Editorial

Optimal pembrolizumab dosing for non-small cell lung cancer: further studies still needed

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Provenance: This is an invited Editorial commissioned by Section Editor Dr. Shangwen Dong (Thoracic Oncology, Journal of Thoracic Disease, Tianjin Medical University General Hospital, Tianjin, China).

Comment on: Herbst RS, Baas P, Kim DW, *et al*. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387:1540-50.

Submitted Sep 18, 2017. Accepted for publication Oct 16, 2017.
doi: 10.21037/jtd.2017.10.152
View this article at: http://dx.doi.org/10.21037/jtd.2017.10.152

The advent of programmed cell death 1 (PD-1)/PD-1 ligand 1 (PD-L1) checkpoint inhibitors has made dramatic progress for the treatment of non-small cell lung cancer (NSCLC). In several series of clinical studies, anti-PD-1/PD-L1 antibodies have generated durable effects, leading to long-term survival with manageable toxicity for patients with advanced NSCLC (1-6). The potential of these agents to generate durable clinical responses has led to their rapid uptake as standard therapy.

Both pembrolizumab (Keytruda, Merck & Co., NJ, USA) and nivolumab (Opdivo, BMS, NJ, USA), which are highly selective anti-PD-1 humanized monoclonal IgG4 kappa isotype antibodies, can prevent PD-1 from engaging PD-L1 and PD-L2 and subsequently hinder inhibitory signals from T cells, allowing tumor cells recognized by cytotoxic T cells. In early clinical trials, to minimize individual variability, patients were treated with these two PD-1 inhibitors at doses based on weight. However, employing a uniform dose has become standard practice in furthermore trails and clinical practice (1-4,6-8). As an example, in previous clinical trials with pembrolizumab, the body weight scheme was used to evaluate its safety and response, but recent trials, such as KEYNOTE-024 (6), have used 200 mg every 3 weeks (Q3W). As a result of KEYNOTE-024, treatment with pembrolizumab 200 mg Q3W was approved as a first-line therapy for advanced NSCLC patients with PD-L1 expression by the USA Food and Drug Administration (FDA). Analogously, the FDA determined that a regimen with a fixed dose of 240 mg nivolumab was similar to 3 mg/kg dosing, and any differences were not clinically significant in safety or response (9).

However, controversies still remain regarding on optimal dosage and regimen. How to determine the optimum dose for these monoclonal antibodies is indeed a challenge. Two kinds of pharmacokinetic and pharmacodynamic (PK/PD) models have contributed to deciding the minimum dose in a clinical trial. The first evaluation is based on an immune-related biomarker (IL-2 release), and the second is a translational PK/PD model derived from the clinical response of anti-PD-1 antibodies in a preclinical study. An initial phase I trial demonstrated complete target engagement with full saturation at 1 mg/kg, which was continued for more than 21 days, and there was no difference in pharmacodynamics with doses at 1, 3, or 10 mg/kg. In addition, the dose-limiting toxicities were not observed. Translational models of intratumor exposure identified the strong efficacy at a dose of 2 mg/kg Q3W (10). In a multicenter expansion cohort of a phase I trial, a randomized comparison melanoma cohort demonstrated similar effects and toxicity for 2 and 10 mg/kg Q3W pembrolizumab; however, the lowest and most effective dose for NSCLC remains unknown (11).

KEYNOTE-010, a randomized controlled phase II/

III trial, reported by Herbst and colleagues in *The Lancet*, is the first clinical trial demonstrating that a dose of 2 mg/kg can generate efficacy comparable to 10 mg/kg in NSCLC (4). In this study, more than 1,000 previously treated NSCLC patients whose PD-L1 expression was greater than 1% were randomized (1:1:1) for treatment with 2 mg/kg pembrolizumab, 10 mg/kg pembrolizumab, or 75 mg/m^2 docetaxel Q3W. And the overall survival (OS) and progression-free survival (PFS) of the total cohort and patients carrying more than 50% tumor cells expressing PD-L1 were set as primary endpoints. The median OS was 12.7, 10.4, and 8.5 months for 10 mg/kg pembrolizumab, 2 mg/kg pembrolizumab, and docetaxel, respectively. Both pembrolizumab groups showed significantly longer OS than docetaxel group [hazard ratio (HR) for 2 mg/kg pembrolizumab *vs.* docetaxel: 0.71, P=0.0008; HR for 10 mg/kg pembrolizumab *vs.* docetaxel: 0.61, P<0.0001]. However, neither in the total population nor selective patients whose PD-L1 expression were greater than 50%, significant difference was showed between the two pembrolizumab groups. For the entire population, the median PFS was 3.9–4 months for all three groups, which did not accord with the pre-established criteria for statistical significance (2 mg/kg *vs.* docetaxel: HR =0.88, P=0.070; 10 mg/kg *vs.* docetaxel: HR =0.79, P=0.004). In patients with greater than 50% tumor cells expressing PD-L1, both 2 and 10 mg/kg pembrolizumab treatment were superior to docetaxel for PFS (for 2 mg/kg group: 5.0 *vs.* 4.1 months; HR =0.59, P=0.0001; for 10 mg/kg group: 5.2 *vs.* 4.1 months; HR =0.59, P<0.0001). The frequency of side effects was not significant different between the two pembrolizumab groups but much less than that of docetaxel group. Based on these efficacy and toxicity data, the recommended dose for pembrolizumab from this study was 2 mg/kg Q3W. This result echoes findings from the KEYNOTE-002 trial, which demonstrated similar efficacies for pembrolizumab regardless of dosing in melanoma (12).

In addition to KEYNOTE-010, analyses to explore a truly effective method for pembrolizumab administration are still ongoing. Results from KEYNOTE-010 were available in 2015, and at the same time, the results of the final NSCLC expansion cohort who were treated with 2 mg/kg pembrolizumab Q3W in KEYNOTE-001 were published. This NSCLC expansion cohort comprised patients treated with 2 mg/kg Q3W (n=53), 10 mg/kg Q3W (n=261) and 10 mg/kg Q2W (n=182). The obtained effect information (exploratory regression analyses) and non-linear mixed effects (NLMEs) evaluation based on tumor volume was used for exposure-efficacy analysis to determine the pembrolizumab dose in NSCLC patients. The 95% CI of exposure response parameters hover around zero which corroborates to the non-significant difference results from a flat exposure–response relationship. Based on this analysis, the sanctified 2 mg/kg Q3W pembrolizumab dose was comparable to 10 mg/kg Q2W and Q3W pembrolizumab in the clinical efficacy and safety of the NSCLC patients (7).

Basing on the availability of the PK data from the KEYNOTE-001 (13), -002 (12), and -006 (14) trials for advanced melanoma, NSCLC, and other solid tumors, population PK (popPK) evaluation was proceed using a non-linear mixed effects modeling method. This analysis demonstrated that the pembrolizumab popPK model could be thought to represent the absence of clinically relevant covariates across oncology indications, thus supporting the approved pembrolizumab 2 mg/kg Q3W dose in different subpopulations (15).

Although the 2 mg/kg Q3W regimen was authorized by the FDA to treat advanced NSCLC following first-line therapy, a fixed dose was used in recent clinical trials, e.g., KEYNOTE-024. The popPK model was then utilized to determine the capacity for applying fixed-dose pembrolizumab treatment. Using clinical trial PK data from more than 2,000 patients with different advanced solid tumors who underwent weight–based doses of 2 mg/kg Q3W to 10 mg/kg Q2W or a fixed dose (200 mg Q3W), the necessity for a weight-based dosing strategy was reassessed (16). Weight-based administration did not surpass the fixed dosing in this model. In addition, both weight-based and fixed dosing can possess a sufficient and analogous capability to ensure PK variability. A fixed dose of 154 mg Q3W was identified as showing a nearly equal drug concentration as the weight-based dose of 2 mg/kg Q3W. The AUC distribution of 200 mg Q3W sufficiently overlapped with that observed with the 2 mg/kg Q3W dose. The clinical drug exposure data for 200 mg Q3W observed from patients with various cancers in the KEYNOTE-055, -024, -164, -52, and -045 trials were also consistent with the predicted model. Additionally, the AUC exposures observed in the 200 mg Q3W studies were accordant with the clinically obtained and predicted PK. Nevertheless, these analyses did not answer whether the weight-based or fixed-dose strategies were the most optimal, but they illustrated that both regimens provide similar PK concentration-time profiles.

There are several clinical advantages including reducing dosing complexity and potential contamination, but

personalized dosing has the potential to decrease costs while maintaining efficacy (17). Considering the exorbitant pharmaceutical economics cost and pervasive Asian body weights, the lowest dose is usually recommended.

With regards to the best dosing for pembrolizumab for NSCLC, some uncertain issues remain. First and most importantly, the KEYNOTE-010 study was not designed as a head to head comparison of the two different dosing groups, and its primary objective was to determine if at least one pembrolizumab arm was superior to docetaxel in either PFS or OS. In this study, the PFS and OS were similar but not equal for the two pembrolizumab groups. Therefore, calculations of the sample size and statistical power focused on comparing the two pembrolizumab arms *vs.* the docetaxel arm, but it was not designed to assess the response or tolerance between the two pembrolizumab arms. Second, the study was limited by the short median follow-up time (13.1 months, interquartile range: 8.6–17.7 months). The limited follow-up time and number of events may not be enough to observe superiority between the two dosing groups. Early termination may lead to a small number of participants analyzed and measurement problems, bringing with undependable or unaccountable data. Herbst *et al.* (18) reported an update of the KEYNOTE-010 trial after 12 additional months of follow-up, and pembrolizumab remained superior to docetaxel. With a 1-year longer follow-up, greater than 30% of patients survive at 2 years, but details about which dosing group demonstrated more durable survival is unknown. Therefore, we should be cautious interpreting the results of the KEYNOTE-010 trial. A randomized clinical trial making direct comparisons with different doses would be more convincing.

There are also important issues regarding the exposure-response evaluation of the tumor volume that was used to select an applicable dose. First, due to the heterogeneous patient population (treatment-naïve or previously treated patients) and nonrandom nature of the phase Ib KEYNOTE-001 trial, bias from the imbalance in different dosing cohorts may lead to unreliable analysis results. Second, efficacy was defined as the change from baseline for the sum of the longest diameter (SLD) of target lesions, but non-target lesions were not accounted for. Furthermore, cancer-specific immune responses include several patterns, and continuous stable disease or efficacy after a growth in total tumor burden could not be identified in such an exposure-response model. In actuality, even the irRECIST standard is not a perfect choice based on its nature of examining changes in anatomy rather than the immune statuses of tumors and patients (18).

As we discussed above regarding the proper dose of pembrolizumab in clinical trials, we fully learned about the complexity of this issue. Former anticancer regimens, such as chemotherapeutic agents, always utilized the maximum toxicity dose (MTD) as the optimal dose to ensure the radical ability of drugs to kill tumor cells. However, for immunotherapy, with complicated mechanisms for controlling tumor growth, higher doses may not mean higher responses in patients. Additionally, the low toxicity of immunotherapy has also made it hard to achieve the true MTD. Therefore, by integrating preclinical model evaluation, prolonged multiple time points clinical data analysis of drug concentrations and immune biomarkers will be a more powerful methodology for identifying the optimal dose. It appears that a series of well-designed, randomized dose-ranging studies would be an ideal way to realize this integration.

Many early-stage clinical trials involving checkpoint inhibitors are currently ongoing in China (19). How to select an optimal dose for further research is an emerging issue for Chinese industries. We expect innovative designs for immunotherapy clinical trials in the future.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Tu HY, Zhang Q, Wu YL. Optimal pembrolizumab dosing for non-small cell lung cancer: further studies still needed. J Thorac Dis 2017;9(12):4821-4824. doi: 10.21037/jtd.2017.10.152

