17 May 2021

WHO Expert Committee on the Selection and Use of Essential Medicines

Email: emlsecretariat@who.int

RE: Application for Inclusion of tislelizumab injectable solution for the treatment of relapsed/refractory (R/R) classical Hodgkin lymphoma (cHL) and locally advanced or metastatic urothelial bladder cancer in the next WHO List of Essential Medicine

Dear WHO Expert Committee:

As an inventor of tislelizumab, I am writing to provide you the scientific point of view and the discussions about the unique attribute of the PD-1 antibody engineered with removal of Fc effector function.

Beside the target modulation, PD-1 antibodies of IgG4 subtype also elicit Fcγ receptor-induced effector function. Tislelizumab was engineered to remove the effector function, therefore, preventing macrophage-mediated phagocytosis that may negatively impact the anti-cancer activity of $CD8^+$ T-cells (Zhang, T., et al., 2018). Recent studies cross examined the mechanism and impact of effector function to PD-1 antibodies. The results indicated that the effector function of PD-1 antibodies and activation of macrophage-mediated phagocytosis exerts adverse effect on PD-1 antibody therapeutic activity (Dahan, R., et al., 2015; Arlauckas, SP., et al., 2017; La Russo, G., et al., 2019).

The first pivotal study of tislelizumab completed for the treatment of relapsed/refractory classical Hodgkin lymphoma (r/r cHL) showed much better than expected clinical benefit to the late stage cHL patients (Song, Y., et al., 2020), which may be attributed to the fact that tislelizumab is an effector-functionless PD-1 antibody (Song, Y., et al., 2020 ASH).

In light of the unique feature and potentially better than expected clinical benefit, please make your considerations for inclusion of tislelizumab in Essential Medicine List.

Sincerely Yours

Kang Li, PhD

References:

1. Arlauckas SP, Garris CS, Kohler RH, Kitaoka M, Cuccarese MF, Yang KS, Miller MA, Carlson JC, Freeman GJ, Anthony RM, Weissleder R, Pittet MJ. In vivo imaging reveals a tumor-

2. Dahan R, Sega E, Engelhardt J, Selby M, Korman AJ, Ravetch JV. FcgammaRs **Modulate** the **Anti-tumor Activity** of **Antibodies Targeting** the PD-1/PD-L1 Axis. Cancer Cell. 2015 Sep 14;28(3):285-95. doi: 10.1016/j.ccell.2015.08.004. PMID: 26373277 **Free article.**

3. Lo Russo G, Moro M, Sommariva M, Cancila V, Boeri M, Centonze G, Ferro S, Ganzinelli M, Gasparini P, Huber V, Milione M, Porcu L, Proto C, Pruneri G, Signorelli D, Sangaletti S, Sfondrini L, Storti C, Tassi E, Bardelli A, Marsoni S, Torri V, Tripodo C, Colombo MP, Anichini A, Rivoltini L, Balsari A, Sozzi G, Garassino MC. Antibody-Fc/FcR Interaction on Macrophages as a Mechanism for Hyperprogressive Disease in Non-small Cell Lung Cancer Subsequent to PD-1/PD-L1 Blockade. Clin Cancer Res. 2019 Feb 1;25(3):989-999. doi: 10.1158/1078-0432.CCR-18-1390. Epub 2018 Sep 11.PMID: 30206165 **Free article.**

4. Song Y, Gao Q, Zhang H, Fan L, Zhou J, Zou D, Li W, Yang H, Liu T, Wang Q, Lv F, Guo H, Yang L, Elstrom R, Huang J, Novotny W, Wei V, Zhu J. Treatment of relapsed or refractory classical Hodgkin lymphoma with the anti-PD-1, tislelizumab: results of a phase 2, single-arm, multicenter study. Leukemia. 2020 Feb; 34(2):533-542. doi: 10.1038/s41375-019-0545-2. Epub 2019 Sep 13 **Free PMC article.**

5. Song Y et al., 2020 62nd ASH Oral and Poster Presentation #1116. Tumor Microenvironment Associated with Complete Response to Tislelizumab Monotherapy in Relapsed/ Refractory Classical Hodgkin Lymphoma Reveals a Potentially Different Mechanism of Action. Abstract:

   Conclusions: Tislelizumab demonstrated a high CR rate regardless of the FcγRI expressing macrophage abundance in the cHL tumor microenvironment, which may be a functional consequence of its engineered Fc region and may differentiate its MOA from the MOAs of other anti-PD-1 agents. CD8+ T-cell abundance and tumor inflammatory gene signatures in the microenvironment may be associated with higher CR rate for cHL patients treated with tislelizumab.

6. Zhang T, Song X, Xu L, Ma J, Zhang Y, Gong W, Zhang Y, Zhou X, Wang Z, Wang Y, Shi Y, Bai H, Liu N, Yang X, Cui X, Cao Y, Liu Q, Song J, Li Y, Tang Z, Guo M, Wang L, Li K. The binding of an **anti-PD-1 antibody** to FcgammaRiota has a profound impact on its biological functions. Cancer Immunol Immunother. 2018 Jul;67(7):1079-1090. doi: 10.1007/s00262-018-2160-x. Epub 2018 Apr 23.PMID: 29687231 **Free PMC article.**