ANNOUNCE prompts questions over the Accelerated Approval process

The negative results of the ANNOUNCE trial, resulting in withdrawal of olaratumab from the market, illustrate the difficulties in balancing access to novel therapies with the need for proven benefit.

On reviewing the highlights of another exciting ASCO Annual Meeting, our thoughts naturally turn to the prestigious plenary session, which usually features studies of 'blockbuster' therapies set to change treatment paradigms. This year, however, we were perhaps most struck by the conspicuous reporting of negative results of ANNOUNCE[1]. This phase III trial was conducted as a condition of the FDA Accelerated Approval of the anti-PDGFRα antibody olaratumab in order to confirm the survival benefits of adding this agent to doxorubicin for patients with advanced-stage soft-tissue sarcoma, as previously observed in a randomized phase Ib/II trial.

The decision of the ASCO Scientific Program Committee to highlight the ANNOUNCE trial must be commended and perfectly encapsulates the theme of this year's meeting: "Caring for every patient, learning from every patient". The findings of ANNOUNCE are, arguably, no less practice-changing than those of trials with positive results, although the nature of the changes in patient care will admittedly be different and somewhat more sobering — namely, removal of an inefficacious treatment from the global market[2]. Moreover, the high-profile coverage of this negative study emphasizes that we can only truly 'learn from every patient' if we adequately capture and actually report their data. Timely and honest reporting of negative trials, ideally in peer-reviewed journals (which the manufacturer of olaratumab has committed to do[2]), can enable lessons to be learnt from past mistakes, inform the direction of future research and, most importantly, limit the exposure of patients to the physiological and financial harms of ineffective treatments, and should therefore be mandatory. Thus, the ANNOUNCE investigators should also be praised for their commitment to candidly describing the late-phase failure of olaratumab.

More broadly, the fallout from ANNOUNCE prompts scrutiny of the rigour and value of some Accelerated Approvals. Drug regulatory authorities have a difficult remit in balancing patients' needs and expectations with regard to access to novel therapies against the requirement for adequate evidence of safety and true clinical benefit. As outlined by patient advocate Bettina Ryll in this issue[3], patients nowadays are better informed and are becoming 'emancipated'. Accordingly, the perceived demand for early access to promising new treatments has never been higher. Some patients might even feel that assignment to the control arm of a randomized trial is a hazard that should be avoided[3], which might further complicate evidence gathering and put more pressure on regulators. It is certainly true that initial approvals are increasingly based on single-arm trials. Regardless, to avoid subsequent failures and harms, the biological and clinical rationale for conditional approvals must be solid and perhaps regulators need to be more resistant to such pressures and set higher bars.

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In the initial approval of olaratumab, regulators were presented with phase Ib/II trial data showing an unprecedented 1-year prolongation of median overall survival (OS), in the context of a disease for which therapeutic advances have been limited, with dismal outcomes. In retrospect, warning signs might have warranted further investigations prior to initial approval, such as a large unexplained discrepancy between the progression-free survival and OS benefits, and a trend towards worse OS associated with tumour positivity for PDGFRα.

The safety profiles of the experimental and control treatments in ANNOUNCE were similar, thus any patients treated with the olaratumab combination are unlikely to have suffered physiological harm (although this will not be the case for all ineffective treatments). The financial costs relating to the approval, however, are likely to have been considerable. The manufacturer has reportedly stated that the total worldwide sales of olaratumab through the first quarter of 2019 amounted to US$562 million[4]. The magnitude of the potential financial (and physiological) costs of approved but ineffective agents will increase with the duration of the interval to reporting of a confirmatory trial. Thus, regulators must do their best to ensure that post-marketing trials are timely, as well as appropriately designed, and perhaps could also, for example, consider linking the prices of agents granted Accelerated Approval to their clinical value or R&D costs, as discussed by Gyawali and Kesselheim in this journal[5].

1. Tap, W. D. et al. *J. Clin. Oncol.* **37** (Suppl.), abstr LBA3 (2019).
2. Lilly to Establish an Access Program for Patients as it Prepares to Withdraw Lartruvo from the Global Market. *Eli Lilly and Company*, https://investor.lilly.com/news-releases/news-release-details/lilly-establish-access-program-patients-it-prepares-withdraw (2019).
3. Ryll, B. *Nat. Rev. Clin. Oncol*. https://doi.org/10.1038/s41571-019-0230-4 (2019).
4. Hernandez, R. *The Accelerated Rise and Fall of Olaratumab in Sarcoma. Cancer Therapy Advisor*, https://www.cancertherapyadvisor.com/home/news/conference-coverage/american-society-of-clinical-oncology-asco/asco-2019/sarcoma-olaratumab-rise-and-fall-treatment/ (2019).
5. Gyawali, B. & Kesselheim, A. S. *Nat. Rev. Clin. Oncol.* **15**, 596–597 (2018).