Breakthrough Therapy Designation Criteria Identify Drugs that Improve Clinical Outcomes for Patients: A Case for More Streamlined Coverage of Promising Therapies

Grace Collins, Mark Stewart, Brittany McKelvey, Hillary Stires, and Jeff Allen

ABSTRACT

The breakthrough therapy designation (BTD) process was created to expedite clinical development timelines for drugs intended to treat serious conditions and preliminary clinical evidence indicates the drug may demonstrate substantial improvement over existing therapies. This analysis demonstrates that BTD is a valuable tool for expediting approval of promising therapies in oncology. By comparing drugs indicated to treat non–small cell lung cancer (NSCLC) approved with BTD or without BTD between January 2013 and October 2021, BTD drugs reduced the risk of death by a median of 31% and progression by a median of 48%, while drugs never receiving BTD reduced the risk of death and progression by a median of 15% and 41.9%, respectively. These findings show that BTD criteria accurately identify drugs that improve long-term outcomes for patients with cancer and warrant coordinated efforts to ensure timely coverage decisions and access for patients.

Since its inception, breakthrough therapy designation (BTD) has helped expedite clinical development timelines for drugs intended to treat a serious condition with preliminary clinical evidence indicating the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s). Several analyses have shown BTD facilitates earlier approval of therapies compared with therapies without BTD (1, 2). To date, the use of BTD has helped sponsors and the FDA streamline development and approval of 225 drugs, over 56% of which were oncology indications (3).

Despite faster FDA approval of these therapies, processes associated with coverage and reimbursement by insurance programs, including the Centers for Medicare and Medicaid Services (CMS), do not follow the same expedited timelines. This is particularly true for entirely novel treatments, such as first-in-class products, that involve new mechanisms of action or new technologies altogether, many of which are approved through an expedited program such as BTD. When payment processes are not finalized immediately following FDA approval, barriers to timely patient access can occur (4). While coverage of oncology drugs has not historically been an impediment to access, determinations of add-on payments or code sets can potentially delay patient access if not done in a timely fashion. This issue was most notable with the recent introduction of chimeric antigen receptor (CAR) T-cell therapies for certain blood cancers (5).

In disease areas where recent innovations in treatment have contributed to lowered population mortality, such as in non–small cell lung cancer (NSCLC), delays between FDA approval and initiation of processes for coverage of new treatments could impede public health benefit (6). Recent discussions on CMS coverage processes for expedited approvals provide an opportunity to consider ways to align CMS and FDA procedures to ensure drugs qualifying for expedited programs, such as BTD, are covered at the time of approval. In oncology, clinical guidelines included in the National Comprehensive Cancer Network's (NCCN) Drugs and Biologics Compendium are used by insurers to inform coverage decisions. This has helped streamline reimbursement following the approval of new cancer drugs, but does not extend to other therapeutic areas, medical devices, and diagnostics, nor address timely coding processes, budgeting, or other procedures associated with payment.

As such, it is necessary to identify appropriate triggers that can help select novel products early in development to support more streamlined discussions regarding coverage. To assess whether BTD criteria identify high-priority drugs that improve outcomes for patients with cancer, and thereby evidence to support the importance of timely coverage, we compared outcomes data supporting approvals of and clinical guidelines for drugs with and without BTD indicated to treat NSCLC. NSCLC was chosen as a case study due to the high number of BTDs given to lung cancer indications and availability of long-term follow-up data. The results demonstrate that BTD drugs indicated for NSCLC improve outcomes and have more recommendations based on higher-quality data suggesting the treatments were more appropriate compared to drugs that never received a BTD. These findings support the notion that the qualifying criteria for BTD support the identification of drugs that improve outcomes for patients with NSCLC.

These findings demonstrate that BTD drugs provide improved clinical utility suggesting it would be beneficial to establish a

Friends of Cancer Research, Washington, D.C.

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Corresponding Author: Mark Stewart, Friends of Cancer Research, 1800 M Street NW, Suite 1050 South, Washington, DC 20036. E-mail: mstewart@focr.org

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Translational Relevance

The breakthrough therapy designation (BTD) process was created to expedite clinical development timelines for drugs intended to treat serious conditions and preliminary clinical evidence indicates the drug may demonstrate substantial improvement over existing therapies. This analysis demonstrates that BTD is a valuable tool for expediting approval of promising therapies in oncology. By comparing drugs indicated to treat non-small cell lung cancer (NSCLC) approved with BTD or without BTD between January 2013 and October 2021, BTD drugs reduced the risk of death by a median of 31% and progression by a median of 48%, while drugs never receiving BTD reduced the risk of death and progression by a median of 15% and 41.9%, respectively. These findings show that BTD criteria accurately identify drugs that improve long-term outcomes for patients with cancer and warrant coordinated efforts to ensure timely coverage decisions and access for patients.

mechanism through which a BTD would initiate processes to expedite CMS coverage. An expedited program at CMS would not include automatic coverage, but rather enable processes to ensure BTD therapies and novel technologies sufficiently meet approval and reimbursement requirements more quickly, and as appropriate, have processes in place for ensuring a product is covered at the time of approval to not delay patient access. An initial pilot of this program would provide valuable information around whether these processes are feasible, the value they bring, and identify areas needing improvement prior to wider implementation. The Parallel Review Program, which helps coordinate FDA and CMS reviews for medical devices and was initially run as a pilot for 5 years before permanent implementation, serves as a precedent for a similar process, outlined below (7).

(i) FDA notifies CMS when a novel product (e.g., first indication) receives a BTD or is participating in another expedited regulatory pathway.
   a. This initial notification to CMS would provide awareness of approval timelines for forthcoming products that are beneficial for patients with serious/life threatening illnesses.

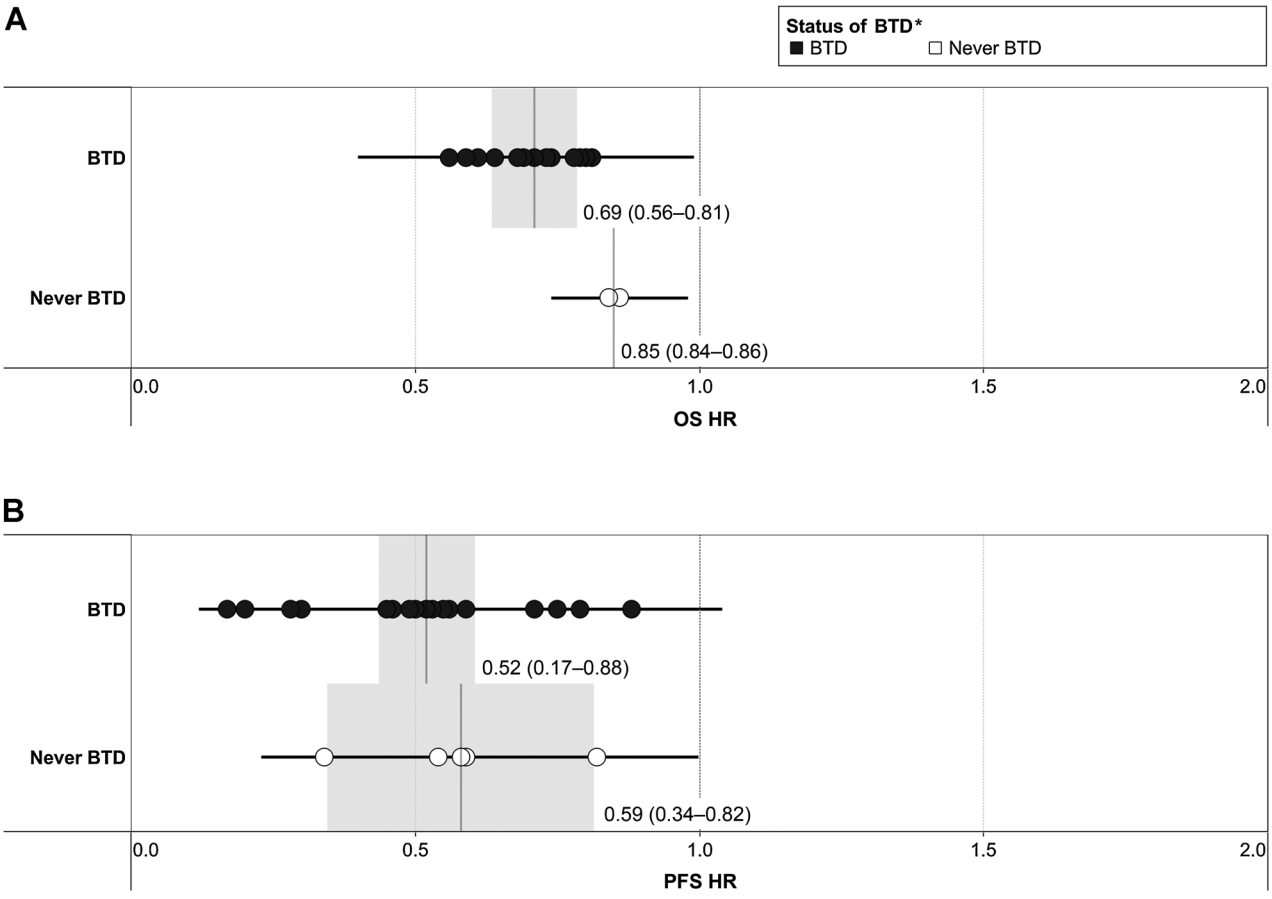

Figure 1.
Outcomes supporting approvals of drugs for NSCLC. Median HR (range) for approvals supported by an RCT with the primary or coprimary endpoint of OS (**A**) and/or PFS (**B**). *"BTD", approvals for a drug or a combination of drug(s) including drugs that have ever received BTD for any indication; "Never BTD", approvals for drugs that have never received BTD for any indication.

Early notification about these products would allow additional time for CMS to coordinate resources necessary to support timely coverage decisions.

(ii) Sponsors of products that receive BTD would have the opportunity to participate in an Expedited Coverage pilot.
   a. The sponsor for a novel product or class of products could apply for the Expedited Coverage pilot prior to FDA approval. CMS would then evaluate whether the product or class (i) has important implications for Medicare beneficiaries and (ii) does not have a clear path to reasonable coverage (e.g., there are gaps in evidence or unique approaches to coverage may be necessary). Should CMS determine the product or product class meet the above requirements, an expedited process would begin.
   b. This process would enable earlier discussions regarding topics such as coverage decisions, coding, eligibility for New Technology Add-On Payment (NTAP), and/or CMS budgeting implications. Sponsors would have earlier opportunities to coordinate and communicate with CMS regarding premarket data necessary to support initial coverage at the time of FDA approval and to receive guidance from CMS on the longer-term path to coverage, including additional data that may be needed to support a national coverage decision. This would ensure clinical trials are designed to provide appropriate data supporting FDA approval and to inform coverage decisions.

Expediting development is a resource intensive process for both the FDA and sponsors, and more drugs are approved using BTD and/or other expedited pathways each year (2). For the processes proposed above to be successful, CMS will need additional resources to support their involvement. A coordinated, well-supported, and timely process for determining coverage of BTD products is necessary to ensure the value brought by BTD facilitates earlier patient access to effective treatments.

Approach

We identified 52 drug and biologics applications approved between January 1, 2013 and October 1, 2021, for an NSCLC indication and collected key clinical trial and outcomes data from

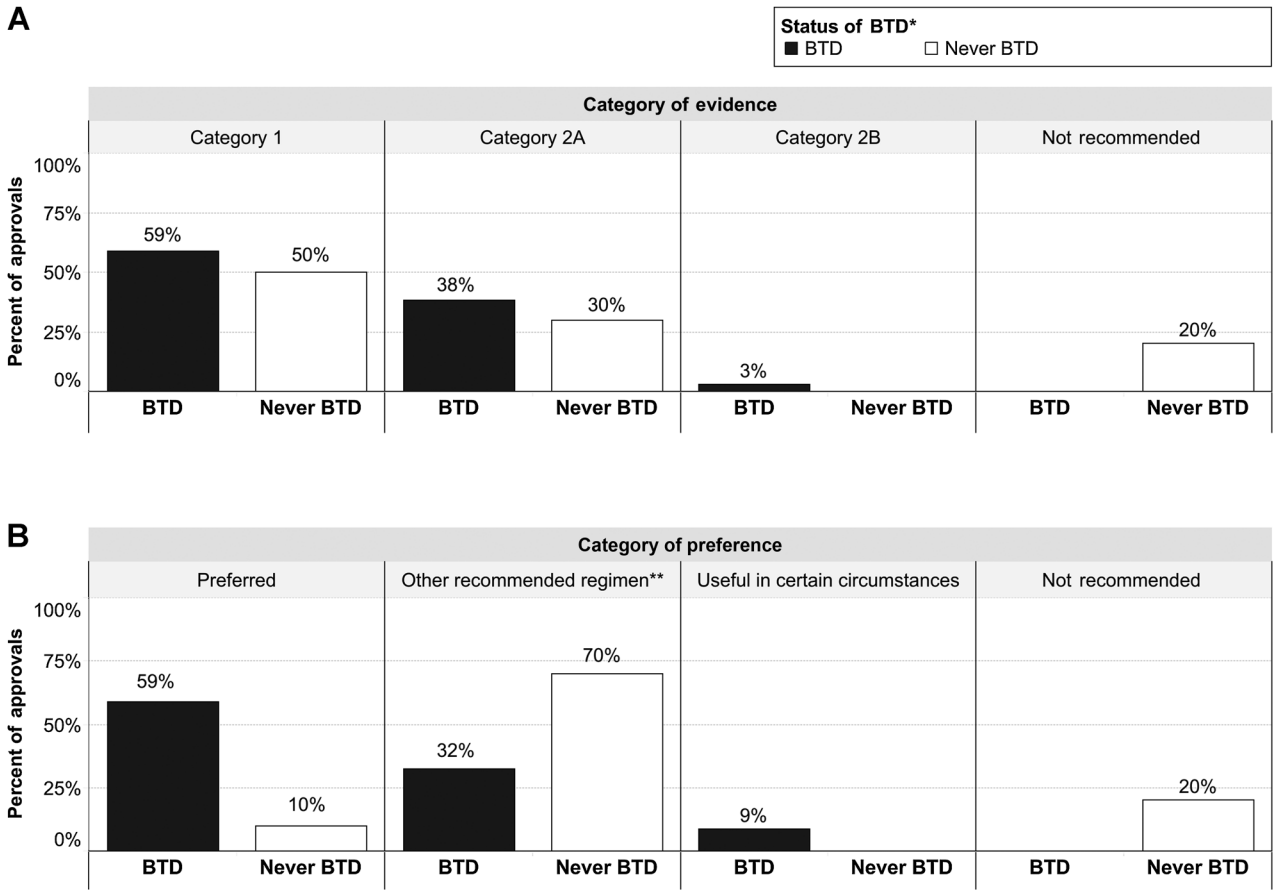

Figure 2.

Characteristics of NCCN recommendations for NSCLC approvals from 2013 to 2021. **A,** Percentage of BTD approvals and percentage of Never BTD approvals by category of evidence. **B,** Percentage of BTD approvals and percent of Never BTD approvals by category of preference. *"BTD", approvals for a drug or a combination of drug(s) including drugs that have ever received BTD for any indication; "Never BTD", approvals for drugs that have never received BTD for any indication. **Other recommended regimens are uses that are more toxic, less affordable, less efficacious, and/or are based on less mature data (8).

publicly available review documents and labels published online in the Drugs@FDA database (Supplementary Table S1). We also collected recommended uses for these approvals from the NCCN Guidelines for NSCLC (version 7.2021) and noted the assigned category of preference and category of evidence.

The sample included 41 applications for drugs that had ever received BTD (BTD) and 11 applications for drugs that had never received a BTD for any indication (Never BTD). Thirty-four percent of BTD applications were also reviewed under the Accelerated Approval pathway.

Thirty-one approvals (59.6%) were supported by data from a randomized clinical trial(s; RCT) with the primary endpoint (pEP) or coprimary endpoint(s; cpEP) of progression-free survival (PFS) and/or overall survival (OS). Twenty-one approvals (40.4%) were excluded from the outcomes analysis because their labels were supported by data from nonrandomized trials and eight were excluded from the NCCN analysis to avoid double counting the same indication (Supplementary Table S1). Twenty-three approvals supported by an RCT (74.2%) included a BTD drug. The remaining eight approvals supported by an RCT were for Never BTD drugs.

Of the 16 approvals supported by trials with OS as a pEP or cpEP (14 BTD, 2 Never BTD), patients receiving BTD drugs had a 31% lower risk of death than those assigned to standard of care (SOC; median HR = 0.69; range: 0.56–0.81) whereas patients receiving a Never BTD drug had a 15% lower risk of death (median HR = 0.85; range: 0.84–0.86; **Fig. 1A**). Similarly, among approvals supported by a trial(s) with the pEP or cpEP of PFS (16 BTD, 6 Never BTD), patients receiving a BTD drug had a 48% reduced risk of progression than those assigned to receive SOC (median HR = 0.52; range: 0.17–0.88) compared with only 41.9% reduced risk of progression for patients receiving a Never BTD drug (median HR = 0.59; range: 0.34–0.82; **Fig. 1B**).

The NCCN Compendium serves as a source of information to support clinical decision making about the appropriate use of drugs in patients with cancer. A Category 1 recommendation is based on high-quality data and a high level of consensus among experts that the use is appropriate. Among NSCLC approvals between 2013 and 2021, including those supported by data from non-RCTs, 59% of BTD drugs, and 50% of Never BTD drugs met the bar for a Category 1 recommendation. For preference, 59% of BTD drugs are preferred interventions based on superior evidence of safety, efficacy, and, in some cases, affordability, while only 10% of Never BTD drugs were given a preferred recommendation (**Fig. 2B**; ref. 8)

This analysis is limited as the drugs included were all indicated only for treatment of NSCLC. A comprehensive analysis comparing outcomes data supporting approvals of BTD and non-BTD drugs for all oncology indications is warranted to further evaluate whether the qualifying criteria for BTD are generalizable across cancer types. In addition, the sample is necessarily limited to BTD and Never BTD drugs that reached approved status and therefore have publicly available labels.

Authors' Disclosures

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