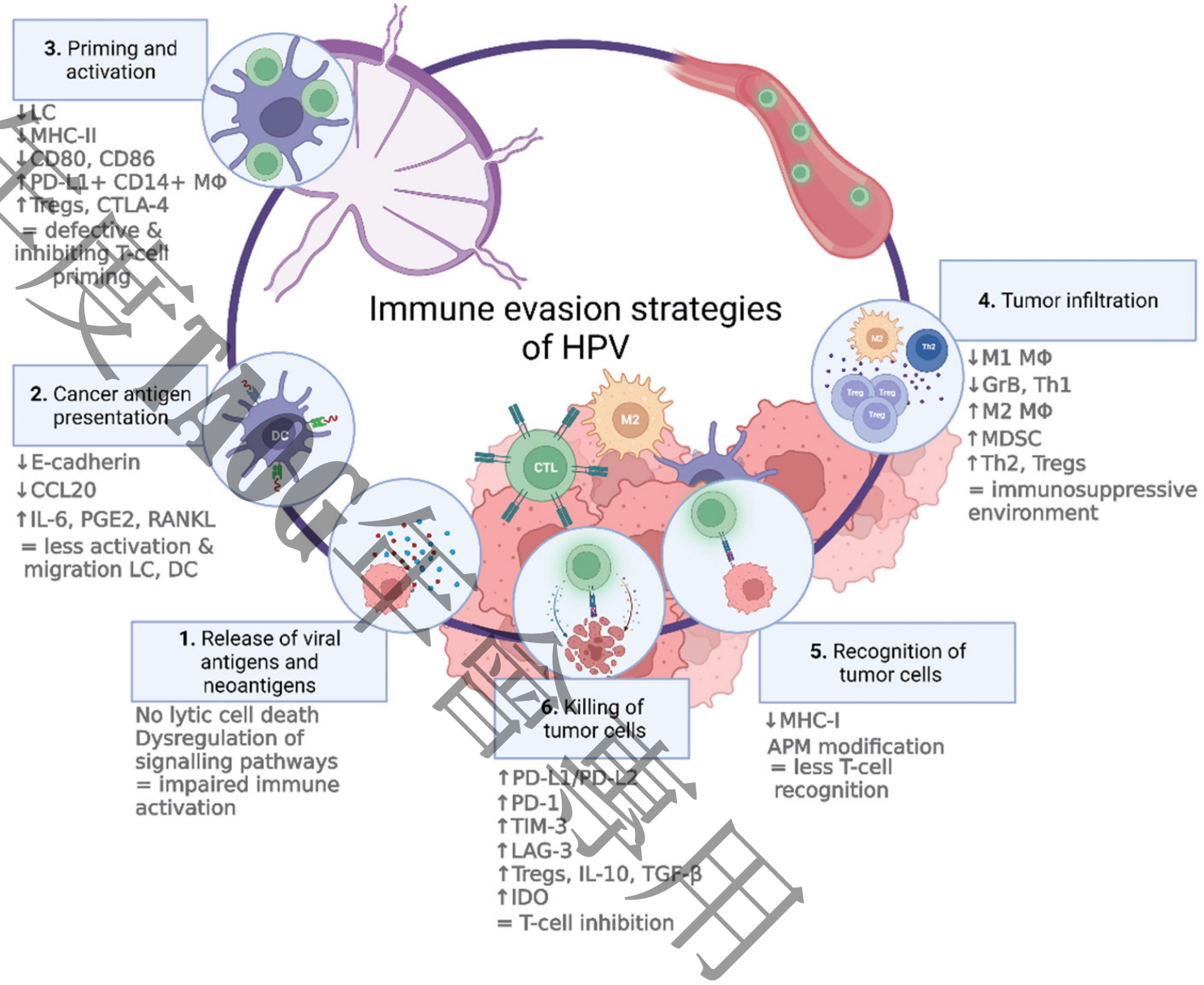
2023 ESMO meeting

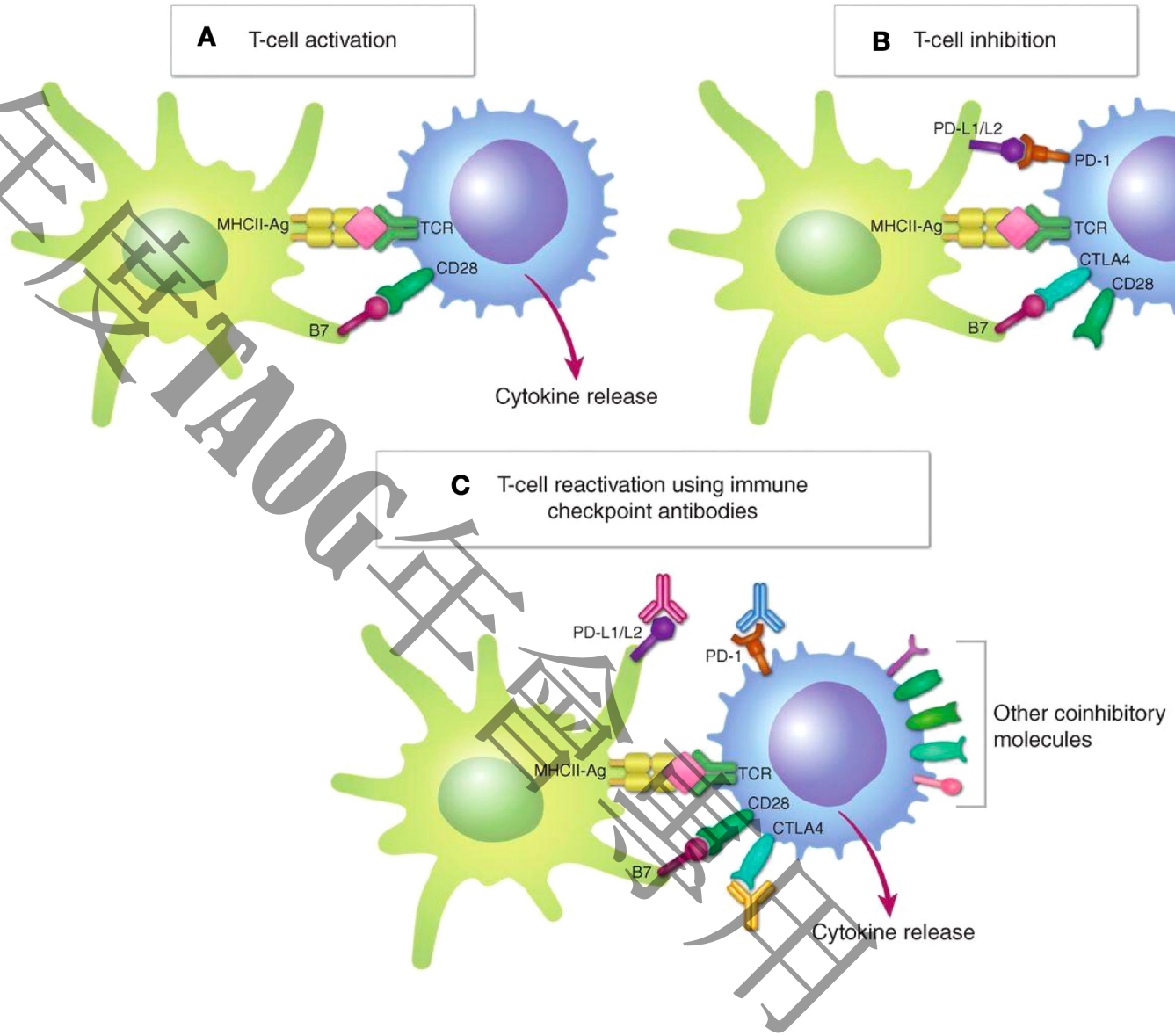
Patterns of Relapse

	CRT alone (n=250)	Induction Chemo + CRT (n=250)
	No. of patients (%)	
Local/pelvic	21 (8)	26 (10)
Local/pelvic & distant	20 (8)	14 (6)
Distant	30 (12)	16 (6)
Total local/pelvic relapses	41 (16)	40 (16)
Total distant relapses	50 (20)	30 (12)

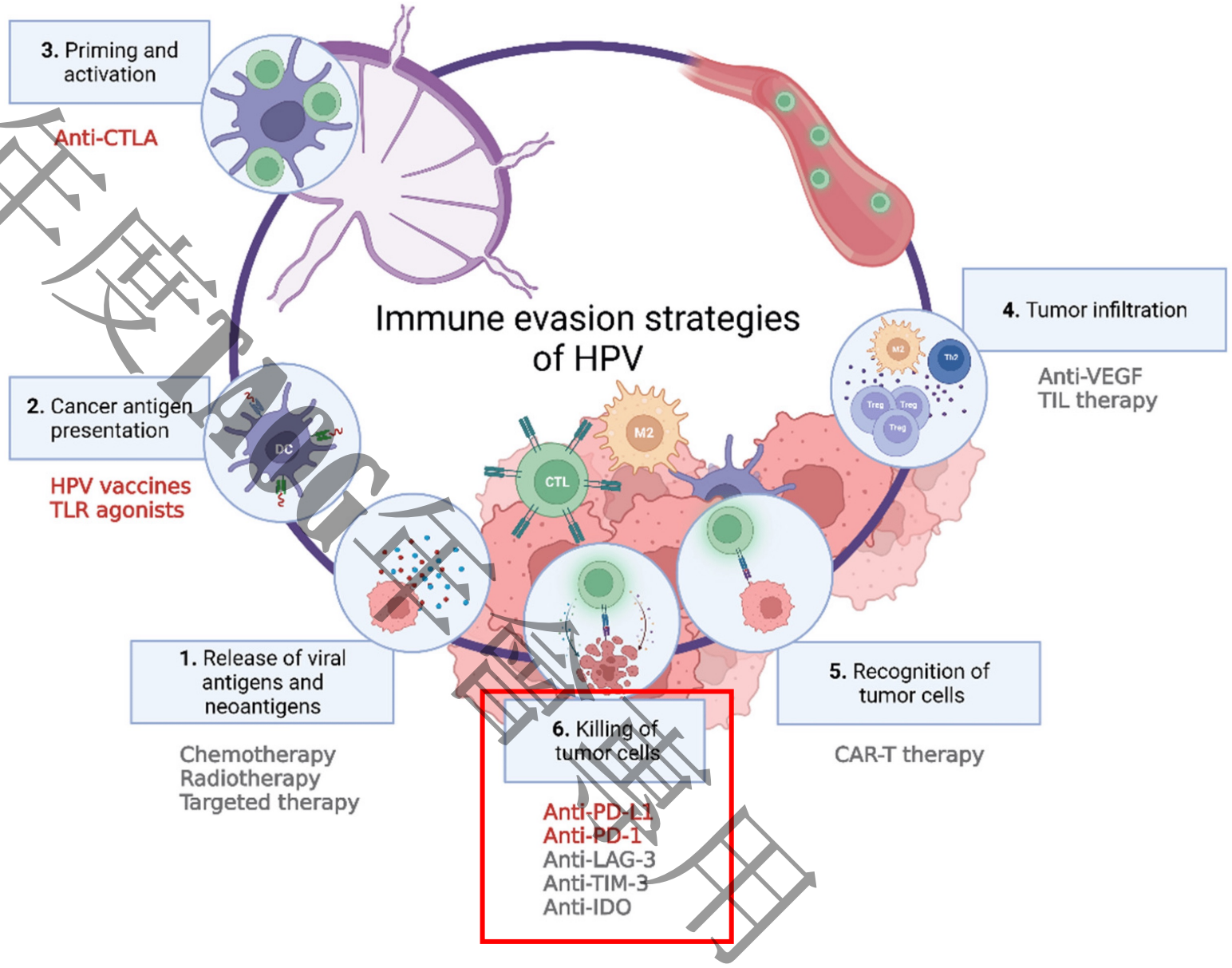
Cancer immunity cycle to illustrate the intracellular and extracellular evasion strategies of HPV



Regulation of T-cell activation



Cancer immunity cycle to illustrate the intracellular and extracellular evasion strategies of HPV



Clinical trials evaluating ICIs in LACC

Clinical trial	CALLA	KEYNOTE-A18	ATOMICC	ATEZOLACC	NiCOL
ClinicalTrials.gov	NCT03830866	NCT04221945	NCT03833479	NCT03612791	NCT03298893
Study design	Randomized, double-blind, global, placebo-controlled, phase III	Randomized, double-blind, placebo-controlled, phase III	Randomized, open-label, phase II	Randomized, open-label, phase II	Phase I
Estimated *N*	770	980	132	189	21
Population	Stages IB2–IIB with N+ or IIIA–IVA any node (FIGO 2009)	Stages IB2–IIB with N+ or III–IVA (FIGO 2014)	Stages IB2–IIB with pelvic N+, any stage with para-aortic N+ or III–IVA (FIGO 2009)	Stages IB1–IIA with pelvic N+, stages IIB–IVA, any stage with para-aortic N+ (FIGO 2009)	Stages IB2 to IVA with or without nodal involvement (FIGO 2009)
ICI	Anti-PD-L1 durvalumab	Anti-PD-1 pembrolizumab	Anti-PD-1 dostarlimab	Anti-PD-L1 atezolizumab	Anti-PD-1 nivolumab
ICI intervention and maximum duration of adjuvant therapy	Concurrent to CRT followed by maintenance up to 24 months	Concurrent to CRT during 5 cycles Q3W and maintenance Q6W for 15 cycles (20 months approx.)	Maintenance after response to concurrent CRT for up to 24 months	Concurrent to CRT followed by maintenance for 20 cycles (12 months approx.).	Concurrent to CRT Q2W and maintenance for 5 months
Primary endpoint	PFS	PFS and OS	PFS	PFS	Rate of DLT, secondary: ORR and PFS

CRT, chemoradiation; DLT, dose-limiting toxicity; ICI, immune checkpoint inhibitor; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Ther Adv Med Oncol. 2023 Mar 28:15

Clinical trials evaluating ICIs in LACC

Clinical trial	CALLA	KEYNOTE-A18	ATOMICC	ATEZOLACC	NiCOL
ClinicalTrials.gov	NCT03830866	NCT04221945	NCT03833479	NCT03612791	NCT03298893
Study design	Randomized, double-blind, global, placebo-controlled, phase III	Randomized, double-blind, placebo-controlled, phase III	Randomized, open-label, phase II	Randomized, open-label, phase II	Phase I
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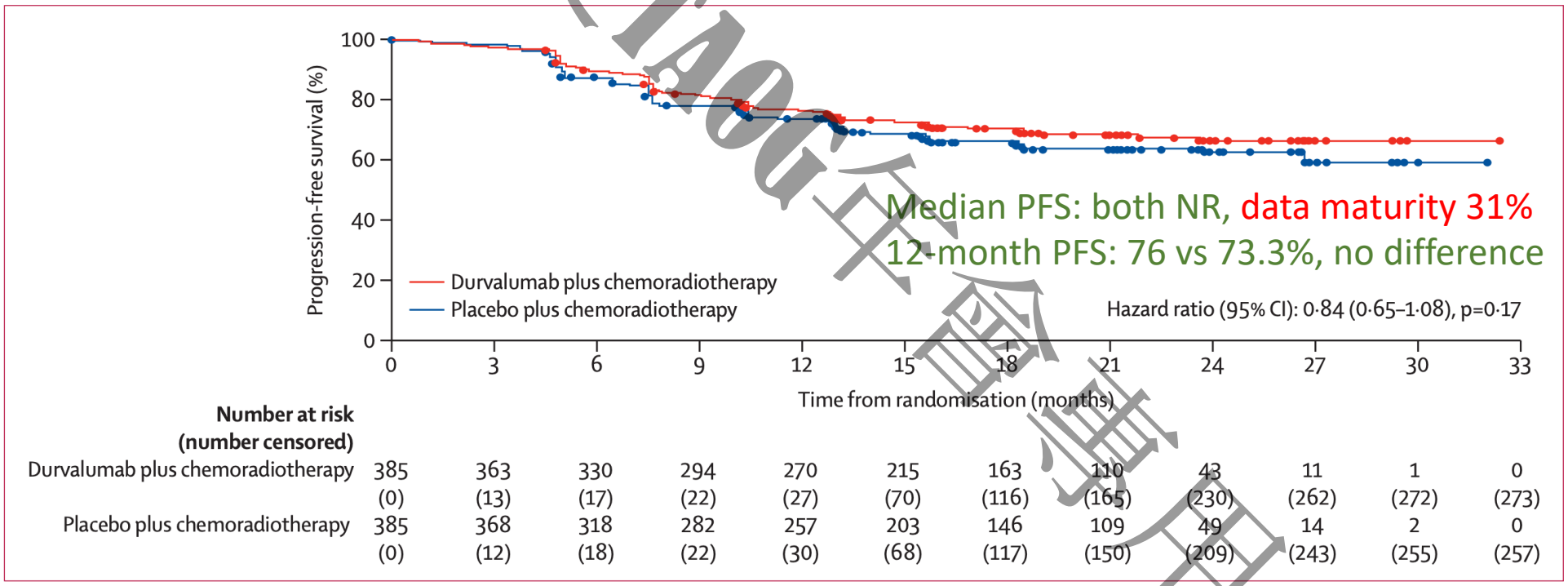
Ther Adv Med Oncol. 2023 Mar 28:15

Result of CALLA trial

- Durvalumab concurrent with CCRT was well tolerated in participants with locally advanced CC, however it did not significantly improve progression-free survival in a biomarker unselected, all-comers population.
- Concurrent durvalumab plus CCRT warrants further exploration in patients with high tumoral PD-L1 expression.
- Rigorous monitoring ensured **high chemoradiotherapy compliance** with advanced technology and allowed patients to receive optimal care.



Number at risk (number censored)												
Durvalumab plus chemoradiotherapy	385	363	330	294	270	215	163	110	43	11	1	0
	(0)	(13)	(17)	(22)	(27)	(70)	(116)	(165)	(230)	(262)	(272)	(273)
Placebo plus chemoradiotherapy	385	368	318	282	257	203	146	109	49	14	2	0
	(0)	(12)	(18)	(22)	(30)	(68)	(117)	(150)	(209)	(243)	(255)	(257)

Lancet Oncol. 2023 Dec;24(12):1334-1348.

Clinical trials evaluating ICIs in LACC

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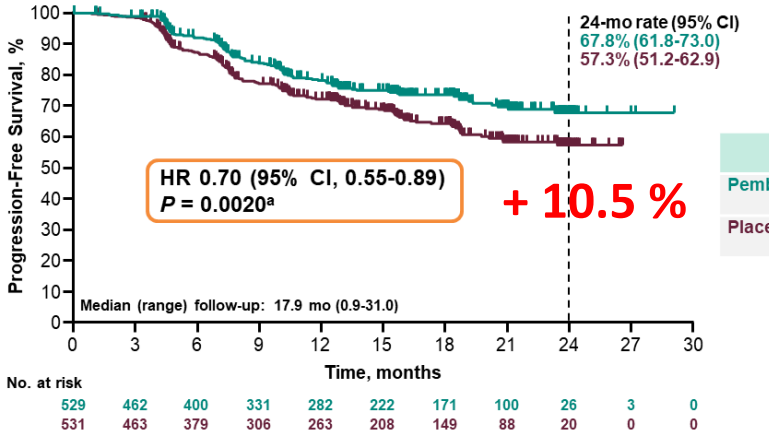
Locally Advanced Cervical Cancer

KEYNOTE-A18

D Lorusso KNA18 ESMO 2023

Primary Endpoint: Progression-Free Survival



	Pts w/ Event	Median, mo (95% CI)
Pembro Arm	21.7%	NR (NR-NR)
Placebo Arm	29.0%	NR (NR-NR)

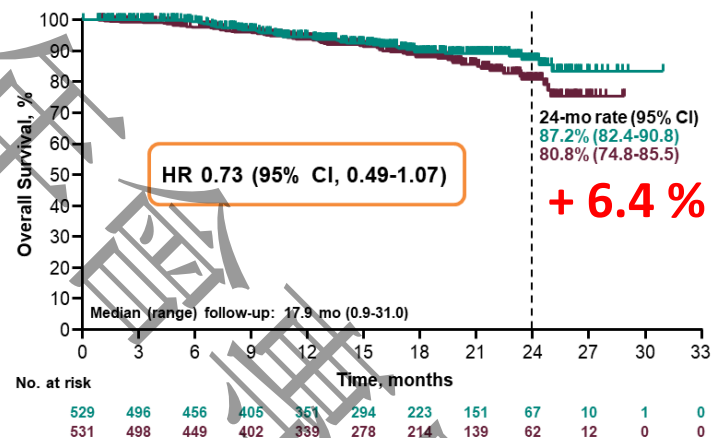
Response assessed per RECIST v1.1 by investigator review or histopathologic confirmation. [a]With 269 events (88.5% information fraction), the observed *P* = 0.0020 (1-sided) crossed the prespecified nominal boundary of 0.0172 (1-sided) at this planned first interim analysis. The success criterion of the PFS hypothesis was met, and thus no formal testing of PFS will be performed at a later analysis. Data cutoff date: January 9, 2023.

MADRID 2023 ESMO congress

Presented by: Domenica Lorusso

D Lorusso KNA18 ESMO 2023

Primary Endpoint: Overall Survival



	Pts w/ Event*	Median, mo (95% CI)
Pembro Arm	8.3%	NR (NR-NR)
Placebo Arm	11.1%	NR (NR-NR)

*42.9% information fraction[a]

[a]At this analysis, 103 of the 240 deaths expected at the final analysis had occurred. Data cutoff date: January 9, 2023.

MADRID 2023 ESMO congress

Presented by: Domenica Lorusso

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2023 ESMO meeting

Clinical trials evaluating ICIs in LACC

Clinical trial	CALLA	KEYNOTE-A18	ATOMICC	ATEZOLACC	NiCOL
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Ther Adv Med Oncol. 2023 Mar 28:15

Result of NiCOL Trial

- 16 pts, ORR is 93.8%, 2-year PFS of 75%
- Compared to patients with PD, progression-free subjects show a brisker stromal immune infiltrate, higher proximity of tumor infiltrating CD3+ T cells to PD-L1+ tumor cells and of FOXP3+ T cells to proliferating CD11c+ myeloid cells--> adaptive immune activation in a subset of pts with LACC

nature communications

Article

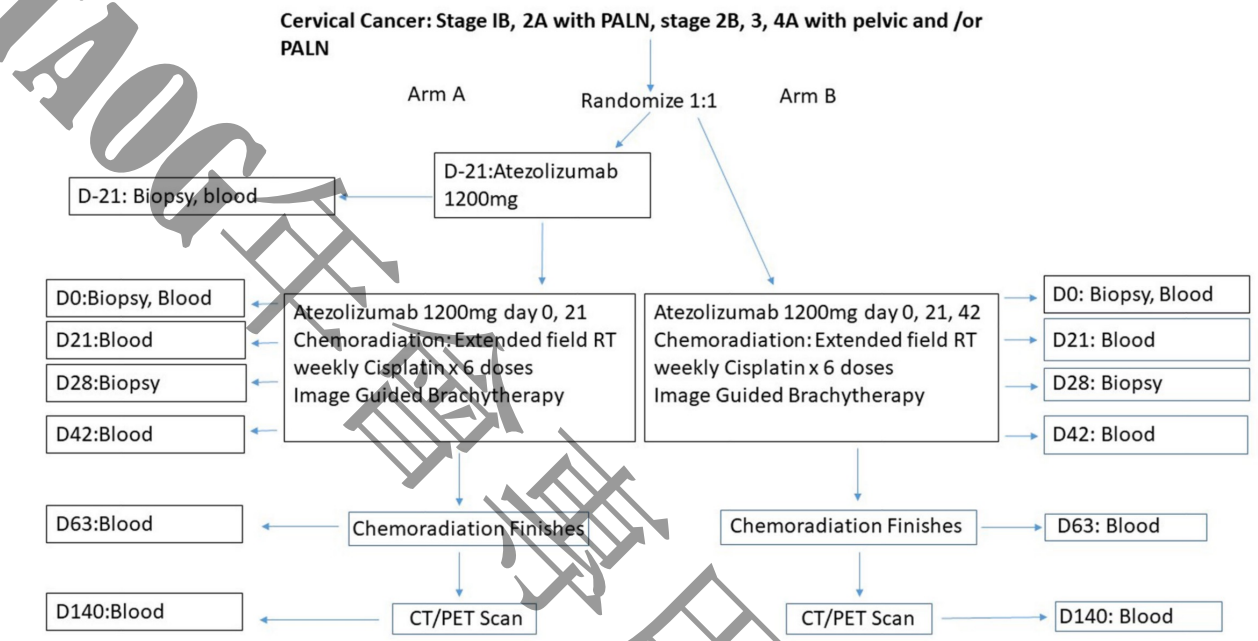
https://doi.org/10.1038/s41467-023-39383-8

Nivolumab plus chemoradiotherapy in locally-advanced cervical cancer: the NICOL phase 1 trial

Nat Commun. 2023 Jun 22;14(1):3698.

Locally Advanced Cervical Cancer

- A primer for chemoradiation has been recently explored in the **NRG-GY017 trial**, and findings demonstrated improved immunogenicity with neoadjuvant compared to concurrent administration of atezolizumab.



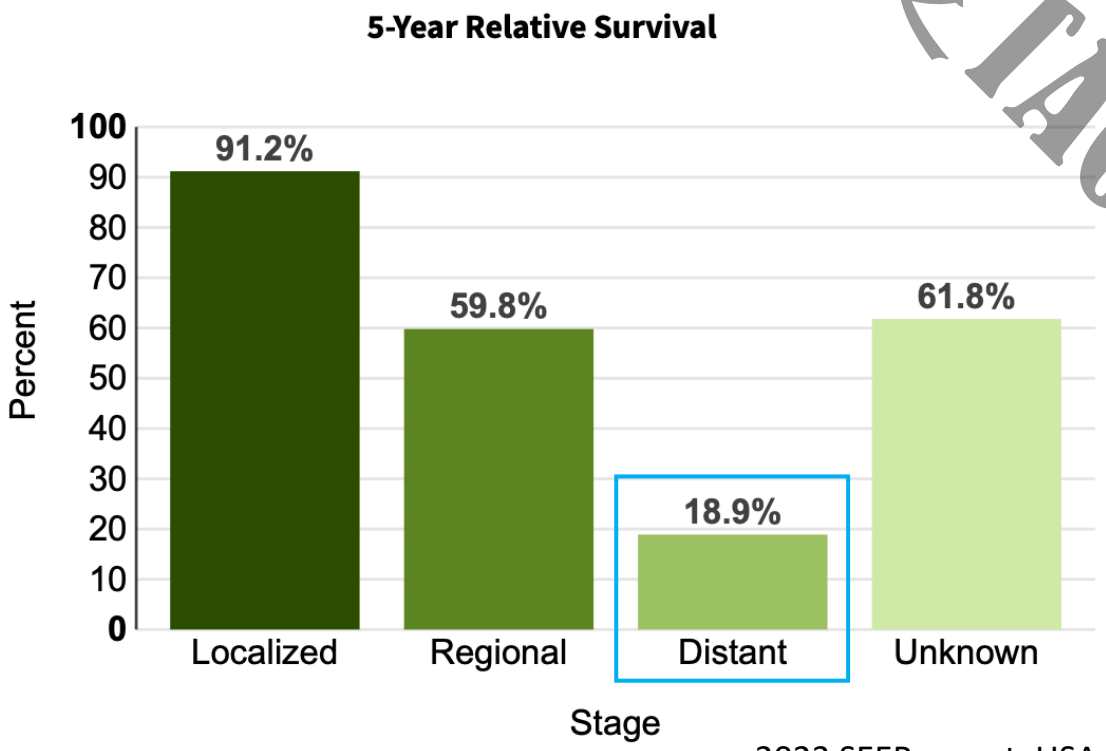
Int J Gynecol Cancer. 2020 May; 30(5): 701–704.

Agenda

- Background
- **Therapy by treatment setting**
  - Early stage
  - Locally advanced disease
  - **Metastatic/recurrent disease**
  - Future directions
- Conclusions

Photo from https://www.trs.texas.gov

Challenge in metastatic/recurrent CC



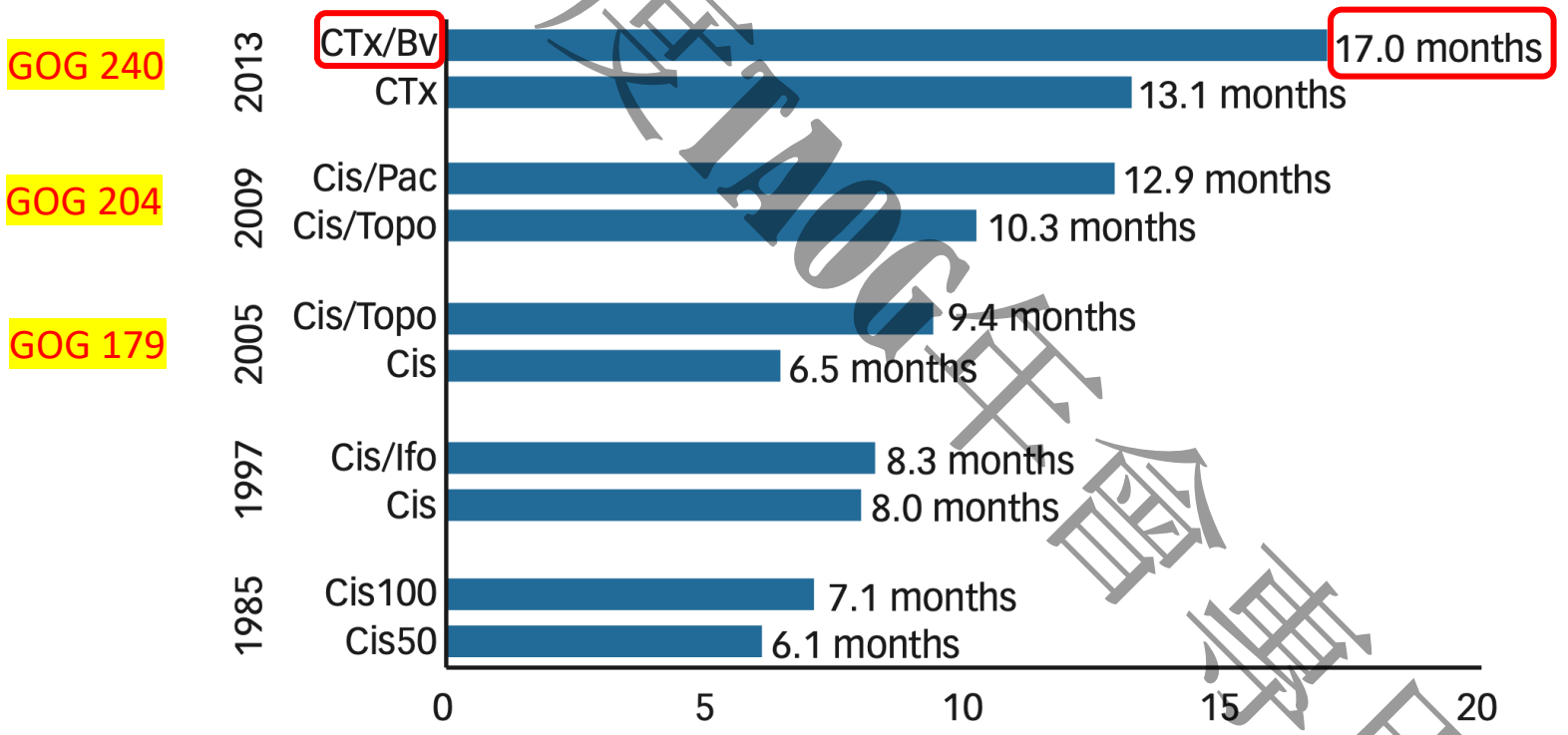
2023 SEER report, USA

FIGO 期別 [2]											
0	期	2229	66.02	-	-	2229	66.02	1189	61.61	1040	71.92
1	期	6	0.18	-	-	6	0.18	5	0.26	1	0.07
1A	期	8	0.24	-	-	8	0.24	3	0.16	5	0.35
1A1	期	73	2.16	-	-	73	2.16	53	2.75	20	1.38
1A2	期	13	0.39	-	-	13	0.39	6	0.31	7	0.48
1B	期	11	0.33	-	-	11	0.33	7	0.36	4	0.28
1B1	期	103	3.05	-	-	103	3.05	78	4.04	25	1.73
1B2	期	102	3.02	-	-	102	3.02	66	3.42	36	2.49
1B3	期	46	1.36	-	-	46	1.36	26	1.35	20	1.38
2	期	1	0.03	-	-	1	0.03	0	0.00	1	0.07
2A	期	8	0.24	-	-	8	0.24	0	0.00	8	0.55
2A1	期	22	0.65	-	-	22	0.65	16	0.83	6	0.41
2A2	期	19	0.56	-	-	19	0.56	10	0.52	9	0.62
2B	期	113	3.35	-	-	113	3.35	66	3.42	47	3.25
3	期	2	0.06	-	-	2	0.06	0	0.00	2	0.14
3A	期	21	0.62	-	-	21	0.62	13	0.67	8	0.55
3B	期	30	0.89	-	-	30	0.89	19	0.98	11	0.76
3C1	期	268	7.94	-	-	268	7.94	184	9.53	84	5.81
3C2	期	43	1.27	-	-	43	1.27	32	1.66	11	0.76
4	期	4	0.12	-	-	4	0.12	2	0.10	2	0.14
4A	期	49	1.45	-	-	49	1.45	23	1.19	26	1.80
4B	期	147	4.35	-	-	147	4.35	98	5.08	49	3.39
不詳		58	1.72	-	-	58	1.72	34	1.76	24	1.66

13.5% of CC

2023-11 國健署癌症年報

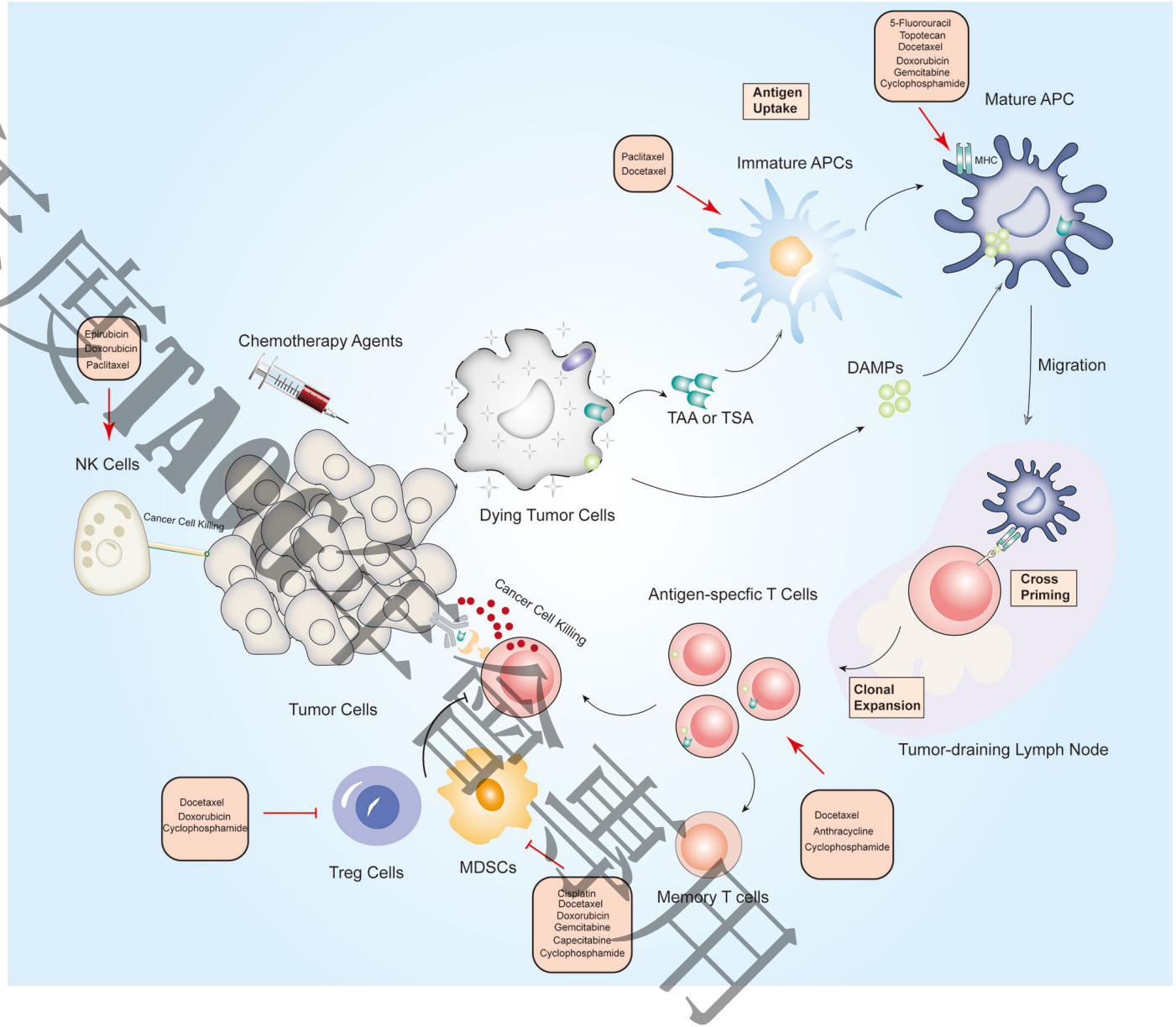
Metastatic/recurrent cervical cancer, 1st line



Bv = bevacizumab; Cis = cisplatin; CTx = chemotherapy; Ifo = ifosfomide; OS = overall survival; Pac = paclitaxel; Topo = topotecan.

2020-06-01
健保給付
Bevacizumab在
轉移/持續/復發
之子宮頸癌

Immunostimulatory properties of chemotherapy in cancer



Front Immunol. 2022 Jan 5:12:819405.

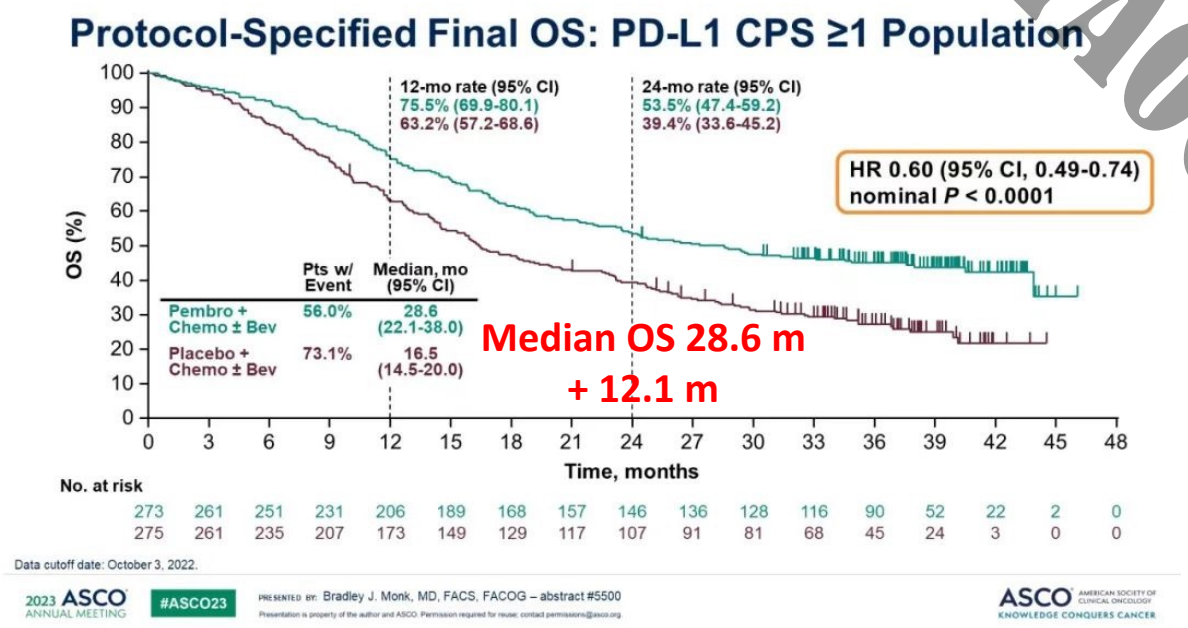
Efficacy data of immune checkpoint inhibitors in the persistent, recurrent, and metastatic cervical cancer setting

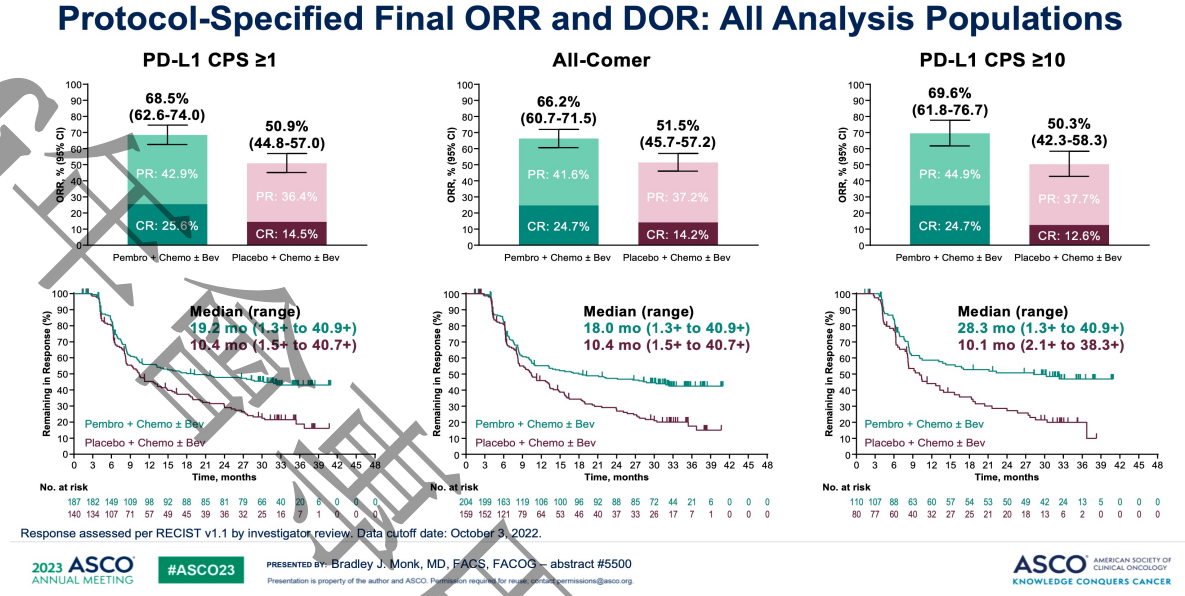
Trial	Disease setting	Drugs and schemes	PD-(L)1 antibody for IHC	PD-(L)1 scoring method Cut-off point	% PD-(L)1-positive patients	ORR, % (95% CI)	Median PFS (m) (95% CI)	Median OS (m) (95% CI)
EMPOWER-Cervical 1[14 22] Phase III Randomized	Post-platinum PD	Cemiplimab 350 mg q3w for up to 96 w vs standard chemotherapy	SP263	TPS 1%	38.9%	PD-L1+: 21.6% vs 5.8% OR 4.5 (1.85 to 10.98) PD-L1−: 13.6% vs 5.9% OR 2.74 (0.76 to 9.86)	Overall population: 2.8 m vs 2.9 m; HR=0.75 (0.63 to 0.89; p<0.001)	PD-L1+: 12.2 m vs 7.7 m HR=0.61 (0.45 to 0.83) PD-L1−: 10.8 m vs 7.0 m HR=0.65 (0.42 to 0.98)
KEYNOTE-158[18] Phase II basket	Post-platinum PD	Pembrolizumab 200 mg q3w for up to 2 y	22C3	CPS 1%	83.7%	PD-L1+: 17.1% (9.7 to 27.0) PD-L1−: 0.0% (0.0 to 21.8)	All-comers: 2.1 m (2.1 to 2.2)	All-comers: 9.3 m (7.6 to 11.7)
CheckMate-358[19 20] Phase I/II	First line and post-platinum PD	Nivolumab 240 mg q2w for up to 2 y	28–8	TPS 1%	58%	PD-L1+: 27% PD-L1−: 14%	All-comers: 5.1 m (1.9 to 9.1)	All-comers: 21.6 m (8.3 to 46.9)
		Nivo 3 mg/kg q2w+Ipi 1 mg/kg q6w for up to 2 y			56%	PD-L1+: 36% PD-L1−: 20%	All-comers: 3.8 m (2.1 to 10.3)	All-comers: 15.2 m (9.0 to 36.2)
		Nivo 1 mg/kg q2w+Ipi 3 mg/kg q3w×4 cycles followed by Nivo 240 mg q2w for up to 2 y			47%	PD-L1+: 36% PD-L1−: 31%	All comers: 5.8 m (3.8 to 9.3)	All-comers: 20.9 m (14.4 to 32.8)
C-700-01[21] Phase II	Post-platinum PD	Balstilimab 3 mg/kg q2w for up to 2 y	22C3	CPS 1%	62%	PD-L1+: 20% (12.9 to 29.7) PD-L1−: 7.9%	Not reported	Not reported
C-550-01[25] Phase II	Post-platinum PD	Balstilimab 3 mg/kg q2w+zalifrelimab 1 mg/kg q6w for up to 2 y	22C3	CPS 1%	57%	PD-L1+: 32.8% (22.8 to 44.7) PD-L1−: 9.1%	All-comers: 2.7 m (1.5 to 3.7)	All-comers: 12.8 m (8.8 to 17.6)
AK104-210[26] Phase II	Post-platinum PD	Cadonilimab 6 mg/kg q2w	22C3	CPS 1%	58%	All comers: 33% (23.9 to 43.1) PD-L1+: 43.8% (31.4 to 56.7) PD-L1−: 16.7% (3.6 to 41.4)	All comers: 3.75 m (2.00 to 6.41) PD-L1+: 6.34 m (3.12 to 11.17)	All comers: 17.51 m (11.37 to NE) PD-L1+: NR (17.51 to NE)
KEYVIBE-001[28] Phase II Randomized	Post-platinum PD	Vibostolimab 700 mg or 200 mg+pembrolizumab 200 mg q3w for up to 35 cycles	22C3	CPS 1%	61%	PD-L1+: 20% (10 to 34) PD-L1−: 14% (3 to 36)	PD-L1+: 4 m (2 to 4) PD-L1-: 2 m (1 to 4)	Not reported
KEYNOTE-826[15 31] Phase III Randomized	First line	Pembrolizumab 200 mg q3w for up to 35 cycles vs placebo+platinum doublet+/-bevacizumab 15 mg/kg q3w	22C3	CPS 1%	88.81%	ITT: 65.9% (60.3 to 71.2) vs 50.8% (45.1 to 56.5) PD-L1+: 68.1% (62.2 to 73.6) vs 50.2% (44.1 to 56.2)	ITT: 10.4 m vs 8.2 m HR=0.65 (0.53 to 0.79; p<0.001) PD-L1+: 10.4 m vs 8.2 m; HR=0.62 (0.50 to 0.77; p<0.001)	ITT: 24.4 m vs 16.5 m HR=0.67 (0.54 to 0.84; p<0.001) PD-L1+: NR vs 16.3 m HR=0.64 (0.50 to 0.81; p<0.001)

Int J Gynecol Cancer. 2023 Mar 6;33(3):403-413.

Metastatic/recurrent cervical cancer, 1st line

KEYNOTE-826





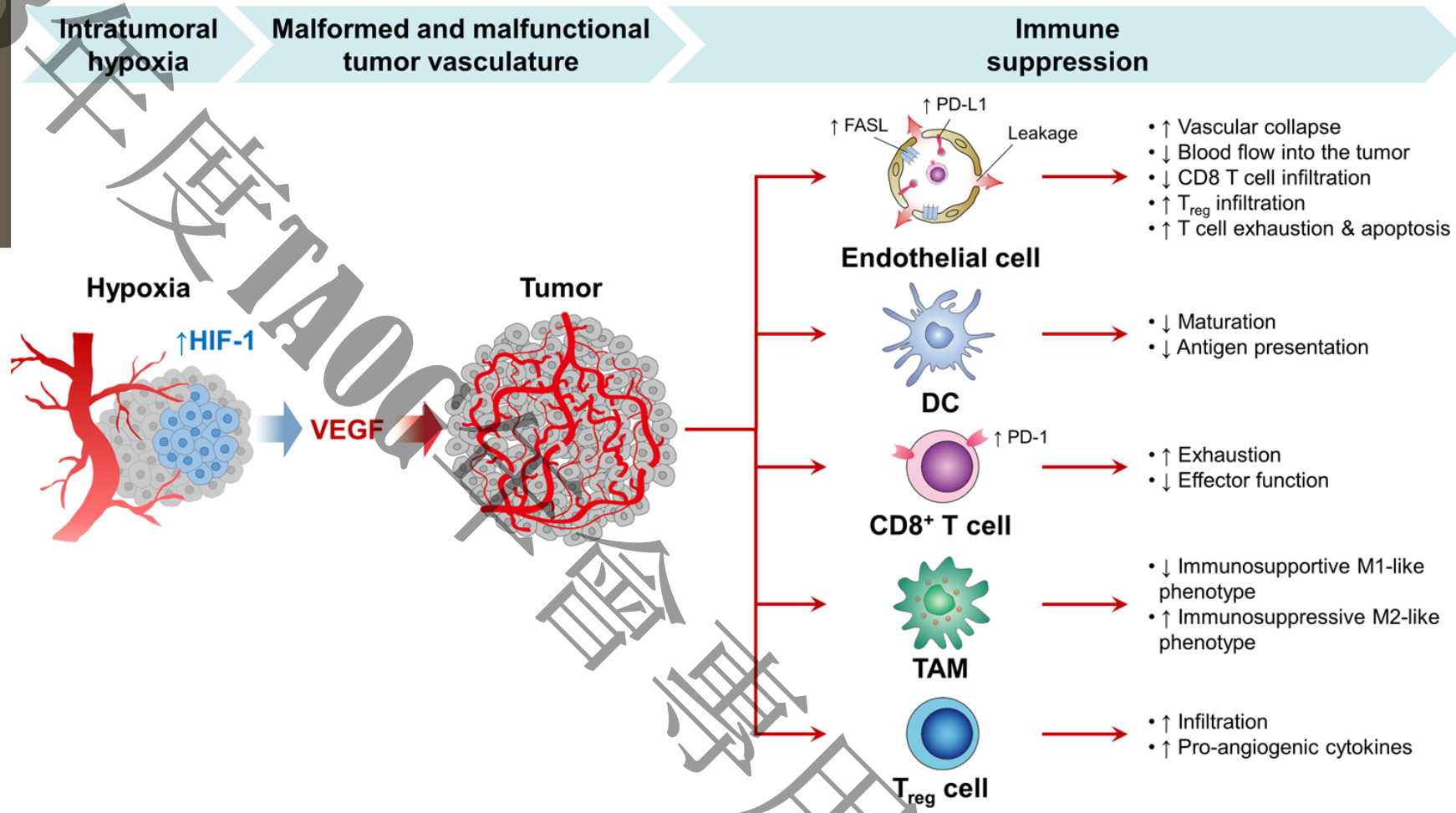
2023 ASCO annual meeting

Subgroup analysis of KEYNOTE-826

Subgroup (N)	Median PFS (mo) Pembro	Median PFS (mo) Pbo	PFS, HR (95% CI)	Median OS (mo) Pembro	Median OS (mo) Pbo	OS, HR (95% CI)
With bev (389)	15.2	10.2	0.61 (0.47-0.79)	Not reached	24.7	0.63 (0.47-.87)
Without bev (228)	6.3	6.2	0.74 (0.54-1.01)	16.8	12.6	0.74 (0.53-1.04)
Squamous (447)	10.4	6.9	0.63 (0.50-0.80)	23.5	14.2	0.61 (0.47-0.80)
Non-squamous (169)	11.6	8.4	0.66 (0.43-1.00)	Not reached	21.3	0.76 (0.47-1.23)
Carboplatin (495)	10.2	7.4	0.69 (0.55-0.86)	21.4	15.9	0.69 (0.54-0.89)
Cisplatin (120)	15.2	8.4	0.47 (0.28-0.77)	Not reached	21.3	0.59 (0.32-1.09)
Prior CRT (243)	10.3	6.3	0.62 (0.45-0.86)	21.3	12.6	0.64 (0.45-0.91)

2022 ASCO annual meeting

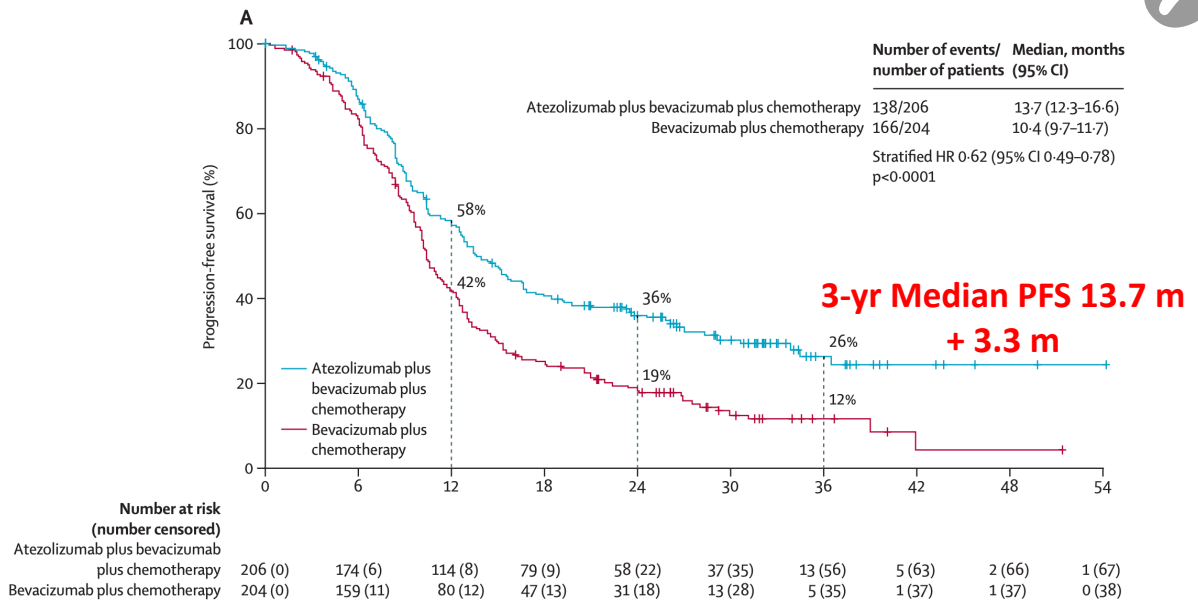
Antitumor immune response modulation -- combining immune checkpoint inhibitors with antiangiogenic drugs



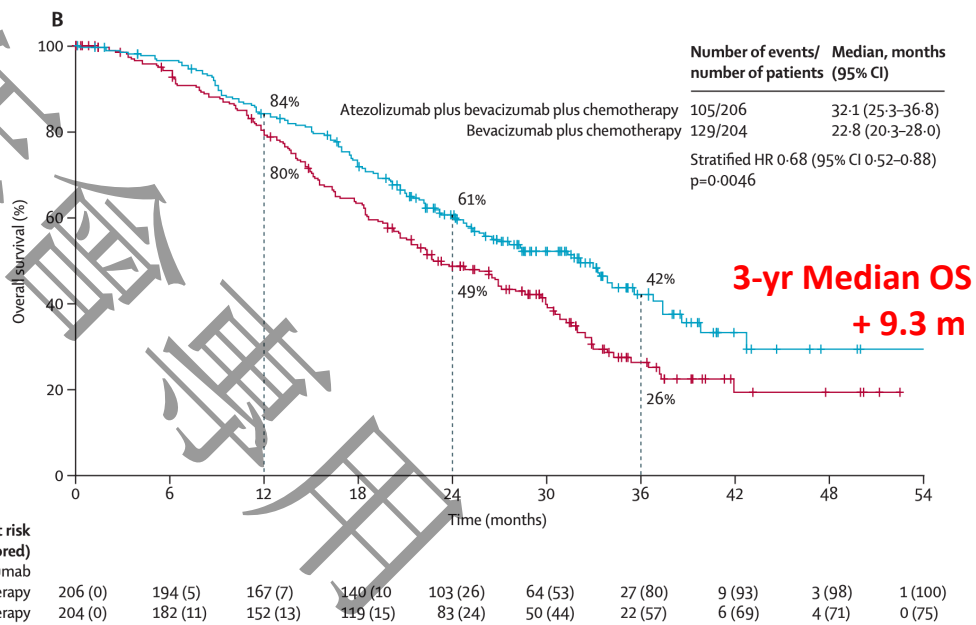
Exp Mol Med. 2020 Sep;52(9):1475-1485.

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**



3-yr Median PFS 13.7 m
+ 3.3 m

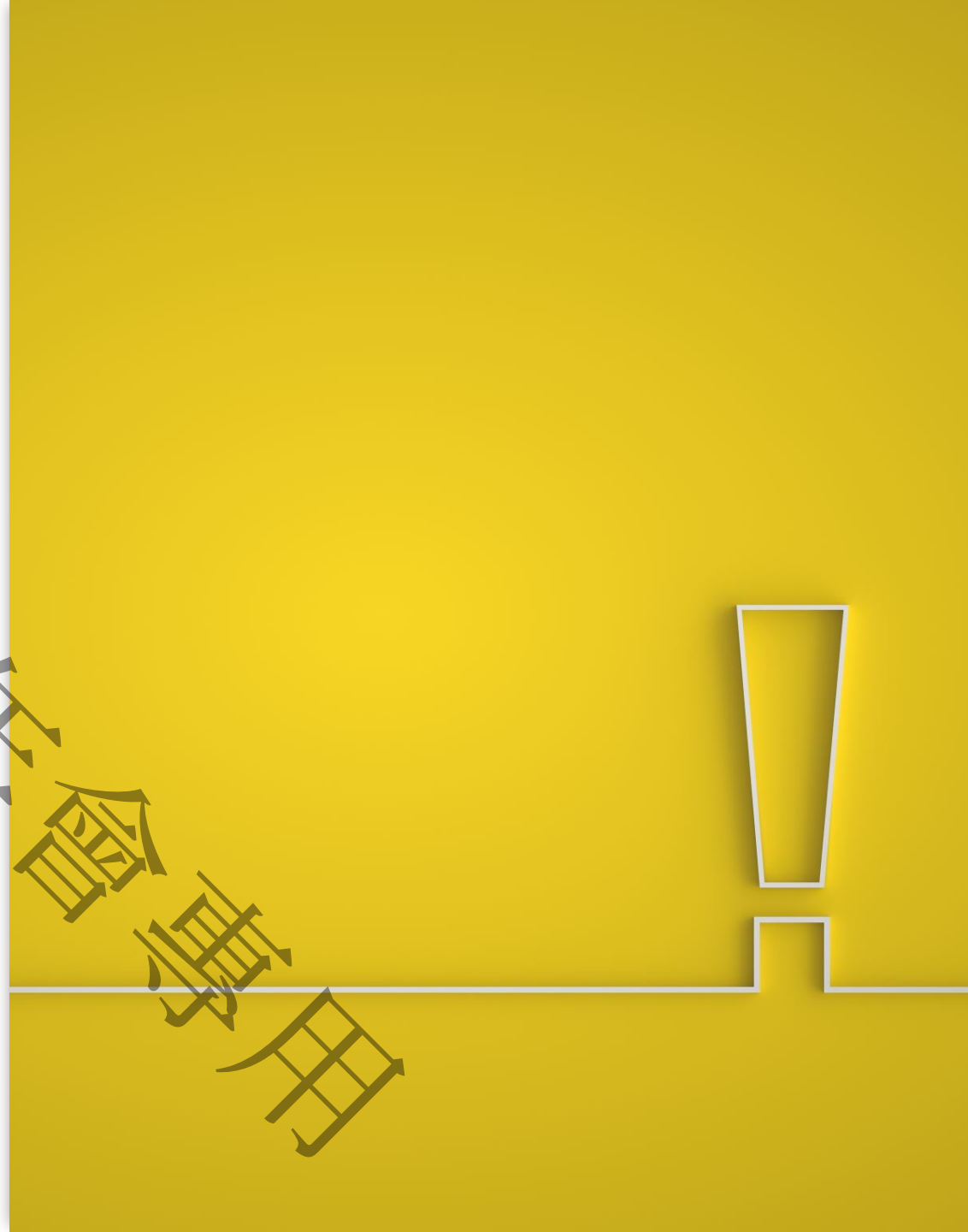


3-yr Median OS 32.1 m
+ 9.3 m

Lancet. 2024 Jan 6;403(10421):31-43.

Recurrent cervical cancer, 2nd/3rd line

- Chemo
- Immune checkpoint inhibitors monotherapy
- Target monotherapy (ADC, anti-HER2 antagonist)
- PD-1 or PD-L1 D CTLA-4 inhibitors
- ICIs + angiogenesis inhibitors



Recurrent cervical cancer, 2nd/3rd line chemotherapy only

Table 2. Chemotherapeutic agents evaluated in clinical trials after progression from first-line therapy

Authors	Year published	Agent	*n*	ORR (%)	PFS (months)	OS (months)
Verschraegen *et al.*[21]	1997	Irinotecan	42	21	4.5	6.4
Bookman *et al.*[22]	2000	Topotecan	45	13	2.1	6.4
Muderspach *et al.*[23]	2001	Topotecan	49	19	2.4	6.6
Schilder *et al.*[24]	2005	Gemcitabine	22	5	2.1	6.5
Rose *et al.*[25]	2006	Pegylated Liposomal Doxorubicin	27	11	3.2	8.9
Garcia *et al.*[26]	2007	Docetaxel	23	9	3.8	7
Lorusso *et al.*[27]	2010	Pemetrexed	43	15	3.1	8.8
Alberts *et al.*[28]	2012	Albumin-bound Paclitaxel	35	29	5	9.4

Recurrent cervical cancer, 2nd/3rd line

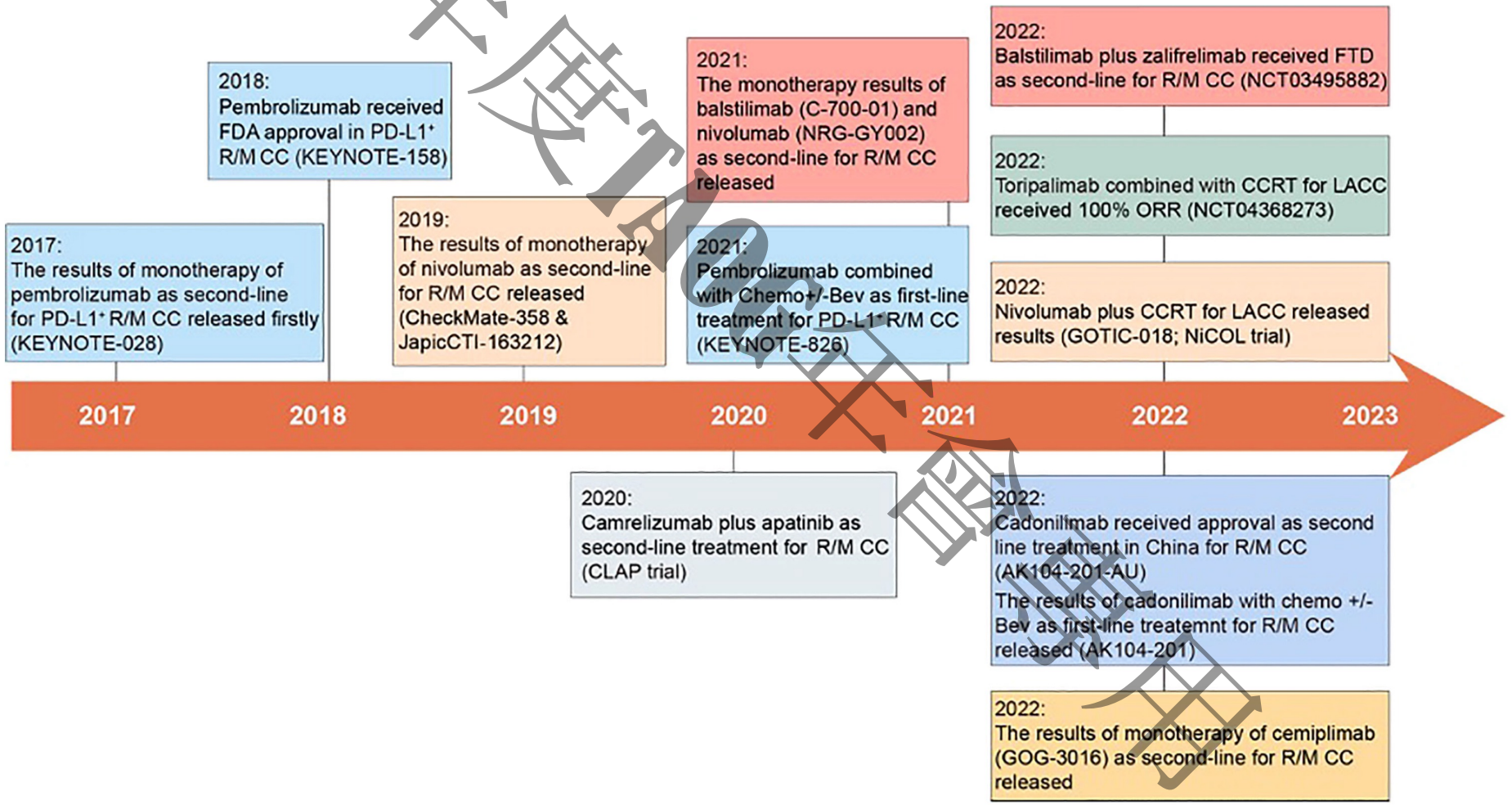
ICIs monotherapy

Table 1. Monotherapy clinical trials

Drug	Trial	Phase	*N*	Population	Histology (%)	Prior RT (%)	Prior bevacizumab (%)	PD-L1 expression (%)	Number of prior lines (%)	ORR (%)	mDOR (months)	mPFS (months)	mOS (months)	Grade 3-4 TRAEs (%) Discontinuation (%)
Pembrolizumab	KEYNOTE-028	Ib	24	Locally advanced or metastatic; PD-L1+; progression after prior therapy	SCC = 96 ADK = 4	92	42	TC = 75 TC + stroma = 25	1 = 38 2 = 25 ≥3 = 38	17	5.4	2	11	20.8 8.3
	KEYNOTE-158	II	98	Advanced disease; progression during or intolerance to ≥1 lines of prior therapy	SCC = 93.9 ADK = 5.1 ADSC = 1.0	86.7	41.8	CPS ≥1 = 83.7	1 = 30.6 2 = 34.7 ≥3 = 30.6	All = 12.2 PD-L1+ = 14.6 PD-L1− = 0	NR	2.1	9.4	12.2 4.1
Nivolumab	CheckMate-358	I/II	19	Recurrent or metastatic; HPV+; SCC	SCC = 100	89.5	31.6	CPS ≥1 = 62.5	1 = 42.1 2 = 42.1 3 = 15.8	26.3	NR	5.1	21.9	21.1 5.3
	NRG-GY002	II	26	Persistent, recurrent, or metastatic disease; progression after 1 prior line of CT	SCC = 60 ADK = 24 ADSC = 16	92	—	CPS ≥1 = 77.3	1 = 100	4	3.8	3.5	14.5	32 —
Balstilimab	NCT03104699	II	161	Metastatic, persistent, or recurrent disease; after a first line	SCC = 62.7 ADK = 32.3 ADSC = 4.3	—	29.2	CPS ≥1 = 61.5	1 = 100	All = 15 SCC = 17.6 ADK = 12.5 PD-L1+ = 20 PD-L1− = 7.9	15.4	NE	NE	11.8 4.3
Cemiplimab	EMPOWER-Cervical 1/ GOG-3016/ ENGOT-cx9	III	Cemiplimab arm = 304 CT arm = 304	Recurrent and metastatic resistant to platinum-based CT ≥2 lines	SCC = 77.8 ADK = 19.1 ADSC = 3.1	—	48.7	Cemiplimab arm/CT arm TC = 41.4/42.1	1 = 56.9 >1 = 42.6	Cemiplimab arm/CT arm (all) 16.4/6.3	Cemiplimab arm/CT arm (all) 16.9/6.9	All = 2.8	All = 12	Cemiplimab arm/CT arm 45/53.4 8.7/5.2
Ipilimumab	NCT01693783	I/II	42	Metastatic disease; progression after at least 1 line of platinum CT	SCC = 69 ADK = 31	83	—	PD-L1+ = 19	2 or 3 = 50	8.8	NE	2.5	8.5	28.5 —

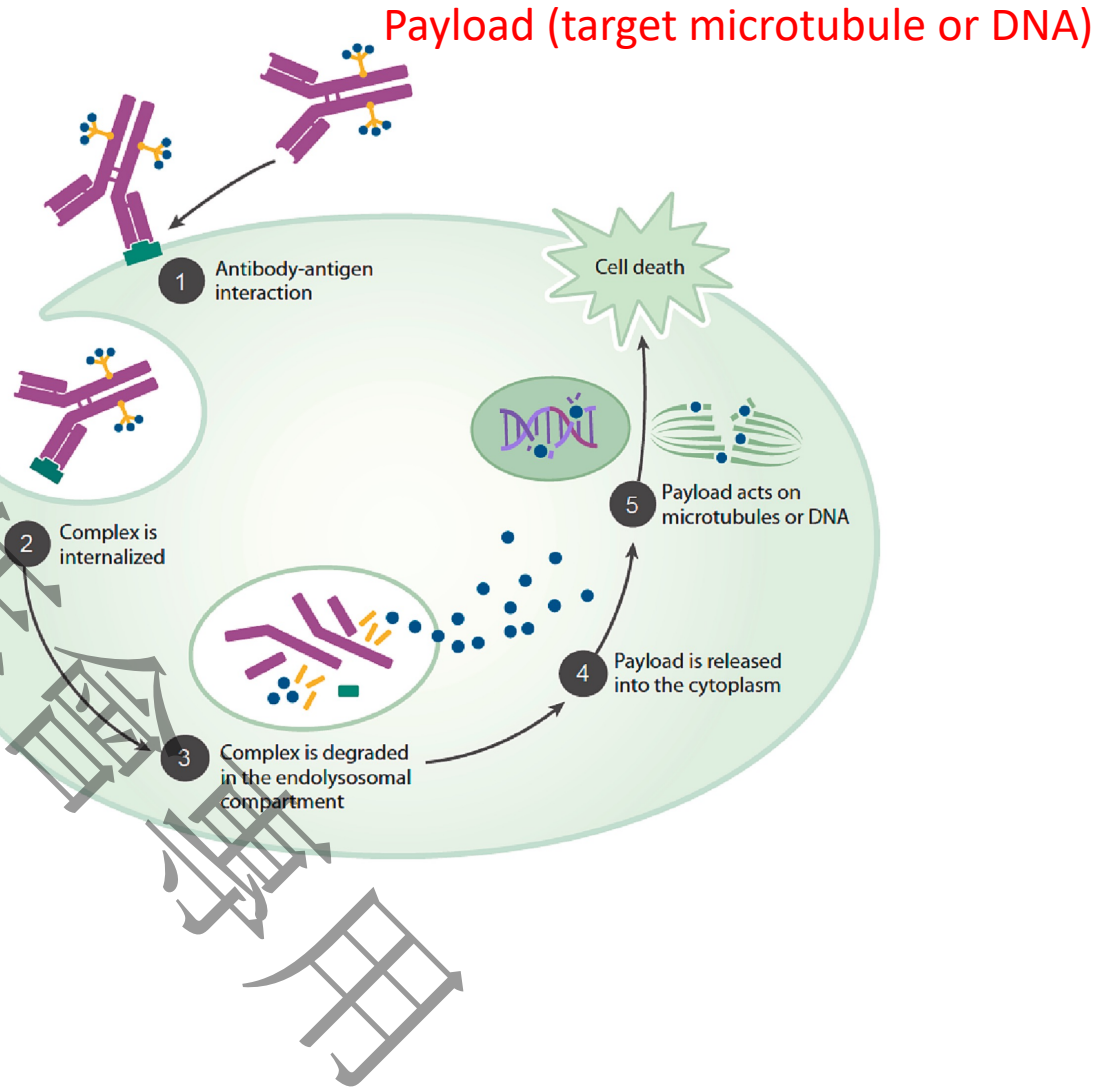
2023 ESMO OPEN

Milestones in the treatment of cervical cancer with anti-PD-1



Antibody-drug conjugates (ADCs)

- More precise drug delivery by using antibody-antigen interactions to specifically release cytotoxic agents directly to tumor cells and/or the tumor microenvironment
- May have the potential to improve clinical efficacy while minimizing toxicity



Cancer Treat Rev. 2023 May:116:102546.

ADCs approved in gynecologic malignancies

ADCs currently approved in oncology in the United States and the European Union.

ADC	Target Antigen	mAb	Linker	Payload	Indication	Approval
Tisotumab vedotin (Tivdak®)	Tissue factor	IgG1	Val-Cit	MMAE	Recurrent or metastatic cervical cancer	FDA: September 2021
Brentuximab vedotin (Adcetris®)	CD30	Chimeric IgG1	Val-Cit	MMAE	Relapsed/refractory and previously untreated stage III/IV Hodgkin lymphoma Relapsed/refractory and untreated systemic anaplastic large cell lymphoma	FDA: August 2011 EMA: October 2012
Trastuzumab emtansine (Kadcyla®)	HER2	IgG1k	MCC	DM1	Metastatic HER2-positive breast cancer	FDA: February 2013 EMA: November 2013
Inotuzumab ozogamicin (Besponsa®)	CD22	IgG4	Cleavable acid-labile acetyl butyrate	Calicheamicin	Relapsed/refractory B-cell acute lymphoblastic lymphoma	FDA: August 2017 EMA: June 2017
Gemtuzumab ozogamicin (Mylotarg®)	CD33	IgG4 k	Cleavable acid-labile acetyl butyrate	Calicheamicin	CD33-positive acute myeloid leukemia	FDA: September 2017 EMA: April 2018
Polatuzumab vedotin (Polivy®)	CD79b	IgG1	Val-Cit	MMAE	Diffuse large B-cell lymphoma	FDA: June 2019 EMA: January 2020
Enfortumab vedotin (Padcev®)	Nectin-4	IgG1 k	Val-Cit	MMAE	Locally advanced/metastatic urothelial cancer	FDA: December 2019 EMA: April 2022
Trastuzumab deruxtecan (Enhertu®)	HER2	IgG1	Maleimide-GGFG	DXd	Unresectable/metastatic HER2-positive and HER2-low breast cancer; unresectable/ metastatic non-small cell lung cancer	FDA: December 2019 EMA: January 2021
Sacituzumab govitecan (Trodelvy®)	Trop-2	IgG1 k	CL2A	SN-38	Unresectable/metastatic triple negative breast cancer	FDA: April 2020 EMA: November 2021
Belantamab mafodotin (Blenrep®)	BCMA	IgG1	MC	MMAF	Relapsed or refractory multiple myeloma	FDA: August 2020 then withdrawn[a] EMA: August 2020
Loncastuximab tesirine (Zynlonta®)	CD19	IgG1 k	Val-Ala	SG3199/PBD dimer	Relapsed/refractory large B-cell lymphoma, diffuse large B-cell lymphoma	FDA: April 2021
Mirvetuximab soravtansine (Elahere™)	FRα	IgG1	Sulfo-SPDB cleavable linker	DM4	FRα-positive platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer	FDA: November 2022

Cervical cancer: 1st

Ovarian cancer: 2nd

Cancer Treat Rev. 2023 May:116:102546.

Tisotumab vedotin

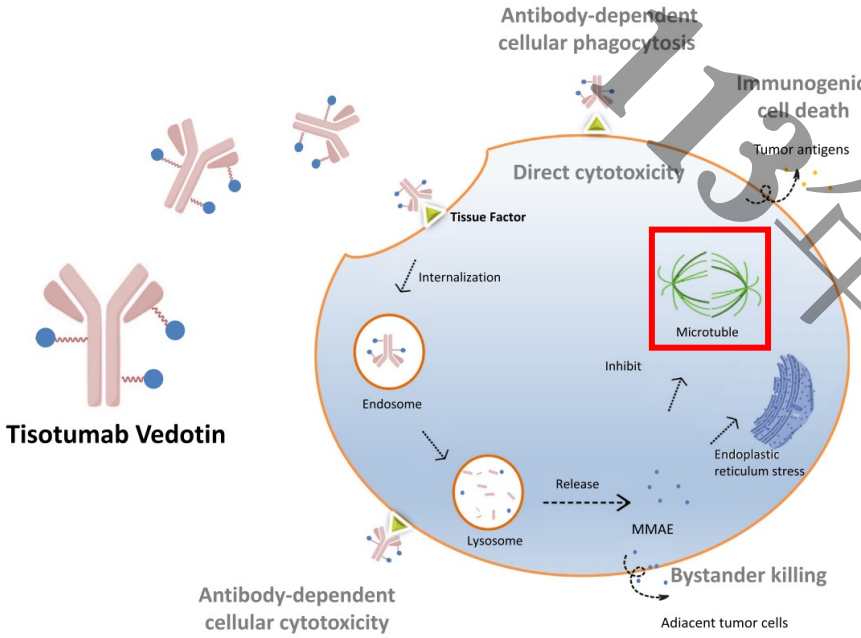
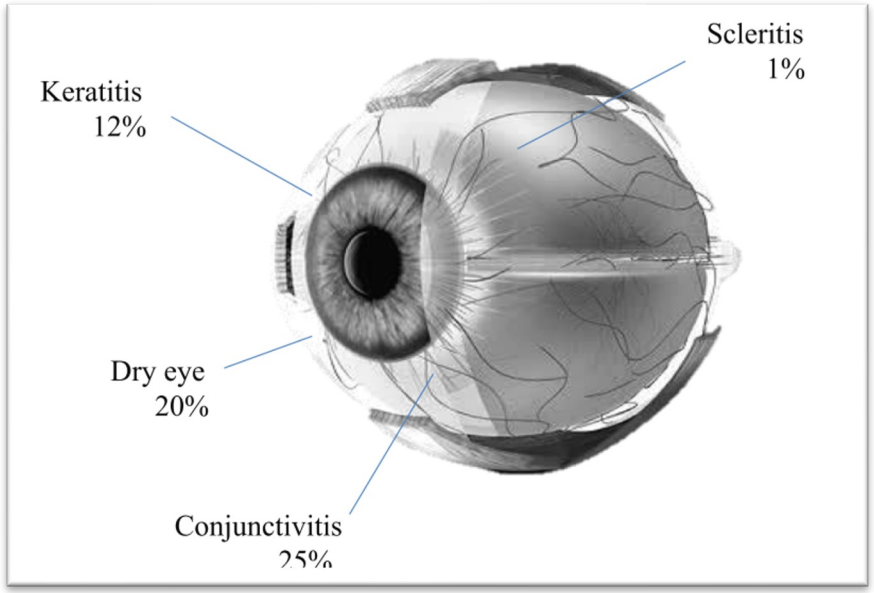


Fig. 1. Mechanism of action of tisotumab vedotin.



	KEYNOTE-158[9]	EMPOWER-cervical 1[10]		InnovaTV-204[14]
Study details	Phase II	Phase III		Phase II
Number of patients receiving experimental drug	98	304		101
Drug	Pembrolizumab	Cemiplimab		Tisotumab vedotin
Mechanism of action	PD-1 inhibitor	PD-1 inhibitor		ADC
Patients received 2 + previous lines of therapies	64 (65.3%)	124 (40.8%)		30 (30%)
Median (range) follow-up	10.2 (0.6, 22.7) mo	18.2 (6, 38.2) mo		10 (6.1, 13) mo
Response rate				
Complete response	3 (3.1%)	10 (3.3%)		7 (7%)
Partial response	9 (9.2%)	40 (13.2%)		17 (17%)
Stable disease	18 (18.4%)	125 (41.1%)		49 (49%)
Progressive disease	55 (56.1%)	105 (34.5%)		24 (24%)
Unknown	13 (13.2%)	24 (7.9%)		4 (4%)
Objective response rate	12.2% (95%CI: 6.5 - 20.4)	16.4% (95%CI: 12.5 - 21.1)	ORR	24% (95%CI: 16 - 33)
Objective response rate in PD-L1 positive (>1%)	14.6% (95%CI: 7.8 - 24.2)	18% (95%CI: 11 - 28)		/
Objective response rate in PD-L1 negative	0% (95%CI: 0 - 21.8)	11% (95%CI: 4 - 25)		/
Disease control rate	30 (95%CI: 21.7 - 40.7)	57.5% (95%CI: NR)	DCR	72% (95%CI: 63-81)
Median progression-free survival	2.1 mo	2.8 mo		4.2 mo
6-mo progression-free survival	25%	NR		30%
Median overall survival	9.4 mo	12 mo	OS	12.1 mo
12-mo overall survival	41.4%	NR		51%
Median (range) time to response	2.1 (1.6, 4.1)	2.7 (1.2, 11.4)		1.4 (1.3, 1.5)
Patients experiencing severe adverse events (grade 3 or worse)	12.2%	45%		28%

MADRID 2023 ESMO congress

DESTINY-PanTumor02

Trastuzumab deruxtecan for pretreated patients with HER2-expressing solid tumors: primary analysis from the DESTINY-PanTumor02 study

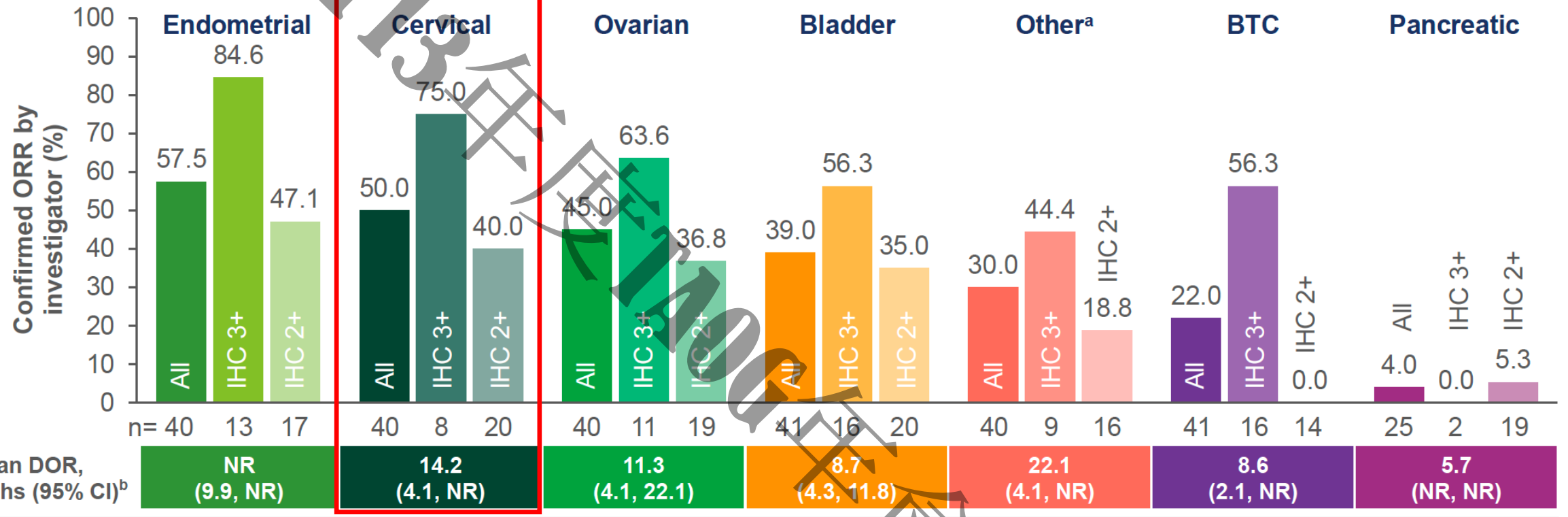
Funda Meric-Bernstam, MD;[a] Vicky Makker; Ana Oaknin; Do-Youn Oh; Susana Banerjee; Antonio González-Martín; Kyung Hae Jung; Iwona Ługowska; Luis Manso; Aránzazu Manzano; Bohuslav Melichar; Salvatore Siena; Daniil Stroyakovskiy; Anitra Fielding; Yan Ma; Soham Puvvada; Jung-Yun Lee

On behalf of the DESTINY-PanTumor02 investigators

[a]University of Texas MD Anderson Cancer Center, Houston, TX, USA

October 23, 2023 | 16:40–16:45 CEST

Objective response and duration of response



	All patients (N=267)	IHC 3+ (n=75)	IHC 2+ (n=125)
ORR, % (95% CI)	37.1 (31.3, 43.2)	61.3 (49.4, 72.4)	27.2 (19.6, 35.9)
Median DOR, months (95% CI)[b]	11.3 (9.6, 17.8)	22.1 (9.6, NR)	9.8 (4.3, 12.6)

Analysis of ORR by investigator was performed in patients who received ≥1 dose of T-DXd; all patients (n=267; including 67 patients with IHC 1+ [n=25], IHC 0 [n=30], or unknown IHC status [n=12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=75) or IHC 2+ (n=125) status. Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd; all patients (n=99; including 19 patients with IHC 1+ [n=6], IHC 0 [n=9], or unknown IHC status [n=4] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=46) or IHC 2+ (n=34) status. [a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer; [b]includes patients with a confirmed objective response only

BTC, biliary tract cancer; CI, confidence interval; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NR, not reached; ORR, objective response rate; T-DXd, trastuzumab deruxtecan

Agenda

- Background
- **Therapy by treatment setting**
  - Early stage
  - Locally advanced disease
  - Metastatic/recurrent disease
- **Future directions**
- Conclusions

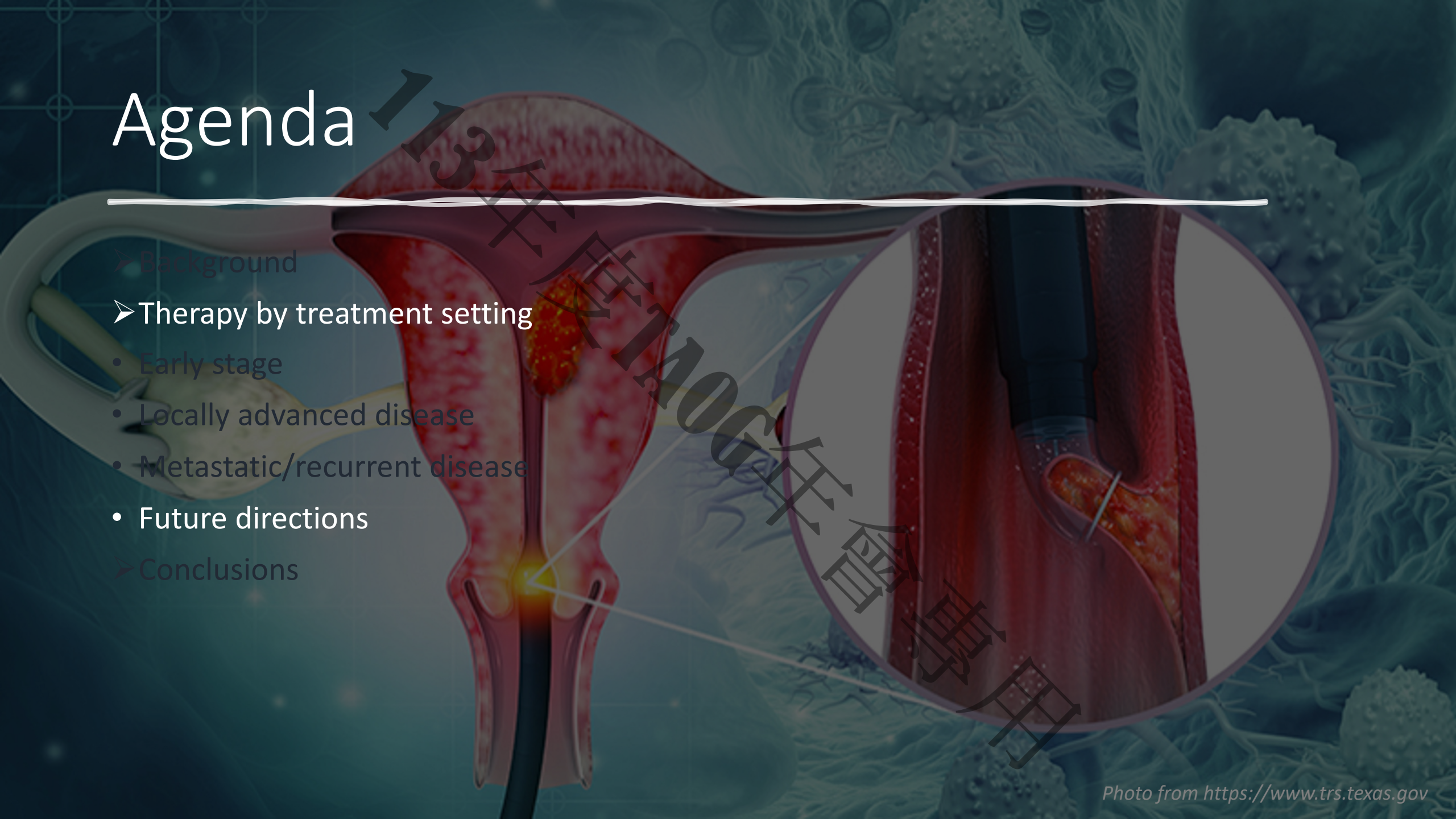


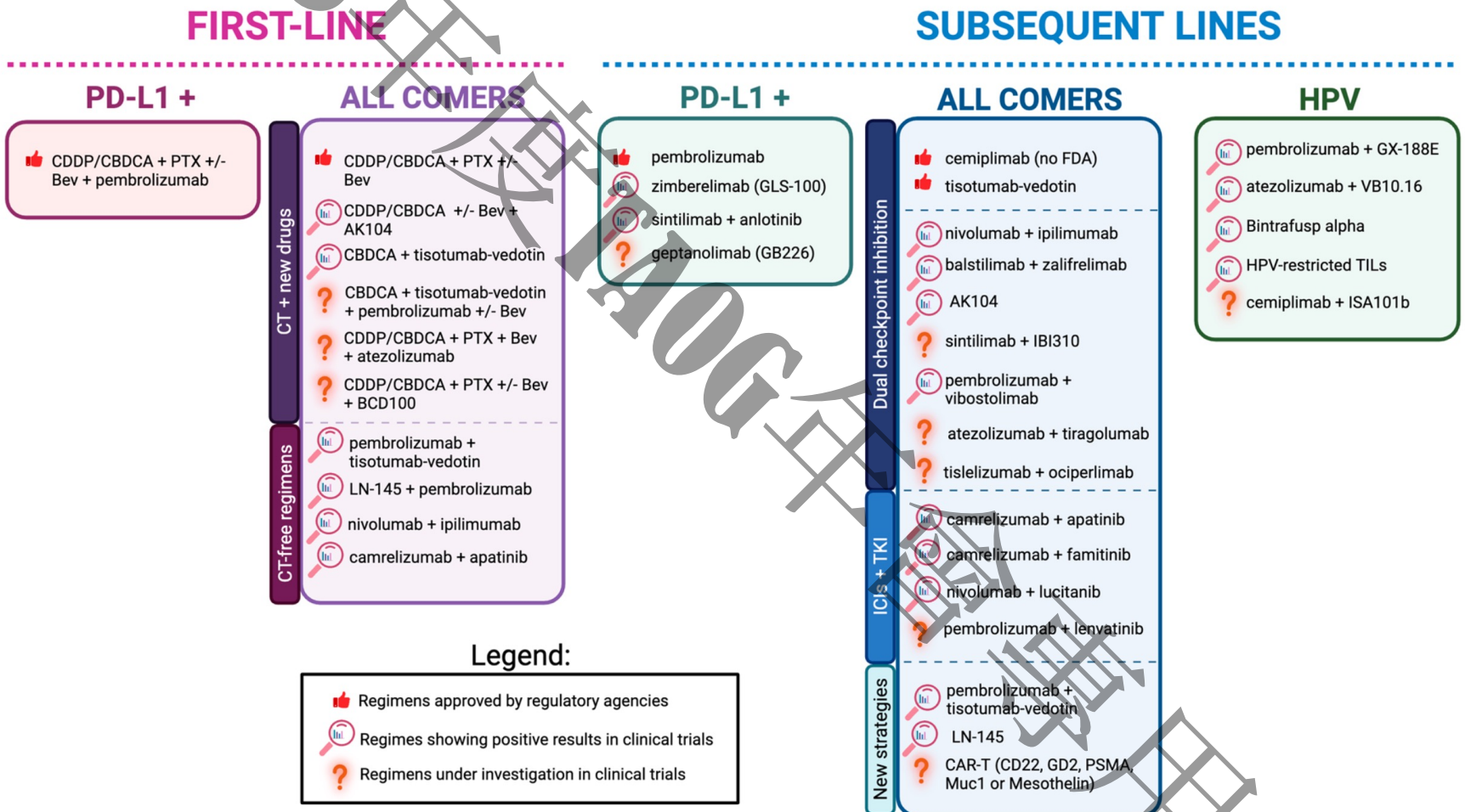
Photo from https://www.trs.texas.gov

Future directions

	Title	Study population	Phase	Treatment	Primary outcome	Secondary outcome
Advanced/ Induction	Pembrolizumab and Chemoradiation Treatment for Advanced Cervical Cancer [NCT02635360]	Locally advanced cervical cancer	II	Pembrolizumab with CRT	Change in immunologic markers, DLT	Metabolic response rate on PET/CT, incidence of distant metastasis, PFS, OS
	TSR-042 (Dostralimab) as Maintenance Therapy for Patients With High-risk Locally Advanced Cervical Cancer After Chemo-radiation (ATOMICC) [NCT03833479]	Stage IB/IIA/IIB/III/IVA cervical cancer with pelvic and PALNs	II	CRT, maintenance dostarlimab	PFS	AE, OS
	Atezolizumab Before and/or With Chemoradiotherapy in Immune System Activation in Patients with Node Positive Stage IB2, II, IIB, or IVA Cervical Cancer [NCT03738228]	Stage IB/II cervical cancer with PALNs or IIB/III/IVA cervical cancer with pelvic or para-aortic lymph nodes	I	Atezolizumab with CRT, atezolizumab before CRT	DLT	DFS, AE, ORR, PFS
	Trial Assessing the Inhibitor of Programmed Cell Death Ligand 1 (PD-L1) Immune Checkpoint Atezolizumab (ATEZOLACC) [NCT03612791]	Locally advanced cervical cancer	II	Atezolizumab with CRT and adjuvant atezolizumab	PFS	
	Nivolumab-ipilimumab and Chemoradiation for Cervical Cancer [NCT05492123]	Stage IB2-IB3 with positive nodes, or stage IIB-IVA	II	Nivolumab/ipilimumab induction with CRT	PFS	ORR, OS, HRQOL, AE, DOR
Recurrent/ Metastatic	Platinum Chemotherapy Plus Paclitaxel With Bevacizumab and Atezolizumab in Metastatic Carcinoma of the Cervix (BEATcc) [NCT03556839]	Metastatic/persistent/-recurrent	III	Platinum/taxane/-bevacizumab+/−atezolizumab	PFS, OS	ORR, DOR, AE, FST, PFS, HRQOL
	Efficacy and Safety of BCD-100 (Anti-PD-1) in Combination With Platinum-Based Chemotherapy With and Without Bevacizumab as First-Line Treatment of Subjects with Advanced Cervical Cancer (FERMATA) [NCT03912415]	Metastatic/persistent/-recurrent	III	BCD-100 (anti-PD-1) + platinum/taxane +/− bevacizumab	OS	PFS, ORR, DCR, TTR, DOR
	Niraparib in Combination With Dostarlimab in Patients With Recurrent or Progressive Cervix Cancer (STAR) [NCT04068753]	Recurrent/progressive	II	Niraparib + dostarlimab	Proportion of patients with response	AE, DOR, PFS, OS
	Niraparib Combined With Brivanib or Toripalimab in Patients With Cervical Cancer (CQGOG0101) [NCT04395612]	Recurrent/progressive	II	Niraparib + brivanib or toripalimab	ORR	PFS, DCR
	Bevacizumab and Rucaparib in Recurrent Carcinoma of the Cervix or Endometrium (Clovis-001) [NCT03476798]	Recurrent/progressive	II	Rucaparib + bevacizumab	PFS	ORR, AE, OS
	Anti-PD-1 Independently or in Combination with Anti-CTLA-4 in Second-line Cervical Cancer (RaPiDS) [NCT03894215]	Recurrent/progressive	II	Balstilimab + zalifrelimab	ORR	DOR, AE

Gynecol Oncol 2023-11 SGO statement

PRESENT AND FUTURE TREATMENT OPTIONS FOR R/M CC PATIENTS



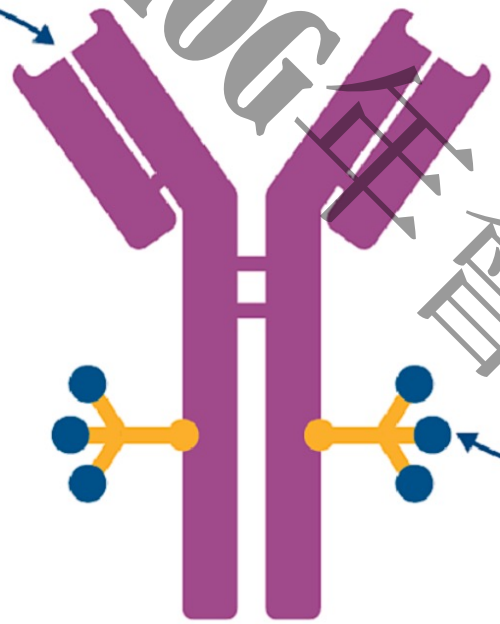
Curr Oncol Rep. 2023 Nov;25(11):1307-1326.

ADCs resistance

Mechanisms of ADC Resistance in Tumor Cells at Each Step in the ADC Mechanism of Action

Antigen binding:
- Antigen **downregulation** ↓
- Binding site **alterations** ✣

Trafficking/ADC degradation:
- **Reduced** lysosomal processing ↓
- **Increased** efflux ↑



Internalization:
- **Altered** intracellular trafficking ✣
- Altered cell-surface recycling kinetics ✣

Payload:
- **Alterations** to target ✣
- **Increased** DNA repair ↑
- Apoptotic **resistance** ↓

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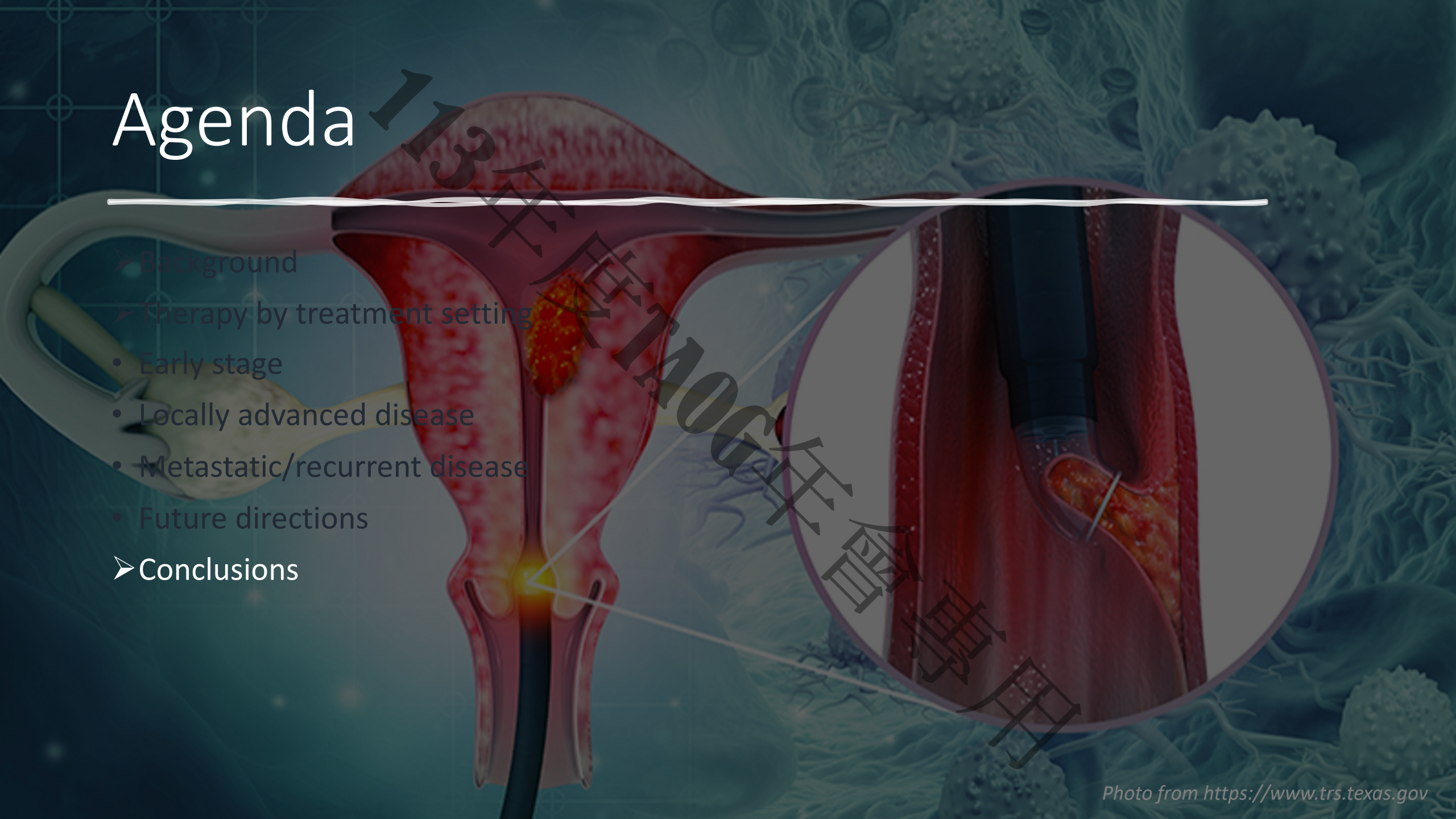

Photo from https://www.trs.texas.gov

SYSTEMIC THERAPY FOR CERVICAL CANCER[a]

Squamous Cell Carcinoma, Adenocarcinoma, or Adenosquamous Carcinoma		
Chemoradiation[b]	Recurrent or Metastatic Disease	
	First-line Therapy[b,f]	Second-line or Subsequent Therapy[j]
<u>Preferred Regimens</u> • Cisplatin[c,d,1] • Carboplatin if patient is cisplatin intolerant[c,d] <u>Other Recommended Regimens[e] (if cisplatin and carboplatin are unavailable)</u> • Capecitabine/ mitomycin[2] • Gemcitabine[3] • Paclitaxel[4,5]	<u>Preferred Regimens</u> • PD-L1–positive tumors ‣ Pembrolizumab + cisplatin/paclitaxel ± bevacizumab (category 1)[d,g,h,i,6] ‣ Pembrolizumab + carboplatin/paclitaxel ± bevacizumab (category 1)[d,g,h,i,6] • Cisplatin/paclitaxel/bevacizumab[d,g,7] (category 1) • Carboplatin/paclitaxel/bevacizumab[d,g] <u>Other Recommended Regimens</u> • Cisplatin/paclitaxel (category 1)[8,9] • Carboplatin/paclitaxel[10,11] (category 1 for patients who have received prior cisplatin therapy) • Topotecan/paclitaxel/bevacizumab[d,g,7,12] (category 1) • Topotecan/paclitaxel[12] • Cisplatin/topotecan[12] • Cisplatin[9] • Carboplatin[13,14]	<u>Preferred Regimens</u> • Pembrolizumab for TMB-H tumors[h,k] or PD-L1–positive[i] or MSI-H/dMMR tumors[h,15] • Tisotumab vedotin-tftv[16] • Cemiplimab[h,17] <u>Other Recommended Regimens</u> • Bevacizumab[g] • Paclitaxel[14,18] • Albumin-bound paclitaxel • Docetaxel • Fluorouracil • Gemcitabine • Pemetrexed • Topotecan • Vinorelbine • Irinotecan <u>Useful in Certain Circumstances</u> • PD-L1–positive tumors ‣ Nivolumab[h,i,19] • HER2-positive tumors (IHC 3+ or 2+) ‣ Fam-trastuzumab deruxtecan-nxki[20] • RET gene fusion-positive tumors ‣ Selpercatinib • *NTRK* gene fusion-positive tumors ‣ Larotrectinib ‣ Entrectinib

Quality of life, financial toxicity and disparity

謝謝聆聽