TISOTUMAB VEDOTIN VS INVESTIGATOR'S CHOICE CHEMOTHERAPY IN SECOND- OR THIRD-LINE RECURRENT OR METASTATIC CERVICAL CANCER (innovaTV 301/ENGOT CX12/GOG 3057, TRIAL IN PROGRESS)

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DISEASE BACKGROUND

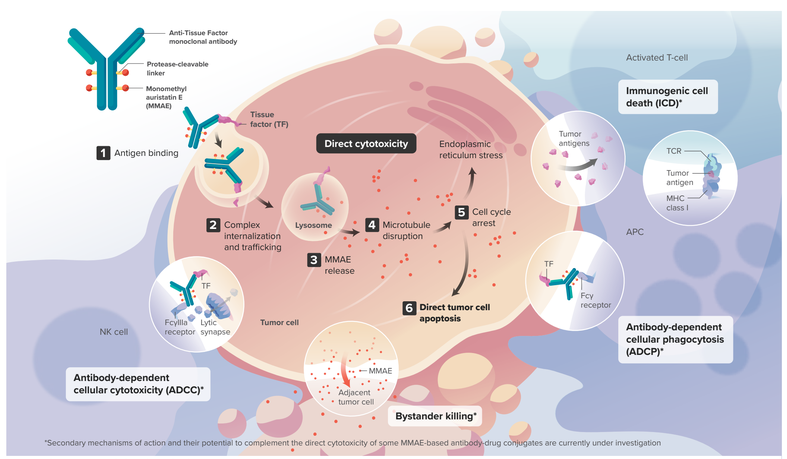
- Cervical cancer poses a significant medical issue worldwide with an estimated yearly incidence of more than 500,000 new cases and is the fourth most frequently diagnosed and fourth most deadly cancer in women worldwide[1]
- Cervical cancer is the most frequently diagnosed cancer amongst women in the United States (US) aged 35 to 44 years[2]
  - In 2020, an estimated 13,800 new cases of invasive cervical cancer were diagnosed, and 4,290 women died from the disease in the US[3]
- Women with recurrent or metastatic cervical cancer (r/mCC) face a devastating disease with significant morbidity, poor prognosis (5-year overall survival [OS] <16.5%), and no standard of care following initial therapy
- Doublet chemotherapy (paclitaxel plus either platinum or topotecan) with bevacizumab (if eligible) is approved for first-line treatment of women with metastatic cervical cancer (Food and Drug Administration 2014; European Medicines Agency 2015; Japan 2016).[4–8] However, intolerance and eventual resistance associated with this regimen limits its utility and often results in disease progression. Currently, guidelines only provide recommendations for second-line treatment in a limited patient population
- Although there are therapeutic agents currently in development, women with r/mCC who progress on first-line treatment options require novel second-line therapies that are both effective and tolerable

TISOTUMAB VEDOTIN

- Tissue Factor (TF) is prevalent in several solid tumors, including cervical cancer. In these tumors where TF is present, levels are elevated relative to normal tissue[9,10]
- Tisotumab vedotin (TV) is an investigational TF-directed antibody-drug conjugate (ADC) with antitumor activity
- TV is composed of 1) a fully human monoclonal antibody specific for TF, 2) the microtubule-disrupting agent monomethyl auristatin E (MMAE) which induces target cell death, and 3) a protease-cleavable linker that covalently links MMAE to the antibody and releases it upon internalization
- The antibody portion of TV is fully human (immunoglobulin G1κ)[11]

Proposed Mechanism of Action

- TV is directed to cells expressing TF and releases MMAE upon internalization, resulting in cell cycle arrest and apoptotic cell death[12,13]
- TV has antitumor activity on multiple tumor types and kills target cells by direct cytotoxicity, bystander cytotoxicity, antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and immunogenic cell death[13]



*Secondary mechanisms of action and their potential to complement the direct cytotoxicity of some MMAE-based antibody-drug conjugates are currently under investigation

Tisotumab vedotin is an investigational agent, and its safety and efficacy have not been established.

TISOTUMAB VEDOTIN: PRELIMINARY EFFICACY AND SAFETY

- In the phase 2 innovaTV 204 trial, TV demonstrated clinically meaningful and durable activity in r/mCC patients with disease progression on or after chemotherapy[14]
  - Responses that were clinically meaningful and durable occurred as early as the first assessment, and were observed regardless of histology, prior treatment, or TF expression
  - Objective response rate (ORR) of 24% by Independent Review Committee
  - Median duration of response (DOR) of 8.3 months
  - A manageable safety profile
    - Most adverse events (AEs), including peripheral neuropathy, ocular, and bleeding events, were mild to moderate

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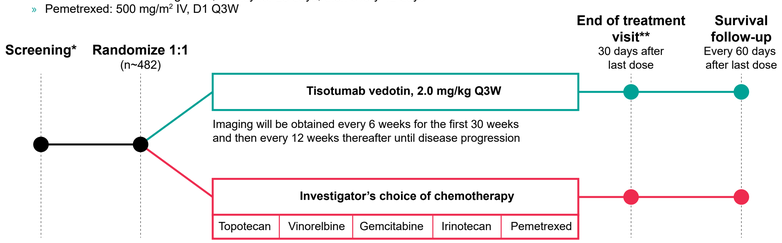
STUDY DESIGN

- innovaTV 301 (NCT04697628) is an open-label, global, phase 3 trial to evaluate the efficacy and safety of TV in patients with r/mCC
- Approximately 482 patients will be randomized 1:1 to receive either TV or investigator's choice of chemotherapy:
  - TV: 2.0 mg/kg intravenously (IV) every 3 weeks (Q3W)
  - Investigator's choice of chemotherapy:
    - Topotecan: 1 or 1.25 mg/m^2 IV; day (D)1 to D5 Q3W
    - Vinorelbine: 30 mg/m^2 IV; D1 and D8 Q3W
    - Gemcitabine: 1000 mg/m^2 IV; D1 and D8 Q3W
    - Irinotecan: 100 or 125 mg/m^2 IV; weekly for 28 days, then every 42 days
    - Pemetrexed: 500 mg/m^2 IV, D1 Q3W



*The proportion of patients who have not received prior bevacizumab in combination with chemotherapy as 1L treatment may be capped at 50%
** Some AESIs may be followed longer than 30 days until resolution, improvement, or stabilization
Abbreviations: 1L = first-line; AESI = adverse event of special interest; n = number of partients; Q3W = every 3 weeks

OBJECTIVES

Primary Objective

- Demonstrate improvement in clinical efficacy of TV compared to chemotherapy in patients with second- or third-line (2L–3L) cervical cancer

Secondary Objectives

- Assess improvement in clinical efficacy of TV compared to chemotherapy in patients with 2L–3L cervical cancer
- Demonstrate improvement in antitumor activity of TV compared to chemotherapy in patients with 2L–3L cervical cancer
- Characterize the antitumor response of TV and chemotherapy in patients with 2L–3L cervical cancer
- Evaluate the safety and tolerability of TV
- Assess health-related quality of life

ENDPOINTS

Primary Endpoint

- OS

Secondary Endpoints

Efficacy

- Progression-free survival and confirmed ORR based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by the investigator
- Time-to-response and DOR as assessed by the investigator

Safety

- Incidence of AEs

Health-Related Quality-of-Life Outcomes

- 5-level version of the European Quality of Life 5-Dimensional (EQ-5D) index
- EQ-5D (visual analog scale)
- European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30)
- EORTC Quality of Life Questionnaire Cervical Cancer Module (QLQ-CX24)

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EN has no relationships to disclose.

KEY ELIGIBILITY CRITERIA

Key Inclusion Criteria

- Age ≥18 years (≥20 years in Japan only)
- r/mCC with squamous cell, adenocarcinoma, or adenosquamous histology, and
  - Disease progression during or after treatment with a standard of care systemic chemotherapy doublet, or platinum-based therapy (if eligible)
  - 1 or 2 prior systemic therapy regimens for r/mCC
  - Not eligible for curative therapy, including but not limited to radiotherapy or exenterative surgery
- Measurable disease by RECIST v1.1 criteria per investigator
- Eastern Cooperative Oncology Group (ECOG) performance status ≤1
- Life expectancy ≥3 months

Key Exclusion Criteria

- Primary neuroendocrine, lymphoid, sarcomatoid, or other histologies not mentioned as part of the inclusion criteria
- Clinically significant bleeding issues or risks
- Any history of intracerebral arteriovenous malformation, cerebral aneurysm, or stroke (transient ischemic attack >1 month prior to screening is allowed)
- Active ocular surface disease or a history of cicatricial conjunctivitis or inflammatory conditions that predispose to cicatrizing conjunctivitis, ocular Stevens-Johnson syndrome or toxic epidermal necrolysis, mucus pemphigoid, and penetrating ocular transplants
  - Cataracts alone is not an exclusion criterion
- Major surgery within 4 weeks or minor surgery within 7 days prior to the first study treatment administration
- Peripheral neuropathy ≥ Grade 2
- Any prior treatment with MMAE-containing drugs

ASSESSMENTS

Efficacy

- Imaging will be obtained every 6 weeks (±7 days) for the first 30 weeks and then every 12 weeks (±7 days) thereafter, calculated from Cycle 1 D1 of treatment administration
- Imaging until evidence of radiographic disease progression per RECIST v1.1 as assessed by investigator
- Survival status every 60 days (±7 days) beginning from the day of the last dose of study treatment, or more frequently around the time of a database lock

Safety and Tolerability

- Recording of AEs, concomitant medications, electrocardiograms, ECOG performance status, physical examination findings, vital signs, clinical laboratory tests, eye examinations, and ocular assessments

SUMMARY

- The innovaTV 301 trial is a phase 3 clinical trial evaluating the efficacy and safety of TV in patients with previously treated r/mCC
- The study is currently enrolling and will have sites open in North America, Europe, Latin America and Asia Pacific within the next year
  - 13/165 sites are active or enrolling
- Study start date: February 2021
- Estimated study completion date: April 2024

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