Genmab Announces European Commission Approval of TEPKINLY® (epcoritamab) for Adults with Relapsed or Refractory (R/R) Diffuse Large B-cell Lymphoma (DLBCL)

Company Announcement

- **TEPKINLY® (epcoritamab) is the first and only subcutaneous bispecific antibody approved as a monotherapy for adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy**
- **Conditional marketing authorization approval from the European Commission is supported by data from the pivotal phase 1/2 EPCORE™ NHL-1 clinical trial, which demonstrated 62 percent overall response rate, 39 percent complete response, and 15.5-month median duration of response in challenging-to-treat R/R DLBCL patients**
- **Epcoritamab represents the eighth approved medicine incorporating Genmab innovation and fourth created via Genmab's DuoBody® technology platform**

COPENHAGEN, Denmark; September 25, 2023 – Genmab A/S (Nasdaq: GMAB) announced today that the European Commission (EC) has granted conditional marketing authorization for TEPKINLY® (epcoritamab) as a monotherapy for the treatment of adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy. TEPKINLY is the first and only subcutaneous T-cell engaging bispecific antibody approved for the treatment of this patient population in the European Union (EU), as well as Liechtenstein, Norway and Iceland.

DLBCL is the most common type of B-cell non-Hodgkin's lymphoma worldwide. While patients may have access to chemoimmunotherapy regimens to treat their disease, they face limited treatment options, with few readily available, off-the-shelf medicines, especially for those whose disease has relapsed or become refractory to prior treatments.[i]

"With TEPKINLY, people in Europe living with relapsed or refractory diffuse large B-cell lymphoma who are in need of additional treatment options now have a readily available, innovative therapeutic option for this aggressive cancer," said Jan van de Winkel, Ph.D., Chief Executive Officer of Genmab. "Today's approval underscores our commitment to bringing our bispecific antibody to more patients worldwide. We're excited to continue working with our partner AbbVie to further explore epcoritamab as potential core therapy across B-cell malignancies."

This conditional approval is supported by data from the pivotal EPCORE™ NHL-1 phase 1/2 open-label, multi-cohort, multi-center, single-arm trial evaluating the preliminary efficacy and safety of TEPKINLY in patients with R/R large B-cell lymphoma (LBCL), including its subtype DLBCL. In this study, DLBCL patients treated with TEPKINLY (n=139) achieved an overall response rate of 62 percent (n=86) and a complete response rate of 39 percent (n=54), with a median duration of response of 15.5 months (range: 9.7, not reached).

Results from the trial showed that TEPKINLY demonstrated a manageable safety profile across the LBCL patient cohort (n=167), which included the DLBCL patient population. The most common adverse reactions (≥ 20 percent) were cytokine release syndrome, fatigue, neutropenia, injection site reaction, musculoskeletal pain, abdominal pain, pyrexia, nausea and diarrhea.

"Relapsed or refractory DLBCL is an aggressive cancer and patients can face a difficult and emotional treatment journey. At this point in the journey, a patient may have had multiple lines of therapy and will already have experienced relapse," said Anna Sureda, M.D., Ph.D., head of clinical hematology department, Institut Català d'Oncologia – L'Hospitalet, Barcelona, Spain. "This European Commission approval represents an important moment for the DLBCL patient community and brings with it a potential opportunity for effective disease management for a condition with limited available treatment options."

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Conditional marketing authorization is granted to medicines that address an unmet medical need, where the benefit of its immediate availability to patients outweighs the risk of limited data availability, and where confirmatory comprehensive data will need to be provided subsequently to maintain the marketing authorization.[ii]

Epcoritamab is being co-developed by AbbVie and Genmab as part of the companies' oncology collaboration. The companies will share commercial responsibilities in the U.S. and Japan, with AbbVie responsible for further global commercialization. AbbVie will continue to pursue regulatory submissions for epcoritamab across international markets throughout the year.

About the EPCORE™ NHL-1 Trial
EPCORE™ NHL-1 is an open-label, multi-center preliminary efficacy and safety trial of epcoritamabthat includes a phase 1 first-in-human, dose escalation part; a phase 2a expansion part; and a dose optimization part. The trial was designed to evaluate subcutaneous epcoritamab in patients with relapsed, progressive or refractory CD20+ mature B-cell non-Hodgkin's lymphoma (NHL), including large B-cell lymphoma (LBCL) and diffuse large B-cell lymphoma (DLBCL).[iii] Data from the dose escalation part of the study, which determined the recommended phase 2 dose, were published in September 2021.[iv] In the phase 2 expansion part, additional patients were treated with epcoritamab to further explore the efficacy and safety of epcoritamab in three cohorts of patients with different types of relapsed or refractory (R/R) B-cell NHLs who had limited therapeutic options.[iiii]

The median number of prior therapies was three (range: 2 to 11), with 30 percent receiving two prior therapies, 30 percent receiving three prior therapies, and 40 percent receiving four or more prior therapies. Eighteen percent had prior autologous hematopoietic stem cell transplantation (HSCT), and 39 percent had prior chimeric antigen receptor (CAR) T-cell therapy. Eighty-two percent of patients had disease refractory to last therapy and 29 percent of patients were refractory to CAR T-cell therapy.

The primary endpoint of the phase 2 expansion part was overall response rate as assessed by an independent review committee. Secondary efficacy endpoints included duration of response, complete response rate, progression-free survival, overall survival, time to response, time to next therapy, and rate of minimal residual disease negativity. More information can be found on www.clinicaltrials.gov.

About TEPKINLY (epcoritamab)
Epcoritamab is an IgG1-bispecific antibody created using Genmab's proprietary DuoBody® technology. Genmab's DuoBody-CD3 technology is designed to direct cytotoxic T-cells selectively to elicit an immune response toward target cell types. Epcoritamab is designed to simultaneously bind to CD3 on T-cells and CD20 on B-cells and induces T-cell mediated killing of CD20+ cells.[v] CD20 is expressed on B-cells and is a clinically validated therapeutic target in many B-cell malignancies, including DLBCL, follicular lymphoma, mantle cell lymphoma and chronic lymphocytic leukemia.[vi,vii]

Epcoritamab-bysp (EPKINLY™) was approved under accelerated approval in the United States in May 2023. Continued approval is contingent upon verification and description of clinical benefit in a confirmatory trial(s). For more information, please see the Full Prescribing Information and Medication Guide, including Important Warnings.

Genmab and AbbVie continue to evaluate the use of epcoritamab as a monotherapy, and in combination, across lines of therapy in a range of hematologic malignancies. This includes three ongoing phase 3,

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open-label, randomized trials including a trial evaluating epcoritamab as a monotherapy in patients with R/R DLBCL (NCT: 04628494) compared to investigators choice chemotherapy, a phase 3, trial evaluating epcoritamab in combination with R-CHOP in adult participants with newly diagnosed DLBCL (NCT: 05578976), and a phase 3, open-label clinical trial evaluating epcoritamab in combination in patients with R/R follicular lymphoma (FL) (NCT: 05409066). Epcoritamab is not approved to treat newly diagnosed patients with DLBCL or FL. The safety and efficacy of epcoritamab has not been established for these investigational uses. Please visit clinicaltrials.gov for more information.

EU Indications and Important Safety Information about Tepkinly® ▼ (epcoritamab)

Indications
Tepkinly (epcoritamab) as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

Important Safety Information

Contraindications
Hypersensitivity to the active substance or to any of the excipients.

Special warnings and precautions for use
Cytokine release syndrome (CRS)
CRS, which may be life-threatening or fatal, occurred in patients receiving Tepkinly. The most common signs and symptoms of CRS include pyrexia, hypotension and hypoxia. Other signs and symptoms of CRS in more than two patients include chills, tachycardia, headache and dyspnoea.

Most CRS events occurred in Cycle 1 and were associated with the first full dose of Tepkinly. Administer prophylactic corticosteroids to mitigate the risk of CRS. Patients should be monitored for signs and symptoms of CRS following Tepkinly administration. Patients should be hospitalised for 24 hours after administration of the Cycle 1 Day 15 dose of 48 mg to monitor for signs and symptoms of CRS. At the first signs or symptoms of CRS, institute treatment of supportive care with tocilizumab and/or corticosteroids as appropriate. Patients should be counselled on the signs and symptoms associated with CRS and patients should be instructed to contact their healthcare professional and seek immediate medical attention should signs or symptoms occur at any time. Management of CRS may require either temporary delay or discontinuation of Tepkinly based on the severity of CRS.

Immune effector cell-associated neurotoxicity syndrome (ICANS)
ICANS, including a fatal event, have occurred in patients receiving Tepkinly. ICANS may manifest as aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral oedema. The majority of cases of ICANS occurred within Cycle 1 of Tepkinly treatment, however some occurred with delayed onset. Patients should be monitored for signs and symptoms of ICANS following Tepkinly administration. Patients should be hospitalised for 24 hours after administration of the Cycle 1 Day 15 dose of 48 mg to monitor for signs and symptoms of ICANS. At the first signs or symptoms of ICANS treatment with corticosteroids and non-sedating-anti-seizure medicinal products should be instituted as appropriate. Patients should be counselled on the signs and symptoms of ICANS and that the onset of events may be delayed. Patients should be instructed to contact their healthcare professional and seek immediate medical attention should signs or symptoms occur at any time. Tepkinly should be delayed or discontinued as recommended.

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Serious infections
Treatment with Tepkinly may lead to an increased risk of infections. Serious or fatal infections were observed in patients treated with Tepkinly in clinical studies. Administration of Tepkinly should be avoided in patients with clinically significant active systemic infections. As appropriate, prophylactic antimicrobials should be administered prior to and during treatment with Tepkinly. Patients should be monitored for signs and symptoms of infection, before and after Tepkinly administration, and treated appropriately. In the event of febrile neutropenia, patients should be evaluated for infection and managed with antibiotics, fluids and other supportive care, according to local guidelines.

Tumour Lysis Syndrome (TLS)
TLS has been reported in patients receiving Tepkinly. Patients at an increased risk for TLS are recommended to receive hydration and prophylactic treatment with a uric acid lowering agent. Patients should be monitored for signs or symptoms of TLS, especially patients with high tumour burden or rapidly proliferative tumours, and patients with reduced renal function. Patients should be monitored for blood chemistries and abnormalities should be managed promptly.

Tumour flare
Tumour flare has been reported in patients treated with Tepkinly. Manifestations could include localized pain and swelling. Consistent with the mechanism of action of Tepkinly, tumour flare is likely due to the influx of T-cells into tumour sites following Tepkinly administration. There are no specific risk factors for tumour flare that have been identified; however, there is a heightened risk of compromise and morbidity due to mass effect secondary to tumour flare in patients with bulky tumours located in close proximity to airways and/or a vital organ. Patients treated with Tepkinly should be monitored and evaluated for tumour flare at critical anatomical sites.

CD20-negative disease
There are limited data available on patients with CD20-negative DLBCL treated with Tepkinly, and it is possible that patients with CD20-negative DLBCL may have less benefit compared to patients with CD20-positive DLBCL. The potential risks and benefits associated with treatment of patients with CD20-negative DLBCL with Tepkinly should be considered.

Immunisation
Live and/or live-attenuated vaccines should not be given during Tepkinly therapy. Studies have not been conducted in patients who received live vaccines.

Fertility, pregnancy and lactation
Tepkinly is not recommended during pregnancy and in women of childbearing potential not using contraception.

Effects on ability to drive and use machines
Tepkinly has minor influence on the ability to drive and use machines. Due to the potential for ICANS, patients should be advised to exercise caution while (or avoid if symptomatic) driving, cycling or using heavy or potentially dangerous machines.

Undesirable effects
Summary of the safety profile
The most common adverse reactions (≥ 20%) were CRS, fatigue, neutropenia, injection site reactions, musculoskeletal pain, abdominal pain, pyrexia, nausea, and diarrhoea.

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Serious adverse reactions occurred in 52% of patients. The most frequent serious adverse reaction (≥ 10%) was cytokine release syndrome (31%). Seven patients (4.2%) experienced a fatal adverse reaction (pneumonia in 3 (1.8%) patients, viral infection in 3 (1.8%) patients and ICANS in 1 (0.6%) patient). Adverse reactions that led to discontinuation occurred in 6.6% of patients. Discontinuation of Tepkinly due to pneumonia occurred in 6 (3.6%) patients, viral infection in 3 (1.8%) patients, and CRS, ICANS, or fatigue in 1 (0.6%) patient each. Dose delays due to adverse reactions occurred in 32% of patients. Adverse reactions leading to dose delays (≥ 3%) were viral infections (9.6%), CRS (7.2%), neutropenia (4.8%), pyrexia (3.0%), and thrombocytopenia (3.0%).

This is not a complete summary of all safety information.
See Tepkinly® full Summary of Product Characteristics (SmPC) at www.ema.europa.eu
Globally, prescribing information varies; refer to the individual country product label for complete information.

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.

Contact:
Marisol Peron, Senior Vice President, Global Communications & Corporate Affairs
T: +1 609 524 0065; E: mmp@genmab.com

Andrew Carlsen, Vice President, Head of Investor Relations
T: +45 3377 9558; E: acn@genmab.com

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.

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