



# Pembrolizumab weight based dosing – A call for policy change

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## Introduction

Immuno-oncology (IO) drugs are now approved for use in metastatic, adjuvant, and/or neoadjuvant setting for a growing list of cancers including non-small cell lung cancer, small cell lung cancer, melanoma, urothelial cancer, renal cell carcinoma, head and neck squamous cell carcinoma, esophageal cancer, gastric cancer, cervical cancer, endometrial cancer, hepatocellular cancer, Merkel cell carcinoma, microsatellite instability-high or mismatch repair deficient colorectal cancer and other cancers, tumor mutational burden-high cancer, cutaneous squamous cell carcinoma, triple-negative breast cancer, classical Hodgkin lymphoma, and primary mediastinal large B cell lymphoma. This list continues to expand at an impressive speed. The benefits in improving progression-free survival (PFS) and overall survival are a welcome advance beyond the plateau that we seem to have reached with conventional chemotherapy treatment. The biggest challenge is to identify biomarkers that would help select the 20 to 40% patients who respond to immunotherapy drugs, thereby limiting treatment to those

most likely to benefit, avoiding toxicity among the patients unlikely to respond. This has very important pharmaco-economic implications, especially because immunotherapy drugs are very expensive.

The important question is whether we can do something substantial to address unnecessary wastage of expensive medicines. The answer is yes. It is based on a long established principle of using dose according to the individual's weight/surface area. It is based on avoiding “flat” dosing—a flawed strategy that leads to unnecessary wastage of expensive medicines and subjects our patients to avoidable toxicity. There is a strong rationale to integrate the concepts of pharmaco-economics.<sup>1</sup> We present here our policy brief on rational use of pembrolizumab that optimizes patient benefit as well as utilization of resources.

## Pharmacokinetics and Pharmacodynamics of Pembrolizumab

Pembrolizumab is a completely humanized monoclonal antibody immunoglobulin G 4 against the programmed

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death-1 tumor-derived antigen. Similar to other monoclonal antibodies, it has peculiar pharmacokinetics and pharmacodynamics (PK/PD) properties such as a very long half-life, linear clearance at doses above 0.3 mg/kg, and steady-state levels being achieved after 18 weeks of therapy.<sup>2</sup> Using the half-life of 23.72 days for pembrolizumab, the complete washout period will be 237 days.<sup>3</sup> Washout period is generally 10 half-lives.<sup>4</sup> In phase 1 pharmacokinetic study of pembrolizumab, the complete interleukin 2 target engagement was seen at doses of 1 mg/kg and above.<sup>5</sup> Durability of this action was documented till day 21 in all the three-dose cohorts, that is, 1, 3, or 10 mg/kg and responses lasted beyond stopping the drug.<sup>5</sup> The modeling-based studies by Chatterjee et al in melanoma and metastatic non-small cell lung cancer (mNSCLC) provided additional evidence that 2 mg/kg q3 weeks was the optimal dose.<sup>6,7</sup> The use of pembrolizumab beyond 2 mg/kg q3 weeks has not shown to improve response rates. Safety, adverse effects, and activity of pembrolizumab were studied at 2 mg/kg every 2 weeks, 10 mg/kg every 2 weeks, and 10 mg/kg every 3 weeks in advanced or mNSCLC.<sup>8</sup> It is important to note that, in this study, the response rate was highest for the dose of 2 mg/kg every 2 weeks (33.3%; albeit with limited data from 6 patients). Also, it was identical for pembrolizumab 10 mg/kg q3 weeks (19.2%;  $n=287$ ) and 10 mg/kg q2 weeks (19.3%;  $n=202$ ) schedules, irrespective of histology.

The phase 2/3 KEYNOTE-010 study enrolled 1,034 patients of previously treated mNSCLC across 24 countries. Pembrolizumab 2 and 10 mg/kg (doses selected on the basis of the previous studies—vide supra) was compared with docetaxel. Overall survival was the primary end point, being 10.4, 12.7, and 8.4 months in pembrolizumab 2 mg/kg, 10 mg/kg, and docetaxel groups, respectively. Hazard ratios (HRs) were 0.71 (2 mg/kg q3w) and 0.61 (10 mg/kg q3w) in comparison with docetaxel. In patients with 50% and more programmed death ligand 1 (PD-L1) expression, HRs were 0.54 and 0.50 for overall survival in pembrolizumab 2 and 10 mg/kg groups, respectively. The authors therefore had sufficient evidence to support the dose of 2 mg/kg q3 weeks for pembrolizumab.<sup>9</sup>

Similarly, a phase 2 randomized trial in ipilimumab refractory metastatic melanoma studied pembrolizumab at 2 and 10 mg/kg every 3 weeks. The HR for PFS was 0.57 and 0.50 in 2 and 10 mg/kg dose and 6-month PFS rate was 34 and 38%, respectively. The authors recommended the minimal effective dose of 2 mg/kg q3 weeks for further use, although the trial was not designed to compare outcome between the two dose schedules.<sup>10</sup>

Factors known to affect the metabolism of pembrolizumab include age, sex, serum albumin, and performance status.<sup>2</sup> Turner et al's PK/PD study concluded that patients with slow clearance have almost double the overall survival as compared with those who had rapid clearance, with identical benefit in cohorts of 2 and 10 mg/kg dose.<sup>11</sup> With all this evidence, 2 mg/kg every 3 weeks is an optimal dose.

## Standard of Care and Approved Dosing

In the landmark KEYNOTE-024 trial of pembrolizumab in advanced lung cancer,<sup>12</sup> the flat dose of 200 mg was used

every 3 weeks, citing pharmacokinetic modeling by Freshwater et al. Freshwater et al used data from population-based pharmacokinetic properties based on 2 and 10 mg/kg and compared them to data from newer trials using fixed doses. In fact, they found no difference between weight based and flat dose regimens.<sup>13</sup>

Food and Drug Administration approved pembrolizumab 400 mg dose every 6 weeks across all indications. This approval was based on pharmacokinetic modeling study which compared 6 weekly 400 mg schedule to 200 mg 3 weekly and 2 mg/kg 3 weekly schedules and concluded that the three schedules were expected to produce similar efficacy and safety across all diseases.<sup>14</sup> This work was supported by Merck Sharp & Dohme Corp. The authors specified that a fixed dose of 200 mg q3 weeks would be more convenient by reducing cost in respect of logistics (reducing cost of manufacturer and hospitals). They conveniently missed the adverse implication on payors (patients, insurance companies, government) by shutting out the weight-based schedule of 2 mg/kg. Further phase 3 trials continued to propagate flat doses of 200 mg across various cancer groups—without any efficacy, safety, or cost-benefit rationale.

The present standard of care for dose differs with different indications. Based on the patent holding company's dossier submission to Indian drug regulatory authorities (Drug Controller General of India), pembrolizumab has been approved since 2016 for use in lung cancer and melanoma at the dose of 2 mg/kg q3 weeks (in previously treated patients of mNSCLC and melanoma). In contrast, for treatment naïve patients of mNSCLC, the submission dossier recommended a flat dose of 200 mg q3 weeks.<sup>15</sup> National Comprehensive Cancer Network recommended 2 mg/kg every 3 weeks for malignant melanoma in addition to flat dose of 200 mg.<sup>16</sup>

## Weight-Based versus Flat Dosing of Pembrolizumab

The flat dose of 200 mg every 3 weeks was derived from the modeling-based study.<sup>13</sup> The Canadian Agency for Drugs and Technologies in Health (CADTH) extensively reviewed the pharmacokinetics and modeling-based studies of pembrolizumab and nivolumab<sup>3</sup> and derived that 2 mg/kg every 3 weeks is the optimal dose of pembrolizumab. In CADTH report, blood levels of pembrolizumab for a patient of 70 kg patient were identical between the four cohorts viz. 98% at the dose of 2 mg/kg q3 weeks; 97% for 4 mg/kg q6h weeks dosing; 99.31% at 200 mg q3 weeks; and 98.16% for 400 mg q6 weeks.<sup>3</sup>

Studies have shown that pembrolizumab is well tolerated up to doses of 10 mg/kg q2 weeks. Toxicities are similar between weight-based (2 mg/kg q3 weeks) and fixed-dose (200 mg q3 weeks) schedules. Recent meta-analysis showed that 2 mg/kg dose of pembrolizumab was better tolerated. Interestingly, in this meta-analysis, pembrolizumab discontinuation rate was higher (9.2%; 95% CI: 6.9–12%) in flat 200 mg dose as compared with weight-based dosing schedule (6.5%; 95% CI: 4.8–8.8%).<sup>17</sup>

## Real-World Studies

Mukherjee et al studied the flat dose versus weight-based dose of pembrolizumab and nivolumab. A total of 60/137 patients received weight-based dosing. There was no difference in overall survival, even after adjusting for other study variables.<sup>18</sup> In a similar study from Singapore, 100 mg (low dose) of pembrolizumab was compared with 200 mg dose in mNSCLC. Sixty-five patients received 100 mg pembrolizumab and 49 patients received 200 mg flat dose. Again, there was no difference in response rate, PFS and overall survival.<sup>19</sup>

Goldstein et al analyzed the cost implications for United States if pembrolizumab is used with weight-based 2 mg/kg dose in PD-L1-positive lung cancer treatment. They estimated savings of \$82.5 million every year without compromising patient outcomes in any way.<sup>20</sup> Using this approach for all labeled indications of pembrolizumab would multiply this saving many folds, saving billions of dollars every year in the United States alone. Another publication also supported the weight-based 4 mg/kg every 6 weeks schedule during coronavirus disease 2019 (COVID-19) pandemic, with additional benefits. It would deliver similar results (efficacy and safety), save cost, and reduce the risk of COVID-19 exposure by reducing hospital visits.<sup>21</sup>

## Worldwide Challenges and Solutions

The 23rd expert committee of World Health Organization on use of essential medicines has considered cost as a major factor for nonconsidering the application for pembrolizumab as essential medicine and also stated that mg/kg dosing may be preferred to flat dose without compromising on disease outcomes.<sup>22</sup> CADTH is an independent organization which helps the Canadian authorities by providing objective evidence on optimal use of dose, devices, and procedures.<sup>3</sup> It has recommended use of pembrolizumab as 2 mg/kg (with 200 mg capping dose) for first line in NSCLC and melanoma. Vial sharing option was suggested specifically as the 50 mg vial was not available. Recently, Israel and Denmark approved weight-based dosing of pembrolizumab.

## Access to Immuno-oncology Drug in Indian Setting

In a real-world study of more than 9,000 patients, only 1.61% of eligible patients received immunotherapy from 2015 to 2018. The cost remains a major deterrent for access to costly medicines.<sup>23</sup> Average weight of Indian lung cancer patients is 55 kg as compare with 75 kg of average American patients.<sup>24,25</sup> The average weight of Indian male is 59.6 kg and female is 52.5 kg.<sup>26</sup> In studies from north Indian lung cancer patients, almost 45% of patients were underweight (body mass index <18.49 kg/m<sup>2</sup> and at 70 percentiles, weight was less than 60 kg).

The cost of pembrolizumab is around INR 235,000 per 100 mg vial (with one vial free). This price might differ

marginally across various states and institutions. Cost of 100 mg, that is, one vial of pembrolizumab is more than India's per capita gross domestic product. A 100-mg vial is ideal for a patient weighing 50 kg, saving a vial for a vial. If conventional doses are used, there is huge monetary loss to the payers. For patients, more than 60 kg, vial sharing remains an option and same vial can be used multiple times as drug is available in liquid form.

## Practical Challenges and Remedies for Practicing the mg/kg Dosing

### The Dose Banding

Dose banding is a well-established methodology wherein the weight-based calculations are simplified by rounding off, taking into consideration available vial size/strength. Ogungbenro et al have shown how this strategy in the usage of pembrolizumab and nivolumab is cost effective.<sup>27</sup> In fact, the National Health Service of the United Kingdom has adopted the strategy of dose banding for nivolumab and pembrolizumab.<sup>28,29</sup> They round off to allow 10% variation. Thus, for a typical 45 to 55 kg patient, the dose range would be 90 to 110 mg of pembrolizumab and one vial of 100 mg would be sufficient, and for majority of Indian patients, the cost of treatment will be halved.

### Stability of IO Drugs

Stability has been studied at 2 to 8°C, at 40°C, and using freezing/thawing cycles. This has been documented for both 10 and 2 mg/mL concentrations. Pembrolizumab is stable in normal saline 0.9% at 2 to 8°C for up to 7 to 14 days in polyolefin infusion bags.<sup>30,31</sup> Nivolumab is stable at 2 to 8°C for 30 days and at 40°C for 7 days.<sup>32</sup>

### The Implications of the 50-mg Vial

Key advantage of weight-based dosing is dependent on the availability of a 50-mg vial. Curiously, the 50 mg vial was withdrawn from the U.S. market, while continuing to be available in certain European countries. In the absence of the 50 mg vial, the application (and resultant cost saving) of weight-based dosing disappears in most countries. It would still be possible (but shall increase complexity) in countries that permit vial sharing, where a central pharmacy prepares chemotherapy infusions. Weight-based dosing is the only way of using pembrolizumab in the pediatric population—approved dose being 2 mg/kg q3 weeks.<sup>33</sup> This is applicable to several cancers including classical Hodgkin lymphoma, primary mediastinal B cell lymphoma, metastatic Merkel cell carcinoma, and high-level microsatellite instability tumors.<sup>34</sup> For a 25-kg child, the dose of 50 mg is adequate. The nonavailability of the 50 mg vial in countries where pediatric use is licensed results in wastage of up to half the drug.

### Recommendations by the Authors

1. Pembrolizumab is recommended as 2 mg/kg every 3 weekly or 4 mg/kg every 6 weekly across all indications

in cost constraint situations, and 200 mg every 3 weeks schedule remains an option.

2. The 50 mg vial of pembrolizumab should be made available in all countries to reduce cost and prevent wastage.
3. Sharing of vials will provide additional saving and should be used where feasible, especially when the government is the payor.

## Conclusion

The usage of IO drugs is expected to rise exponentially in coming years. We provide existing evidence and rationale for usage of pembrolizumab in a manner that optimizes benefit, minimizes toxicity, and prevents unnecessary wastage of resources. These recommendations need to be implemented and governing authorities are requested to take the case forward.

## Methodology

We initially surveyed the challenges associated with practice of mg/kg dosing of pembrolizumab. We discussed this issue with imminent and various medical oncologists of India. We formulated a group of 14 medical oncologists representing nationwide academic and nonacademic institutes, corporate and government hospitals. First author wrote the initial manuscript and the manuscript was circulated to all members of the group through emails. The consensus was accepted and approved unanimously.

### Conflict of Interest

None declared.

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