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NCCN Guidelines Panels: Kidney Cancer

Specific Change: On behalf of *Vi3C*, we respectfully request the *Kidney Cancer Guideline Panel* to amend the NCCN guidelines to include the option of dosing pembrolizumab at 2mg/kg every three weeks as an alternative option to 200mg every 3 weeks.

Rationale: Weight based dosing at 2mg/kg q3 weeks and fixed dosing at 200mg q3 weeks are considered by the FDA and the manufacturer to have equivalent safety and efficacy. For patients with body weight $\leq$ 55kg, dosing at 2 mg/kg (accepting standard dose-rounding) would permit treatment with one 100mg vial, thereby reducing the drug cost in these patients by 50%.

As a matter of precedent, we note that modifications of other NCCN guidelines for purposes of mitigating financial toxicity have occurred. For example, NCCN updated the prostate cancer guidelines to allow the option of dosing of abiraterone in prostate cancer at 250 mg daily with food, as an alternative to 1000mg daily without food, when financial toxicity is felt to be a major concern and/or is felt to be a potential impediment to compliance. We also note that that the Canadian Agency of Drugs and Technologies in Health (CADTH) concluded that "2 mg/kg every three weeks, with a 200 mg upper dose cap, is the most efficient dosage to deliver target engagement of 95% based on the trough or end of dosage interval concentration."[1]

Practical Issues: For patients who weigh more than 55 kg, there would be some practical challenges to the implementation of weight-based dosing. Although the manufacturer distributes the drug in 50mg and 100 mg vial sizes in Europe, only the 100 mg vial is currently available in the United States. These large sizes would necessitate vial sharing in patients over 55 kg. In some US settings this may be challenging, given that vials, once opened and refrigerated, must be used within 24 hours, thereby creating logistical obstacles. However, in high-volume settings, especially in which the payer also acts as the provider, such as the Veterans Affairs system, vial sharing would be expected to be feasible and preferable. While the NCCN guidelines originate from the USA, they also have extensive global influence, and we would expect that many healthcare systems around the world may also wish to pursue this strategy.

Summary of literature: Initial Pharmacologic and Clinical Studies
Pembrolizumab was first approved by the FDA for advanced melanoma in 2014 at a dose of 2 mg/kg every three weeks. The initial phase 1 trial of pembrolizumab aimed to identify the maximal tolerated dose and to assess pharmacodynamics with a wide range of doses.[2] This study demonstrated complete target engagement with full saturation at a dose of 1 mg/kg,

which was durable for at least 21 days and there was no difference in pharmacodynamics with alternative doses of 1, 3 or 10 mg/kg. Translational models of intratumor exposure predicted robust responses at doses of 2 mg/kg every 3 weeks leading to a recommended phase 2 dose of 2 mg/kg every 3 weeks, which was ultimately the first FDA approved dose. Other clinical trials and population pharmacokinetic models have clearly established that there was no difference in efficacy in the range between 2 mg/kg to 10 mg/kg.[3–6]

Population Pharmacokinetic studies and FDA label changes

Recent changes in dosing strategy moved away from weight based dosed to fixed dosing, with the first fixed dose approval of 200 mg every 3 weeks coming as a result of the positive findings for *PD-L1* positive lung cancer in 2016.[7] Subsequent label changes recommended this dosing strategy for all adult indications. However, recognizing that the mean weight of a patient with lung cancer was 75kg, and 2 mg/kg and 200 mg fixed dose are considered equivalent by both the manufacturer and the FDA, significant financial savings can be made by using weight based dosing.[8] From the perspective of an individual it is reasonable to expect that weight based dosing will lead to reduced personal financial toxicity.

References

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