FDA Grants Full Approval for TIVDAK® to Treat Recurrent or Metastatic Cervical Cancer

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- *TIVDAK is the first antibody-drug conjugate (ADC) to have positive overall survival data for patients with previously treated recurrent or metastatic cervical cancer*
- *Conversion to full approval from accelerated approval is based on positive results from global Phase 3 study demonstrating overall survival benefit of TIVDAK compared to chemotherapy*

NEW YORK & COPENHAGEN, Denmark--(BUSINESS WIRE)--Pfizer Inc. (NYSE: PFE) and Genmab A/S (Nasdaq: GMAB) today announced the U.S. Food and Drug Administration (FDA) approves the supplemental Biologics License Application (sBLA) granting full approval for TIVDAK® (tisotumab vedotin-tftv) for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy.

"Recurrent or metastatic cervical cancer is a particularly devastating and mostly incurable disease, and patients are in need of survival-extending treatment options," said Chris Boshoff, M.D., Ph.D., Chief Oncology Officer, Executive Vice President at Pfizer. "Today's full approval by the FDA reinforces the important role of TIVDAK for these patients, as the first antibody-drug conjugate with statistically significant prolonged overall survival data."

The approval is based on results from the global, randomized, Phase 3 innovaTV 301 clinical trial (NCT04697628), which met its primary endpoint, demonstrating overall survival (OS) benefit in adult patients with previously treated recurrent or metastatic cervical cancer treated with TIVDAK compared to chemotherapy. Secondary endpoints of progression-free survival (PFS) and confirmed objective response rate (ORR) were also met. In October 2023, results from the innovaTV 301 study were presented during the Presidential session at the European Society of Medical Oncology (ESMO) Congress.

The innovaTV 301 study demonstrated a 30% reduction in the risk of death compared to chemotherapy (hazard ratio [HR]: 0.70 [95% CI: 0.54-0.89], two-sided p=0.0038)[i]. Median OS for patients treated with TIVDAK was 11.5 months [95% CI: 9.8-14.9] versus chemotherapy 9.5 months [95% CI: 7.9-10.7].

"The full FDA approval of TIVDAK represents a significant achievement for women with recurrent and metastatic cervical cancer, reinforcing TIVDAK as a treatment option that has proven to extend survival in patients whose disease has advanced after initial treatments," said Jan van de Winkel, Ph.D., Chief Executive Officer of Genmab. "This milestone underscores the importance of our ongoing clinical development program to assess the full potential of tisotumab vedotin as a treatment option in other indications."

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.

The safety profile of TIVDAK in innovaTV 301 was consistent with its known safety profile as presented in the U.S. prescribing information. No new safety issues were identified. The most common (≥25%) adverse reactions, including laboratory abnormalities, in patients receiving TIVDAK were hemoglobin decreased (41%), peripheral neuropathy (38%), conjunctival adverse reactions (37%), aspartate aminotransferase increased (34%), nausea (33%), alanine aminotransferase increased (30%), fatigue (28%), sodium decreased (27%), epistaxis (26%), and constipation (25%).

"As a treating physician, it is encouraging to see overall survival data among these patients and a manageable safety profile with tisotumab vedotin," said Brian Slomovitz, M.D., Director of Gynecologic Oncology and Co-Chair of the Cancer Research Committee at Mount Sinai Medical Center, Miami Beach. "Treatment options for patients with advanced or recurrent cervical cancer are limited. The five-year survival rate for patients who have metastatic disease at diagnosis is less than 20% in the U.S.[ii] There is a high unmet need for more treatment options that have demonstrated survival benefit in the contemporary treatment landscape. The approval of tisotumab vedotin brings us a step closer to fulfilling that need."

The sBLA application received a Priority Review Designation, which is granted by the FDA to medicines that may offer significant advances in treatment or may provide a treatment where no adequate therapy exists.[iii] TIVDAK was originally granted accelerated approval in the U.S. by the FDA in September 2021, based on tumor response and durability of response from the innovaTV 204 pivotal Phase 2 single-arm clinical trial evaluating TIVDAK in patients with previously treated recurrent or metastatic cervical cancer. The FDA's approval of the sBLA converts the accelerated approval for TIVDAK to full approval in the U.S.

"Today marks a great day for patients, especially adults battling advanced cervical cancer," said Tamika Felder, cervical cancer patient advocate, and Founder and Chief Visionary Officer, Cervivor, Inc. "This full approval opens up new treatment paths for this patient community who have long faced limited options."

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 15% of adults with cervical cancer present with metastatic disease at diagnosis[iv,v] and, for adults diagnosed at earlier stages who receive

treatment, up to 61%[vi] will experience disease recurrence. It was estimated that, in 2023, more than 13,960 new cases of invasive cervical cancer were diagnosed in the U.S. and 4,310 adults would die from the disease.[vii]

About the innovaTV 301 Trial

The innovaTV 301 trial (NCT04697628) is a global, 1:1 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 with recurrent or metastatic cervical cancer who received chemotherapy in the recurrent or metastatic setting.

Patients with recurrent or metastatic cervical cancer with squamous cell, adenocarcinoma, or adenosquamous histology, and disease progression during or after treatment with chemotherapy doublet +/- bevacizumab and an anti-PD-(L)1 agent (if eligible) are included. The primary endpoint was overall survival. The main secondary outcomes were progression-free survival and objective response rate.

The study was conducted by Seagen, which was acquired by Pfizer in December 2023, 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), as well as other global gynecological oncology cooperative groups. 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 Pfizer's ADC technology that utilizes a protease-cleavable linker that covalently attaches the microtubule-disrupting agent monomethyl auristatin E (MMAE) to the antibody. Nonclinical data suggest that the anticancer activity of tisotumab vedotin-tftv 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, tisotumab vedotin-tftv also mediates antibody-dependent cellular phagocytosis and antibody-dependent cellular cytotoxicity. TIVDAK received accelerated approval from the U.S. FDA in September 2021 for adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy.

Indication

TIVDAK is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer (r/mCC) with disease progression on or after chemotherapy.

Important Safety Information

BOXED WARNING: OCULAR TOXICITY

TIVDAK can cause severe ocular toxicities resulting in changes in vision, including severe vision loss, and corneal ulceration. Conduct an ophthalmic exam, including an assessment of ocular symptoms, visual acuity, and slit lamp exam of the anterior segment of the eye prior to initiation of TIVDAK, prior to every cycle for the first nine cycles, and as clinically indicated. Adhere to the required premedication and 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: TIVDAK can cause severe ocular adverse reactions, including conjunctivitis, keratopathy (keratitis, punctate keratitis, and ulcerative keratitis), and dry eye (increased lacrimation, eye pain, eye discharge, pruritus, irritation, and foreign body sensation), that may lead to changes in vision and/or corneal ulceration.

Ocular adverse reactions occurred in 55% of patients with cervical cancer treated with TIVDAK across clinical trials. The most common were conjunctivitis (32%), dry eye (24%), keratopathy (17%), and blepharitis (5%). Grade 3 ocular adverse reactions occurred in 3.3% of patients, including severe ulcerative keratitis in 1.2% of patients. Nine patients (2.1%) experienced ulcerative keratitis (including one with perforation requiring corneal transplantation), six (1.4%) conjunctival ulcer, four (0.9%) corneal erosion, two (0.5%) conjunctival erosion, and two (0.5%) symblepharon.

In innovaTV 301, 8 patients (3.2%) experienced delayed ocular adverse reactions occurring more than 30 days after discontinuation of TIVDAK. These adverse reactions included 3 patients with ulcerative keratitis, and one patient (each) with keratitis, punctate keratitis and corneal erosion, blepharitis and conjunctival hyperemia, conjunctival scar, and conjunctivitis and xerophthalmia.

Refer patients to an eye care provider to conduct an ophthalmic exam prior to initiation of TIVDAK, prior to every cycle for the first nine cycles, and as clinically indicated. The exam should include visual acuity, slit lamp exam of the anterior segment of the eye, and an assessment of normal eye movement and ocular signs or symptoms which include dry or irritated eyes, eye secretions, or blurry vision.

Adhere to the required premedication and eye care before, during, and after infusion to reduce the risk of ocular adverse reactions. Monitor for ocular toxicity and promptly refer patients to an eye care provider for any new or worsening ocular signs and symptoms. Withhold, reduce, or permanently discontinue TIVDAK based on the severity or persistence of the ocular adverse reaction.

Peripheral Neuropathy (PN) occurred in 39% of cervical cancer patients treated with TIVDAK across clinical trials; 6% of patients experienced Grade 3 PN. PN adverse reactions included peripheral sensory neuropathy (23%), PN (5%), paresthesia (3.8%), peripheral sensorimotor neuropathy (3.3%), muscular weakness (2.8%), and peripheral motor neuropathy (2.4%). One patient with another tumor type treated with TIVDAK at the recommended dose developed Guillain- Barre syndrome.

Monitor patients for signs and symptoms of neuropathy such as paresthesia, tingling or a burning sensation, neuropathic pain, muscle weakness, or dysesthesia. For new or worsening PN, withhold, then dose reduce, or permanently discontinue TIVDAK based on the severity of PN.

Hemorrhage occurred in 51% of cervical cancer patients treated with TIVDAK across clinical trials. The most common all grade hemorrhage adverse reaction was epistaxis (33%). Grade 3 hemorrhage occurred in 4% of patients.

Monitor patients for signs and symptoms of hemorrhage. For patients experiencing pulmonary or central nervous system 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 cervical cancer patients treated with TIVDAK across clinical trials, 4 patients (0.9%) 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 such 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 (SCAR), including events of fatal or life-threatening Stevens-Johnson syndrome (SJS), can occur in patients treated with TIVDAK. SCAR occurred in 1.6% of cervical cancer patients treated with TIVDAK across clinical trials. Grade ≥3 SCAR occurred in 0.5% of patients, including 1 patient who had a fatal outcome.

Monitor patients for signs or symptoms of SCAR, 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 SCAR 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 SCAR, 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

Across clinical trials of TIVDAK in 425 patients with r/mCC, the most common (≥25%) adverse reactions, including laboratory abnormalities, were hemoglobin decreased (45%), PN (39%), conjunctival adverse reactions (38%), nausea (37%), fatigue (36%), aspartate aminotransferase increased (33%), epistaxis (33%), alopecia (31%), alanine aminotransferase increased (30%), and hemorrhage (28%).

innovaTV 301 Study: 250 patients with r/mCC with disease progression on or after systemic therapy

Serious adverse reactions occurred in 33% of patients receiving TIVDAK; the most common (≥2%) were urinary tract infection (4.8%), small intestinal obstruction (2.4%), sepsis, abdominal pain, and hemorrhage (each 2%). **Fatal adverse reactions** occurred in 1.6% of patients who received TIVDAK, including acute kidney injury, pneumonia, sepsis, and SJS (each 0.4%).

Adverse reactions leading to permanent discontinuation occurred in 15% of patients receiving TIVDAK; the most common (≥3%) were PN and ocular adverse reactions (each 6%). **Adverse reactions leading to dose interruption** occurred in 39% of patients receiving TIVDAK; the most common (≥3%) were ocular adverse reactions (16%) and PN (6%). **Adverse reactions leading to dose reduction** occurred in 30% of patients receiving TIVDAK; the most common (≥3%) were PN and ocular adverse reactions (each 10%). The ocular adverse reactions included conjunctival disorders (4.8%), keratopathy (4%), and dry eye (0.8%).

innovaTV 204 Study: 101 patients with r/mCC with disease progression on or after chemotherapy

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, and hemorrhage (each 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%).

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 Pfizer Oncology

At Pfizer Oncology, we are at the forefront of a new era in cancer care. Our industry-leading portfolio and extensive pipeline includes game-changing mechanisms of action to attack cancer from multiple angles, including antibody-drug conjugates (ADCs), small molecules, bispecific antibodies and other immunotherapy biologics. We are focused on delivering transformative therapies in some of the world's most common cancers, including breast cancer, genitourinary cancer, hematology-oncology and thoracic cancers, which includes lung cancer. Driven by science, we are committed to accelerating breakthroughs to extend and improve patients' lives.

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 25 years, its passionate, innovative and collaborative team has invented next-generation antibody technology platforms and leveraged translational, quantitative, and data sciences, resulting 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 LinkedIn and X.

About the Pfizer and Genmab Collaboration

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

Pfizer Disclosure Notice

The information contained in this release is as of April 29, 2024. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments.

This release contains forward-looking information about Pfizer Oncology and TIVDAK® (tisotumab vedotin-tftv), including its potential benefits and its ongoing clinical development program, that involves substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, uncertainties regarding the commercial success of TIVDAK; the uncertainties inherent in research and development, including the ability to meet anticipated clinical endpoints, commencement and/or completion dates for our clinical trials, regulatory submission dates, regulatory approval dates and/or launch dates, as well as the possibility of unfavorable new clinical data and further analyses of existing clinical data; the risk that clinical trial data are subject to differing interpretations and assessments by regulatory authorities; whether regulatory authorities will be satisfied with the design of and results from our clinical studies; whether and when drug applications may be filed in particular jurisdictions for TIVDAK; whether and when any applications that may be pending or filed for TIVDAK may be approved by regulatory authorities, which will depend on myriad factors, including making a determination as to whether the product's benefits outweigh its known risks and determination of the product's efficacy and, if approved, whether TIVDAK will be commercially successful; decisions by regulatory authorities impacting labeling, manufacturing processes, safety and/or other matters that could affect the availability or commercial potential of TIVDAK; whether the collaboration between Pfizer and Genmab will be successful; uncertainties regarding the impact of COVID-19 on Pfizer's business, operations and financial results; and competitive developments.

A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2023 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at www.sec.gov and www.pfizer.com.

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.comand 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.

[i] The threshold for statistical significance is 0.0226 (two-sided).

[ii] Cervical Cancer: Statistics. American Society of Clinical Oncology (ASCO). September 2023. https://www.cancer.net/cancer-types/cervical-cancer/statistics

[iii] Priority Review. U.S. Food and Drug Administration. January 4, 2018. https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review

[iv] National Cancer Institute. SEER Cancer Stat Facts: Cervical Cancer. 2023. https://seer.cancer.gov/statfacts/html/cervix.html

[v] 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.

[vi] Pfaendler KS, Tewari KS. Changing paradigms in the systemic treatment of advanced cervical cancer. Am J Obstet Gynecol. 2016 Jan;214(1):22-30. doi: 10.1016/j.ajog.2015.07.022. Epub 2015 Jul 26. PMID: 26212178; PMCID: PMC5613936.

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

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