Taiwan Food and Drug Administration

Assessment Report

Trade Name：

力汰瘤濃縮輸注液/

Libtayo concentrate for solution for infusion

Active Ingredient：Cemiplimab

License Number：MOHW-BI 001233

Applicant：賽諾菲股份有限公司 / Sanofi Taiwan Co., Ltd.

Approval Date：2023.07.07

Indication：

LIBTAYO 單一療法用於第一線治療有 PD-L1 表現(Tumor Proportion Score [TPS]≥50%)且無 EGFR、ALK 或 ROS1 基因異常之局部晚期(且不適合手術切除或接受根除性化學放射治療)或轉移性非小細胞肺癌 (NSCLC)成人病人。

LIBTAYO as monotherapy is indicated for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing PD-L1 (Tumor Proportion Score [TPS]≥50%), with no EGFR, ALK or ROS1 aberrations, who have:

- **locally advanced NSCLC who are not candidates for surgical resection or definitive chemoradiation, or**
- **metastatic NSCLC.**

Background Information

Trade Name	力汰瘤濃縮輸注液 50 毫克/毫升 / Libtayo 50mg/ml concentrate for solution for infusion
Active Ingredient(s)	Cemiplimab
Applicant	賽諾菲股份有限公司 / Sanofi Taiwan Co., Ltd.
Dosage Form & Strengths	注射液劑
Indication	LIBTAYO 單一療法用於第一線治療有 PD-L1 表現(Tumor Proportion Score [TPS]≥50%)且無 EGFR、ALK 或 ROS1 基因異常之局部晚期(且不適合手術切除或接受根除性化學放射治療)或轉移性非小細胞肺癌 (NSCLC)成人病人。 LIBTAYO as monotherapy is indicated for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing PD-L1 (Tumor Proportion Score [TPS]≥50%), with no EGFR, ALK or ROS1 aberrations, who have: ● locally advanced NSCLC who are not candidates for surgical resection or definitive chemoradiation, or ● metastatic NSCLC.
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Pharmacological Category ATC Code	L01FF06

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Cemiplimab is a recombinant human IgG4 isotype monoclonal antibody that binds specifically to programmed cell death 1 receptor (PD-1) blocking the interaction with its ligands, PD-L1 and PD-L2.

Cemiplimab is produced using CHO cell lines. Cemiplimab DS is manufactured under current good manufacturing practice. Manufacturing process is sufficiently described including the material inputs, critical process parameters, and process outputs (in-process controls, microbial controls, and performance attributes) and supported process robustness, as demonstrated during process validation. The structural, physiochemical and biological characterization of Cemiplimab are considered sufficient. Process-related impurities and product-related impurities are well-controlled. Controls of raw materials are considered adequate to ensure the

safety of Cemiplimab.

The specification of Cemiplimab DS is provided and the acceptance criteria is well-justified. All batch results are within acceptable criteria to demonstrate DS quality consistency. In addition, CoAs show that analytical results meet specification requirements. The stability data provided are enough to support the proposed shelf life and storage conditions for Cemiplimab.

2.1.2 Drug product

Cemiplimab is the active ingredient in LIBTAYO®. LIBTAYO®, is provided as a sterile, preservative-free, clear to slightly opalescent solution intended for intravenous infusion. The drug product is formulated as 50 mg/mL Cemiplimab which is supplied in a single-use 10 mL glass vial equipped with an elastomeric stopper and aluminum seal cap with a flip-off button. Each vial contains 350 mg/7 mL Cemiplimab.

Details of formulation development and manufacturing process development are provided. The drug product manufacturing process is sufficiently described and in-process controls are considered adequate. The compatibility and safety of the container closure system are demonstrated by stability study. The release and stability specifications for Cemiplimab drug product are acceptable. The results of accelerated stability and long-term stability data are provided and supported 36 months of shelf-life for DP stored at 5 ± 3 °C, and protected from light.

In summary, the information on the drug substance and drug product is sufficiently provided.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Pharmacology data showed that cemiplimab has a high affinity to the human PD-1 and blocks the interaction with its endogenous ligands, PD-L1 and PD-L2. REGN2810 was also shown to antagonize PDL1-mediated TCR signaling in vitro. In vivo studies in PD-1-humanized mice demonstrated inhibition of syngeneic MC38 tumor growth by cemiplimab. Safety pharmacology endpoints were integrated into repeated-dose toxicology studies in cynomolgus monkeys. In these studies, no drug-related adverse effects were observed in cardiovascular, respiratory, or central nervous system (CNS) function, nor were any deleterious microscopic changes observed in tissues associated with these systems following intravenous (IV) dosing of cemiplimab at 2, 10 or 50 mg/kg/week for up to 6 months.

2.2.2 Toxicological Studies

In 4-week and 26-week repeated-dose toxicity studies, there were no adverse effects of cemiplimab in monkeys receiving doses of up to 50 mg/kg/week. The observed ADA response is considered the result of administering a heterologous human protein to monkeys and is not

necessarily predictive of responses to cemiplimab in humans. The NOAEL of the 26-week repeated-dose toxicity study was 50 mg/kg/week, providing an approximately 9.6-fold safety margin base on AUC.

In the 13-week fertility assessment toxicology study performed in sexually mature cynomolgus monkeys, there were no REGN2810-related microscopic findings in male or female reproductive tissues or fertility parameters, nor were any effects of REGN2810 exposure observed for either sex. According to ICH S6 and ICH S9, the absence of genotoxicity and carcinogenicity studies is agreed since cemiplimab is an antibody not expected to interact with DNA or to be carcinogenic.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Cemiplimab pharmacokinetic data were collected in 1062 patients with various solid tumors in a population pharmacokinetic analysis. The pharmacokinetics of cemiplimab were linear and dose proportional in the dose range of 1 mg/kg to 10 mg/kg LIBTAYO administered intravenously every 2 weeks. The volume of distribution of cemiplimab at steady state is 5.3 L (26%). Cemiplimab clearance (CV%) after the first dose is 0.29 L/day (33%) and decreases over time by 29%, resulting in a steady-state clearance (CLss) (CV%) of 0.20 L/day (40%). The elimination half-life (CV%) at steady state is 20.3 days (29%).

2.3.2 Interaction Studies

No pharmacokinetic drug-drug interaction studies have been conducted with cemiplimab.

2.3.3 Special Populations

The following factors have no clinically important effect on the exposure of cemiplimab: age (27 to 96 years), sex, body weight (31 to 172 kg), cancer type, albumin level (20 to 93 g/L), renal function (creatinine clearance determined by Cockcroft-Gault 21 mL/min or greater) and hepatic function (total bilirubin greater than 1.0 times up to 3.0 times the ULN). Race [White (N=931), Black (N=47), Asian (N=21)] appears to have no clinically important effect on the exposure of cemiplimab. LIBTAYO has not been studied in patients with severe hepatic impairment.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

In this submission, a Phase III, randomized, open-label, multi-national, multi-center study ([R2810-ONC-1624]) was conducted to support the efficacy of Libtayo for the first-line treatment of patients NSCLC whose tumors have high PD-L1 expression (Tumor Proportion Score (TPS)≧50%), with no EGFR, ALK or ROS1 aberrations and is locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or metastatic.

The primary endpoints for this study were OS and IRC-assessed PFS, and the key secondary efficacy endpoint was IRC-assessed ORR. Per the protocol, there were 5 pre-planned interim analyses for OS in addition to the final analysis. The results of pre-planned 2nd interim analysis (data cut-off date: 01 March 2020) of OS was the final analysis for this study. There were 249 deaths included in the analysis and the alpha spending for OS was adjusted to 0.00255.

Results based on pre-specified efficacy endpoints (OS, PFS and ORR) are primarily presented for the ITT population (N = 710), as well as for the mITT-1 (N = 563) and the mITT-2 (N = 475) populations.

Results of the ITT population (N = 710) are summarized below:

- The difference in IRC-assessed PFS between the two arms was statistically significant (stratified log-rank test p-value < 0.0001; HR = 0.593 [95% CI: 0.491 to 0.718]).
- The difference in OS between the two arms was statistically significant (stratified log-rank test p-value = 0.0022; HR = 0.676 [95% CI: 0.525 to 0.870]).
- The IRC-assessed ORR was 36.5% in the Libtayo arm versus 20.6% in the chemotherapy arm. The difference was statistically significant (stratified CMH test p-value < 0.0001).

Consistent results were observed from the mITT-1 and mITT-2 populations.

In summary, results from the pivotal study ([R2810-ONC-1624]) have provided sufficient evidence to support the efficacy of Libtayo for the claimed indication.

2.4.2 Safety Results

At the time of data cutoff for Study R2810-ONC-1624, 355 subjects were treated with cemiplimab for a median duration of 27.3 weeks and 342 subjects were treated with chemotherapy for a median duration of 17.7 weeks. The proportion of subjects with treatment-emergent adverse events (TEAEs) of any grade was lower in the cemiplimab arm (88.2%) compared to the chemotherapy arm (94.2%). The most common TEAEs (occurring in ≥ 10% of subjects) in the cemiplimab arm were anemia (14.6%), decreased appetite (11.8%), and fatigue (10.1%). The majority of TEAEs reported were of grade 1 or 2 in severity. Grade ≥ 3 TEAEs were reported in a lower proportion of subjects in the cemiplimab arm (37.2%) compared to the chemotherapy arm (48.5%).

Similar proportion of subjects experienced serious TEAEs in the cemiplimab arm (28.2%) compared to the chemotherapy arm (27.5%). In both arms, the most common serious TEAE was pneumonia (4.8% in the cemiplimab arm and 5.0% in the chemotherapy arm). The proportion of deaths due to TEAEs was similar between the cemiplimab arm (9.6%) and the chemotherapy arm (9.1%).

The proportion of subjects who discontinued study treatment due to TEAEs was slightly higher in the cemiplimab arm (6.5%) compared to the chemotherapy arm. The most common TEAE leading to discontinuation of cemiplimab was pneumonitis (1.1%).

Infusion reactions and immune-mediated AEs were well-known adverse reactions associated with immune-oncolgy (IO) therapies. In Study R2810-ONC-1624, 6.5% subjects treated with cemiplimab had infusion reactions and only 1 subject had a grade 3 dyspnea. Overall, 17.5% subjects in the cemiplimab arm experienced at least one immune-mediated adverse event (imAE). The most common imAEs included hypothyroidism (5.6%), hyperthyroidism (4.2%), pneumonitis (2.3%), hepatitis (1.7%), skin adverse reactions (1.4%), and colitis (1.1%). Few (3.7%) subjects had grade ≥ 3 imAEs and the most frequently reported grade ≥ 3 imAE was hepatitis (1.4%).

2.5 Bridging Study Evaluation

The population pharmacokinetic analysis result indicated that the exposure of cemiplimab is similar between Taiwan and non-Asian population. The steady-state C_{max} is 184 mg/L and the C_{trough} is 59 mg/L in Taiwan population. The steady-state C_{max} is 164 mg/L and the C_{trough} is 52 mg/L in non-Asian population. Another pharmacokinetics study conducted in Japanese also indicated the exposure of cemiplimab is similar between Japanese and Taiwan population. There is no significant difference in cemiplimab exposure between the race.

The clinical bridging study evaluation of cemiplimab was based on Study 1624 which was a multinational, multicenter, randomized, open-label, active controlled study in patients with advanced or metastatic non-small cell lung cancer (NSCLC).

A total of 710 subjects were enrolled (356 subjects in the cemiplimab arm and 354 subjects in the chemotherapy arm). Among these subjects, 77 (10.8%) subjects (39 [10.9%] subjects in the cemiplimab arm and 38 [10.7%] subjects in the chemotherapy arm) were from Asian countries (China, Malaysia, Philippines, Taiwan, and Thailand).

The efficacy and safety results were generally comparable between the Asian subgroup and the overall population.

In brief summary, the Sponsor submitted adequate data for evaluation and the bridging study of cemiplimab was waived.

2.6 Conclusion

Based on the above multidiscipline review, CDE review team leader recommends approval of cemiplimab (LIBTAYO®).

1. Recommended indication: LIBTAYO® as a single agent is indicated for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) whose tumors have PD-L1 expression (tumor proportion score ≥ 50%), with o EGFR, ALK or ROS1 aberrations, and is:
   (1) locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or
   (2) metastatic
2. The recommended does of cemiplimab is 350 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

3. Post-Marketing Requirements

Not required.