TIVDAK® (tisotumab vedotin-tftv) Significantly Prolonged Overall Survival in Patients with Recurrent or Metastatic Cervical Cancer Compared with Chemotherapy in Global Phase 3 innovaTV 301 Trial

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TIVDAK demonstrated superior overall survival, progression-free survival and objective response rate compared to chemotherapy in late-breaking results presented at ESMO 2023 congress

Results from innovaTV 301 intended to serve as pivotal confirmatory trial for U.S. accelerated approval and to support global regulatory application

BOTHELL, Wash., & COPENHAGEN, Denmark--(BUSINESS WIRE)--Seagen Inc. (Nasdaq: SGEN) and Genmab A/S (Nasdaq: GMAB) announced results today from the Phase 3 innovaTV 301 randomized global trial, which showed treatment with TIVDAK demonstrated a statistically significant and clinically meaningful 30% reduction in the risk of death in recurrent or metastatic cervical cancer patients with disease progression on or after first-line therapy, compared with chemotherapy (HR: 0.70, 95% CI: 0.54-0.89, p=0.0038[1]). Data were presented during the Presidential Symposium at the European Society of Medical Oncology (ESMO) Congress 2023.

“Patients with cervical cancer have few treatment options once their cancer comes back or spreads after initial treatment,” said Ignace B. Vergote, M.D., Ph.D., co-founder of European Network of Gynaecological Oncological Trial groups (ENGOT), and lead investigator on the innovaTV 301/ENGOT cx-12/GOG 3057 clinical trial. “The positive data, seen in a representative patient population of recurrent or metastatic cervical cancer, demonstrate the potential for TIVDAK to reshape clinical practice and provide hope for patients who need a new treatment option.”

TIVDAK demonstrated the following results compared with chemotherapy across primary and key secondary efficacy endpoints:

- Overall survival (OS) was statistically significantly prolonged with TIVDAK, demonstrating a 30% reduction in the risk of death compared with chemotherapy (Hazard ratio [HR]: 0.70 [95% CI: 0.54, 0.89], p=0.0038[1]).
- Progression-free survival (PFS) results were statistically significant with TIVDAK, demonstrating a 33% reduction in the risk of disease worsening or death compared with chemotherapy (HR: 0.67 [95% CI, 0.54-0.82], p<0.0001).
- The confirmed objective response rate (ORR) was also statistically significantly improved with TIVDAK (17.8%) compared with chemotherapy (5.2%); odds ratio: 4.0 [95% CI, 2.1-7.6], p<0.0001). All the complete responses were seen in the TIVDAK arm, defined as patients with no detectable evidence of a tumor over a specified time period.
- The disease control rate (DCR), defined as the percentage of patients who achieved complete response, partial response, or stable disease, was 75.9% (95% CI, 70.1-80.0) in the TIVDAK arm compared with 58.2% (95% CI, 51.8-64.4) in the chemotherapy arm.

The safety profile of TIVDAK in innovaTV 301 was consistent with its known safety profile as presented in the U.S. prescribing information, and no new safety signals were observed.

The U.S. Prescribing Information for TIVDAK includes a **BOXED WARNING** for **Ocular Toxicity** as well as the following Warnings and Precautions: peripheral neuropathy, hemorrhage, pneumonitis, severe cutaneous adverse reactions, and embryo-fetal toxicity. **Please see below for additional Important Safety Information.**

In innovaTV 301, treatment-related adverse events (TRAEs) occurring in patients with TIVDAK were generally low grade and manageable with supportive care and dose modifications. The proportion of patients who experienced TRAEs of grade 3 or higher with chemotherapy was 45.2% compared with TIVDAK (29.2%), and grade 3 or higher treatment-related adverse events of special interest with TIVDAK were peripheral neuropathy (5.2%), ocular events (3.2%), and bleeding events (0.8%).

The results of innovaTV 301, a global, randomized, open-label Phase 3 trial, add to the previous results of innovaTV 204, which served as the basis for the accelerated approval of TIVDAK in the U.S. Subject to discussions with regulatory authorities, the results from innovaTV 301 are intended to serve as the confirmatory trial for the U.S. accelerated approval and support potential global regulatory applications.

“Recurrent or metastatic cervical cancer is a devastating disease,” said Roger Dansey, M.D., President of Research and Development and Chief Medical Officer at Seagen. “In this study, TIVDAK was proven to extend the lives of patients with advanced cervical cancer, demonstrating its value as the first-ever antibody drug conjugate approved in the U.S. for this hard-to-treat patient population.”

“We are excited to share the results of the innovaTV 301 trial, which demonstrated benefit in prolonging survival in patients with recurrent or metastatic cervical cancer compared with chemotherapy,” said Jan van de Winkel, Ph.D., Chief Executive Officer, Genmab. “Together with our partners at Seagen, we look forward to discussing the results of this pivotal confirmatory trial with regulatory authorities with a view to potentially delivering TIVDAK to more patients in need of alternative treatment options in the future.”

About Cervical Cancer

Cervical cancer remains a disease with high unmet need despite advances in effective vaccination and screening practices to prevent and diagnose pre-/early-stage cancers for curative treatment. Recurrent and/or metastatic cervical cancer is a particularly devastating and mostly incurable disease; up to approximately 16% of adults with cervical cancer are diagnosed with metastatic disease at diagnosis[2,3] and, for adults diagnosed at earlier stages who receive treatment, up to 61% will experience disease recurrence and progress to metastatic cervical cancer.[4] It is estimated that in 2023, more than 13,960 new cases of invasive cervical cancer will be diagnosed in the U.S. and 4,310 adults will die from the disease.[5]

About the innovaTV 301 Trial

The innovaTV 301 trial (NCT04697628) is a global, randomized, open-label Phase 3 trial evaluating TIVDAK® (tisotumab vedotin-tftv) versus investigator's choice of single agent chemotherapy (topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed) in 502 patients (n=253 TIVDAK; n=249 chemotherapy) with recurrent or metastatic cervical cancer who received no more than two prior systemic regimens, with a median survival follow-up of 10.8 months (95% CI, 10.3-11.6). The treatment arms were balanced for demographics and disease characteristics, and reflective of the real-world patient population in advanced cervical cancer.

Patients with recurrent or metastatic cervical cancer 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) are included. The main efficacy outcome measure is overall survival. The key secondary endpoints are progression-free survival and objective response rate, as assessed by the investigator, as well as safety and quality of life outcomes.

The study was conducted by Seagen in collaboration with Genmab, European Network of Gynaecological Oncological Trial Groups (ENGOT, study number ENGOT cx-12) and the Gynecologic Oncology Group (GOG) Foundation (study number GOG 3057). For more information about the Phase 3 innovaTV 301 clinical trial and other clinical trials with tisotumab vedotin, please visit www.clinicaltrials.gov.

About TIVDAK® (tisotumab vedotin-tftv)

TIVDAK® (tisotumab vedotin-tftv) is an antibody-drug conjugate (ADC) composed of Genmab's human monoclonal antibody directed to tissue factor (TF) and Seagen's ADC technology that utilizes a protease-cleavable linker that covalently attaches the microtubule-disrupting agent monomethyl auristatin E (MMAE) to the antibody. Determination of TF expression is not required. Nonclinical data suggest that the anticancer activity of TIVDAK is due to the binding of the ADC to TF-expressing cancer cells, followed by internalization of the ADC-TF complex, and release of MMAE via proteolytic cleavage. MMAE disrupts the microtubule network of actively dividing cells, leading to cell cycle arrest and apoptotic cell death. In vitro, TIVDAK also mediates antibody-dependent cellular phagocytosis and antibody-dependent cellular cytotoxicity.

In September 2021, the U.S. Food and Drug Administration granted accelerated approval for TIVDAK in adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy. TIVDAK is the first and only approved ADC for the treatment of these patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy.

Indication

TIVDAK is indicated in the U.S. for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials**.**

Important Safety Information

BOXED WARNING: OCULAR TOXICITY

TIVDAK caused changes in the corneal epithelium and conjunctiva resulting in changes in vision, including severe vision loss, and corneal ulceration. Conduct an ophthalmic exam at baseline, prior to each dose, and as clinically indicated. Adhere to premedication and required eye care before, during, and after infusion. Withhold TIVDAK until improvement and resume, reduce the dose, or permanently discontinue, based on severity.

WARNINGS AND PRECAUTIONS

Ocular adverse reactions occurred in 60% of patients with cervical cancer treated with TIVDAK across clinical trials. The most common were conjunctival adverse reactions (40%), dry eye (29%), corneal adverse reactions (21%), and blepharitis (8%). Grade 3 ocular adverse reactions occurred in 3.8% of patients, including severe ulcerative keratitis in 3.2% of patients. One patient experienced ulcerative keratitis with perforation requiring corneal transplantation. Cases of symblepharon were reported in patients with other tumor types treated with TIVDAK at the recommended dose.

In innovaTV 204, 4% of patients experienced visual acuity changes to 20/50 or worse including 1% of patients who experienced a visual acuity change to 20/200. Of the patients who experienced decreased visual acuity to 20/50 or worse, 75% resolved, including the patient who experienced decreased visual acuity to 20/200.

Refer patients to an eye care provider for an ophthalmic exam, including visual acuity and slit lamp exam, at baseline, prior to each dose, and as clinically indicated. Adhere to premedication and required eye care to reduce the risk of ocular adverse reactions. Promptly refer patients to an eye care provider for any new or worsening ocular signs and symptoms. Withhold dose, reduce the dose, or permanently discontinue TIVDAK based on the severity of the adverse reaction.

Peripheral Neuropathy (PN) occurred in 42% of cervical cancer patients treated with TIVDAK across clinical trials; 8% of patients experienced Grade 3 PN. PN adverse reactions included peripheral neuropathy (20%), peripheral sensory neuropathy (11%), peripheral sensorimotor neuropathy (5%), motor neuropathy (3%), muscular weakness (3%), and demyelinating peripheral polyneuropathy (1%). One patient with another tumor type treated with TIVDAK at the recommended dose developed Guillain- Barre syndrome.

Hemorrhage occurred in 62% of cervical cancer patients treated with TIVDAK across clinical trials. The most common all grade hemorrhage adverse reactions were epistaxis (44%), hematuria (10%), and vaginal hemorrhage (10%). Grade 3 hemorrhage occurred in 5% of patients.

Monitor patients for signs and symptoms of hemorrhage. For patients experiencing pulmonary or central nervous system (CNS) hemorrhage, permanently discontinue TIVDAK. For Grade ≥2 hemorrhage in any other location, withhold until bleeding has resolved, blood hemoglobin is stable, there is no bleeding diathesis that could increase the risk of continuing therapy, and there is no anatomical or pathologic condition that can increase the risk of hemorrhage recurrence. After resolution, either resume treatment or permanently discontinue TIVDAK.

Pneumonitis that is severe, life-threatening, or fatal can occur in patients treated with antibody-drug conjugates containing vedotin, including TIVDAK. Among patients with cervical cancer treated with TIVDAK across clinical trials, 2 patients (1.3%) experienced pneumonitis, including 1 patient who had a fatal outcome.

Monitor patients for pulmonary symptoms of pneumonitis. Symptoms may include hypoxia, cough, dyspnea or interstitial infiltrates on radiologic exams. Infectious, neoplastic, and other causes for symptoms should be excluded through appropriate investigations. Withhold TIVDAK for patients who develop persistent or recurrent Grade 2 pneumonitis and consider dose reduction. Permanently discontinue TIVDAK in all patients with Grade 3 or 4 pneumonitis.

Severe cutaneous adverse reactions, including events of fatal or life-threatening Stevens-Johnson syndrome (SJS), can occur in patients treated with TIVDAK.

Monitor patients for signs or symptoms of severe cutaneous adverse reactions, which include target lesions, worsening skin reactions, blistering or peeling of the skin, painful sores in mouth, nose, throat, or genital area, fever or flu-like symptoms, and swollen lymph nodes. If signs or symptoms of severe cutaneous adverse reactions occur, withhold TIVDAK until the etiology of the reaction has been determined. Early consultation with a specialist is recommended to ensure greater diagnostic accuracy and appropriate management. Permanently discontinue TIVDAK for confirmed Grade 3 or 4 severe cutaneous adverse reactions, including SJS.

Embryo-fetal toxicity: TIVDAK can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TIVDAK and for 2 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TIVDAK and for 4 months after the last dose.

Adverse Reactions

Serious adverse reactions occurred in 43% of patients; the most common (≥3%) were ileus (6%), hemorrhage (5%), pneumonia (4%), PN, sepsis, constipation, and pyrexia (each 3%). Fatal adverse reactions occurred in 4% of patients who received TIVDAK, including septic shock, pneumonitis, sudden death, and multisystem organ failure (each 1%).

Adverse reactions leading to permanent discontinuation occurred in 13% of patients receiving TIVDAK; the most common (≥3%) were PN (5%) and corneal adverse reactions (4%). Adverse reactions leading to dose interruption occurred in 47% of patients; the most common (≥3%) were PN (8%), conjunctival adverse reactions (4%), and hemorrhage (4%). Adverse reactions leading to dose reduction occurred in 23% of patients; the most common (≥3%) were conjunctival adverse reactions (9%) and corneal adverse reactions (8%).

The most common (≥25%) adverse reactions, including laboratory abnormalities, were hemoglobin decreased (52%), fatigue (50%), lymphocytes decreased (42%), nausea (41%), PN (39%), alopecia (39%), epistaxis (39%), conjunctival adverse reactions (37%), hemorrhage (32%), leukocytes decreased (30%), creatinine increased (29%), dry eye (29%), prothrombin international normalized ratio increased (26%), activated partial thromboplastin time prolonged (26%), diarrhea (25%), and rash (25%).

Drug Interactions

Strong CYP3A4 inhibitors: Concomitant use with strong CYP3A4 inhibitors may increase unconjugated monomethyl auristatin E (MMAE) exposure, which may increase the risk of TIVDAK adverse reactions. Closely monitor patients for TIVDAK adverse reactions.

Use in Specific Populations

Moderate or severe hepatic impairment: MMAE exposure and adverse reactions are increased. Avoid use.

Lactation: Advise lactating women not to breastfeed during TIVDAK treatment and for at least 3 weeks after the last dose**.**

Please see full prescribing information, including BOXED WARNING for TIVDAK here.

About Seagen

Founded 25 years ago, Seagen Inc. is a global biotechnology company that discovers, develops, manufactures and commercializes targeted cancer therapeutics, with antibody-drug conjugates (ADCs) at our core. Our colleagues work together with urgency to improve and extend the lives of people living with cancer. An ADC technology trailblazer, approximately one-third of FDA-approved and marketed ADCs use Seagen technology. Seagen is headquartered in Bothell, Washington and has locations in California, Canada, Switzerland and across Europe. For additional information, visit www.seagen.com and follow us on Twitter and LinkedIn.

About Genmab

Genmab is an international biotechnology company with a core purpose guiding its unstoppable team to strive towards improving the lives of patients through innovative and differentiated antibody therapeutics. For more than 20 years, its passionate, innovative and collaborative team has invented next-generation antibody technology platforms and leveraged translational research and data sciences, which has resulted in a proprietary pipeline including bispecific T-cell engagers, next-generation immune checkpoint modulators, effector function enhanced antibodies and antibody-drug conjugates. To help develop and deliver novel antibody therapies to patients, Genmab has formed 20+ strategic partnerships with biotechnology and pharmaceutical companies. By 2030, Genmab's vision is to transform the lives of people with cancer and other serious diseases with Knock-Your-Socks-Off (KYSO™) antibody medicines.

Established in 1999, Genmab is headquartered in Copenhagen, Denmark with locations in Utrecht, the Netherlands, Princeton, New Jersey, U.S. and Tokyo, Japan. For more information, please visit Genmab.com and follow us on Twitter.com/Genmab.

About the Seagen and Genmab Collaboration

Tisotumab vedotin is being co-developed by Genmab and Seagen, under an agreement in which the companies share costs and profits for the product on a 50:50 basis.

Seagen Forward Looking Statements

Certain of the statements made in this press release are forward looking, such as those, among others, relating to the potential for results from the innovaTV 301 clinical trial to serve as the confirmatory trial for the U.S. accelerated approval and support global regulatory applications; plans to discuss results with regulatory authorities; the conduct of the ongoing innovaTV 301 trial; and the therapeutic potential of TIVDAK, including its efficacy, safety and therapeutic uses. Actual results or developments may differ materially from those projected or implied in these forward-looking statements. Factors that may cause such a difference include the possibility that results from the innovaTV 301 trial may not be sufficient to support the conversion of the U.S. accelerated approval of TIVDAK to full approval or any global regulatory approvals; that adverse events or safety signals may occur; that adverse regulatory actions may occur; the possibility of delays, setbacks or failures in clinical development activities, the submission of regulatory applications and the regulatory review process for a variety of reasons, including the inherent difficulty and uncertainty of pharmaceutical product development; the inability to provide information and institute safety mitigation measures as may be required by the FDA or other regulatory authorities from time to time; and failure to properly conduct or manage clinical trials. More information about the risks and uncertainties faced by Seagen is contained under the caption "Risk Factors" included in the Company's Quarterly Report on Form 10-Q for the quarter ended June 30, 2023 filed with the Securities and Exchange Commission. Seagen disclaims any intention or obligation to update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

Genmab Forward Looking Statements

This Company Announcement contains forward looking statements. The words "believe", "expect", "anticipate", "intend" and "plan" and similar expressions identify forward looking statements. Actual results or performance may differ materially from any future results or performance expressed or implied by such statements. The important factors that could cause our actual results or performance to differ materially include, among others, risks associated with pre-clinical and clinical development of products, uncertainties related to the outcome and conduct of clinical trials including unforeseen safety issues, uncertainties related to product manufacturing, the lack of market acceptance of our products, our inability to manage growth, the competitive environment in relation to our business area and markets, our inability to attract and retain suitably qualified personnel, the unenforceability or lack of protection of our patents and proprietary rights, our relationships with affiliated entities, changes and developments in technology which may render our products or technologies obsolete, and other factors. For a further discussion of these risks, please refer to the risk management sections in Genmab's most recent financial reports, which are available on www.genmab.com and the risk factors included in Genmab's most recent Annual Report on Form 20-F and other filings with the U.S. Securities and Exchange Commission (SEC), which are available at www.sec.gov. Genmab does not undertake any obligation to update or revise forward looking statements in this Company Announcement nor to confirm such statements to reflect subsequent events or circumstances after the date made or in relation to actual results, unless required by law.

Genmab A/S and/or its subsidiaries own the following trademarks: Genmab®; the Y-shaped Genmab logo®; Genmab in combination with the Y-shaped Genmab logo®; HuMax®; DuoBody®; HexaBody®; DuoHexaBody® and HexElect®.

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[1] The threshold for statistical significance is 0.0226 (2-sided).

[2] National Cancer Institute. SEER Cancer Stat Facts: Cervical Cancer. 2020. https://seer.cancer.gov/statfacts/html/cervix.html

[3] McLachlan J, Boussios S, Okines A, et al. The impact of systemic therapy beyond first-line treatment for advanced cervical cancer. Clin Oncol (R Coll Radiol). 2017;29(3):153-60.

[4] Pfaendler KS, Tewari KS. Changing paradigms in the systemic treatment of advanced cervical cancer. Am J Obstet Gynecol. 2016;214(1):22-30.

[5] Key Statistics for Cervical Cancer. American Cancer Society. Atlanta, GA. 2023. https://www.cancer.org/cancer/types/cervical-cancer/about/key-statistics.html

Contacts

INVESTOR & MEDIA CONTACTS

Seagen Contacts:
For Media:
David Caouette
Vice President, Corporate Communications
(310) 430-3476
dcaouette@seagen.com

For Investor Relations:
Douglas Maffei, Ph.D.
Vice President, Head of Investor Relations & ESG
(425) 527- 4881
dmaffei@seagen.com

Genmab A/S Contacts:
For Media:
David Freundel
Senior Director, Communications & Corporate Affairs
(609) 613-0504

dafr@genmab.com

For Investor Relations:
Andrew Carlsen
Vice President, Head of Investor Relations
+45 3377-9558
acn@genmab.com

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