Phase Ib/II Trial of Tisotumab Vedotin ± Bevacizumab, Pembrolizumab, or Carboplatin in Recurrent or Metastatic Cervical Cancer (innovaTV 205/ENGOT-cx8/GOG-3024)

Ignace Vergote,[1] Nicole Concin,[1] Mansoor Raza Mirza,[2] Camilla Mondrup Andreassen,[3] Domenica Lorusso,[4] Christine N. Gennigens,[5] Susana N. Banerjee,[6] Roisin Eilish O'Cearbhaill,[7] Susana Campos,[8] Leonardo Viana Nicacio,[9] Lamar Eaton,[10] David M. O'Malley,[11] Ibrahima Soumaoro,[10] Bradley J. Monk[12]

[1]Belgium and Luxembourg Gynaecological Oncology Group, University of Leuven, Leuven Cancer Institute, Leuven, Belgium; [2]Nordic Society of Gynaecological Oncology – Clinical Trial Unit, and Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [3]Genmab A/S, Copenhagen, Denmark; [4]Fondazione IRCCS, Foundation Policlinico Universitario Agostino Gemelli IRCCS, Istituto Nazionale dei Tumori, Milan, Italy; [5]Centre Hospitalier Universitaire de Liège, Liège, Belgium; [6]The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, UK; [7]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [8]Dana-Farber Cancer Institute, Boston, MA, USA; [9]Seattle Genetics, Inc., Bothell, WA, USA; [10]Genmab US, Inc., Princeton, NJ, USA; [11]The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA; [12]Arizona Oncology (US Oncology Network), University of Arizona College of Medicine, Creighton University School of Medicine, Phoenix, AZ, USA

BACKGROUND

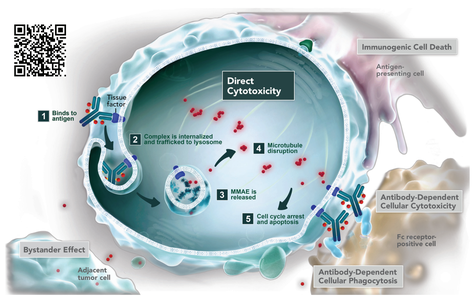
Treatment of Recurrent or Metastatic Cervical Cancer (r/mCC)

- With an estimated 570,000 new cases and 311,000 deaths globally in 2018, cervical cancer is a significant medical problem in women worldwide[1]
- In the United States there will be an estimated 13,800 new cases and nearly 4,300 deaths in 2020[2,3]
- In 2018, 61,072 new cases of cervical cancer were diagnosed in Europe, with 25,829 deaths[4]
- r/mCC is highly incurable, with a 5-year survival rate of only 17%.[5] Therefore, there is an urgent unmet need for effective therapies and novel treatment combinations
- Beyond traditional chemotherapy, monoclonal antibodies, including bevacizumab and pembrolizumab, have displayed activity in r/mCC[6,7]

Tissue Factor (TF) and Tisotumab Vedotin (TV)

- TV is an investigational TF-directed antibody–drug conjugate comprising the following three components:
  1. A fully human monoclonal antibody specific for TF
  2. The microtubule-disrupting agent monomethyl auristatin E (MMAE), which induces apoptosis of dividing cells
  3. A protease-cleavable linker that covalently attaches MMAE to the antibody and releases it upon internalization[8,9]
- TV is designed to bind to TF on target cells and to release MMAE upon internalization, resulting in cell-cycle arrest and apoptotic cell death.[8,9] Antitumor effects of TV are further potentiated by bystander cytotoxicity and multiple immune-mediated activity, including immunogenic cell death, antibody-dependent cellular toxicity, and antibody-dependent cellular phagocytosis[8-10] (**Figure 1**)

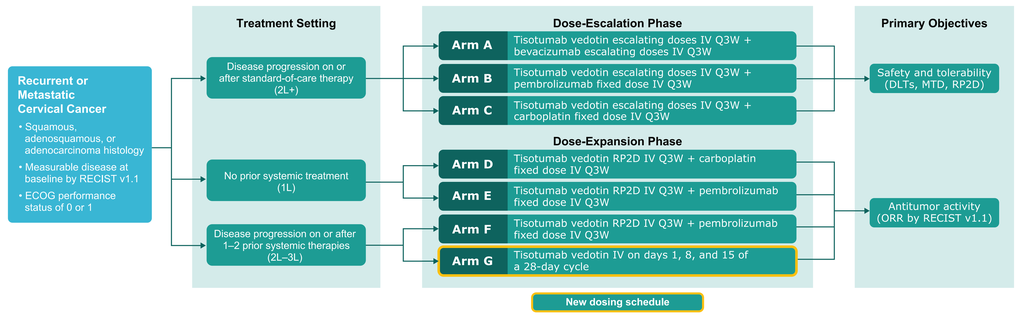
Figure 1. Proposed Mechanism of Action of TV[8-10]



- The phase I/II innovaTV 201 study (NCT02001623) evaluated TV administered every 3 weeks (Q3W) in patients with previously treated, locally advanced, or metastatic solid tumors, including r/mCC[11,12]
- In the cervical cancer expansion phase (N=51), TV demonstrated a manageable safety profile and encouraging antitumor activity in an advanced, previously treated cervical cancer patient population[12]

TRIAL DESIGN

Figure 2. innovaTV 205 Study Design



2L, second-line; 3L, third-line; DLTs, dose-limiting toxicities; ECOG, Eastern Cooperative Oncology Group; IV, intravenously; MTD, maximum tolerated dose; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; RP2D, recommended phase 2 dose.

Study Interventions

- Evidence to support investigation of combinations of standards of care (SOCs) with TV and for an alternative dosing schedule of TV is shown in **Table 1**

Table 1. Supporting Evidence for Study Regimens

TV + Bevacizumab
• Bevacizumab in combination with chemotherapy has been established as 1L treatment for patients with r/mCC and has been associated with an improvement in overall survival[6]
• Preclinical studies have shown that the TF-FVIIa protease complex can promote tumor and developmental angiogenesis through protease-activated receptor-2 (PAR2) signaling[13]
• TV has been shown to interefere with TF-FVIIa downstream PAR2 signaling.[9] PAR2 has been shown to induce VEGF expression[14]; therefore, targeting the TF-FVIIa downstream signaling pathway through PAR2 via TV may enhance angiogenesis inhibitors by reducing the amount of bioavailable VEGF in the tumor
TV + Pembrolizumab
• Approximately 80% of the patients with r/mCC in the KEYNOTE-158 (NCT02628067) clinical trial with pembrolizumab were PD-L1–positive (combined positive score ≥1%),[7,15] and most patients (92%) enrolled in this trial had cervical cancer with squamous cell histology[7]
• Immunogenic cell death induced by TV, in addition to pembrolizumab mechanism of action releasing PD-1 pathway-mediated inhibition of T cells, may enhance T cell–mediated antitumor activity in cervical cancer
TV + Carboplatin
• Platinum doublet chemotherapy regimens (eg, cisplatin plus paclitaxel, carboplatin plus paclitaxel) are considered a 1L SOC treatment for r/mCC when patients are ineligible for bevacizumab[2,16]
• The MMAE-mediated microtubule inhibition of TV may complement carboplatin DNA replication-inhibition mechanism of action
TV Monotherapy: Alternative Dosing Schedule
• The innovaTV 201 study showed that TV 2.0 mg/kg administered Q3W had a half-life of 1.71 days as well as encouraging safety and antitumor activity[12]
• The newly added arm G is exploring TV monotherapy in a more frequent weekly dosing schedule on days 1, 8, and 15 of a 28-day cycle to determine whether this provides improved efficacy in patients with cervical cancer

1L, first-line; PD-1, programmed cell death-1; PD-L1, programmed death ligand 1.

KEY TAKEAWAYS

- **The study has been amended to incorporate the addition of arm G, which will evaluate a new weekly dosing schedule of TV monotherapy on days 1, 8, and 15 of each 28-day cycle**
- **innovaTV 205 is an ongoing international study evaluating novel regimens of TV alone and in combination for patients with r/mCC**

https://bit.ly/2zDtmjq

STUDY DESIGN

Study Objectives

Primary

- Dose-escalation phase (arms A–C): safety and tolerability
  - DLTs to establish the MTD and the RP2D of TV (arms A–C) and bevacizumab (arm A only)
- Dose-expansion phase (arms D–G): antitumor activity
  - ORR by RECIST v1.1

Secondary

- Antitumor activity as determined by duration of response, time to response, progression-free survival (per RECIST v1.1), and overall survival
- Safety as determined by the frequency, duration, and severity of adverse events

Eligibility Criteria

- The key inclusion and exclusion criteria are shown in **Table 2**

Table 2. Key Inclusion and Exclusion Criteria

Key Inclusion Criteria
Recurrent or metastatic squamous, adenosquamous, or adenocarcinoma of the cervix
Measurable disease at baseline by RECIST v1.1
ECOG performance status of 0 or 1
Not pregnant, breastfeeding, or expecting to conceive children within the projected duration of the trial and for >6 months after the last trial treatment administration
Dose-escalation phase (arms A-C) • Disease progression on or after SOC treatments or ineligible for or intolerant of SOC for r/mCC
Dose-expansion phase (arms D-G) • Arms D and E: No prior systemic therapy for r/mCC • Arms F and G: Disease progression on or after 1 or 2 prior systemic therapies for r/mCC

Table 2. Key Inclusion and Exclusion Criteria (cont'd)

Key Exclusion Criteria
Clinically relevant bilateral hydronephrosis that cannot be alleviated by ureteral stents or percutaneous drainage
Clinical signs or symptoms of gastrointestinal obstruction that requires parenteral hydration and/or nutrition[a]
Clinically significant bleeding issues or risks
Active ocular surface disease at baseline or history of cicatricial conjunctivitis
Clinically significant cardiac disease
Arm A only • Prior history (≤3 months) or current evidence of hemoptysis (≥0.5 tea-spoon) • Recent (≤4 weeks of first dose of trial treatment) clinically significant gastrointestinal or vaginal bleeding requiring transfusion of packed red blood cells • Recent (≤4 weeks of first dose of trial treatment) evidence of wound-healing complications that require medical intervention • Requires anticoagulation therapy

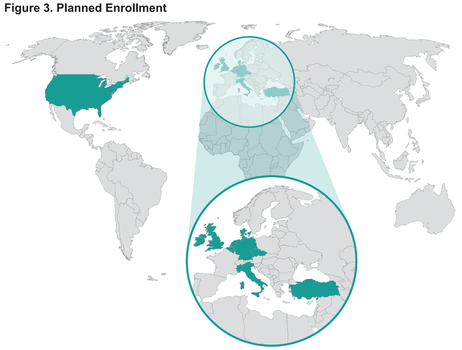
[a]Postoperative obstructions within 4 weeks of abdominal surgery are permitted.

- The innovaTV 205 study (NCT03786081, ENGOT-cx8, and GOG-3024) is a phase Ib/II, open-label, multicenter trial of TV monotherapy or TV in combination with bevacizumab, pembrolizumab, or carboplatin in patients with r/mCC
- The innovaTV 205 trial consists of two parts: a dose-escalation phase and a dose-expansion phase (**Figure 2**)
  - The dose-expansion phase will be initiated once the RP2D of the drug combinations have been determined in the dose-escalation phase
  - A new arm (Arm G) has been added to the study evaluating TV monotherapy using an alternative weekly dosing schedule

ENROLLMENT

- The innovaTV 205 study, which is currently recruiting in the United States and Europe, will enroll approximately 170 patients (**Figure 3**)

Figure 3. Planned Enrollment



Additional Information

- For more information about the innovaTV 205 study, please visit https://clinicaltrials.gov/ct2/show/NCT03786081

REFERENCES

1. Bray F et al. *CA Cancer J Clin*. 2018;68:394-424.
2. NCCN Guidelines. CervicalCancer.v1.2020. https://www.nccn.org/professionals/physician_gls/PDF/cervical.pdf. Accessed April 17, 2020.
3. Siegel RL et al. *CA Cancer J Clin*. 2020;70:7-30.
4. Ferlay J et al. Lyon, France: International Agency for Research on Cancer. https://gcoiarcfr/today. Accessed September 27, 2019.
5. National Cancer Institute. Cancer stat facts: cervical cancer. Seer.cancer.gov/statfacts/html/cervix.html. Accessed April 17, 2020.
6. Avastin [package insert]. South San Francisco, CA: Genentech, Inc; 2019.
7. Keytruda [package insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; 2020.
8. de Goeij BE et al. *Mol Cancer Ther*. 2015;14:1130-40.
9. Breij EC et al. *Cancer Res*. 2014;74:1214-26.
10. Alley SC et al. *Cancer Res*. 2019;79(13_suppl):221.
11. de Bono JS et al. *Lancet Oncol*. 2019;20(3):383-93.
12. Hong DS et al. *Clin Cancer Res*. 2020;26:1220-28.
13. Belting M et al. *Nat Med*. 2004;10:502-9.
14. Rasmussen TL et al. *PLoS One*. 2012;7:e50103.
15. Chung HC et al. *J Clin Oncol*. 2018;36:5522.
16. Marth C et al. *Ann Oncol*. 2017;28:iv72-83.

ACKNOWLEDGMENTS

- The authors thank the patients and their families and caregivers for participating in this trial as well as all investigators and study site personnel
- This study is funded by Genmab A/S (Copenhagen, Denmark)
- Tisotumab vedotin is being developed in collaboration with Seattle Genetics, Inc.
- Medical writing assistance was provided by Nicholas Gast, PharmD (ApotheCom, Boston, MA), and funded by Genmab A/S

Presented at ASCO20 Virtual Scientific Program; May 29-31, 2020.