Editorial

New cancer breakthrough therapies at the United States Food and Drug Administration

Nigel S. B. Rawson[1,2,3]

[1]Eastlake Research Group, Oakville, Ontario, Canada; [2]Fraser Institute, Vancouver, British Columbia, Canada; [3]Canadian Health Policy Institute, Toronto, Ontario, Canada

Correspondence to: Nigel S. B. Rawson, PhD. Eastlake Research Group, Oakville, Ontario 91710, Canada. Email: EastlakeRG@gmail.com.

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Cancer is an emotive word that strikes fear into many people. This is hardly surprising since premature death due to cancer is the leading cause of mortality in Canada, the United States and many other countries. Approximately one in two Canadians are expected to develop cancer in their lifetime (1) and, despite improvements in survival of breast, colorectal, prostate, kidney and liver cancer patients and those with non-Hodgkin's lymphoma, leukemias and multiple myeloma, the 5-year age-standardized survival rate in people over the age of 15 years in Canada is below 75% for many common cancers, much lower (<20%) for lung, brain and pancreas cancers. As a result, pharmaceutical manufacturers are working to develop new and better oncology drugs and patients and healthcare providers want them as soon as possible.

However, when regulatory approval to allow the marketing of a drug is sought, the efficacy evidence for oncology drugs is frequently limited and, when drugs are used in everyday oncology care, the benefits are usually modest at best (2). Nevertheless, huge resources are devoted to trying to find more effective oncology medications because they are vitally important to patients needing hope and to physicians seeking even moderately effective therapies (3-5), and oncology drugs are more likely to receive an expedited review from regulatory agencies in the United States, Canada and Europe (6).

The United States Food and Drug Administration (FDA) has four methods to expedite the review of a new drug through its review and approval process: priority review, accelerated approval, fast track, and breakthrough therapy.

Priority review: once the FDA receives a new drug application, the agency decides whether the drug will receive a priority or standard review. Priority review status directs resources to the evaluation of the application for a drug that, if approved, would be a significant improvement in "the safety or effectiveness of the treatment, diagnosis or prevention of a serious condition" (7). The FDA aims to make a decision on a priority review application within 6 months compared with 10 months for a standard review. However, priority review status does not alter "the scientific/medical standard for approval or the quality of evidence required" (7).

Accelerated approval: an accelerated approval is designed to enable the FDA to expedite approval of new drugs for serious conditions that fill unmet medical needs on the basis of whether the product has an effect on a surrogate marker (a measure that is thought to predict clinical benefit), or an intermediate clinical endpoint (a measure of therapeutic effect considered to be reasonably likely to predict the benefit of a drug) (8). The pharmaceutical manufacturer is required to conduct post-approval studies to confirm that the surrogate or intermediate endpoint predicts the drug's benefit. When these studies verify the clinical benefit, the FDA will normally terminate the requirement but, if they fail, the drug's approval may be withdrawn or the indication changed.

Fast track: fast track is yet another process intended to "expedite the review of new drugs to treat serious conditions and fill an unmet medical need" (9). Fast track designation must be requested by the drug's manufacturer, which can

make the request at any time during the development of the drug. Early and frequent communication between the FDA and manufacturer is encouraged throughout both the development and review processes of fast track drugs to ensure that issues are resolved quickly.

Breakthrough therapy: this is the most recently introduced (in 2012) process designed to "expedite the development and review of new drugs intended to treat a serious condition" for which "preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy" based on a clinically significant endpoint, usually one that measures an effect on irreversible morbidity or mortality (10). Breakthrough therapy designation is requested by the pharmaceutical manufacturer, although the FDA may suggest that the company consider submitting a request.

In a recent publication, Hwang *et al.* evaluated the efficacy and safety of 58 new oncology drugs approved by the FDA between 2012 and 2017 (25 with breakthrough designation and 23 without) and compared the "review times" of the two groups to assess the association between breakthrough designation and speed of drug development (11). I have put quotation marks around review times because Hwang *et al.* defined this measure as the duration between the date of the Investigational New Drug (IND) application, which marks the start of human trials, and first approval by the FDA. As far as I am aware, all previous analyses of the time required to review a new drug have defined the extent of the review as the time between submission of the marketing application and regulatory approval; this measures the time taken by the agency for its regulatory review work, with the exception of any period during which the agency is waiting for a response from the manufacturer. The duration between the IND application and regulatory approval encompasses the time required by the manufacturer to complete its clinical trials, which can vary widely and is beyond the control of the regulatory agency.

Using their measure of review time, Hwang *et al.* found that oncology drugs with breakthrough designation were approved by the FDA almost 2 years earlier than non-breakthrough drugs (11). However, it is important to note that 95% of the 58 oncology drugs received some type of expedited review, with at least 37 receiving more than one type (only combinations of programs with more than two observations were reported). The authors do not provide separate numbers of the combinations with the other expedited programs for breakthrough and non-breakthrough drugs, which would have been useful. More than 72% of the drugs also received orphan drug status, which although this does not imply an expedited review, focuses attention on a drug. While multivariable analyses designed to control for all these different programs were performed, residual confounding resulting from some unexplained impact of multiple programs remains possible.

Only 1 (4%) of the 25 breakthrough oncology drugs was approved on the basis of overall survival; approval of the other 24 (96%) was based on progression-free survival or response rates. In contrast, overall survival was the basis for the approval of 9 (27%) of the 23 non-breakthrough oncology drugs. No statistically significant differences in progression-free survival, response rates, proportion of drugs with clinically meaningful improvements in progression-free survival, or innovative mechanism of action were found between breakthrough and non-breakthrough drugs.

Hwang *et al.* concluded that patients, clinicians, regulators and other stakeholders should be given an opportunity to redefine the minimum level of expected clinical benefit needed to qualify for breakthrough therapy status in order to provide a more reliable signal of truly transformative drugs that achieves both legislative intent and patient expectations (11). More stringent criteria for breakthrough status by the FDA may result in fewer products receiving the designation, but a reduction in the number of new cancer drugs given breakthrough therapy designation could also free-up resources at the FDA.

Since 95% of the oncology drugs approved within the study observation period received one or more of the other three types of expedited programs, this conclusion may be logical and even reasonable, especially if reducing the number of breakthrough oncology drugs would result in more drugs for other important therapeutic indications, such as rare diseases, receiving breakthrough designation. However, cancer has strong political and emotional dimensions so that decisions about whether oncology drugs should be prioritized, no matter whether they deserve it, may be based more on these elements than a balanced approach. Whether the political and emotional aspects are encouraged by the pharmaceutical industry, as some authors have suggested (12), or are simply the result of the fear that cancer provokes, or both, is unresolved. Regardless of the reasons, new cancer treatments, such as immunotherapies (13) which have shown benefits against several cancers including some that until now have lacked effective therapy, are raising patients' hopes so that the demand for the rapid approval of new

oncology drugs, whether under breakthrough therapy designation and/or other expedited programs, will continue.

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Footnote

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