.cáncer. XII FORO DE ovario
Y OTROS TUMORES GINECOLÓGICOS

Inmunoterapia en cáncer de cérvix ¿es una realidad?

Dra. Lydia Gaba Garcia
Hospital Clínic, Barcelona

Disclousures

- Speaker: Astra Zeneca, Clovis Oncology, GlaxoSmithKline, Roche, Merck Sharp & Dohme, Pharmamar

- Consulting or advisory role: AstraZeneca, Clovis Oncology, GlaxoSmithKline, MerckSharp & Dohme, Pharmamar

- Travel, accomodation, expenses: Astra Zeneca, Clovis Oncology, GlaxoSmithKline, Roche, Merck Sharp & Dohme, Roche, Pharmamar

In 2022…

Córdoba 05 MAYO • 2022 •

cáncer. XI FORO DE ovario
Y OTROS TUMORES GINECOLÓGICOS

La Inmunoterapia en Cáncer de Cervix: ¿Tendremos un nuevo estándar?

Ana Oaknin, MD PhD
Head of Gynecologic Cancer Program.
Vall d´Hebron Institute of Oncology (VHIO)
Vall d'Hebron University Hospital
Barcelona, Spain

La respuesta que yo anticipo es que SÍ, pero…

In 2023…

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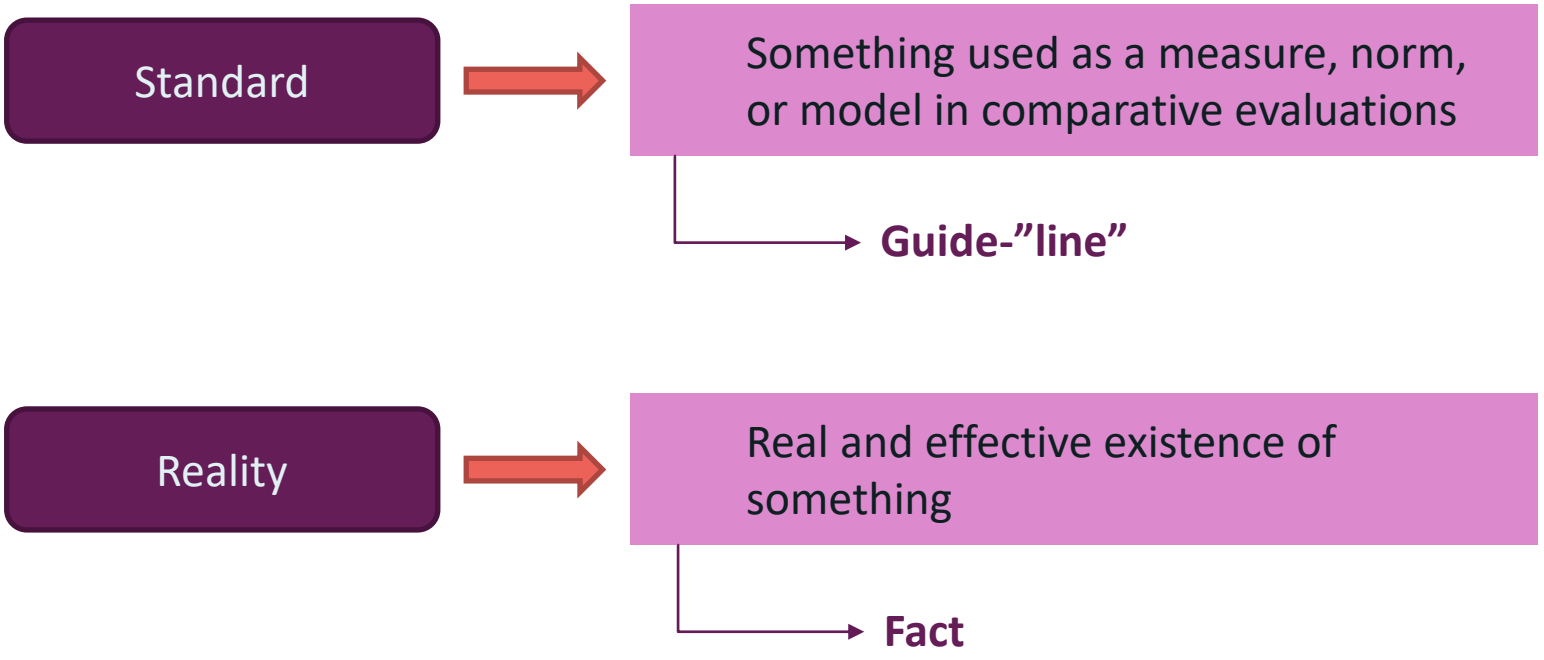
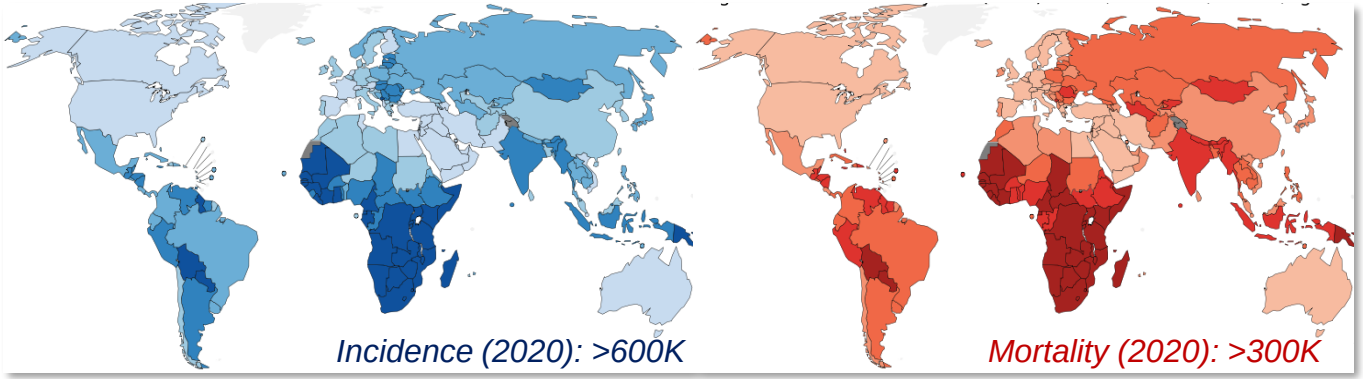
Definitions



CERVICAL CANCER: THE FACTS

- 1st FACT: Cervical cancer is a major public health problem
  - 4th most common cancer and the 4th cause of cancer death in women worldwide
  - 2nd leading cause in incidence and mortality in low and low-middle income countries



Global Cancer Observatory (https://gco.iarc.fr) (1st May 2023)

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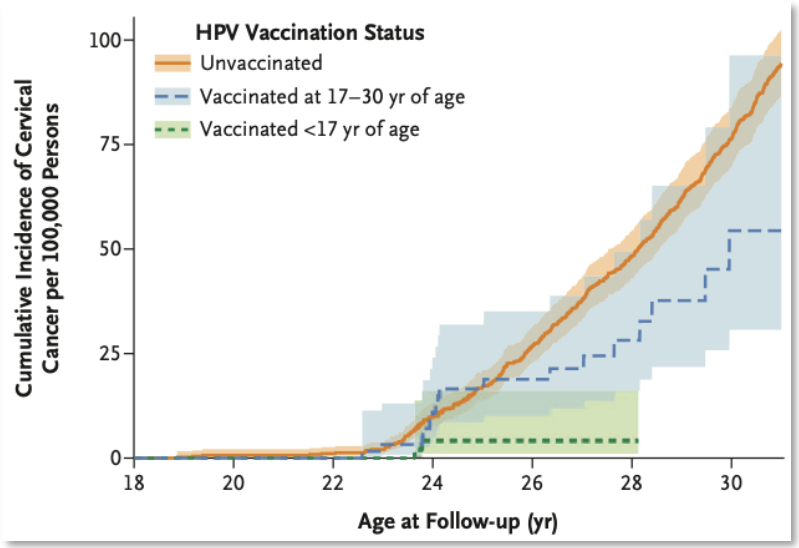
- 2nd FACT: Cervical cancer is a largely preventable disease
  - High-risk subtypes of HPV cause almost all (>95%) cervical cancers
  - Screening and vaccination programs are effective strategies in disease prevention



Lei J, et al. N Engl J Med 2020; 383:1340-48

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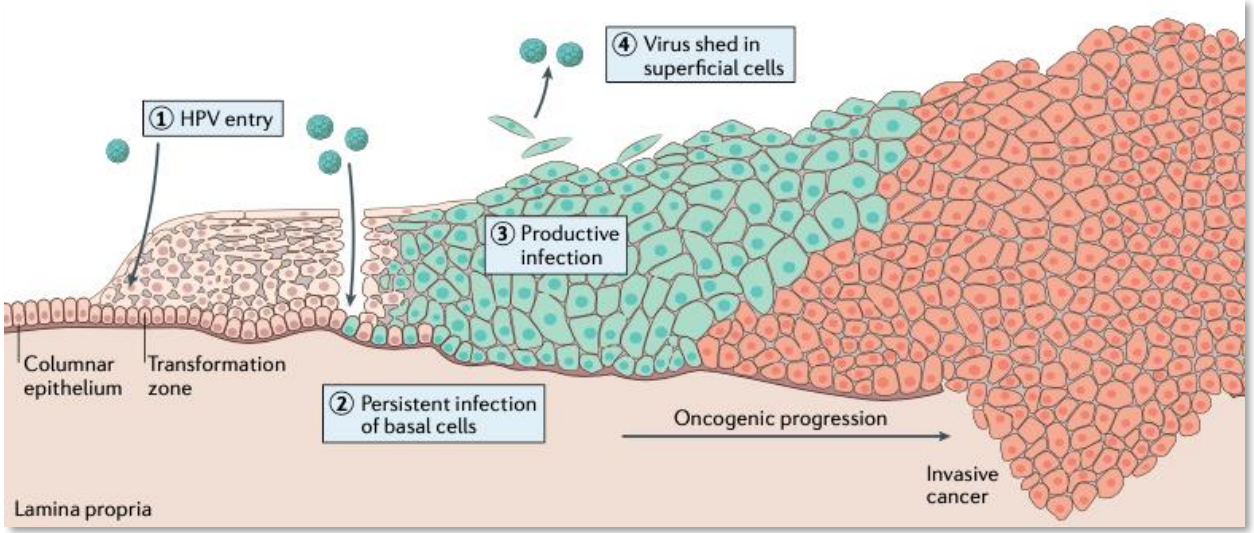
- 3rd FACT: Cervical cancer can be cured if diagnosed and treated at an early stage by radical surgery with tailored adjuvant therapy
  - Despite radical chemoradiation in locally advanced disease, 5-year OS is 41-83%
  - The management of advanced and recurrent disease still represents an unmet clinical need, with median OS of ~17 months

Cohen PA, et al. Lancet 2019; 393: 169–82

CERVICAL CANCER: WHY IMMUNOTHERAPY??

- Cervical Cancer is the consequence of persistent infection by oncogenic HPV subtypes
  - HPV should be recognized by the immune system as being foreign
  - The acquisition of immunosuppressive mechanisms leads to tumor immune evasion and development of invasive cancer

A multistep carcinogenesis model is widely accepted in a long process that may last up to 15 years



McBride AA. Nat Rev Microbiol 2022; 20:95-108

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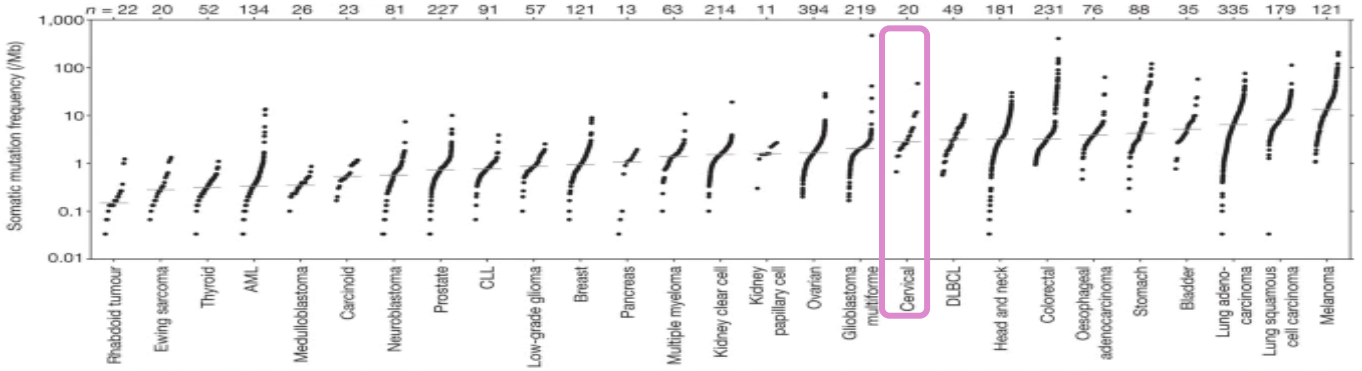
- Cervical Cancers have an increased Tumor Mutational Burden (TMB) Rate: 5-6 Mut/Mb
  - Increased TMB lead to the presence of more neoantigens that then stimulate the immune system



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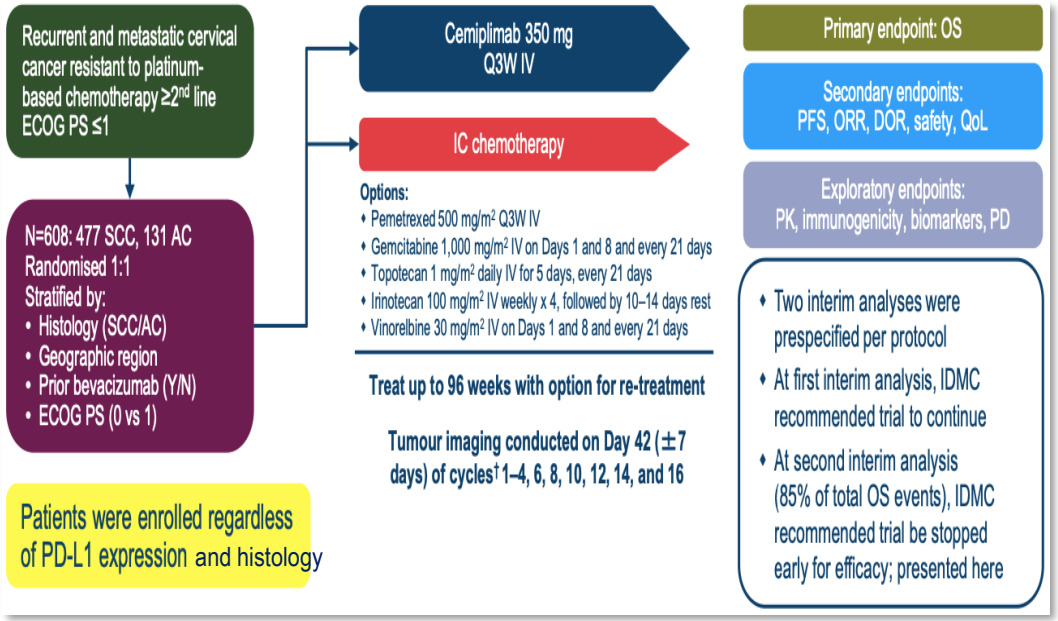
- Immune-Privilege State: PD-L1 expression and Tumor Infiltrating Lymphocytes(TILs)
  - PD-L1 is a solid biomarker of HPV infection and is overexpressed in SCC (19-88%) and Adenocarcinoma (14%)
  - CC shows higher lymphocyte infiltration compared to HPV-negative malignancies

Otter SJ, et al. Clin Oncol 2019; 31:834-843

IMMUNOTHERAPY FOR CERVICAL CANCER: THE MOST RELEVANT EVIDENCE

4th FACT: Cemiplimab demonstrated OS benefit in second-line monotherapy after platinum-chemotherapy

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



	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)

KS Tewari, et al at ESMO Virtual Plenary 2021

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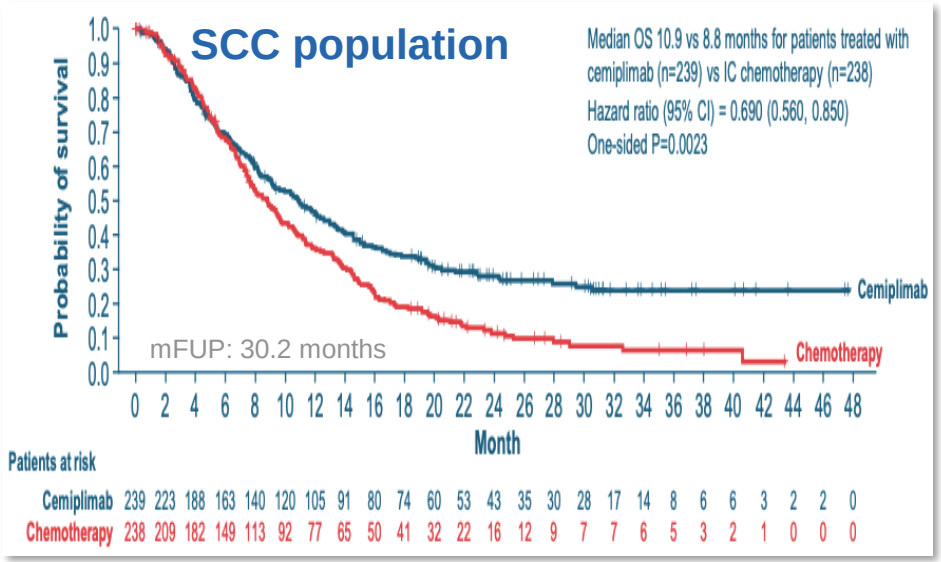
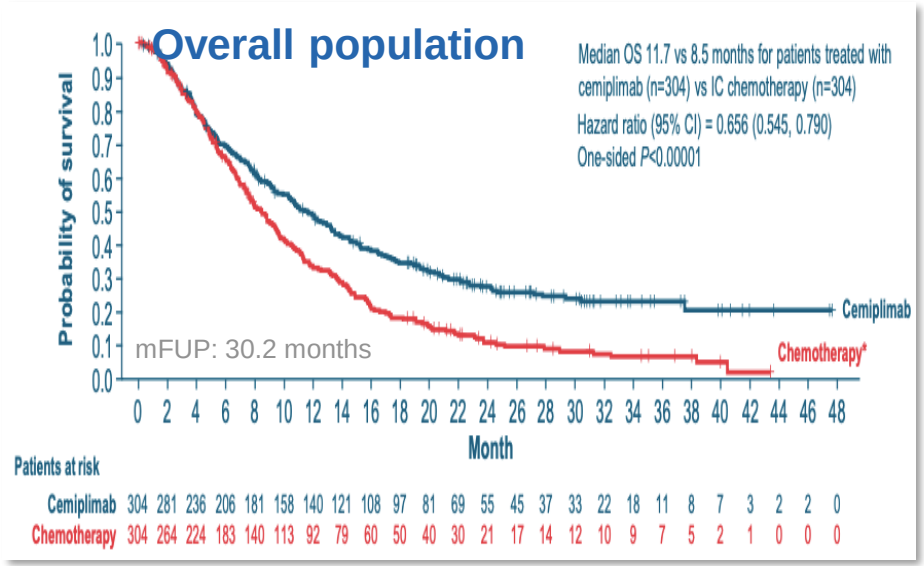
Primary Endpoint





Oaknin A, et al at ESMO Congress 2022

IMMUNOTHERAPY FOR CERVICAL CANCER: THE MOST RELEVANT EVIDENCE

4th FACT: Cemiplimab demonstrated OS benefit in second-line monotherapy after platinum-chemotherapy

(Regardless of histology or PD-L1 status)

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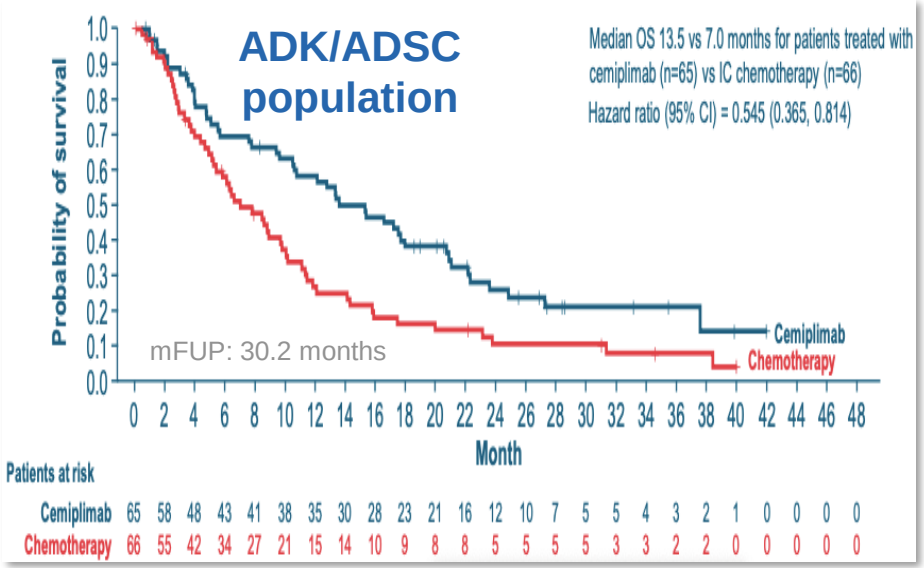
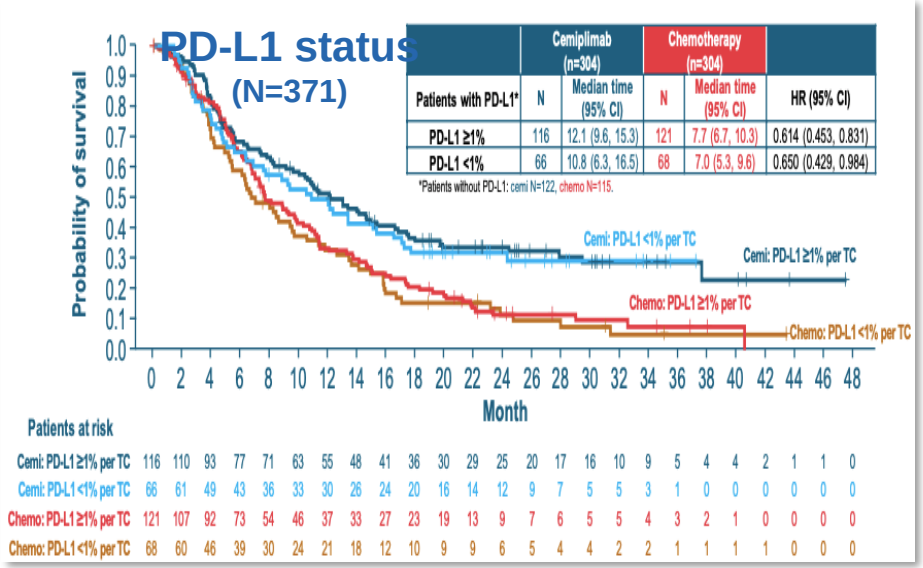
Exploratory Analysis





Patients with PD-L1*	Cemiplimab (n=304) N	Cemiplimab (n=304) Median time (95% CI)	Chemotherapy (n=304) N	Chemotherapy (n=304) Median time (95% CI)	HR (95% CI)
PD-L1 ≥1%	116	12.1 (9.6, 15.3)	121	7.7 (6.7, 10.3)	0.614 (0.453, 0.831)
PD-L1 <1%	66	10.8 (6.3, 16.5)	68	7.0 (5.3, 9.6)	0.650 (0.429, 0.984)

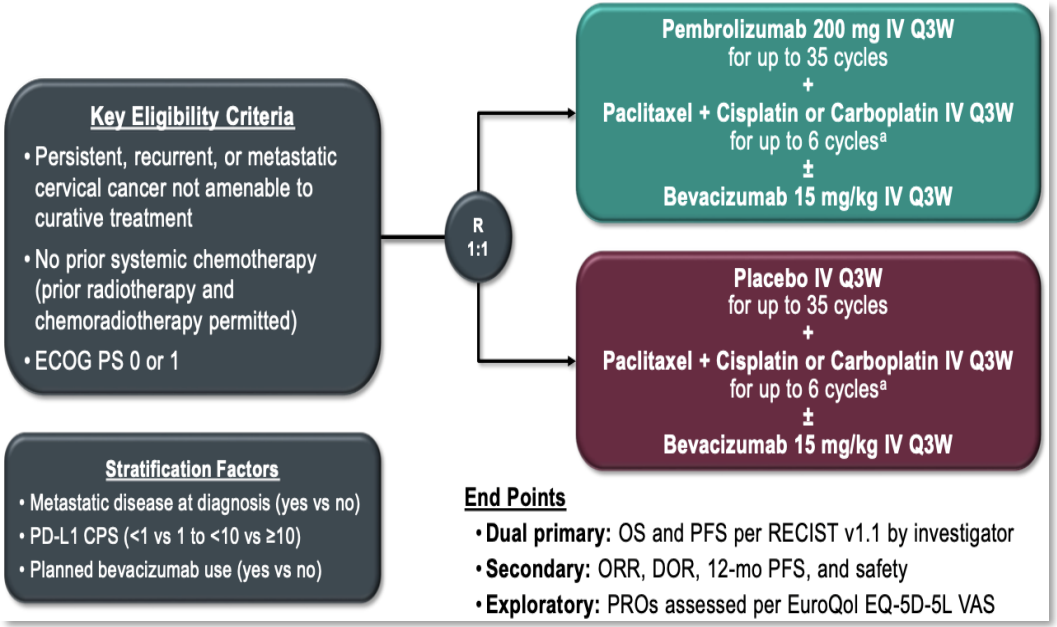
*Patients without PD-L1: cemi N=122, chemo N=115.

Oaknin A, et al at ESMO Congress 2022

IMMUNOTHERAPY FOR CERVICAL CANCER: THE MOST RELEVANT EVIDENCE

5th FACT: Pembrolizumab added to ChT +/- bevacizumab demonstrated OS benefit in first-line

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



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

N Colombo, et al at ESMO Congress 2021

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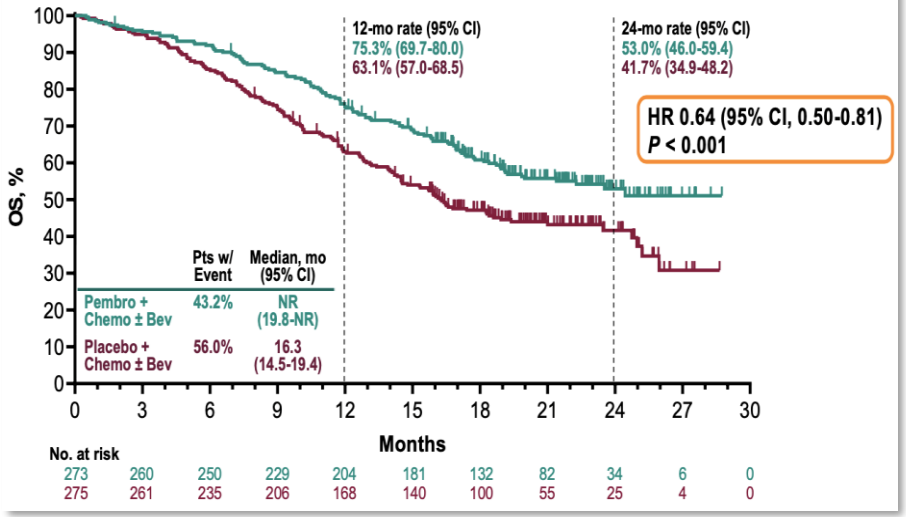
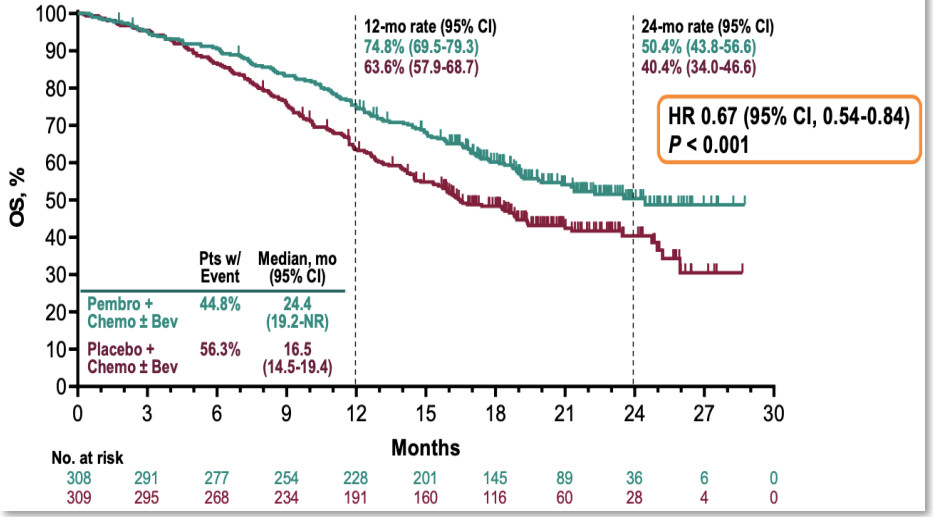
Primary Endpoint

OS: PD-L1 CPS ≥1 Population



OS: All-Comer Population



N Colombo, et al at ESMO Congress 2021

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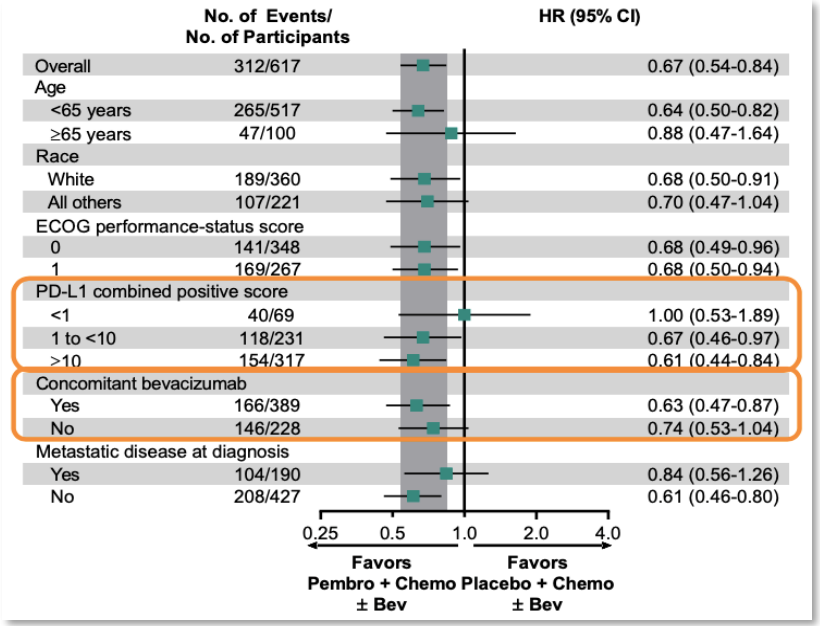
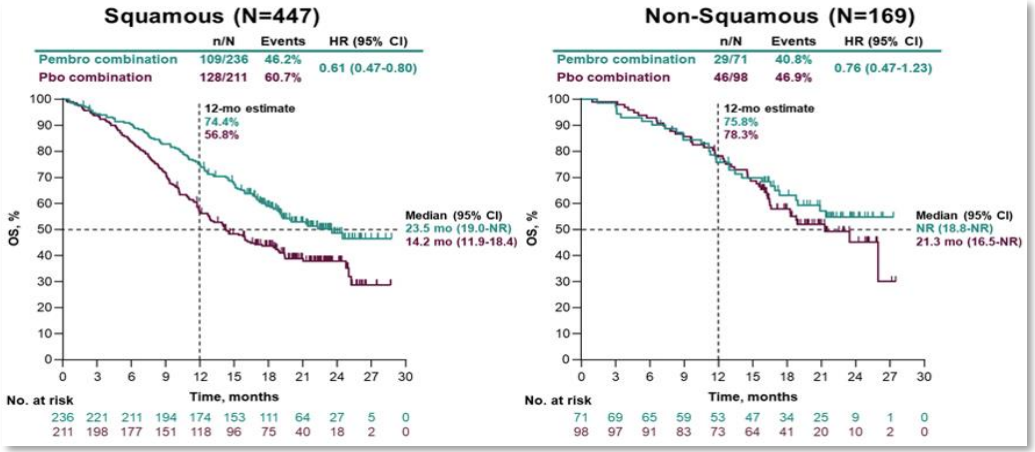
(Some subgroups appear not to benefit from addition of pembrolizumab)



Subgroup Analysis



- Study was not powered to detect differences according to histology
- Only 69 (11%) of patients were PD-L1 negative
- Up to 35% did not received bevacizumab

KS Tewari, et al at ASCO 2022

IMMUNOTHERAPY FOR CERVICAL CANCER: A REAL REALITY??

6th FACT: Cemiplimab and Pembrolizumab were both approved by EMA…

…but with some unexpected limitations

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

November 22, 2022

European Commission Approves Merck's KEYTRUDA® (pembrolizumab) Plus Chemotherapy, With or Without Bevacizumab, for Patients With Persistent, Recurrent or Metastatic Cervical Cancer Whose Tumors Express PD-L1 (CPS ≥1)

4/29/2022

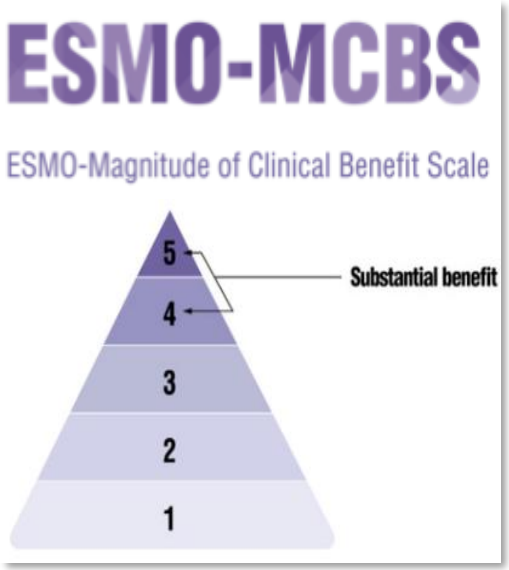
"To decide the lack of benefit on a small population of 69 (11%) patients is both scientifically and methodologically INCORRECT"

(N. Colombo at 2022 ESMO Gyn Cancer Congress)

IMMUNOTHERAPY FOR CERVICAL CANCER: A REAL REALITY??

7th FACT: Cemiplimab and Pembro were both considered to be associated to substantial benefit…

…which means considered to trigger rapid consideration for reimbursement



Tested Agent(s)	Combined Agent(s)	Control Arm	Treatment Setting
Cemiplimab	-	Investigator's choice of ChT	Indicated for the treatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy

4
Agent Score
ESMO-MCBS v1.1
Scorecard version: 1

Tested Agent(s)	Combined Agent(s)	Control Arm	Treatment	Tumour Sub-group
Pembrolizumab	ChT with our without bevacizumab	Placebo + ChT with our without bevacizumab	First-line treatment	PD-L1 (CPS ≥1)

4
Agent Score
ESMO-MCBS v1.1
Scorecard version: 1

ESMO-MCBS Scorecards (https://www.esmo.org) (2nd May 2023)

IMMUNOTHERAPY FOR CERVICAL CANCER: A REAL REALITY??

8th FACT: …But the real reality is that Cemiplimab and Pembrolizumab are not a reality in Spain…

BIFIMED: Buscador de la Información sobre la situación de financiación de los medicamentos - Nomenclátor de MAYO - 2023

Indicación autorizada	Situación expediente indicación
LIBTAYO en monoterapia está indicado para el tratamiento de pacientes adultas con cáncer de cuello uterino metastásico o recurrente cuya enfermedad ha progresado durante o después de quimioterapia basada en platino.	En estudio
KEYTRUDA, en combinación con quimioterapia con o sin bevacizumab, está indicado para el tratamiento del cáncer de cuello uterino persistente, recurrente o metastásico en mujeres adultas cuyos tumores expresen PD-L1 con una CPS mayo o igual a 1.	En estudio

Ministerio de Sanidad (https://www.sanidad.gob) (2nd May 2023)

IMMUNOTHERAPY FOR CERVICAL CANCER: OPEN QUESTIONS

9th FACT: No benefit from immunotherapy in locally advanced cervical cancer

CALLA: Durvalumab Added to Standard-of-Care CCRT
Study Design

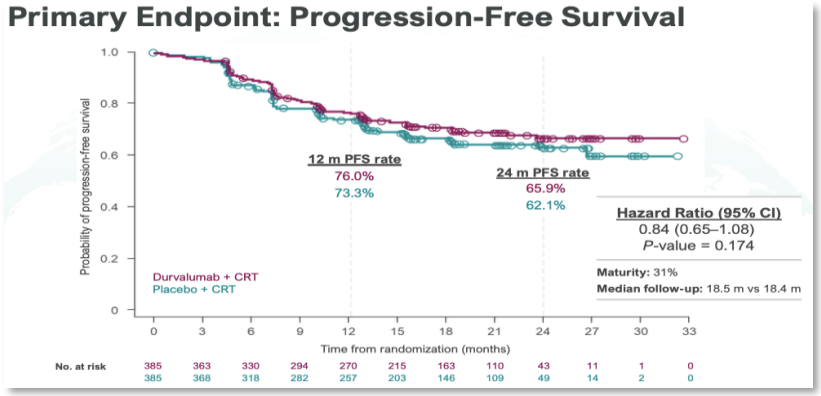
- Primary locally advanced carcinoma of the cervix (IB2-IIB node-positive or IIIA-IVA any nodal status)
- Measurable disease by RECIST v1.1
- ECOG PS: 0-1
- N=714 pts

R 1:1

- CCRT + DURVALUMAB up to 24 months or until progression
- CCRT + PLACEBOup to 24 months or until progression

Primary Endpoints:
Progression-free survival (PFS)
Secondary Endpoints:
- OS
- ORR
- DOR
- Safety
- HRQOL

Primary Endpoint: Progression-Free Survival



Monk BJ, et al at IGCS 2022

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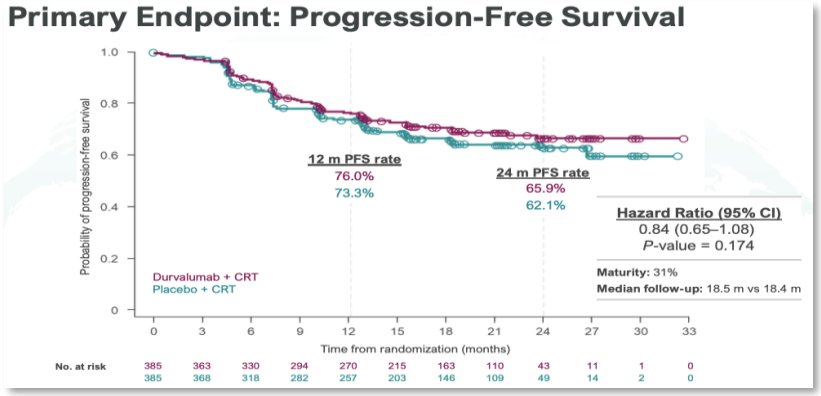

Considering the benefit observed with immunotherapy in first and second-line, what was "wrong" in LACC setting??

- Should we select a different population?? Stage ≥III?? LN+??
- Should the timing of administration be considered?? Previous?? Concomitant?? After chemoradiation??
- Would anti-PD-1 therapy be different from anti-PD-L1??

Monk BJ, et al at IGCS 2022

IMMUNOTHERAPY FOR CERVICAL CANCER: OPEN QUESTIONS

10th FACT: Promising activity with dual checkpoint inhibitors… but phase 3 trials are missing

Study	N	Population	ORR	mDoR	mPFS	mOS
CheckMate 358 Nivolumab + Ipilimumab (1L)	87	SCC HPV+/ukn 1st line	ORR: 39-41% PD-L1+ve: 33-39% PD-L1-ve: 32-67%	25.6-34.6 months	8.5-13.8 months	NR
CheckMate 358 Nivolumab + Ipilimumab (2L)	70	SCC HPV+/ukn ≤2 prior lines	ORR: 26-35% PD-L1+ve: 30-38% PD-L1-ve: 8-29%	21.1-NR months	3.6-5.8 months	10.3-25.4 months
Balstilimab + Zalifrelimab	155	All types 1 prior line All PD-L1	ORR: 25.6% PD-L1+ve: 33% PD-L1-ve: 9% PD-L1 ukn: 28%	NR (9.7-NR)	2.7 months	12.8 months
Cadonilimab (Bi-specific antibody)	111	All types ≤2 lines All PD-L1	ORR: 33% PD-L1+ve: 44% PD-L1-ve: 17%	NR	3.8 months	17.5 months
Vibostolimab (anti-TIGIT) + Pembro	80	All types <1 line All PD-L1	ORR: 15-23% PD-L1+ve: 20% PD-L1-ve: 14%	NR	2.0 months	NR

Oaknin A at ESMO Congress 2022; O'Malley DM et al. J Clin Oncol 2022;40:762-71; Wu X at SGO 2022; Shapira-Frommer R at AACR, 2022

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- Could Anti-PD1/Anti-CTL4 or Anti-TIGIT combinations be a choice for immunotherapy pre-treated patients??
- Could Ant-PD1/Anti-CTL4 agents combination replace platinum-based therapy??
- Could dual ICIs combination be a choice for those patients PD-L1 negative??

Oaknin A at ESMO Congress 2022; O'Malley DM et al. J Clin Oncol 2022;40:762-71; Wu X at SGO 2022; Shapira-Frommer R at AACR, 2022

Conclusions

Something used as a measure, norm, or model in comparative evaluations

→ **YES**

Real and effective existence of something

→ **NOT YET**

.cáncer. XII FORO DE ovario
Y OTROS TUMORES GINECOLÓGICOS

Muchas gracias por vuestra atención!!

Dra. Lydia Gaba Garcia
Hospital Clínic, Barcelona