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Keeping Checkpoint Inhibitors in Check

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Immune checkpoint inhibitors (ICIs) have stormed oncology clinics in recent years. In many ways, the excitement and public acclaim are justified, particularly for programmed cell death receptor 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors. In select tumor types, including non–small cell lung cancer (NSCLC), microsatellite instability–high tumors, and melanoma, ICIs have affected the natural history of these diseases and resulted in treatment paradigm shifts. Approvals and expanded indications for ICIs are occurring routinely, but lay excitement does not always align with clinical data. Therefore, the study by Haslam and Prasad[1] is timely and may assist physicians, patients, and policy makers in estimating how many patients with cancer are eligible for ICIs and, critically, estimating the percentage expected to actually derive significant benefit.

To this end, the authors performed a retrospective cross-sectional analysis providing annual estimations of the percentage of US patients with cancer who are eligible for ICIs and estimates of what percentage may benefit. The methods by which they performed these analyses were previously described in a similar assessment[2] concerning genomically targeted therapies. Briefly, the authors used annual cancer deaths from the American Cancer Society as an estimate of annual incidence of advanced metastatic disease. These incidences were considered the pool of potential candidates and adjusted per the US Food and Drug Administration (FDA) labels and qualifiers by tumor type (eg, PD-L1–positive tumors only) to determine the percentage eligible to receive ICIs. As surrogates for expected efficacy, overall response rates (ORRs) in the FDA label by indication were applied when the ICI was used as monotherapy, or the differential improvement in ORR when used in combination with backbone therapies, compared with the treatment backbone alone. Benefit estimates always used the highest value if there was either more than 1 study evaluating a given ICI in a given indication or when multiple different ICIs were used in the same indication. The cancer-specific benefit was derived by multiplying the number of people eligible in each cancer type by the expected efficacy reported in the FDA label for that indication for that cancer type, and overall ICI benefit estimate was the summative analysis. This was comparatively performed annually based on approvals as they accumulated from January 2011 to August 2018 (ultimately 6 ICIs in 14 total indications).

The point estimates for ICI eligibility increased from 1.54% of US patients with cancer initially in 2011 with ipilimumab for melanoma to 26.86% by 2015 with ICI approvals in NSCLC, and then to 43.63% in 2018. At the same time, the percentage estimated to respond to ICIs was 0.14% in 2011, 5.86% in 2015, and 12.46% by 2018. Concerningly, the ratio of the percentage benefit from ICIs to the percentage of cancers affected by ICIs over time peaked in 2014 but then dropped as more approvals ensued, indicating that the percentage of individuals who are eligible for ICIs through FDA approvals has grown at a higher rate than the percentage of individuals who may actually benefit from them.

The observations in this article are sobering and remind us to keep expectations of ICIs realistic. As the dust settles and the wave of hysteria ebbs, studies like this lend support to physicians as they attempt to explain to most of their patients with cancer the reason they are not receiving ICIs—because these drugs are not appropriate for them.

The authors acknowledge several study limitations, including overestimates of overall eligibility owing to lack of adjustment for approvals in later-line treatment. For instance, although many patients die annually of gastroesophageal cancer, approximately two-thirds of them die before getting to third-line therapy and therefore those affected by immuno-oncology would be only

one-third of the deaths from gastroesophageal cancer, not all of them. In contrast, the methods used also lead to significant underestimation of overall eligibility in the setting of approval for stage III NSCLC, representing about 30% of all NSCLC, because approximately 20% of these patients have long-term survival with standard chemoradiotherapy alone and, therefore, would not die or be accounted for as eligible for immunotherapy by the authors' methods.[3] Also, the benefit in earlier lines or stages of therapy may be more substantial than in later lines.[4] Other subtleties include patients with clinical ascites who are not technically eligible by the FDA label for diseases like gastric cancer (where they were excluded due to observed lack of benefit in earlier studies), yet this is rarely followed in practice, leading to underestimation of patients who are actually treated while simultaneously not likely benefiting. Along these lines, the authors describe "desperation oncology," which was difficult to quantify, but not including that underestimates the numbers of patients affected by ICIs, with very few of those, if any, deriving benefit. Importantly, the benefit estimates are biased at the high end, leading to gross overestimate of benefit for ICIs among those considered eligible. Additionally, although tumor response may be associated with symptomatic improvement, ORR does not necessarily translate into long-term benefits of progression-free and overall survival. Recent negative phase III hepatocellular cancer (KEYNOTE-240) and gastroesophageal (KEYNOTE-061) trials[5] highlight the pitfalls of using conditional approvals based on ORRs in analyzing eligibility and benefit. Although yet to occur for ICIs, these negative phase III trials may lead to fewer eligible patients (appropriately) because they could lead to rescinded approvals or, alternatively, modified approvals based on higher PD-L1 cutoff scores. More optimistically, the authors may mildly underestimate benefit for patients who did not experience tumor regression, as stable disease can be clinically significant but not captured by the methods used.

Overall, considering these concerns in aggregate, in this study there is general underestimation of eligibility for ICIs and overestimation of benefit. Even so, while lacking some context and clear survival data, the reported benefit ratios are still underwhelming, with an estimated 43.63% of cancer patients ultimately eligible by August 2018 but only 12.46% deriving benefit as defined. Figure 1 in the article by Haslam and Prasad[1] shows that the gap is widening. This current gap between eligibility and benefit is larger than that found in the similar assessment of genomic-based therapy (8.33% vs 4.9%, respectively).[2] The oft-cited potential for longer-term benefit of ICIs and the inherently restricted eligibility for genomically-matched therapies likely influenced these differences. In fact, the reality is that the tail of the curve only represents very few patients (fewer than approximately 2% of patients with gastroesophageal cancer, for example, while 50%-60% of patients are ICI eligible by PD-L1 criteria, with only 13.3% of these patients having any response)[6]; this ultimately leads to merely "chasing our tails" in most situations. As such, immunotherapy is not immune to the concept of targeted therapies for targeted populations. With better patient selection and earlier disease indications, there is no doubt that eligibility and benefit estimates will change over time, and one need look no further than the recent ICI approval in first-line PD-L1–positive triple-negative breast cancer.[7] Notably, going forward, the methods used by Haslam and Prasad[1] would not be appropriate for approvals in the adjuvant setting, as for melanoma recently. Adjuvantly, ORR is not measurable, while cancer death rates are not accurate to determine eligibility, as mentioned previously relating to stage III NSCLC.[3,4]

Notwithstanding these limitations, this study quantitates the disturbing trend that, despite the expansion in the number of patients eligible for expensive and potentially toxic ICIs, the ratio of those benefitting is decreasing. As responsible and informed oncologists, it is vital that we use ICI judiciously with an eye to maximizing benefit, as difficult as this may be while patients demand ICI based on the press, the current buzz, and patient-directed advertising. This article indirectly highlights the importance of rational biomarker evaluation to improve the ICI therapeutic window. For example, biomarkers such as PD-L1 immunohistochemistry, with good negative predictive value, are imperative because patients with PD-L1–negative cancers derive minimal benefit with monotherapy ICI, thereby limiting eligibility via this selection. Predictive tools to pinpoint optimal benefit within the PDL1–positive group remain an unmet need toward realizing precision

immunotherapy. In addition, attempts to convert immune nonresponders to responders with various approaches are currently an active area of research that will hopefully not only increase the number of patients eligible, but also close the gap between those eligible and those benefiting from harnessing the power of the immune system.

ARTICLE INFORMATION

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