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# TIVDAK® Supplemental Biologics License Application Accepted for Priority Review by FDA for Patients with Recurrent or Metastatic Cervical Cancer

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*– Submission based on positive results from global phase 3 study demonstrating overall survival benefit of TIVDAK over chemotherapy –*

NEW YORK & COPENHAGEN, Denmark--(BUSINESS WIRE)-- Pfizer Inc. (NYSE: PFE) and Genmab A/S (Nasdaq: GMAB) announced today that the U.S. Food and Drug Administration (FDA) has accepted the supplemental Biologics License Application (sBLA) seeking to convert the accelerated approval of TIVDAK® (tisotumab vedotin-tftv) to full approval, for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after first-line therapy. The application has been granted Priority Review with a Prescription Drug User Fee Act (PDUFA) goal date of May 9, 2024.

“The Phase 3 innovaTV 301 trial demonstrated a favorable benefit/risk profile, including improvement in overall survival, and adds to the overall data supporting TIVDAK as a treatment option for people with recurrent and metastatic cervical cancer who have limited treatment options,” said Roger Dansey, M.D., Chief Development Officer, Oncology at Pfizer. “The FDA acceptance of our sBLA for review is important progress toward continuing to offer an option that can extend the lives of more adults with cervical cancer.”

The sBLA is supported by efficacy and safety data from the global, randomized, Phase 3 innovaTV 301 trial (NCT04697628), in which TIVDAK demonstrated superior overall survival (OS), progression-free survival (PFS) and confirmed objective response rate (ORR), as assessed by the investigator, in patients with previously treated recurrent or metastatic cervical cancer compared to chemotherapy. The safety profile of TIVDAK in innovaTV 301 was consistent with its known safety profile as presented in the U.S. prescribing information. In October 2023, results from the innovaTV 301 study were presented during a Presidential Symposium at the European Society of Medical Oncology (ESMO) Congress.

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.**

“Therapeutic options for metastatic cervical cancer that not only demonstrate a survival advantage but also include a novel approach to treating this condition are needed,” said Jan van de Winkel, Ph.D., Chief Executive Officer at Genmab. “This milestone underscores our commitment to continuing to deliver TIVDAK as a treatment option to women in the U.S. diagnosed with cervical cancer whose disease has progressed after first-line treatment.”

TIVDAK was granted accelerated approval in the U.S. by the FDA in September 2021. The accelerated approval is based on tumor response and durability of response from the innovaTV 204 pivotal Phase 2 single-arm clinical trial evaluating TIVDAK as monotherapy in patients with previously treated recurrent or metastatic cervical cancer. The data from innovaTV 301 will support global regulatory submissions.

**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 percent of adults with cervical cancer are diagnosed with metastatic disease at diagnosis[1,2] and, for adults diagnosed at earlier stages who receive treatment, up to 31.5 percent will experience disease recurrence.[3] 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.[4]

**About the innovaTV 301 Trial**
The innovaTV 301 trial (NCT04697628) is a global, 1:1 randomized, open-label Phase 3 trial evaluating (tisotumab vedotin-tftv) versus investigator's choice of chemotherapy alone (topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed) in 502 randomized patients with recurrent or metastatic cervical cancer who received one or two prior systemic regimens 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 is overall survival. The main secondary outcomes are progression-free survival, confirmed objective response rate, time to response, and duration of response, as assessed by the investigator, as well as safety and quality of life outcomes.

The study was conducted by Seagen, recently acquired by Pfizer, 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. Determination of TF expression is not required. 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.

**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-Barré 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, includinglaboratory 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%), andrash (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 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, bispecifics and other immunotherapies. We are focused on delivering transformative therapies in some of the world's most common cancers, including breast cancer, genitourinary cancer and hematologic malignancies, as well as melanoma, gastrointestinal, gynecological and thoracic cancers, which includes lung cancer. Driven by science, we are committed to accelerating breakthroughs to extend and improve patients' lives. We routinely post information that may be important to investors on our website at www.Pfizer.com. In addition, to learn more, please visit us on www.Pfizer.com and follow us on X (Twitter) at @Pfizer and @Pfizer News, LinkedIn, YouTube and like us on Facebook at Facebook.com/Pfizer.

**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 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 *January 9, 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 potential to convert the accelerated approval of TIVDAK to full approval, potential benefits and plans for data from innovaTV 301 to support global regulatory submissions*, 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 (including the sBLA seeking to convert the accelerated approval of TIVDAK to full approval, for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after first-line therapy),* 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, 2022 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.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®.*

Category: Medicines

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

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.
[3] de Foucher T, Bendifallah S, Ouldamer L, et al. Patterns of recurrence and prognosis in locally advanced FIGO stage IB2 to IIB cervical cancer: retrospective multicentre study from the FRANCOGYN Group. Eur J Surg Oncol. 2019;45:659–665. doi: 10.1016/j.ejso.2018.11.014.
[4] 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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