The role of immunotherapy in cervical cancer

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Disclosures

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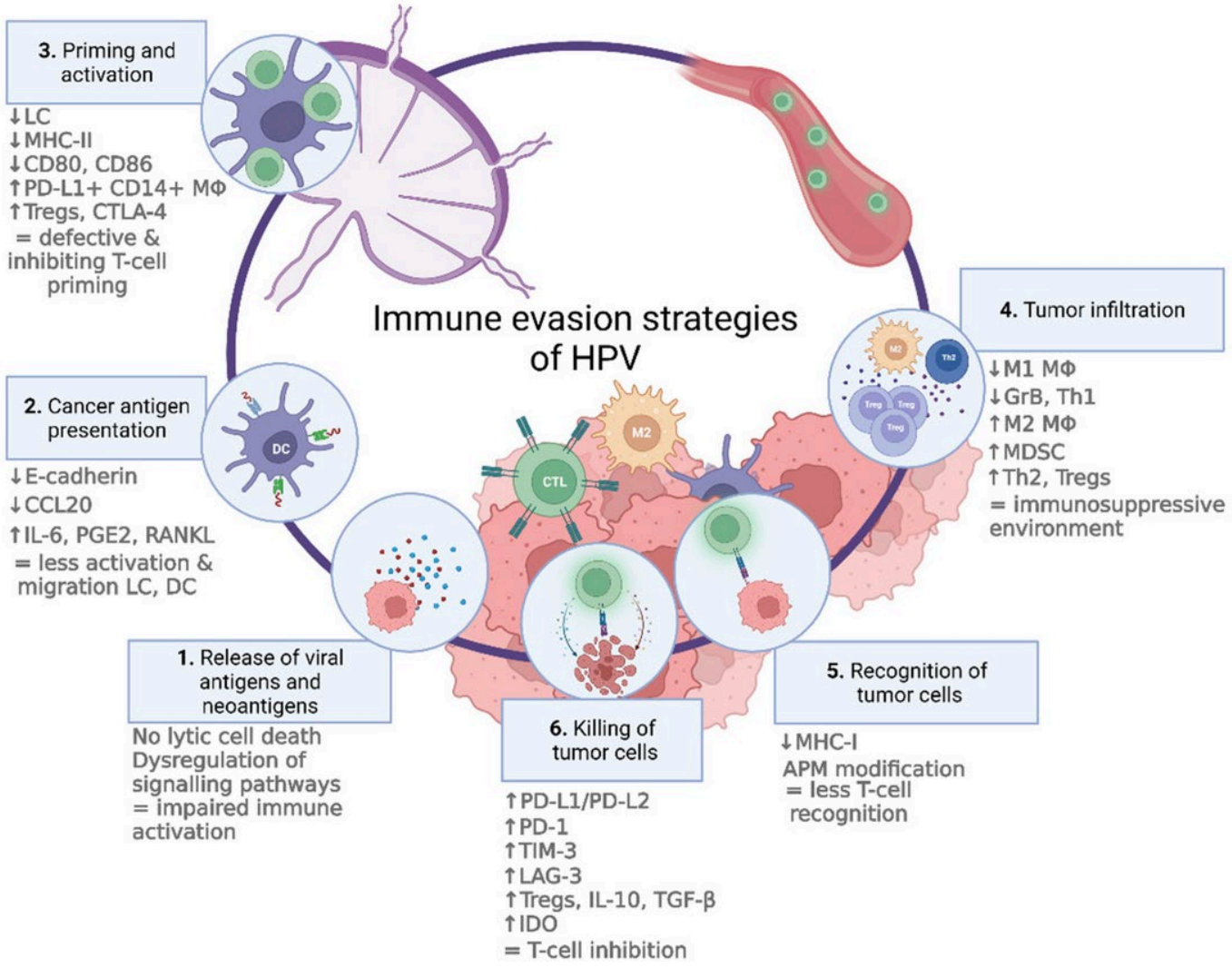
Speakers fee: MSD, Nycode

Rational for immunotherapy in cervical cancer



Rafael et al, J Clin Med 2022

Immunotherapy: Strategies

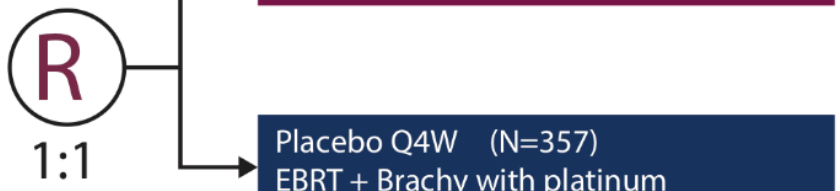
- First-line in locally advanced disease: CALLA, ENGOT-Cx11, Atezo LACC, GEICO-72C/ATOMICC
- First-line in metastatic/recurrent disease: ENGOT-Cx10, ENGOT-Cx13, Keynote 826
- Multiple-line metastatic disease:
  - Single agent checkpoint blockade
  - Dual checkpoint blockade
  - Vaccine strategies
  - Targeting TGFβ & PD-L1
  - Adoptive cell transfer (TILs)

First line locally advanced disease

CALLA trial

Study population

- FIGO 2009 Stages IB2 to IIB (N ≥1) OR IIIA to IVA (N ≥0)
- Nodal staging (pelvic and/or para-aortic) may be either surgical or by imaging (RECIST v1.1)
- No evidence of metastatic disease (M0)



Primary endpoint

PFS

Secondary endpoints

OS, ORR, CR rate, incidence of local progression, distant disease recurrence, secondary malignancy, HRQoL, PK, ADAs

Stratification

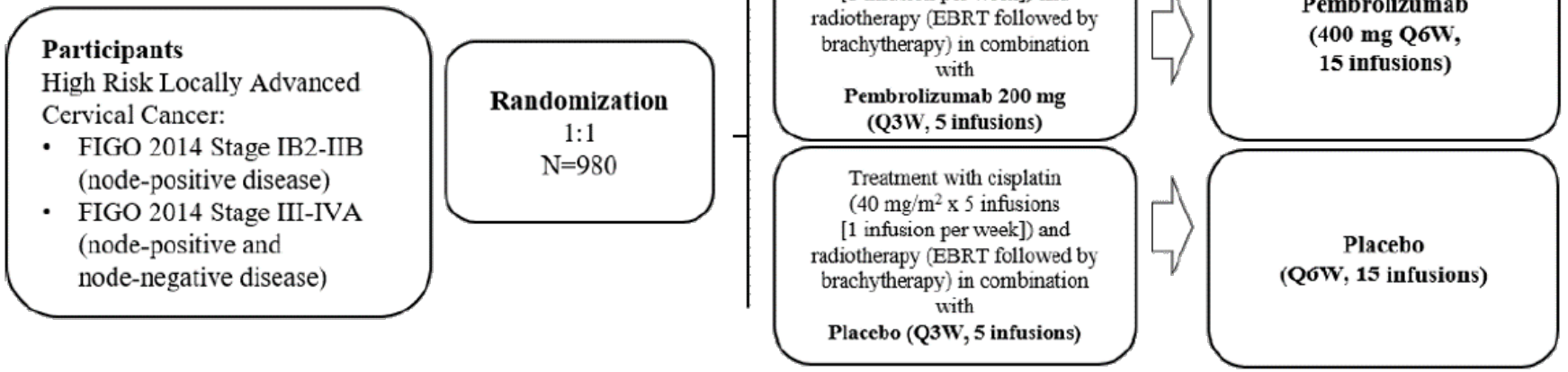
- Stage: Stage <III and N positive, Stage ≥III and N negative, or Stage ≥III and N positive
- Region: United States, Canada, European Union, South Korea, and Japan versus rest of the world

24 March 2022 07:00 GMT

The CALLA Phase III trial for AstraZeneca's *Imfinzi* (durvalumab) given concurrently with chemoradiotherapy (CRT) did not achieve statistical significance for the primary endpoint of improving progression-free survival (PFS) versus CRT alone in the treatment of patients with locally advanced cervical cancer.

KEYNOTE-A18/ENGOT-Cx11

A Randomized Phase III Study of Chemoradiotherapy with or without Pembrolizumab for High-risk, Locally Advanced Cervical Cancer

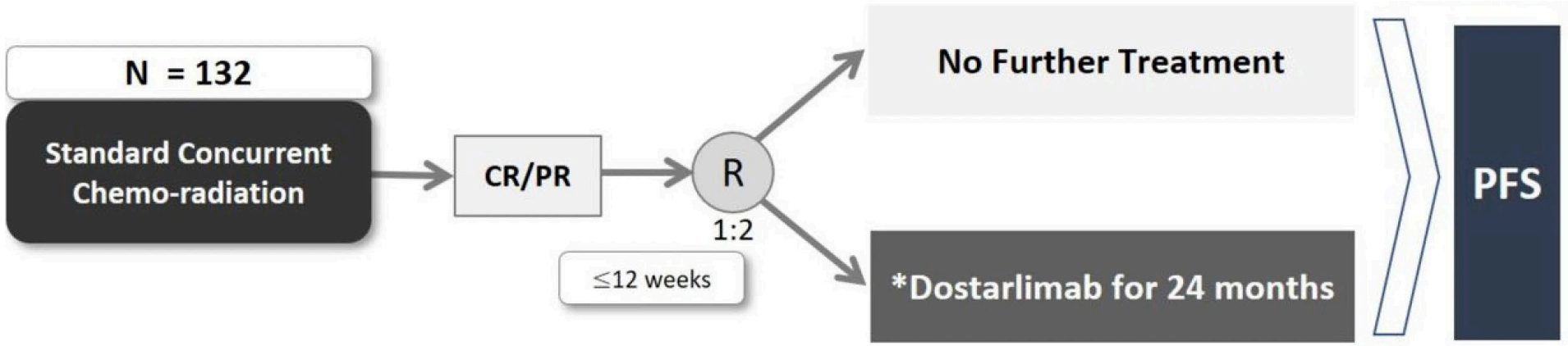


ENGOT model: C
Status: Recruiting
Planned number of patients: 980
Number of total patients recruited: 978
Number of ENGOT patients recruited: 315
Sponsor: Merck/MSD
ENGOT Lead Group: MITO
NSGO-CTU Lead PI: Kristina Lindemann
NSGO-CTU PM: Johanne Hestvang
Primary Endpoints: Progression Free Survival (PFS) and Overall Survival (OS)

<u>Stratification factors</u>

- Radiotherapy technique; IMRT or VMAT (yes/no)
- Total radiation dose
- Early-stage versus late-stage disease (IB2-II vs III-IVA)

GEICO-72C/ATOMICC and ATEZOLACC trial



Stratification factors

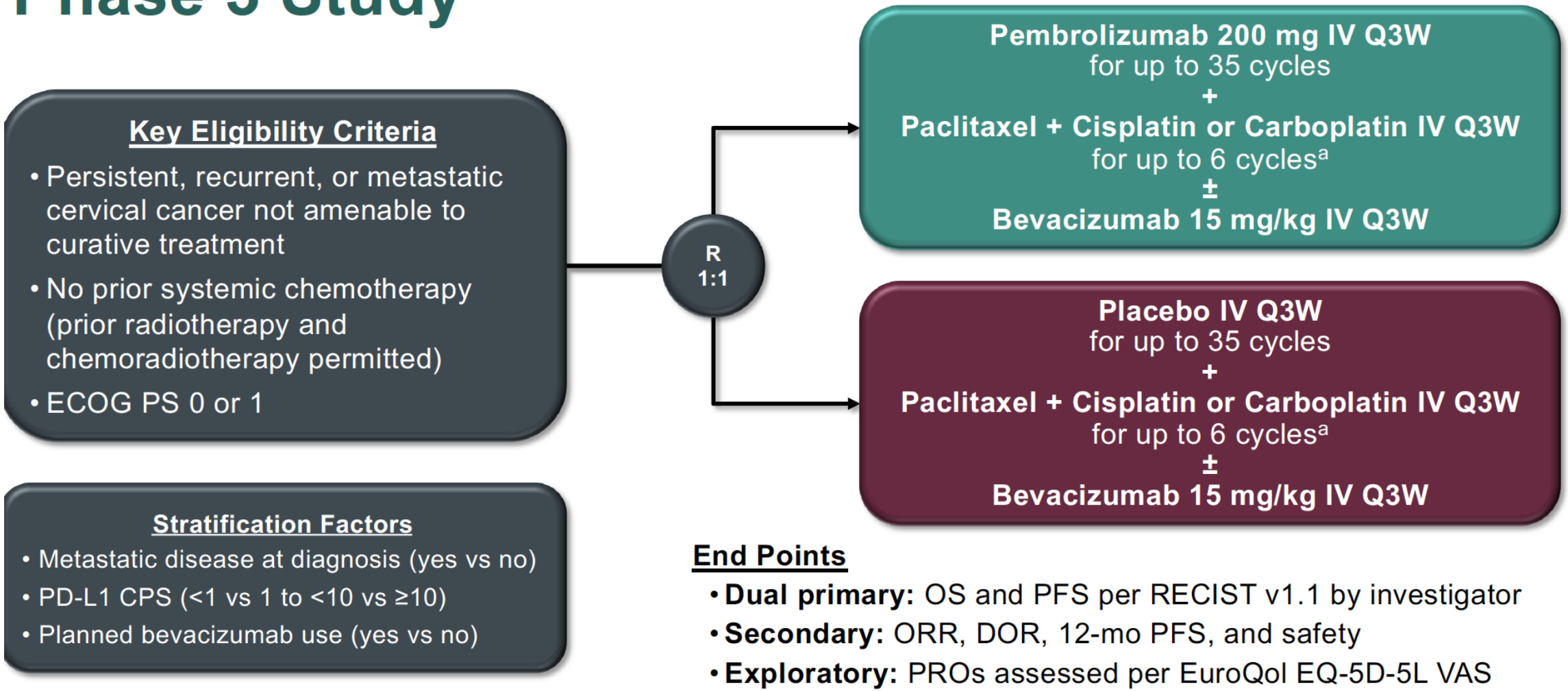
- Histology (squamous vs. adenosquamous adenocarcinoma)
- FIGO Stage: IB2, IIA2 or IIB with pelvic positive lymph nodes vs. III/IVA vs. any Stage with positive ParaAortic Lymph nodes
- Partial Response vs. Complete Response by RECIST Criteria v1.1

AtezoLACC
Randomized Phase II Trial Assessing the Inhibitor of Programmed Cell Death Ligand 1 (PD-L1) Immune Checkpoint Atezolizumab in Locally Advanced Cervical Cancer

Concomitant and maintenance

Multiple-line metastatic disease

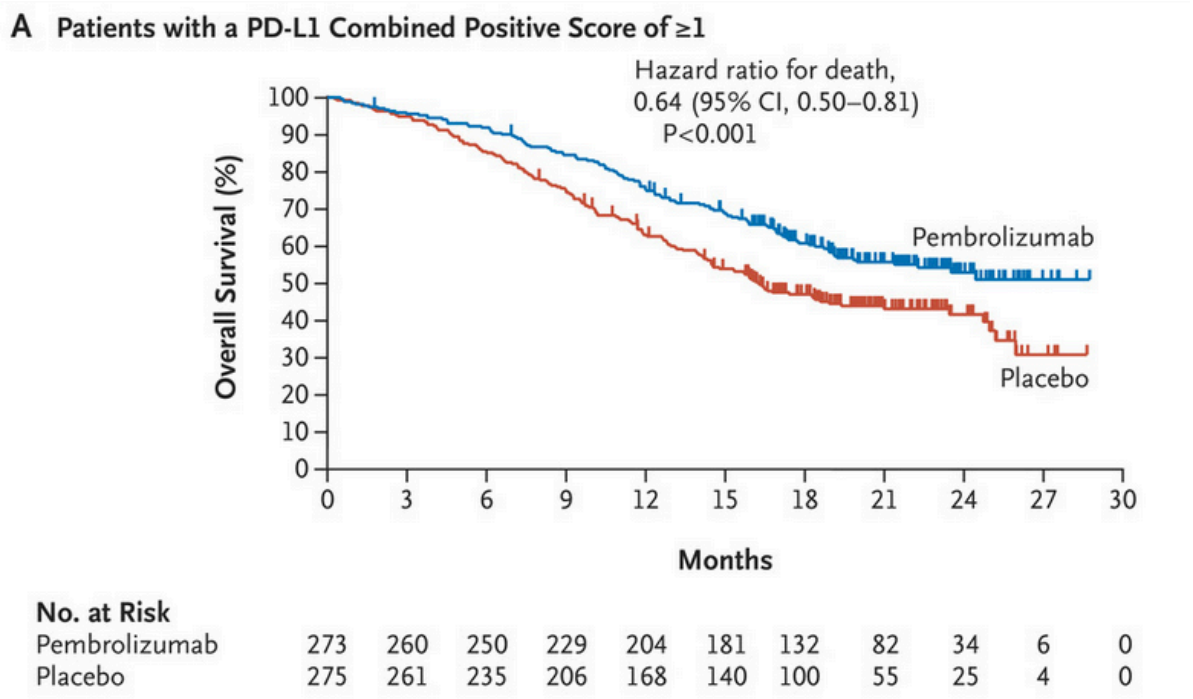
KEYNOTE-826: Randomized, Double-Blind, Phase 3 Study

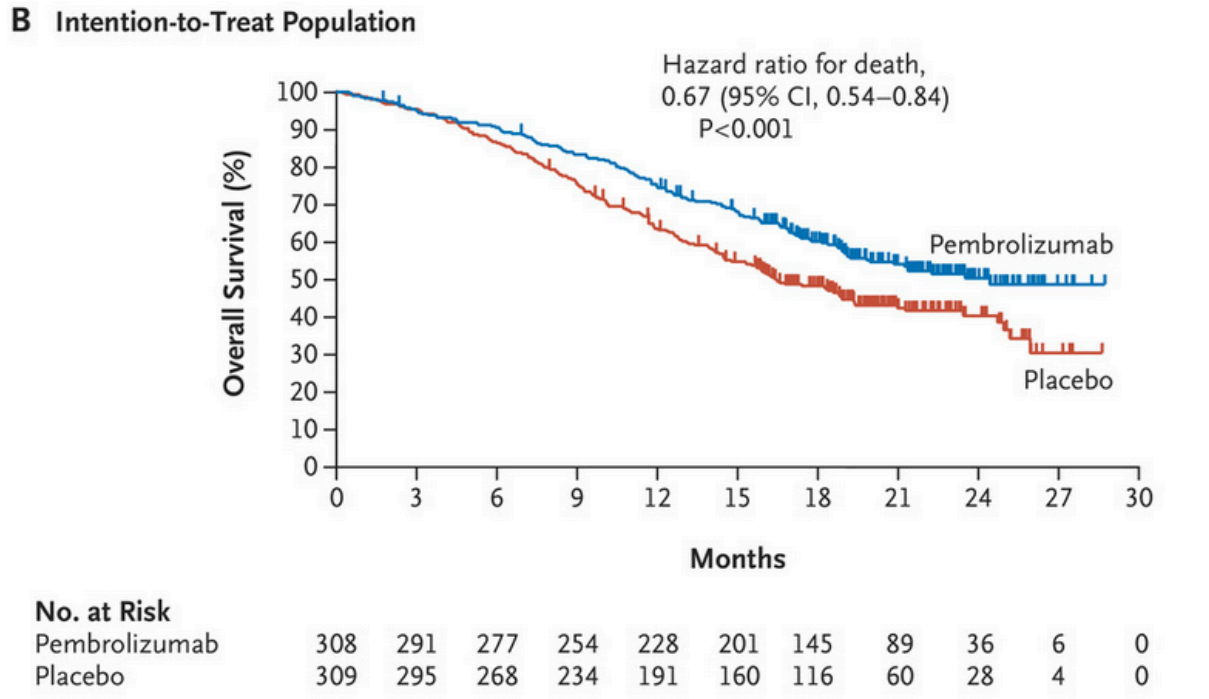


End Points

- **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

Overall survival

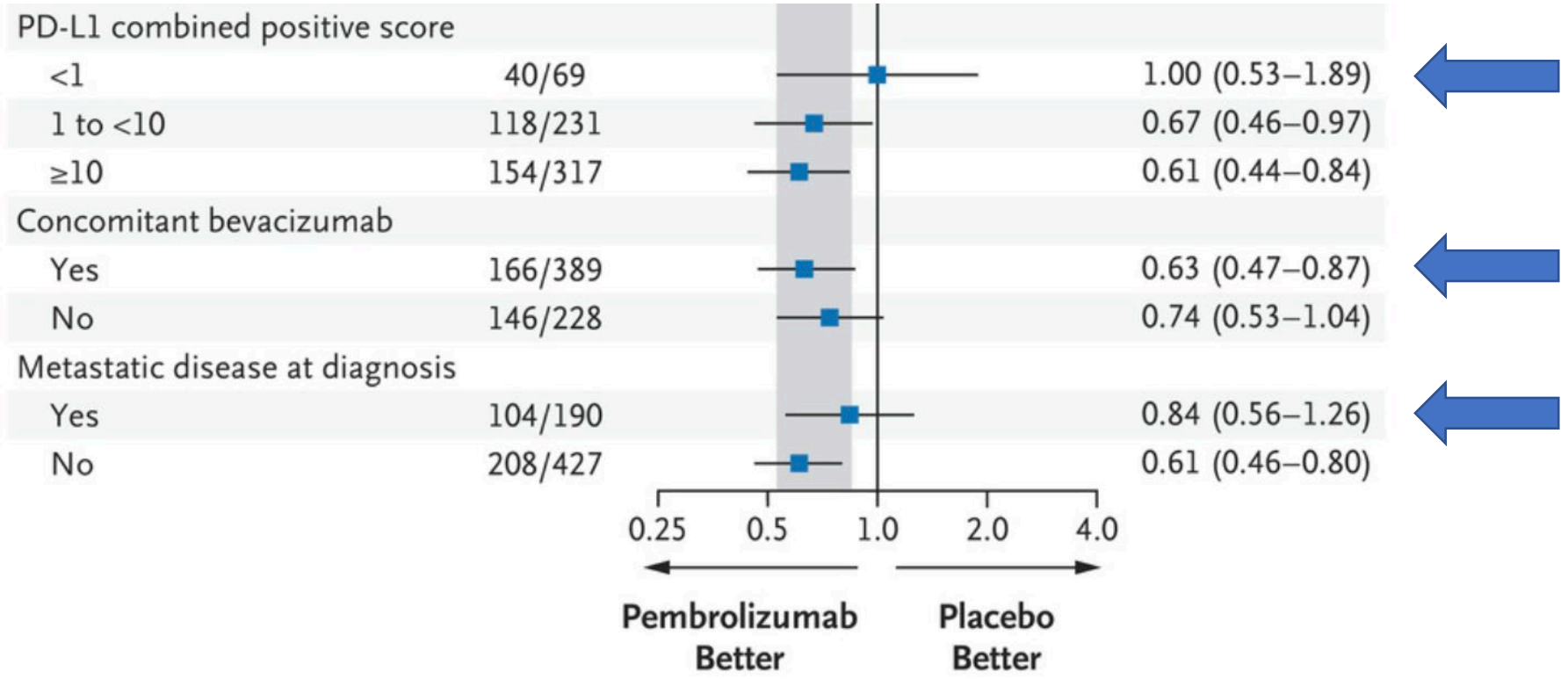




- @24 months 53% alive vs 41.7%
- Median OR NR in pembrolizumab arm

- @24 months 50.4% alive vs 40.4%
- Median OS 24.4 months for pembrolizumab, vs 16.3 to 16.5 months for placebo
- QoL: @12 months 58.2% vs. 44.8% free from deterioration

Subgroup analysis



ENGOT-Cx10/GEICO 68-C/JGOG1084/GOG-3030/BEAT cc

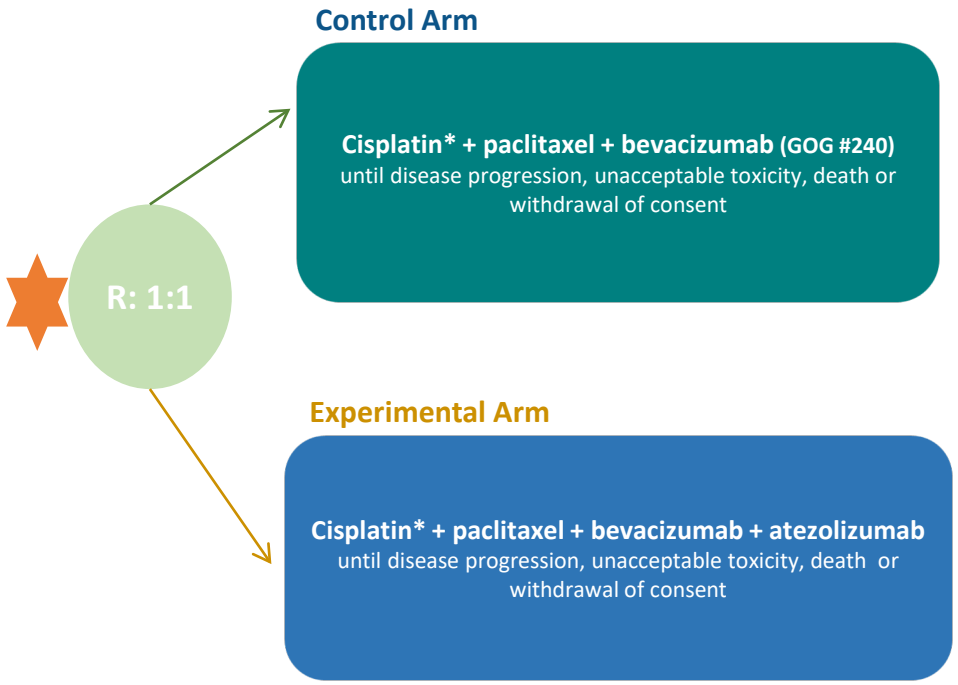
A Randomized Phase III Trial of Platinum Chemotherapy plus Paclitaxel with Bevacizumab and Atezolizumab versus Platinum Chemotherapy plus Paclitaxel and Bevacizumab in Metastatic (stage IVB), Persistent or Recurrent Carcinoma of the Cervix

Eligibility Criteria:

- Persistent/recurrent/ metastatic cervical cancer
- ECOG PS 0-1
- No prior systemic anti-cancer therapy for metastatic or recurrent disease
- Available archival or fresh tumor tissue for PD-L1 expression

Stratification factors:

- Prior concurrent cisplatin-RT
- Histology: SCC vs. ADK (including adenosquamous)
- Chemotherapy backbone (cisplatin vs carboplatin)



*carboplatin allowed in amended protocol

ENGOT model: B

Status: Recruitment ended 31.08.2021

Number of total patients recruited: 410

Number of ENGOT patients recruited: 339

Sponsor: GEICO

ENGOT Lead Group: GEICO

NSGO-CTU Lead PI: Kristina Lindemann

NSGO-CTU PM: Johanne Hestvang

Primary Endpoint: Progression Free Survival and Overall Survival

Oslo University Hospital

UiO : University of Oslo

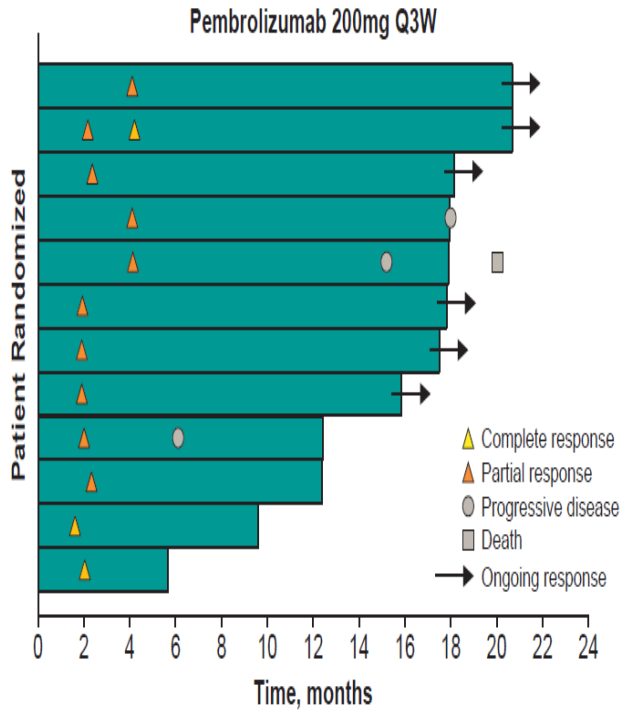
First-line in metastatic/recurrent disease

Keynote-158 Pembrolizumab:
Phase 2, Multi Cohort, Multi center study. Cervical Cancer

TABLE 2. Antitumor Activity Assessed by RECIST v1.1 per Independent Central Review

Antitumor Activity	Total Population (N = 98)*	PD-L1–Positive Population		PD-L1–Negative Population
		Total (n = 82)	Previously Treated (n = 77)†	(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	
Estimated rate of response duration, months‖¶				—
≥ 6	10 (90.9)	10 (90.9)	10 (90.9)	
≥ 9	9 (90.9)	9 (90.9)	9 (90.9)	
≥ 12	7 (79.5)	7 (79.5)	7 (79.5)	

Duration of response in patients who responded to treatment (n=12)



Includes patients whose best overall response was complete or partial response. The length of the bars represents the time to the last imaging assessment.

Chung et al. JCO 2019

CHECKMATE-358
Single-agent nivolumab in virus-associated tumours

	All patients (N = 24)	Cervical (n = 19)	Vaginal/ Vulvar (n = 5)
Best overall response, n (%)			
Complete response	1 (4.2)	1 (5.3)	0
Partial response	4 (16.7)	4 (21.1)	0
Stable disease	12 (50.0)	8 (42.1)	4 (80.0)
Progressive disease	7 (29.2)	6 (31.6)	1 (20.0)
ORR, n (%) [95% CI]	5 (20.8) [7.1, 42.2]	5 (26.3) [9.1, 51.2]	0 [0.0, 52.2]
Disease control rate, n (%)	17 (70.8)	13 (68.4)	4 (80.0)
Duration of response, median (range), months	NR[a] (0.0–5.8+)	NR[a] (0.0–5.8+)	NA

EMPOWER-CERVICAL 1/GOG-3016/ENGOT-CX9 (NCT03257267)

Recurrent and metastatic cervical cancer resistant to platinum-based chemotherapy ≥2nd line
ECOG PS ≤1

N=608: 477 SCC, 131 AC
Randomised 1:1
Stratified by:
- Histology (SCC/AC)
- Geographic region
- Prior bevacizumab (Y/N)
- ECOG PS (0 vs 1)

Patients were enrolled regardless of PD-L1 expression

Cemiplimab 350 mg Q3W IV

IC chemotherapy

Options:
- Pemetrexed 500 mg/m^2 Q3W IV
- Gemcitabine 1,000 mg/m^2 IV on Days 1 and 8 and every 21 days
- Topotecan 1 mg/m^2 daily IV for 5 days, every 21 days
- Irinotecan 100 mg/m^2 IV weekly x 4, followed by 10–14 days rest
- Vinorelbine 30 mg/m^2 IV on Days 1 and 8 and every 21 days

Treat up to 96 weeks with option for re-treatment

Tumour imaging conducted on Day 42 (±7 days) of cycles† 1–4, 6, 8, 10, 12, 14, and 16

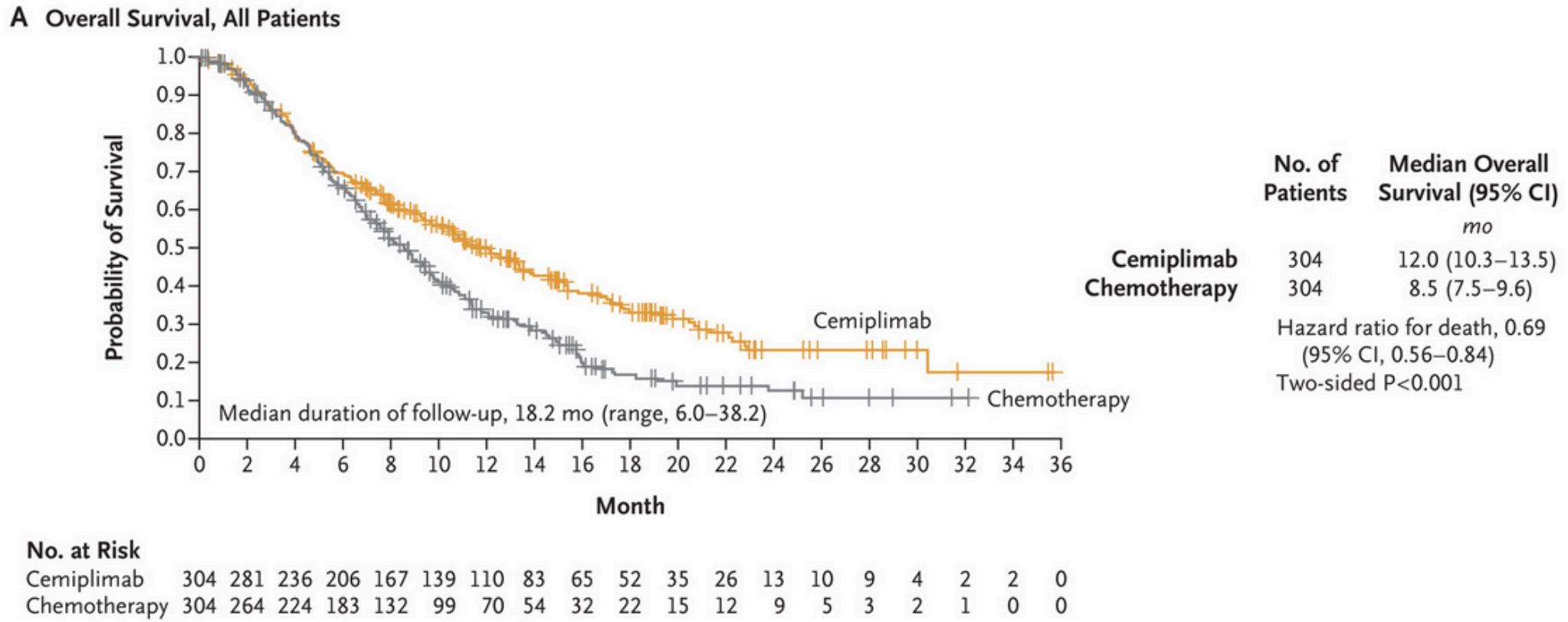
Primary endpoint: OS

Secondary endpoints:
PFS, ORR, DOR, safety, QoL

Exploratory endpoints:
PK, immunogenicity, biomarkers, PD

- Two interim analyses were prespecified per protocol
- At first interim analysis, IDMC recommended trial to continue
- At second interim analysis (85% of total OS events), IDMC recommended trial be stopped early for efficacy; presented here

Final OS results



	No. of Patients	Median Overall Survival (95% CI)
		mo
Cemiplimab	304	12.0 (10.3–13.5)
Chemotherapy	304	8.5 (7.5–9.6)

Hazard ratio for death, 0.69 (95% CI, 0.56–0.84)
Two-sided P<0.001

OVERALL SURVIVAL BY HISTOLOGY

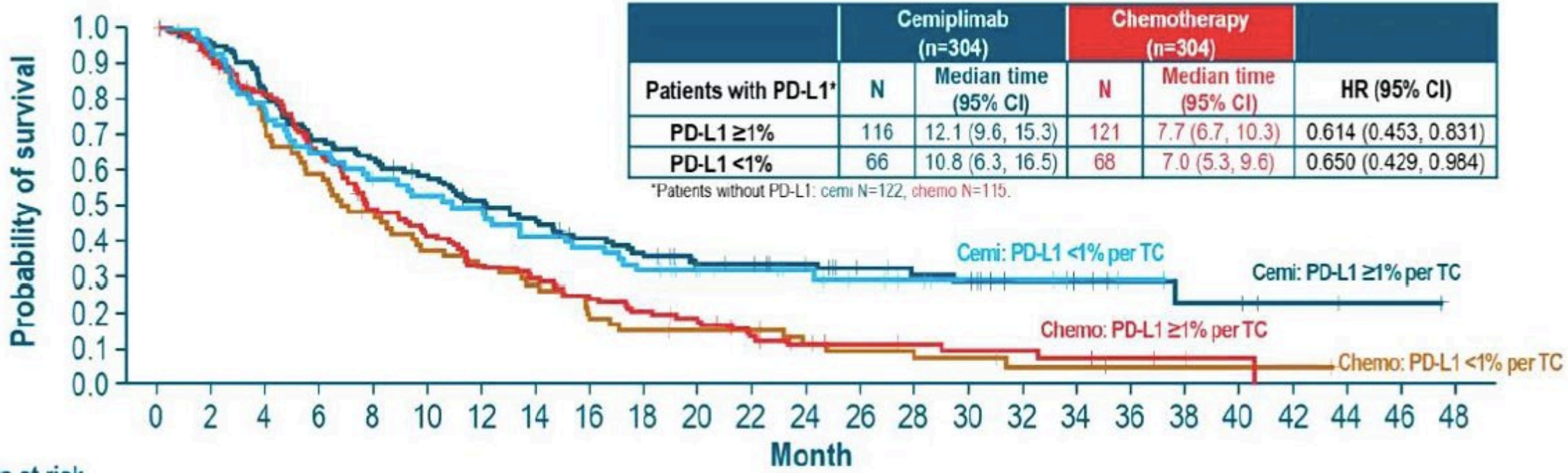
Squamous carcinoma

Adenocarcinoma

And again...the biomarker question

	Cemiplimab (n=304)		Chemotherapy (n=304)		
Patients with PD-L1*	N	Median time (95% CI)	N	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.

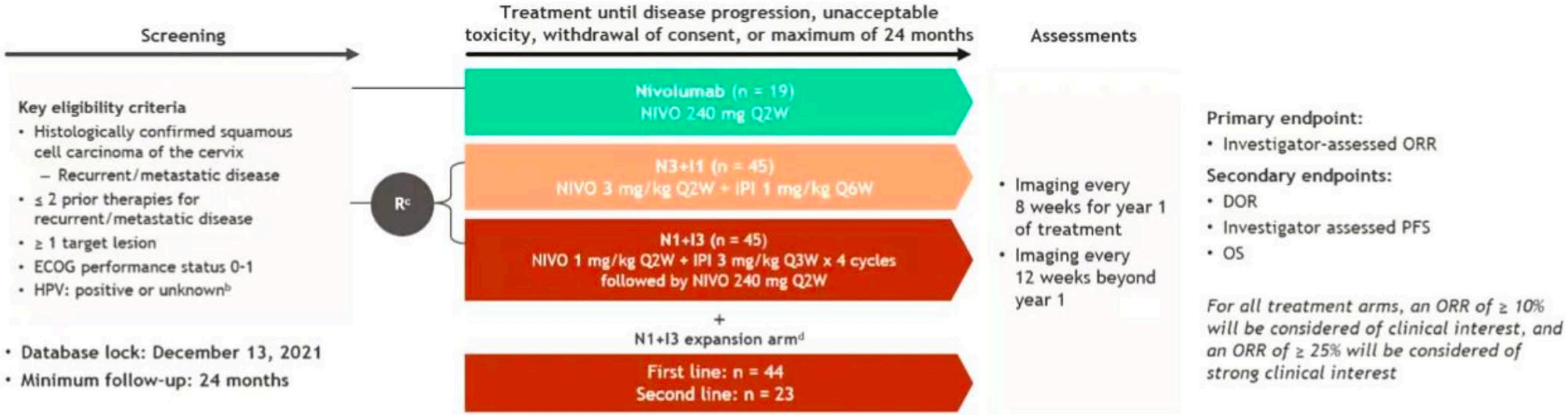


Patients at risk

Cemi: PD-L1 ≥1% per TC	116	110	93	77	71	63	55	48	41	36	30	29	25	20	17	16	10	9	5	4	4	2	1	1	0
Cemi: PD-L1 <1% per TC	66	61	49	43	36	33	30	26	24	20	16	14	12	9	7	5	5	3	1	0	0	0	0	0	0
Chemo: PD-L1 ≥1% per TC	121	107	92	73	54	46	37	33	27	23	19	13	9	7	6	5	5	4	3	2	1	0	0	0	0
Chemo: PD-L1 <1% per TC	68	60	46	39	30	24	21	18	12	10	9	9	6	5	4	4	2	2	1	1	1	1	0	0	0

Immunotherapy combinations

Checkmate 358: Nivolumab-ipilimumab combination



- Squamous carcinoma only
- 42-52% of patients had no prior line for metastatic disease

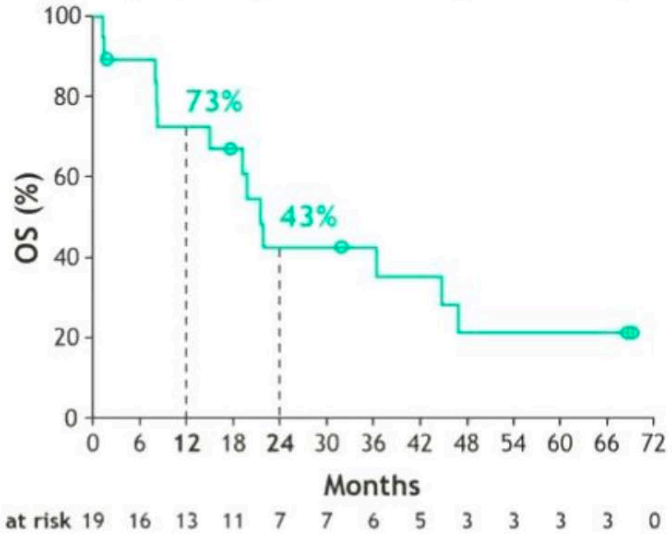
Response single agent vs combination

	NIVO	N3+I1 (randomized)			N1+I3 Pooled (randomized + expansion)		
	All (n = 19)	All (n = 45)	1L (n = 18)	≥ 2L (n = 27)	All (n = 112)	1L (n = 69)	≥ 2L (n = 43)
ORR, % (95% CI)	26 (9-51)	31 (18-47)	39 (17-64)	26 (11-46)	38 (29-48)	41 (29-53)	35 (21-51)
PD-L1[a] ≥ 1%, responders/evaluable (%)	3/11 (27)	9/25 (36)	4/12 (33)	5/13 (38)	19/53 (36)	13/33 (39)	6/20 (30)
PD-L1[a] < 1%, responders/evaluable (%)	1/7 (14)	3/15 (20)	2/3 (67)	1/12 (8)	11/36 (31)	6/19 (32)	5/17 (29)
Median DOR, months (95% CI)	NR (35.3-NR)	24.4 (8.7-NR)	34.6 (6.6-NR)	21.1 (7.5-NR)	34.1 (11.5-NR)	25.6 (9.2-NR)	NR (5.2-NR)

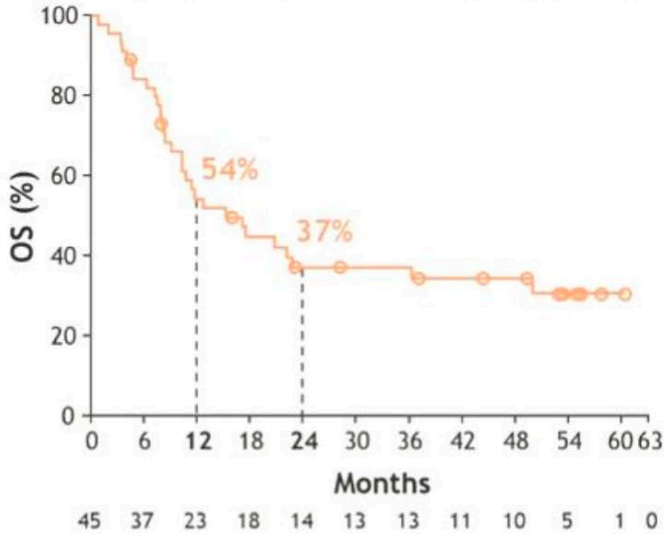
Oaknin A, et al. *ESMO* 2022

Overall survival

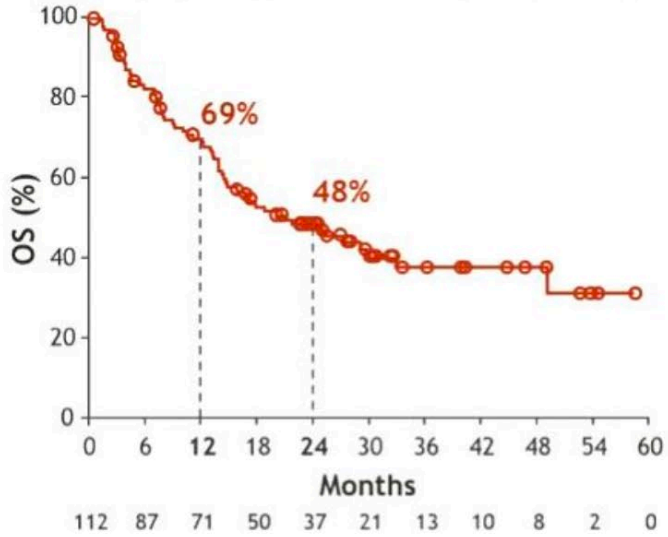
	NIVO (n = 19)
Median OS, mo (95% CI)	21.6 (8.3-46.9)
12-month OS, % (95% CI)	73 (46-88)
24-month OS, % (95% CI)	43 (20-64)



	N3+I1 (randomized) (n = 45)
Median OS, mo (95% CI)	15.2 (9.0-36.2)
12-month OS, % (95% CI)	54 (38-68)
24-month OS, % (95% CI)	37 (23-51)

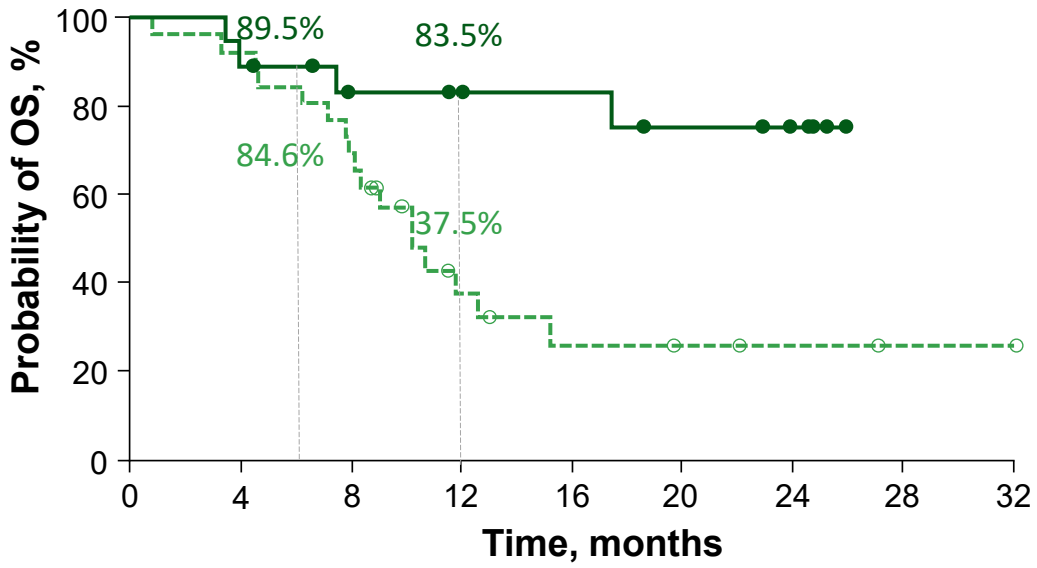


	N1+I3 pooled (randomized + expansion) (n = 112)
Median OS, mo (95% CI)	20.9 (14.4-32.8)
12-month OS, % (95% CI)	69 (60-77)
24-month OS, % (95% CI)	48 (38-57)



Nivolumab + Ipilimumab: Overall Survival

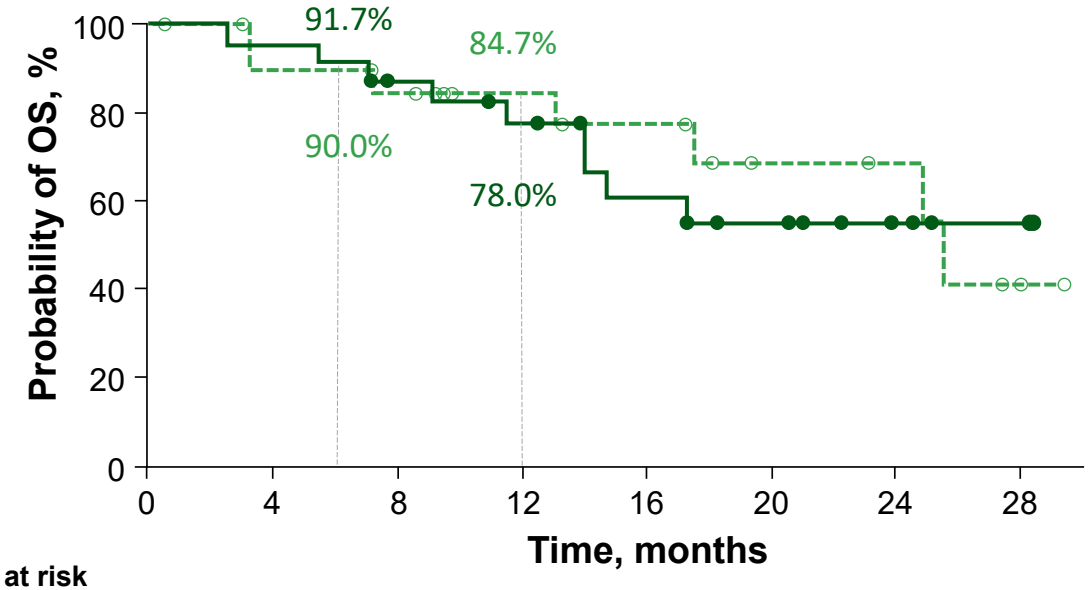
NIVO3+IPI1	
Median OS, mo (95% CI)	
No PST for R/M disease	NR (17.4–NR)
PST for R/M disease	10.3 (7.9–15.2)



No. at risk

No PST	19	17	13	12	11	9	6	0	0
PST	26	24	18	7	4	3	2	1	1

NIVO1+IPI3	
Median OS, mo (95% CI)	
No PST for R/M disease	NR (13.9–NR)
PST for R/M disease	25.4 (17.5–NR)



No. at risk

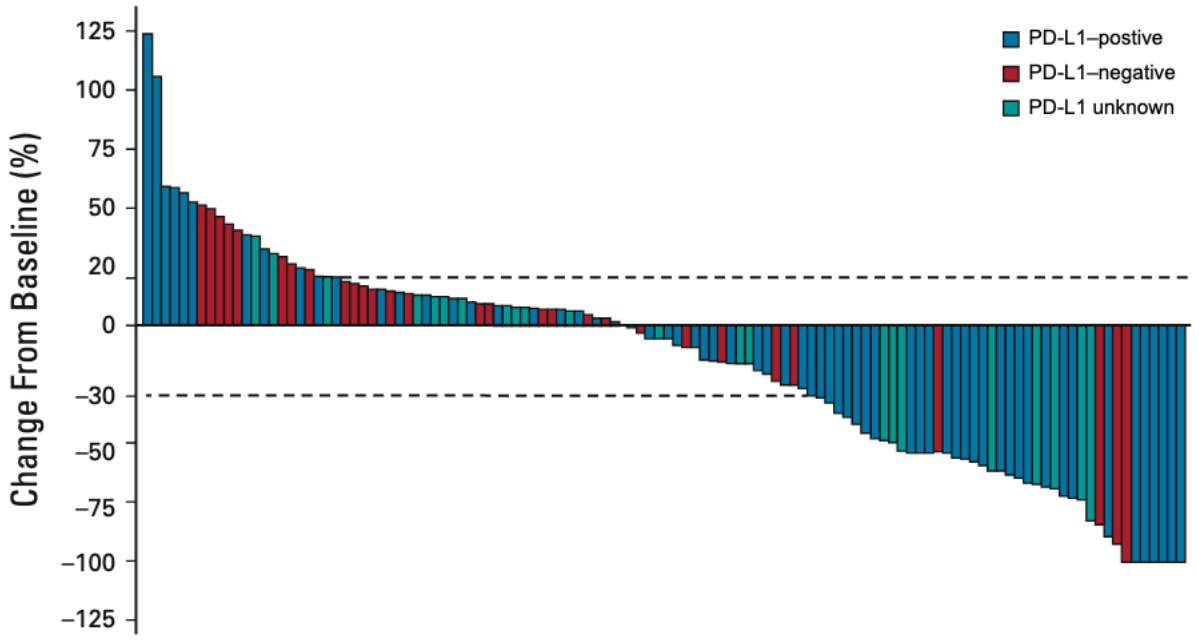
No PST	24	23	19	16	11	8	4	2
PST	22	18	16	12	10	6	5	1

Safety

No. of patients, n (%)	NIVO (n = 19)		N3+I1 (randomized) (n = 45)		N1+I3 pooled (randomized + expansion) (n = 112)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Any treatment-related AE (TRAE)	12 (63)	4 (21)	36 (80)	13 (29)	99 (88)	52 (46)
TRAEs leading to discontinuation, n (%)	2 (11)	1 (5)	8 (18)	4 (9)	27 (24)	21 (19)
Serious TRAEs, n (%)	3 (16)	3 (16)	12 (27)	8 (18)	47 (42)	34 (30)
IMAE[a,b]						
Endocrine						
Hypothyroidism/thyroiditis	1 (5)	0	11 (24)	1 (2)	27 (24)	0
Hyperthyroidism	0	0	5 (11)	1 (2)	15 (13)	1 (1)
Diabetes mellitus	0	0	2 (4)	1 (2)	0	0
Hypophystitis	0	0	1 (2)	0	5 (4)	1 (1)
Adrenal insufficiency	0	0	1 (2)	0	1 (1)	0
Nonendocrine						
Pneumonitis	1 (5)	1 (5)	1 (2)	0	12 (11)	4 (4)
Rash	0	0	4 (9)	0	17 (15)	4 (4)
Hepatitis	0	0	3 (7)	3 (7)	20 (18)	18 (16)
Diarrhea/colitis	0	0	2 (4)	1 (2)	18 (16)	6 (5)
Nephritis and renal dysfunction	0	0	1 (2)	1 (2)	2 (2)	1 (1)
Hypersensitivity	0	0	0	0	1 (1)	1 (1)
Treatment-related deaths, n	0		0		1[c]	

Balstilimab+zalifrelimab: anti-PD1 + anti-CTLA4

A



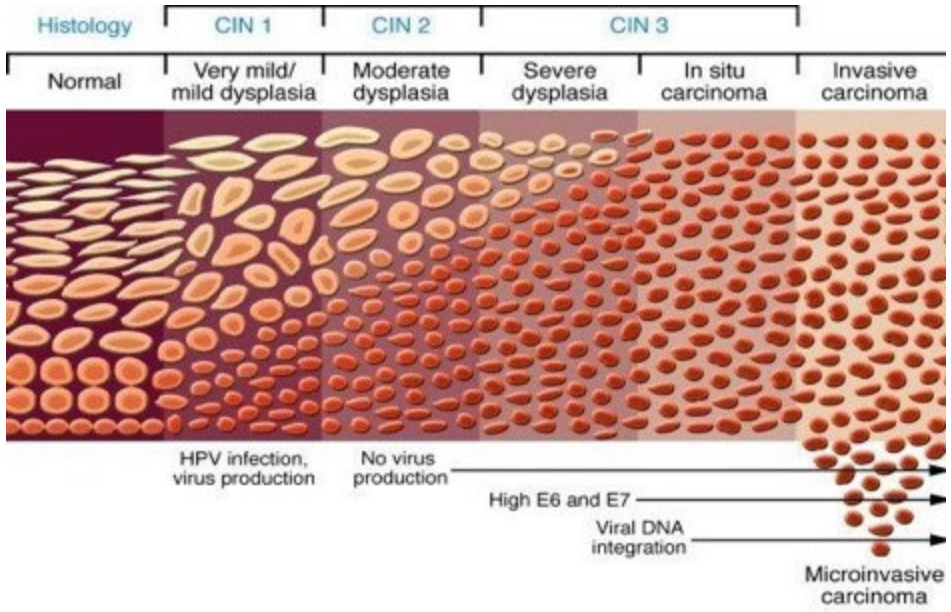
ORR	32 (25.6)
95% CI	18.8 to 33.9
Best overall response	
CR	10 (8.0)
PR	22 (17.6)
SD	39 (27.2)
Progressive disease	50 (40.0)
Not available[a]	9 (7.2)
DCR[b]	65 (52.0)
95% CI	43.3 to 60.6
DOR, (median) months[c]	NR
95% CI	9.7 to NR

- Modest increment in ORR by adding CTLA4
- 20% G3/4 TRAE

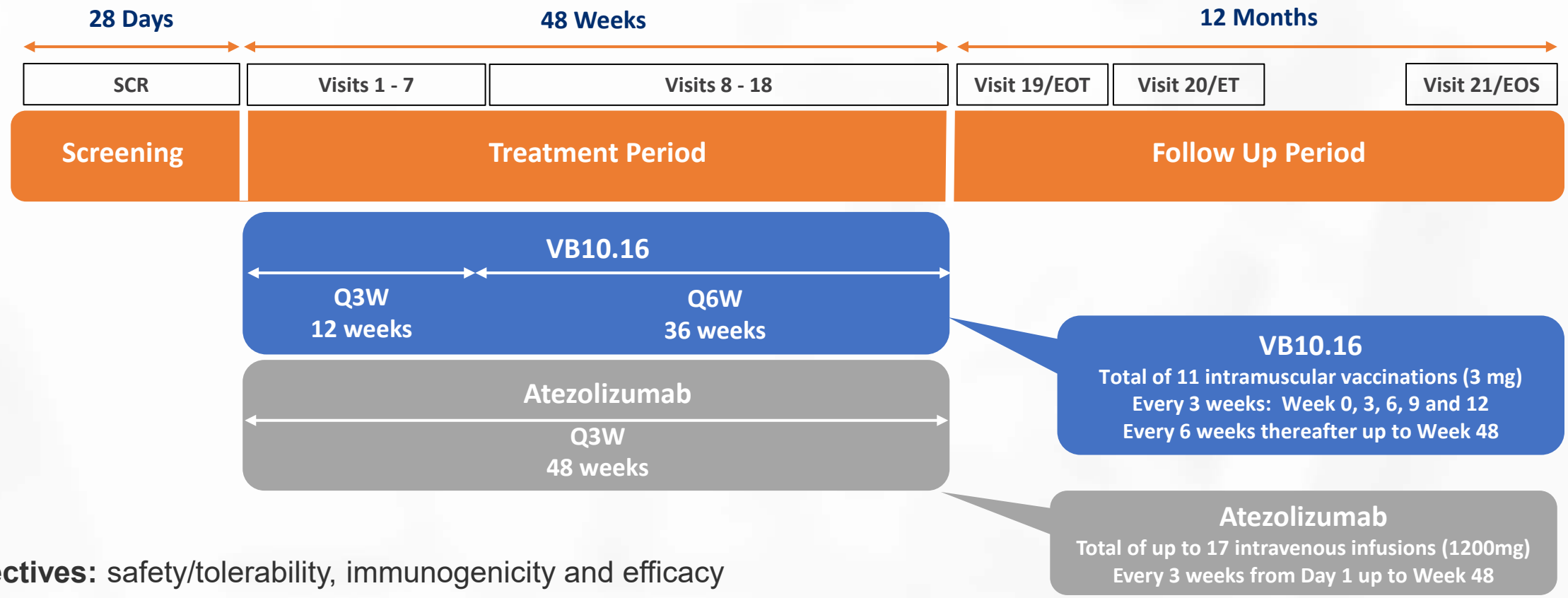
O'Malley D, et al. *JCO 2022*

HPV16 is an ideal target for off-the-shelf cancer vaccines

- High-grade cervical intraepithelial neoplasia (CIN) caused by infection with human papillomavirus (HPV) often precedes the development of cervical cancer
- Almost all cervical cancers are caused by HPV infection and HPV16 accounts for more than half of all cases
- HPV E6 and E7 viral antigens are only expressed by HPV-infected cells and thus act as tumor-specific antigens that are attractive targets for therapeutic cancer vaccines like VB10.16



VB C-02: VB10.16 in combination with atezolizumab in advanced cervical cancer – A multi-center single arm phase 2a trial (NCT04405349)



Objectives: safety/tolerability, immunogenicity and efficacy

Primary endpoints: incidence/severity of AEs, ORR (based on RECIST 1.1 by blinded independent central review)

Fully enrolled with 52 patients

Best overall response by blinded independent central review

BOR rate	N (%)
Complete Response	2 (5%)
Partial Response	6 (15%)
Stable Disease *SD+*	17 (44%) *9*
Progressive Disease	13 (33%)
NE	1 (3%)

- *Assessment using RECIST v1.1 criteria*
- *SD+ = Stable Disease with shrinkage in target lesion(s)*
- *NE = non-evaluable*

ORR = 21% (8/39 patients)

DCR = 64% (25/39 patients)

DOR: Median DOR not yet reached (range 2.3 – 10.8 months)

PD-L1 status	ORR (n/N)	DCR (n/N)
Positive (TIC 1-2)	**27%** (6/22)	**77%** (17/22)
Negative (TIC 0)	**17%** (2/12)	**58%** (7/12)

Thank you!