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MEDIA & INVESTOR RELEASE

Novartis expands Kymriah® manufacturing footprint with first-ever approved site for commercial CAR-T cell therapy manufacturing in Asia

- *Foundation for Biomedical Research and Innovation (FBRI) in Kobe, Japan becomes first CAR-T cell therapy commercial manufacturing site in Asia*
- *Novartis global CAR-T manufacturing footprint now spans four continents, bringing Kymriah closer to patients and healthcare professionals around the world*
- *Prestigious FBRI is recognized for its world-class expertise and established practice in CAR-T cell therapy*
- *Global CAR-T manufacturing growth includes recent FDA approval for further capacity expansion in the US, which enables increased production of Kymriah*

Basel, October 30, 2020 — Novartis today announced the receipt of marketing authorization from Japan's Ministry of Health, Labor and Welfare (MHLW) for Foundation for Biomedical Research and Innovation at Kobe ("FBRI") to manufacture and supply commercial Kymriah® (tisagenlecleucel) for patients in Japan. This approval makes FBRI the first and only approved commercial manufacturing site for CAR-T cell therapy in Asia.

"Behind our efforts to reimagine medicine with CAR-T cell therapy lies a commitment to build a manufacturing network that brings treatment closer to patients," commented Steffen Lang, Global Head of Novartis Technical Operations. "The expertise and infrastructure of FBRI, a world-leading manufacturing organization, allows us to bring CAR-T manufacturing to Asia. With the Japan MHLW commercial manufacturing approval, the recent capacity expansion in the US and our ongoing efforts to optimize and evolve our processes, we are well-positioned to deliver this potentially curative treatment option to more patients around the world."

Novartis has the largest geographical CAR-T cell therapy manufacturing network in the world, including seven CAR-T manufacturing facilities, across four continents. Commercial manufacturing for Kymriah now takes place at five sites globally including at the Morris Plains, New Jersey facility, where the US Food and Drug Administration (FDA) recently approved a further increase in manufacturing capacity.

Kymriah is the first-ever FDA-approved CAR-T cell therapy, and the first-ever CAR-T to be approved in two distinct indications. It is a one-time treatment designed to empower patients' immune systems to fight their cancer. Kymriah is currently approved for the treatment of r/r pediatric and young adult (up to 25 years of age) acute lymphoblastic leukemia (ALL), and r/r adult diffuse large B-cell lymphoma (DLBCL)[1]. Kymriah, approved in both indications by the

Japan MHLW in 2019, is currently the only CAR-T cell therapy approved in Asia. Clinical manufacturing began at FBRI in 2019 and will continue alongside commercial manufacturing.

Kymriah was developed in collaboration with the Perelman School of Medicine at the University of Pennsylvania, a strategic alliance between industry and academia, which was first-of-its-kind in CAR-T research and development.

About Novartis Commitment to Oncology Cell & Gene
Novartis has a mission to reimagine medicine by bringing curative cell & gene therapies to patients worldwide. Novartis has a deep CAR-T pipeline and ongoing investment in manufacturing and supply chain process improvements. With active research underway to broaden the impact of cell and gene therapy in oncology, Novartis is going deeper in hematological malignancies, reaching patients with other cancer types and evaluating next-generation CAR-T cell therapies that focus on new targets and utilize new technologies.

Novartis was the first pharmaceutical company to significantly invest in pioneering CAR-T research and initiate global CAR-T trials. Kymriah, the first approved CAR-T cell therapy, developed in collaboration with the Perelman School of Medicine at the University of Pennsylvania, is the foundation of Novartis' commitment to CAR-T cell therapy. Kymriah is currently approved for use in at least one indication in 26 countries and at more than 260 certified treatment centers, with the ambition for further expansion to help fulfill the ultimate goal of bringing CAR-T cell therapy to every patient in need.

The Novartis global CAR-T manufacturing footprint spans seven facilities, across four continents. This comprehensive, integrated footprint strengthens the flexibility, resilience and sustainability of the Novartis manufacturing and supply chain. Commercial and clinical trial manufacturing is now ongoing at Novartis-owned facilities in Stein, Switzerland, Les Ulis, France and Morris Plains, New Jersey, USA, as well as at the contract manufacturing sites at Fraunhofer-Institut for cell therapy and immunology (Fraunhofer-Institut für Zelltherapie und Immunologie) facility in Leipzig, Germany, and now FBRI in Kobe, Japan. Manufacturing production at Cell Therapies in Australia and Cellular Biomedicine Group in China is forthcoming.

Important Safety information from the Kymriah SmPC

EU Name of the medicinal product:

Kymriah 1.2 x 10^6 – 6 x 10^8 cells dispersion for infusion

Important note: Before prescribing, consult full prescribing information.

Presentation: Cell dispersion for infusion in 1 or more bags for intravenous use (tisagenlecleucel).

Indications: Treatment of pediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse. Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

Dosage and administration:

B-cell patients: For patients 50 kg and below: 0.2 to 5.0 x 10^6 CAR-positive viable T-cells/kg body weight. **For patients above 50 kg**: 0.1 to 2.5 x 10^8 CAR-positive viable T-cells (non-weight based).

DLBCL Patients: 0.6 to 6.0×10^8 CAR-positive viable T-cells (non-weight based).

Pre-treatment conditioning (lymphodepleting chemotherapy): Lymphodepleting chemotherapy is recommended to be administered before Kymriah infusion unless the white blood cell (WBC) count within one week prior to infusion is ≤1,000 cells/µL. The availability of Kymriah must be confirmed prior to starting the lymphodepleting regimen.

Precautions before handling or administering Kymriah®: Kymriah contains genetically modified human blood cells. Healthcare professionals handling Kymriah should therefore take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases.

Preparation for infusion
The timing of thaw of Kymriah and infusion should be coordinated. Once Kymriah has been thawed and is at room temperature (20°C -25°C), it should be infused within 30 minutes to maintain maximum product viability, including any interruption during the infusion.

Administration
Kymriah should be administered as an intravenous infusion through latex-free intravenous tubing without a leukocyte depleting filter, at approximately 10 to 20 mL per minute by gravity flow. If the volume of Kymriah to be administered is ≤20 mL, intravenous push may be used as an alternative method of administration.

All contents of the infusion bag(s) should be infused.

Clinical assessment prior to infusion: Kymriah treatment should be delayed in some patient groups at risk (see Special warnings and precautions for use).

Monitoring after infusion: Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential cytokine release syndrome, neurological events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs/symptoms of CRS and/or neurological events. After the first 10 days following the infusion, the patient should be monitored at the physician's discretion. Patients should be instructed to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion.

Elderly (above 65 years of age): Safety and efficacy have not been established in B-cell patients. No dose adjustment is required in patients over 65 years of age in DLBCL patients.

Paediatric patients: No formal studies have been performed in paediatric patients with B-cell ALL below 3 years of age. The safety and efficacy of Kymriah in children and adolescents below 18 years of age have not yet been established in DLBCL. No data are available.

Patients seropositive for hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV): There is no experience with manufacturing Kymriah for patients with a positive test for HIV, active HBV, or active HCV infection. Leukapheresis material from these patients will not be accepted for Kymriah manufacturing.

Contraindications: Hypersensitivity to the active substance or to any of the excipients of Kymriah. Contraindications of the lymphodepleting chemotherapy must be considered.

Warnings and precautions: **Reasons to delay treatment**: Due to the risks associated with Kymriah treatment, infusion should be delayed if a patient has any of the following conditions: Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions or hypotension) from preceding chemotherapies, active uncontrolled infection, active graft versus host disease (GVHD), significant clinical worsening of leukaemia burden or rapid progression of lymphoma following lymphodepleting chemotherapy. **Blood, organ, tissue and cell donation**: Patients treated with Kymriah should not donate blood, organs, tissues or cells.

Active central nervous system (CNS) leukaemia or lymphoma: There is limited experience of use of Kymriah in patients with active CNS leukaemia and active CNS lymphoma. Therefore the risk/benefit of Kymriah has not been established in these populations. **Risk of CRS**: Occurred in almost all cases within 1 to 10 days post infusion with a median time to onset of 3 days and a median time to resolution of8 days. See full prescribing information for management algorithm of CRS. **Risk of neurological events:** Majority of events, in particular encephalopathy, confusional state or delirium, occurred within 8 weeks post infusion and were transient. The median time to onset of neurological events was 8 days in B-cell ALL and 6 days in DLBCL; the median time to resolution was 7 days for B-cell ALL and 13 days for DLBCL. Patients should be monitored for neurological events. **Risk of infections**: Delay start of therapy with Kymriah until active uncontrolled infections have resolved. As appropriate, administer prophylactic antibiotics and employ surveillance testing prior to and during treatment with Kymriah. Serious infections were observed in patients, some of which were life threatening or fatal. After Kymriah administration observe patient and ensure prompt management in case of signs of infection **Risk of febrile neutropenia:** Frequently observed after Kymriah infusion, may be concurrent with CRS. Appropriate management necessary. **Risk of prolonged cytopenias**: Appropriate management necessary. Prolonged cytopenia has been associated with increased risk of infections. Myeloid growth factors, particularly granulocyte macrophage colony stimulating factor (GM CSF), not recommended during the first 3 weeks after Kymriah infusion or until CRS has been resolved. **Risk of secondary malignancies**: Patients treated with Kymriah may develop secondary malignancies or recurrence of their cancer and should be monitored life-long for secondary malignancies. **Risk of hypogammaglobulinemia or agammaglobulinemia**: Infection precautions, antibiotic prophylaxis and immunoglobulin replacement should be managed per age and standard guidelines. In patients with low immunoglobulin levels preemptive measures such as immunoglobulin replacement and rapid attention to signs and symptoms of infection should be implemented. **Live vaccines:** The safety of immunisation with live viral vaccines during or following Kymriah treatment was not studied. Vaccination with live virus vaccines is not recommended at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Kymriah treatment, and until immune recovery following treatment with Kymriah. **Risk of tumor lysis syndrome (TLS)**: Patients with elevated uric acid or high tumor burden should receive allopurinol or alternative prophylaxis prior to Kymriah infusion. Continued monitoring for TLS following Kymriah administration should also be performed. **Concomitant disease**: Patients with a history of active CNS disorder or inadequate renal, hepatic, pulmonary or cardiac function are likely to be more vulnerable to the consequences of the adverse reactions of Kymriah and require special attention. **Prior stem cell transplantation**: Kymriah infusion is not recommended within 4 months of undergoing an allogeneic stem cell transplant (SCT) because of potential risk of worsening GVHD. Leukapheresis for Kymriah manufacturing should be performed at least 12 weeks after allogeneic SCT. **Serological testing**: There is currently no experience with manufacturing Kymriah for patients testing positive for HBV, HCV and HIV. Screening for HBV, HCV and HIV, must be performed before collection of cells for manufacturing. Hepatitis B virus (HBV) reactivation, can occur in patients treated with medicinal products directed against B cells and could result in fulminant hepatitis, hepatic failure and death. **Prior treatment with anti CD19 therapy**: There is limited experience with Kymriah in patients exposed to prior CD19 directed therapy. Kymriah is not recommended if the patient has relapsed with CD19 negative leukaemia after prior anti-CD19 therapy. **Interference with serological testing**: Due to limited and short spans of identical genetic information between the lentiviral vector used to create Kymriah and HIV, some commercial HIV nucleic acid tests (NAT) may give a false positive result. **Sodium and potassium content:** This medicinal product contains 24.3 to 121.5 mg sodium per dose, equivalent to 1 to 6% of the WHO recommended maximum daily intake of 2 g sodium for an adult. This medicinal product contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially “potassium free”. **Content of dextran 40 and dimethyl sulfoxide (DMSO)**: Contains 11 mg dextran 40 and 82.5 mg dimethyl sulfoxide (DMSO) per mL. Each of these excipients are known to possibly cause anaphylactic reaction following parenteral administration. Patients not previously exposed to dextran and DMSO should be observed closely during the first minutes of the

infusion period.

Interaction with other medicinal products and other forms of interaction

Live vaccines: The safety of immunisation with live viral vaccines during or following Kymriah treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Kymriah treatment, and until immune recovery following treatment with Kymriah.

Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females: Pregnancy status for females of reproductive potential should be verified prior to starting treatment with Kymriah. Consider the need for effective contraception in patients who receive the lymphodepleting chemotherapy. There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with Kymriah.

Pregnancy: There are no data from the use of Kymriah in pregnant women. It is not known whether Kymriah has the potential to be transferred to the foetus via the placenta and could cause foetal toxicity, including B cell lymphocytopenia. Kymriah is not recommended during pregnancy and in women of childbearing potential not using contraception. Pregnant women should be advised on the potential risks to the foetus. Pregnancy after Kymriah therapy should be discussed with the treating physician. Pregnant women who have received Kymriah may have hypogammaglobulinaemia. Assessment of immunoglobulin levels is indicated in newborns of mothers treated with Kymriah.

Breast feeding: It is unknown whether Kymriah cells are excreted in human milk, a risk to the breast fed infant cannot be excluded. Women who are breast feeding should be advised of the potential risk to the breast fed infant. Breast-feeding should be discussed with the treating physician.

Fertility: There are no data on the effect of Kymriah on fertility.

Effects on ability to drive and use machines
Driving and engaging in hazardous activities in the 8 weeks following infusion should be refrained due to risks for altered or decreased consciousness or coordination.

Adverse drug reactions:

B-Cell ALL patients and DLBCL patients:

Very common (≥10%): Infections - pathogen unspecified, viral infections, bacterial infections, fungal infections, anaemia, haemorrhage, febrile neutropenia, neutropenia, thrombocytopenia, cytokine release syndrome, hypogammaglobulinaemia, decreased appetite, hypokalaemia, hypophosphataemia, hypomagnesaemia, hypocalcaemia, anxiety, delirium, sleep disorder, headache, encephalopathy, arrhythmia, hypotension, hypertension, cough, dyspnoea, hypoxia, diarrhoea, nausea, vomiting, constipation, abdominal pain, rash, arthralgia, acute kidney injury, pyrexia, fatigue, oedema, pain, chills, lymphocyte count decreased, white blood cell count decreased, haemoglobin decreased, neutrophil count decreased, platelet count decreased, aspartate aminotransferase increased.

Common (1 to 10%): Haemophagocytic lymphohistiocytosis, leukopenia, pancytopenia, coagulopathy, lymphopenia, infusion-related reactions, graft versus host disease, hypoalbuminaemia, hyperglycaemia, hyponatraemia, hyperuricaemia, fluid overload, hypercalcemia, tumor lysis syndrome, hyperkalaemia, hyperphosphataemia, hypernatraemia, hypermagnesaemia, dizziness, peripheral neuropathy, tremor, motor dysfunction, seizure, speech disorder, neuralgia, ataxia, visual impairment, cardiac failure, cardiac arrest, thrombosis, capillary leak syndrome, oropharyngeal pain, pulmonary oedema, nasal congestion, pleural effusion, tachypnea, acute respiratory distress syndrome, stomatitis,

abdominal distension, dry mouth, ascites, hyperbilirubinaemia, pruritus, erythema, hyperhidrosis, night sweats, back pain, myalgia, musculoskeletal pain, influenza-like illness, asthenia, multiple organ dysfunction syndrome, alanine aminotransferase increased, blood bilirubin increased, weight decreased, serum ferritin increased, blood fibrinogen decreased, international normalized ratio increased, fibrin D dimer increased, activated partial thromboplastin time prolonged, blood alkaline phosphate increased, prothrombin time prolonged.

Uncommon: B-cell aplasia, ischaemic cerebral infarction, flushing, lung infiltration.

Packs and prices: Country-specific.

Legal classification: Country-specific.

Disclaimer

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About Novartis

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References

1. Kymriah (tisagenlecleucel) Summary of Product Characteristics (SmPC), 2018.

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