ADVANCED CERVICAL CANCER/ CURRENT TREATMENTS AND FUTURE STRATEGIES

04/12/2021

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Medical Oncology Department

INSTITUT DE CANCÉROLOGIE ARSÈNE BURNY

CHU de Liège

LOCALLY ADVANCED STAGE

IB3 - IVA

Cisplatin-based chemoradiation followed by brachytherapy

EXPERT REVIEW OF ANTICANCER THERAPY
https://doi.org/10.1080/14737140.2021.1879646

REVIEW

OPEN ACCESS Check for updates

Optimal treatment in locally advanced cervical cancer

Christine Gennigens [a], Marjolein De Cuypere[b], Johanne Hermesse[c], Frédéric Kridelka[d,^] and Guy Jerusalem [e,^]

[a]Department of Medical Oncology, CHU Liège, Liège, Belgium; [b]Department of Obstetrics and Gynecology, CHU Liège, Liège, Belgium; [c]Department of Radiotherapy, CHU Liège, Liège, Belgium; [d]Department of Obstetrics and Gynecology, CHU Liège and Liège University, Liège, Belgium; [e]Department of Medical Oncology, CHU Liège and Liège University, Liège, Belgium

Optimal treatment in locally advanced cervical cancer *(Gennigens et al., 2021)*

- « step by step » approach
- several phases
- multidisciplinary

- Around 30% of recurrence
- 5y OS = 17%

INITIAL WORKUP	• Anamnesis • Biology • Clinical examination • Biopsy (colposcopy-oriented) • Pelvic MRI • [^{18}F]FDG-PET/CT		
NODAL WORKUP	Pelvic LN [^{18}F]FDG-PET/CT status	→ Negative →	STOP
		→ Positive →	PAo LN laparoscopic
TREATMENT PHASE	OTT < 50-55 days		
	EBRT	Anamnesis IMRT or VMAT + IGRT (1.8 Gy/day; 25 days; total = 45 Gy) • With pelvic +/- PAo extended-field RT according to PAo status • With LN boost: 10-15 Gy to involved LN by sequential or simultaneous integrated	
	CHEMOTHERAPY	Anamnesis Weekly biology • Weekly cisplatin 40 mg/m^2/week X 5 cycles • If unfit for cisplatin: carboplatin AUC 2 X 5 cycles	
	BRACHYTHERAPY	• IGABT (PDR or HDR) intra-cavitary + interstitial if residual disease and/or parametrium involved • EBRT + BT = 85 Gy	
EVALUATION	First evaluation : 3 months after the end of the treatment with • Anamnesis • Biology • Clinical examination • Pelvic MRI • [^{18}F]FDG-PET/CT		

OUTBACK TRIAL

2021 ASCO ANNUAL MEETING

Adjuvant chemotherapy following chemo-radiation as primary treatment for locally advanced cervical cancer compared to chemo-radiation alone: The randomised phase 3 OUTBACK Trial (ANZGOG 0902, RTOG 1174, NRG 0274)

Linda Mileshkin*, Kathleen N Moore*, Elizabeth H Barnes, Val Gebski, Kailash Narayan, Nathan Bradshaw Yeh Chen Lee, Katrina Diamante, Anthony Fyles, William Small Jr, David K Gaffney, Pearly Khaw, Susan Brooks, Spencer Thompson, Warner Huh, Matthew J Carlson, Cara Matthews, Danny Rischin, Martin Stockler, Bradley J Monk

* Equal; first authors

6th June, 2021

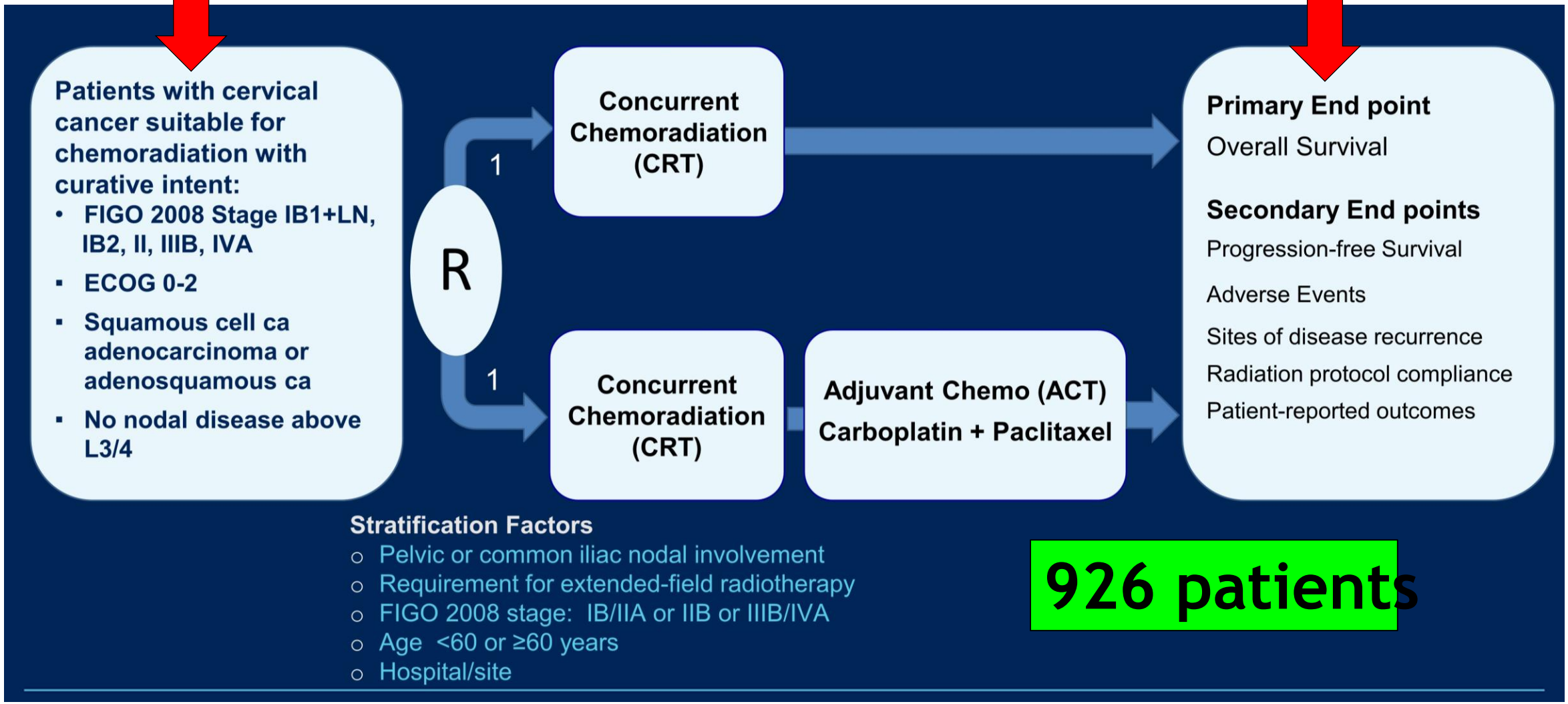
ANZ GOG

NRG ONCOLOGY
Advancing Research. Improving Lives.™

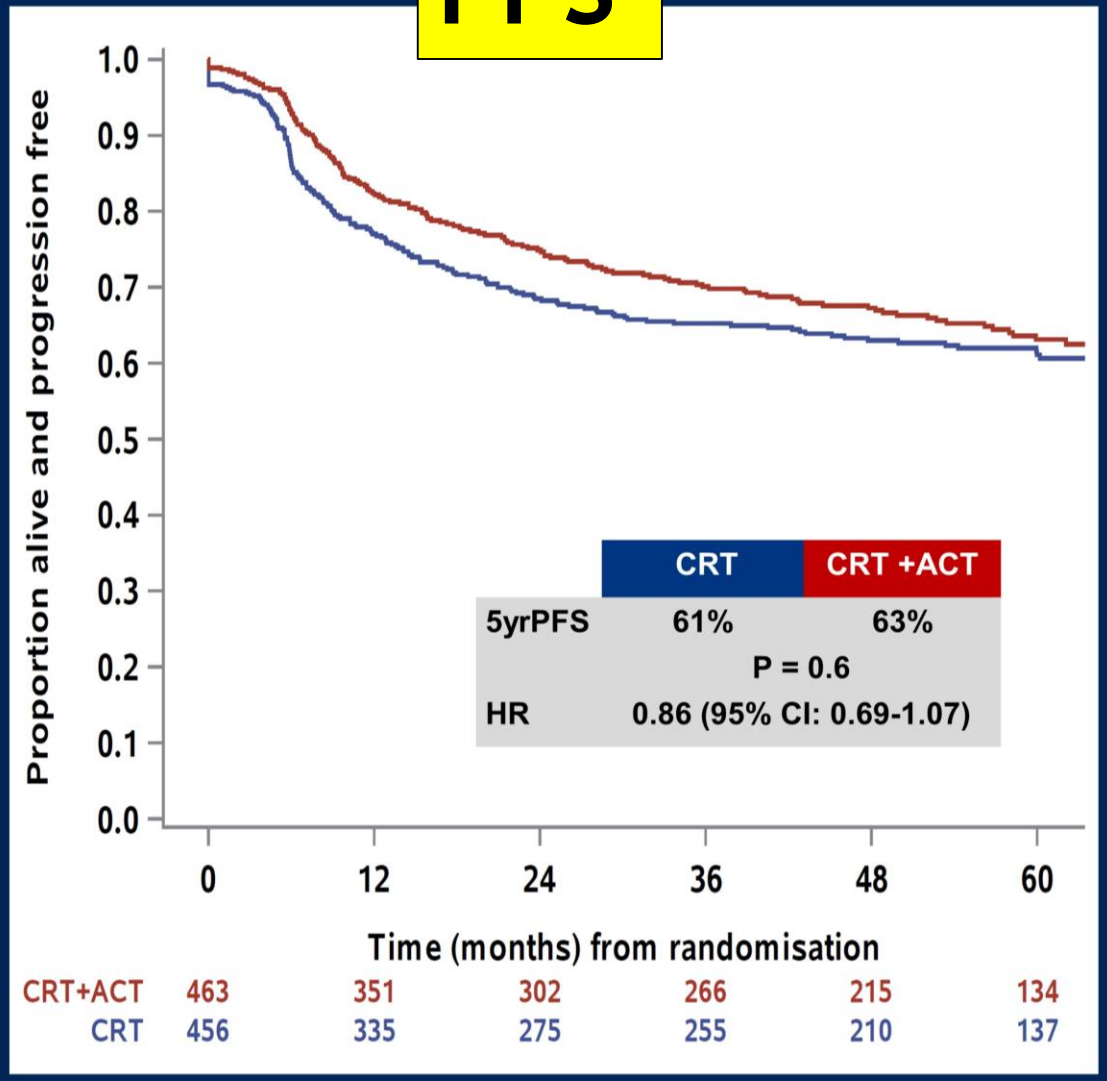
GCIG GYNECOLOGIC CANCER INTERGROUP

NHMRC Clinical Trials Centre

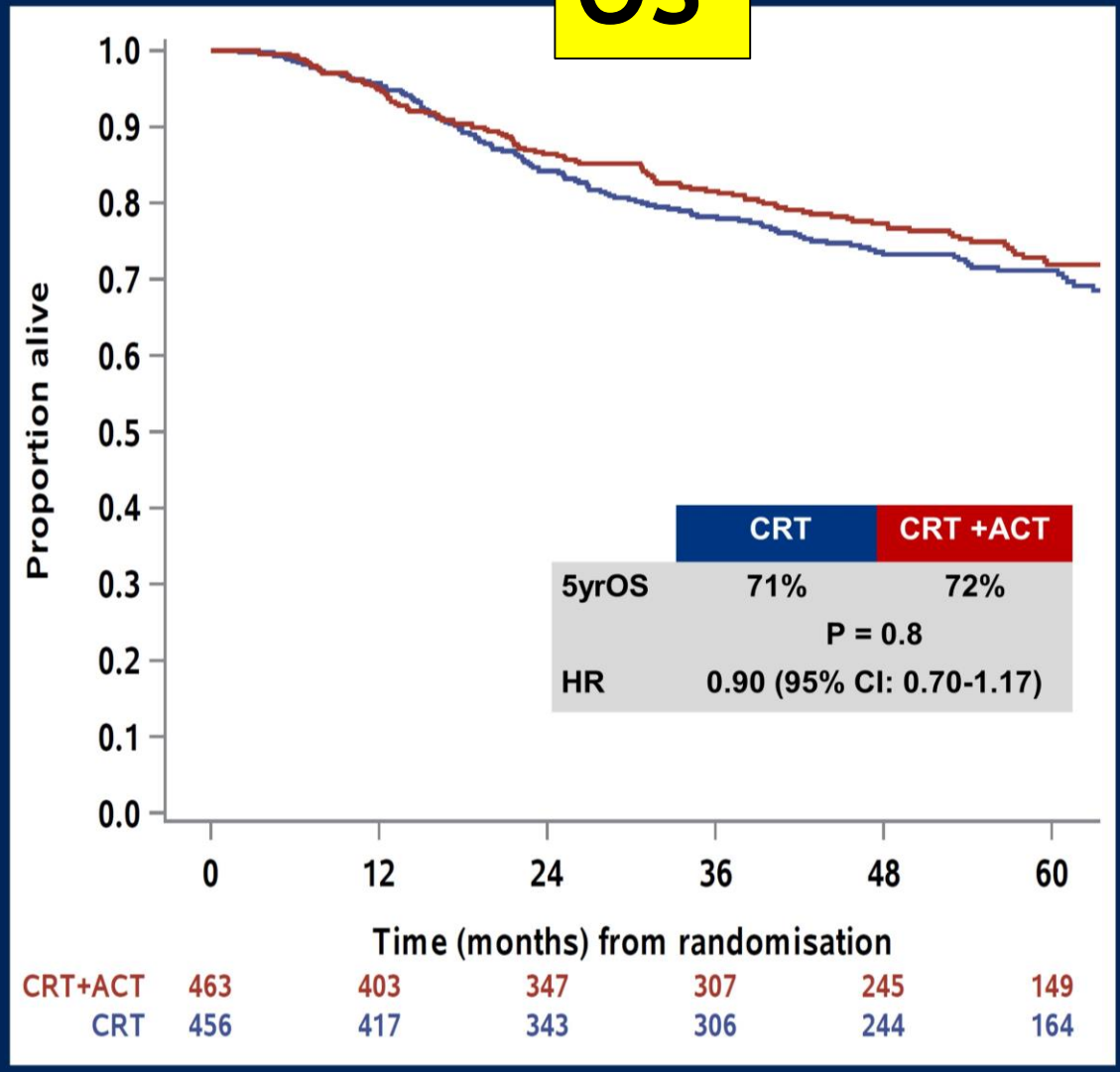
DESIGN


Patients with cervical cancer suitable for chemoradiation with curative intent:
• FIGO 2008 Stage IB1+LN, IB2, II, IIIB, IVA
▪ ECOG 0-2
▪ Squamous cell ca adenocarcinoma or adenosquamous ca
▪ No nodal disease above L3/4
R
1
1
Concurrent Chemoradiation (CRT)
Concurrent Chemoradiation (CRT)
Adjuvant Chemo (ACT)
Carboplatin + Paclitaxel
Primary End point
Overall Survival
Secondary End points
Progression-free Survival
Adverse Events
Sites of disease recurrence
Radiation protocol compliance
Patient-reported outcomes
Stratification Factors
o Pelvic or common iliac nodal involvement
o Requirement for extended-field radiotherapy
o FIGO 2008 stage: IB/IIA or IIB or IIIB/IVA
o Age <60 or ≥60 years
o Hospital/site
926 patients

PFS


Proportion alive and progression free
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
12
24
36
48
60
Time (months) from randomisation
CRT
CRT +ACT
5yrPFS
61%
63%
P = 0.6
HR
0.86 (95% CI: 0.69-1.07)
CRT+ACT 463 351 302 266 215 134
CRT 456 335 275 255 210 137

OS


Proportion alive
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
12
24
36
48
60
Time (months) from randomisation
CRT
CRT +ACT
5yrOS
71%
72%
P = 0.8
HR
0.90 (95% CI: 0.70-1.17)
CRT+ACT 463 403 347 307 245 149
CRT 456 417 343 306 244 164

RECURRENT / METASTATIC

IVB or RECURRENT

. Isolated central recurrences = pelvic exenterati
. Others = chemotherapy / unmet clinical need !!

GOG 204 TRIAL

513 pts

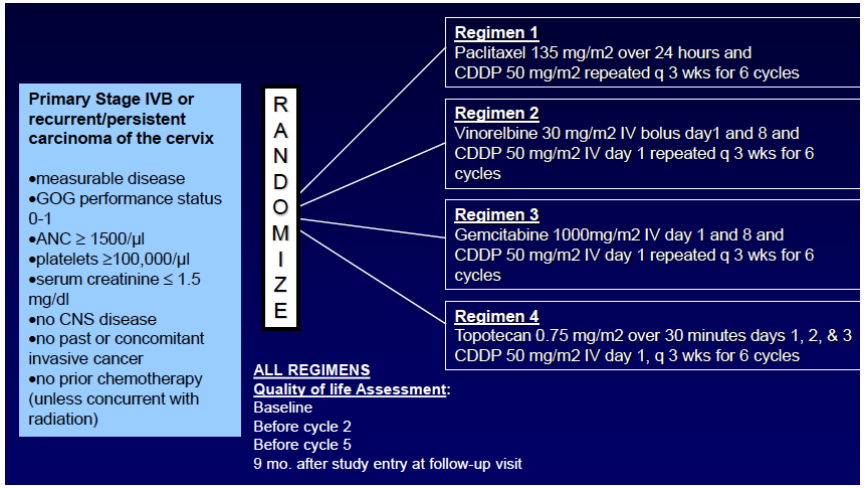
Phase III Trial of Four Cisplatin-Containing Doublet Combinations in Stage IVB, Recurrent, or Persistent Cervical Carcinoma: A Gynecologic Oncology Group Study

Bradley J. Monk, Michael W. Sill, D. Scott McMeekin, David E. Cohn, Lois M. Ramondetta, Cecelia H. Boardman, Jo Benda, and David Cella

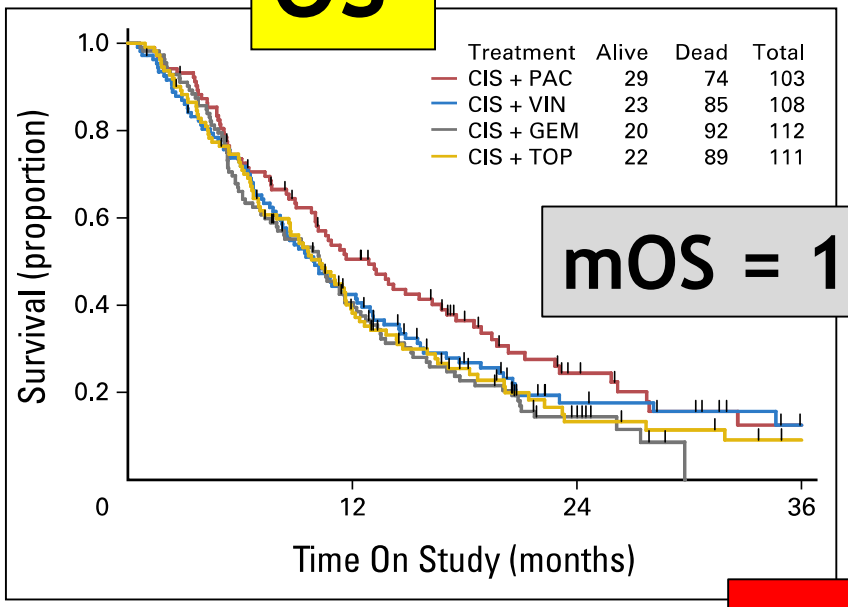
J Clin Oncol 27:4649-4655. © 2009

PHASE III

70% = prior CT-RT



OS



mOS = 12.9mths

ORR

Tumor Response	Cis+Pac No.	Cis+Pac %	Cis+Vin No.	Cis+Vin %	Cis+Gem No.	Cis+Gem %	Cis+Top No.	Cis+Top %	Total
Responders	30	29.1	28	25.9	25	22.3	26	23.4	109
Complete	[illegible]	2.9	8	7.4	1	0.9	2	1.8	14
Partial	2[illegible]	26.2	20	18.5	24	21.4	24	21.6	95
Stable disease	50	48.4	46	42.6	54	48.2	53	47.8	203
Progressive disease/ other	23	22.3	34	31.5	33	29.5	32	28.8	122
Total	103		108		112		111		434
Odds ratio*		—		1.17		1.43		1.34	
95% CI†		—		0.54 to 2.58		0.65 to 3.19		0.61 to 2.98	

CISPLATIN + PACLITAXEL

JCOG 0505 TRIAL

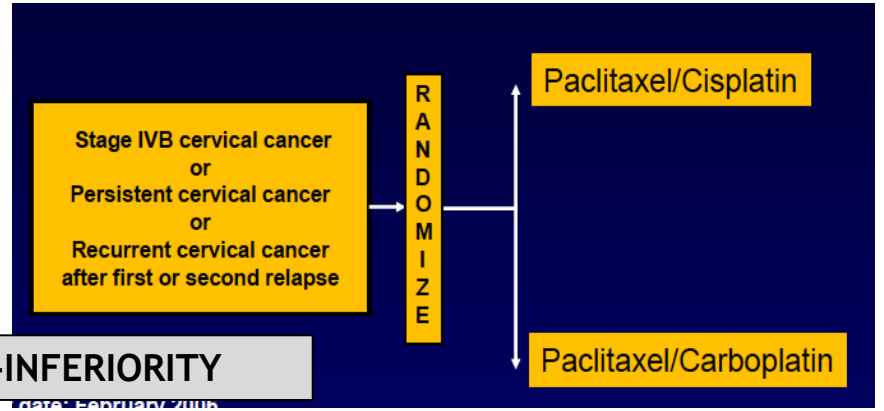
253 pts

PHASE III

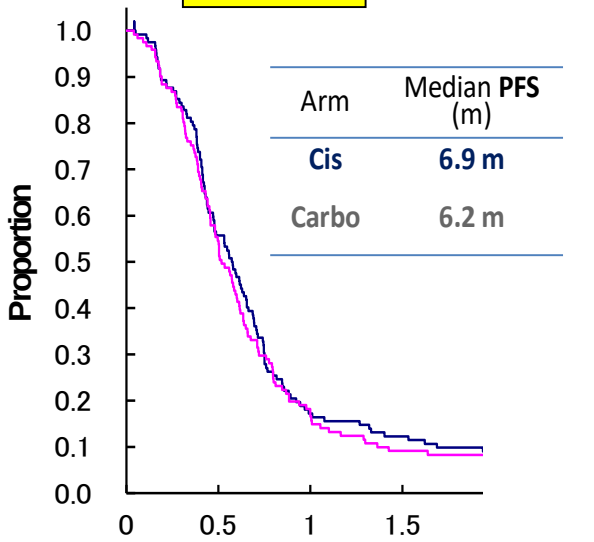
Paclitaxel Plus Carboplatin Versus Paclitaxel Plus Cisplatin in Metastatic or Recurrent Cervical Cancer: The Open-Label Randomized Phase III Trial JCOG0505

Ryo Kitagawa, Noriyuki Katsumata, Taro Shibata, Toshiharu Kamura, Takahiro Kasamatsu, Toru Nakanishi, Sadako Nishimura, Kimio Ushijima, Masashi Takano, Toyomi Satoh, and Hiroyuki Yoshikawa

J Clin Oncol 33:2129-2135. © 2015

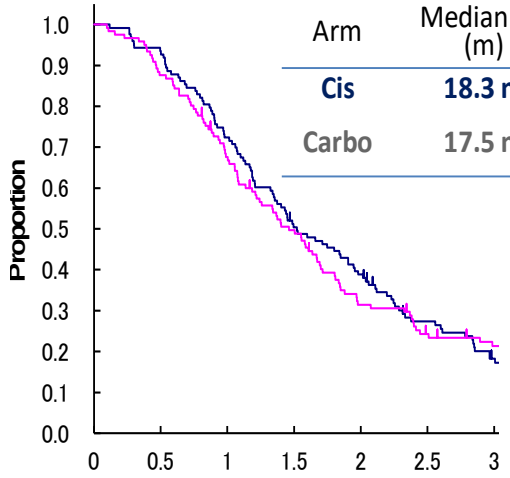


PFS



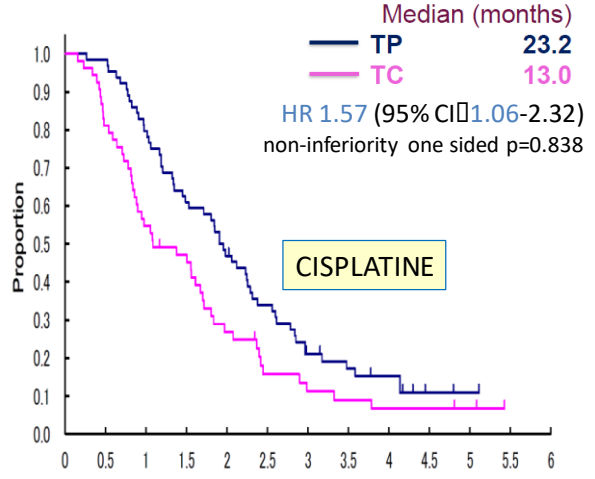
Arm	Median **PFS** (m)
Cis	6.9 m
Carbo	6.2 m

OS

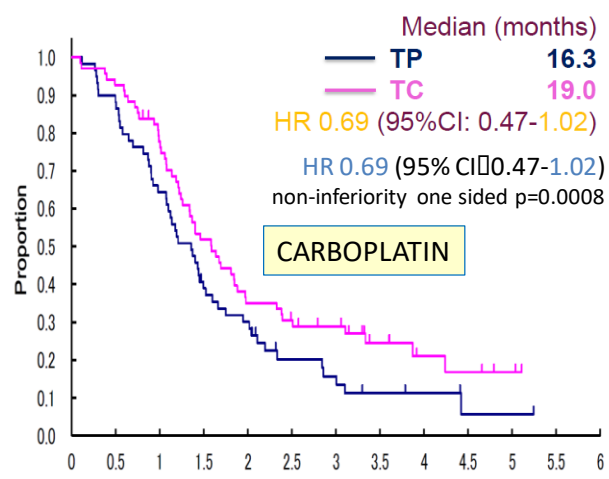


Arm	Median **OS** (m)
Cis	18.3 m
Carbo	17.5 m

No prior cisplatinum (n=117)



Prior cisplatinum (n=127)



Acquired platinum resistance in pts exposed to prior

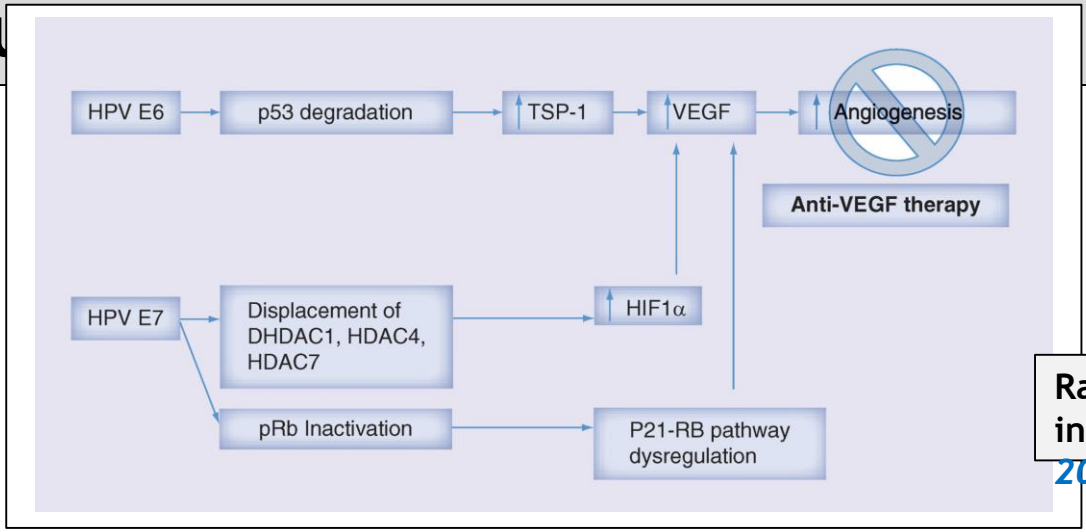
HOW TO IMPROVE BEYOND PLATINUM DOUBLETS ??

1

TARGETING ANGIOGENESIS

RATIONALE (1)

- Angiogenesis plays a central role in the development and growth of these tu



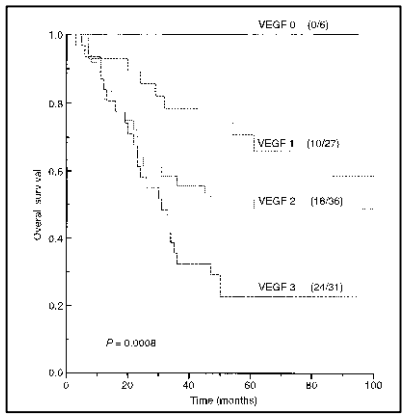
Rationale for use of angiogenesis inhibitors in CC *(Eskander and Tewari, 2015)*

- VEGF overexpression is a poor prognostic factor in CC

Vascular endothelial growth factor (VEGF) expression is a prognostic factor for radiotherapy outcome in advanced carcinoma of the cervix

JA Loncaster[1], RA Cooper[2], JP Logue[2], SE Davidson[2], RD Hunter[2] and CML West[1]

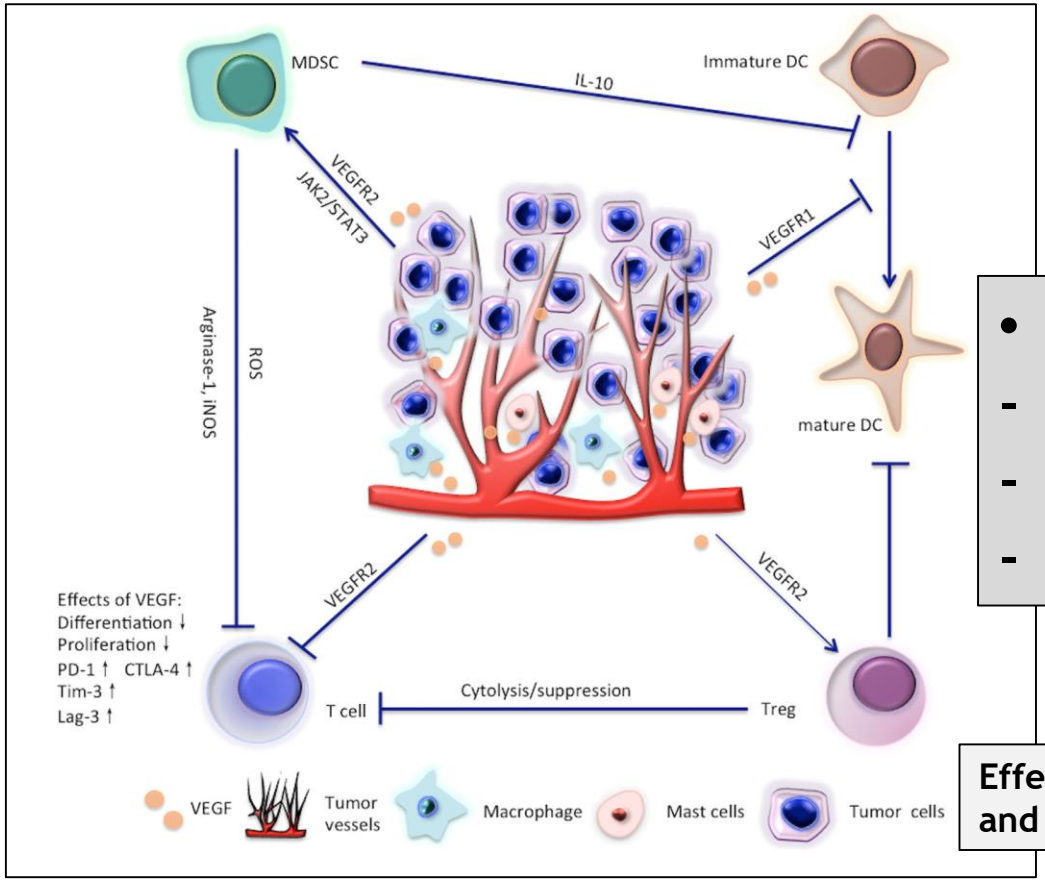
British Journal of Cancer (2000) ***83***(5), 620–625



100 pts

RATIONALE (2)

- VEGF = immunosuppressive role
- Inhibiting T^{eff}
- Increasing T^{reg} and MDSC in the TME



- Anti-VEGF therapy may modulate the TME by
- Increasing T cell trafficking
- Increasing T^{eff} to T^{reg} ratio
- Reducing suppressive cytokines

Effects of VEGF on T cells, Tregs, MDSC and DC *(Yang et al., 2018)*

GOG-240 TRIAL

452 pts

PHASE III

2014

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

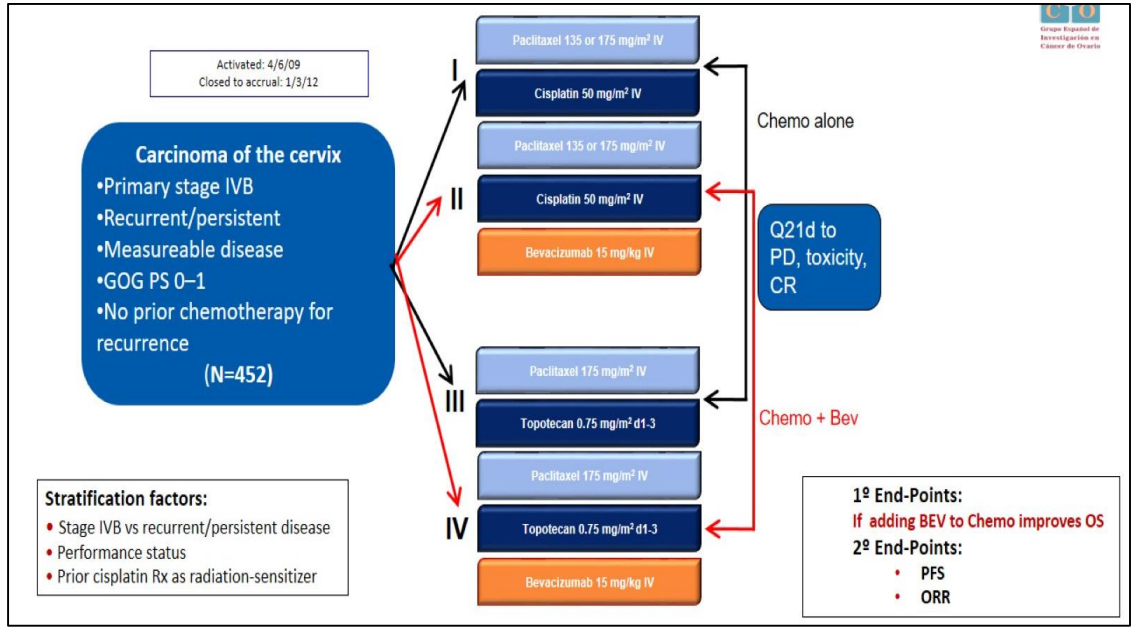
Improved Survival with Bevacizumab in Advanced Cervical Cancer

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

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

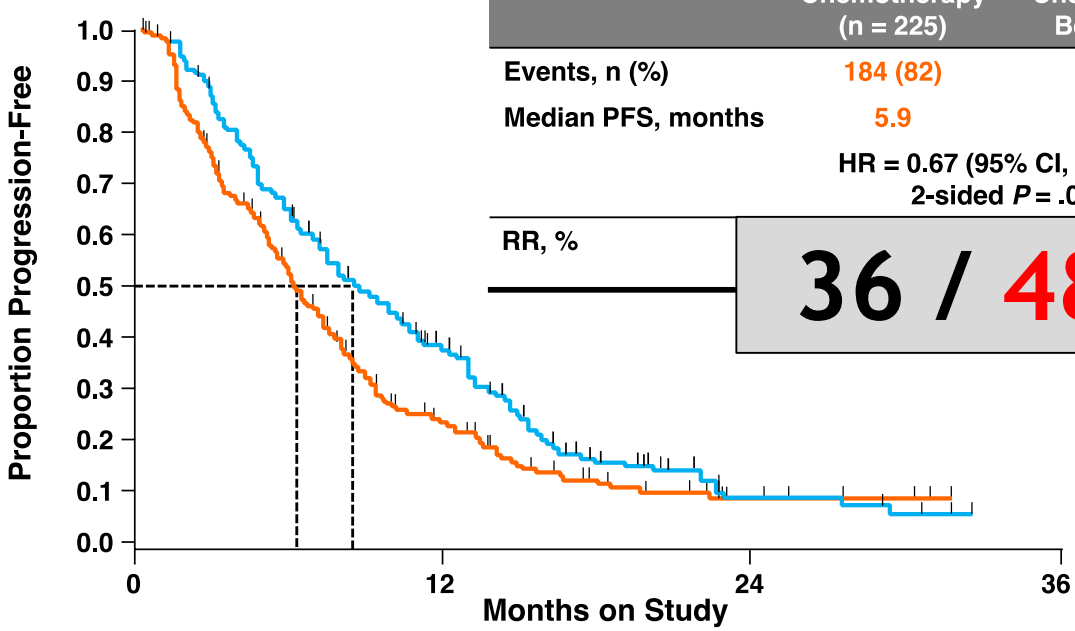
Krishnansu S Tewari, Michael W Sill, Richard T Penson, Helen Huang, Lois M Ramondetta, Lisa M Landrum, Ana Oaknin, Thomas J Reid, Mario M Leitao, Helen E Michael, Philip J DiSaia, Larry J Copeland, William T Creasman, Frederick B Stehman, Mark F Brady, Robert A Burger, J Tate Thigpen, Michael J Birrer,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

Lancet 2017



75% = prior CT with

RR

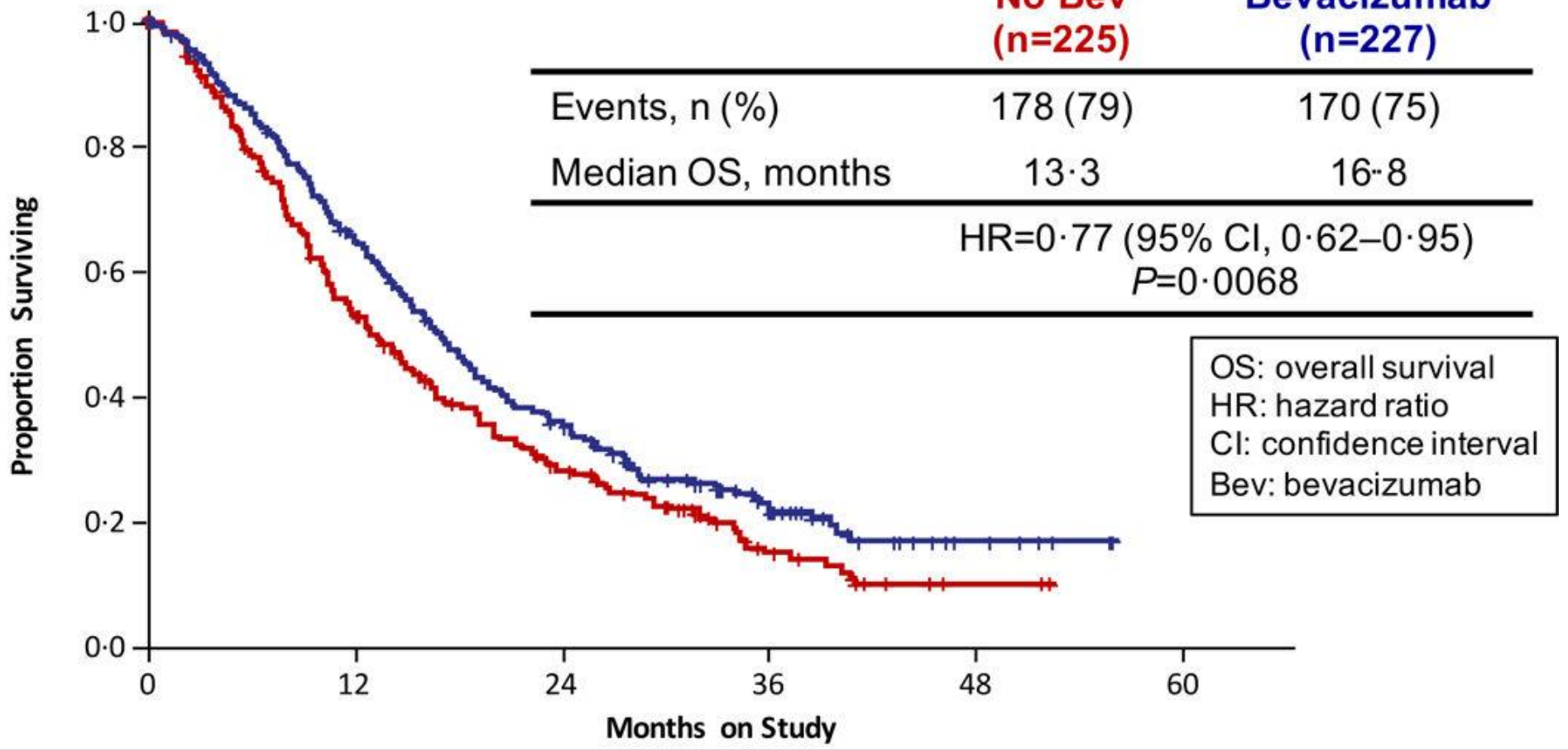


	Chemotherapy (n = 225)	Chemotherapy + Bev (n = 227)
Events, n (%)	184 (82)	183 (81)
Median PFS, months	5.9	8.2

HR = 0.67 (95% CI, 0.54-0.82)
2-sided *P* = .0002

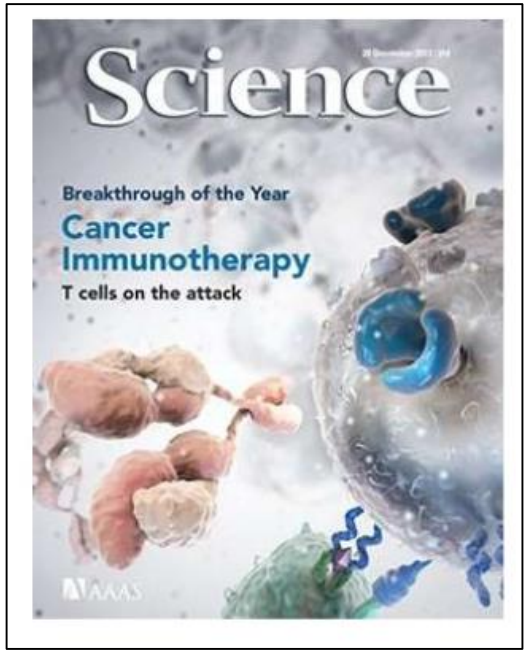
RR, % 36 / 48 %

OS = CHEMO +/- BEVA



PACLITAXEL + CISPLATIN or TOPOTECAN + BEVACIZUMAB

2 IMMUNOTHERAPY



RATIONALE (1)

- T cells play a central role in the control of viral infections and prevention of virus-associated tumors

- Nearly every case of CC is the consequence of persistent infection by oncogenic HPV high-risk subtypes (e.g. 16 and 18)

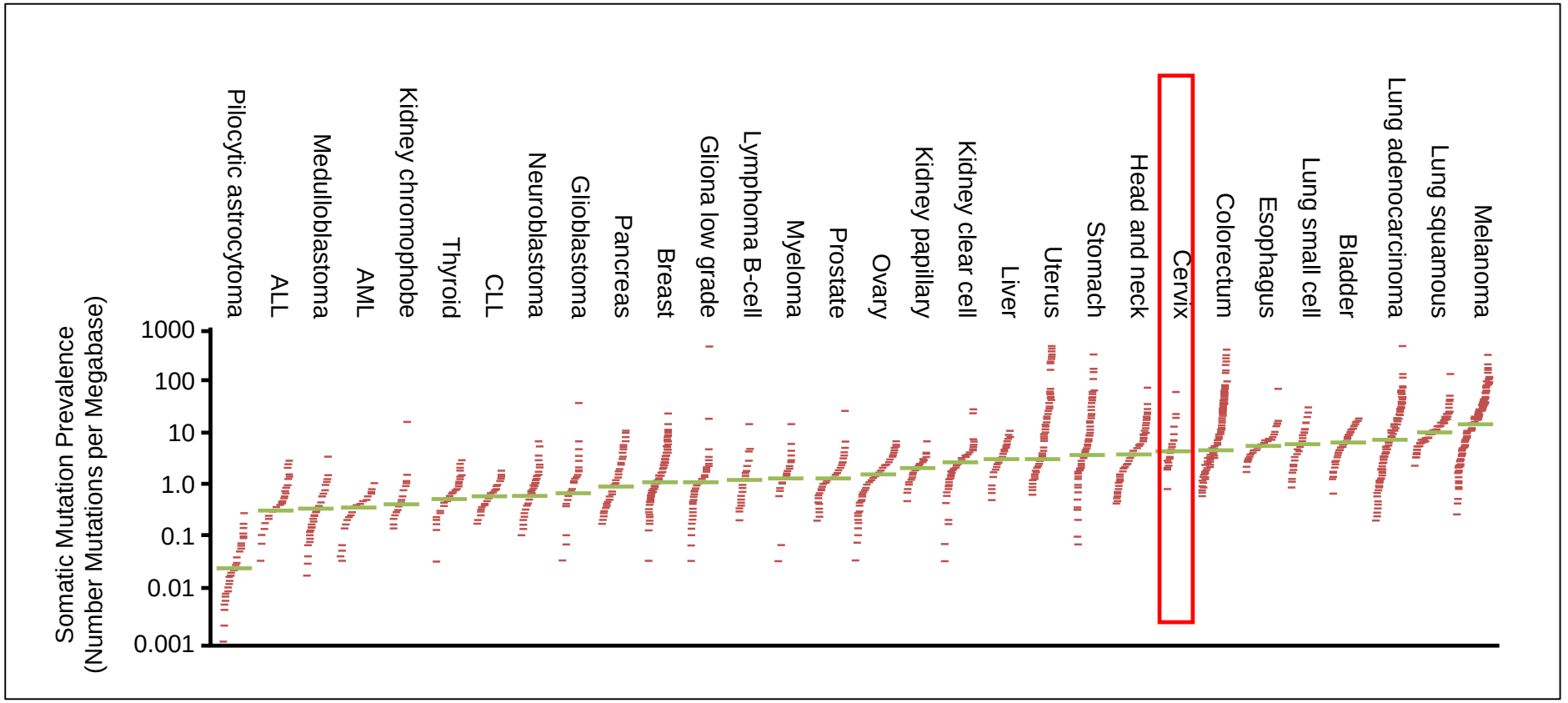
- CC expresses PD-L1 (up-regulation)
  - Normal cervical tissue = 0%
  - Squamous (SCC) = 54-80%; Adenocarcinoma (ADC) = 14%

- TME has an impact on prognosis
  - Increased TILs associated with improved survival

- CC is associated with the expression of other immune inhibitory molecules as CTLA-4 or TIM-3, …

RATIONALE (2)

- CC have an increased TMB (5-6 mutations per mega-base)



The prevalence of somatic mutations across human cancer types *(Alexandrov LB et al., 2013)*

IMMUNOTHERAPY STRATEGIES

STRATEGIES TO GENERATE AND ENHANCE CC SPECIFIC T CELLS

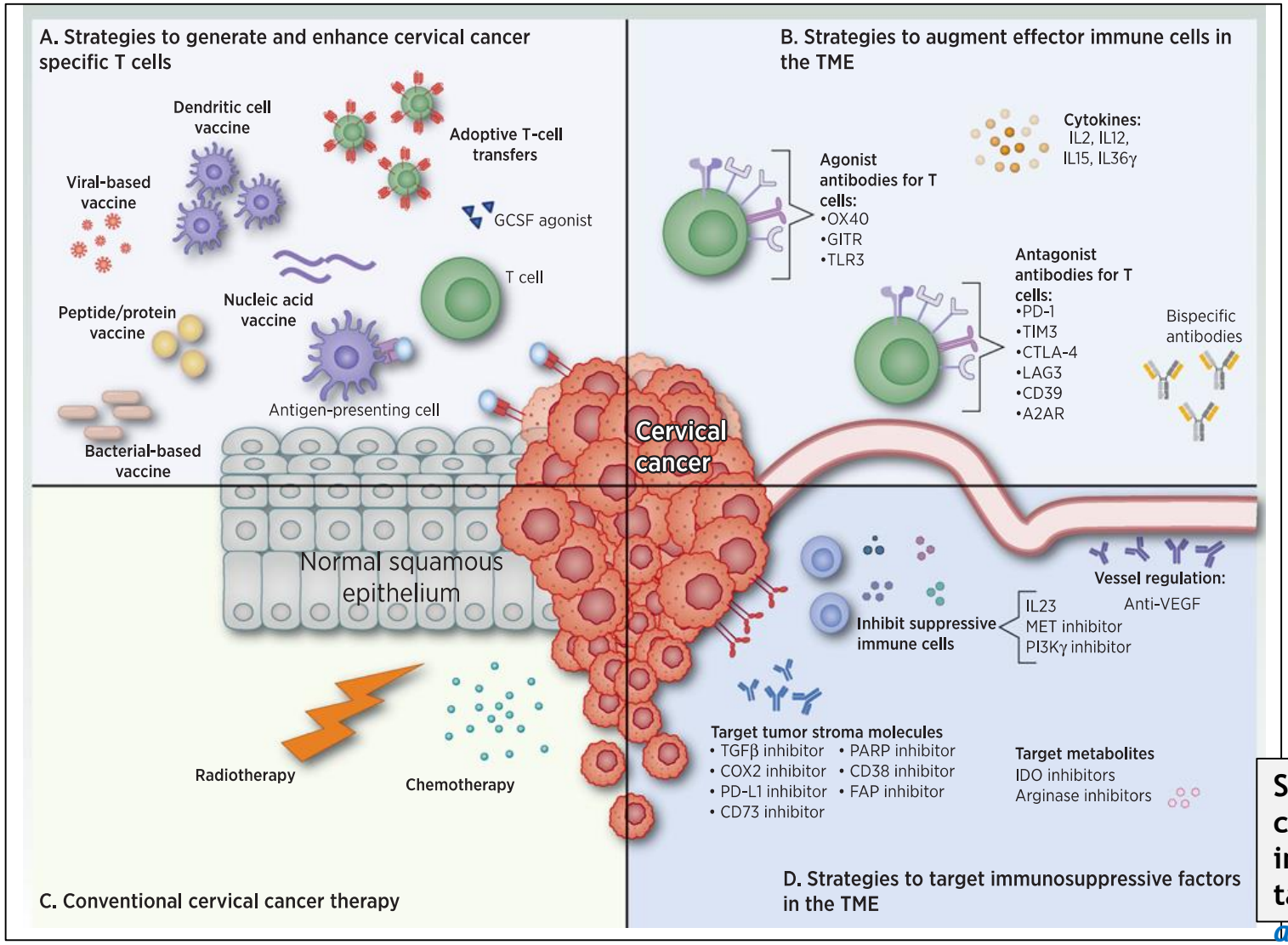
1

VACCINATION

2

ADOPTIVE TRANSFERS
TILs / CAR-T

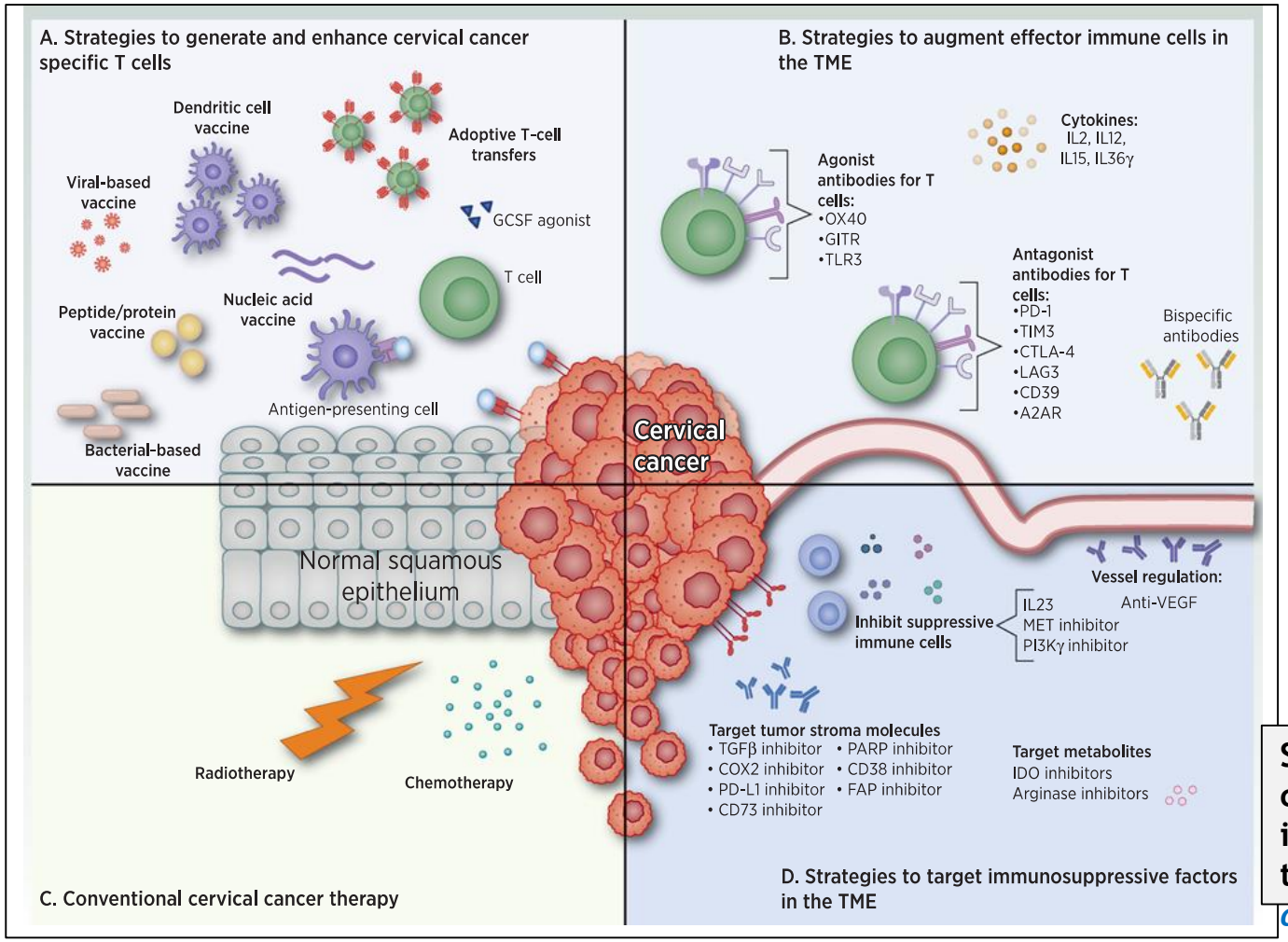
Limited data
Ongoing trials



Schematic overview of cancer immunotherapies to target CC *(Ferrall et al., 2021)*

IMMUNOTHERAPY STRATEGIES

STRATEGIES TO AUGMENT EFFECTOR IMMUNE CELLS IN THE TME



3

IMMUNE CHECKPOINT INHIBITORS (ICIs)

Schematic overview of cancer immunotherapies to target CC *(Ferrall et al., 2021)*

STRATEGIES TO TARGET IMMUNOSUPPRESSIVE FACTORS IN THE TME

ICIs ' ACTIVITY AFTER FAILURE TO PLATINUM

BEFORE ESMO 2021

STUDY	PHASE	TREATMENT	NUMBER OF PATIENTS	PATIENT POPULATION	RESULTS
MONOTHERAPY					
KEYNOTE-028	Ib	Pembrolizumab 10 mg/kg q2w x 2y	24	PD-L1+ previously treated	ORR 17% DCR 17% mPFS 2 mos mOS 11 mos
KEYNOTE-158	II	Pembrolizumab 200 mg q2w x 2y	98	Previously treated	ORR 12.2% DCR 30.6% mPFS 2.1 mos mOS 9.4 mos
CHECKMATE- 358	I-II	Nivolumab 240 mg q2w	19	Previously treated	ORR 26.3% DCR 70.8% mPFS 5.5 mos
NRG-GY002	II	Nivolumab 3 mg/kg q2w	25	Persistent or recurrent	ORR 4% DCR 38%
LHEUREUX et al.	I-II	Ipilimumab 3 mg/kg q3w x 4 cycles or Ipilimumab 10 mg/kg q3w x 4 cycles followed by maintenance q12w	42	Stage IV	ORR 2.9% DCR 32.4% mPFS 2.5 mos mOS 8.5 mos
O'MALLEY et al.	II	Balstilimab 3 mg/kg	160	Previously treated	ORR 14% DOR 15.4 mos
COMBINATIONS					
O'MALLEY et al.	II	Balstilimab 3 mg/kg + Zalifrelimab 1 mg/kg q6w	143	Previously treated	ORR 22% DOR NR
FRIEDMAN et al.	II	Atezolizumab 1200 mg q3w + Bevacizumab 15 mg/kg q3 w	10	Stage IV CC	DCR 50% mPFS 2.9 mos mOS 9 mos
NAUMAN et al.	I	COMBO A Nivolumab 3 mg/kg q2w + Ipilimumab 1mg/kg q6w	45	Not previously treated	ORR 32% mPFS 13.8 mos mOS NR
				Previously treated	ORR 36% mPFS 3.6 mos mOS 10.3 mos
		COMBO B Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg X 4 cycles followed by Nivolumab 240 mg q2w	46	Not previously treated	ORR 46% mPFS 8.5 mos mOS NR
				Previously treated	ORR 23% mPFS 5.5 mos mOS 25.4 mos

KEYNOTE-158 TRIAL

98pts (84% PD-L1+)

PHASE II

JCO 2019

original report

Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Cervical Cancer: Results From the Phase II KEYNOTE-158 Study

Hyun Cheol Chung, MD, PhD[1]; Willeke Ros, MSc[2]; Jean-Pierre Delord, MD, PhD[3]; Ruth Perets, MD, PhD[4]; Antoine Italiano, MD, PhD[5]; Ronnie Shapira-Frommer, MD[6]; Lyudmila Manzuk, MD[7]; Sarina A. Piha-Paul, MD[8]; Lei Xu, PhD[9]; Susan Zeigenfuss, RN[9]; Scott K. Pruitt, MD, PhD[9]; and Alexandra Leary, MD, PhD[10]

- **Key eligibility criteria**:
  - ECOG: 0 or 1
  - Advanced cervical **squamous carcinomas on progression or intolerance to ≥1 line of standard therapy**
- **Main Demographics and Disease Characteristics**
  - 65% ≥2 prior therapies for recurrent/metastatic CC
  - 84% PD-L1-positive; 77/98 (79%) had CPS ≥1*
- **Treatment**: **pembrolizumab 200 mg once every 3 weeks (Q3W) for 2 years** or until disease progression, intolerable toxicity, patient withdrawal, or investigator decision

*CPS(Combined Positive Score):number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the number of viable tumor cells, multiplied by 100

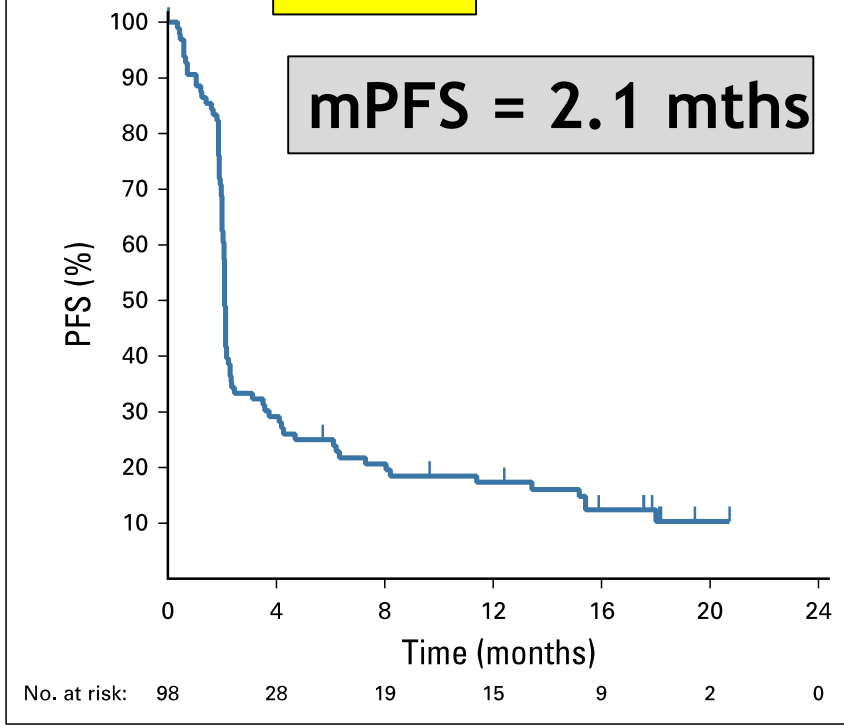
Primary endpoint: IRC-assessed ORR (RECIST v1.1)

Secondary endpoints: DoR, IRC-assessed PFS, OS, safety

ORR / DoR

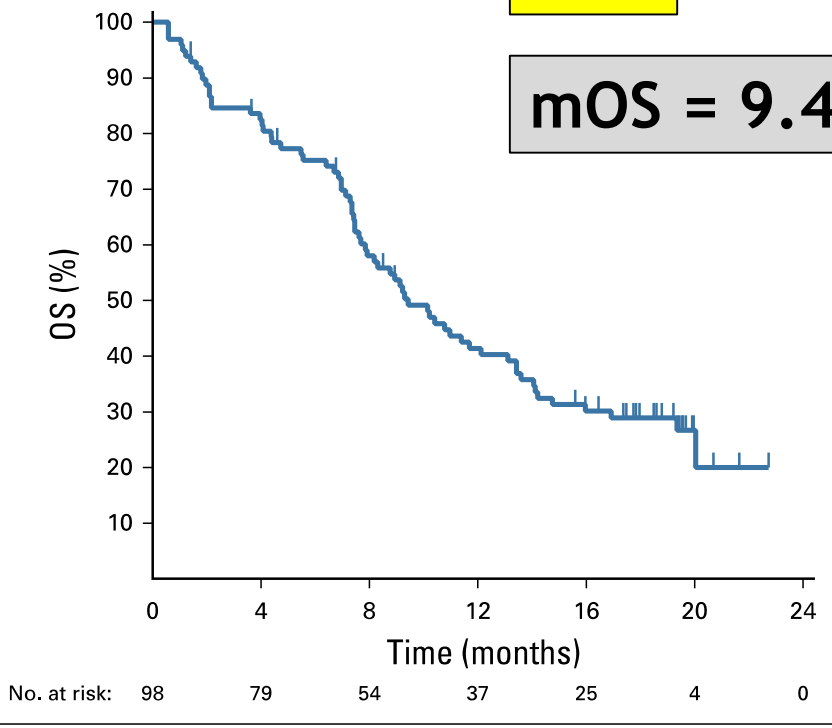
Antitumor Activity	Total Population (N = 98)*	PD-L1–Positive Population: Total (n = 82)	PD-L1–Positive Population: Previously Treated (n = 77)†	PD-L1–Negative Population (n = 15)
ORR	12 (12.2)	12 (14.6)	11 (14.3)	0 (0.0)
95% CI	6.5 to 20.4	7.8 to 24.2	7.4 to 24.1	0.0 to 21.8
DCR	30 (30.6)	27 (32.9)	24 (31.2)	3 (20.0)
95% CI	21.7 to 40.7	22.9 to 44.2	21.2 to 42.7	4.3 to 48.1
Best overall response				
CR	3 (3.1)	3 (3.7)	2 (2.6)	0 (0.0)
PR	9 (9.2)	9 (11.0)	9 (11.7)	0 (0.0)
SD	18 (18.4)	15 (18.3)	13 (16.9)	3 (20.0)
Progressive disease	55 (56.1)	44 (53.7)	42 (54.5)	10 (66.7)
Not able to be evaluated‡	5 (5.1)	4 (4.9)	4 (5.2)	1 (6.7)
Not able to be assessed§	8 (8.2)	7 (8.5)	7 (9.1)	1 (6.7)
Time to response, months‖				—
Median	2.1	2.1	2.2	
Range	1.6-4.1	1.6-4.1	1.6-4.1	
Duration of response, months‖¶				—
Median	NR	NR	NR	
Range	≥ 3.7 to ≥ 18.6	≥ 3.7 to ≥ 18.6	4.1 to ≥ 18.6	

PFS



mPFS = 2.1 mths

OS



mOS = 9.4 mths

12/06/2018

For patients with recurrent or metastatic CC with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS >=1)

ICIs ' ACTIVITY

AFTER ESMO 2021

Randomized Phase III Trial of Cemiplimab [illegible] Choice of Chemotherapy in Cervical Cancer:

ENGOT

GOG FOUNDATION, INC.

Metastatic cervical cancer resistant to platinum-based chemotherapy, [illegible] Line (N = 436) ECOG PS 0 or 1

[illegible] choice

Options:
- **Antifolate**: Pemetrexed
- **Nucleoside analogue**: Gemcitabine
- **Topisomerase 1 inhibitor**: Topotecan or Irinotecan
- **Vinca Alkaloid**: Vinorelbine

Primary Endpoint is OS

Statistical Considerations for Study Design	
Power	90%
Median Survival	7 months
Hazard Ratio	0.7
Timing of Final Analysis (Ha)	30.5 months

All treatment regimens are for up to 96 weeks, with option for retreatment

Cemiplimab

Cemiplimab 350 mg IV every 3 weeks

National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT03257267. Accessed 16 January 2018.

PI Tewari KS
Dec 11, 2018:
194 screened, 146 enrolled

PHASE III

PRACTICE CHANGING TRIALS

KEYNOTE-826

- **Untreated persistent, recurrent, or metastatic cervical**
- **Measurable disease per RECIST 1.1**
- **Available archival tumor tissue**
- **Performance status of 0 to1**
- **Adequate organ function**

1:1

Every 3 week pembrolizumab 200 mg PLUS investigator choice of chemotherapy*

Every 3 week placebo PLUS investigator choice of chemotherapy*

N = 600
57 Sites as of Jan 12, 2018

Stratification:
[illegible]

All treatments are administered until disease progression or toxicity, for up to 35 cycles (up to approximately 2 years)

*paclitaxel 175 mg/m2 PLUS cisplatin 50 mg/m2 WITH or WITHOUT bevacizumab 15 mg/kg OR paclitaxel 175 mg/m2 PLUS carboplatin AUC 5, WITH or WITHOUT bevacizumab 15 mg/kg

Primary endpoints: 1) Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) as assessed by blinded independent central review (BICR), or, 2) overall survival (OS)
Secondary endpoints: ORR, DOR, PFS, AEs, PROs

National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT03635567. Accessed 24 January 2018.

EMPOWER-CERVICAL 1 / GOG-3016 / ENGOT-cx9 TRIAL

ESMO 2021

EMPOWER GOG FOUNDATION ENGOT European Network of Gynaecological Oncological Trial groups

EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9: Results of Phase 3 trial of cemiplimab vs investigator's choice (IC) chemotherapy (chemo) in recurrent/metastatic (R/M) cervical carcinoma

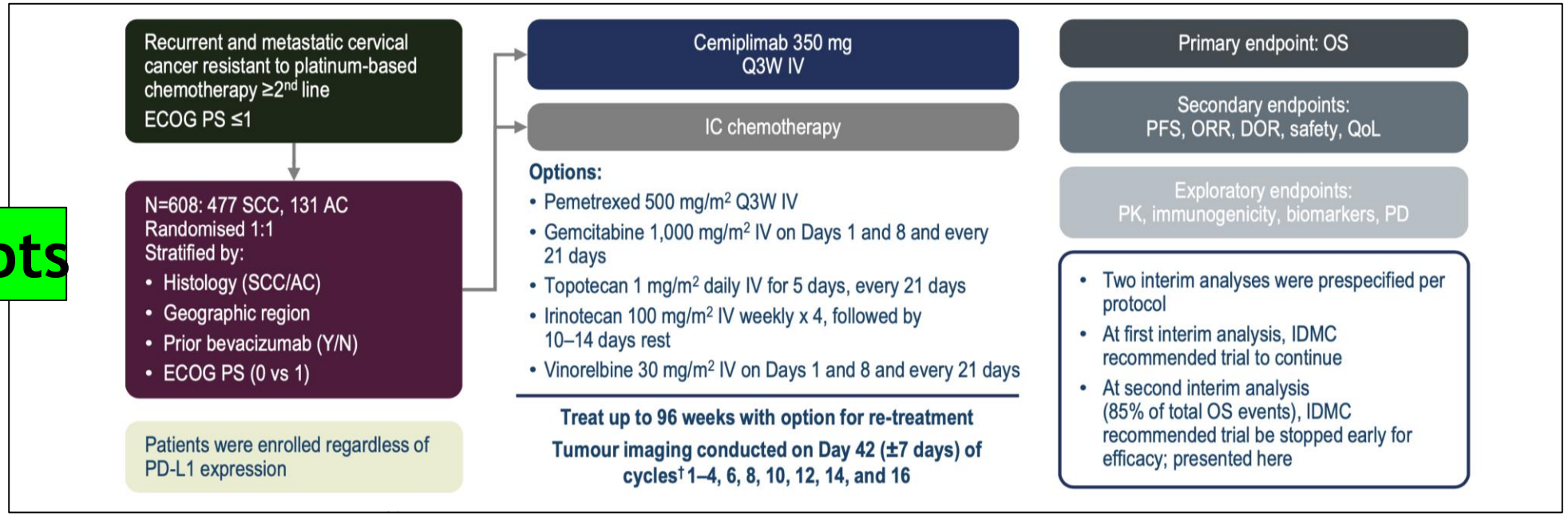
Krishnansu S Tewari,*† Bradley J Monk,* Ignace Vergote, Austin Miller, Andreia Cristina de Melo, Hee Seung Kim, Yong Man Kim, Alla Lisyanskaya, Vanessa Samouëlian, Domenica Lorusso, Fernanda Damian, Chih-Long Chang, Evgeniy A Gotovkin, Shunji Takahashi, Daniella Ramone, Joanna Pikiel, Beata Maćkowiak-Matejczyk,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

*Contributed equally to this presentation.
†Department of Obstetrics & Gynecology, University of California, Irvine.
Portions of the following were previously presented at the May 2021 ESMO Virtual Plenary.
This study (NCT03257267) was sponsored by Regeneron Pharmaceuticals, Inc. and Sanofi.

PD-1 INHIBITOR

DESIGN

608 pts



STATISTICAL ANALYSES

Hierarchical testing†

Primary endpoint

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

Secondary endpoints

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

BASELINE CHARACTERISTICS

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

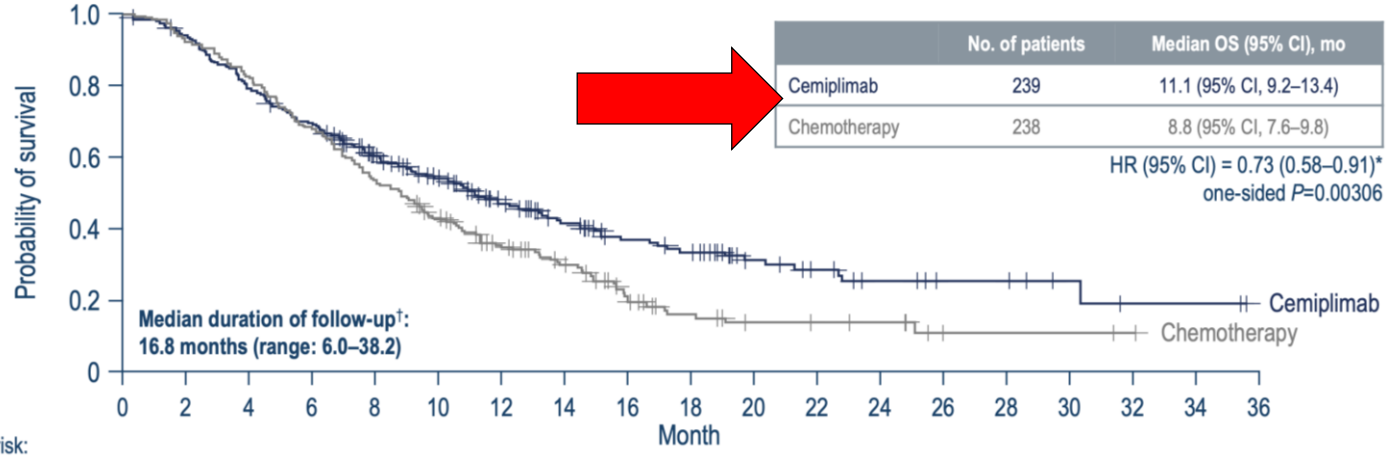
	Cemiplimab (n=304)	Chemotherapy (n=304)	Total (N=608)
Histology/cytology, n (%)			
SCC	240 (78.9)	233 (76.6)	473 (77.8)
Adenocarcinoma	54 (17.8)	62 (20.4)	116 (19.1)
Adenosquamous carcinoma	10 (3.3)	9 (3.0)	19 (3.1)
Extent of disease, n (%)			
Metastatic	284 (93.4)	290 (95.4)	574 (94.4)
Recurrent/persistent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

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

Rate of prior chemoradiation not reported

SURVIVAL FOR SCC POPULATION

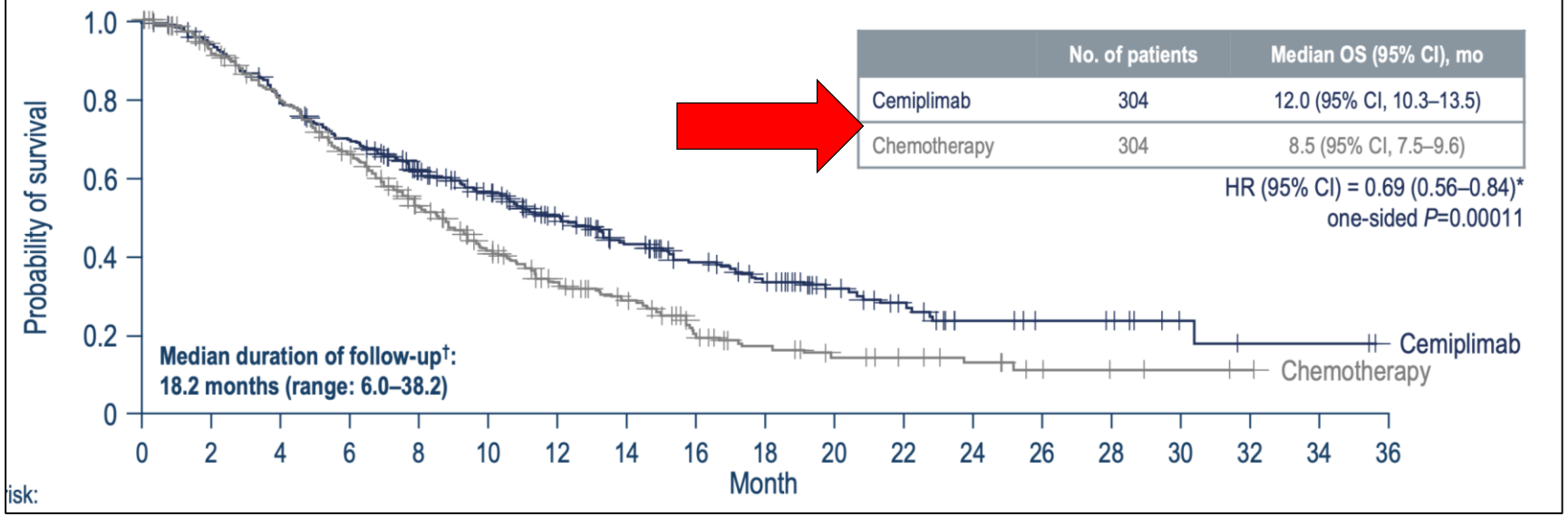
- At second interim analysis (85% of total OS events), IDMC recommended trial be stopped early for efficacy



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

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

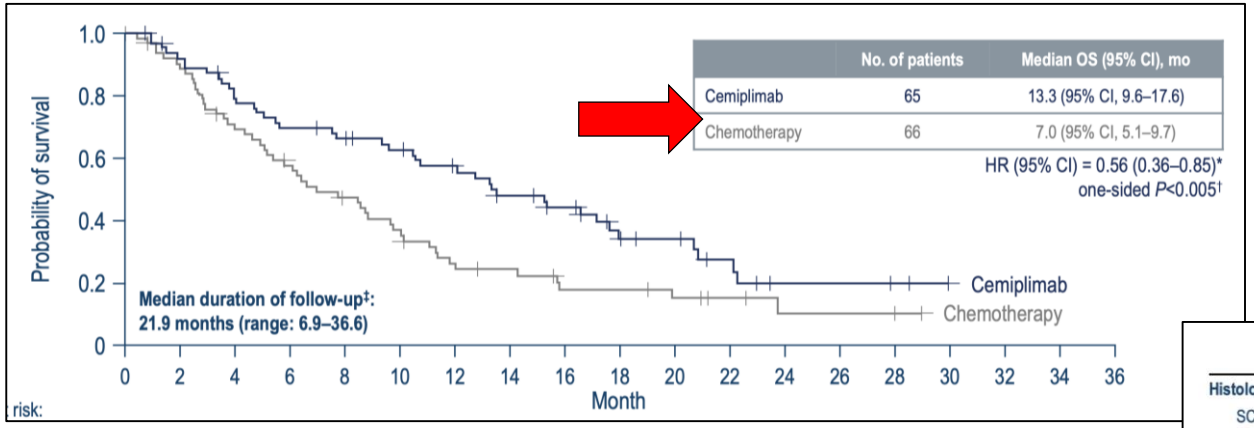
SURVIVAL FOR TOTAL POPULATION



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

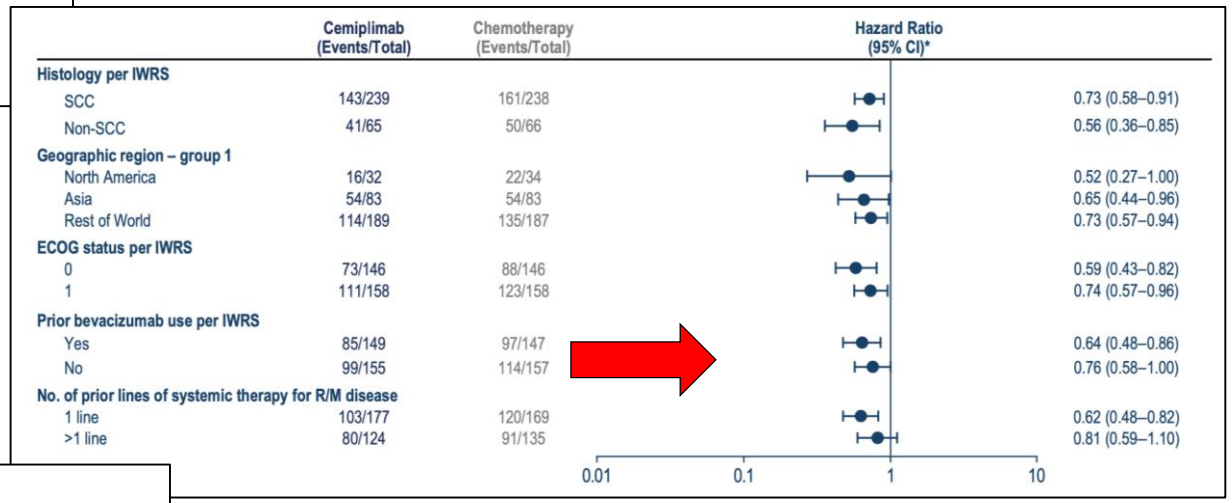
HR (95% CI) = 0.69 (0.56–0.84)*
one-sided *P*=0.00011

SURVIVAL FOR ADC POPULATION



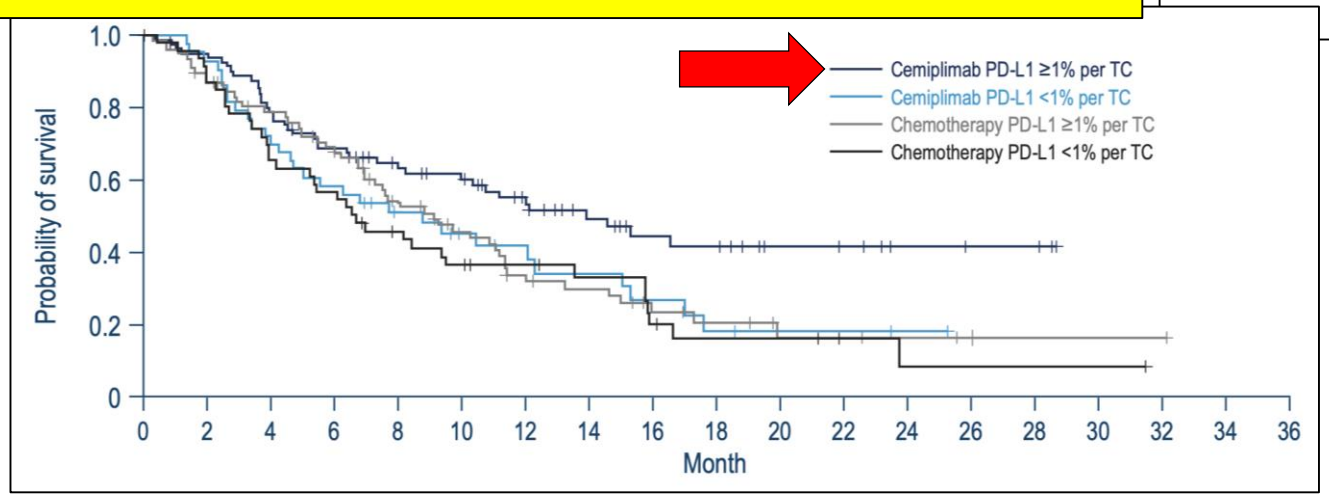
	No. of patients	Median OS (95% CI), mo
Cemiplimab	65	13.3 (95% CI, 9.6–17.6)
Chemotherapy	66	7.0 (95% CI, 5.1–9.7)

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



	Cemiplimab (Events/Total)	Chemotherapy (Events/Total)	Hazard Ratio (95% CI)*
Histology per IWRS			
SCC	143/239	161/238	0.73 (0.58–0.91)
Non-SCC	41/65	50/66	0.56 (0.36–0.85)
Geographic region – group 1			
North America	16/32	22/34	0.52 (0.27–1.00)
Asia	54/83	54/83	0.65 (0.44–0.96)
Rest of World	114/189	135/187	0.73 (0.57–0.94)
ECOG status per IWRS			
0	73/146	88/146	0.59 (0.43–0.82)
1	111/158	123/158	0.74 (0.57–0.96)
Prior bevacizumab use per IWRS			
Yes	85/149	97/147	0.64 (0.48–0.86)
No	99/155	114/157	0.76 (0.58–1.00)
No. of prior lines of systemic therapy for R/M disease			
1 line	103/177	120/169	0.62 (0.48–0.82)
>1 line	80/124	91/135	0.81 (0.59–1.10)

SURVIVAL BY PD-L1 STATUS



No new irAEs that are not well described for the PD-1/PDL1 inhibitor class

PRACTICE CHANGING !!!

28/09/2021

U.S. FOOD & DRUG ADMINISTRATION

- FDA has accepted for priority review, to treat

patients with recurrent or metastatic CC whose disease progressed on or after CT

- Target action date for the FDA decision = 30/01/2022

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Submission planned by end of 2021

KEYNOTE-826 STUDY

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

ESMO 2021

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

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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer

10/2021

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

DESIGN

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

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

Stratification Factors

- Metastatic disease at diagnosis (yes vs no)
- PD-[illegible]
- Planned bevacizumab use (yes vs no)

End Points

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

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

617

mFU = 22 mths

STATISTICAL ANALYSES

Hypothesis 1
PFS, CPS ≥1 Population
α = 0.004

Hypothesis 2
PFS, All-Comer Population
α = 0

Hypothesis 3
PFS, CPS ≥10 Population
α = 0.001

Hypothesis 4
OS, CPS ≥1 Population
α = 0.016

Hypothesis 5
OS, All-Comer Population
α = 0

Hypothesis 6
OS, CPS ≥10 Population
α = 0.004

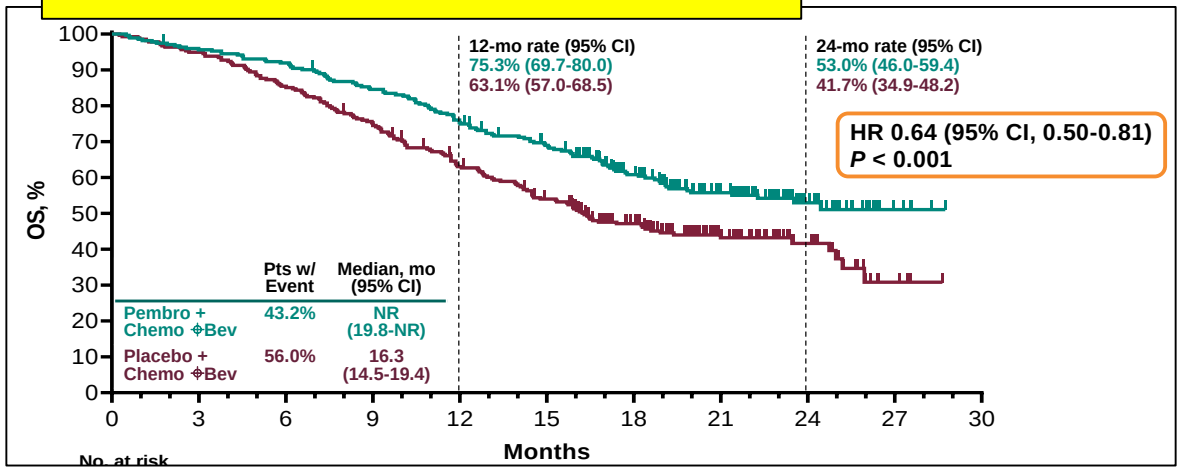
Prespecified analysis plan allows alpha from successful hypotheses to be passed to other hypotheses

BASELINE CHARACTERISTICS / ALL-COMER

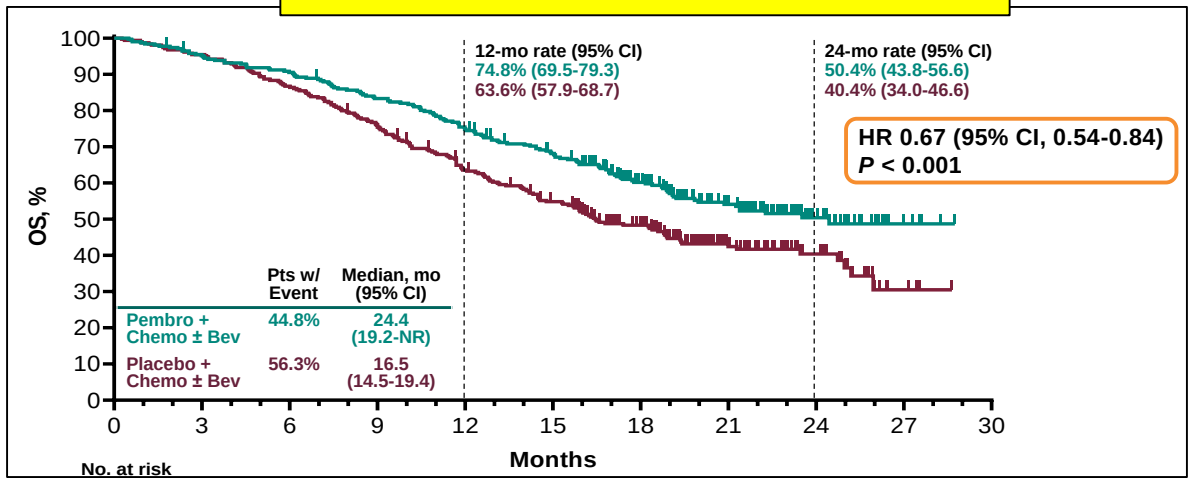
	Pembro Arm[a] (N = 308)	Placebo Arm[a] (N = 309)
Age, median (range)	51 y (25-82)	50 y (22-79)
ECOG PS 1	128 (41.6%)	139 (45.0%)
Squamous cell carcinoma	235 (76.3%)	211 (68.3%)
PD-L1 CPS		
<1	35 (11.4%)	34 (11.0%)
1 to <10	115 (37.3%)	116 (37.5%)
▯	158 (51.3%)	159 (51.5%)
Prior therapy		
Chemoradiation 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%)

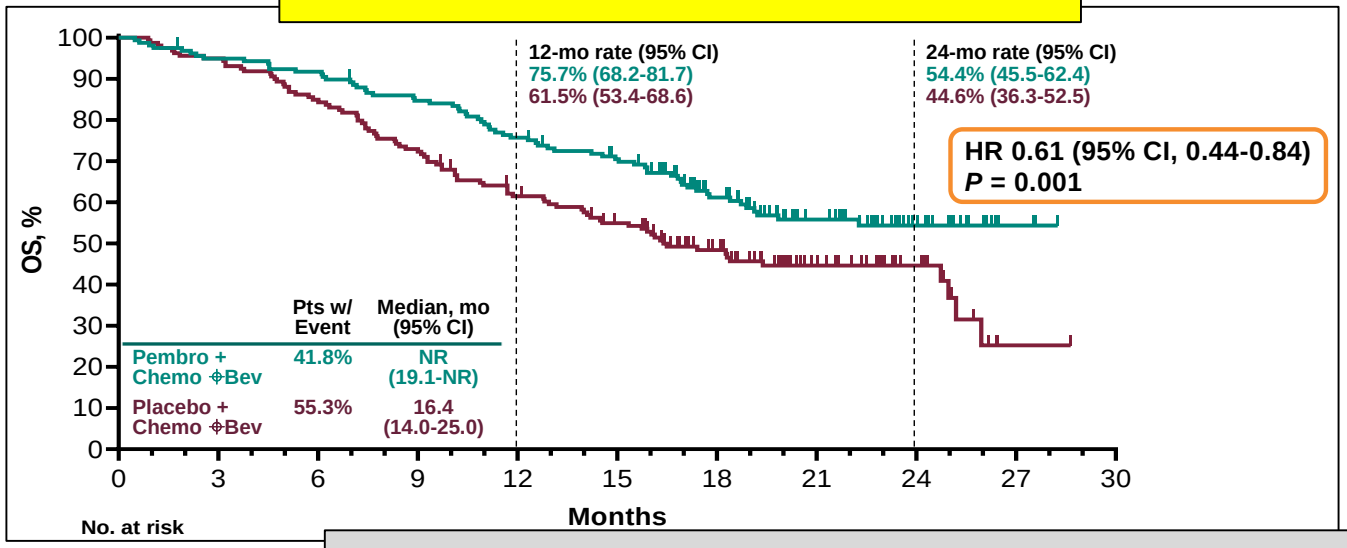
OS : PD-L1 CPS ≥1

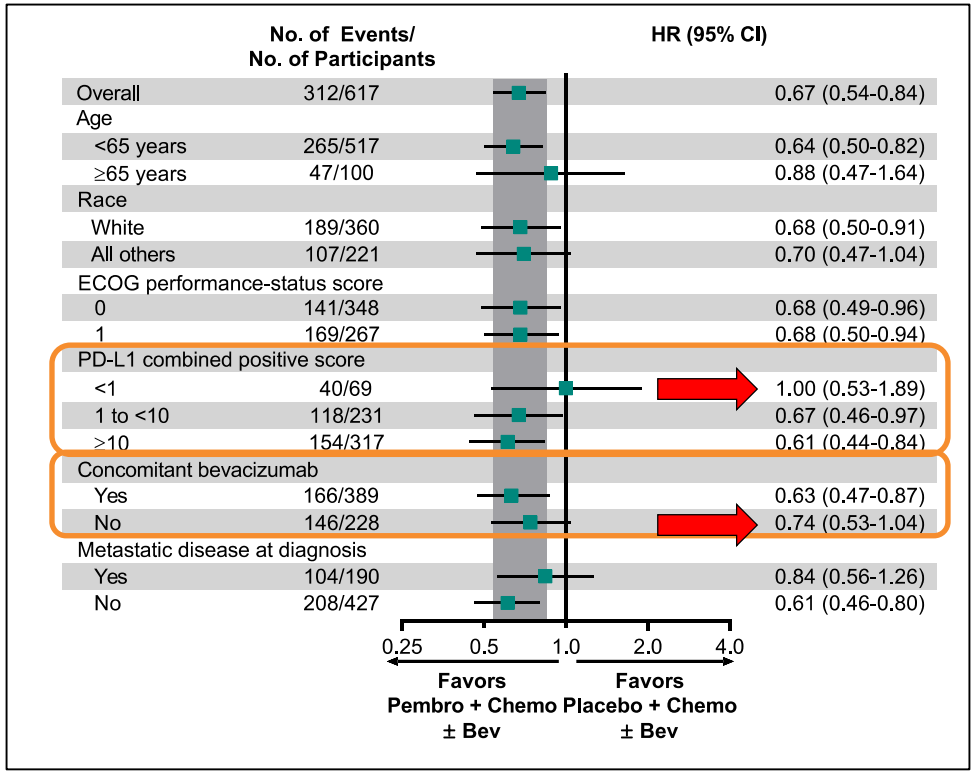


OS : ALL-COMER



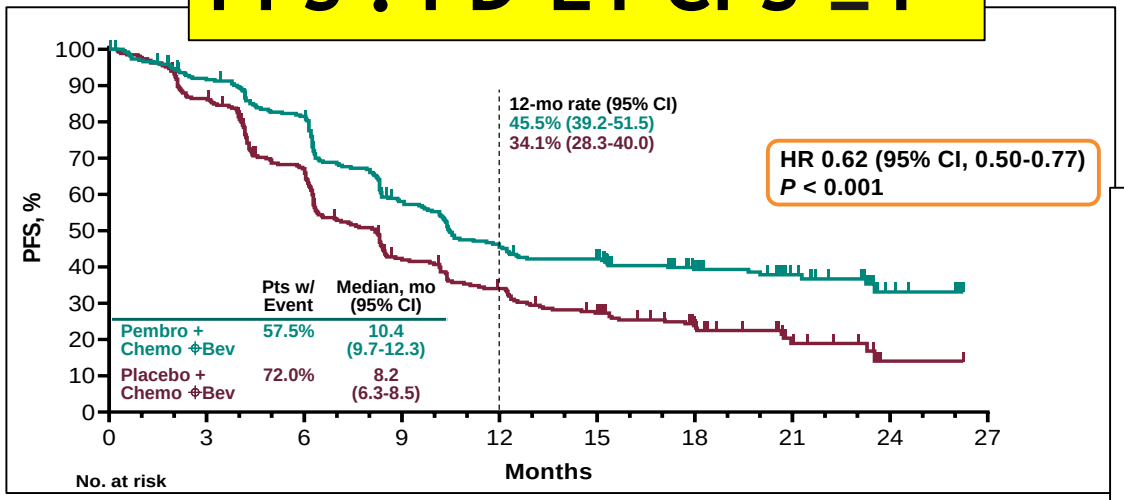
OS : PD-L1 CPS ≥10



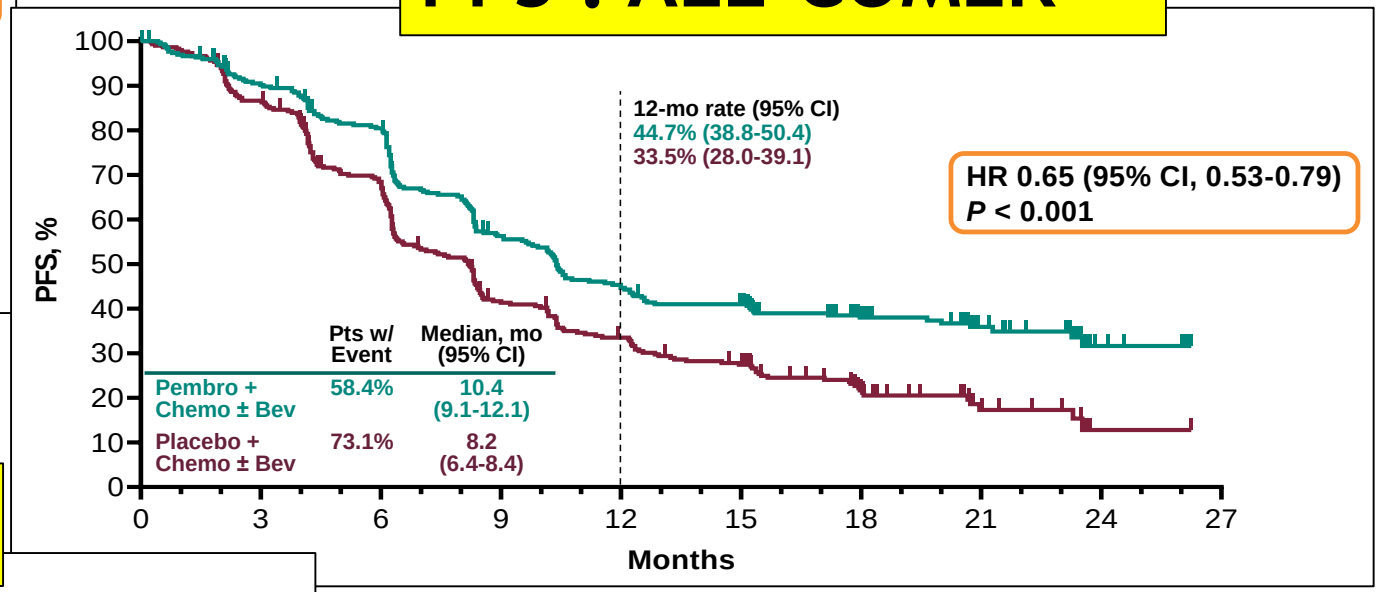


No new irAEs that are not well described for the PD-1/PDL1 inhibitor class

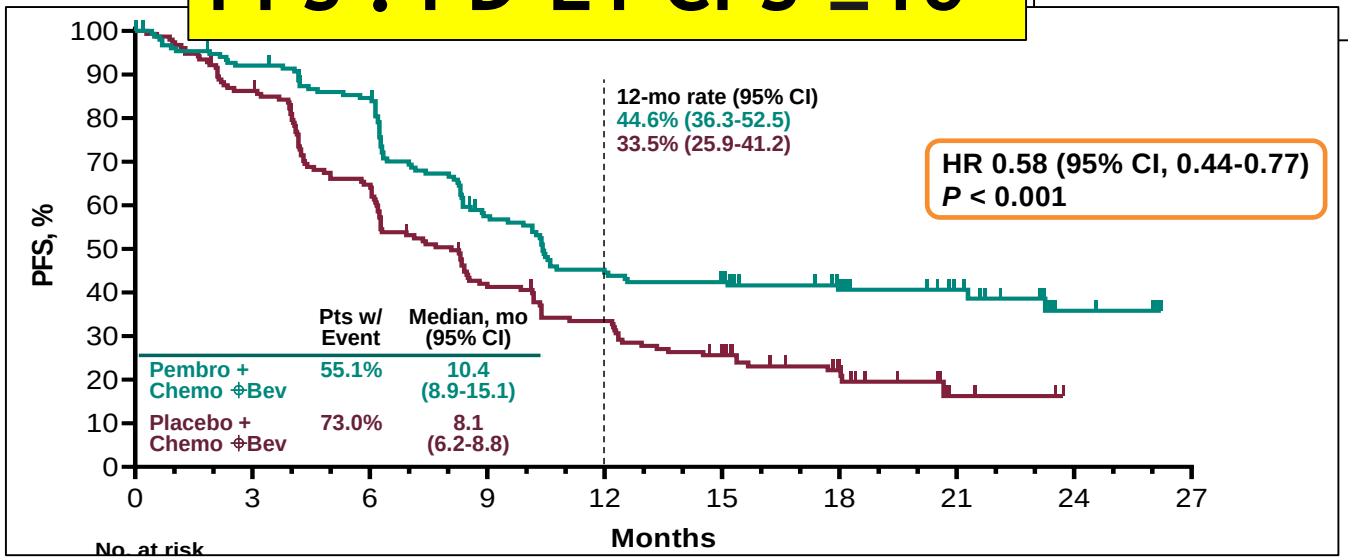
PFS : PD-L1 CPS ≥1



PFS : ALL-COMER



PFS : PD-L1 CPS ≥10



PRACTICE CHANGING !!!

The author *Nicoletta Colombo*: « Pembrolizumab plus chemotherapy with or without bevacizumab may be a new standard of care for women with persistent, recurrent, or metastatic cervical cancer »

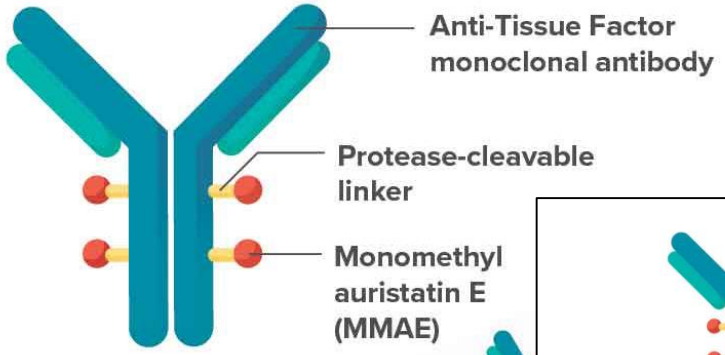
13/10/2021

Pembrolizumab in combination with chemotherapy, with or without bevacizumab, for patients with persistent, recurrent or metastatic CC whose tumors express PD-L1 (CPS ≥1), as determined by an FDA-approved test…

3

TISOTUMAB VEDOTIN

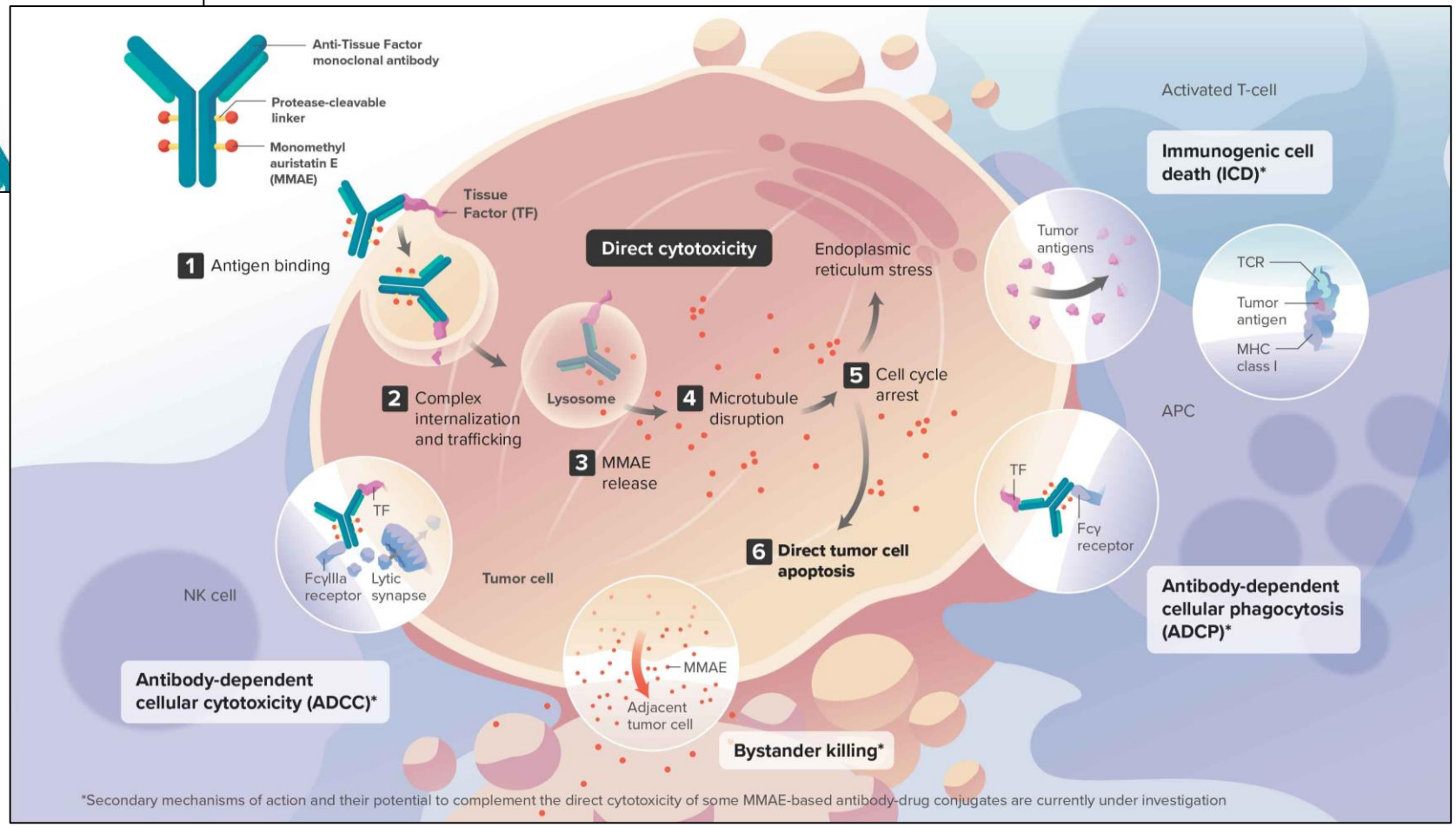
ANTIBODY-DRUG CONJUGATE



Directed to TISSUE FACTOR (TF)

CC = 94-100%

- Aberrantly expressed in a broad range of solid tumors
- Associated with poor prognosis
- Role in tumor angiogenesis, proliferation, metastases, thrombotic events



INNOVA TV201 TRIAL

PHASE I/II

55pts

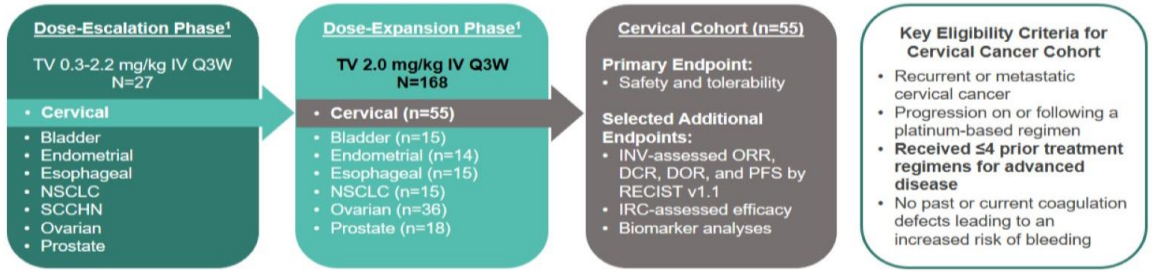
CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

CLIN CANCER RES. March 2020

Tisotumab Vedotin in Previously Treated Recurrent or Metastatic Cervical Cancer AC

David S. Hong[1], Nicole Concin[2], Ignace Vergote[2], Johann S. de Bono[3], Brian M. Slomovitz[4], Yvette Drew[5], Hendrik-Tobias Arkenau[6], Jean-Pascal Machiels[7], James F. Spicer[8], Robert Jones[9], Martin D. Forster[10], Nathalie Cornez[11], Christine Gennigens[12], Melissa L. Johnson[13], Fiona C. Thistlethwaite[14], Reshma A. Rangwala[15], Srinivas Ghatta[16], Kristian Windfeld[17], Jeffrey R. Harris[18], Ulrik Niels Lassen[19], and Robert L. Coleman[20]

DESIGN



- TV 2.0 mg/kg every 3 weeks was the recommended phase II dose
- Patients with clinical benefit (SD or better) at the end of 4 cycles could continue TV for an additional 8 cycles (12 cycles total) or until disease progression or unacceptable toxicity
  - After 12 cycles, patients with clinical benefit could continue in an extension study (NCT03245736)
- Confirmed responses were defined with repeat imaging ≥4 weeks after initial response

RESPONSE

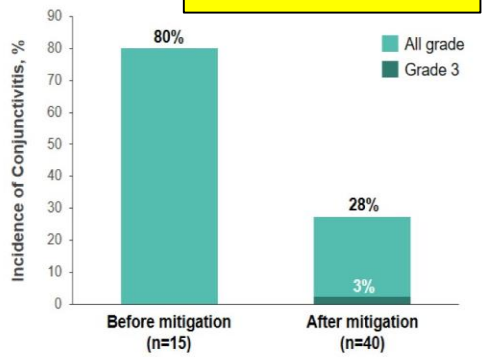
	N=55	
	IRC-Assessed[a]	INV-Assessed
ORR confirmed + unconfirmed (95% CI), %	35 (22–49)	31 (19–45)
ORR confirmed (95% CI), %	22 (12–35)	24 (13–37)
CR, n (%)	1 (2)	0
PR, n (%)	11 (20)	13 (24)
SD, n (%)	19 (35)	21 (38)
PD, n (%)	17 (31)	17 (31)
Not evaluable,[b] n (%)	5 (9)	4 (7)
DCR confirmed (95% CI), %	56 (42–70)	62 (48–75)
Median DOR (range), months	6.0 (1.0+–9.7)	4.2 (1.0+–9.7)
Median PFS (95% CI), months	4.1 (1.7–6.7)	4.2 (2.1–5.3)
6-month PFS rate (95% CI), %	40 (24–55)	29 (17–43)

- Overall 95% agreement on IRC- and INV-assessed confirmed objective response (Cohen's kappa 0.84)

SAFETY

AESIs in ≥10% of Patients, n (%)	N=55	
	Any Grade	Grade 3
Neuropathies[a]	**30 (55)**	**6 (11)**
Peripheral neuropathy	20 (36)	2 (4)
Bleeding-related events[b]	**40 (73)**	**3 (5)**
Epistaxis	28 (51)	0
Vaginal hemorrhage	7 (13)	2 (4)
Ocular events[c]	**36 (65)**	**1 (2)**
Conjunctivitis	23 (42)	1 (2)
Dry eye	13 (24)	0

- No grade ≥4 AESIs were observed



- **Incidence of conjunctivitis was reduced with mitigation measures, which included:**
  - Eye drops (vasoconstricting, steroid, lubricating)
  - Cooling eye masks
  - Dose modification

INNOVA TV204 TRIAL

PHASE II **101pts**

mFU = 10 mths

Efficacy and safety of tisotumab vedotin in previously treated recurrent or metastatic cervical cancer (innovaTV 204/ GOG-3023/ENGOT-cx6): a multicentre, open-label, single-arm, phase 2 study

*Robert L Coleman, Domenica Lorusso, Christine Gennigens, Antonio González-Martín, Leslie Randall, David Cibula, Bente Lund, Linn Woelber, Sandro Pignata, Frederic Forget, Andrés Redondo, Signe Diness Vindeløv, Menghui Chen, Jeffrey R Harris, Margaret Smith, Leonardo Viana Nicacio, Melinda S L Teng, Annouschka Laenen, Reshma Rangwala, Luis Manso, Mansoor Mirza, Bradley J Monk, Ignace Vergote, on behalf of the innovaTV 204/GOG-3023/ENGOT-cx6 Collaborators**

LANCET ONCOLOGY. May 2021

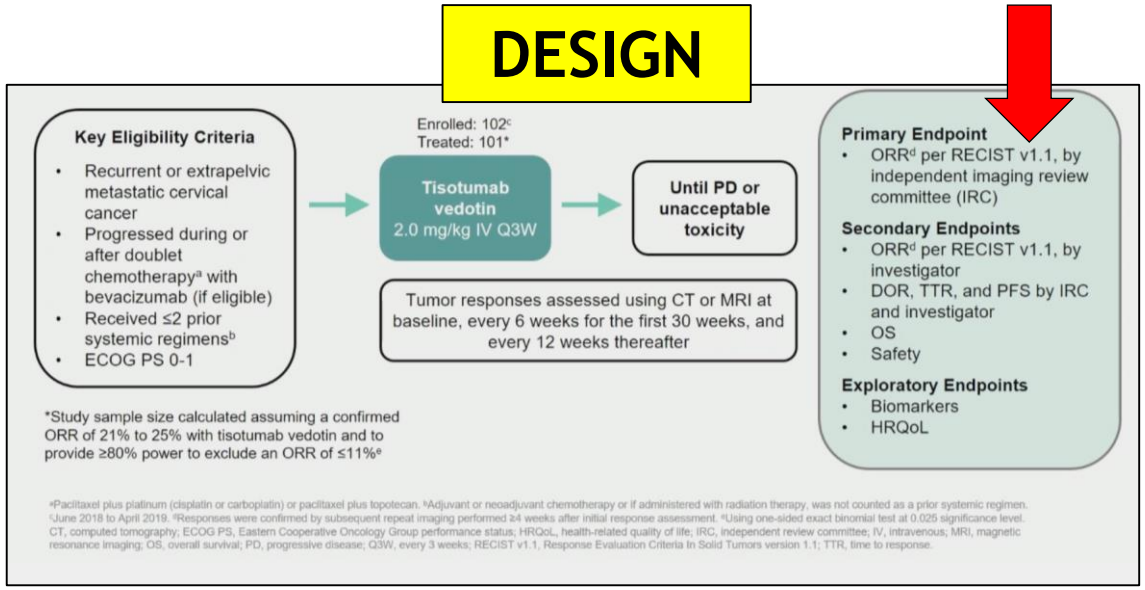
CHARACTERISTICS

	N=101
Age, median (range), years	50 (31–78)
Race, (n %)	
White	96 (95)
Asian	2 (2)
Black or African American	1 (1)
Other	2 (2)
ECOG PS, n (%)	
0	59 (58)
1	42 (42)
Histology, n (%)	
Squamous cell carcinoma	69 (68)
Adenocarcinoma	27 (27)
Adenosquamous carcinoma	5 (5)
Extrapelvic metastatic disease at baseline, n (%)	95 (94)

	N=101
Prior cisplatin plus radiation, n (%)	
Yes	55 (54)
No	46 (46)
Prior lines of systemic regimen for recurrent/metastatic disease,[a] n (%)	
1	71 (70)
2	30 (30)
Prior bevacizumab plus doublet chemotherapy as 1L therapy,[b] n (%)	64 (63)
Response to last systemic regimen,[a] n (%)	
Yes	38 (38)
No	57 (56)
Unknown	6 (6)
Biopsy evaluable, n (%)	80 (79)
Positive membrane TF expression,[c] n (%)	77 (96)

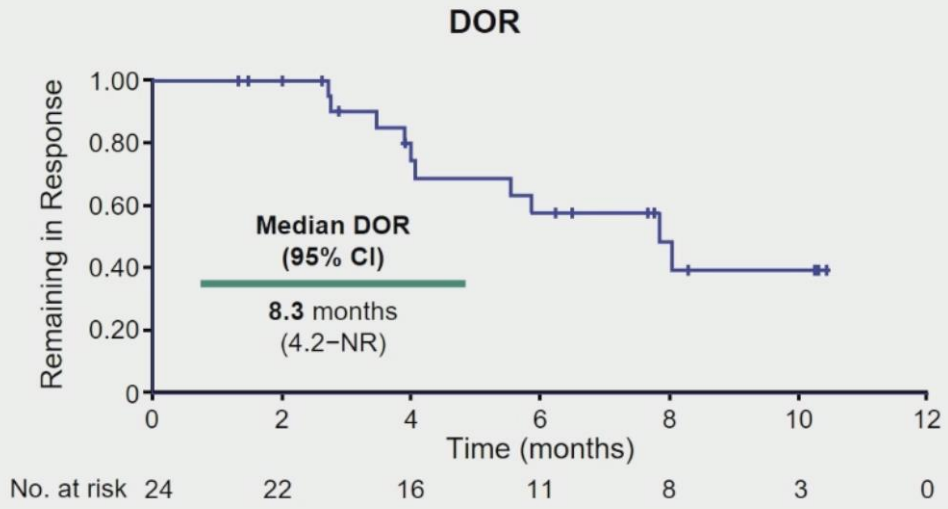
Data cutoff: February 06, 2020.
[a]Systemic regimen administered in the metastatic or recurrent setting. [b]Doublet chemotherapy defined as paclitaxel-platinum or paclitaxel-topotecan. [c]Positive TF expression defined as any positive membrane staining on tumor cells out of biopsy-evaluable population (n=80).
1L, first-line; ECOG PS, Eastern Cooperative Group performance status; TF, tissue factor.

DESIGN

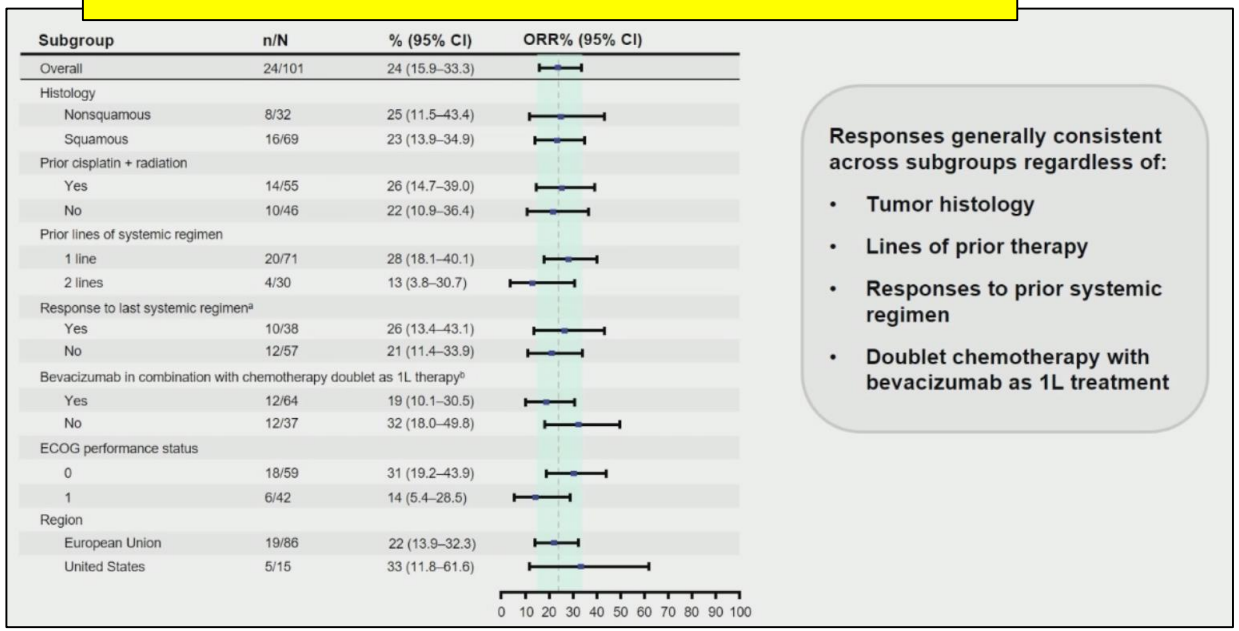


ANTITUMOUR ACTIVITY by IRC

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



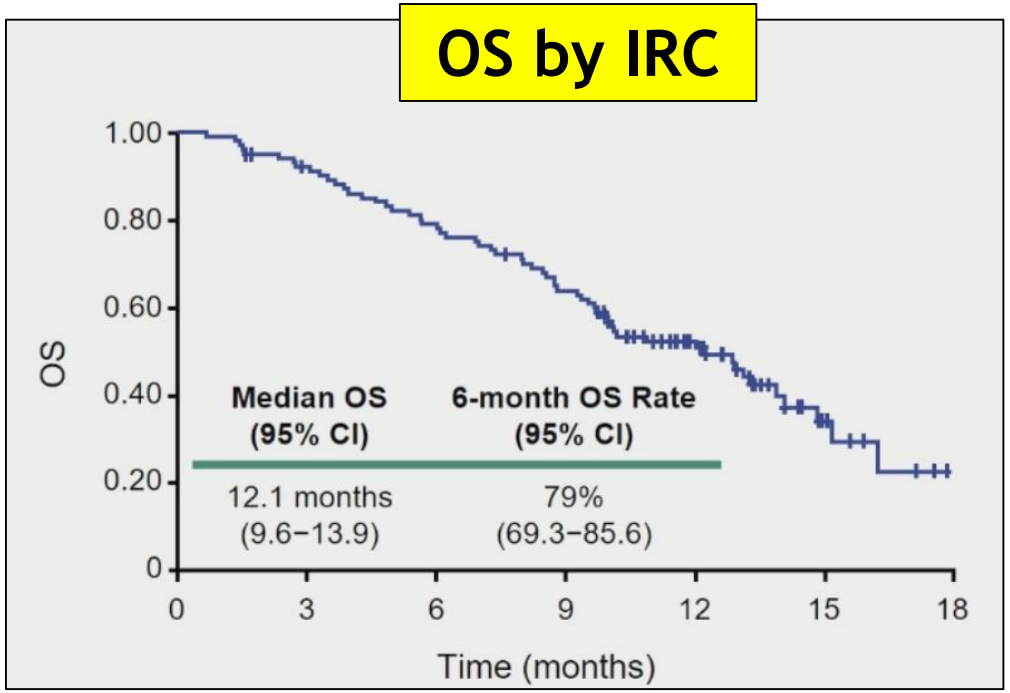
ORR SUBGROUP ANALYSIS



Responses generally consistent across subgroups regardless of:

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

OS by IRC



INNOVA TV205 TRIAL

PHASE I/II (expansion)

1L = 33 pts
2L/3L = 35 pts

Tisotumab Vedotin + Carboplatin in First-Line or + Pembrolizumab in Previously Treated Recurrent/Metastatic Cervical Cancer: Interim Results of ENGOT-Cx8/GOG-3024/innovaTV 205

Ignace Vergote,[1] Bradley J. Monk,[2] Roisin E. O'Cearbhaill,[3] Anneke Westermann,[4] Susana Banerjee,[5] Dearbhaile Catherine Collins,[6] Mansoor Raza Mirza,[7] David O'Malley,[8] Christine Gennigens,[9] Sandro Pignata,[10] Bohuslav Melichar,[11] Azmat Sadozye,[12] Frederic Forget,[13] Krishnansu S. Tewari,[14] Eelke Gort,[15] Ibrahima Soumaoro,[16] Camilla Mondrup Andreassen,[17] Leonardo Viana Nicacio,[18] Els Van Nieuwenhuysen,[1] Domenica Lorusso[19]

[1]Belgium and Luxembourg Gynaecological Oncology Group, University of Leuven, Leuven Cancer Institute, Leuven, Belgium; [2]Arizona Oncology (US Oncology Network), University of Arizona College of Medicine, Creighton University School of Medicine, Phoenix, AZ, USA; [3]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA; [4]Amsterdam University Medical Centers, Amsterdam, Netherlands; [5]The Royal Marsden NHS Foundation Trust, London, UK; [6]Cork University Hospital/Oncology Trials Unit, Cork, Ireland; [7]Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark; [8]Division of Gynecology Oncology, Department of Gynecology and Obstetrics, The Ohio State University College of Medicine, Columbus, Ohio, USA; [9]Department of Medical Oncology, Liège University Hospital, Liège, Belgium; [10]Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, Naples, Italy; [11]Palacký University Medical School and Teaching Hospital, Olomouc, Czech Republic; [12]NHS Greater Glasgow and Clyde, Glasgow, United Kingdom; [13]Centre Hospitalier de l'Ardenne, Libramont, Belgium; [14]University of California, Irvine Medical Center, Orange, CA, USA; [15]University Medical Center Utrecht, Utrecht, Netherlands; [16]Genmab US, Inc., Princeton, NJ, USA; [17]Genmab A/S, Copenhagen, Denmark; [18]Seagen Inc., Bothell, WA, USA; [19]Fondazione IRCCS, Foundation Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

2021 ESMO congress

Ignace Vergote

DESIGN

1L TV + carbo	Patients with no prior systemic therapy for r/mCC	N=33	TV 2.0 mg/kg IV (Q3W) + Carbo AUC 5 IV (Q3W)
2L/3L TV + pembro	Patients with r/mCC, with disease progression on/after 1–2 prior systemic therapies	N=35	TV 2.0 mg/kg IV (Q3W) + Pembro 200 mg IV (Q3W)

Primary endpoint:
- ORR per RECIST v1.1

Secondary endpoints:
- Adverse events and laboratory parameters
- Duration of Response
- Time to Response
- Progression free survival
- Overall survival
- PK-concentrations and anti-drug antibodies associated with TV

BASELINE CHARACTERISTICS

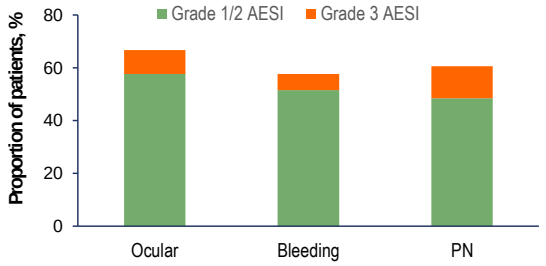
Parameter	TV + Carboplatin (N=33)	TV + Pembrolizumab (N=35)
Age, median (range), years	51.0 (25 – 78)	47.0 (31 – 73)
ECOG performance status, n (%)		
0	21 (63.6)	22 (62.9%)
1	12 (36.4)	13 (37.1%)
Histology, n (%)		
Squamous	24 (72.7)	19 (54.3)
Adenocarcinoma	8 (24.2)	15 (42.9)
Other	1 (3.0)	1 (2.9)
PD-L1 positive,[a] n (%)	N/A	22 (81.5)[b]
Prior chemoradiation, n (%)	21 (63.6)	18 (51.4)
Prior lines of systemic regimen,[c] n (%)		
0	33 (100)	0
1	0	26 (74.3)[d]
2	0	9 (25.7)[e]
Prior bevacizumab,[f] n (%)	N/A	18 (51.4)

EFFICACY/ SAFETY 1L TV + CARBO

Parameters	1L TV + Carbo (N = 33) Median FU: 7.9 months
Median duration of exposure, months (range)	TV: 4.9 (1 – 9) Carbo: 4.1 (1 – 9)
Median number of cycles initiated (range)	TV: 6.0 (1 – 12) Carbo: 6.0 (1 – 12)
Confirmed response rate, n (%) [95% CI] Complete response, n (%) Partial response, n (%) Stable disease, n (%) Progressive disease, n (%) Not evaluable, n (%)	18 (55) [36 – 72] 4 (12) 14 (42) 12 (36) 2 (6) 1 (3)
Median duration of response, months (95% CI)	8.3 (4.2 – NR)
Median time to response, months (range)	1.4 (1.1 – 4.4)
Median PFS, months (95% CI)	9.5 (4.0 – NR)
Median OS, months (range)	NR (0.8+ – 14.1+)

Treatment ongoing in 9 patients. +, censored.

	TV + Carbo (N=33)
Patients with ≥1 TEAE, n (%) AE related to TV	33 (100.0) 32 (97.0)
Grade ≥3 AE, n (%) Grade ≥3 AE related to TV	26 (78.8) 19 (57.6)
SAE, n (%) SAE related to TV	14 (42.4) 5 (15.2)
Fatal AE, n (%) Fatal AE related to TV	0 0



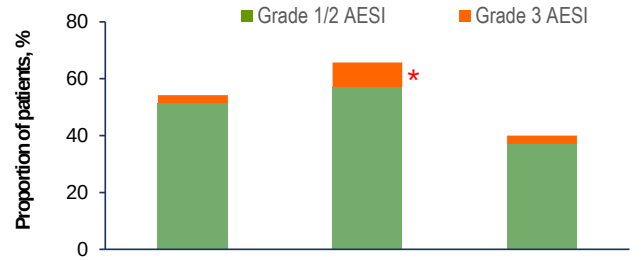
- Limited sample size
- Encouraging and durable antitumor activity
- Acceptable safety

EFFICACY/ SAFETY 2-3L TV + PEMBRO

Parameters	2L/3L TV + Pembro (N = 34)[a] Median FU: 13.0 months
Median duration of exposure, months (range)	TV: 4.1 (1 – 16) Pembro: 4.3 (1 – 17)
Median number of cycles initiated (range)	TV: 6.0 (1 – 21) Pembro: 6.0 (1 – 25)
Confirmed response rate, n (%) [95% CI] Complete response, n (%) Partial response, n (%) Stable Disease, n (%) Progressive disease, n (%) Not evaluable, n (%)	13 (38) [22 – 56] 2 (6) 11 (32) 12 (35) 7 (21) 2 (6)
Median DOR, months (95% CI)	13.8 (2.8 – NR)
Median time to response, months (range)	1.4 (1.3 - 5.8)
Median PFS, months (95% CI)	5.6 (2.7 – 13.7)
Median OS, months (range)	NR (1.3 – 17.5+)

[a]1 pt was excluded from the full analysis set as they didn't have any target or non-target lesions at baseline.
Treatment ongoing in 4 patients.

	TV + Pembro (N = 35)
Patients with ≥1 TEAE, n (%) AE related to TV	35 (100.0) 34 (97.1)
Grade ≥3 AE, n (%) Grade ≥3 AE related to TV	26 (74.3) 16 (45.7)
SAE, n (%) SAE related to TV	18 (51.4) 5 (14.3)
Fatal AE, n (%) Fatal AE related to TV	1 (2.9) 0



*One patient had a grade 4 bleeding event.

PRACTICE CHANGING !!!

20/09/2021

Tisotumab vedotin (brand name Tivdak®), for adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy…

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Submission planned very soon…

4 GENOMIC DIVERSITY

Integrated genomic and molecular characterization of cervical cancer

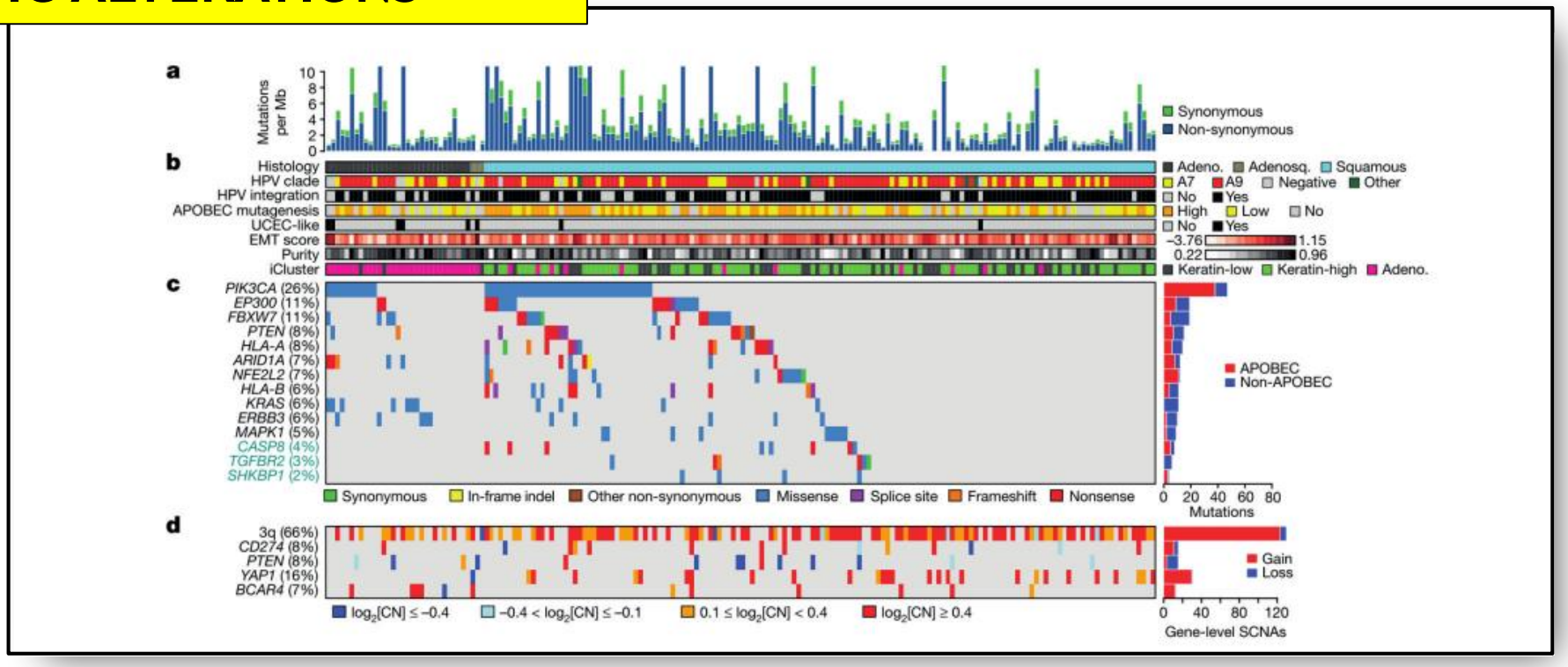
The Cancer Genome Atlas Research Network*

NATURE | VOL 543 | 16 MARCH 2017

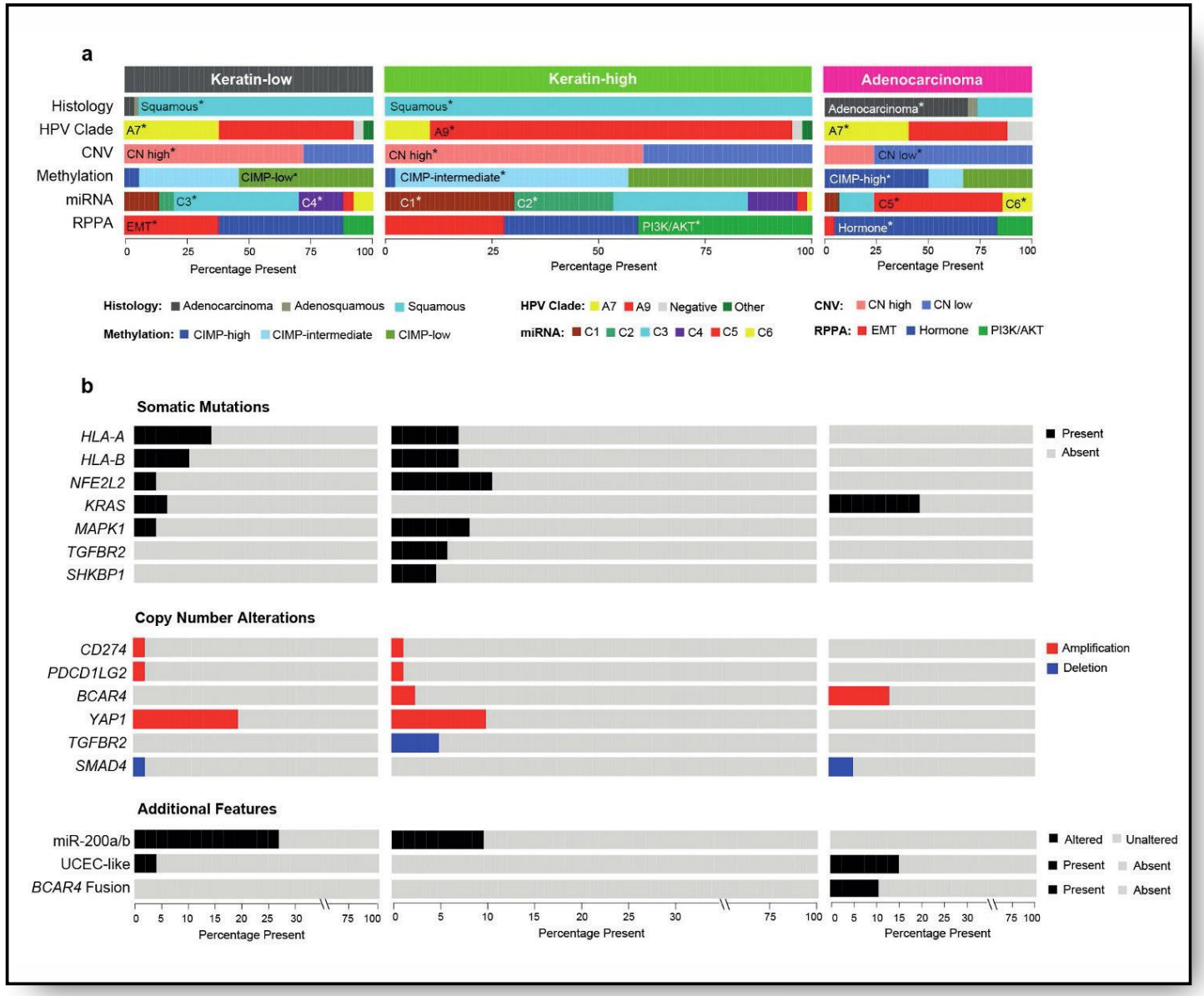
228 pts

- report the extensive molecular characterization of primary CCs
- one of the largest comprehensive genomic studies of CC to date

SOMATIC ALTERATIONS



DISTINGUISHING FEATURES OF CC INTEGRATED MOLECULAR SUBTYPES



KEEP CALM ITS THE CONCLUSION

LOCALLY ADVANCED STAGE

IB3 - IVA

CURRENTLY

Cisplatin-based chemoradiation followed by brachytherapy

- Around 30% of recurrence
- 5y OS = 17%

STUDY	STUDY TITLE	Phase	Treatment arms	Target accrual goal	Radiation therapy	Primary endpoints
NCT02635360	Pembrolizumab and CCRT treatment for advanced CC	II	**Arm 1:** CCRT then pembrolizumab **Arm 2:** CCRT with pembrolizumab	88	EBRT with weekly cisplatin and BT	Change in immunologic markers, toxicity
NCT03298893 (NiCOL)	Nivolumab in association with radiation therapy and cisplatin in LACC followed by adjuvant nivolumab for up to 6 months	I	CCRT with nivolumab, then nivolumab	21	IMRT with SIB to bulky nodes, weekly cisplatin, and BT	Toxicity
NCT03527264 (BrUOG 355)	Nivolumab to tailored Radiation therapy with concomitant cisplatin in the treatment of patients with CC	II	**Cohort 1A:** CCRT with concurrent nivolumab **Cohort 1B:** extended-field CCRT with concurrent nivolumab **Cohort 2:** CCRT then nivolumab **Cohort 3:** CCRT with nivolumab, then nivolumab	24	Whole pelvis or extended-field RT 45 Gy in 25 fractions with weekly cisplatin and BT	Toxicity, PFS
NCT03612791 (ATEZOLACC)	Trial assessing atezolizumab (with CCRT vs CCRT alone)	II	**Arm 1:** CCRT **Arm 2:** CCRT with atezolizumab, then atezolizumab	190	Whole pelvis or extended-field RT using IMRT 45 Gy in 25 fractions (SIB to bulky nodes) with weekly cisplatin and BT	PFS
NCT03738228 (NRG-GY017)	Atezolizumab before and/or with CCRT in immune system activation in patients with node positive stage IB2, II, IIIB, or IVA CC	I	**Arm 1:** atezolizumab day - 21 then CCRT with atezolizumab **Arm 2:** CCRT with atezolizumab	40	Extended-field RT using IMRT 45 Gy in 25 fractions (SIB to gross nodes) with weekly cisplatin and BT	TCRB clonal expansion in peripheral blood
NCT03830866 (CALLA)	Study of durvalumab with CCRT for women with LACC	III	**Arm 1:** CCRT with durvalumab, then durvalumab Arm 2: CCRTwith placebo, then placebo	714	EBRT 45 Gy in 25 fractions PFS (boost to bulky nodes) with weekly cisplatin or carboplatin and BT	PFS
NCT03833479 (ATOMICC)	TSR-042 (anti-PD-1) as maintenance for patients with high-risk LACC after CCRT	II	**Arm 1:** no further treatment Arm 2: TSR-042 q6w for up to 24 months	132	Curative-intent chemoRT with >=4 doses weekly cisplatin before enrollment	PFS
NCT04221945 (MK-3475-A 18/KEYNOTE-A18/ENGOT-cx11)	Study of CCRT with or without pembrolizumab for the treatment of LACC	III	**Arm 1:** CCRT with pembrolizumab, then pembrolizumab Arm 2: CCRT with placebo, then placebo	980	EBRT 45-50 Gy then 25-30 Gy BT; total radiation treatment < 56 days	PFS, OS

FUTURE ?

IMMUNOTHERAPY ?

ADJUVANT ?

CONCO and ADJUVANT ?

NEO-ADJUVANT ?

RECURRENT / METASTATIC

CURRENTLY

FIRST-LINE

CISPLATIN or TOPOTECAN + PACLITAXEL + BEVACIZUMAB (if no CI)

SECOND-LINE AFTER PLATINUM

- CLINICAL TRIALS
- VINORELBINE
- GEMCITABINE
- PEMETREXED

« NEAR » FUTURE

PRACTICE CHANGING

FIRST-LINE

CARBOPLATIN + PACLITAXEL + PEMBROLIZUMAB +/- BEVACIZUMAB

SECOND-LINE AFTER PLATINUM

CEMIPLIMAB (if no previous ICI)

TISOTUMAB

UNRESOLVED QUESTIONS

- When may the patient most benefit from anti-PD1 therapy: LACC or second or first-line in recurrent setting

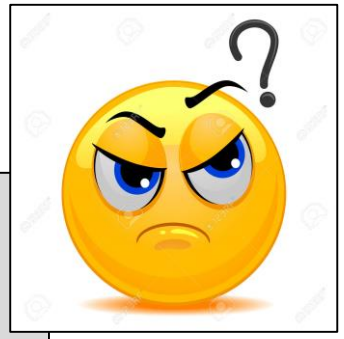
ARGUMENTS FOR « EARLY » USE

- Healthy immune system : diverse T cell repertoire, competent bone marrow
- Sensitive tumor : fewer mechanisms of immune escape earlier in the disease course
- Healthy host : better tolerance of irAEs

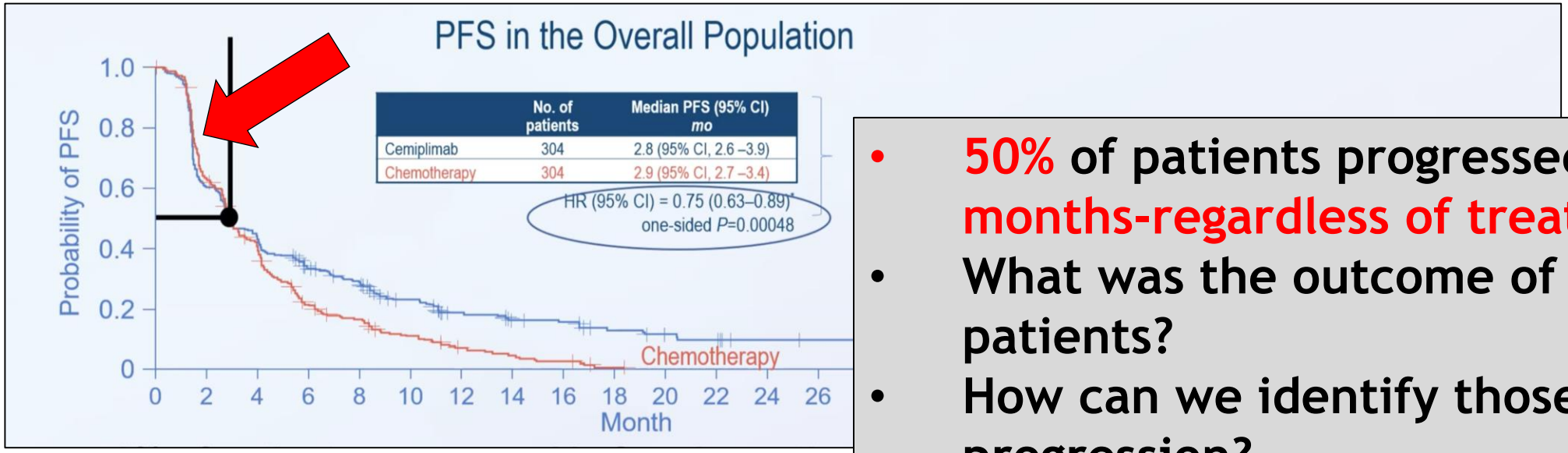
ARGUMENTS FOR « LATE » USE

- The majority of patients with LACC disease are cured with CTRT alone; addition of ICI may increase toxicities without overall increase in benefit, though data are still pending
- ICI in the upfront setting will require 1-2 years of maintenance
- Expensive

UNRESOLVED QUESTIONS



- Is there any rationale to use anti-PD1 agents after anti-PD1?
- Could anti-PD1 agents replace by themselves platinum-based therapy?
- If use of anti-PD1 in first-line of recurrent setting, what is the best next agent?



- 50% of patients progressed before 3 months-regardless of treatment
- What was the outcome of these patients?
- How can we identify those with rapid progression?

THANKS !!!