MacroGenics Announces Publication of SOPHIA Trial Results for MARGENZA™ in JAMA Oncology

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- *Primary endpoint of Phase 3 study met with MARGENZA (margetuximab-cmkb) showing a 24% Progression Free Survival (PFS) relative risk reduction compared to Herceptin® (trastuzumab), both with chemotherapy*
- *In the U.S., MARGENZA is approved, in combination with chemotherapy, for the treatment of adult patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease*

ROCKVILLE, MD, Jan. 25, 2021 (GLOBE NEWSWIRE) -- MacroGenics, Inc. (Nasdaq: MGNX), a biopharmaceutical company focused on developing and commercializing innovative monoclonal antibody-based therapeutics for the treatment of cancer, today announced the publication of results from the SOPHIA trial of MARGENZA™ (margetuximab-cmkb) in the *Journal of the American Medical Association (JAMA) Oncology*. SOPHIA is a pivotal Phase 3 clinical trial of 536 adult patients with metastatic HER2-positive breast cancer previously treated with two or more anti-HER2 regimens and from one to three lines of therapy for metastatic disease. In the study, MARGENZA demonstrated a statistically significant 24% reduction in the risk of disease progression or death compared to Herceptin, each in combination with chemotherapy (Hazard Ratio [HR] = 0.76; 95% CI, 0.59-0.98; p=0.03; median PFS 5.8 vs. 4.9 months).

“MARGENZA is the first HER2-targeted therapy to reduce the risk of disease progression in metastatic breast cancer patients over trastuzumab in a head-to-head comparison involving a heavily pretreated patient population,” said Scott Koenig, M.D., Ph.D., President and CEO of MacroGenics. “These data represent years of research and clinical development at MacroGenics leading to the forthcoming commercialization of this innovative antibody-based therapeutic for the treatment of metastatic HER2-positive breast cancer.”

In addition to the statistically significant improvement in primary endpoint of PFS by centrally blinded review, investigator-assessed PFS (based on 337 events) was also greater with MARGENZA compared to trastuzumab with a 30% PFS relative risk reduction compared to trastuzumab (HR=0.70; 95% CI, 0.56-0.87; P=0.001; median investigator-assessed PFS 5.6 vs 4.2 months). Among 524 response-evaluable patients, the objective response rates for MARGENZA plus chemotherapy and trastuzumab plus chemotherapy were 22% and 16%, respectively (P=0.06) and the clinical benefit rates were 37% for MARGENZA and 25% for trastuzumab, (P=0.003).

At the prespecified interim Overall Survival (OS) analysis, based on 270 events, median OS was 21.6 months with MARGENZA and 19.8 months with trastuzumab (HR=0.89; 95% CI, 0.69-1.13; P=0.33). The stopping threshold was not reached. The final OS analysis will occur after 385 events, and it is expected in the second half of 2021.

Adverse reactions occurring in greater than twenty percent of patients with MARGENZA in combination with chemotherapy were fatigue/asthenia (57%), nausea (33%), diarrhea (25%), and vomiting (21%). The MARGENZA U.S. Prescribing Information has a BOXED WARNING for left ventricular dysfunction and embryo-fetal toxicity. In addition, MARGENZA can cause infusion related reactions (IRRs). IRRs occurred in 13% of patients treated with MARGENZA, with the majority reported as Grade 2 or less. Grade 3 IRRs occurred in 1.5% of patients. See below for Important Safety Information.

“Up to one-fifth of all breast cancers are HER2-positive, and identifying new treatment options for patients in the metastatic setting represents a serious unmet medical need,” said SOPHIA principal investigator Hope S. Rugo, M.D., Professor of Medicine and Director of Breast Oncology and Clinical Trials Education, University of California San Francisco Helen Diller Family Comprehensive Cancer Center. “These results show that MARGENZA provides improvement, for this patient population, beyond what we can achieve with trastuzumab, which is good news for patients with advanced disease.”

MacroGenics anticipates that MARGENZA will be available to patients in the U.S. in March of 2021.

About the SOPHIA Study

The SOPHIA study (NCT02492711) is a randomized, open-label Phase 3 clinical trial evaluating MARGENZA plus chemotherapy compared to trastuzumab plus chemotherapy in patients with HER2-positive metastatic breast cancer, who have previously been treated with anti-HER2-targeted therapies. All study patients had previously received trastuzumab, all but one patient had previously received pertuzumab, and 91% had previously received ado-trastuzumab emtansine, or T-DM1.

The study enrolled 536 patients who were randomized 1:1 to receive either MARGENZA (n=266) given intravenously at 15 mg/kg every three weeks or trastuzumab (n=270) given intravenously at 6 mg/kg (or 8 mg/kg for loading dose) every three weeks in combination with one of four chemotherapy agents (capecitabine, eribulin, gemcitabine or vinorelbine) given at the standard dose. Intent-to-treat PFS analysis occurred after 265 PFS events.

The primary endpoints of the study were sequentially-assessed PFS, determined by blinded, centrally-reviewed radiological review, followed by OS. Additional key secondary endpoints are PFS by investigator assessment and ORR. Tertiary endpoints include ORR by investigator assessment and safety. PFS and ORR were assessed according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

About HER2-positive Breast Cancer

Human epidermal growth factor receptor 2 (HER2) is a protein found on the surface of some cancer cells that promotes growth and is associated with aggressive disease and poor prognosis. Approximately 15-20% of breast cancer cases are HER2-positive. Monoclonal antibodies targeting HER2 have greatly improved outcomes; however, a significant number of patients progress to later lines of therapy. Effective treatments for metastatic HER2-positive breast cancer continue to remain an unmet need.

About MARGENZA

MARGENZA (margetuximab-cmkb) is an Fc-engineered, monoclonal antibody that targets the HER2 oncoprotein. HER2 is expressed by tumor cells in breast, gastroesophageal and other solid tumors. Similar to trastuzumab, margetuximab-cmkb inhibits tumor cell proliferation, reduces shedding of the HER2 extracellular domain and mediates antibody-dependent cellular cytoxicity (ADCC). However, through MacroGenics' Fc Optimization technology, margetuximab-cmkb has been engineered to enhance the engagement of the immune system. In vitro, the modified Fc region of margetuximab-cmkb increases binding to the activitating Fc receptor FCGR3A (CD16A) and decreases binding to inhibitor Fc receptor FCGR2B (CD32B). These changes lead to greater in vitro ADCC and NK cell activation. The clinical significance of in vitro data is unknown.

Margetuximab-cmkb is also being evaluated in combination with checkpoint blockade in the Phase 2/3 MAHOGANY trial for the treatment of patients with HER2-positive gastroesophageal cancer (NCT04082364), and in combination with tebotelimab (PD-1 × LAG-3 bispecific DART® molecule) in various HER2+ tumors (NCT03219268). For more information, please visit www.clinicaltrials.gov.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: LEFT VENTRICULAR DYSFUNCTION AND EMBRYO-FETAL TOXICITY

- **Left Ventricular Dysfunction:** MARGENZA may lead to reductions in left ventricular ejection fraction (LVEF). Evaluate cardiac function prior to and during treatment. Discontinue MARGENZA treatment for a confirmed clinically significant decrease in left ventricular function.
- **Embryo-Fetal Toxicity:** Exposure to MARGENZA during pregnancy can cause embryo-fetal harm. Advise patients of the risk and need for effective contraception.

WARNINGS & PRECAUTIONS:

Left Ventricular Dysfunction

- Left ventricular cardiac dysfunction can occur with MARGENZA.
- MARGENZA has not been studied in patients with a pretreatment LVEF value of <50%, a prior history of myocardial infarction or unstable angina within 6 months, or congestive heart failure NYHA class II-IV.
- Withhold MARGENZA for ≥16% absolute decrease in LVEF from pre-treatment values or LVEF below institutional limits of normal (or 50% if no limits available) and ≥10% absolute decrease in LVEF from pretreatment values.
- Permanently discontinue MARGENZA if LVEF decline persists greater than 8 weeks, or dosing is interrupted more than 3 times due to LVEF decline.
- Evaluate cardiac function within 4 weeks prior to and every 3 months during and upon completion of treatment. Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan.
- Monitor cardiac function every 4 weeks if MARGENZA is withheld for significant left ventricular cardiac dysfunction.

Embryo-Fetal Toxicity

- Based on findings in animals and mechanism of action, MARGENZA can cause fetal harm when administered to a pregnant woman. Post-marketing studies of other HER2 directed antibodies during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death.
- Verify pregnancy status of women of reproductive potential prior to initiation of MARGENZA.
- Advise pregnant women and women of reproductive potential that exposure to MARGENZA during pregnancy or within 4 months prior to conception can result in fetal harm.
- Advise women of reproductive potential to use effective contraception during treatment and for 4 months following the last dose of MARGENZA.

Infusion-Related Reactions (IRRs)

- MARGENZA can cause IRRs. Symptoms may include fever, chills, arthralgia, cough, dizziness, fatigue, nausea, vomiting, headache, diaphoresis, tachycardia, hypotension, pruritus, rash, urticaria, and dyspnea.
- Monitor patients during and after MARGENZA infusion. Have medications and emergency equipment to treat IRRs available for immediate use.
- In patients experiencing mild or moderate IRRs, decrease rate of infusion and consider premedications, including antihistamines, corticosteroids, and antipyretics. Monitor patients until symptoms completely resolve.
- Interrupt MARGENZA infusion in patients experiencing dyspnea or clinically significant hypotension and intervene with supportive medical therapy as needed. Permanently discontinue MARGENZA in all patients with severe or life-threatening IRRs.

MOST COMMON ADVERSE REACTIONS:

The most common adverse drug reactions (≥10%) with MARGENZA in combination with chemotherapy are fatigue/asthenia, nausea, diarrhea, vomiting, constipation, headache, pyrexia, alopecia, abdominal pain, peripheral neuropathy, arthralgia/myalgia, cough, decreased appetite, dyspnea, infusion-related reactions, palmar-plantar erythrodysesthesia, and extremity pain.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch or to MacroGenics at (844)-MED-MGNX (844-633-6469).

Link to full Prescribing Information, including Boxed Warning.

About MacroGenics, Inc.

MacroGenics is a biopharmaceutical company focused on developing and commercializing innovative monoclonal antibody-based therapeutics for the treatment of cancer. The Company generates its pipeline of product candidates primarily from its proprietary suite of next-generation antibody-based technology platforms, which have applicability across broad therapeutic domains. The combination of MacroGenics' technology platforms and protein engineering expertise has allowed the Company to generate promising product candidates and enter into several strategic collaborations with global pharmaceutical and biotechnology companies. For more information, please see the Company's website at www.macrogenics.com. MacroGenics, the MacroGenics logo, MARGENZA and DART are trademarks or registered trademarks of MacroGenics, Inc.

Cautionary Note on Forward-Looking Statements

Any statements in this press release about future expectations, plans and prospects for the Company, including statements about the Company's strategy, future operations, clinical development of the Company's therapeutic candidates, commercial prospects of or product revenues from MARGENZA, milestone or opt-in payments from the Company's collaborators, the Company's anticipated milestones and other statements containing the words "subject to," "believe," "anticipate," "plan," "expect," "intend," "estimate," "project," "may," "will," "should," "would," "could," "can," the negatives thereof, variations thereon and similar expressions, or by discussions of strategy constitute forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, including: risks that MARGENZA revenue, expenses and costs may not be as expected, risks relating to MARGENZA's market acceptance, competition, reimbursement and regulatory actions the uncertainties inherent in the initiation and enrollment of future clinical trials, expectations of expanding ongoing clinical trials, availability and timing of data from ongoing clinical trials, expectations for regulatory approvals, other matters that could affect the availability or commercial potential of the Company's product candidates and other risks described in the Company's filings with the Securities and Exchange Commission. In addition, the forward-looking statements included in this press release represent the Company's views only as of the date hereof. The Company anticipates that subsequent events and developments will cause the Company's views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, the Company specifically disclaims any obligation to do so, except as may be required by law. These forward-looking statements should not be relied upon as representing the Company's views as of any date subsequent to the date hereof.

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Contacts:
Jim Karrels, Senior Vice President, CFO
+1-301-251-5172
info@macrogenics.com

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