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Novartis receives European Commission approval of its CAR-T cell therapy, Kymriah® (tisagenlecleucel)

- *The EC approval is based on the first global CAR-T registration trials, which included patients from eight European countries and demonstrated durable responses and a consistent safety profile in r/r pediatric B-cell ALL and r/r DLBCL*

- *Novartis is the only company with an approved CAR-T cell therapy for pediatric r/r B-cell ALL and the first to receive approval in two distinct indications, both in the EU and the US*

- *Novartis continues its strategy to expand manufacturing facilities with agreements with external collaborators, such as CELLforCURE in France*

Basel, August 27, 2018 – Novartis today announced that the European Commission (EC) has approved Kymriah® (tisagenlecleucel, formerly CTL019). The approved indications are for the treatment of pediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse; and 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. Kymriah – developed in collaboration with the University of Pennsylvania (Penn) – is a ground-breaking one-time treatment that uses a patient's own T cells to fight cancer, and the only chimeric antigen receptor T cell (CAR-T) therapy to receive regulatory approval in the EU for these two distinct B-cell malignancies. Kymriah was also the first CAR-T cell therapy ever approved by the US Food and Drug Administration (FDA).

“The Kymriah approval is a transformational milestone for patients in Europe in need of new treatment options,” said Liz Barrett, CEO, Novartis Oncology. “Novartis will continue to build a global infrastructure for delivering CAR-T cell therapies where none existed before – remaining steadfast in our goal of reimagining cancer.”

Kymriah, a cell dispersion for infusion with doses varying between 1.2 x 10^6 – 6 x 10^8 CAR-positive viable T cells, is a living medicinal product, manufactured individually for each patient by reprogramming the patient's own immune system cells. Kymriah is the only approved CAR-T cell therapy built using the 4-1BB costimulatory domain, which is critical for full activation of the therapy, enhancement of cellular expansion and durable persistence of the cancer-fighting cells.

This approval was based on the review of the only two global registration CAR-T clinical trials, JULIET and ELIANA, which included patients from eight European countries. In these trials, Kymriah demonstrated strong and durable response rates and a consistent safety profile in two difficult-to-treat patient populations[1]. In 2012, Novartis and Penn entered into a global collaboration to further research, develop and commercialize CAR-T cell therapies, including Kymriah, for the investigational treatment of cancers. This collaboration between industry and academia was the first-of-its-kind in CAR-T research and development.

“When the University of Pennsylvania and Novartis agreed to work together to develop CAR-T therapy, our main goal was clear and ambitious – to address unmet needs for patients and to extend, improve and save lives,” said Carl June, MD, the Richard W. Vague Professor in Immunotherapy in the Department of Pathology and Laboratory Medicine at Penn and Director of the Center for Cellular Immunotherapies in the Abramson Cancer Center. “We are

proud that our efforts in CAR-T now offer the European blood cancer community a breakthrough that brings new hope."

Kymriah was designated as an orphan medicinal product and is one of the first PRIME-designated therapies to receive EU approval; PRIME (PRIority MEdicines) is a program launched by the European Medicines Agency (EMA) to enhance support for the development of medicines that target an unmet medical need and help patients benefit as early as possible from therapies that may significantly improve their quality of life.

"Bringing Kymriah to patients in the EU advances the treatment paradigm in an unprecedented way and delivers a lifesaving therapy to young patients with ALL who have not been successfully treated with existing therapies, and who have limited options left[2]," said Prof. Peter Bader, Head of the Division for Stem Cell Transplantation and Immunology and Principal Investigator of the ELIANA study at the University Hospital for Children and Adolescents in Frankfurt/Main.

Both B-cell ALL and DLBCL are aggressive malignancies with significant treatment gaps for patients. In Europe, ALL accounts for approximately 80% of leukemia cases among children[3], and for patients who relapse from standard of care therapies, the outlook is poor[2]. This low survival rate is in spite of patients having to undergo multiple treatments, including chemotherapy, radiation, targeted therapy or stem cell transplant, and further highlights the need for new treatment options. DLBCL is the most common form of non-Hodgkin lymphoma, accounting for up to 40% of all cases globally[4]. For patients who relapse or don't respond to initial therapy, there are limited treatment options that provide durable responses, and survival rates are low for the majority of patients due to ineligibility for autologous stem cell transplant (ASCT) or because salvage chemotherapy or ASCT have failed[5].

Novartis expects to launch initially in the pediatric ALL indication, as we continue to ramp up capacity. Moreover, timing for Kymriah availability in each country will depend on multiple factors, including the onboarding of qualified treatment centers for the appropriate indications, as well as the completion of national reimbursement procedures. Training is already underway at key qualified treatment centers to facilitate safe and seamless delivery to patients; and Novartis continues to collaborate with national health and reimbursement authorities across Europe on a fair, value-based pricing approach that is sustainable for national healthcare systems.

As this innovative treatment is made available to more patients globally, Novartis has been actively pursuing options to expand manufacturing capabilities beyond our facility in Morris Plains, New Jersey. This includes our agreement with CELLforCURE, based in France and one of the first and largest contract development and manufacturing organizations (CDMOs) producing cell and gene therapies in Europe, the expanded alliance with Fraunhofer Institute – which currently supports the manufacturing of Kymriah for global clinical trials and for post approval manufacturing –, as well as technology transfer efforts to a CDMO in Japan.

About Kymriah ELIANA Pivotal Study
The EC approval of Kymriah in pediatric and young adult patients with r/r B-cell ALL is based on the pivotal Phase II ELIANA clinical trial, the first pediatric global CAR-T cell therapy registration study for Kymriah in children and young adults with r/r B-cell ALL. ELIANA was conducted in collaboration with the University of Pennsylvania and Children's Hospital of Philadelphia, evaluating Kymriah in patients in 25 centers in the US, Canada, Australia, Japan, and in Europe, in Austria, Belgium, France, Germany, Italy, Norway and Spain.

In this Novartis-sponsored, global, multi-center study evaluating 75 patients infused with Kymriah with three or more months of follow-up, 81% of patients achieved overall remission (95% CI: 71% - 89%) with 80% of responders still in remission at 6 months. Sixty percent of patients achieved complete response (CR) and 21% of patients achieved CR with incomplete

blood count recovery (CRi). Of those patients in remission, 100% had no minimal residual disease (MRD) detected in the bone marrow[1]. Overall survival (OS) was 90% at six months, and 76% at 12 months. Median OS was 19.1 months (95% CI: 15.2 - NE) in this difficult-to-treat patient population.

In ELIANA, 47% percent of patients experienced Grade 3 or 4 CRS. CRS was managed according to the global CRS management protocol at clinical sites adequately trained for the safe administration and management of Kymriah. There were two deaths within 30 days of Kymriah infusion: one due to progressive disease with CRS and one death with resolving CRS from intracranial hemorrhage. Within eight weeks of treatment, 13% of patients experienced Grade 3 or 4 neurological events. The most common severe (Grade 3 or 4) neurological events were encephalopathy and/or delirium. Severe (Grade 3 or 4) febrile neutropenia and infection occurred in 36% and 44% of patients, respectively[1].

About Kymriah JULIET Pivotal Study
The EC approval of Kymriah in adult patients with r/r DLBCL is based on the pivotal Phase II JULIET clinical trial, the first multi-center global registration study for Kymriah in adult patients with r/r DLBCL. JULIET was conducted in collaboration with the University of Pennsylvania, and is the largest study examining a CAR-T therapy in DLBCL, enrolling patients from 27 sites in 10 countries across the US, Canada, Australia, Japan, and Europe in Austria, France, Germany, Italy, Norway and the Netherlands. In the JULIET trial, patients were infused in the inpatient and outpatient setting.

In this Novartis-sponsored, global, multi-center study, among 93 evaluable patients who were followed for at least three months or discontinued earlier, Kymriah demonstrated an overall response rate (ORR) of 52% (95% confidence interval [CI], 41% - 62%), with 40% achieving a complete response (CR) and 12% achieving a partial response (PR). The relapse-free probability at 6 and 12 months was 68% and 65%, respectively; and the median duration of response was not reached at the time of data cut-off, indicating sustainability of response[1]. The OS rate at 12 months was 49% and median OS was 11.7 months among all infused patients (n=111) (95% CI, 6.6-NE).

In JULIET, 22% of all treated patients experienced Grade 3 or 4 CRS within eight weeks of infusion with Kymriah, as defined by the Penn Grading Scale, a rigorous scale for grading CRS. CRS was successfully managed globally using site education on implementation of the CRS treatment protocol. Twelve percent of patients had Grade 3 or 4 neurologic adverse events, which were managed with supportive care. Grade 3 or 4 cytopenias lasting more than 28 days were reported based on laboratory findings and included thrombocytopenia (41%), lymphopenia (28%), neutropenia (24%), leukopenia (21%) and anemia (14%), Grade 3 or 4 infections and Grade 3 or 4 febrile neutropenia occurred in 32% and 15% of patients, respectively[1].

Important Safety information from the Kymriah SmPC
Kymriah (tisagenlecleucel) is an autologous, immunocellular cancer therapy which involves reprogramming a patient's own T-cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19-expressing cells. It is administered as intravenous infusion.

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

Kymriah must not be administered in case of hypersensitivity to the active substance or to any of the excipients of the product. In addition, contraindications of the lymphodepleting chemotherapy that is usually preceding the Kymriah infusion to prepare the patient's body, must be considered.

For details please see the Summary of Product Characteristics (SmPC).

Reasons to delay Kymriah treatment
Kymriah treatment 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 leukemia burden or lymphoma following lymphodepleting chemotherapy.

Monitoring after Kymriah infusion
Kymriah may cause side effects that could be severe, life-threatening or fatal. Therefore, 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 hospitalization for the first 10 days post infusion or at the first signs/symptoms of cytokine release syndrome 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 (i.e., 2 hours of travel) of a qualified clinical facility for at least 4 weeks following infusion. They should be advised to contact their healthcare provider right away, if they experience any of signs and symptoms of cytokine release syndrome, neurological events, infections and tumor lysis syndrome or if other severe or serious side effects occur.

Patients are advised to take their body temperature twice a day for 3-4 weeks after treatment with Kymriah, and if the temperature is high to contact their doctor immediately.

Important side effects
Kymriah may cause side effects that could be severe, life-threatening or fatal. They usually happen in the first eight weeks after the infusion, but can also develop later. The following main side effects can occur after Kymriah infusion:

Cytokine release syndrome has been frequently observed and almost always occurred within the first 10 days after Kymriah infusion. Patients may experience high fever, chills, difficulty breathing, nausea, vomiting, diarrhea, muscle pain, joint pain, low blood pressure, dizziness/light headedness, and issues with blood coagulation. Adverse reactions of multiple body organs, such as the heart, the liver or kidney, may occur.

Neurological events, in particular encephalopathy, confusional state or delirium, can occur frequently with Kymriah. Other manifestations can also include altered or decreased consciousness, agitation, seizures, difficulty speaking, understanding speech, or loss of balance. The majority of neurological events occurred within eight weeks following Kymriah infusion and were transient. Because of the risk of neurological side effects, patients should not drive, operate heavy machinery, or do other activities that require alertness for eight weeks after receiving Kymriah.

Infections can occur frequently after Kymriah infusion. As appropriate, prophylactic antibiotics should be administered and surveillance testing should be employed prior to and during treatment with Kymriah. Infections are known to complicate the course and management of concurrent cytokine release syndrome. Vaccination with live virus vaccines is not recommended at least six weeks prior to the start of lymphodepleting chemotherapy, during Kymriah treatment, and until immune recovery following treatment with Kymriah.

Febrile neutropenia was frequently observed in patients after Kymriah infusion. In the event of febrile neutropenia, infection should be evaluated and managed appropriately with broad-spectrum antibiotics, fluids and other supportive care, as medically indicated.

Tumor lysis syndrome is a rapid breakdown of tumor cells and release of their contents into the bloodstream. This can interfere with the workings of various body organs, especially the kidneys, heart and nervous system. To minimize risk of tumor lysis syndrome, patients with elevated uric acid or high tumor burden should receive allopurinol, or an alternative prophylaxis, prior to Kymriah infusion.

Prolonged cytopenias, which is a low count of one or more types of blood cells such as red blood cells, white blood cells, or platelets, can persist for several weeks following Kymriah. The majority of patients who had cytopenias at day 28 following Kymriah treatment improved or resolved within three months after treatment. Prolonged neutropenia has been associated with increased risk of infection.

Hypogammaglobulinemia or Agammaglobulinemia, a condition in which the level of immunoglobulins (antibodies) in the blood is low and the risk of infections is increased, can occur in patients treated with Kymriah. Infection precautions, antibiotic prophylaxis and immunoglobulin replacement should be managed per age and standard guidelines.

Secondary malignancies: After treatment with Kymriah, patients will be monitored life-long by their healthcare provider, as they may develop secondary cancers.

Pregnancy and breast-feeding: It is not known, whether Kymriah has the potential to be transferred to the fetus via the placenta and could cause fetal toxicity, including B-cell lymphocytopenia. Kymriah is not recommended during pregnancy and in women of childbearing potential not using contraception. It is unknown, whether Kymriah is 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.

Blood, organ, tissue and cell donation: Patients treated with Kymriah should not donate blood, organs, tissues and cells for transplantation.

Please see the full Summary of Product Characteristics (SmPC) for KYMRIAH, www.KYMRIAH.com

Disclaimer

This press release contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements can generally be identified by words such as “launches,” “launching,” “strategy,” “potential,” “can,” “will,” “plan,” “expect,” “investigational,” “launched,” “transformational milestone,” “goal,” “breakthrough,” “hope,” “may,” “underway,” or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for Kymriah, regarding our ability to scale and sustain commercial manufacturing for Kymriah, regarding our ability to onboard and sustain a network of qualified treatment centers, regarding our ability to obtain reimbursement approval from national health and reimbursement authorities, or regarding potential future revenues from Kymriah. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that Kymriah will be submitted or approved for sale or for any additional indications or labeling in any market, or at any particular time. Neither can there be any guarantee that we will successfully scale and sustain commercial manufacturing for Kymriah, or successfully onboard and sustain a network of qualified treatment centers to offer Kymriah. Nor can there be any guarantee that we will

successfully obtain reimbursement approval for Kymriah from relevant national health and reimbursement authorities, or at any particular time. Neither can there be any guarantee that Kymriah will be commercially successful in the future. In particular, our expectations regarding Kymriah could be affected by, among other things, our ability to successfully scale and sustain commercial manufacturing; our ability to onboard and sustain a network of treatment centers; our ability to obtain reimbursement approval from national health and reimbursement authorities; the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; regulatory actions or delays or government regulation generally; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; general political and economic conditions; safety, quality or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

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Novartis provides innovative healthcare solutions that address the evolving needs of patients and societies. Headquartered in Basel, Switzerland, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, cost-saving generic and biosimilar pharmaceuticals and eye care. Novartis has leading positions globally in each of these areas. In 2017, the Group achieved net sales of USD 49.1 billion, while R&D throughout the Group amounted to approximately USD 9.0 billion. Novartis Group companies employ approximately 125,000 full-time-equivalent associates. Novartis products are sold in approximately 155 countries around the world. For more information, please visit http://www.novartis.com.

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