TPS 5603

Trial in Progress Update on ENGOT-cx8/GOG-3024/innovaTV 205: Addition of a New Cohort With First-Line Tisotumab Vedotin + Pembrolizumab + Carboplatin ± Bevacizumab in Recurrent/ Metastatic Cervical Cancer

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BACKGROUND

- The prognosis for recurrent/metastatic cervical cancer (r/mCC) is poor, with a 5-year survival rate of 18% in patients with distant metastases[1]
- Until recently, first-line (1L) treatment for r/mCC was limited to taxane-platinum combinations with bevacizumab, per regional guidelines[2-4]
- After the approval of KN-826, the immune checkpoint inhibitor pembrolizumab was approved in the United States and Europe in combination with chemotherapy, with or without bevacizumab, for patients with r/mCC whose tumors express programmed death ligand 1 (PD-L1; with a combined positive score of ≥1)[5-8]
  - With the use of pembrolizumab + chemotherapy ± bevacizumab investigators saw a survival benefit over placebo (overall survival [OS] hazard ratio [HR], 0.64; profession-free survival [PFS] HR, 0.62)
  - The 24-month OS of 53% and 42% in the pembrolizumab group and placebo group, respectively, suggests a need for options that are more effective and result in long-term improvement
- Additional treatment approaches are necessary so clinical benefit is achieved in more patients, regardless of biomarker selection

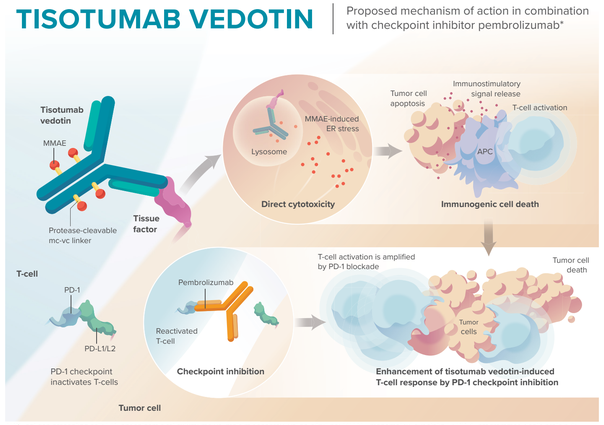
Tisotumab Vedotin

- Tissue factor (TF) plays a role in the tumor growth, angiogenesis, and metastasis of cancer[9] and is highly prevalent in cervical cancer, including squamous and adenocarcinoma histologic subtypes[9-11]
- Tisotumab vedotin (TV) is a TF-directed antibody-drug conjugate comprisinga fully human monoclonal antibody specific for TF, the microtubule-disrupting agent monomethyl auristatin E (MMAE), and a protease-cleavable linker that covalently links MMAE to the antibody (**Figure 1**)[12,13]
  - Once internalized by TF-expressing cells, MMAE is released in the endolysosome, resulting in cell cycle arrest and apoptotic cell death in actively dividing cells
  - TV exerts antitumor activity in multiple tumor types and kills tumor cells by direct cytotoxicity, by bystander cytotoxicity, by antibody-dependent cellular cytotoxicity, by antibody-dependent cellular phagocytosis, and in a manner consistent with immunogenic cell death
- Based on clinically meaningful and durable tumor response from the innovaTV 204 study (NCT03438396; objective response rate, 24%; median duration of response, 8.3 months), TV monotherapy received accelerated approval from the US Food and Drug Administration for use in patients with previously treated r/mCC[14,15]

Study Rationale

- To further improve outcomes in r/mCC, the authors combined TV with other agents that had nonoverlapping modes of action and known activity in cervical cancer
- The ENGOT-cx8/GOG-3024/innovaTV 205 (NCT03786081) study was conducted to explore the combination of TV + pembrolizumab, TV + carboplatin, and TV + bevacizumab; early results suggest potentially enhanced antitumor activity with a tolerable safety profile[14]
  - After dose escalation, the safety and recommended phase 2 dose (RP2D) of TV were confirmed in **1L/2L TV + bevacizumab** (Arm A), **2L/3L TV + pembrolizumab** (Arm B), and **2L+ TV + carboplatin** (Arm C) patients with r/mCC (2.0 mg/kg once every three weeks)[16]
  - Interim safety and efficacy data from 2 dose-expansion cohorts, **1L TV + carboplatin** (Arm D) and **2L/3L TV + pembrolizumab** (Arm F), were reported thereafter[17]
  - Safety and efficacy data of a third dose-expansion cohort for **1L TV + pembrolizumab** (Arm E) was recently reported, as was updated safety and efficacy data from Arm D and Arm F[18]
- This report describes the design of Arm H (**Figure 2**), a new, ongoing dose-expansion cohort in the innovaTV 205 study to evaluate the combination of **1L TV, pembrolizumab, and carboplatin, ± bevacizumab** (if permitted per local practice and if the patient is eligible per investigator assessment) in a mixed population of patients with PD-L1+ and PD-L1- tumors (see **Figure 3** for participating countries)

Figure 1. Proposed Mechanism of Action of TV



APC, antigen presenting cell; ER, endoplasmic reticulum; mc-vc, maleimidocaproyl-valine-citrulline; MMAE, monomethyl auristatin E; PD-1, programmed death protein 1; PD-L1/L2, programmed death ligands 1/2.

ELIGIBILITY

Key Inclusion Criteria

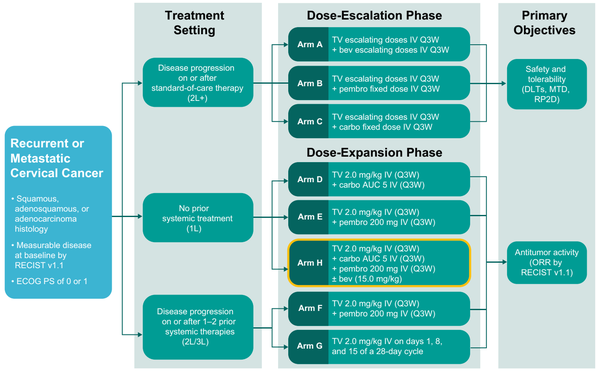
- Squamous, adenosquamous, or adenocarcinoma of the cervix
- Must not have received prior systemic therapy for recurrent or stage IVB cervical cancer
- Aged ≤18 years on the day of signing informed consent
- Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1

Key Exclusion Criteria

- Active ocular surface disease or a history of cicatricial conjunctivitis or inflammatory conditions that predispose the patient to cicatrizing conjunctivitis
- Clinically relevant bilateral hydronephrosis that cannot be alleviated by ureteral stents or percutaneous drainage
- Clinical signs or symptoms of gastrointestinal obstruction, necessitating parenteral hydration and or nutrition; postoperative obstructions within 4 weeks of abdominal surgery are permitted
- Clinically significant bleeding issues or risks
- History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, or interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating investigator or sponsor
- Known allergies, hypersensitivity, or intolerance to any part of the specific trial treatment regimen selected for the patient or other platinum-containing compounds as applicable to the assigned treatment regimen

STUDY DESIGN

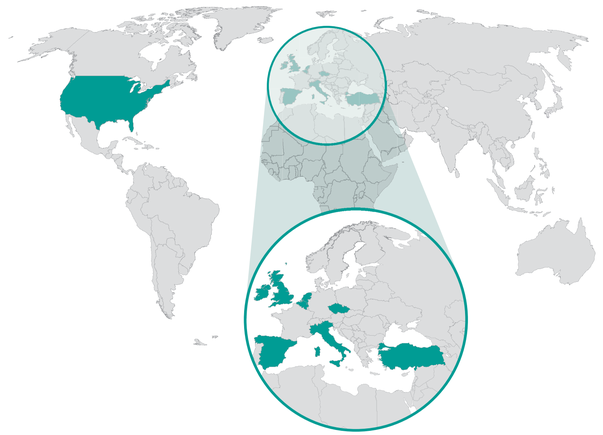
Figure 2. Study Design of ENGOT-cx8/GOG-3024/innovaTV 205 Arm H



Arm H (outlined in yellow box) is described in this presentation. After the first 6 patients treated with the quadruplet combination in Arm H have undergone the 21-day dose-limiting toxicity (DLT) evaluation by the safety committee and there are fewer than 2 DLTs, enrollment will be expanded to approximately 30 patients (including those eligible [quadruplet combination] and ineligible [triplet combination] to receive bev). If ≥ 2 patients experience DLT during the DLT period, enrollment will be paused, and the safety committee will perform a comprehensive review to determine whether treatment will be continued further with or without a modified dose or schedule or be discontinued. Data will be reviewed on an ongoing basis throughout the trial.

1/2/3L, first-, second-, third-line; AUC, area under the curve; bev, bevacizumab; carbo, carboplatin; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; MTD, maximum-tolerated dose; ORR, objective response rate; pembro, pembrolizumab; Q3W, once every three weeks; RP2D, recommended phase 2 dose; TV, tisotumab vedotin.

Figure 3. Countries Participating in ENGOT-cx8/GOG-3024/innovaTV 205 (green)



OBJECTIVES

Primary Objective	Endpoint
Evaluate the antitumor activity of 1L TV in combination in patients with r/mCC	Confirmed ORR per RECIST v1.1
Secondary Objectives	**Endpoints**
Assess safety and tolerability of TV in combination	Adverse events and safety laboratory parameters
Evaluate durability of response of TV in combination	Duration of response per RECIST v1.1 Time to response per RECIST v1.1
Evaluate clinical efficacy with TV in combination	PFS per RECIST v1.1 OS
Evaluate the pharmacokinetics and immunogenicity of TV in combination	Pharmacokinetics concentrations and anti-drug antibodies associated with TV
Exploratory Objectives	**Endpoints**
Explore the relationship between biomarkers and clinical response	TF and PD-L1 expression in tumor biopsies, circulating TF, proteomic analyses, and genomic signatures
Assess potential pharmacodynamic biomarkers	Circulating TF and proteomic analyses

ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; r/mCC, recurrent/metastatic cervical cancer; RECIST, Response Evaluation Criteria in Solid Tumors; TF, tissue factor; TV, tisotumab vedotin.

SUMMARY

- This study is enrolling adult patients with recurrent or stage IVb squamous,adenosquamous, or adenocarcinoma of the cervix with an ECOG PS of 0 or 1
- Patients will be treated every 3 weeks with the **RP2D of TV (2.0 mg/kg)**
  - **+ carboplatin (area under the curve 5 mg/mL), pembrolizumab (200 mg), and bevacizumab (15 mg/kg), or**
  - **+ carboplatin (area under the curve 5 mg/mL) and pembrolizumab (200 mg)**
- The expansion of enrollment of the quadruplet regimen to 30 patients is contingent on the occurrence of fewer than 2 DLTs among the first 6 patients enrolled over a treatment evaluation period of 21 days
  - If there are fewer than 2 DLTs, enrollment will be expanded to approximately 30 patients
- The primary endpoint of this dose-expansion phase is confirmed ORR per RECIST v1.1
- Secondary endpoints are duration of response, time to response, PFS, OS, and safety
- Enrollment is ongoing in the United States and Europe

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REFERENCES

1. The American Cancer Society. Survival rates for cervical cancer. Accessed August 23, 2022. https://www.cancer.org/cancer/cervical-cancer/detection-diagnosis-staging/survival.html.
2. Kitagawa R et al. *J Clin Oncol.* 2015;33:2129-2135.
3. Tewari KS et al. *N Engl J Med.* 2014;370:734-743.
4. Ebina Y et al. *Int J Clin Oncol.* 2019;24:1-19.
5. Keytruda. Prescribing information. Merck Sharp & Dohme Corp.; 2022.
6. 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). News release. Business Wire; April 29, 2022. Accessed August 23, 2022. https://www.nasdaq.com/press-release/european-commission-approves-mercks-keytruda-pembrolizumab-plus-chemotherapy-with-or.
7. National Comprehensive Cancer Network. NCCN guidelines for patients: cervical cancer. Version 2022. Accessed August 23, 2022. https://www.nccn.org/patients/guidelines/content/PDF/cervical-patient.guideline.pdf.
8. Colombo N et al. *N Engl J Med.* 2021;385:1856-1867.
9. Vansteeg HH et al. *Mol Med.* 2004;10:6-11.
10. Zhao X et al. *Exp Ther Med.* 2018;16:4075-4081.
11. Cocco E et al. *BMC Cancer.* 2011;11:263.
12. Breij EC et al. *Cancer Res.* 2013;74:1214-1226.
13. de Goeij BE et al. *Mol Cancer Ther.* 2016;14:1130-1140.
14. Coleman RL et al. *Lancet Oncol.* 2021;22:609-619.
15. Tivdak (tisotumab vedotin-tftv) for injection, for intravenous use. Prescribing information. Seagen Inc.; 2022.
16. Monk BJ et al. Abstract presented at: IGCS Annual Global Meeting; August 30-September 2, 2021; Virtual. OO13:IST3
17. Vergote I et al. Abstract presented at: ESMO; September 16-21, 2021; Paris, France; Abstract 723MO
18. Lorusso D et al. Abstract presented at: ASCO Annual Meeting; June 3-7, 2022; Chicago, IL. Abstract 5507

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