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EDITORIAL

The FDA approval of pembrolizumab for patients with TMB >10 mut/Mb: was it a wise decision? No

There are 12 reasons why the US FDA's approval of pembrolizumab for patients with ≥10 mutations/megabase (mut/Mb) progressing on one prior line without satisfactory alternatives is an unwise decision.

1. *There is nothing logical about the cut off of 10 mut/Mb.* The underlying data from KEYNOTE-158 suggest the cut off is arbitrary and capricious. Below 10 mut/Mb, pembrolizumab's response rate (RR) is 6.7%. From 10 to 13 mut/Mb, the RR is 12.5%, and above 13 mut/Mb, the RR is 37%[1] (numerator/denominators not reported). The current approval sanctions a cut point (10 mut/Mb) that does not separate responders from non-responders. Moreover, tumor mutational burden (TMB), so far, has failed to show predictive value for overall survival across cancers.[2–4]
2. *We do not know if patients live longer or better.* The goal of cancer drugs is improving overall survival, quality of life or both. Given that the approval for pembrolizumab for TMB >10 mut/Mb lacks a control arm, we do not know if that is achieved. RR is a poor surrogate for survival,[5] and several PD-1/PD-L1 Ab (including pembrolizumab) drug approvals were made on the basis of RRs in uncontrolled studies, but later failed to improve survival in randomized trials.[6] Caution and randomized trials are warranted.
3. *Patients who want survival benefits are not satisfied, nor are patients happy with responses.* Patients have different appetites for risk and uncertainty.[7] Some desire randomized trials assessing survival gains, while others may be happy with evidence of responses. Here, there is no proof of survival or quality-of-life benefit. Alternatively, if one thinks responses are sufficient, one must explain why 12.5% is a permitted chance to take, while 6.7% is not. Remember, the FDA did not approve Pembrolizumab for patients with <10mut/Mb, despite 6.7% having responses. Neither patients wanting better evidence nor those tolerant of risk will be satisfied with this approval.
4. *The cut off has fallen from prior publications, which means more prescriptions and more profits.* TMB in KEYNOTE-158 was provided by Foundation Medicine's assay, which was approved as a companion diagnostic.[8] Until recently, a cut off of >20 mut/Mb had been used in reports by this company as 'high TMB,' where it was associated with a 46% RR[9] for PD-1/PD-L1 drugs. Lowering the cut off to 10 mut/Mb means a lower RR, but more prescriptions.
5. *Overall survival was longer in the TMB-low cohort, i.e. where the drug was not approved.* The median overall survival for patients with <10 mut/Mb was 13.0 months (95% CI, 11.5—14.6) while it was 11.7 months (95% CI, 8.2—19.1) among patients with TMB ≥10 mut/mb. Landmark analyses support this paradox—survival is longer where the drug *was not* approved. Although these cohorts are not randomly generated and covariate imbalance may exist, this finding raises concern that the cut point is irrational and does not denote a group with clear long-term benefit.
6. *The data supporting drug approval are weaker than you think.* The FDA excludes patients with microsatelite instability (MSI)-high from their calculation of TMB RRs for good reason. We already have an approval for pembrolizumab in MSI-high tumors. Now, we want to know the RR in microsatelite stable (MSS)/TMB-high tumors. However, bizarrely, the FDA does not extend this logic to tumor types that already have PD-1 or PD-L1 Ab approvals. Specifically, the three most common cancers—small cell lung cancer [34 patients (pts)], cervical cancer (16 pts), and endometrial cancer (15 pts) account for 64% of 102 patients for which approval is based, but all three cancers already have approvals for pembrolizumab as a single agent or in combination.[10–13] Just 37 pts (with anal, vulvar, neuroendocrine, salivary, and thyroid mesothelioma) and 8 responses support the use of TMB among cancers where it is not used. These data are insufficient to sanction widespread use of a costly medication.
7. *We know nothing about prostate cancer, for instance.* No patients with prostate cancer >10 mut/Mb are included in data supporting approval, but ∼5% of prostate cancer meets this threshold.[14] Roughly one in three such patients are MSS, and some will be treated based on this approval. Yet, there are no data documenting the RR for these patients. The TMB approval ensures unproven extrapolations to tumors for which no data has been provided.
8. *An agnostic approval, but tumor seems to matter.* The sample size is too small to rule in or rule out a meaningful interaction by tissue. Notably, the RR ranges from 0/1 (0%) in mesothelioma to 1/14 (7%) in anal cancer up to 2/2 for thyroid cancer (100%), among cancers without prior pembrolizumab approval. Much

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larger samples are needed to prove or disprove that all tissues respond similarly at the same TMB score.[15]

9. *Low regulatory standards did not considerably speed this drug to market.* A common argument from those who favor the use of uncontrolled, surrogate endpoint studies for drug approvals is that it 'speeds drugs to market.' This claim is overstated. In an analysis of 188 approvals, Chen et al. find that the acceptance of surrogate endpoints speeds drugs to market by 11 months against a background of 7.3 years of drug development, and this diminishes in later lines of therapies.[16] In the current approval 50% of responders have been followed for >24 months. This time—spent documenting duration of response—could instead have been spent on running randomized trials and assessing survival.
10. *Costs matter.* Pembrolizumab earned 11.9 billion dollars in 2019, and is priced variably throughout the world.[17] Given the crushing price of cancer medicines,[18] society has an obligation to know if those dollars are a wise use of health care resources. We simply do not know that here.
11. *Accurate cost effectiveness cannot be calculated until you study efficacy.* The simple fact is many countries will not pay for this approval until it has been shown to be cost effective. Those calculations cannot be reliably carried out based on retrospective uncontrolled studies documenting response rate. We need prospective randomized trials to quantify survival gains (or decrements) to know (i) is this drug effective and (ii) is it cost effective over alternatives.
12. *Patients and oncologists do not just want options, they want good options.* Some physicians praise every drug approval—no matter how toxic or how low the RR—as 'providing another option'. However, this attitude confuses options with good options. We want good options—drugs that improve outcomes beyond available therapies. If one merely desires unfettered choice, one should lobby for the FDA and EMA to be dissolved. In fact, a world without drug regulation would have the most options. However, life would be poor, nasty, brutish, and short.

For these 12 reasons, the approval of pembrolizumab for tumors with >10 mut/Mb after one prior line of therapy is unwise.

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