# The Role of ADCs in Cervical Cancer and the Evolving Treatment Landscape

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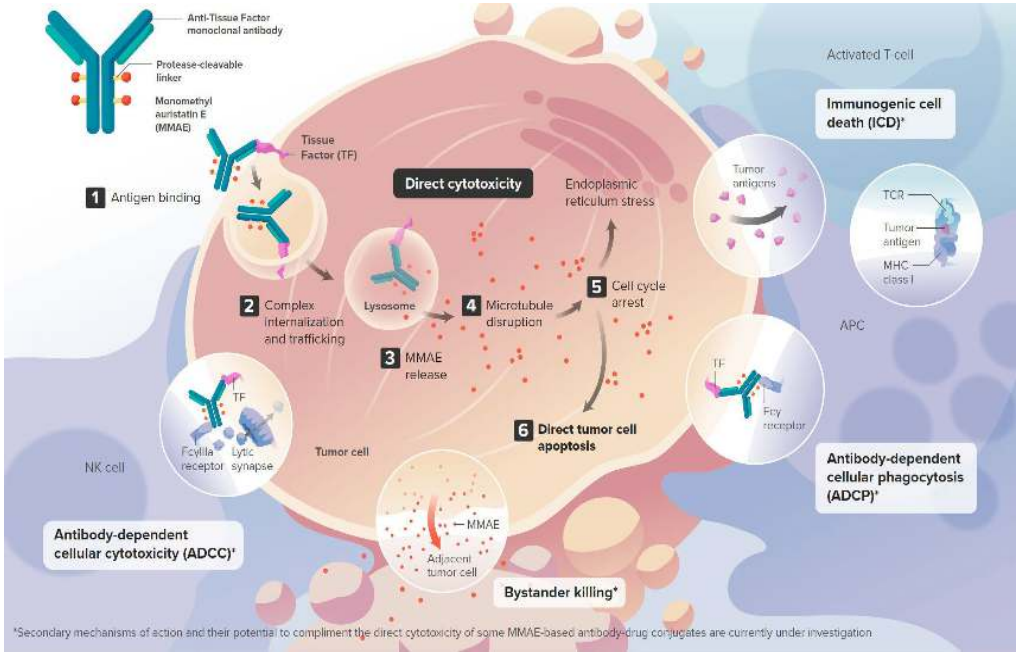
## SYSTEMIC THERAPY FOR CERVICAL CANCER[a]

**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**<br>• Cisplatin<br>• Carboplatin if patient is cisplatin intolerant | **Preferred Regimens**<br>• Pembrolizumab + cisplatin/paclitaxel ± bevacizumab for PD-L1–positive tumors (category 1)[d,e,f,1]<br>• Pembrolizumab + carboplatin/paclitaxel ± bevacizumab for PD-L1–positive tumors (category 1)[d,e,f,1]<br>• Cisplatin/paclitaxel/bevacizumab[d,2] (category 1)<br>• Carboplatin/paclitaxel/bevacizumab[d]<br><br>**Other Recommended Regimens**<br>• Cisplatin/paclitaxel (category 1)[3,4]<br>• Carboplatin/paclitaxel[5,6] (category 1 for patients who have received prior cisplatin therapy)<br>• Topotecan/paclitaxel/bevacizumab[d,2] (category 1)<br>• Topotecan/paclitaxel[2]<br>• Cisplatin/topotecan[7] | **Preferred Regimens**<br>• Cisplatin[4]<br><br>**Other Recommended Regimens**<br>• Carboplatin[8]<br>• Paclitaxel[9,10] | **Preferred Regimens**<br>• Pembrolizumab for PD-L1–positive or MSI-H/dMMR tumors[e,f,11]<br>• Nivolumab for PD-L1–positive tumors[e,f,12]<br><br>**Other Recommended Regimens**<br>(All agents listed here are category 2B unless otherwise noted)<br>• Bevacizumab[d]<br>• Albumin-bound paclitaxel<br>• Docetaxel<br>• Fluorouracil<br>• Gemcitabine<br>• Ifosfamide<br>• Irinotecan<br>• Mitomycin<br>• Pemetrexed<br>• Topotecan<br>• Vinorelbine<br>• Tisotumab vedotin-tftv (category 2A)[13]<br><br>**Useful in Certain Circumstances**<br>• Pembrolizumab for TMB-H tumors[e,h]<br>• Larotrectinib or entrectinib for *NTRK* gene fusion-positive tumors (category 2B) |

# 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

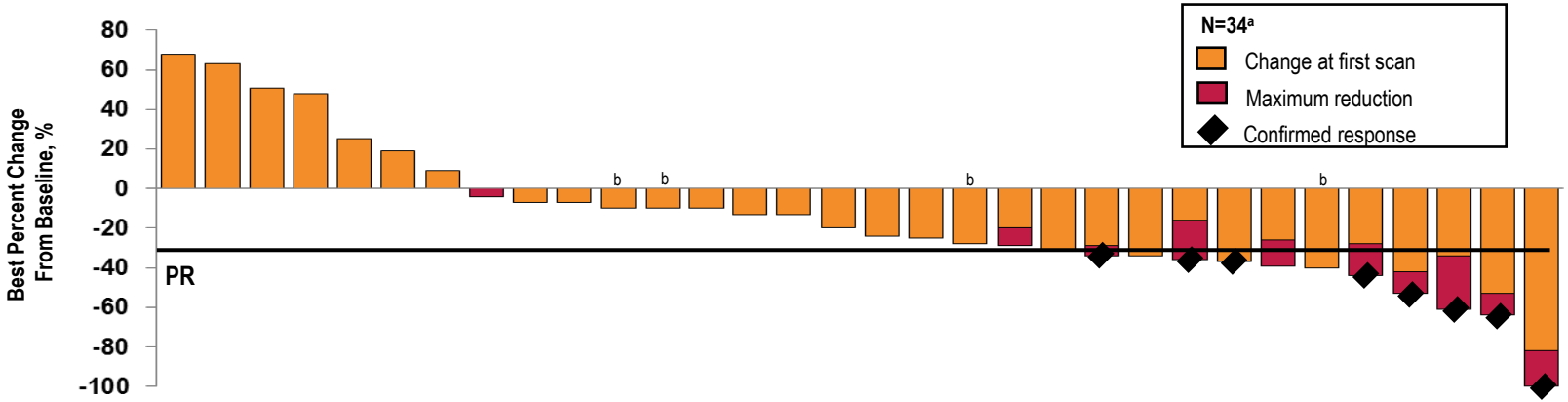



.ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; MMAE, monomethyl auristatin E; MOA, mechanism of action; TF, tissue factor

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.

# Phase I expansion in ≥ 2nd line recurrent Cxca (Vergote et al ESMO 2017)

## RECURRENT/ADVANCED CERVICAL CANCER TISOTUMAB VEDOTIN ORR 32%



# 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

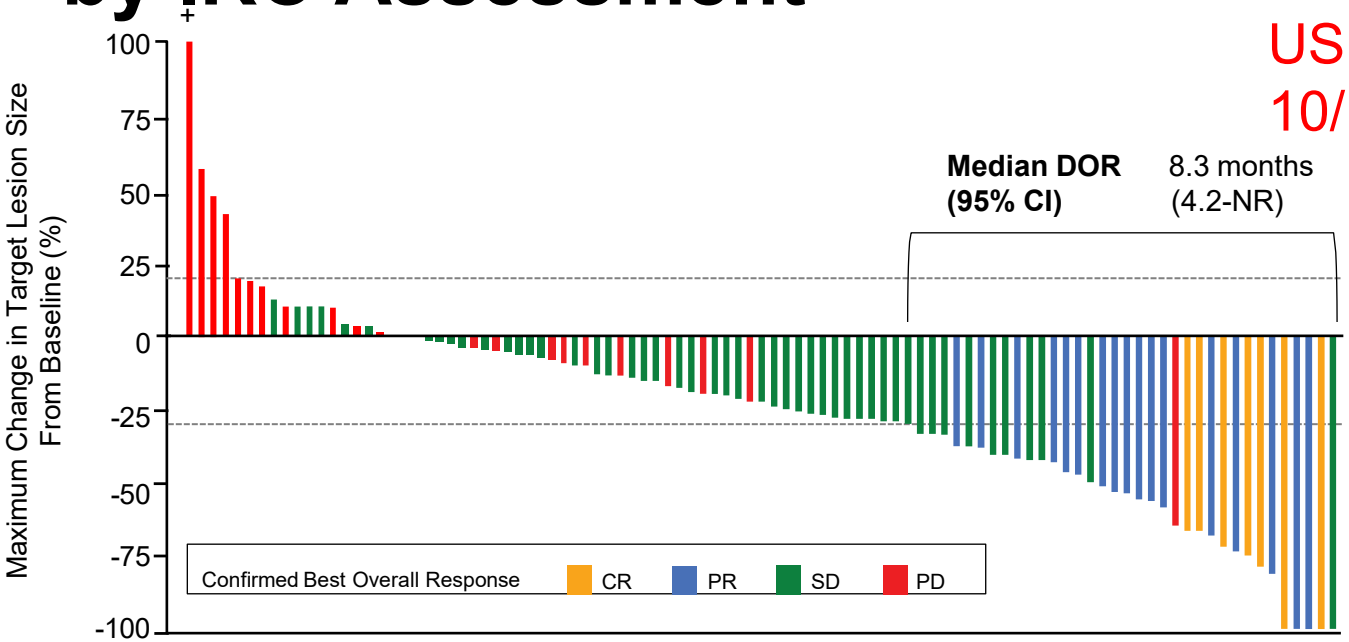
**Exploratory Endpoints**
- Biomarkers
- HRQoL

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.

## Genmab Announces Very Favorable Topline Results from Phase 2 Clinical Trial of Tisotumab Vedotin in Recurrent or Metastatic Cervical Cancer

Jun 29, 2020 at 10:29 PM CEST


## 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

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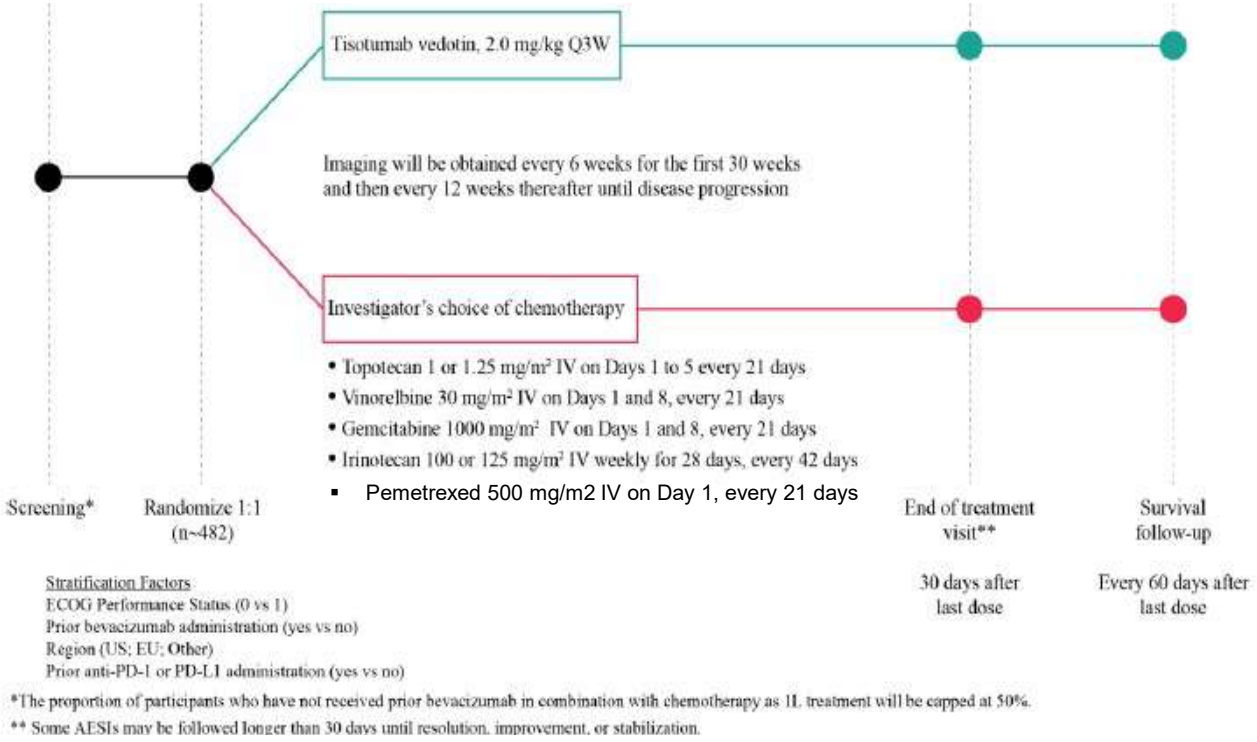
# ENGOT cx12/GOG-3057/innovaTV 301: Schema




**Primary Endpoint = OS**

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/carbo/Pembro +/- Bev | TV weekly x 3 q28d* |

*Completed enrollment 2021
Enrollment in start up

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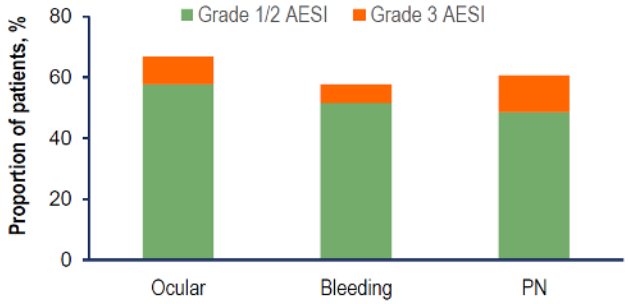
# Summary of Efficacy & Safety for 1L TV + Carbo

| Parameters | 1L TV + Carbo (N = 33)<br>Median FU: 7.9 months |
|---|---|
| Median duration of exposure, months (range) | TV: 4.9 (1 – 9)<br>Carbo: 4.1 (1 – 9) |
| Median number of cycles initiated (range) | TV: 6.0 (1 – 12)<br>Carbo: 6.0 (1 – 12) |
| Confirmed response rate, n (%) [95% CI]<br>Complete response, n (%)<br>Partial response, n (%)<br>Stable disease, n (%)<br>Progressive disease, n (%)<br>Not evaluable, n (%) | 18 (55) [36 – 72]<br>4 (12)<br>14 (42)<br>12 (36)<br>2 (6)<br>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 (%)<br>AE related to TV | 33 (100.0)<br>32 (97.0) |
| Grade ≥3 AE, n (%)<br>Grade ≥3 AE related to TV | 26 (78.8)<br>19 (57.6) |
| SAE, n (%)<br>SAE related to TV | 14 (42.4)<br>5 (15.2) |
| Fatal AE, n (%)<br>Fatal AE related to TV | 0<br>0 |







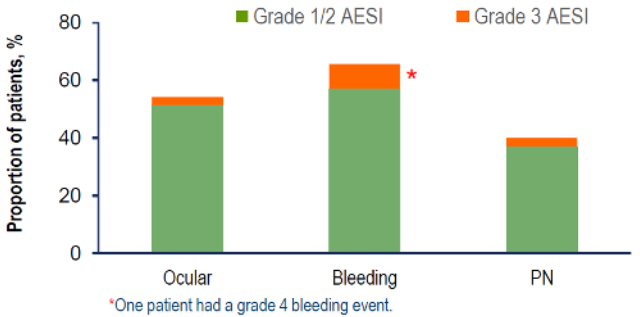
1L, first-line; AE, adverse event; AESI, adverse event of special interest; carbo, carboplatin; FU, follow-up; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PN; peripheral neuropathy; r/mCC, recurrent/metastatic cervical cancer; SAE, serious adverse 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)<br>Pembro: 4.3 (1 – 17) |
| Median number of cycles initiated (range) | TV: 6.0 (1 – 21)<br>Pembro: 6.0 (1 – 25) |
| Confirmed response rate, n (%) [95% CI]<br>Complete response, n (%)<br>Partial response, n (%)<br>Stable Disease, n (%)<br>Progressive disease, n (%)<br>Not evaluable, n (%) | 13 (38) [22 – 56]<br>2 (6)<br>11 (32)<br>12 (35)<br>7 (21)<br>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 (%)<br>AE related to TV | 35 (100.0)<br>34 (97.1) |
| Grade ≥3 AE, n (%)<br>Grade ≥3 AE related to TV | 26 (74.3)<br>16 (45.7) |
| SAE, n (%)<br>SAE related to TV | 18 (51.4)<br>5 (14.3) |
| Fatal AE, n (%)<br>Fatal AE related to TV | 1 (2.9)<br>0 |



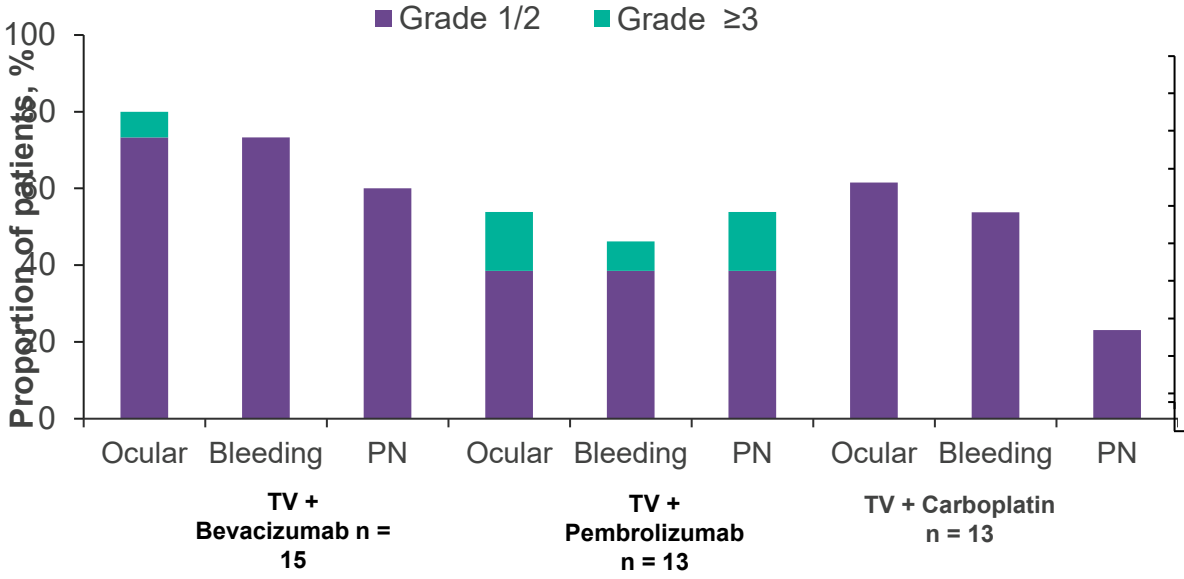

*One patient had a grade 4 bleeding event.




+, 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.

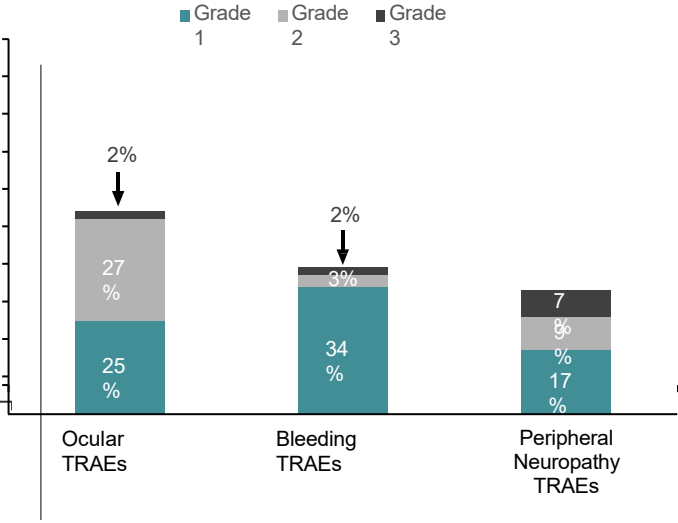
# Prespecified AEs of Special Interest

## GOG 3024/innovaTV 205
## IGCS 2021




Monk et.al Virtual IGCS 2021

## GOG 3023/innovaTV 204




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

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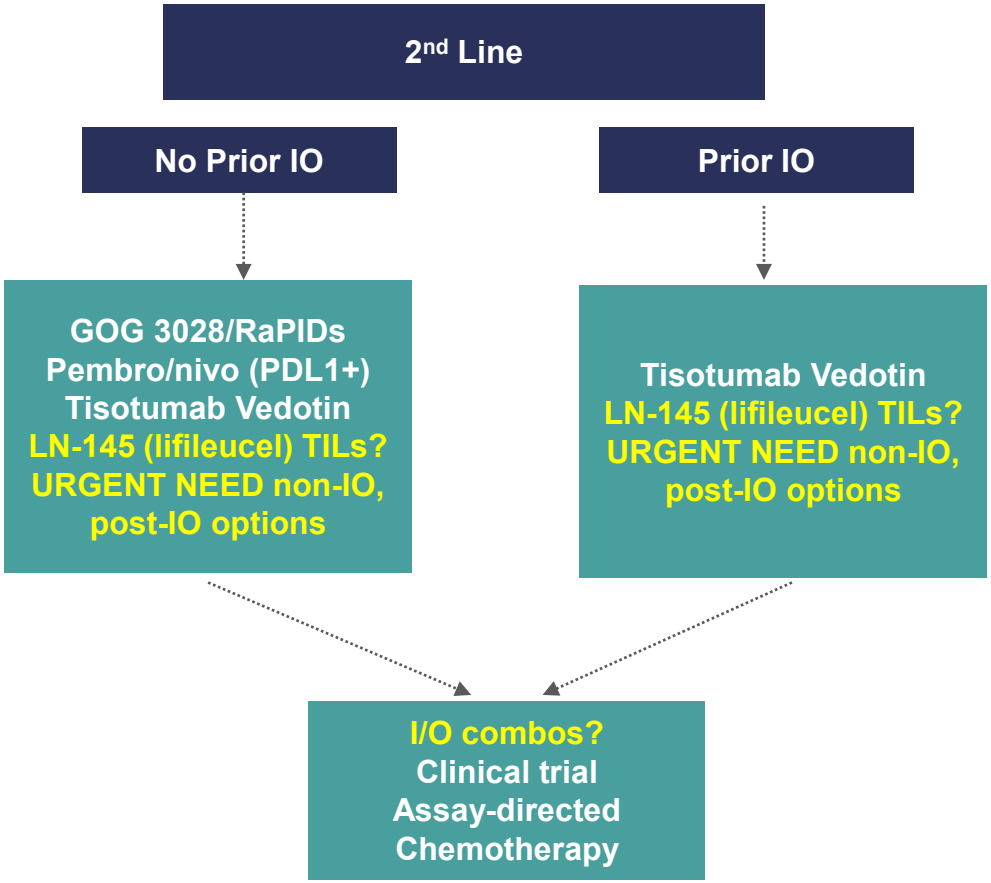
# Cervical Cancer: Projected Treatment Landscape

# Cervical Cancer: Projection of Treatment

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