Cervical Cancer and the Evolving Therapeutic Landscape

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Cervical Cancer

NCCN Guidelines Index
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Discussion

SYSTEMIC THERAPY FOR CERVICAL CANCER[a]

Squamous Cell Carcinoma, Adenocarcinoma, or Adenosquamous Carcinoma			
Chemoradiation	Recurrent or Metastatic Disease		
	First-line Combination Therapy[b,c]	Possible First-line Single-agent therapy[c]	Second-line or Subsequent Therapy[g]
Preferred Regimens • Cisplatin • Carboplatin if patient is cisplatin intolerant	**Preferred Regimens** • Pembrolizumab + cisplatin/paclitaxel ± bevacizumab for PD-L1–positive tumors (category 1)[d,e,f,1] • Pembrolizumab + carboplatin/paclitaxel ± bevacizumab for PD-L1–positive tumors (category 1)[d,e,f,1] • Cisplatin/paclitaxel/bevacizumab[d,2] (category 1) • Carboplatin/paclitaxel/bevacizumab[d] **Other Recommended Regimens** • Cisplatin/paclitaxel (category 1)[3,4] • Carboplatin/paclitaxel[5,6] (category 1 for patients who have received prior cisplatin therapy) • Topotecan/paclitaxel/bevacizumab[d,2] (category 1) • Topotecan/paclitaxel[2] • Cisplatin/topotecan[7]	**Preferred Regimens** • Cisplatin[4] **Other Recommended Regimens** • Carboplatin[8] • Paclitaxel[9,10]	**Preferred Regimens** • Pembrolizumab for PD-L1–positive or MSI-H/dMMR tumors[e,f,11] • Nivolumab for PD-L1–positive tumors[e,f,12] **Other Recommended Regimens** (All agents listed here are category 2B unless otherwise noted) • Bevacizumab[d] • Albumin-bound paclitaxel • Docetaxel • Fluorouracil • Gemcitabine • Ifosfamide • Irinotecan • Mitomycin • Pemetrexed • Topotecan • Vinorelbine • Tisotumab vedotin-tftv (category 2A)[13] **Useful in Certain Circumstances** • Pembrolizumab for TMB-H tumors[e,h] • Larotrectinib or entrectinib for *NTRK* gene fusion-positive tumors (category 2B)

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

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

Stratification Factors

- Metastatic disease at diagnosis (yes vs no)
- PD-L1 CPS (<1 vs 1 to <10 vs ≥10)
- Planned bevacizumab use (yes vs no)

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

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.

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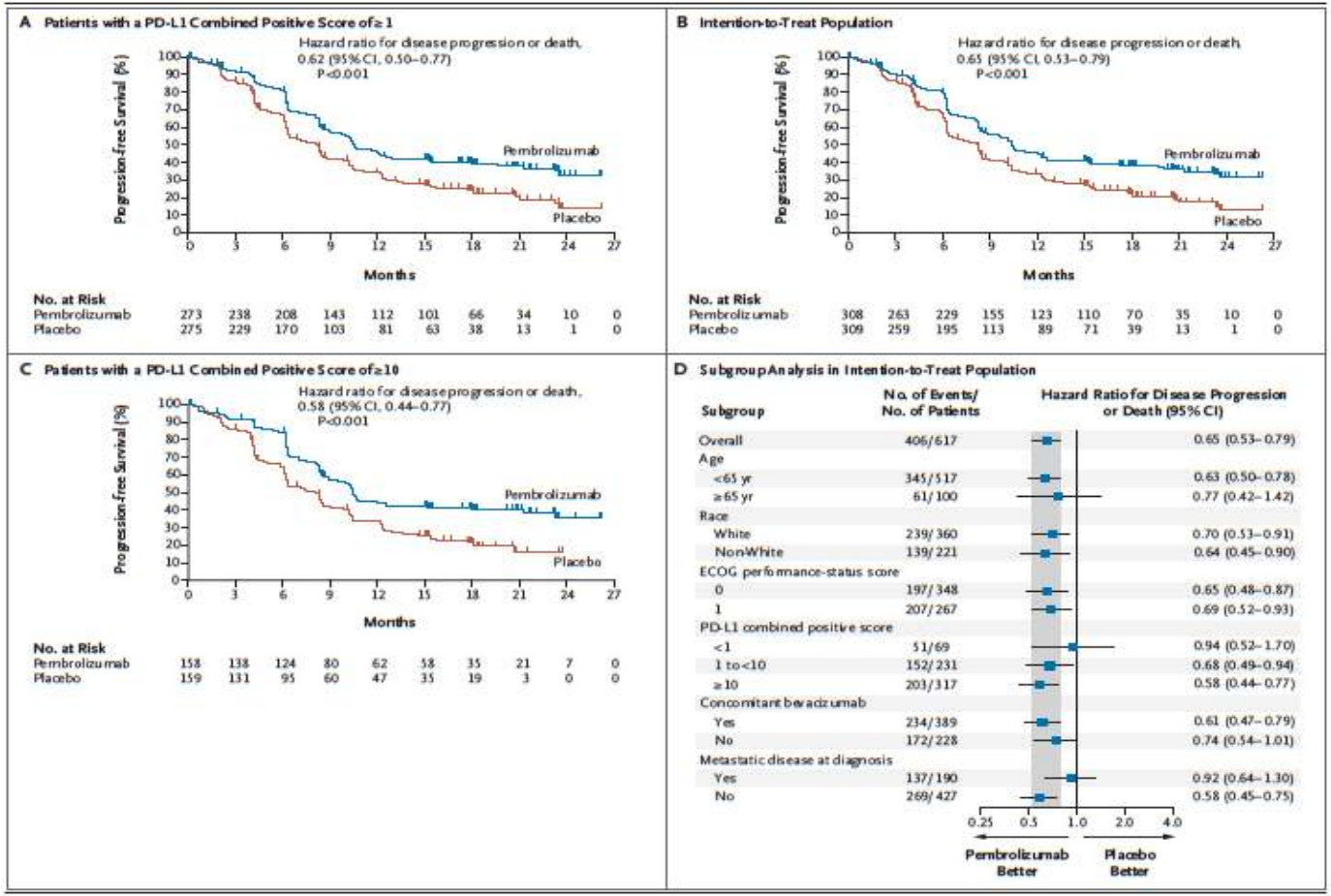
Keynote 826 PFS by PD-L1

1. CPS ≥ 1
2. ITT
3. CPS ≥ 10



Colombo et al NEJM 2021

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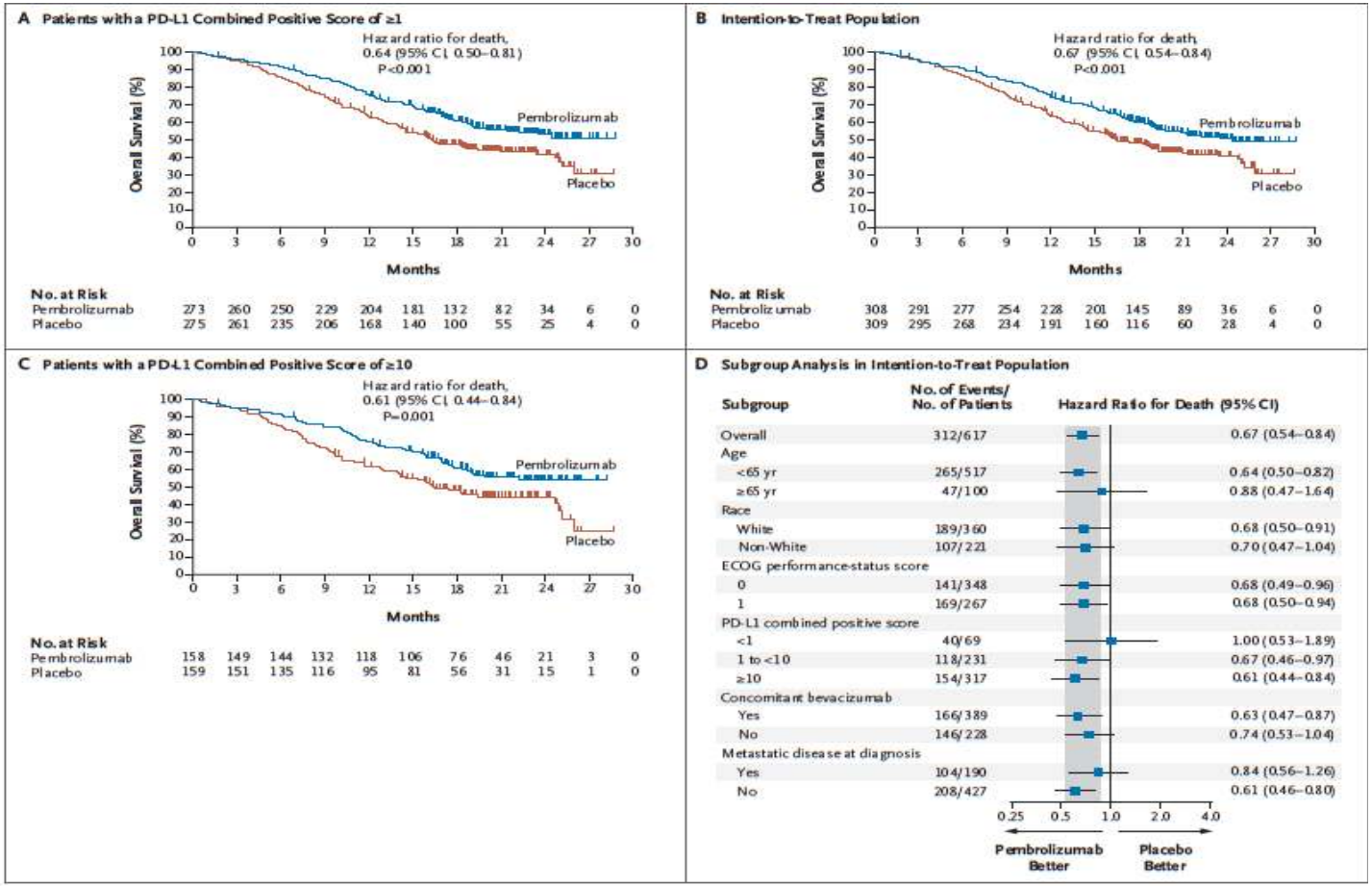
Keynote 826 OS by PD-L1

1. CPS ≥ 1
2. ITT
3. CPS ≥ 10



Colombo et al NEJM 2021

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GEICO 68-C/GOG 3030/BEATcc

- Primary Stage IVB, persistent or recurrent carcinoma of the cervix
- Measurable disease by RECIST v1.1
- ECOG-PS: 0-1
- No previous systemic chemotherapy for advanced or recurrent disease
- Available tissue (archival or fresh)
- N=404 pts

R: 1:1

Control Arm

Cis- or carboplatin + paclitaxel + bevacizumab (GOG 240)
until disease progression, unacceptable toxicity, death or withdrawal of consent

Experimental Arm

Cis- or carboplatin + paclitaxel + bevacizumab + atezolizumab until disease progression, unacceptable toxicity, death or withdrawal of consent

Primary Endpoint:
Overall survival (OS)

Secondary Endpoints:
- PFS
- ORR
- DOR
- Safety
- HR-QOL

Stratification Factors:
- Prior ChemoRT
- Histology: SCC vs Adeno (including AdenoSquamous)
- Chemotherapy Backbone: Cisplatin vs Carboplatin

ClinicalTrials.gov Identifier: NCT03556839

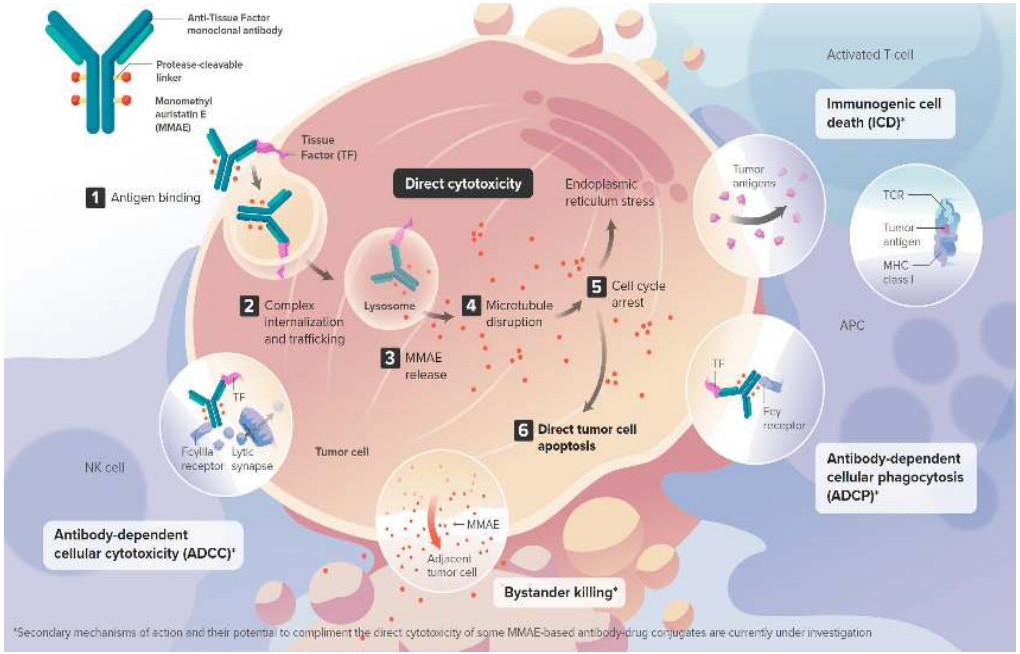
Randomized Phase III ICI Trials in the Locally-advanced Setting

Frontline ICI trial	Population	Agent (n)	Design	Primary endpoint(s)
CALLA (NCT03830866)	• FIGO 2009 IB2-IIB node+ • IIIA-IVA any nodal status • Measurable RECIST v1.1 • ECOG PS: 0-1	Durva (714)	2 arm 1:1 CRT control 24 months	• PFS
ENGOT cx11/GOG 3047/ KEYNOTE-A18 (NCT04221945)	• FIGO 2009 IB2-IIB node+ • IIIA-IVA any nodal status • Measurable RECIST v1.1 • ECOG PS: 0-1	Pembro (980)	2 arm 1:1 CRT control 24 months	• PFS • OS

CRT, chemoradiotherapy; durva, durvalumab; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics; ICI, immune checkpoint inhibitor; OS, overall survival; pembro, pembrolizumab; RECIST, Response Evaluation Criteria in Solid Tumours

Tisotumab Vedotin (TV)

- Tisotumab vedotin is an investigational antibody–drug conjugate directed to TF and covalently linked to the microtubule-disrupting agent, MMAE, via a protease-cleavable linker[1,2]
  - TF is a protein highly expressed in cervical cancer and other solid tumors[3-6]
- Multimodal MOA of tisotumab vedotin[1,2,7]
  - Direct cytotoxicity
  - Bystander killing
  - Immunogenic cell death
  - ADCC
  - ADCP



.ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; MMAE, monomethyl auristatin E; MOA, mechanism of action; TF, tissue factor

1. Breij EC et al. *Cancer Res*. 2014;74(4):1214-1226. 2. De Goeij BE et al. *Mol Cancer Ther*. 2015;14(5):1130-1140. 3. Forster Y et al. *Clin Chim Acta.* 2006;364:12-21. 4. Pan L et al. *Mol Med Rep*. 2019;19:2077-2086. 5. Cocco E et al. *BMC Cancer.* 2011;11:263. 6. Zhao X et al. *Exp Ther Med.* 2018;16:4075-4081. 7. Alley SC et al. AACR 2019; Abstract 221.

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innovaTV 204/GOG 3023/ENGOT cx6 Study Design

innovaTV 204 (NCT03438396) is a pivotal phase 2 single-arm, multicenter (United States and Europe) study evaluating tisotumab vedotin in patients with previously treated recurrent and/or metastatic cervical cancer

Key Eligibility Criteria

- Recurrent or extrapelvic metastatic cervical cancer
- Progressed during or after doublet chemotherapy with bevacizumab (if eligible)
- Received ≤2 prior systemic regimens
- ECOG PS 0-1

Enrolled: 102
Treated: 101

Tisotumab vedotin
2.0 mg/kg IV Q3W

Until PD or unacceptable toxicity

Tumor responses assessed using CT or MRI at baseline, every 6 weeks for the first 30 weeks, and every 12 weeks thereafter

*Study sample size calculated assuming a confirmed ORR of 21% to 25% with tisotumab vedotin and to provide ≥80% power to exclude an ORR of ≤11%

Primary Endpoint
- ORR per RECIST v1.1, by independent imaging review committee (IRC)

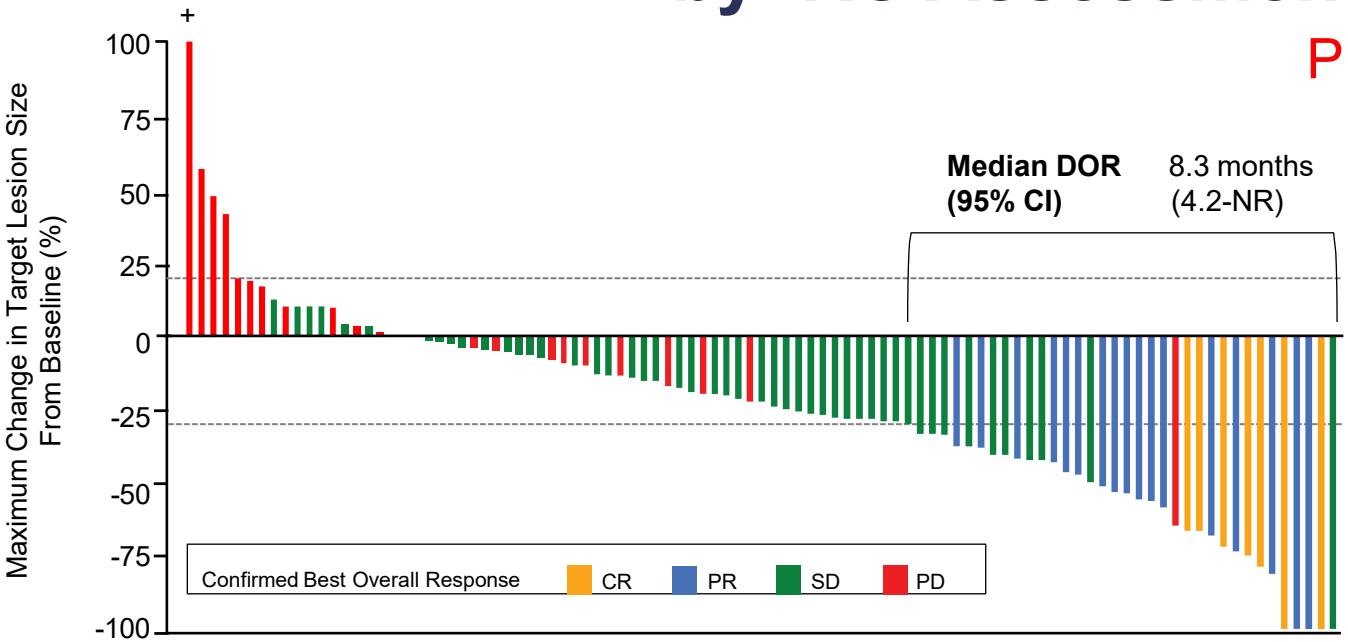
Secondary Endpoints
- ORR per RECIST v1.1, by investigator
- DOR, TTR, and PFS by IRC and investigator
- OS
- Safety

Exploratory Endpoints
- Biomarkers
- HRQoL

CT, computed tomography; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HR QoL, health-related quality of life; MRI, magnetic resonance imaging; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours, TTR; time to relapse; Q3W, every 3 weeks

Coleman RL et al. ESMO 2020. Abstract LBA32.
Coleman RL. *Lancet Oncol.* 2021:S1470-2045(21)00056-5.

Maximum Change in Target Lesion Size by IRC Assessment



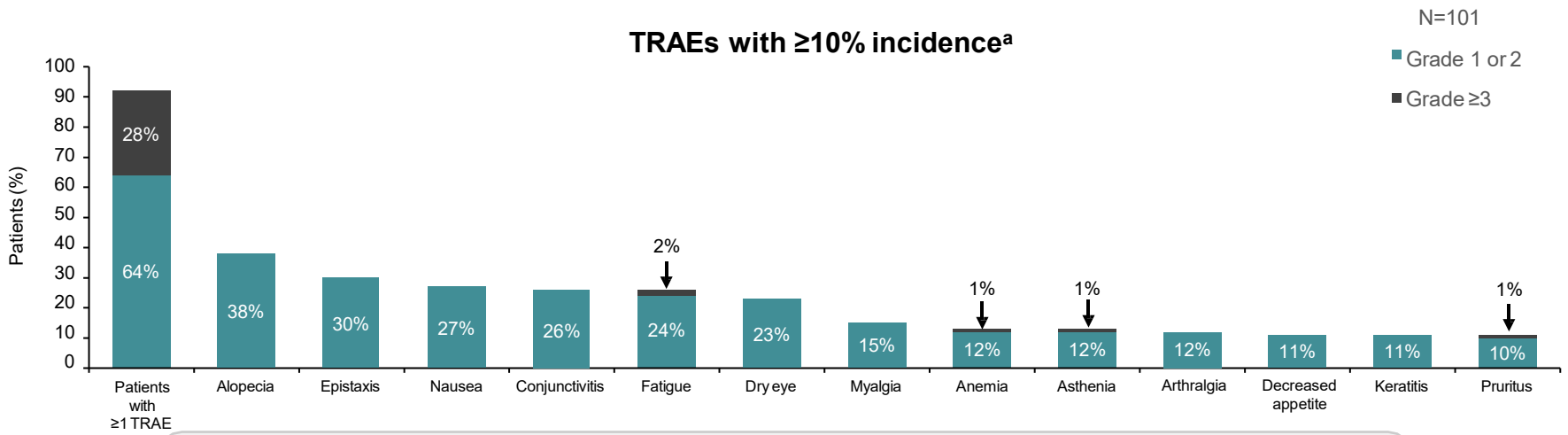
PDUFA for accelerated US FDA approval 10/10/2021

	N=101
Confirmed ORR (95% CI), %	**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)

Data cutoff: February 06, 2020. Median duration of follow-up: 10.0 months. + indicates a change greater than 100%. Horizontal dashed lines indicate 20% increase and 30% decrease in target lesion diameters from baseline for RECIST v1.1 assessment. Colored bars represent the best overall confirmed response. CR, PR, SD, and PD were based on RECIST v1.1 as evaluated by IRC.
CR, complete response; IRC, independent review committee; PD, disease progression; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; SD, stable disease.

Coleman RL et al. ESMO 2020. Abstract LBA32.
Coleman RL. *Lancet Oncol.* 2021:S1470-2045(21)00056-5.

Most Common TRAEs with TV



- **Most TRAEs were grade 1 or 2 and no new safety signals were reported**
- **One death due to septic shock was considered by the investigator to be related to therapy[b]**

Data cutoff: February 06, 2020. Median duration of follow-up: 10.0 months. Median duration of treatment: 4.2 months (range, 1–16).
[a]Any-grade AEs included if ≥10%. [b]Three treatment-emergent deaths unrelated to therapy included one case of ileus and two with unknown causes. TRAE, treatment-related adverse event.

Coleman RL et al. ESMO 2020. Abstract LBA32.
Coleman RL. *Lancet Oncol.* 2021:S1470-2045(21)00056-5.

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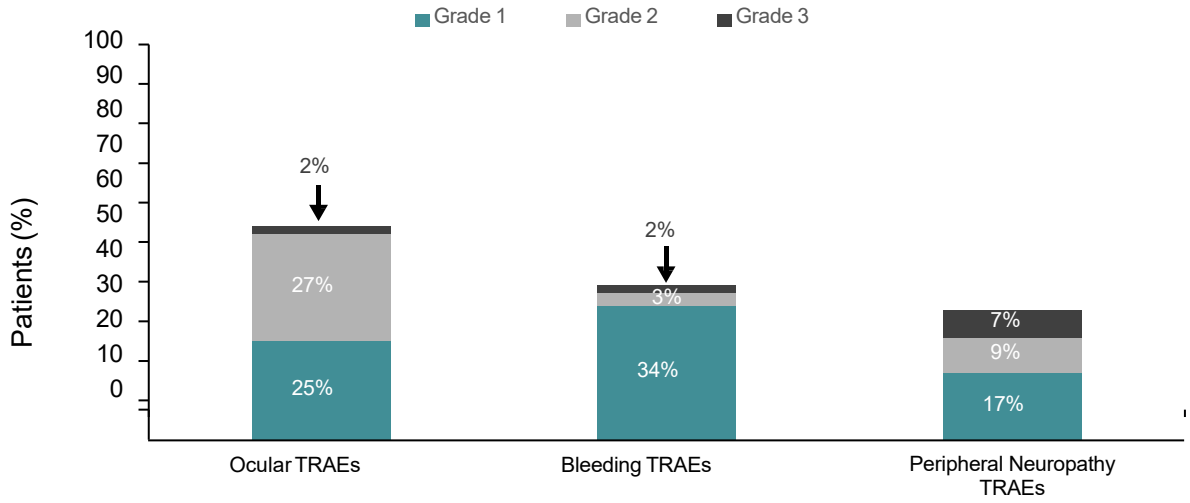
Prespecified AEs of Interest of TV



- **Ocular AEs were mostly mild to moderate, resolved, and were manageable with an eye care plan**
- **Most bleeding events were grade 1 epistaxis (28%) of which majority resolved**
- **Most peripheral neuropathy events (known MMAE-related toxicity) were grade 1 and manageable with dose modifications; resolution was limited by follow-up period**

Coleman RL et al. ESMO 2020. Abstract LBA32.
Coleman RL. *Lancet Oncol.* 2021:S1470-2045(21)00056-5.

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ENGOT cx12/GOG-3057/innovaTV 301: Schema

Genmab

Genmab and Seagen Announce FDA Accelerated Approval for TIVDAK™ (tisotumab vedotin-tftv) in Previously Treated Recurrent or Metastatic Cervical Cancer

September 20, 2021 17:00 ET | Source: Genmab A/S

Prior bevacizumab administration (yes vs no)
Region (US; EU; Other)
Prior anti-PD-1 or PD-L1 administration (yes vs no)

*The proportion of participants who have not received prior bevacizumab in combination with chemotherapy as 1L treatment will be capped at 50%.

** Some AESIs may be followed longer than 30 days until resolution, improvement, or stabilization.

innovaTV 301. Updated April 28, 2021. Accessed April 30, 2021. https://www.clinicaltrials.gov/ct2/show/NCT04697628

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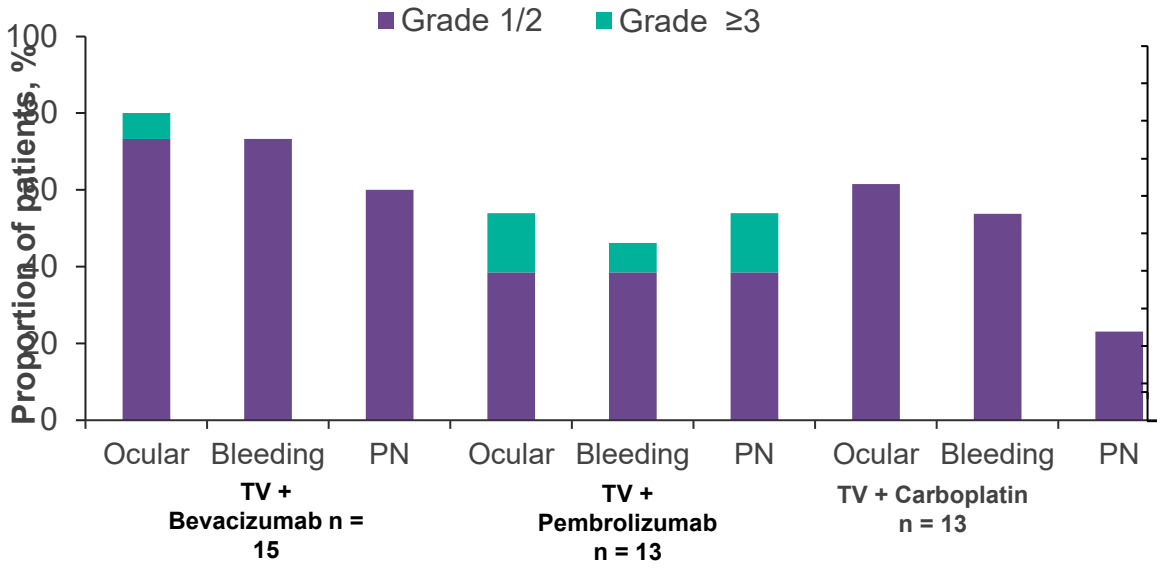
innovaTV 205/ENGOT cx8/GOG 3024: TV Combinations and 1L

2L+ escalation	Frontline expansion	2L+ expansion
TV + bevacizumab		
TV + pembrolizumab	TV + pembrolizumab	TV + pembrolizumab
TV + carboplatin	TV + carboplatin	
		TV weekly x 3 q28d

Completed enrollment 2021

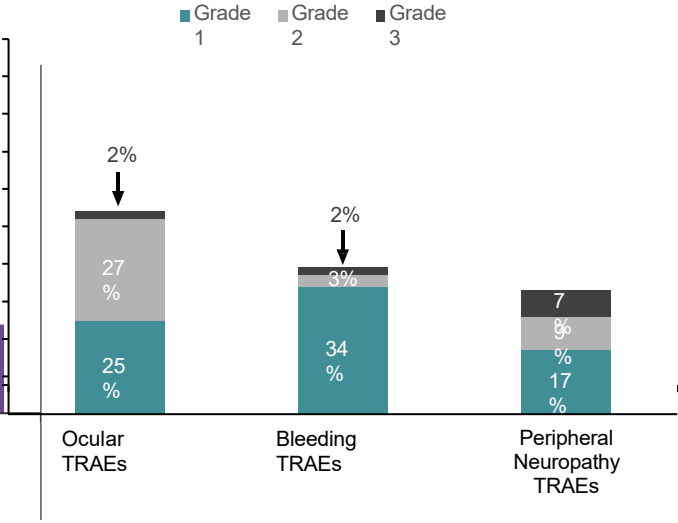
Prespecified AEs of Special Interest

GOG 3024/innovaTV 205 IGCS 2021



Monk et.al Virtual IGCS 2021

GOG 3023/innovaTV 204



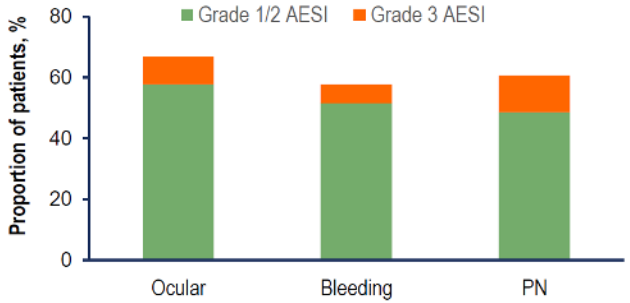
Coleman RL. *Lancet Oncol.* 2021:S1470-2045(21).

Summary of Efficacy & Safety for 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



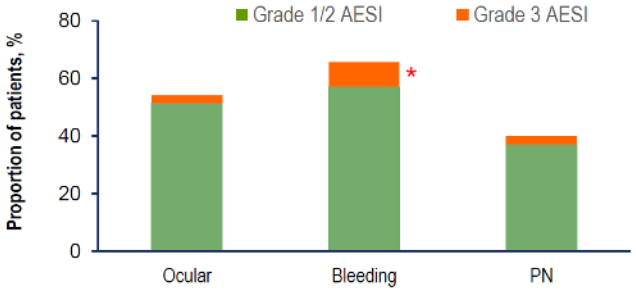
1L, first-line; AE, adverse event; AESI, adverse event of special interest; carbo, carboplatin; FU, follow-up; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PN; peripheral neuropathy; r/mCC, recurrent/metastatic cervical cancer; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TV, tisotumab vedotin.

Summary of Efficacy & Safety for 2L/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.

2021 ESMO congress

Vergote I., et al.

+, censored; 1L, first-line; AE, adverse event; AESI, adverse event of special interest; DOR, duration of response; FU, follow-up; NR, not reached; ORR, objective response rate; OS, overall survival; pembro, pembrolizumab; PFS, progression-free survival; PN; peripheral neuropathy; r/mCC, recurrent/metastatic cervical cancer; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TV, tisotumab vedotin.

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GOG 3016/ENGOT-cx9: Randomized Phase III Trial of Cemiplimab Versus Investigator's Choice Chemotherapy in Cervical Cancer: "EMPOWER- CERVICAL 1" NCT03257267

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

Primary Endpoint is OS

Investigators' choice

Options:

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

Cemiplimab

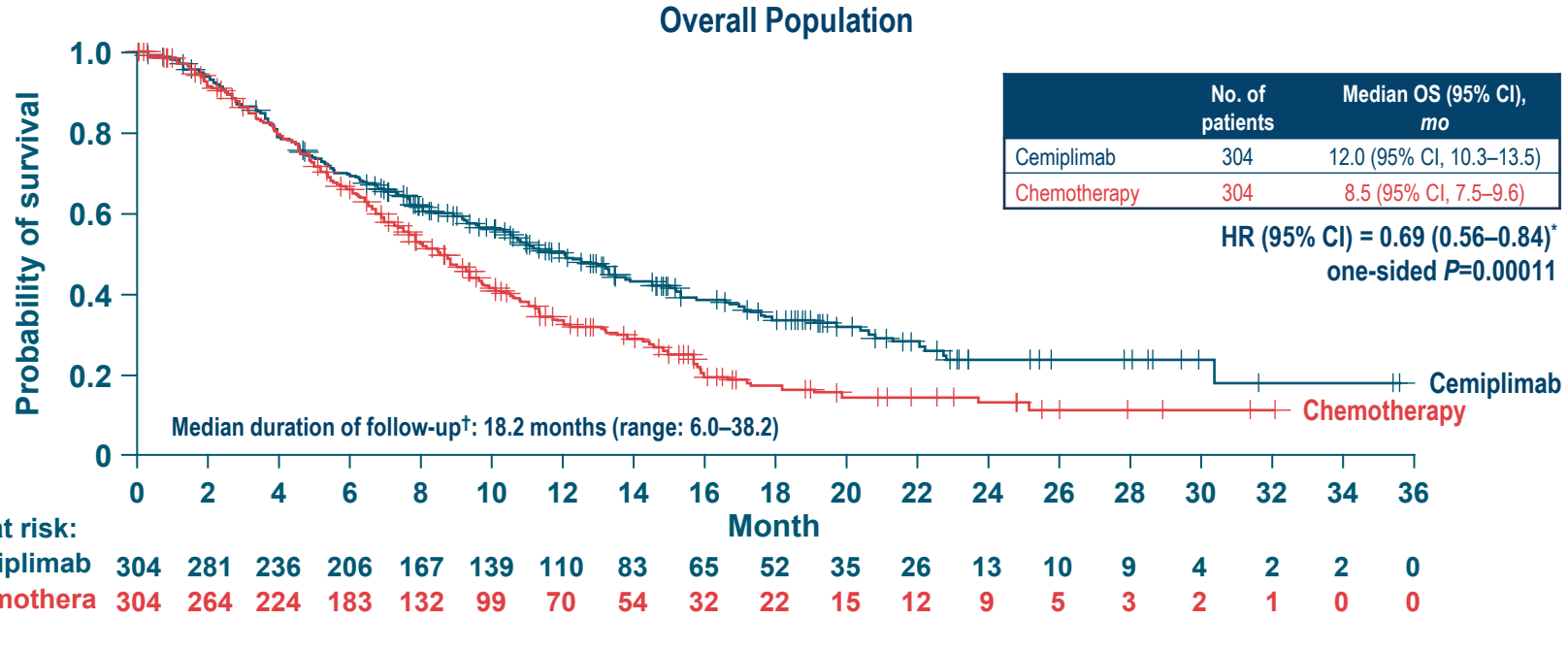
Cemiplimab 350 mg IV every 3 weeks

Statistical Considerations for Study Design

Power	90%
Median Survival	7 months
Hazard Ratio	0.7
Timing of Final Analysis (Ha)	30.5 months

Accrual completed 5/29/2020

Overall survival

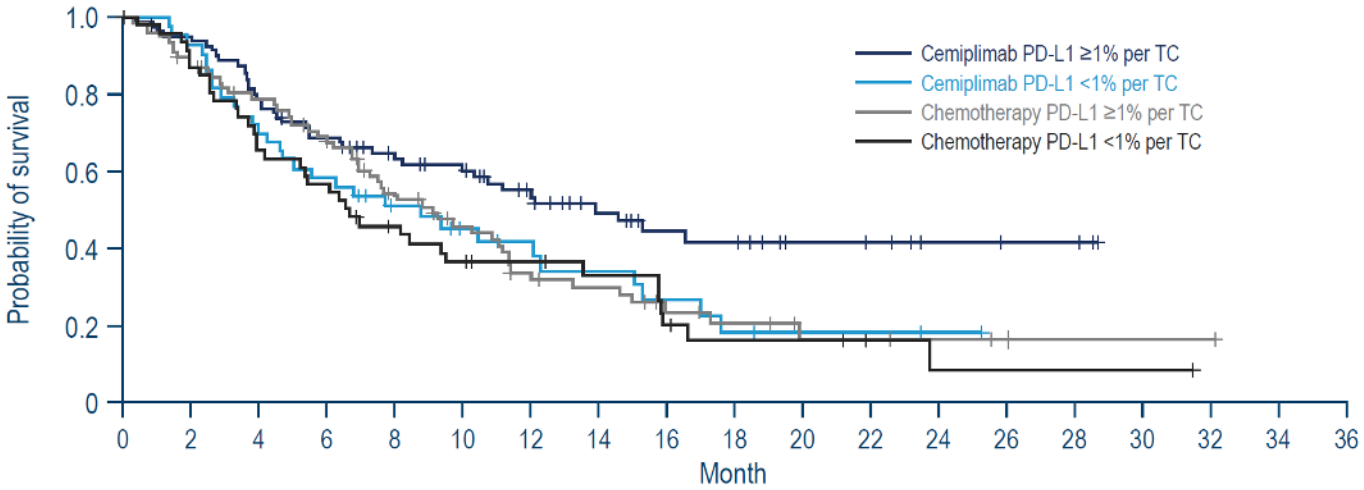


*Stratified by geographic region (North America vs Asia vs ROW) and Histology (SCC vs AC) according to interactive web response system. †From randomisation to data cutoff date.
AC, adenocarcinoma or adenosquamous carcinoma; CI, confidence interval; HR, hazard ratio; mo, month; OS, overall survival; ROW, rest of world; SCC, squamous cell carcinoma..

Tewari KS et al. Virtual Interim ESMO 2021

Data cutoff date: 4 Jan 2021

Survival analysis by PD-L1 status*



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

*Associations between efficacy outcomes and PD-L1 expression (detected using the SP263 monoclonal antibody) in tumor cells was evaluated using exploratory analyses.
Of 608 randomized patients, 254 had valid baseline PD-L1 samples: cemiplimab (n=126) and chemotherapy (n=128).
Data cutoff date: 4 Jan 2021.
PD-L1, programmed cell death-ligand 1; TC, tumor cells.

2021 ESMO congress

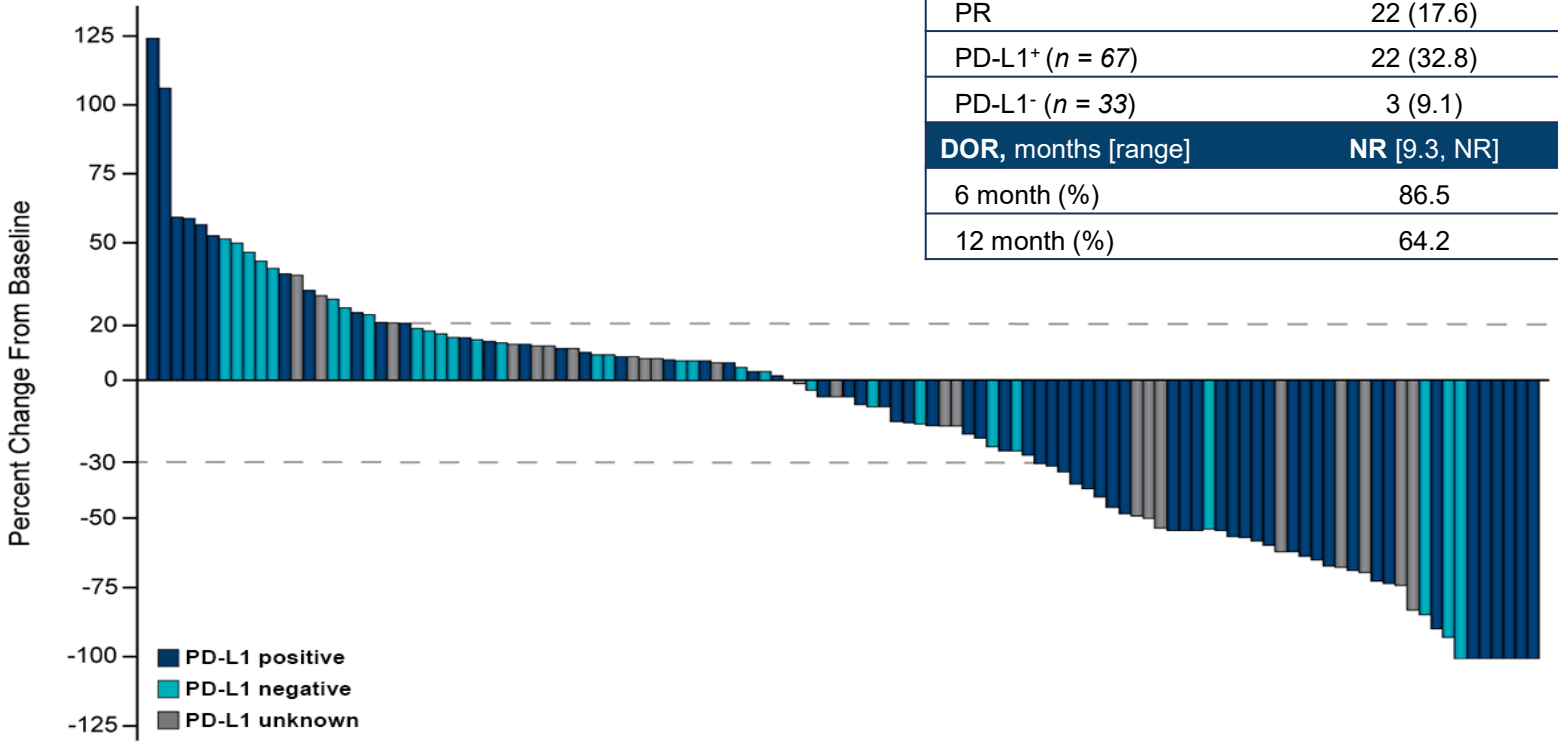
Balstilimab (anti-PD-1) in combination with zalifrelimab (anti-CTLA-4): final results from a Phase 2 study in patients (pts) with recurrent/metastatic (R/M) cervical cancer (CC)

D.M. O'Malley[1], M. Neffa[2], B.J. Monk[3], T. Melkadze[4], A. Kryzhanivska[5], I. Bulat[6], T.M. Meniawy[7], I. Bondarenko[8], W. Ortuzar Feliu[9], M. Ancukiewicz[9], I. Lugowska[10]

[1]Division of Gynecologic Oncology, The Ohio State University/James Comprehensive Cancer Center, Columbus, Ohio; [2]Department of Surgery, CI of Healthcare Regional Clinical Specialized Dispensary of the Radiation Protection, Kharvik, Ukraine; [3]Arizona Oncology (US Oncology Network), University of Arizona College of Medicine, Creighton University School of Medicine, Phoenix, Arizona; [4]Medical Oncology, Research Institute of Clinical Medicine, Tbilisi, Georgia; [5]Regional Clinical Oncology Center, Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine; [6]ARENSIA Exploratory Medicine, Institute of Oncology Unit, Chisinau, Moldova; [7]Linear Clinical Research, Nedlands, Australia; [8]Department of Chemotherapy, Dnipropetrovsk Medical Academy of Ministry of Health of Ukraine, Dnipropetrovsk, Ukraine; [9]Clinical Development, Agenus Inc., Lexington, Massachusetts; [10]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Memorial Cancer Center, Warsaw, Poland.

Clinical Activity

ORR, N (%)	**32 (25.6)**
CR	10 (8.0)
PR	22 (17.6)
PD-L1^{+} (*n* = *67*)	22 (32.8)
PD-L1^{-} (*n* = *33*)	3 (9.1)
DOR, months [range]	**NR** [9.3, NR]
6 month (%)	86.5
12 month (%)	64.2

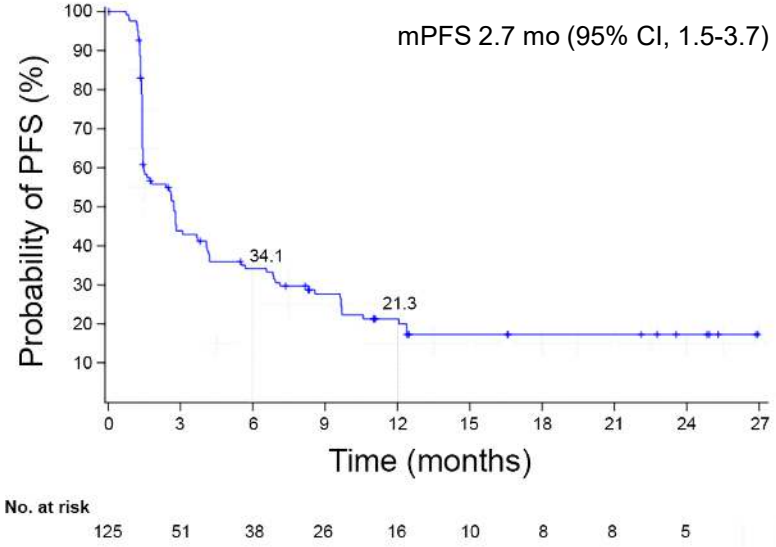


Kaplan-Meier Survival Estimates

Median duration of follow-up: 21 months

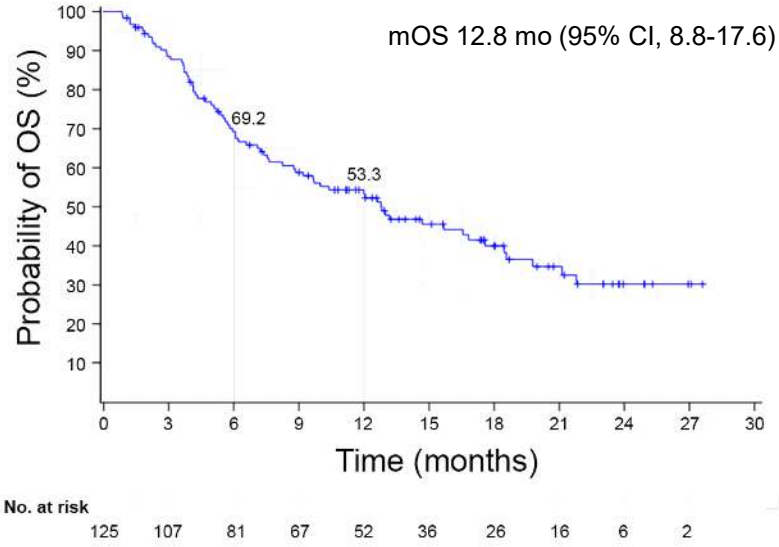
PFS

A



OS

B



PD-L1⁺ subset mOS: 15.7 mo (95% CI, 7.6, 21.1)

GOG-3028 - A Two Arm, Randomized, Non Comparative Blinded Phase 2 Trial of Balstilimab +/- Zalifrelimab in Second Line Cervical Cancer

RaPiDS

Patient Eligibility

- Cervical cancer that has relapsed after a platinum-based treatment (first line) regimen for advanced (recurrent, unresectable, or metastatic) disease
- Measurable disease on imaging based on RECIST version 1.1
- ECOG PS ≤1
- sufficient and adequate formalin-fixed paraffin embedded (FFPE)

Randomization 1:1

Treatment up to 24 months

Balstilimab (300 mg) every 3 weeks
Placebo every 6 weeks

Balstilimab (300 mg) every 3 weeks
Zalifrelimab (1 mg/kg) every 6 weeks

Primary Endpoint

- ORR according to RECIST 1.1

GOG Highlight Reel

Cervical Cancer: Projected Treatment Landscape

GOG FOUNDATION

Cervical Cancer: Projection of Treatment