View Point

Accelerated drug approvals in oncology: Pros and cons

Sayanta Thakur, Sandeep Lahiry[1]

Department of Pharmacology, Institute of Postgraduate Medical Education and Research, [1]Independent Scholar, Kolkata, West Bengal, India

Correspondence to: Sayanta Thakur, E-mail: tsayanta83@gmail.com

Abstract

The inevitable surge of the accelerated approval process, especially for oncology drugs, has been a success story. However, the use of surrogate end-points and its validation has been debatable over the years. Over the years, US Food and Drug Administration has been rigorously working for the validation of these end-points to capture the real clinical benefit and appropriateness of clinical study designs. However, the high cost imposed by the manufacturer attributed to the faster drug access can be prohibitive and well undermine the whole process. We discuss issues that must be addressed and solved accordingly for managed care in oncology.

Keywords:
Clinical study, drug approval, medical oncology

Introduction

Any drug or pharmaceutical product is approved for marketing once it succeeds in the adequate and well-controlled phase III trial. Marketing approval of drugs, provided by the US Food and Drug Administration (FDA), could be granted provided the safety, as well as efficacy measures, has been taken care of. Regular approval was the sole mandate of the US FDA until 1992. Eventually, in the context of the Human Immunodeficiency Virus (HIV) crisis, the addition of subpart H to federal regulation paved the way for accelerated approval (AA) as an alternative pathway.[1] It promotes the new drug as having a more meaningful advantage over already approved minuscule drugs in the context of a serious or life-threatening rare condition. It is followed by postapproval studies, which ascertain the clinical benefit as well as risk profile in a more sophisticated way. AA can be revoked if the confirmatory trial is suspended or depicts risk outweighing the benefit. As an example, the approval of bevacizumab for the treatment of metastatic breast cancer was revoked in 2011 as it failed to demonstrate a benefit in overall survival (OS).[2]

The accelerated approval (AA) pathway has paved the way for many of the novel drugs used in oncology in recent years, which seems likely to continue in the near future. However, there are certain issues that may lead to various dilemmas in the process. Therefore, the specific issues involving study methodology as well as regulatory issues of this process need further clarification to avert various dilemma.

Planning and Execution of Study

Selection and validation of surrogate end-points

Drugs in the AA pathway must demonstrate their effect on an end-point that is "reasonably likely" to predict real clinical benefit (changes in symptoms or mortality rate), which is known as a *surrogate* end-point[3] [Table 1].

Surrogate measures can expedite drugs to reach the market more quickly via the approval process. The

Access this article online	
Website: www.indianjcancer.com	**Quick Response Code:**
DOI: 10.4103/ijc.IJC_793_19	

How to cite this article: Thakur S, Lahiry S. Accelerated drug approvals in oncology: Pros and cons. Indian J Cancer 2021;58:114-8.
Submitted: 08-Sep-2019 **Revised:** 27-May-2020
Accepted: 19-Jun-2020 **Published:** 14-Sep-2020

Table 1: Commonly used surrogate end-points in oncology

Surrogate end-points	Description
Response rate (RR)	Percentage of patients showing tumor shrinkage as greater than or equal to 30% decrease in the sum of diameter of target lesion
Progression-free survival (PFS)	Time from randomization to disease progression (defined as ≥20% increase in the sum of diameter of target lesion with an absolute increase of at least 5 mm or appearance of any new lesion) or death
Disease-free survival (DFS)	Time from randomization until tumor recurrence or death from any cause
Time to tumor progression (TTP)	Randomization until tumor progression (death not included)
Invasive DFS	Time from randomization until the date of first occurrence of one of the following: Recurrence of ipsilateral invasive breast tumor Recurrence of ipsilateral locoregional invasive disease A distant disease recurrence Contralateral invasive breast carcinoma Death from any cause relevant to adjuvant treatment of breast carcinoma
Pathological complete response rate (CRR)	Percentage of patients who achieve a pathological complete response, defined as the absence of invasive neoplastic cells at microscopic examination of the primary tumor at surgery Application in neoadjuvant treatment of cancer

choice of surrogate measure to delineate real clinical benefit in the confirmed trial can vary in a diverse disease setting accordingly.[4] For instance, benefit in disease-free survival (DFS) has been well correlated with OS in colorectal carcinoma, whereas another surrogate end-point progression-free survival (PFS) has a poor association with clinical benefit in gastric carcinoma.[5,6] It may also vary with postprogression survival time, that is, the correlation of PFS with OS is poor in case of long survival time, whereas it is stronger in a case with tumor with short survival postprogression.[7] The reverse might be encountered such as DFS being a good trial level surrogate for OS in the adjuvant treatment of colorectal cancer.[5] Therefore, their use cannot be derived from a random indication or population to the intended one or vice versa. In some instances, surrogate measures appear to be subjective, hence tend to introduce bias than measurement.[8]

Postapproval studies form an important safety net for the drugs approved via an AA pathway. Linking and harmonization of these two processes have always remained as a priority. The US FDA's report on 20 years of experience with the AA pathway delineated the fate of 93 oncology drugs approved from 1992 until 2017. Nearly 81 out of 93 AA were based upon response rate (RR) with the rest of the 12 based upon PFS and DFS. Among the 51 out of 93 indications, clinical benefit was verified with 15, demonstrating improvements in OS (16% of the sample). However, for the remaining 37 indications, postapproval evaluation was ongoing.[9]

An updated report related to the continuation of the review done recently depicted the number of confirmatory trials using OS, 19 (20%), with others using different end-points. Among them, studies utilizing different surrogate end-point of that of pre-approval studies (21%) were almost equivalent to studies using same surrogate measures as that of previous pre-approval studies (20%).[4]

It is pertinent to use the same surrogate measures for pre- and postapproval studies given that the surrogate validation has been ascertained.[4] Surrogate validation by investigators needs to be accomplished, which includes two-step determination of the efficacy of drug and confirmation of the effect of surrogate end-points over intended therapeutic outcome.[10] Corroboration of the effect of the same surrogate measure used in AA would then be justified in confirmatory studies done in a larger or more diverse population. So, even if after the approval, confusion could prevail whether it imposes survival benefit or improves the quality of life, hence should be interpreted and judged in a precise manner for a rational clinical decision-making. Delineation of surrogate variability could be possible with the US FDA maintaining a continually updated database of the strength of surrogate validation in diverse tumor types.[4]

The use of RR or PFS has been considered suitable for regular or AA pathway in the context of the magnitude of the effect, safety profile, and disease context. They augment clinical decision-making and may be beneficial to patients with a limited treatment option. A recent update on using RR data for AA pathway prompted a fair conversion (29 out of 53) to regular approval.[11]

Study design

A common approach in oncology involves consideration of a single-arm study that would satisfy the regulatory agency,[9] that is, a high RR. It would not be ethically pertinent to allocate a patient to either an agent with marked activity or to a marginally effective or toxic compound available as the standard therapy as the basic tenet of biomedical ethics known as "clinical equipoise" could be jeopardized.[12]

Oncologists may have some doubts regarding whether improvement in OS should remain as a benchmark

or achieving a durable response in the single-arm trial will suffice. It would be unreasonable to use OS in randomized controlled trial (RCT) in the selected disease area. Use of placebo-controlled trial could not be the avenue in life-threatening rare disease with limited standards available, especially for novel drugs with high biological activity.[12] Moreover, RCT is only realizable when the incidence of carcinoma is 0.7–2.0 per 1,000,000 patients.[13]

The use of OS remains impractical in case of cancers with long natural history, that is, chronic lymphocytic leukemia, multiple myeloma, and chronic myeloid leukemia with 5-year survival of more than 50% due to effective treatment option.[12] It would necessitate long follow-up period imparting patients to switch over to other treatments, confounding the analysis.

Despite the issues over OS encroaching regular approval pathway, a recent study to assess the clinical benefit of cancer drugs approved via AA illustrated RCT (45 out of 93, 48%) using OS (19 of 93, 20%) as an end-point.[4]

Timing of the post-approval trial

Completion of post-marketing trial promptly is a key to provide data to verify the outcome established in AA. Manufacturers should ensure their intention to initiate a confirmatory trial at the very beginning of the procedure.[4] The benefit of post-marketing trial which is underway at the time of AA depicted more than 2 years difference in confirmatory trial completion and verification of benefit compared to those who did not.[9]

Although the present scenario raises definite apprehension, as a recent report suggesting 1 in 10, anticancer therapy remains in the market for >5 years without results from a confirmatory clinical trial. Some of the drugs even stranded for as much as 12.6 years without confirmatory trial.[9] The median time from AA to the demonstration of clinical benefit for a specific indication was 3.4 years (0.5–12.6 years).[14] According to the report of US FDA, a large number (almost 40%) of the confirmatory trials involving drugs approved for 93 different indications, were incomplete.[9] To corroborate the fact stated by FDA as of May 2017, results have shown that only 10 studies were complete with 9 ongoing, 10 pending, and 5 being delayed.[4] Hence, US FDA must try to minimize the period during which patients and physician are using the drugs approved via the AA pathway without any confirmatory evidence over safety and efficacy.

Regulatory Factors

Regulators in the different parts of the globe, whether in developed or developing countries, strive forward to ensure faster access to the novel compounds. Followed by US FDA, regulators in Europe and Japan established their pathway of accelerated development. There has been further dissemination of such pathways to accelerate the review in other agencies such as Health Canada, China Drug Administration, and South Korean Ministry of Food and Drug Safety, to impart conditional approval.[15] However, in most of the developing states, there remains a paucity of such strategy in the context of mature and well-governed regulatory bodies.

Two key concepts, reliance and recognition, has been adopted to ascertain routine acceptance of regulatory decision of other jurisdiction utilizing significant information derived from the agency of reference.[15] Based upon these key principles, there might be an allowance of any product to be marketed in specific countries once they are approved by stringent regulatory authorities (SRA), that is, Argentina, Ecuador, Egypt, and Saudi Arabia.[15]

Some of the regulatory authorities enthuse independent or abridged review of data suitable to their demographics, already reviewed and approved by SRAs, that is, Mexico, Indonesia, Singapore, and Taiwan.[15] In some instance, review procedure is encouraged by few of the authorities in countries other than their own, that is, European Medicines Agency article 58, *SwissMedic.*[15] The key concept in the overall context is to ensure adaptation of the regulatory decision aligned with the region-specific situation and unmet need. Strong collaboration through sharing resource and experience will avert the burden over underresourced regulatory authorities.

The new drugs and clinical trial rule, introduced in March 2019,[16] has provision for AA pathways in India. It justifies approval of a novel drug for serious/life-threatening disease with having special relevance to the country, that is, addressing an unmet need.

An "unmet need," explained judiciously in the rule, is attributed to immediate or long-term need of a population and community in the context of inadequate allocation of specific treatment or diagnosis of a disease of interest. The use of surrogate end-point is encouraged rather than hard clinical outcomes such as survival or disease progression. "Remarkable" efficacy in phase II trial will suffice grant for marketing approval by the regulatory authority. However, what and how much extent of efficacy will satisfy the regulators is not appreciated as the term "remarkable" is not critically appraised in the rule. Subsequently, confirmatory trials in a larger population are envisioned after the AA procedure.

Reimbursement and Price-Related Decision

Reimbursement by government payers could be offered to manufacturers for the cost of developing the drug until confirmatory trial demonstrates its clinical benefit. However, occasionally, proper reimbursement coverage were not covered by such formal payers. This was evident from a systemic review done involving 11 jurisdictions including USA, Canada, Brazil, Australia, and some of the European countries, where 15 drugs were deprived of reimbursement advantage, approved in conditions like melanoma, lung cancer, and hematological cancer.[17] AA might not conduce relaxation of other requirements to hasten timely market access of the novel compounds. Moreover, a formal economic impact analysis intended to ease financial constraints could be done after a product is in the market for 1–2 years.[18]

The manufacturers are prone to increase the price of all drugs approved via AA, far beyond their actual clinical value. This can undermine the performance of the agent approved as well as draw the resource away from the use of other interventions with a stronger level of clinical evidence. Systems could be designed to limit the price of the agent in a predefined range compatible with its clinical value or cost of research and development until a true benefit is being ascertained. Measures like arranging concession to public insurance program by the manufacturers could be implemented.[18] Regulatory agencies might also pose financial penalties or withdraw an approved drug from the market via AA if the manufacturers fail to conduct a confirmatory trial with "due diligence," a benchmark that needs to be clarified by US FDA.[9]

However, in most of the developing countries including India, there are no formal private and government payer structure, for example, National Institute for Health and Care Excellence in the United Kingdom as well as health technology assessment (HTA) bodies, and organized insurance program that would facilitate reimbursement of novel drugs. Therefore, most of the payments are out-of-pocket expenditure carried by patients. It would hinder timely access of novel compounds, approved via AA, driven by low motivation and willingness of manufacturers. Therefore, regulatory collaboration discussed previously, homogeneity in multi-payer engagement should be promulgated in developing and resource-compromised regions.

Comments

AA pathway was implemented by US FDA as a key regulatory mechanism to provide earlier access to novel drugs for the patients amidst of life-threatening and rare disease. For last 50 years, this AA process has leveraged actual clinical benefit in large patient population. However, there are certain issues that could pose hindrance over both AA pathway as well as confirmatory post-approval studies. It obviates to address as well as settle down those factors which otherwise pose a negative impact in the context of patient welfare. Ultimately, the success of novel anticancer therapy could be ascertained not only via premarketing studies but also in the purview of reducing the disease burden for patients and society.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

ORCID iDs
Sayanta Thakur: https://orcid.org/0000-0002-3308-2220
Sandeep Lahiry: https://orcid.org/0000-0002-6919-0530

References

1. Subpart H–Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses [internet]. Electronic Code of Federal Regulations. Available from: https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=989bffc6d5d0dfacace3b9f073beeb84&mc=true&n=sp21.5.314.h&r=SUBPART&ty=HTML. [Last accessed on 2019 Aug 14].
2. Carpenter D, Kesselheim AS, Joffe S. Reputation and precedent in the bevacizumab decision. N Engl J Med 2011;365:e3.
3. Accelerated Approval [internet]. US Food & Drug Administration. Available from: https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval. [Last accessed on 2019 Aug 14].
4. Gyawali B, Hey SP, Kesselheim AS. Assessment of the clinical benefit of cancer drugs receiving accelerated approval. JAMA Intern Med 2019;179:906-13.
5. Buyse M, Burzykowski T, Michiels S, Carroll K. Individual- and trial-level surrogacy in colorectal cancer. Stat Methods Med Res 2008;17:467-75.
6. Paoletti X, Oba K, Bang YJ, Bleiberg H, Boku N, Bouché O, *et al*.; GASTRIC group. Progression-free survival as a surrogate for overall survival in advanced/recurrent gastric cancer trials: A meta-analysis. J Natl Cancer Inst 2013;105:1667-70.
7. Amir E, Seruga B, Kwong R, Tannock IF, Ocaña A. Poor correlation between progression-free and overall survival in modern clinical trials: Are composite endpoints the answer? Eur J Cancer 2012;48:385-8.
8. Kemp R, Prasad V. Surrogate endpoints in oncology: When are they acceptable for regulatory and clinical decisions, and are they currently overused? BMC Med 2017;15:134.
9. Beaver JA, Howie LJ, Pelosof L, Kim T, Liu J, Goldberg KB, *et al*. A 25-year experience of US food and drug administration accelerated approval of malignant hematology and oncology drugs and biologics: A review. JAMA Oncol 2018;4:849-56.
10. Pursuing Accelerated Approval in Oncology Indications: Regulatory, Medical and Logistical Considerations [internet]. Syneos Health 2016. Available from: https://www.syneoshealth.com/sites/default/files/documents/53424_voinv_35_pursuing_accelerated_approval_wp_lo06.pdf. [Last accessed on 2020 Apr 24].
11. Chen EY, Raghunathan V, Prasad V. An overview of cancer drugs approved by the US Food and Drug Administration based on the surrogate end-point of response rate. JAMA Intern Med 2019;179:915-21.

12. Blumenthal GM, Kluetz PG, Schneider J, Goldberg KB, McKee AE, Pazdur R. Oncology drug approvals: Evaluating endpoints and evidence in an era of breakthrough therapies. Oncologist 2017;22:762-7.
13. Fassnacht M, Terzolo M, Allolio B, Baudin E, Haak H, Berruti A, *et al*.; FIRM-ACT Study Group. Combination chemotherapy in advanced adrenocortical carcinoma. N Engl J Med 2012;366:2189-97.
14. Gyawali B, Kesselheim AS. Reinforcing the social compromise of accelerated approval. Nat Rev Clin Oncol 2018; 15:596-7.
15. Expedited Regulatory pathways in established and Emerging Markets. DIA Global forum 2018. Available from: https://globalforum.diaglobal.org/issue/september-2018/expedited-regulatory-pathways-in-established-and-emerging-markets/. [Last accessed on 2020 Apr 24].
16. New Drugs and Clinical Trial Rule. CDSCO MoHFW 2019. Available from: https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/NewDrugs_CTRules_2019.pdf. [Last accessed on 2020 Apr 24].
17. Kanavos P, Tzouma V, Flannelly C. The impact of regulatory accelerated approval schemes and Htas on access to new oncology medicines: Evidence from 11 countries. Value Health 2018;21:S43. DOI: 10.1016/j.jval.2018.04.244.
18. Gellad WF, Kesselheim AS. Accelerated approval and expensive drugs – A challenging combination. N Engl J Med 2017;376:2001-4.