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Loose regulatory standards portend a new era of imprecision oncology

Ali Raza Khaki, MD

Division of Medical Oncology, Department of Medicine, University of Washington School of Medicine, 1100 Fairview Ave. N, D5-100, Seattle, Washington 98109

Abstract

Precision oncology has revolutionized the therapeutic landscape of oncology and is a goal for cancer drug development. However, lenient drug approvals by the United States Food and Drug Administration under the auspices of precision oncology are setting up this therapeutic approach to fail. In this commentary, I review two recent FDA drug approvals (pembrolizumab for tumor mutation burden-high solid tumors and olaparib for castration-resistant prostate cancer with deleterious homologous recombination repair mutations) where the FDA indication is broader than the studied population. I explain how these broad approvals stray from principles of precision oncology and can cause harm to patients.

Keywords

precision oncology; TMB-high; homologous recombination deficiency; Olaparib; pembrolizumab

Over the last 20 years, precision oncology has changed the treatment landscape for patients with specific cancers and has become a much sought-after goal in oncology drug development. However, recent drug approvals by the United States Food and Drug Administration (FDA) under the auspices of precision oncology may be setting up this therapeutic approach to fail.

Early drug development in precision oncology involved identifying molecular alterations in a specific cancer type (e.g. human epidermal growth factor-2 [HER2] in breast cancer) then developing therapeutic agents to target this specific molecular alteration.[1] This approach is well demonstrated by trastuzumab in HER2+ breast cancer, imatinib in chronic myelogenous leukemia, erlotinib and gefitinib in epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer, and others. While this has been successful, it has only benefited a small proportion of oncology patients.[2]

More recently, next generation sequencing and a better understanding of molecular pathways has expanded the population hypothesized to benefit from precision oncology. However, when approved drug indications are broader than a studied population, the approvals can harm patients and the field of precision oncology.

Tel: 206-667-3132, Fax 206-667-4998, (khakia@uw.edu).

In this commentary, I will review two recent drug approvals – pembrolizumab in unresectable or metastatic solid tumors that are tissue tumor mutational burden (TMB)-high (≥10 mutations/megabase) and olaparib for patients with castration-resistant prostate cancer (CRPC) with deleterious germline or somatic homologous recombination repair mutations – where the drug indication strays from the studied population and then explain how this can cause harm to patients and precision oncology.

First, on June 16, 2020, the FDA approved pembrolizumab for TMB-high solid tumors based on a prospectively planned retrospective analysis of ten cohorts in the 11-cohort, open-label, non-randomized KEYNOTE-158 trial. The analysis identified 102 patients with TMB-high tumors with an objective response rate (ORR) with pembrolizumab of 29%. This was significantly higher than in those with non-TMB-high tumors (6.7%), though there was no difference in durability of response or overall survival between the two populations.[3] This approval has been debated by others[4,5] and warrants review in the context of drug approvals in precision oncology.

While these results may appear promising, further consideration of the trial population compared to the FDA drug approval raise concerns about the appropriateness of a tumor agnostic approval. The three largest cancers included in the analysis (small cell lung cancer, cervical cancer, endometrial cancer), comprising 65 of the 102 patients, already had an FDA approval for pembrolizumab. In addition, the next two cancers (anal cancer and vulvar cancer), including 26 patients, also have pembrolizumab and/or an alternate immune checkpoint inhibitor listed in the National Comprehensive Cancer Network (NCCN) guidelines as a recommended treatment. This suggests 89% (91/102) of the patients evaluated had cancers that have already shown efficacy with immune checkpoint inhibitors.

The same responses should not be expected for patients with cancers without a track record of response to immune checkpoint inhibition. This is a key issue. For example, the trial did not include patients from the two cancers with highest incidence rates in the US – breast and prostate cancer - both without broad immune checkpoint inhibitor indications. Trials in these cancers have shown modest results.

In breast cancer, the study that best approximates the setting of the pembrolizumab approval is the phase Ib Javelin solid tumor study.[6] This study enrolled 168 patients with refractory metastatic breast cancer and treated patients with the PD-L1 inhibitor avelumab. ORR was 3.0% for the overall population and 5.2% in the triple negative breast cancer subgroup. Conversely, recent data from the Targeted Agent and Profiling Utilization Registry (TAPUR) showed a 20% ORR in metastatic breast cancer patients with TMB-high tumors (defined as >9 mutations/megabase), though in the poster[7] presented, breast cancer receptor status (estrogen, progesterone, HER2) was not reported, so it is unknown if the responses were in triple negative breast cancer patients – a population that has shown higher efficacy with immune checkpoint inhibitors (and has an approved checkpoint inhibitor[8]) – or in a broader set of patients.

In prostate cancer, patients with metastatic (m)CRPC had ORRs of 5% and 3% among those with PD-L1 positive and PD-L1 negative disease, respectively.[9] A follow-up biomarker

analysis of this trial suggests that TMB may be associated with higher PSA response and longer time to PSA progression, though the same association was not observed for radiographic progression free survival.[10] It is also unclear whether the cutoff of 10 mutations/megabase would be appropriate for this population (median TMB among responders was 70 mutations/exome vs 53 mutations/exome in non-responders). Other studies across diverse tumor types have also suggested that a universal cutoff of 10 mutations/megabase may be inappropriate.[11,12]

Therefore, a blanket tumor agnostic approval without evidence of efficacy in the two most prevalent solid tumors and at a single cut-point strays from the precision aspired with precision medicine.

Second, the olaparib approval for mCRPC also has similar issues where the approval deviates from the study population. This drug was approved for patients with mCRPC with deleterious germline or somatic homologous recombination repair mutations. The approval was based on the phase 3 PROfound trial that randomized patients with mCRPC and an alteration in prespecified genes with a direct or indirect role in homologous recombination repair to receive olaparib or physician's choice of enzalutamide or abiraterone.[13] Overall, the trial showed imaging-based progression-free survival was longer in patients treated with olaparib vs control (5.8 months vs 3.5 months, hazard ratio for progression or death 0.49). Though, a prespecified subgroup analysis shows that the patients with BRCA1 and BRCA2 mutations showed most of the benefit from olaparib treatment. Whereas populations with other mutations like ATM, CDK12, and CHEK2 had a null result and one group (those with PPP2R2A mutations) was inferior to physician's choice therapy. These negative results are particularly concerning given the sub-optimal control arm biased results in favor of olaparib. The same differential response based on mutation type has also been noted in earlier phase studies with olaparib in a similar population[14], leaving some to question this broad approval[15] and others to suggest reconsidering the method with which patients are classified as candidates for olaparib and similar agents targeting Poly ADP-ribose polymerase (PARP).[16]

How are these broad drug approvals harmful? First, use of agents in populations with limited chance of benefit can increase the cost of cancer care and lead to undue toxicity. Second, these agents can divert patients from clinical trials and from other agents that are more likely to be beneficial. For example, treatment of mCRPC patients without BRCA mutations with olaparib prior to other FDA-approved agents shown to improve overall survival, may lead to worse outcomes. Third, if efficacy in the real world is divergent from clinical trial results, this can also lead patients and providers to become more skeptical of precision oncology as a treatment paradigm. Fourth, a higher use of agents near the end of life can also lead to delayed hospice referrals and lead to more intense end of life experiences. This is of particular concern with pembrolizumab, where use near the end of life has been previously advocated[17] but has been shown to be associated with decreased hospice referrals and increased in-hospital deaths.[18-20]

Overall, the goal of precision oncology is to use advanced laboratory methods and biomarkers to better identify patients likely to benefit from a particular therapy. If FDA drug

approvals deviate from the populations most likely to benefit, precision oncology is likely to shepherd in a new era of imprecision.

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