Taiwan Food and Drug Administration

Assessment Report

Trade Name：祈萊亞靜脈輸注用懸浮液/ Kymriah suspension for intravenous infusion

Active Ingredient：Tisagenlecleucel

License Number：MOHW-BI 001176

Applicant：台灣諾華股份有限公司

Approval Date：2021.9.23

Indication：

Kymriah 是一種經過基因修飾的自體免疫細胞療法，適用於治療：

(1) 患有難治型、移植後復發、第二次或二次以上復發之 B 細胞急性淋巴性白血病（ALL）的 25 歲以下兒童和年輕成人病人。

(2) 經兩線或兩線以上全身治療後之復發性或難治性瀰漫性大 B 細胞淋巴瘤（DLBCL）的成人病人。

KYMRIAH is a genetically modified autologous T-cell immunotherapy indicated for the treatment of:

1. **Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.**
2. **Adult patients with relapsed or refractory large diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.**

Background Information

Trade Name	祈萊亞靜脈輸注用懸浮液 / Kymriah suspension for intravenous infusion
Active Ingredient(s)	Tisagenlecleucel
Applicant	台灣諾華股份有限公司
Dosage Form & Strengths	注射劑 $1.2x10^6$-$6x10^8$ cells dispersion for infusion
Indication	Kymria 是一種經過基因修飾的自體免疫細胞療法，適用於治療： 1. 患有難治型、移植後復發、第二次或二次以上復發之B細胞急性淋巴性白血病（ALL)的25歲以下兒童和年輕成人病人。 2. 經兩線或兩線以上全身治療後之復發性或難治性瀰漫性大 B 細胞淋巴瘤（DLBCL）的成人病人。 KYMRIAH is a genetically modified autologous T-cell immunotherapy indicated for the treatment of: 1. Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. 2. Adult patients with relapsed or refractory large diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.
Posology	詳見中文仿單擬稿。
Pharmacological Category **ATC Code**	L01XX71

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

Tisagenlecleucel is an autologous, immuno-cellular cancer therapy which involves reprogramming a patient's own T cells with a transgene using a lentiviral vector. The transgene encodes a chimeric antigen receptor (CAR) to identify and eliminate CD19 expressing cells. The CAR is comprised of a single chain antibody fragment which recognizes CD19, followed by a CD8 hinge and transmembrane region which is fused to intracellular signaling domains from 4-1BB (CD137) and CD3 zeta. The CD3 zeta component is critical for initiating T cell activation and antitumor activity while 4-1BB enhances the expansion and persistence of tisagenlecleucel. Expression of CD19 is restricted to B cells and their precursors with the exception of pluripotent hematopoietic stem cells, and is expressed on most B cell

malignancies. Upon binding to CD19 expressing cells, the CAR transmits a signal to promote T cell expansion, activation, target cell elimination and persistence of tisagenlecleucel.

Manufacturing

Tisagenlecleucel is prepared from the peripheral blood mononuclear cells collected from each patient by leukapheresis procedure. The obtained mononuclear cells are enriched for T cells, which are then transduced with a lentiviral vector containing a transgene encoding CAR directed against human CD19 (CTL019 vector). The transduced T cells are then expanded in culture, adjusted to final formulation formulated, and cryopreserved.

The excipients for tisagenlecleucel solution contain Plasma-Lyte A, dextrose and sodium chloride, human serum albumin, dextran 40, DMSO and water for injection.

Controls

The materials used the viral vector manufacturing and raw and starting materials used in the manufacturing process as well as quality standards are presented. The generation of the production cell and the expression plasmids are described in detail. The in-process controls and critical process parameter including the product related impurities, replication competent lentivirus (RCL) are provided sufficiently.

In addition, the results of tests for adventitious agents and the risk evaluation for transmission of TSE/BSE are considered acceptable.

Characterization

Information on vector characterization, immunological, phenotypic and biological properties characterization as well as the potential produced- and process-related impurities have been analyzed and are considered sufficiently controlled.

Specification

The release testing of tisagenlecleucel includes identity, appearance, purity, potency, impurities, quantity, biological activity and contaminants. The proposed specifications are considered adequate and acceptable.

Process validation

The validation of the manufacturing processes for CTL019 vector and tisagenlecleucel was carried out. Results obtained from these batches meet the pre-defined criteria and demonstrate

the process consistency. The results of shipping validation study were also provided to state that no noticeable impact of the transport on product quality, container closure integrity, stability and suitability of the packaging.

Stability

The stability data revealed that tisagenlecleucel is stable under storage condition for 9 months at the long-term storage condition (≤ -120°C in vapor phase liquid nitrogen).

For post thawed final product, the acceptable in-use time period is 30 minutes at 20 - 25°C and 1 hour at 5°C. The 37°C temperature is not recommended for the in-use period.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

In vitro pharmacology studies demonstrated that (1) tisagenlecleucel scFv is specific for CD19, (2) αCD19 CAR^+ T cells kill both laboratory-engineered and primary tumor cell lines, (3) an intact CD3ζ domain is required for CAR-mediated killing and cytokine production and (4) 4-1BB costimulatory domain provides enhanced proliferative and survival capacity.

In vivo pharmacology studies demonstrated that (1) reduction of leukemia burden by αCD19 CAR T cells, which is dependent upon an intact CD3ζ domain, (2) tisagenlecleucel mediates durable control of leukemia (>6 months), and (3) tisagenlecleucel has a survival advantage conferred by the 4-1BB costimulatory domain.

2.2.2 Toxicological Studies

Standard safety studies (including safety pharmacology and toxicology) conducted for biological drugs was not applicable for tisagenlecleucel. The main areas of potential concern for tisagenlecleucel included (1) malignant transformation of transduced T cells by insertional mutagenesis, (2) abnormal tissue distribution behavior, and (3) unwanted cell/tissue cytotoxicity mediated by the transgene product on the cell surface.

In the in vitro studies, there was no clonal dominance or immortalization observed. In addition, no signs of hyperproliferation in the blood compartment or perfused tissues related to tisagenlecleucel were observed in the in vivo mouse study. Two independent lentivirus insertion site analyses showed that all these tisagenlecleucel products were highly polyclonal and did not reveal evidence for preferential integration near genes of concern, nor preferential outgrowth of cells harboring integration sites of concern. In the mouse model, tisagenlecleucel persisted and/or expanded after administration and distributed throughout the body. The risks of abnormal cell-toxic behavior, derailed cell growth control, and abnormal biodistribution in vivo have been addressed in an immunocompromised mouse model xenografted with human ALL tumor. Cross-reactivity to CD19 expressed on tissues different from B lymphocytes is

extremely unlikely because CD19 is exclusively expressed by these cells. The human cell surface protein array did not reveal any binding other than to CD19. No gene expression of CD19 was detected in human and monkey brain tissues, and there was no specific binding of the CD19-specific scFv of the tisagenlecleucel CAR.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

In this submission, three Phase II, single arm, open-label, multi-national, multi-center studies were provided to support the efficacy of Kymriah for the claimed indications. Study [CCTL019C2201] was conducted in adult patients with r/r DLBCL. Study [CCTL019B2202] and [CCTL019B2205J] were conducted in pediatric and young adult patients with r/r B-cell ALL and B-cell lymphoblastic lymphoma. Key efficacy findings for these three studies are summarized below.

- ***Study [CCTL019C2201]***

The primary efficacy endpoint was IRC-assessed overall response rate, defined as complete response + partial response based on the Lugano Classification, in subjects treated with Kymriah from the US manufacturing facility (Main Cohort).

At the pre-planned interim analysis (20-Dec-2016) from first 51 subjects in the Main Cohort who received Kymriah infusion and were followed for at least 3 months, the IRC-assessed overall response rate was 58.8% (95% confidence interval [CI]: 44.2%, 72.4%) with a *p*-value < 0.0001 to reject H_0: overall response rate ≤ 20%. As the *p*-value was less than the 1-sided critical alpha level of 0.0047, the study met its primary objective at the interim analysis.

At updated analysis (11-Dec-2018), the IRC-assessed overall response rate from 99 subjects was 53.5% (95% CI: 43.2%, 63.6%) and demonstrated consistent result.

- ***Study [CCTL019B2202]***

The primary efficacy endpoint was IRC-assessed overall remission rate during the 3 months after Kymriah administration, which included complete remission and complete remission with incomplete blood count recovery.

One pre-planned interim analysis (17-Aug-2016) was conducted when 50 subjects treated with Kymriah had been followed for at least 3 months or discontinued early. The IRC-assessed overall remission rate was 82.0% (98.9% exact CI: 64.5%, 93.3%). As the lower bound of the 98.9% exact CI was greater than the pre-defined threshold of 20%, the study met its primary objective at this interim analysis. Three key secondary objectives were also met at the interim analysis. The IRC-assessed overall remission rate during 3 months from US manufacturing facility was 82.0% (98.9% CI: 64.5%, 93.3%) with the lower 98.9% exact exceeded the pre-

defined margin of 20%. The proportion of patients who achieved overall remission per IRC during 3 months post-Kymriah infusion and bone marrow minimal residual disease (MRD) negative (MRD < 0.01%) was 82% (98.9% exact CI 64.5%, 93.3%) for all manufacturing facility and for the US manufacturing facility. The lower 98.9% exact CIs exceeded the pre-defined margin of 15%.

The updated analysis (13-Apr-2018), which included 79 subjects, demonstrated the overall remission rate per IRC during 3 months post-Kymriah infusion of 82.3% (95% CI: 72.1%, 90.0%) and was consistent with the pre-planned interim analysis.

- ***Study [CCTL019B2205J]***

The primary efficacy endpoint was IRC-assessed overall remission rate during the 6 months after Kymriah administration, which included complete remission and complete remission with incomplete blood count recovery.

At the pre-planned interim analysis (1-Feb-2016), the IRC-assessed overall remission rate was 69.0% (98.95% exact CI: 43.6%, 88.1%). As the lower bound of the 98.95% exact CI was greater than 20%, the study met its primary objective at interim analysis.

At the updated analysis (6-Oct-2017), the IRC-assessed ORR was 69.0% (95% exact CI: 52.9%, 82.4%), further supported the primary interim analysis.

2.4.2 Safety Results

The safety results were based on Study [CCTL019B2202] and [CCTL019C2201]. The majority of subjects experienced Grade 3/4 adverse events (AEs) and serious AEs (SAEs) after Kymriah infusion in both studies.

The most important AEs observed in clinical studies of Kymriah included cytokine release syndrome (CRS) and related symptoms, serious neurological AEs, hematological cytopenia, infections, and hypogammaglobulinemia.

CRS was the most commonly reported AE, Grade 3/4 AE, and SAE. A proportion of subjects with CRS required admission to intensive care unit, intubation with ventilator support, hemodynamic support or dialysis. The majority of CRS occurred within 8 weeks after Kymriah infusion. High tumor burden was a risk factor for CRS.

Serious neurological AEs could be related CRS. Although most subjects with serious neurological AEs had improved in clinical studies of Kymriah, fatal case was reported in the clinical studies of another anti-CD19 CAR-T product.

Hematological cytopenia and infections were commonly encountered in patients with hematological malignancies. Patients treated with B cell-directed therapy had risk of hypogammaglobulinemia and immunoglobulin replacement therapy should be considered.

The safety data observed currently were limited by low number of patients exposed in clinical studies and short duration of follow-up. Long-term safety data, such as generation of replication competent lentivirus or secondary malignancies were necessary with continuous monitor.

Fourteen Asian (14) subjects with acute lymphoblastic leukemia and 10 Asian subjects with diffuse large B cell lymphoma received Kymriah infusion in Study [CCTL019B2202], [CCTL019B2205J], and [CCTL019C2201]. The efficacy and safety results were generally consistent between Asian and non-Asian subjects.

2.6 Conclusion

Based on the above multidiscipline review and discussion in the Advisory Committee, the benefit-risk assessment for Kymriah for the proposed indications is positive. Approval of Kymriah is recommended. Risk Management Plan (RMP) is necessary to assure safe use.

3. Post-Marketing Requirements

- Submit the final clinical study report of Study [CCTL019C2201], [CCTL019B2202] and [CCTL019H2301]
- Implement the RMP, including the global long-term follow-up Study [CCTL019B2401]. At least 10 Taiwanese patients will be enrolled and followed for 15 years.