Registration and Reimbursement of New Cancer Medicines in Australia—Response to Letter to the Editor by Michael Wonder

We welcome the comments on our article on the regulatory and reimbursement approval of oncology drugs in Australia lacking any supportive phase 3 data [1]. The author of the letter raises a series of discussion points, and a detailed response addressing each of these can be found in the following paragraphs. We believe that the arguments do not detract from the central tenets of our article, which are as follows:

1. To date, a larger number of oncology drugs have been approved on trial packages lacking phase 3 data under the US Food and Drug administration (FDA) and the European Medicines Agency (EMA) than under the Therapeutic Good Administration (TGA).
2. In cases in which the TGA has granted such early approval, the EMA and the FDA have typically approved the same drugs but at an even earlier time, resulting in lost treatment opportunities for Australian patients.
3. Additional expedited programs are being or have recently been implemented by the FDA (Breakthrough Status) and the EMA (Adaptive Pathways) that will increase the number of oncology drugs being approved on such early clinical data packages in the future. No similar plans for any such programs exist in Australia.
4. The EMA’s Adaptive Pathways pilot also includes national payers as part of this process. This means that for those drugs attaining EMA regulatory approval under this program, there is an increased likelihood that this will translate into early European payer reimbursement. In contrast, there are no such plans to change Pharmaceutical Benefits Advisory Committee (PBAC) processes to enable earlier reimbursement and patient access.
5. The result of this is that the delay in access to promising new oncologics for Australian patients is likely to increase, relative to their US and European peers.

We apologize if the author of the letter felt that the objectives were unclear. As stated, the objectives were to define the conditions under which oncology drugs could achieve TGA regulatory and PBAC reimbursement approval on the basis of a clinical data package lacking phase 3 data. To research these issues, there is clearly a need to examine the evidence packages submitted to the TGA and compare the decisions made and the timing of those decisions with similar decision-making bodies elsewhere. The FDA and the EMA provide an objective indication of what the TGA may have decided if it made more use of early data, and so hints at the opportunity cost of delaying a decision.

Without reference to these bodies, we would have little basis to suggest that the TGA could be providing market authorization for drugs at an earlier stage in their clinical development pathway. The author also refers to our discussion and analysis not aligning with our research objectives. Our objective, however, could not be achieved solely by examining these drugs without reference to the wider body of oncology drugs appraised. Otherwise, the factors identified as common to drugs approved on the basis of clinical data packages lacking phase 3 data may not be factors specific to this group, but rather factors common across many oncology drugs. This is especially important in our analysis because the numbers of drugs appraised by the TGA and the PBAC according to our criteria are low. This is epitomized by the authors’ alternative conclusions that the willingness of the TGA and the PBAC to recommend oncology drugs on the basis of such an early data package relates to the severity and orphan status of the disease. As the authors state, 9 out of 10 drugs in our sample were orphan drugs and all were for life-threatening diseases. Almost all oncology drugs, however, address severe, life-threatening diseases, and the proportion of new drugs with orphan designation is very high. Although we are unaware of any Australian-specific data, in 2014, more than 20% of EMA-approved and more than 40% of FDA-approved new drugs had an orphan designation [2,3]. Furthermore, all drugs that received a positive PBAC recommendation on such an early clinical data package received a negative recommendation at first submission, despite being for the same orphan, life-threatening diseases.

The author suggests some clarifications, an instance of data omission, and an incorrect date in our article (listed in bullets below). We thank the author for bringing these points to our attention and will request that we be allowed to amend the journal text as part of an addendum to address these points:

1. PBAC makes “recommendations” rather than “approvals.”
2. “Cost-effectiveness” analysis is more accurate than “cost-benefit” in this setting.
3. The imatinib mesylate PBAC submission included an economic “evaluation” rather than a “model.”
4. Cetuximab was approved in metastatic colorectal cancer in 2005 (not 2004, as we depicted in Fig. 1).
5. Phenasen was recommended by the PBAC in 2009 on the basis of a package lacking phase 3 data.

The letter author queries the date range of the study period. We did not set a defined search date range for the research. To ensure comprehensiveness, we researched all publicly available

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reports published by the PBAC and the TGA. TGA reports have been published only since 2010, and the earliest PBAC submission that we identified according to our extraction criteria was for cetuximab in 2005. There was no exclusion criterion, however, for earlier publications.

We did not assume that the data packages used to support Pharmaceutical Benefits Scheme (PBS) listing was the same as that used to attain registrational approval. Simply, that the data package supporting PBS listing represented the most mature data available. It would be extremely unusual if, as the author insinuates, that phase 3 data would be used to support registrational approval, but then for the PBAC appraisal to be conducted on the basis of phase I/II or case series data.

We welcome the opportunity to provide some additional detail regarding our definition of “restricted approval,” which is defined as medicines that are approved in a restricted subpopulation (as opposed to the full indication as part of the application).

The assertion by the author of the letter that we need a separate study including Australian submission dates to support some of our conclusions while recognizing that these data are not publicly available is odd. The result of the situation in Australia is that drugs are available after the United States and the European Union, and this is demonstrated by the examples presented. The example of crizotinib is particularly prescient because it was approved by the FDA and the EMA on a pivotal phase 2 data package. The TGA did not approve crizotinib until the interim study report of a comparative phase 3 study was made available, delaying marketing authorization until August 2013 (the EMA approved in July 2012 and the FDA approved in August 2011).

There are reasons why drugs may be submitted later in Australia, but companies are often asked to submit early in other countries, and this is part of the expedition process. Australia may get late submissions because the market is smaller, the process is tough, and they are not asking for submissions early. These are just additional reasons, however, suggesting why Australian patients may benefit from improvements in the current system. Alternatively, if Australia was a relatively low-priced market for pharmaceuticals, the quoted examples of dabrafenib and pembrolizumab achieving reimbursement before it was achieved in Europe based on phase 3 data contradict this. Afatinib received a positive PBAC recommendation in July 2013, the same month that FDA approval was granted and a Committee for Medicinal Products for Human Use (CHMP) positive opinion was issued. This suggests that companies can achieve rapid market access and reimbursement in Australia but only when supported by phase 3 data.

The author of the letter also highlights the fact that, subsequent to our article being published, crizotinib has been recommended by the PBAC leading to addition to the PBS in July 2015 [4], though this was substantially after FDA approval in 2011 and positive decisions by other payer bodies (the National Institute for Health and Care Excellence and the pan-Canadian Oncology Drug Review: 2012). It is unclear, then, how this debases any of our conclusions. Similarly, the author points out that, subsequent to publication, pembrolizumab received positive recommendations by the TGA and the PBAC on the basis of a phase 3 data package despite being approved under the new FDA Breakthrough Status program when supported by a dose-ranging phase 1 study over a year beforehand and being only 1 month before a Committee for Medicinal Products for Human Use (CHMP) positive opinion being granted. Although this agent received a positive PBAC recommendation before it was appraised by any European Union–payer body, the author must be mindful that the new EMA Adaptive Pathways program, unlike the new FDA Breakthrough Status pathway, is still in its pilot phase. If this becomes another regular pathway under the EMA (as anticipated), drugs such as pembrolizumab will likely be strong candidates for early European market access on the basis of early clinical data, further exacerbating the delay for Australian patients to access these medicines.

In summary, the author raises a number of interesting discussion points and additional data to be considered. These do not detract, however, from the central narrative of our article or the overall conclusions, nor do they in any way undermine the basis of our proposed recommendations.

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REFERENCES


