Cervical cancer: Immunotherapy in the metastatic disease

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Conclicts of interest

- Honoraria from AZ, Clovis, GSK, Immunogen, MSD, PharmaMar, Pharma&
- Travel & accommodation support from AZ, GSK, MSD
- Research grants from ASCO Conquer Cancer, GEICO, SEOM (funded by KYOWA KIRIN), ISCIII
- Associate editor at the International Journal of Gynecological Cancer (IJGC)

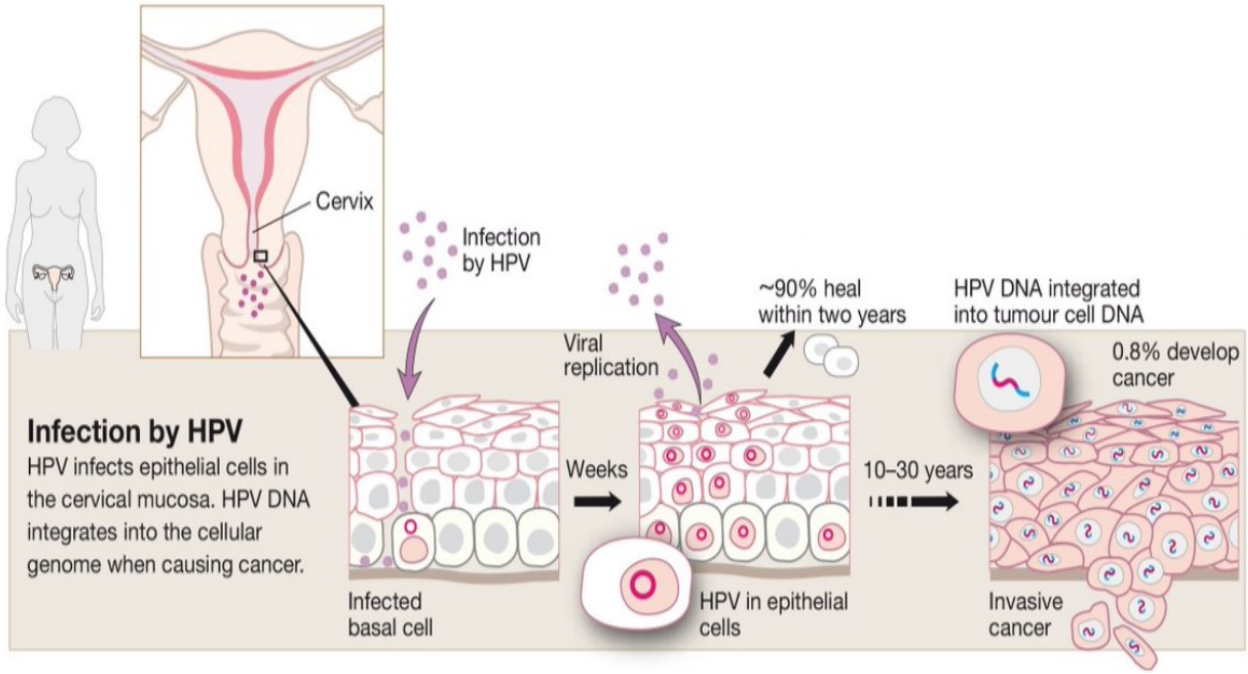
Overview

- Background
- Role of ICI in cervical cancer
  - Post-platinum recurrent
  - 1st line
- ICI combinations
- Emerging strategies
- Conclusions

Background

- Cervical cancer is the 4th most common cancer in women.
- ↑ burden in LMICs, where 85% of cases occur, & with low access to innovative therapies.

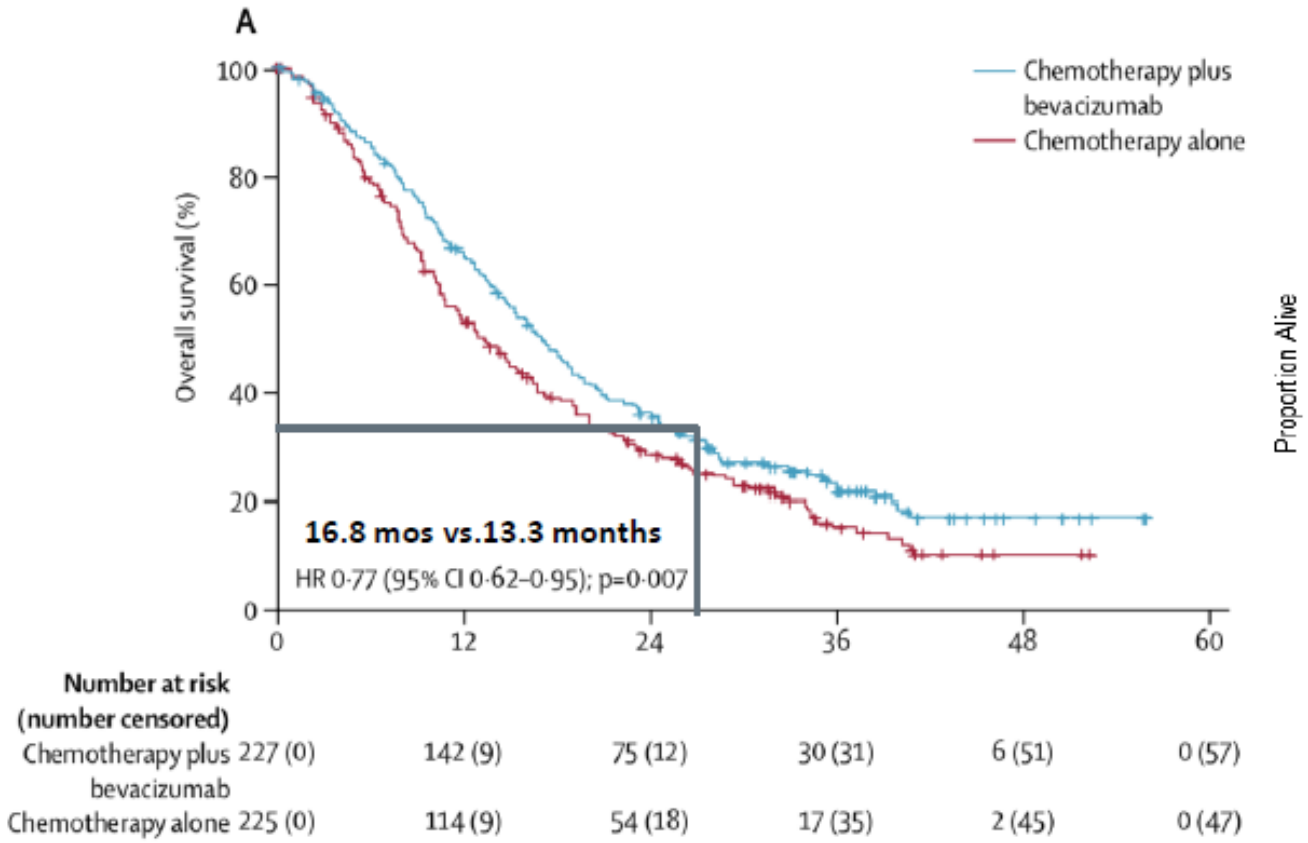
- **Virally Driven Cancer:**
- **HPV** responsible for >95% of cases
  - Most oncogenic: HPV-16, HPV-18



Grau et al. IJGC 2022, WHO 2020

Background

Prior standard in 1st line GOG 240: Platinum-based chemotherapy ± bevacizumab.



Unmet Needs:

- Not all patients are candidate for bevacizumab
- ↑ rates of progression
- Limited durable responses

→ Need for novel systemic therapies to improve survival.

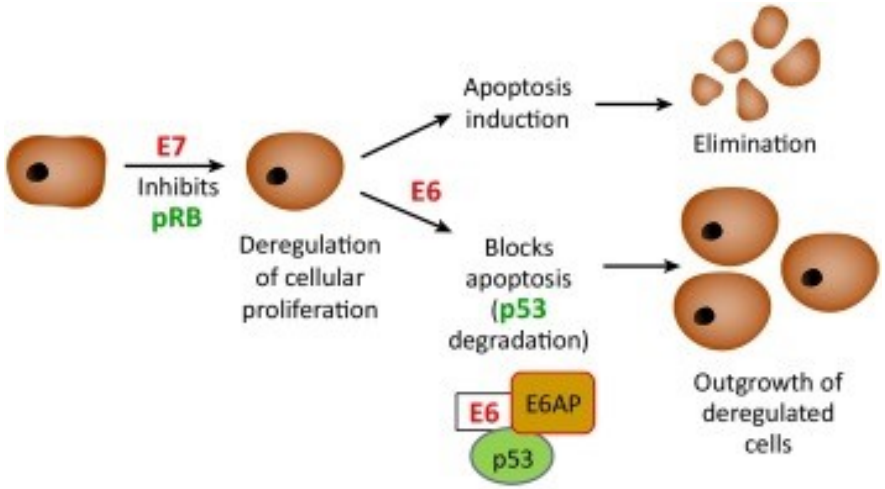
Tewari KS, et al. *Lancet*. 2017

Background

Tumors evade the immune system via immune checkpoint pathways like PD-1/PD-L1

Why immunotherapy in Cervical Cancer?

- Presence of **viral antigens**: strong association with HPV infection – immunogenic.
- HPV related **E6, E7** as potential immune targets.
- Implicated in PD1/PDL1 pathway leading to ↑PD-L1 expression, propagating immune evasion.
- Immune-Privilege State: ↑ PD-L1 expression and TILs



Immune Biomarkers	%
PD-L1 CPS ≥1	>60% (Scc ++)
TMB high	15%
MSI-H	2.6-14%

Meng et al 2018; Enwere et al 2017; Kulungara et al 2019; Chung et al 2001; Bonneville et al 2017; Shao et al 2020; Heeren et al 2006

ICI in recurrent cervical cancer

Early phase trials with single agent ICI in the recurrent, post-platinum setting

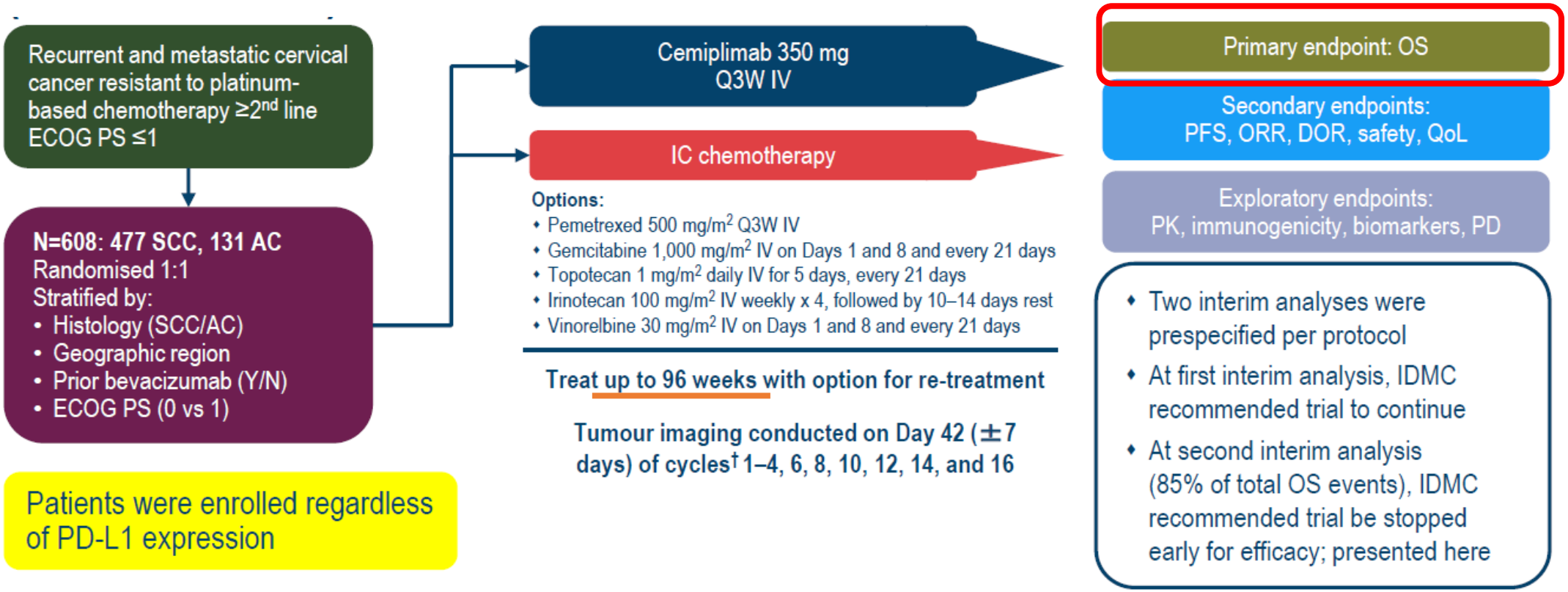
	Keynote-158	Checkmate-358	Ph2 Balstilimab
Treatment	Pembrolizumab (PD1)	Nivolumab (PD1)	Bastilimab (PD1)
N	98	19	140
Histology	Squamous (94%) Adeno (5%)	Squamous (100%)	Squamous (60%) **Adeno/AdenoSq (40%)**
N lines	3+ (31%)	3+ (16%)	1 (99%)
PDL1 CPS	CPS ≥1 : 84%		CPS ≥1 : 61%
ORR	**Overall 14.3%** CPS ≥1: 17% CPS <1: 0%	**Overall 26.3%** PDL1+: 20% PDL1-: 16.7%	**Overall 15%** CPS ≥1: 17% CPS <1: 0%
Median **DoR**	**NR**	**NR**	**15.4 m**
PFS	2.1m	5.1m	NR
OS	9.4m PDL1+ 11m	21.9m	NA

ORR 14-26%
Long dOR

Pembrolizumab FDA approved 2018 in CPS ≥1

ICI in recurrent cervical cancer

EMPOWER: Phase III RCT Cemiplimab vs Chemotherapy



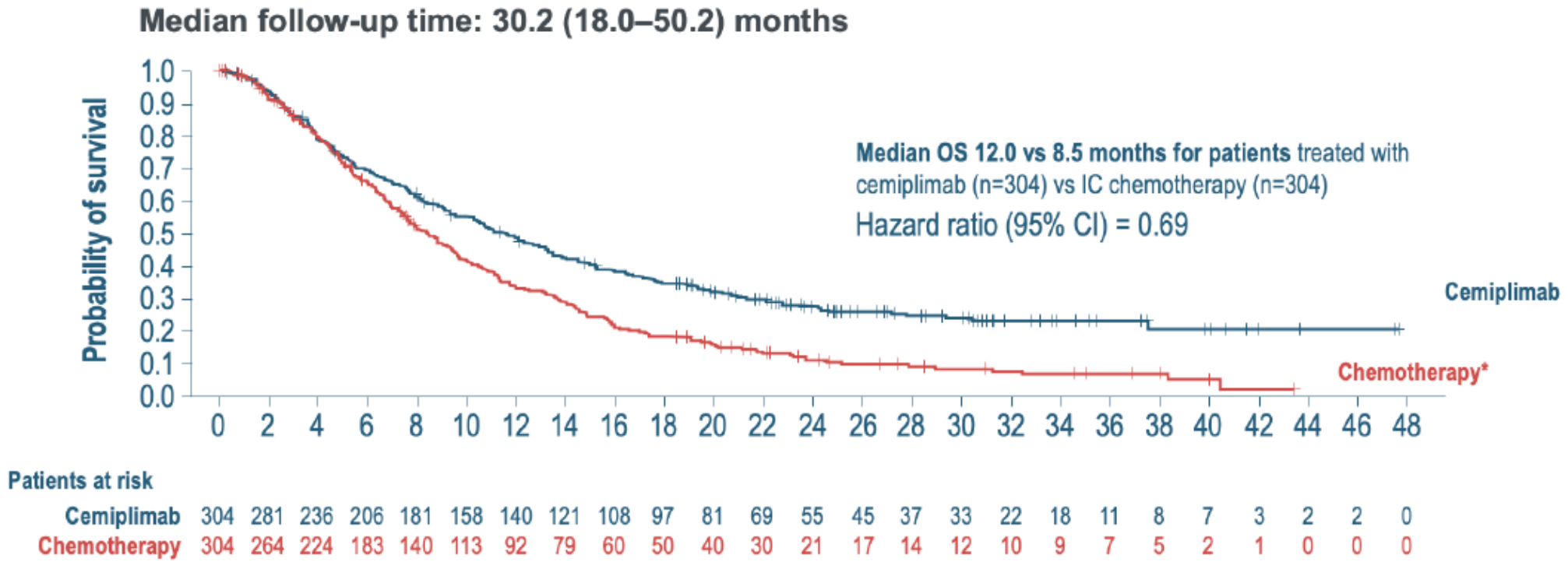
Cemiplimab: PD-1–blocking monoclonal antibody

Population: 78% SCC. 1 prior line of therapy 57%. Prior Bev 50%

Tewari, NEJM 2022

ICI in recurrent cervical cancer

EMPOWER: Phase III RCT Cemiplimab vs Chemotherapy: OS in the **overall population**



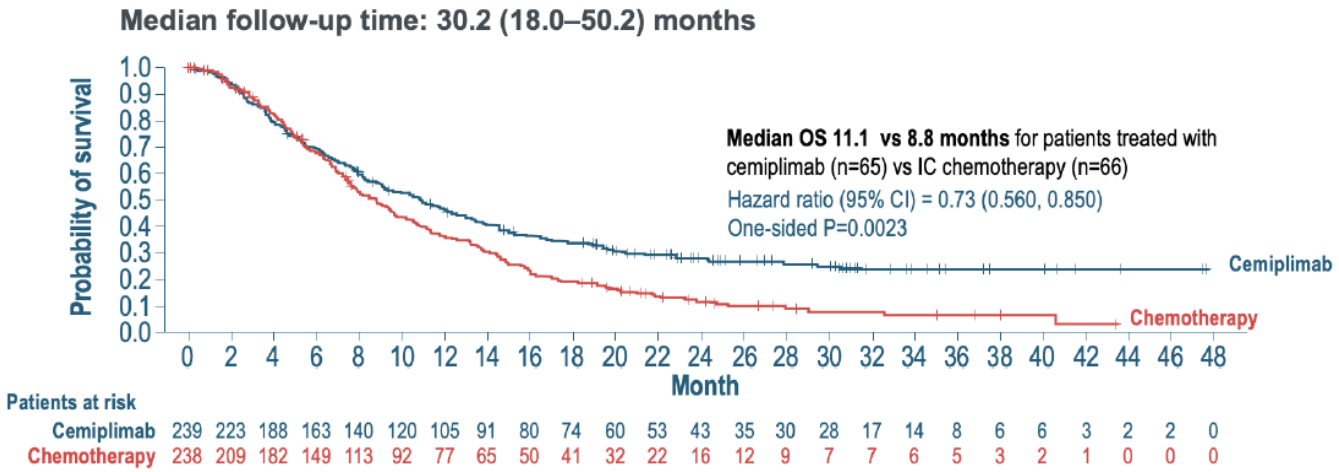
PFS: 2.7m (Cemi) vs 2.8m (Chemo), HR 0.75; 95% CI, 0.63 to 0.89; p<0.001
mDOR: 16.4m (Cemi) vs 6.9m(Ch); **ORR**: 16.4% (Cemi) vs 6.3% (Chemo)

Tewari, NEJM 2022

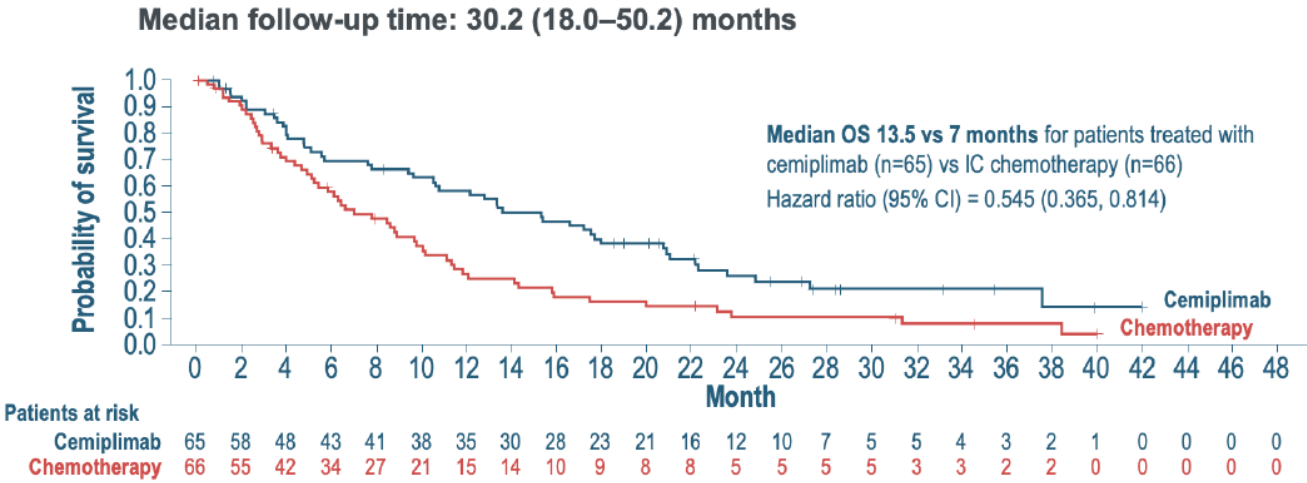
ICI in recurrent cervical cancer

EMPOWER: Phase III RCT Cemiplimab vs Chemotherapy

OS in **squamous cell**
(n= 473, 77.8%)



OS in **adenocarcinoma** or
adeno-squamous
(n= 135, 22.2%)

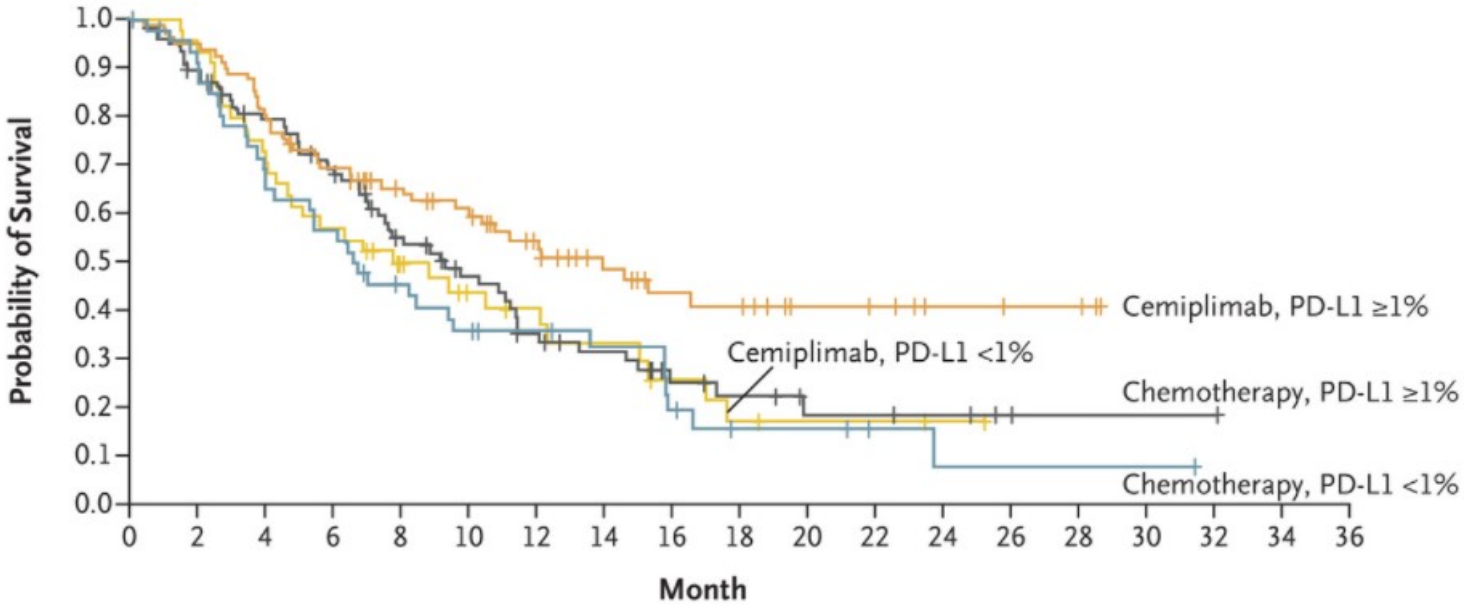


Tewari, NEJM 2022

ICI in recurrent cervical cancer

EMPOWER: Phase III RCT Cemiplimab vs Chemotherapy

Biomarkers



No. at Risk																			
Cemiplimab, PD-L1 ≥1%	82	78	65	55	45	39	30	22	16	15	10	9	4	3	3	0	0	0	0
Cemiplimab, PD-L1 <1%	44	41	30	25	18	13	11	9	6	4	3	3	1	0	0	0	0	0	0
Chemotherapy, PD-L1 ≥1%	80	69	58	50	36	28	20	16	10	8	5	5	4	2	1	1	1	0	0
Chemotherapy, PD-L1 <1%	48	40	30	26	19	15	12	10	6	4	4	2	1	1	1	1	0	0	0

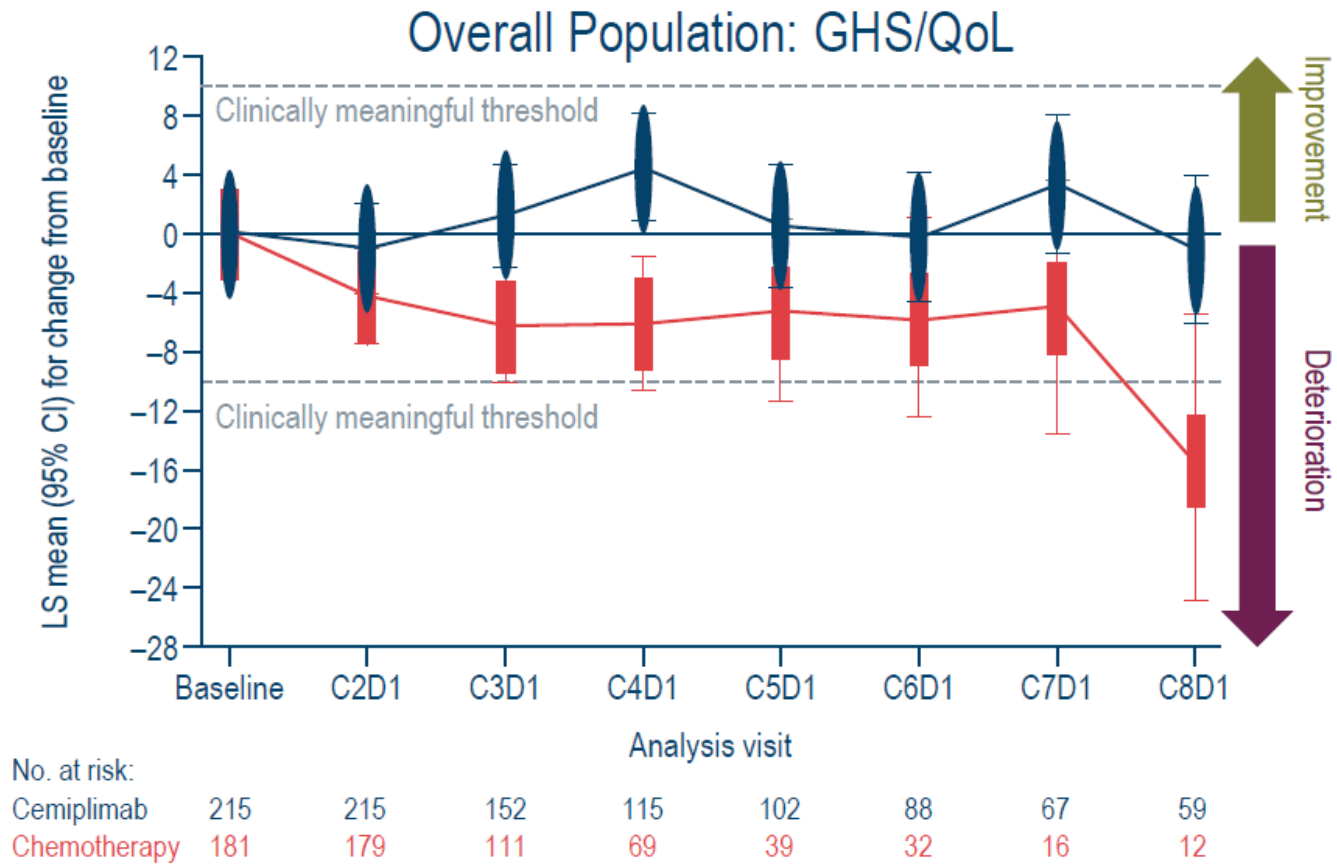
44% tumor samples evaluable for PD-L1 expression

PDL1 CPS ≥1: SCC 70%, Adeno 32.6%

Tewari, NEJM 2022

ICI in recurrent cervical cancer

EMPOWER: Phase III RCT Cemiplimab vs Chemotherapy



Overall (SE)
Cemiplimab: 1.01 (1.54)
Chemotherapy: −6.81 (2.12)
Difference: 7.81, one-sided nominal *P*=0.00040

- Overall population: nominally significant difference in favour of cemiplimab over IC chemotherapy
- **Patients receiving cemiplimab improved or maintained GHS/QoL from baseline**
- Patients receiving chemotherapy generally showed deterioration in these scores

Tewari, NEJM 2022

Can we move ICI to an earlier setting?

Subsequent lines

EMPOWER-Cervical-1
Cemiplimab
Approved: any CPS

KEYNOTE-158 (Phase II)
Pembrolizumab
Approved: PDL1 CPS ≥1

* If not previously treated with ICI

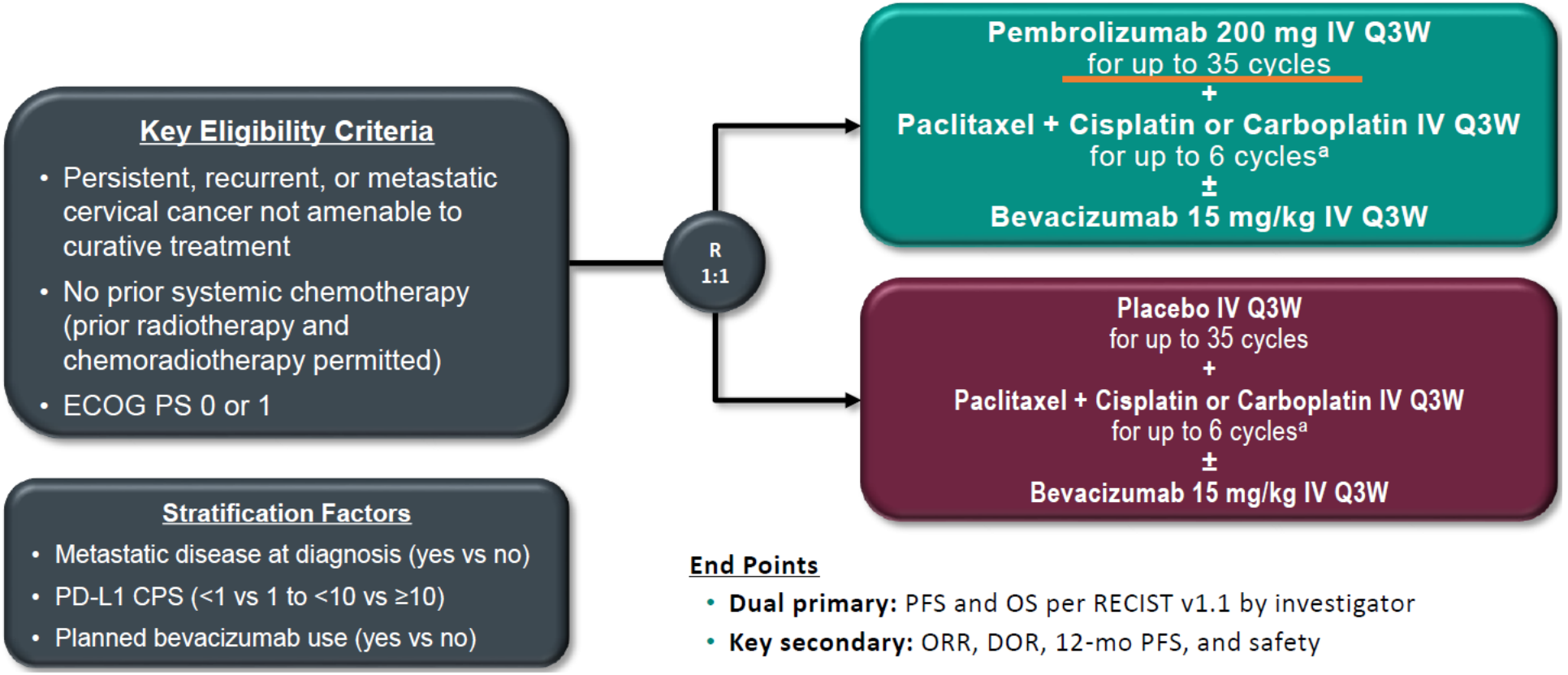
1st line

KEYNOTE-826
Pembrolizumab + Ch +/- Bevacizumab
Approved: PDL1 CPS ≥1

BEATCC
Atezolizumab + Ch + Bevacizumab

ICI in advanced and metastatic cervical cancer

KEYNOTE-826: Phase III RCT Chemo +/- Bev with Pembro vs Pcb

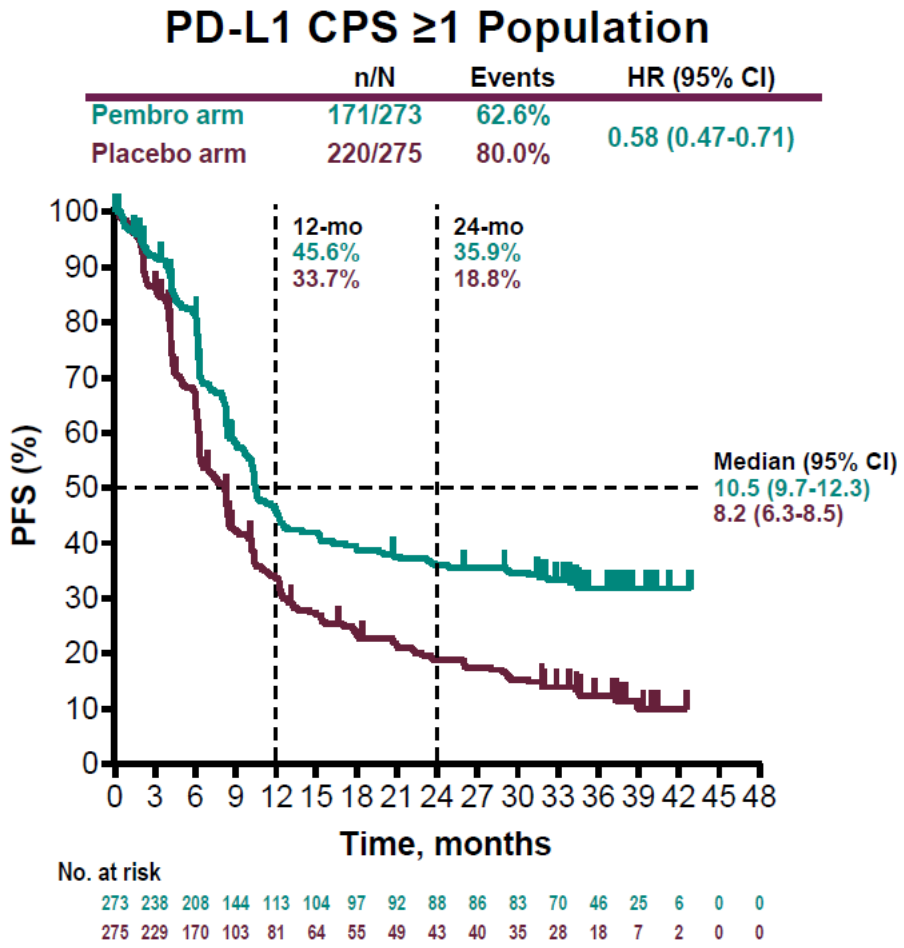


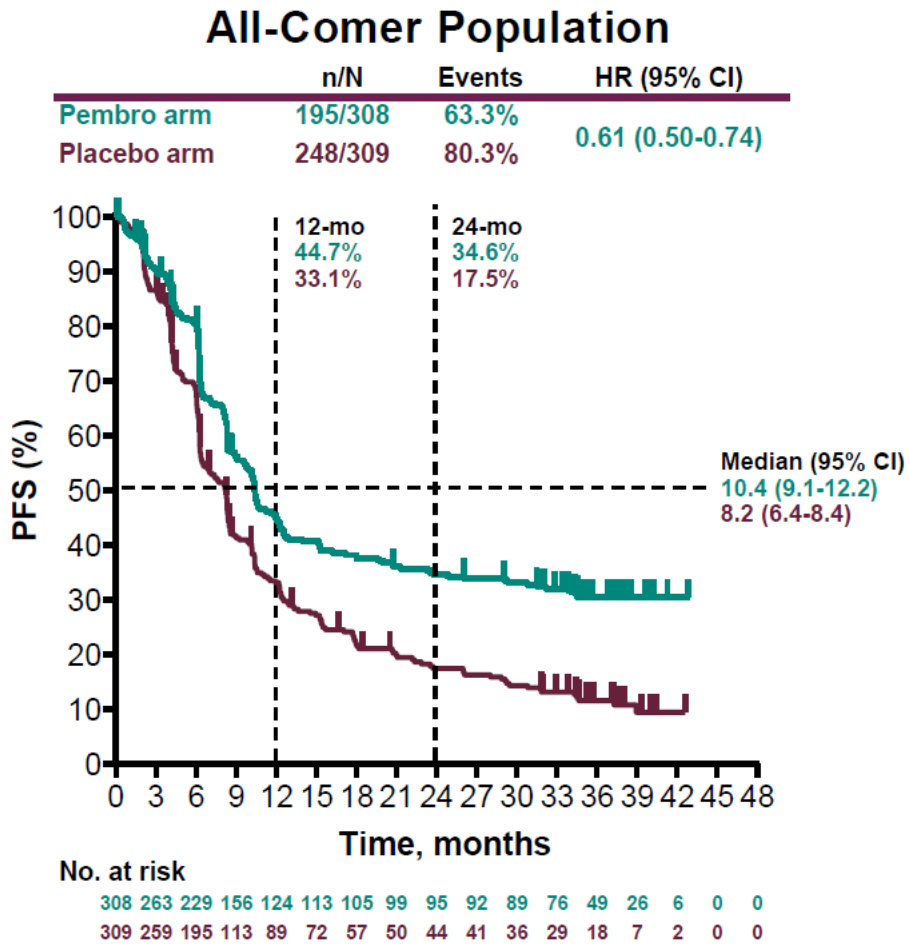
Population: 72% SCC, PD-L1 CPS≥1 89%

Colombo, NEJM 2021

ICI in advanced and metastatic cervical cancer

KEYNOTE-826: Phase III RCT Chemo +/- Bev with Pembro vs Pcb **– Final PFS**

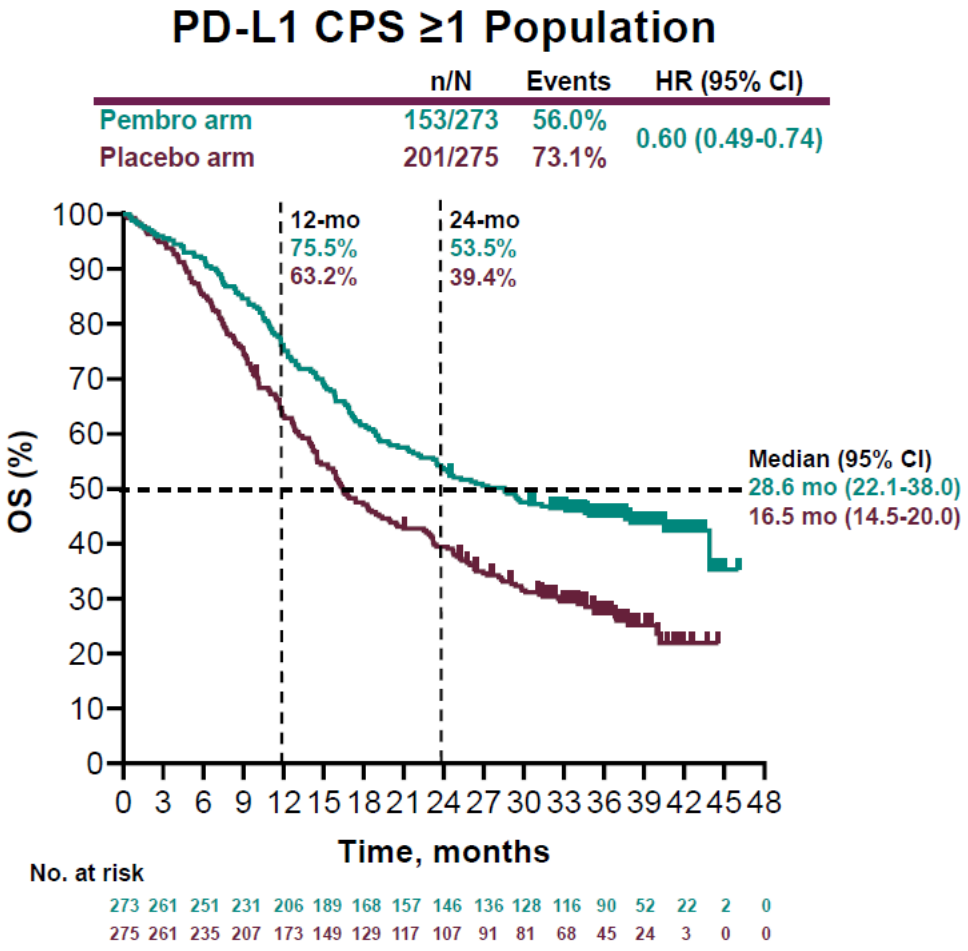


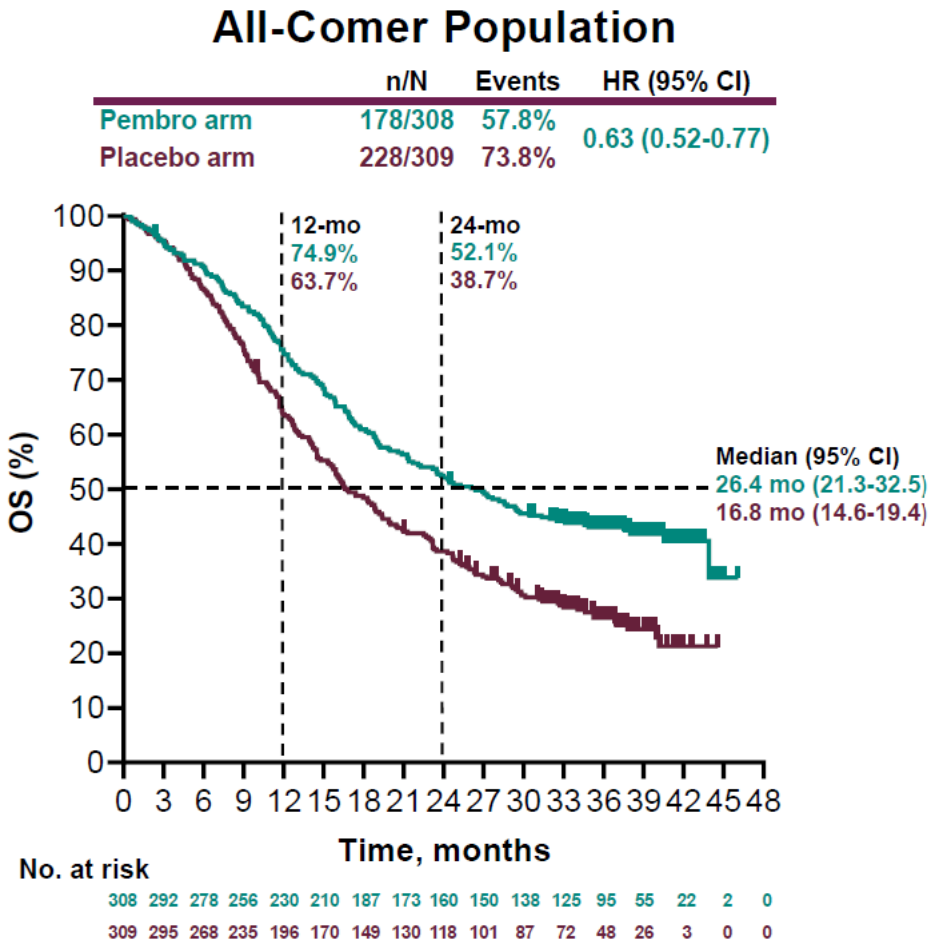


Monk, JCO 2023

ICI in advanced and metastatic cervical cancer

KEYNOTE-826: Phase III RCT Chemo +/- Bev with Pembro vs Pcb **– Final OS**

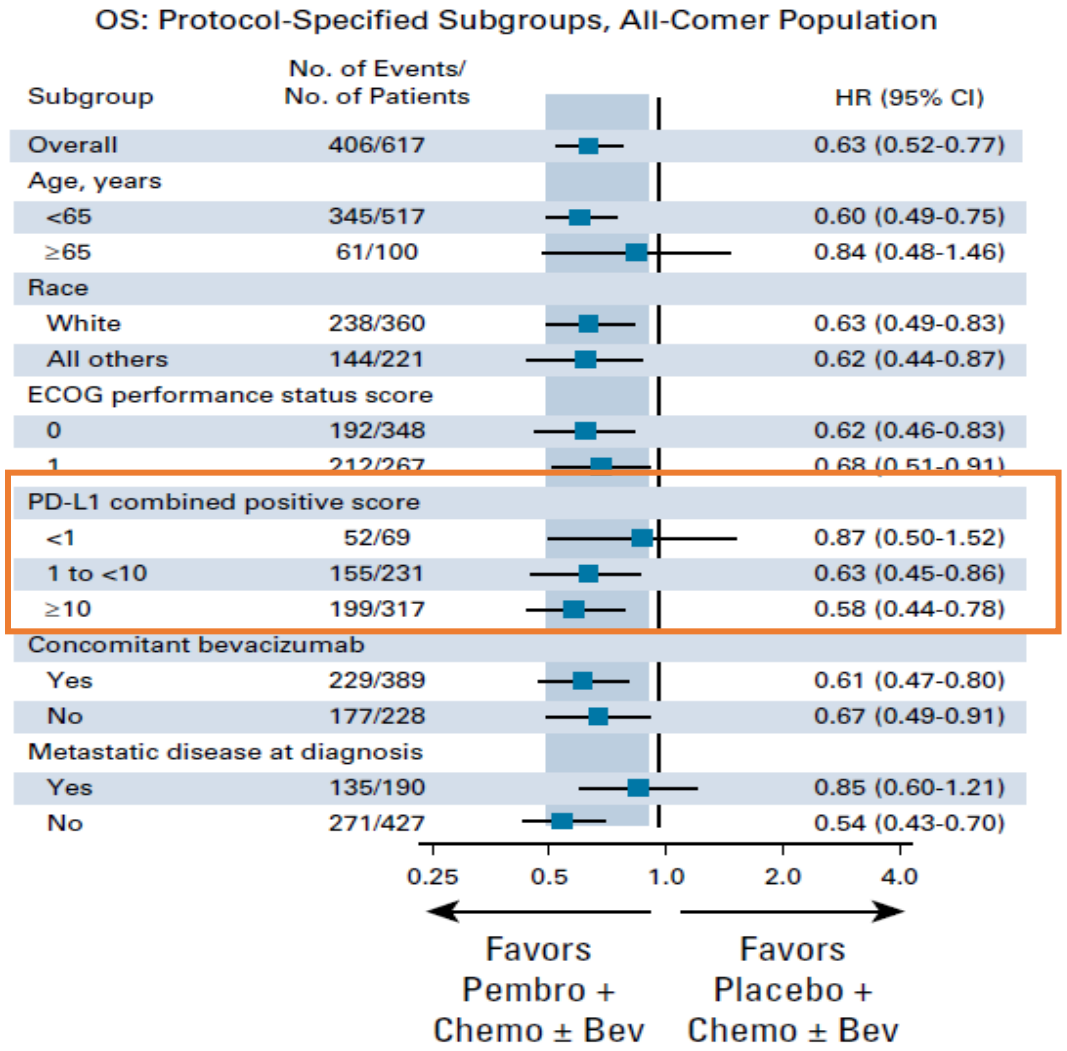




Monk, JCO 2023

ICI in advanced and metastatic cervical cancer

KEYNOTE-826: Phase III RCT Chemo +/- Bev with Pembro vs Pcb



Regulatory agency approval
PD-L1 CPS ≥1

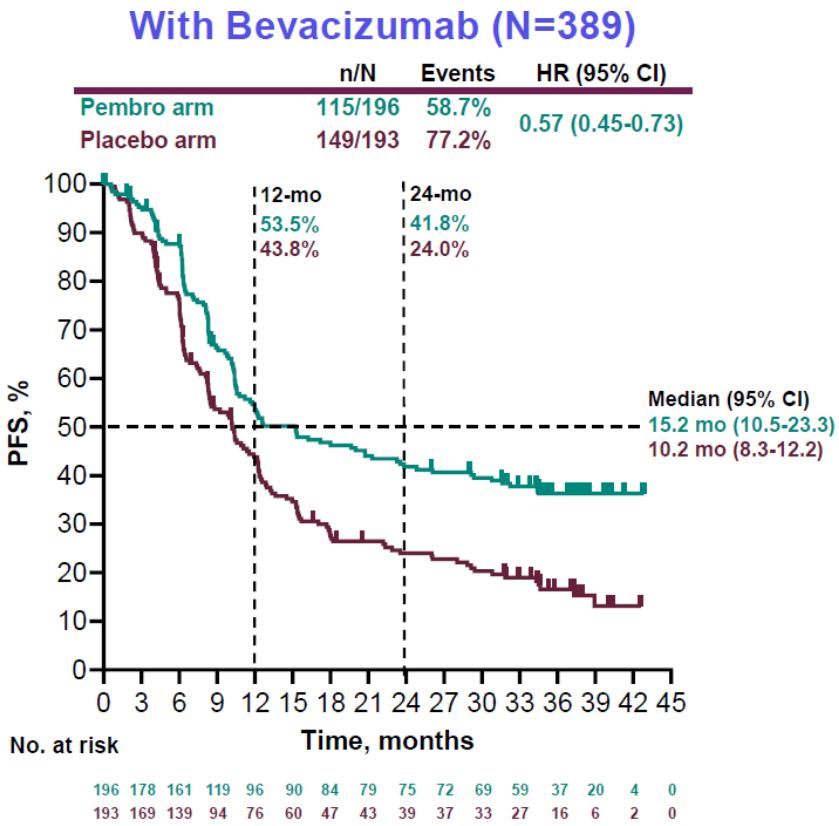
Monk, JCO 2023

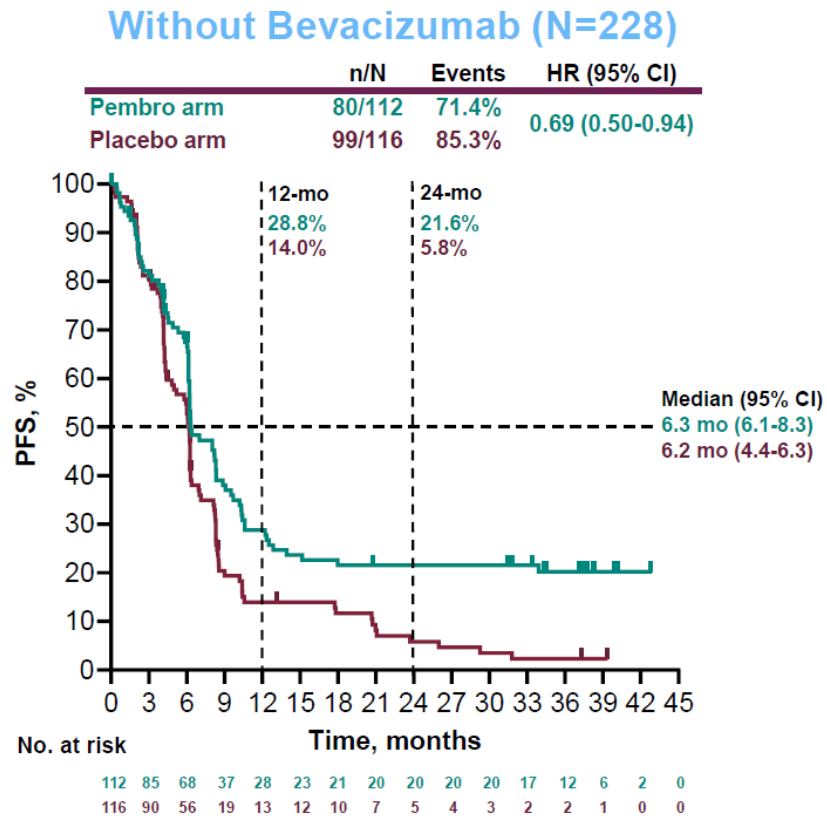
ICI in advanced and metastatic cervical cancer

KEYNOTE-826: Phase III RCT Chemo +/- Bev with Pembro vs Pcb

Bevacizumab use 63%

Reasons for no use:
-Non-medical 19%
-**Medical 76%** (GI perf, fistula risk 35%)
-Other 5%





Lorusso et al. Annals Oncol 2023

ICI in advanced and metastatic cervical cancer

BEATCC: Phase III RCT Chemo **+** Bev **+- Atezolizumab** (open-label)

- Metastatic, persistent or recurrent cervical cancer not amenable to curative therapy
- GOG/ECOG PS ≤1
- No prior systemic anti-cancer therapy for R/M CC
- In patients with pelvic disease, no bladder or rectal mucosa involvement
- Available archival or fresh tumour sample for PD-L1 expression

R 1:1

N=410

Atezolizumab 1200 mg + bevacizumab 15 mg/kg + paclitaxel + cis/carboplatin[a] all IV q3w

Bevacizumab 15 mg/kg + paclitaxel + cis/carboplatin[a] all IV q3w

- Continued until disease progression/unacceptable toxicity
- Patients with CR after ≥6 cycles could stop chemotherapy and continue biological therapy alone
- Crossover from standard arm at progression not permitted

Stratification factors:

- Prior concurrent chemoradiation (yes vs no)
- Histology (squamous cell carcinoma vs adenocarcinoma[b] including adenosquamous carcinoma)
- Chemotherapy backbone (cisplatin vs carboplatin)

Dual primary endpoints

- Investigator-assessed PFS (RECIST 1.1)
- OS

Key secondary endpoints

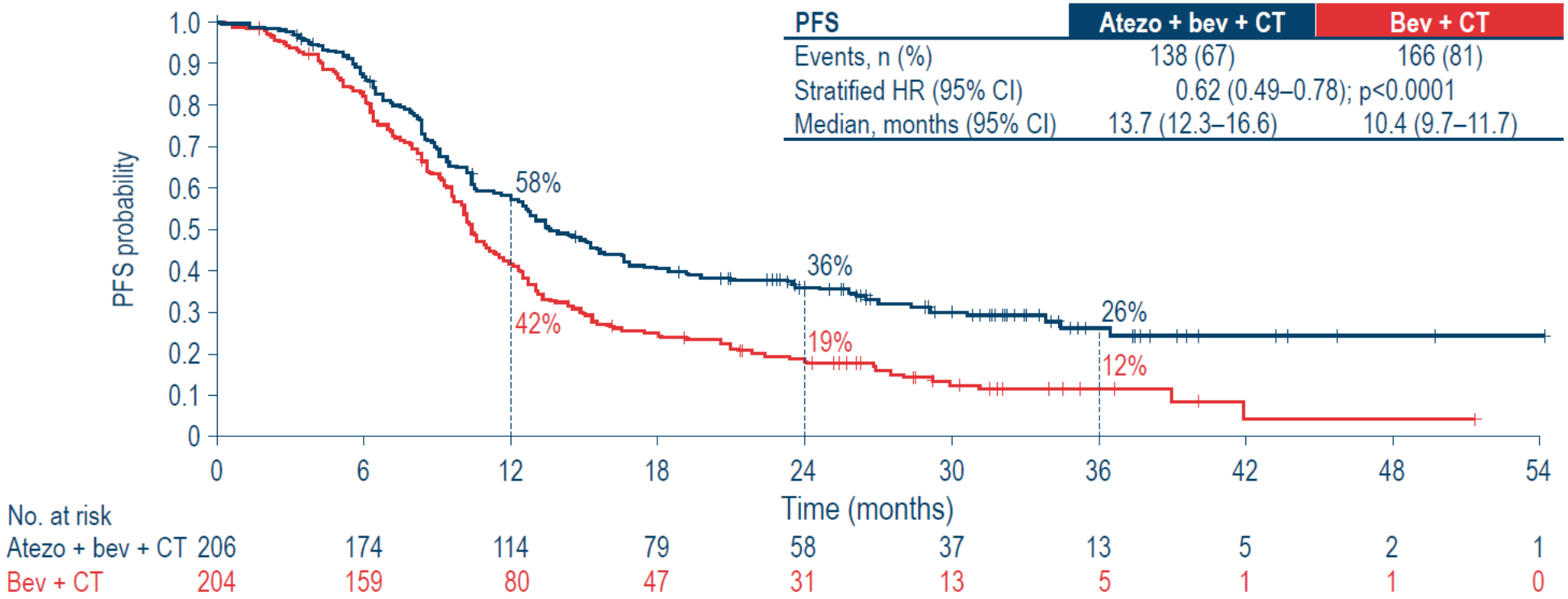
- ORR (RECIST v1.1)
- DoR (RECIST v1.1)
- TFST
- PFS2
- Safety

Population: 78% SCC, PD-L1 status not reported

Oaknin et al. Lancet 2024

ICI in advanced and metastatic cervical cancer

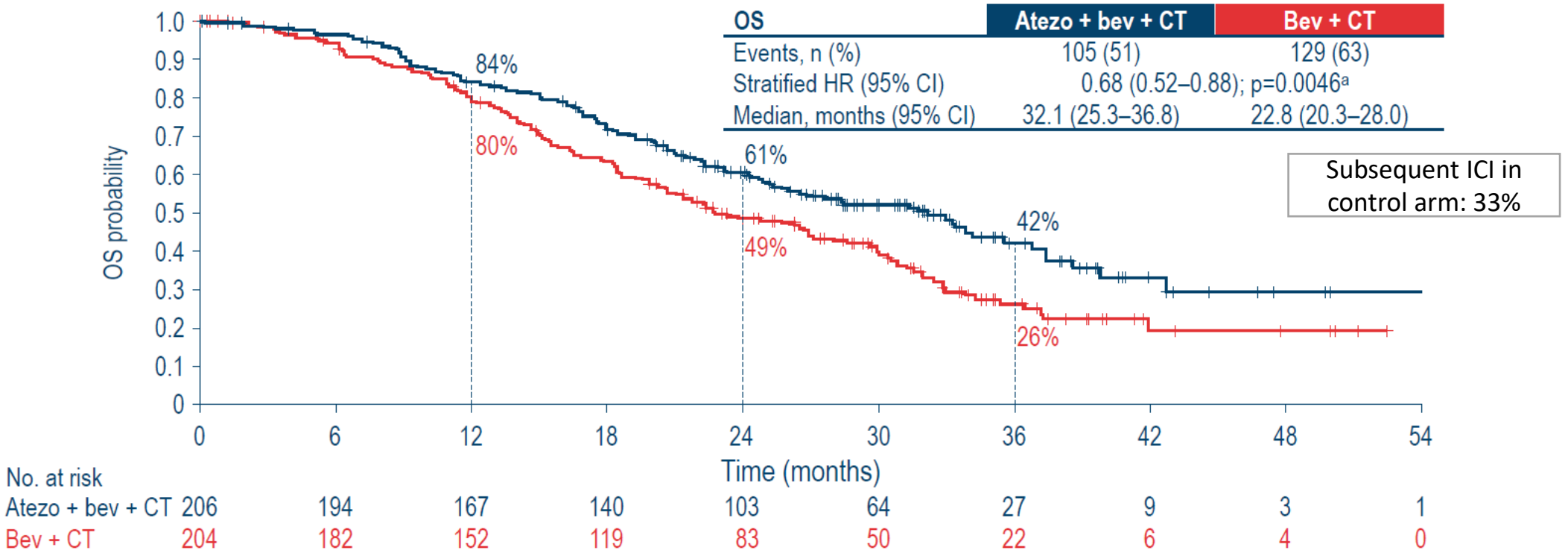
BEATCC: Phase III RCT Chemo + Bev +- Atezolizumab **– Dual primary endpoint PFS (final)**



Oaknin et al. Lancet 2024

ICI in advanced and metastatic cervical cancer

BEATCC: Phase III RCT Chemo + Bev +- Atezolizumab **– Dual primary endpoint OS (intermediate)**



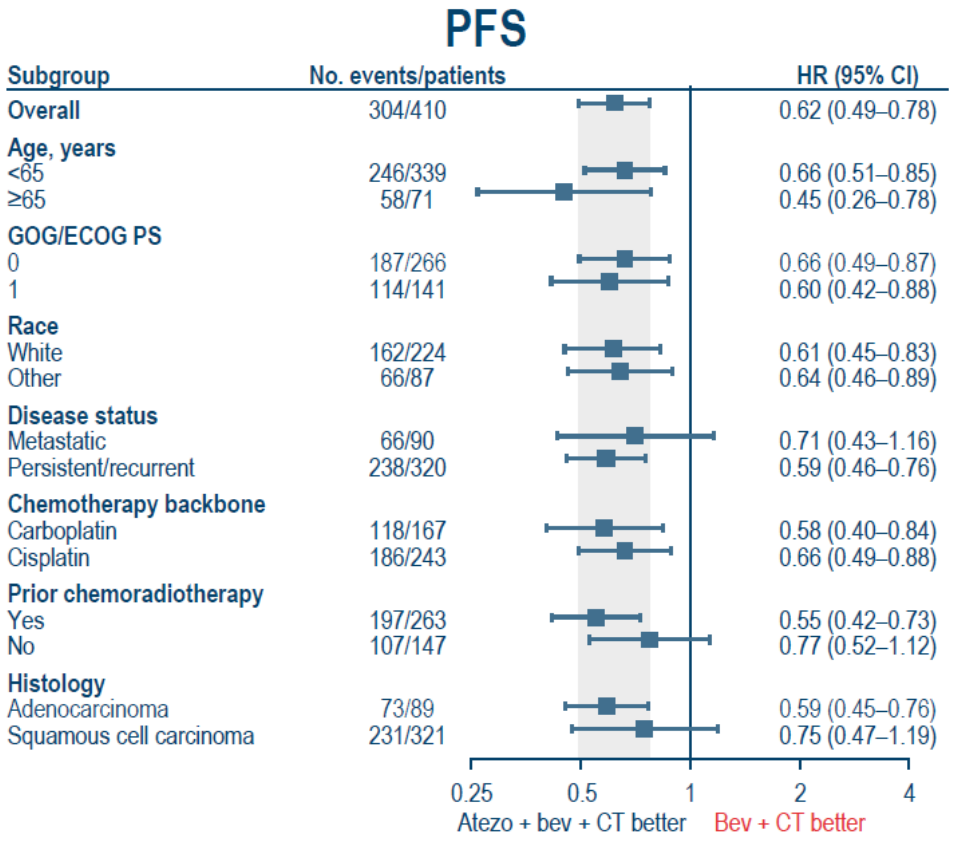
OS	Atezo + bev + CT	Bev + CT
Events, n (%)	105 (51)	129 (63)
Stratified HR (95% CI)	0.68 (0.52–0.88); p=0.0046[a]	
Median, months (95% CI)	32.1 (25.3–36.8)	22.8 (20.3–28.0)

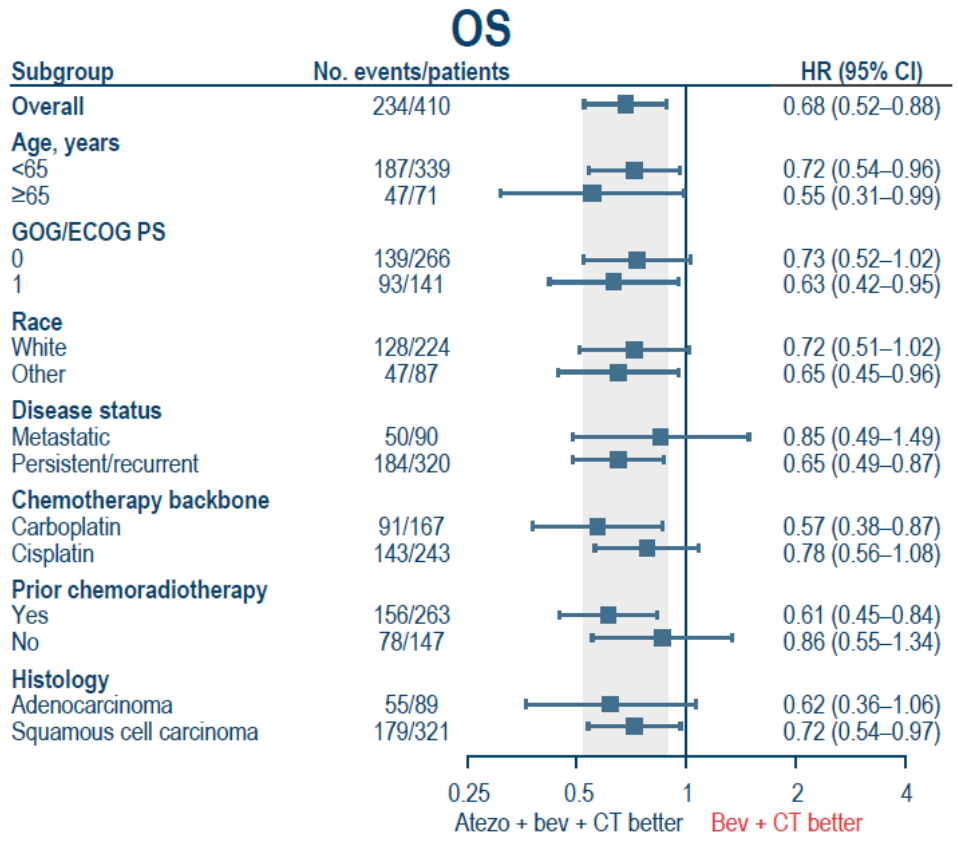
Subsequent ICI in control arm: 33%

Oaknin et al. Lancet 2024

ICI in advanced and metastatic cervical cancer

BEATCC: Exploratory subgroup analyses



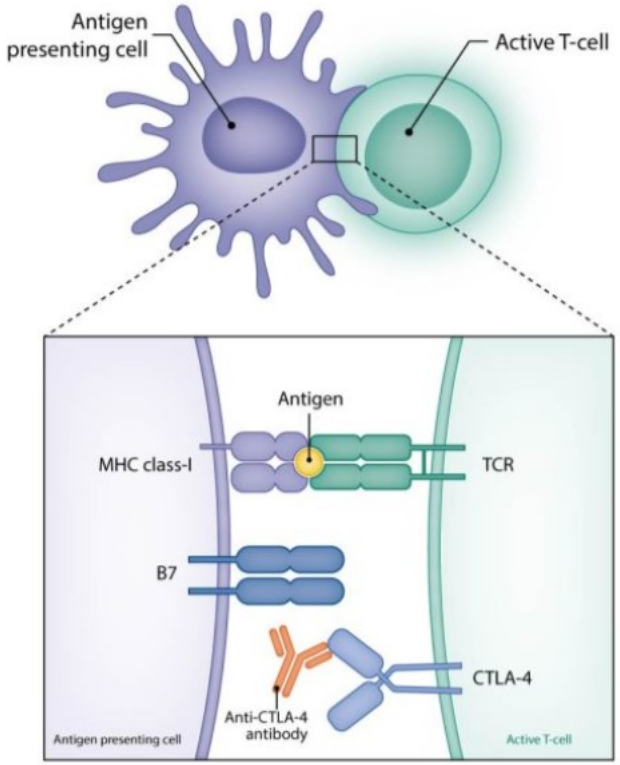


Biomarker studies ongoing – academic trial

Oaknin et al. Lancet 2024

ICI combination approaches: anti-CTLA4

Dual blockade may synergistically enhance antitumor activity



	CheckMate-358	C-550-01	AK104
	Ph I/II: (1) **Nivo** Or (2) **Nivo+Ipi** Or (3) **Nivo+Ipix4→Nivo**	**Balstilimab** (antiPD1) + **Zalifrelimab** (anti-CTLA4)	Phase II **Cadonilimab** (bispecific)
N	176	155	111
ORR	26% vs 31% vs 38% (Chemo-naïve ↑)	25.6%	33%
DoR	NR vs 24.4m vs 34.1m	NR	NR
PFS	NR	2.7m	3.75 m
OS	21.6m vs 15.2m vs 20.9m	12.8m	17.5 1m

O'malley et al. ESMO 2021; Oaknin et al ESMO 2022; Wu X et al. Gynecol Oncol 2022

Can we move ICI to an earlier setting?

Subsequent lines

EMPOWER-Cervical-1
Cemiplimab
Approved: any CPS

KEYNOTE-158 (Phase II)
Pembrolizumab
Approved: PDL1 CPS ≥1

* If not previously treated with ICI

1st line

KEYNOTE-826
Pembrolizumab + Ch +/- Bevacizumab
Approved: PDL1 CPS ≥1

BEAT-CC
Atezolizumab + Ch + Bevacizumab

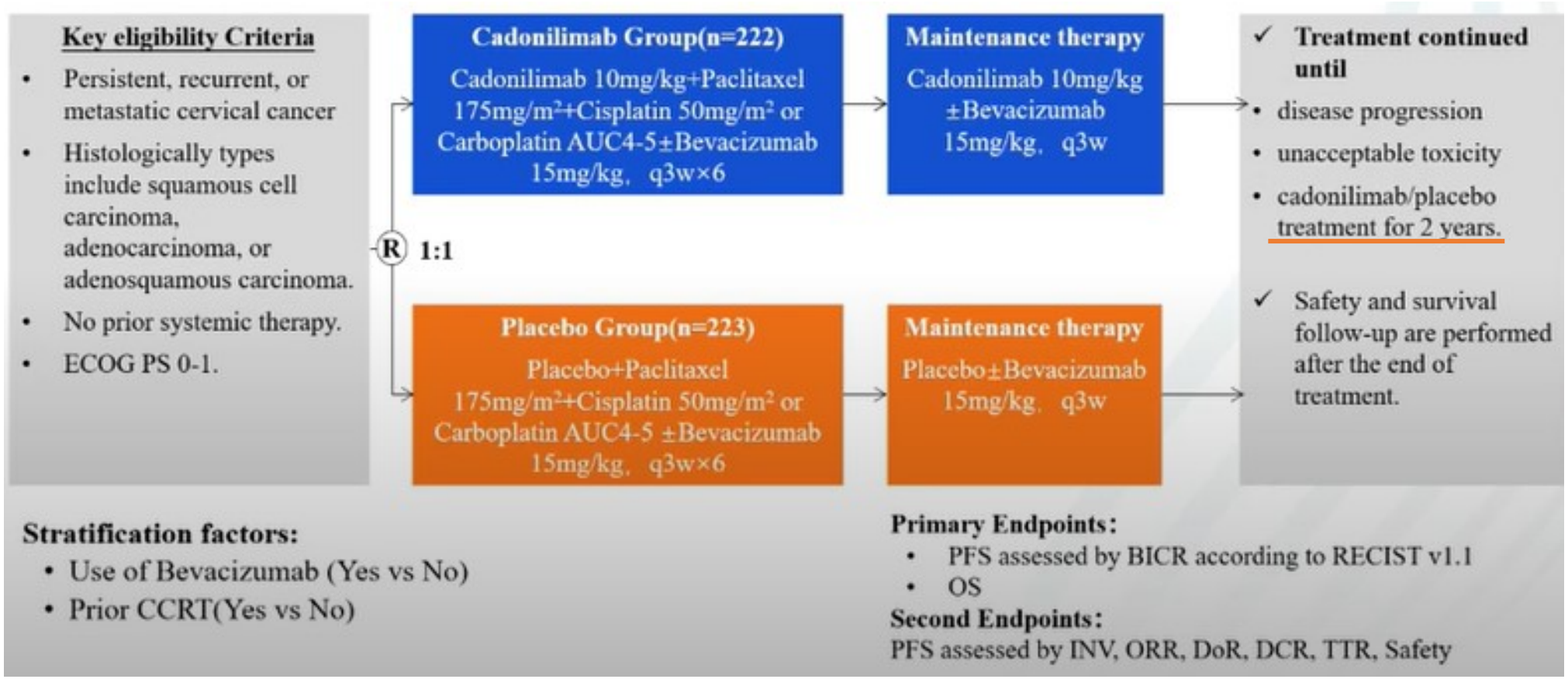
AntiPD1+CTLA4?

COMPASSION-13 (Phase II)
Cadonilimab + Ch +/- Bevacizumab. ORR: 80%

COMPASSION-16
Cadonilimab + Ch +/- Bevacizumab

ICI combination approaches

COMPASSION-16: Phase III RCT Chemo +/- Bev with Cadonilimab vs Pcb

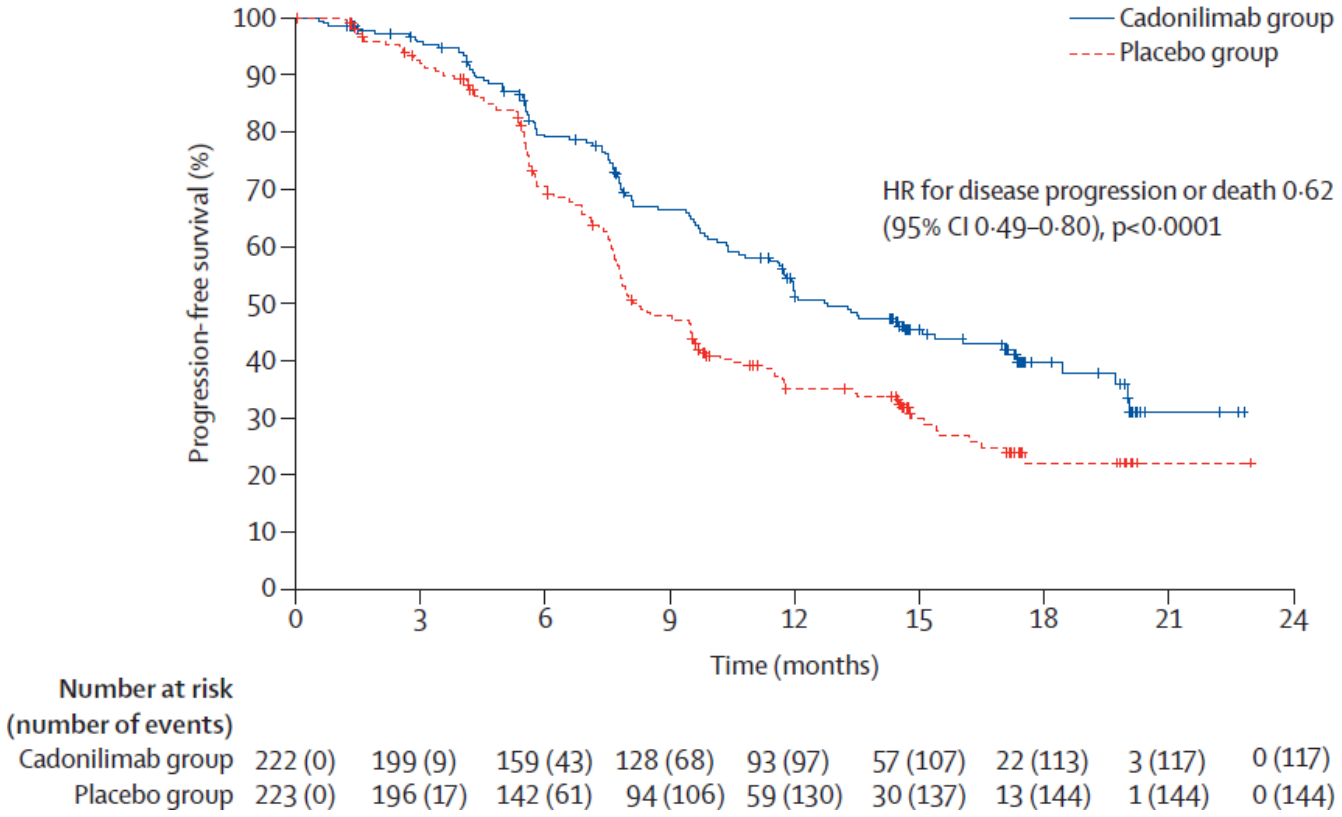


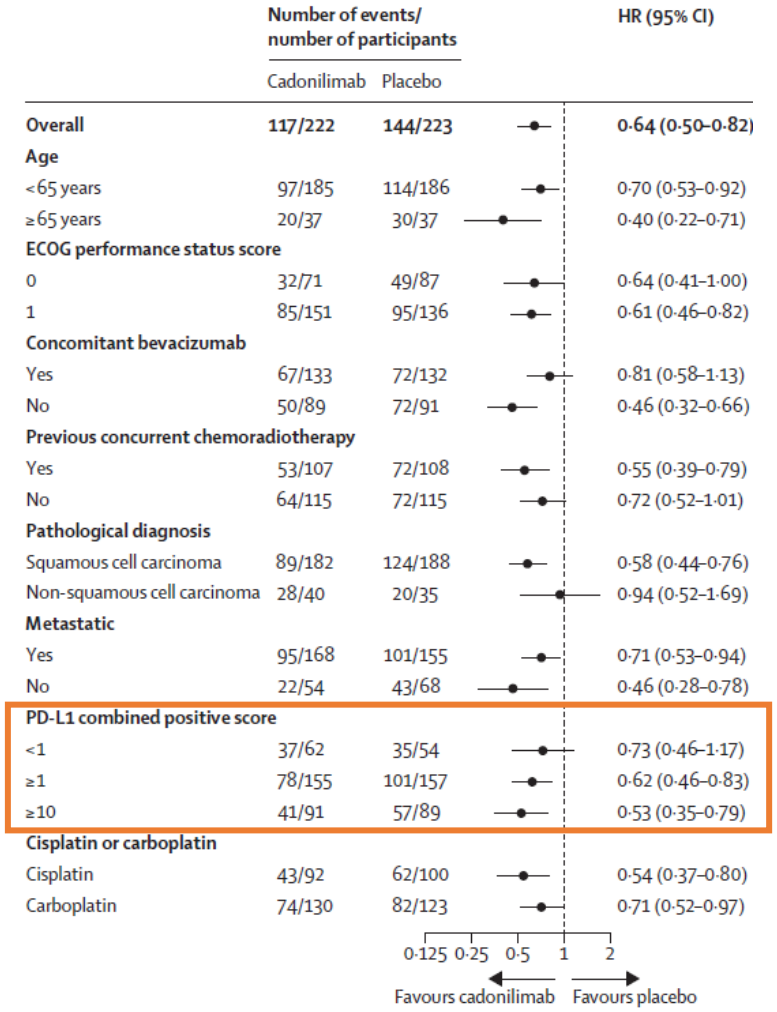
Population (N=445): 83% SCC, prior Ch-Rt 48%, PDL1 CPS <1 25%

Wu et al. Lancet 2024

ICI combination approaches

COMPASSION-16: Phase III RCT Chemo +/- Bev with Pembro vs Pcb – **PFS**

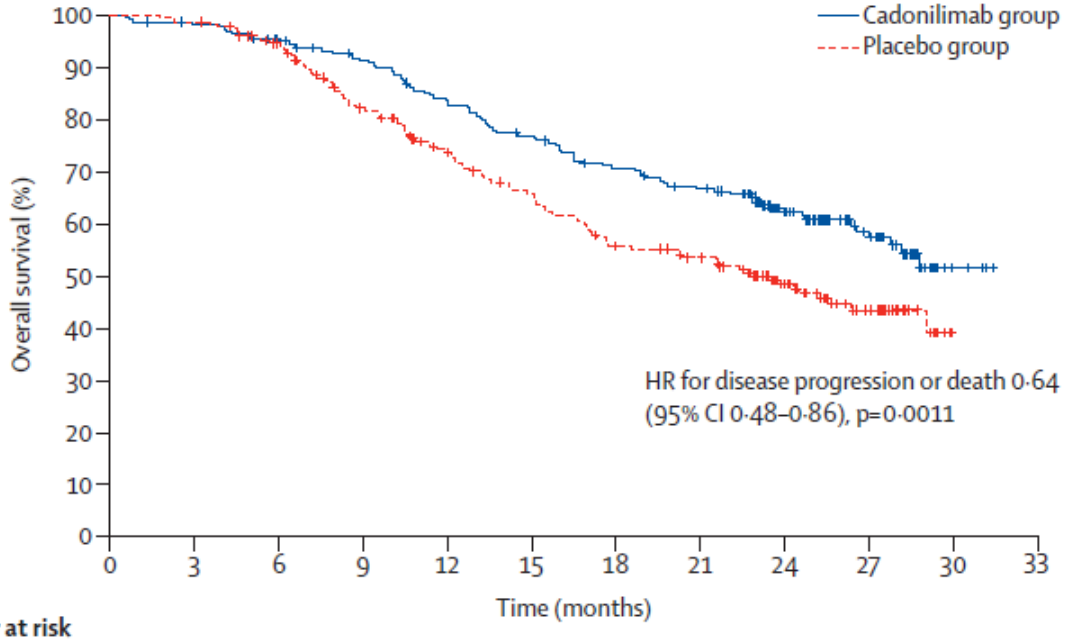




Wu et al. Lancet 2024

ICI combination approaches

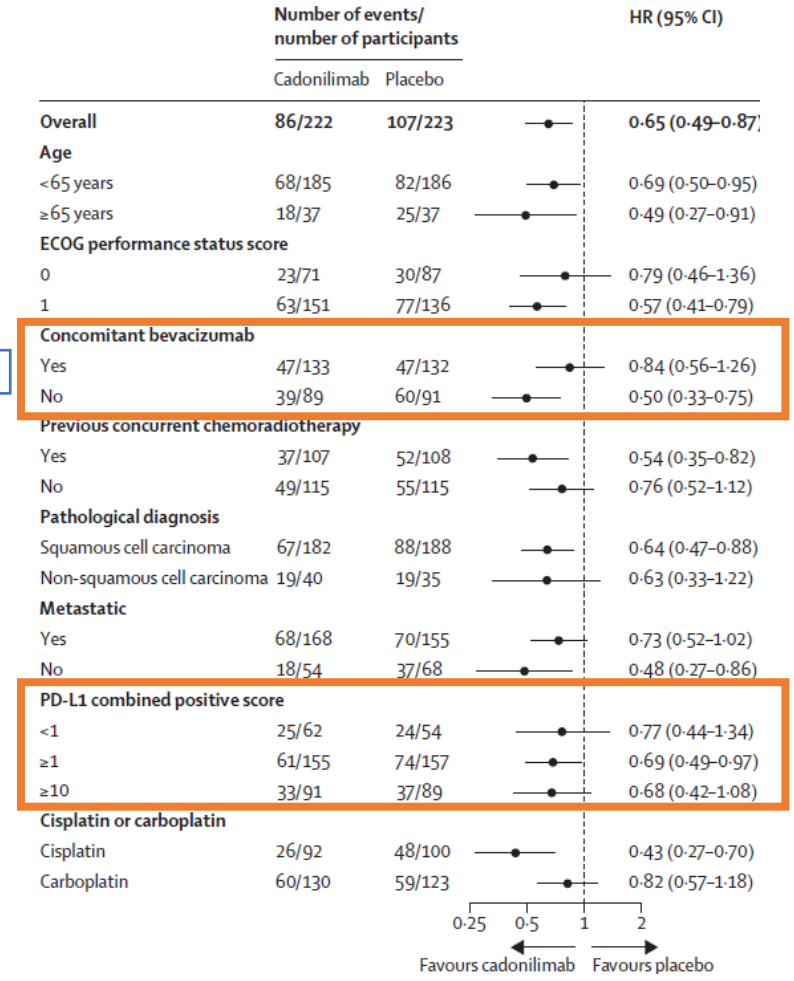
COMPASSION-16: Phase III RCT Chemo +/- Bev with Pembro vs Pcb – **OS**



Number at risk (number of events)

Cadonilimab group	222 (0)	215 (4)	205 (10)	192 (19)	174 (36)	160 (49)	145 (62)	135 (70)	92 (78)	51 (82)	6 (86)	0 (86)
Placebo group	223 (0)	220 (3)	202 (12)	169 (38)	143 (55)	124 (70)	104 (89)	95 (93)	60 (101)	32 (106)	0 (107)	..

60%



	Number of events/ number of participants		HR (95% CI)
	Cadonilimab	Placebo	
Overall	**86/222**	**107/223**	**0·65 (0·49–0·87)**
Age			
<65 years	68/185	82/186	0·69 (0·50–0·95)
≥65 years	18/37	25/37	0·49 (0·27–0·91)
ECOG performance status score			
0	23/71	30/87	0·79 (0·46–1·36)
1	63/151	77/136	0·57 (0·41–0·79)
Concomitant bevacizumab			
Yes	47/133	47/132	0·84 (0·56–1·26)
No	39/89	60/91	0·50 (0·33–0·75)
Previous concurrent chemoradiotherapy			
Yes	37/107	52/108	0·54 (0·35–0·82)
No	49/115	55/115	0·76 (0·52–1·12)
Pathological diagnosis			
Squamous cell carcinoma	67/182	88/188	0·64 (0·47–0·88)
Non-squamous cell carcinoma	19/40	19/35	0·63 (0·33–1·22)
Metastatic			
Yes	68/168	70/155	0·73 (0·52–1·02)
No	18/54	37/68	0·48 (0·27–0·86)
PD-L1 combined positive score			
<1	25/62	24/54	0·77 (0·44–1·34)
≥1	61/155	74/157	0·69 (0·49–0·97)
≥10	33/91	37/89	0·68 (0·42–1·08)
Cisplatin or carboplatin			
Cisplatin	26/92	48/100	0·43 (0·27–0·70)
Carboplatin	60/130	59/123	0·82 (0·57–1·18)

Wu et al. Lancet 2024

ICI combination approaches

COMPASSION-16: Phase III RCT Chemo +/- Bev with Pembro vs Pcb – **PFS**

TEAE	Cadonilimab (N = 226)*	Placebo (N = 219)
Any Grade, n(%)	225 (99.6)	219 (100)
≥Grade 3, n (%)	193 (85.4)	176 (80.4)
SAE, n (%)	126 (55.8)	74 (33.8)
Led to discontinuation of any trial agent, n (%)	63 (27.9)	23 (10.5)
Led to Death, n (%)	12 (5.3)	7 (3.2)
irAE	103 (45.6)	15 (6.8)
≥Grade 3 irAE, n (%)	22 (9.7)	2 (0.9)

No grade 5 irAEs

QoL not reported

Wu et al. Lancet 2024

ICI combination approaches

Current perspective: Phase III studies in the 1st line
– Not for cross trial comparissons

	Keynote-826 Overall	Keynote-826 *Bev cohort	BEATCC	COMPASSION16	COMPASSION16 *Bev cohort
Treatment	Ch+/-Bev -+ **Pembro**/Pcb		Ch+Bev -+ **Atezo**	Ch+/-Bev -+ **Cadonilimab**/Pcb	
N	617	389 (63%)	410	445	265 (60%)
Population	72% scc, PD-L1 CPS≥1 89%		78% scc	83% SCC, PDL1 CPS ≥1 75%	
PFS	10.4 vs 8.2m; **HR 0.61** (0.5-0.74)	15.2 vs.10; HR 0.57 (0.45-0.73)	13.7 vs 10.4m; **HR 0.62** (0.49-0.78)	12.6 vs 8.1m; **HR 0.62** (0.49-0.8)	15.1 vs 11.5m HR 0.81 (0.58-1.1)
OS	26.4 vs 16.8m; **HR 0.63** (0.5-0.77)	37.6 vs. 22.5; HR 0.61 (0.47-0.80)	32.1 vs. 22.8m; **HR 0.68** (0.52-0.88)	NR vs 25.6m; **HR 0.64** (0.48-0.86)	NR. HR 0.84 (0.56-1.36)
			Biomarkers ongoing	Chinese population Control arm Toxicity with anti-CTLA4?	

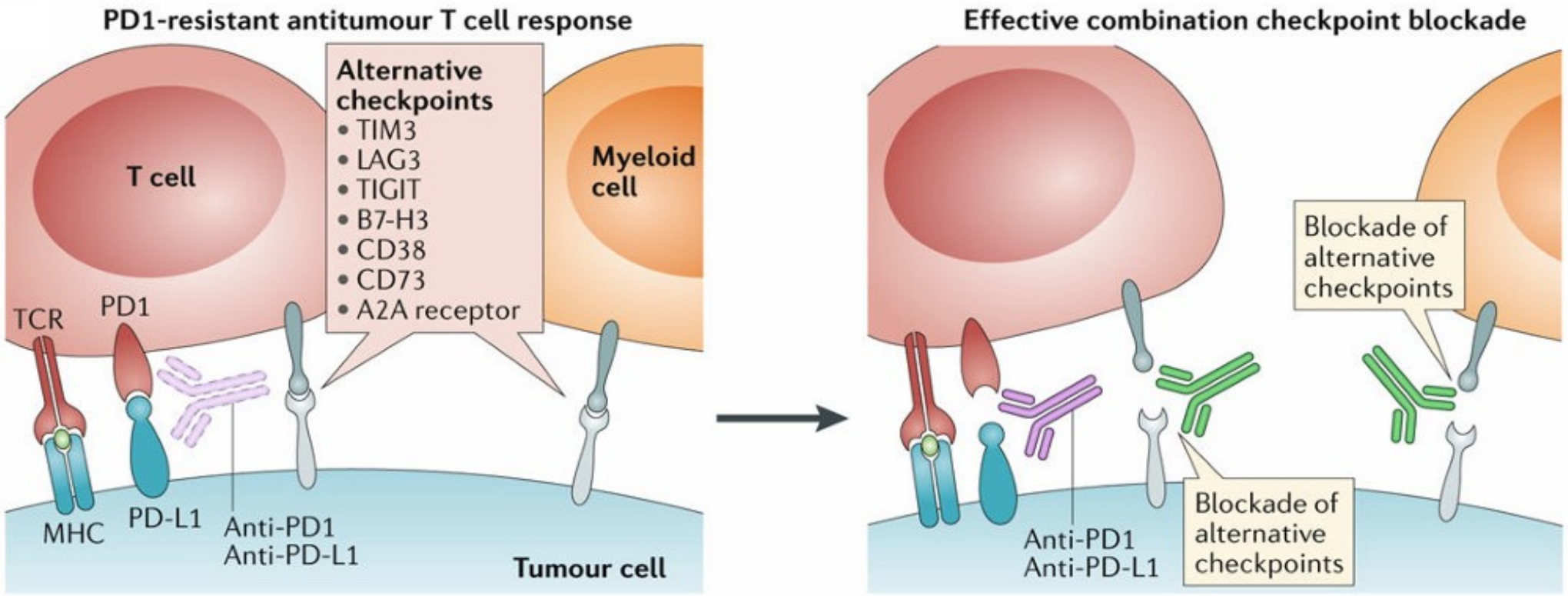
*Exploratory

Wu et al. Lancet 2024, Oaknin Lancet 2024, Colombo NEJM 2021

ICI combination approaches: anti-TIGIT

Dual blockade may synergistically enhance antitumor activity

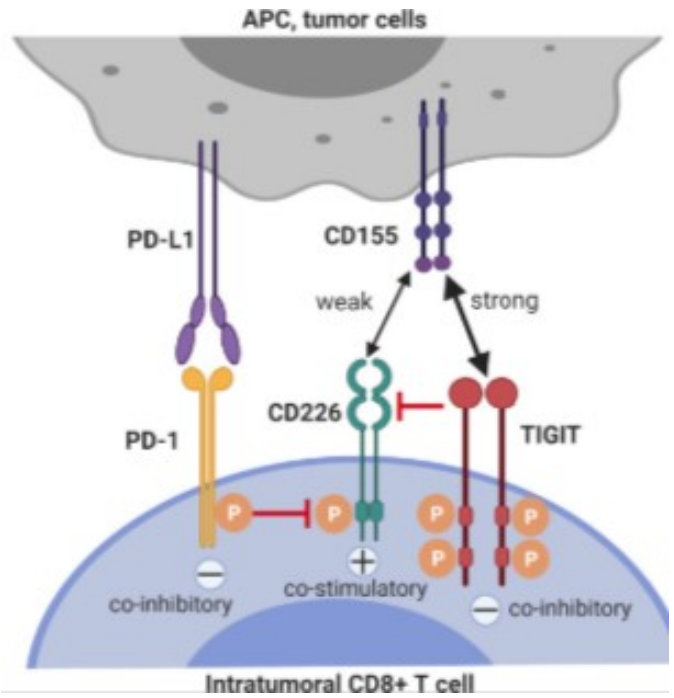
Can we tackle primary or secondary resistances?



Kalbasi et al. Nat Rev Immunol. 2020

ICI combination approaches: anti-TIGIT

Dual blockade may synergistically enhance antitumor activity



TIGIT is a coinhibitory receptor
↑ co-expressed CD4+, CD8+, TILs

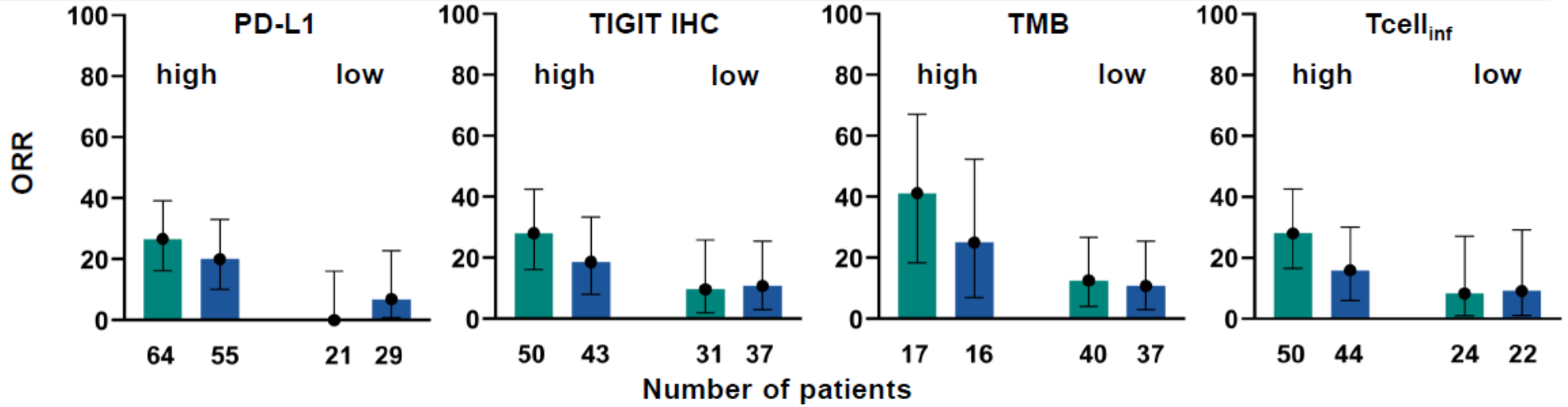
	KEYVIBE-005	SKYSCRAPPER-04
Treatment	RPh II: C1 - R Phase II (ICI naive) **Vibostolimab/Pembro** Vs Pembro. C2 - V/P in PDL1-	RPh II **Atezolizumab + Tiragolumab** vs Atezo *Crossover allowed
N	C1: 169, C2: 31	172
Population	C1: Scc 63%, C2: scc 26% Lines 1: 60%, 3+: 14.5%	Scc 75% Lines 1: 70%
ORR	C1: **20% vs 16%** C2: 16%	**19% vs 15.6%** (p=0.07)
DoR	C1: 10.9m, NR. C2: 10.8m	9.9m vs 7m
PFS	C1: **2.2 vs 2.1 m**. **HR 0.99** C2: 2.2m	2.8m vs 1.9m
OS	C1: 10.2 vs 10.3m. HR 1.0 C2: 12.8m (12m 50%)	11.1m vs 10.6m

Leary et al. ESMO Gyne 2025, Slani et al IJGC 2024

ICI combination approaches: anti-TIGIT

Biomarkers KEYVIBE-005

Arm (P-value[a])	PD-L1	TIGIT IHC	TMB	$Tcell_{inf}$
Vibo/Pembro	0.007	0.074	0.012	0.005
Pembro	0.011	0.076	0.021	0.060

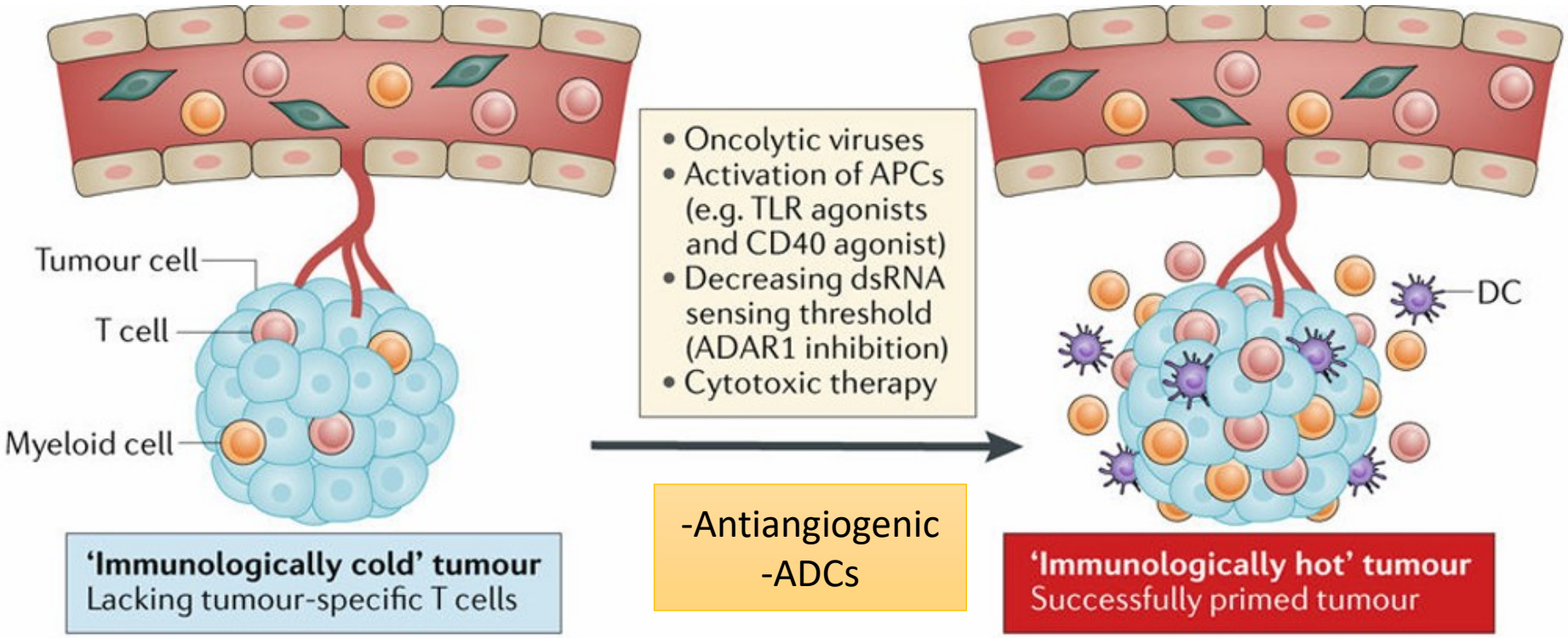


- Higher ORR was observed in PD-L1, TIGIT IHC, TMB and $Tcell_{inf}$ biomarker high subgroups
- Trends to higher ORR were observed with vibo/pembro compared to pembro alone in PD-L1, TIGIT IHC, TMB and $Tcell_{inf}$ biomarker high subgroups

Leary et al. ESMO Gyne 2025

ICI combination approaches: other targets

Can we tackle primary or secondary resistances?



Kalbasi et al. Nat Rev Immunol. 2020

ICI combination approaches: other targets

What about other combination approaches?

- Can we tackle primary or secondary resistances?

	TKI: ALTER-C201	Other Bispecifics	ADC: Sac-TMT
Treatment	Ph II: Sintilimab (PD1) + **anlotinib**	Phase I: PM8002/BNT327 (PDL1/VEGF-A)	Ph I **Sac-TMT** + Pembro *Prior ICI allowed
N	42 PDL1 CPS ≥1	48	38 (**42% prior anti-PD1**)
Histology	Scc 83%	81% PDL1+	Scc 76%
N lines	1: 40%, 3+: 21%	2+ 35%	1 or 2
ORR	**53.8% (scc ++)**	**42.2%**	**57.9%**
Median DoR	19 m (8.7 -NR)	NR	6m 82%
Median PFS	9.4m (8.0 - 14.6)	8.3m	NR
Median OS	17.59 m (12.8-36.2)	12m OS 75%	NR

Xu Q et al ASCO2024; Lingying et al. ASCO 2024, Wu X et al ESMO 2024

Emerging strategies

ADXS11-001: Listeria-based, target HPV16-E7
Phase III LACC closed
ISA101: Peptide vaccine, target HPV16 E6-7
Phase 2 + nivo ORR: 33%.
GX188E: DNA vaccine, target HPV16/18 E6/7
Phase 2 + Pembro ORR 31.7%
Many ongoing trials

Therapeutic vaccines

TCR-T therapy

E6 NCT02280811, NCT03578406
E7 NCT02858310
MAGE-A3: NCT02153905, NCT02111850

LN-145 TIL (Lifileucel): Autologous TIL
C1: Pre-treated, ICI naive (+IL2)
N=27, ORR 44%
C2: Pre-treated, ICI PD (+IL2)
C3: No prior therapy (+IL2, Pembro)
N=14, ORR 57%

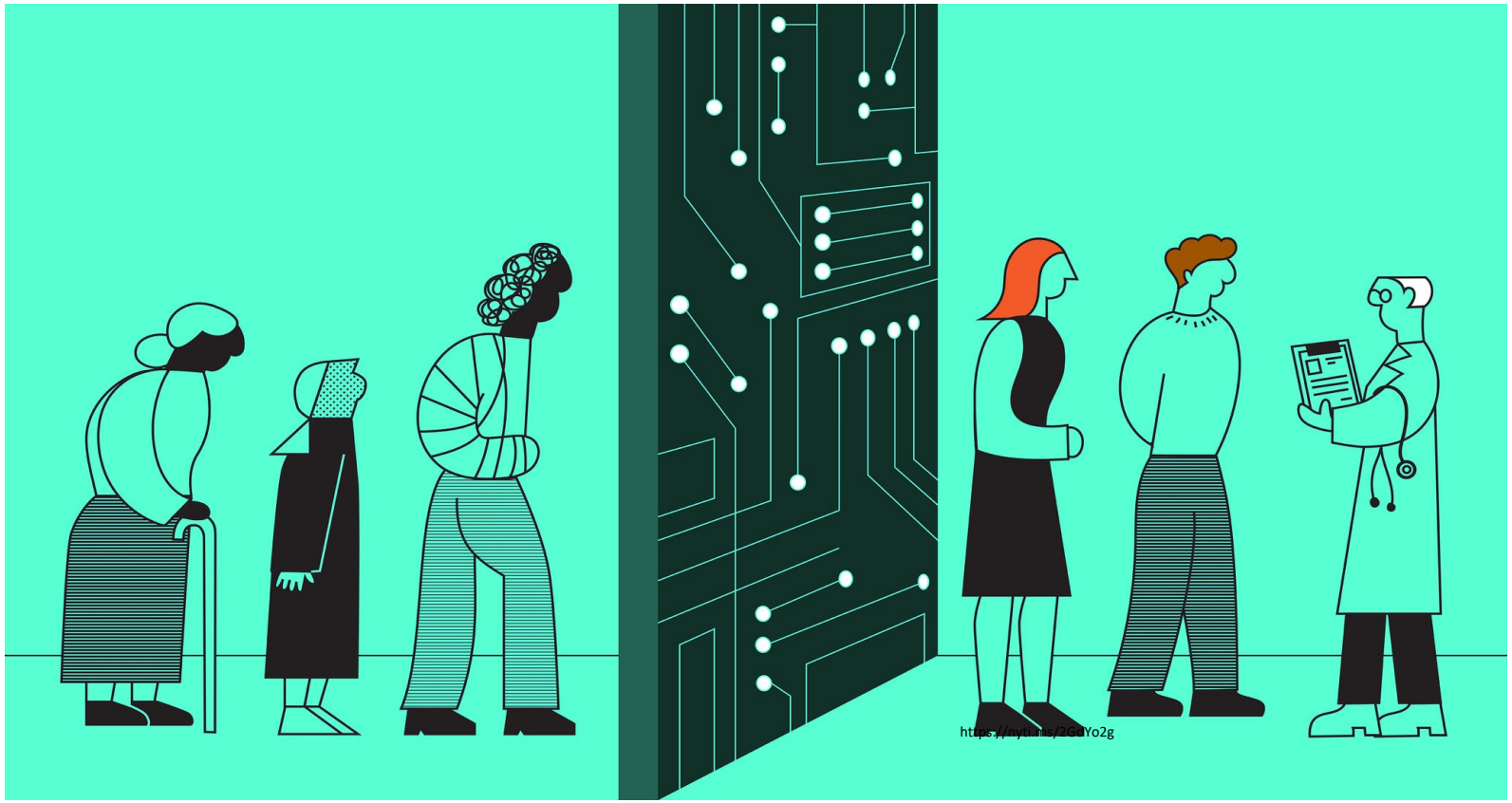
TILs

CAR-T therapy

Mesothelin: NCT01583686
CD22: NCT04556669
Others: NCT03356795

Grau et al. IJGC 2022,

Cervical cancer is a Global Health Challenge
Importance of Racial & Social Equity - Work with LMIC
Global access to preventive strategies is required



World Health Organization

We can eliminate **cervical cancer** as a public health problem through intensified vaccination against HPV, screening and treatment.

Conclusions

- **ICI represents a major breakthrough in cervical cancer**
  - Improvements in OS & PFS compared to standard of care, monotherapy or in combination with chemotherapy
- **ICI moving to earlier setting: ICI post-ICI & novel combination approaches?**
- Unmet need: biomarkers beyond PDL1
- Advances in personalized immunotherapy: TILs, CAR-T

Thank you!

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