Breakthrough Therapy Cancer Drugs and Indications With FDA Approval: Development Time, Innovation, Trials, Clinical Benefit, Epidemiology, and Price

Daniel Tobias Michaeli, MSc, MSc,1,2 and Thomas Michaeli, MD, MSc, MSc2,3,4,5

Abstract

Background: The breakthrough therapy designation (BTD) facilitates the development of drugs with a large preliminary benefit in treating serious or life-threatening diseases. This study analyzes the FDA approval, trials, benefits, unmet needs, and pricing of breakthrough and nonbreakthrough therapy cancer drugs and indications. Patients and Methods: We analyzed 355 cancer indications with FDA approval (2012–2022). Breakthrough and nonbreakthrough indications were compared regarding their FDA approval, innovativeness, clinical trials, epidemiology, and price. Data were extracted from FDA labels, the Global Burden of Disease study, and the Centers for Medicare & Medicaid Services. Hazard ratios (HRs) for overall survival (OS), progression-free survival (PFS), and relative risk (RR) of tumor response were meta-analyzed across randomized controlled trials. Objective response rates (ORRs) were meta-analyzed for single-arm trials. Results: We identified 137 breakthrough and 218 nonbreakthrough cancer indications. The median clinical development time was 3.2 years shorter for breakthrough drugs than for nonbreakthrough drugs (5.6 vs 8.8 years; P = .002). The BTD was more frequently granted to biomarker-directed indications (46% vs 34%; P = .025) supported by smaller trials (median, 149 vs 326 patients; P < .001) of single-arm (53% vs 27%; P < .001) and phase I or II design (61% vs 31%; P < .001). Breakthrough indications offered a greater OS (HR, 0.69 vs 0.74; P = .031) and tumor response (RR, 1.48 vs 1.32; P = .006; ORR, 52% vs 40%; P = .004), but not a PFS benefit (HR, 0.53 vs 0.58; P = .212). Median improvements in OS (4.8 vs 3.2 months; P = .002) and PFS (5.4 vs 3.3 months; P = .005) but not duration of response (8.7 vs 4.7 months; P = .245) were higher for breakthrough than for nonbreakthrough indications. The BTD was more frequently granted to first-in-class drugs (42% vs 28%; P = .001) and first-in-indication treatments (43% vs 29%; P < .001). There were no differences in treatment and epidemiologic characteristics between breakthrough and nonbreakthrough drugs. Breakthrough drugs were more expensive than nonbreakthrough drugs (mean monthly price, $38,971 vs $22,591; P = .0592). Conclusions: The BTD expedites patient access to effective and innovative, but also expensive, new cancer drugs and indications.

Background

In 2012, US Congress introduced the breakthrough therapy designation (BTD) under Section 902 of the FDA Safety and Innovation Act. To keep pace with the biotechnological advances of the 21st century, the US Congress aimed to facilitate the development of and expedite patient access to highly innovative drugs.1 Specifically, patients with serious or life-threatening diseases should be granted access to therapies whose preliminary large benefit can already be observed in phase I or II trials.2,3 Therefore, the BTD permits the FDA to allocate resources to these promising breakthrough drugs by providing pharmaceutical companies with “intensive guidance on … efficient drug development,” which entails shorter response timelines, close collaboration with senior FDA officials, and a rolling review of clinical evidence.3,4 Moreover, the BTD justifies the use of historical controls as control groups and smaller, less time-intensive trials.3,5

Ten years after its inception, the BTD has been vividly lauded by patients, the pharmaceutical industry, and the FDA itself. From 2012 to 2022, the FDA received 1,289 BTD requests, of which 506 (39%) were granted (see Figure S1 in the supplementary material, available online with this article). This led to the approval of 157 breakthrough drugs. The BTD has become an integral part of the FDA’s expedited review process, which includes priority review and fast track.6 However, the new BTD has been heavily criticized by physicians and academics for nurturing the development of potentially unsafe drugs that are approved based on small, nonrandomized, unblinded trials.1,5,7

The efficacy of breakthrough drugs remains disputed. Patients and physicians associate the term “breakthrough” with a major scientific disruption. Consequently, 3 surveys demonstrated that physicians are more inclined to prescribe a breakthrough-designated drug than a similarly effective alternative.8–10 Yet, previous studies that analyzed the first 5 years of the BTD could not confirm a consistent superior clinical benefit of breakthrough compared with nonbreakthrough drugs.11–13 Nonetheless, pharmaceutical companies demand 25% higher list prices for breakthrough drugs.11 Although these studies were limited in sample size and analyzed time horizon,11–13 some authors have criticized the “laudatory [breakthrough] labels [that] promote the use of new drugs that frequently offer limited additional benefits.”7

This study clarifies the role of the BTD in drug development and clinical practice by analyzing a uniquely large sample of 114 cancer drugs and 355 indications with FDA approval over 10 years. Breakthrough and nonbreakthrough cancer drugs and

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1Department of Medical Oncology, National Center for Tumor Diseases, Heidelberg University Hospital, Heidelberg, Germany; 2Schumpeter School of Business and Economics, University of Wuppertal, Wuppertal, Germany; 3Department of Personalized Oncology, University Hospital Mannheim, Heidelberg University, Mannheim, Germany; 4German Cancer Research Center–Hector Cancer Institute, University Medical Center Mannheim, Mannheim, Germany, and 5Division of Personalized Medical Oncology, German Cancer Research Center, Heidelberg, Germany.
indications are compared regarding their clinical development time, clinical trial evidence, efficacy, innovativeness, epidemiology, and pricing.

**Patients and Methods**

**Sample Identification**

We accessed the Drugs@FDA database to identify all new drugs, including New Drug Applications (NDAs) and Biologics License Applications (BLAs), with FDA approval between January 1, 2000, and January 1, 2022 (Supplementary Figure S2). The sample was then restricted to include only anticancer drugs, excluding non-oncology, supportive care, and diagnostic agents, while including gene and cell therapies. For each drug, we identified all anticancer indications, including original and supplemental indications, approved until January 1, 2022. The sample was then restricted to include only drugs and indications approved after January 1, 2013. The breakthrough therapy designation status was linked to each indication using the FDA’s breakthrough drug database (Supplementary Table S1).

**Data Collection**

We collected data on the FDA approval, clinical trial evidence, cancer epidemiology, and price for each cancer drug and indication from publicly available sources (Supplementary Table S1).

**FDA Approval**

For each anticancer indication, FDA labels were accessed to gather data on drug, indication, and clinical trial characteristics. The first reviewer (D.T. Michaeli) independently retrieved data from FDA labels, which was then cross-checked by the second reviewer (T. Michaeli) with data found on ClinicalTrials.gov and associated peer-reviewed publications. Disagreements were resolved in consensus or by consulting an experienced oncologist. Full details of the data extraction method have been described elsewhere.

Drugs were categorized by their number of indications, innovativeness, mechanism of action, and product type. Biotechnological innovation was determined on a drug level based on each compound’s target according to the definition provided by Lanthier et al (first-in-class vs advance-in-class vs addition-to-class). For multi-indication drugs, FDA approvals were classified as original and supplemental indications. For all original indications, we collected data on the date the investigational new drug (IND) application became effective and the FDA approval date from FDA documents or the US Patent and Trademark Office.

Indications were then categorized by clinical novelty, approval type, treatment regimen, cancer type, biomarker status, and line of therapy. Clinical novelty was determined on an indication level based on each indication’s target and treated disease (first-in-indication vs advance-in-indication vs addition-to-indication).

The pivotal trial for each indication was characterized by the number of enrolled patients, phase, design, blinding, number of arms, comparator, and primary endpoint. For randomized controlled trials (RCTs), we extracted hazard ratios (HRs) for overall survival (OS), and/or progression-free survival (PFS), and/or the relative risk (RR) of tumor response with 95% confidence intervals. The number of patients and events were noted for the control and intervention arms. For single-arm trials, we obtained the objective response rate (ORR). Furthermore, we extracted median improvements in OS, PFS, and duration of tumor response with IQRs for each indication.

**Cancer Epidemiology**

For each indication, we retrieved data on the treated cancer’s incidence, prevalence, and disability-adjusted life years (DALYs), composed of years lived with disability and years of life lost from the Global Burden of Disease study. Five-year survival rates and number of available treatment options per cancer entity were extracted from the National Cancer Institute’s list of FDA-approved drugs for specific types of cancer.

**Drug Prices**

Drug prices were retrieved in January 2023 from the Centers for Medicare & Medicaid Services and Medicare’s Plan Finder tool for patients covered under Medicare Parts B and D. Consistent with previous studies, monthly treatment costs were estimated for an average adult with a body surface area of 1.7 m² weighing 70 kg based on the dosing regimen in the FDA label. Full details of the drug price calculation have been described elsewhere.

**Statistical Analysis**

Breakthrough and nonbreakthrough therapy cancer drugs and indications were compared regarding their clinical development time; drug, indication, pivotal clinical trial, and cancer epidemiologic characteristics; efficacy; and price.

First, clinical development times, calculated as the difference between IND application and NDA/BLA approval for original indications, were compared using Kaplan-Meier survival curves, log-rank tests, and a Cox proportional hazard model. Second, the distribution of categorical variables describing the drug, indication, clinical trial, and epidemiology characteristics of breakthrough and nonbreakthrough drugs was compared using Fisher exact tests. Medians were compared with Kruskal-Wallis tests. Third, a series of random effects meta-analyses was conducted for clinical trials with available outcome data. HRs for OS and PFS were meta-analyzed in all RCTs, as were RRs for tumor response. ORRs were meta-analyzed in all single-arm trials. Differences between HRs, RRs, and ORRs for breakthrough and nonbreakthrough therapy indications were compared using the Cochran’s Q test. Fourth, mean monthly drug prices were compared in January 2023. Mean monthly prices were further calculated for all drugs covered under Medicare Part B from 2015 to 2023, and the compounded annual growth rate (CAGR) of drug prices was also calculated from 2015 to 2023. Finally, we reevaluated the comparison between breakthrough and nonbreakthrough drugs through stratification of full and accelerated approvals.

Data were stored in Excel and analyzed with Stata, version 14.2 (StataCorp LP). Two-tailed P values <.05 were considered significant. This study followed the STROBE reporting guidelines where applicable.

**Results**

The FDA approved 720 new drugs from 2000 to 2022, with 170 anticancer drugs with FDA approval in 455 indications. After 2012, a total of 114 drugs and 355 indications received approval and were included in the final sample for analysis. Of these 355
indications, the FDA granted the BTD to 137 (39%) indications (Supplementary Figure S2).

Clinical Development Time
For all original drug approvals, we measured clinical development times as the difference between the IND application date and the first FDA indication approval. The IND application date was available for 106 (93%) of 114 drugs in our sample. The clinical development time was significantly shorter for breakthrough versus nonbreakthrough drugs (median clinical development time, 5.6 vs 8.8 years; \( P = .002; \text{HR} = 1.82; P = .003 \)) (Figure 1).

Drug Characteristics
There were 60 (17%) and 54 (15%) drugs with and without the breakthrough designation for the original FDA indication approval, respectively (Table 1). Breakthrough drugs were more innovative than nonbreakthrough drugs. On a biotechnological level, more breakthrough than nonbreakthrough drugs were first-in-class (42% vs 28%; \( P = .001 \)). Accordingly, breakthrough drugs more frequently acted via a novel mechanism of action than nonbreakthrough drugs: immune-regulatory (37% vs 19%), targeted (63% vs 70%), and cytotoxic (0% vs 11%; \( P = .004 \)). There was a tendency for breakthrough drugs to more frequently be antibodies (27% vs 13%) or antibody–drug conjugates (12% vs 6%; \( P = .147 \)).

Indication Characteristics
On an indication level, the BTD was more often granted to first-in-indication treatments (43% vs 29%; \( P < .001 \)) (Table 2). Breakthrough indications were more likely to be original than supplemental FDA approvals (53% vs 47%; \( P < .001 \)). Breakthrough and nonbreakthrough indications did not significantly differ in treatment type, cancer type, or line of therapy. The FDA more frequently granted breakthrough designation to biomarker-based indications (46% vs 34%; \( P = .025 \)). The breakthrough designation was often granted to treatments for lung (18% vs 15%), breast (10% vs 6%), thyroid (5% vs 1%), and endometrial cancer (2% vs 0%) (Supplementary Table S2).

A total of 69 (19%) indications received fast-track review, 112 (32%) indications received accelerated approval, and 233 (66%) indications received orphan designation. Breakthrough indications were significantly more likely than nonbreakthrough indications to receive accelerated approval (44% vs 24%; \( P < .001 \)) (Table 2). Among these accelerated approvals, there was no difference in the rate of withdrawals between breakthrough and nonbreakthrough indications until March 31, 2023 (10% vs 19%; \( P = .199 \)).

Pivotal Clinical Trial Characteristics
A median of 149 patients (IQR, 84–521 patients) were enrolled in the pivotal clinical trials for breakthrough indications compared with 326 patients (IQR, 137–616 patients; \( P < .001 \)) for nonbreakthrough indications. Breakthrough indications were less frequently supported by double-blind (18% vs 28%; \( P = .022 \)), concurrent RCTs (44% vs 70%; \( P < .001 \)) of phase III design (39% vs 69%; \( P < .001 \)). Instead, clinical evidence for breakthrough indications was commonly gathered in phase II (53% vs 27%; \( P < .001 \)) single-arm trials (50% vs 28%; \( P < .001 \)). The primary endpoint for pivotal clinical trials that supported breakthrough relative to nonbreakthrough indications less frequently involved an assessment of OS (9% vs 20%; \( P = .006 \)) but more frequently assessed tumor response (57% vs 31%; \( P < .001 \)).

Cancer Epidemiology
Breakthrough and nonbreakthrough indications did not significantly differ in disease incidence or prevalence. Disease severity as measured by DALYs as well as 5-year survival and the number
Table 2. Characteristics of Breakthrough and Nonbreakthrough Cancer Indications Approved by the FDA, 2012–2022

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No ( % )</th>
<th>Yes ( % )</th>
<th>P Value*</th>
</tr>
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<td><strong>Breakthrough Therapy</strong></td>
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<td>Indication characteristics</td>
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<td>Clinical novelty</td>
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<tr>
<td>Addition-to-indication</td>
<td>43 (19.7)</td>
<td>5 (3.6)</td>
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<tr>
<td>Advance-in-indication</td>
<td>112 (51.4)</td>
<td>73 (33.3)</td>
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<td>First-in-indication</td>
<td>43 (28.9)</td>
<td>59 (43.1)</td>
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<td>Indication approval sequence</td>
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<td></td>
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<td>Original indication approval</td>
<td>161 (73.9)</td>
<td>72 (52.6)</td>
<td></td>
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<tr>
<td>Supplemental indication approval</td>
<td>57 (26.1)</td>
<td>65 (47.4)</td>
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<tr>
<td>Treatment type</td>
<td>.178</td>
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<tr>
<td>Combination</td>
<td>90 (41.3)</td>
<td>46 (33.6)</td>
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<tr>
<td>Monotherapy</td>
<td>128 (58.7)</td>
<td>91 (66.4)</td>
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<td>Cancer type</td>
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<td>Hematologic</td>
<td>67 (30.7)</td>
<td>47 (34.3)</td>
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<tr>
<td>Solid</td>
<td>151 (69.3)</td>
<td>90 (65.7)</td>
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<td>No</td>
<td>144 (66.1)</td>
<td>74 (54.0)</td>
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<tr>
<td>Yes</td>
<td>74 (33.9)</td>
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<td>Line of therapy</td>
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<tr>
<td>First-line</td>
<td>112 (51.4)</td>
<td>60 (43.8)</td>
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<tr>
<td>Second-line</td>
<td>77 (35.3)</td>
<td>63 (46.0)</td>
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<tr>
<td>≥Third-line</td>
<td>29 (13.3)</td>
<td>14 (10.2)</td>
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</tr>
<tr>
<td><strong>Total no. of indications</strong></td>
<td>218 (61.4)</td>
<td>137 (38.6)</td>
<td></td>
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<tr>
<td>Special FDA designations</td>
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<tr>
<td>Orphan designation</td>
<td>138 (63.3)</td>
<td>95 (69.3)</td>
<td>.253</td>
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<tr>
<td>Fast track</td>
<td>44 (20.2)</td>
<td>25 (18.2)</td>
<td>.682</td>
</tr>
<tr>
<td>Accelerated approval</td>
<td>52 (23.9)</td>
<td>60 (43.8)</td>
<td>&lt;.001</td>
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<td>27</td>
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<tr>
<td>Pending</td>
<td>26</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Withdrawn/Not converted</td>
<td>10</td>
<td>6</td>
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</tr>
<tr>
<td><strong>Clinical trial characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enrolled patients, median (IQR)</td>
<td>326 (137–616)</td>
<td>149 (84–521)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Clinical trial phase</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>9 (4.1)</td>
<td>11 (8.0)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>59 (27.1)</td>
<td>73 (53.3)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>150 (68.8)</td>
<td>53 (38.7)</td>
<td></td>
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<tr>
<td>Trial design</td>
<td>&lt;.001</td>
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<tr>
<td>Single-arm</td>
<td>61 (28.0)</td>
<td>68 (49.6)</td>
<td></td>
</tr>
<tr>
<td>Nonrandomized controlled</td>
<td>2 (0.9)</td>
<td>6 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Randomized controlled</td>
<td>152 (69.7)</td>
<td>60 (43.8)</td>
<td></td>
</tr>
<tr>
<td>Dose-comparison randomized</td>
<td>3 (1.4)</td>
<td>3 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Type of blinding</td>
<td>.022</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open-label</td>
<td>156 (71.6)</td>
<td>113 (82.5)</td>
<td></td>
</tr>
<tr>
<td>Double-blind</td>
<td>62 (28.4)</td>
<td>24 (17.5)</td>
<td></td>
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<tr>
<td>Clinical trial arms</td>
<td>&lt;.001</td>
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</tr>
<tr>
<td>1 arm</td>
<td>61 (28.0)</td>
<td>68 (49.6)</td>
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<tr>
<td>2 arm</td>
<td>152 (69.7)</td>
<td>65 (47.4)</td>
<td></td>
</tr>
<tr>
<td>≥3 arms</td>
<td>5 (2.3)</td>
<td>4 (2.9)</td>
<td></td>
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<tr>
<td>Primary endpoint</td>
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<td></td>
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<tr>
<td>Overall survival</td>
<td>43 (19.7)</td>
<td>12 (8.8)</td>
<td>.006</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>83 (38.1)</td>
<td>40 (29.2)</td>
<td>.109</td>
</tr>
<tr>
<td>Tumor response</td>
<td>67 (30.7)</td>
<td>78 (56.9)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

(continued in next column)

Table 2. Characteristics of Breakthrough and Nonbreakthrough Cancer Indications Approved by the FDA, 2012–2022 (cont.)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No (Median IQR)</th>
<th>Yes (Median IQR)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breakthrough Therapy</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cancer epidemiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease incidence (per 100,000)</td>
<td>8.5 (5.2–67.6)</td>
<td>15.2 (3.9–67.6)</td>
<td>.559</td>
</tr>
<tr>
<td>Disease prevalence (July 31, 2011)</td>
<td>33.7 (17.6–117.8)</td>
<td>74 (13.2–117.8)</td>
<td>.710</td>
</tr>
<tr>
<td>DALYs per person</td>
<td>10 (5.5–16.4)</td>
<td>8.9 (5.5–16.4)</td>
<td>.111</td>
</tr>
<tr>
<td>YLL per person</td>
<td>9.3 (4.8–16.2)</td>
<td>8.3 (4.8–16.2)</td>
<td>.127</td>
</tr>
<tr>
<td>YLD per person</td>
<td>0.5 (0.3–0.7)</td>
<td>0.5 (0.3–0.7)</td>
<td>.514</td>
</tr>
<tr>
<td>5-year survival rate</td>
<td>66.2%</td>
<td>75.2%</td>
<td>.207</td>
</tr>
<tr>
<td>No. of available treatments</td>
<td>16 (11–38)</td>
<td>16 (11–38)</td>
<td>.484</td>
</tr>
</tbody>
</table>

In this table, the breakthrough designation was analyzed on an indication level. Abbreviations: DALYs, disability-adjusted life years; YLD, years lived with disability; YLL, years of life lost.

*P values were calculated based on Fisher exact tests.

**P values were calculated based on Kruskal-Wallis tests.

***Disease incidence and prevalence rates (per 100,000) for the US population in 2019.

of available treatments were the same for nonbreakthrough and breakthrough indications.

**Clinical Benefit**

Breakthrough indications were associated with a lower likelihood of death compared with nonbreakthrough indications (HR, 0.69 [95% CI, 0.66–0.73] vs 0.74 [95% CI, 0.71–0.76]; P = .031) and offered significantly greater improvements in OS (median number of months, 4.8 [IQR, 3.5–9.4 months] vs 3.2 months [IQR, 2.2–4.4 months]; P = .002) (Figure 2). Breakthrough indications were not associated with a lower likelihood of tumor progression (HR, 0.53 [95% CI, 0.47–0.60] vs 0.58 [95% CI, 0.54–0.62]; P = .212), but they provided significantly greater improvements in PFS (median, 5.4 months [IQR, 2.5–9.7 months] vs 3.3 months [IQR, 1.3–5.4 months]; P = .005). Tumor response rates were higher for breakthrough compared with nonbreakthrough indications (RR, 1.48 [95% CI, 1.38–1.58] vs 1.32 [95% CI, 1.27–1.37]; P = .006). The median duration of response was not significantly longer for breakthrough indications (median, 8.7 months [IQR, 2.7–10.1 months] vs 4.7 months [IQR, 2.5–7.6 months]; P = .245). Consistently, more patients responded to treatment with breakthrough than with nonbreakthrough indications in single-arm trials (ORR, 52% [95% CI, 47%–57%] vs 40% [95% CI, 33%–46%]; P = .004). Figure 3 shows that single-arm trials with higher tumor response rates, expressed as ORRs, were at a significantly higher likelihood of receiving the BTD (odds ratio, 4.29; 95% CI, 1.85–6.74; P = .001). The direction and significance of results were confirmed in a series of meta-regression analyses of the BTD on OS, PFS, and tumor response outcomes (Supplementary eTable 3).

**Drug Prices**

Mean monthly prices were 73% higher for breakthrough (mean monthly price, $38,971; 95% CI, $25,547–$52,394) versus nonbreakthrough drugs (mean monthly price, $22,591; 95% CI, $12,387–$32,795; P = .0592) (Figure 4). Quarterly drug price data were available for 48 drugs covered under Medicare Part B. From 2015 to 2023, drug prices increased by an average of 125% for breakthrough and 138% for nonbreakthrough drugs. Inflation
amounted to 2.77% per quarter, but drug prices increased by a quarterly CAGR of 2.67% for breakthrough and 4.08% for non-breakthrough drugs.

Standard Approval Versus Accelerated Approval

The previous analyses were reevaluated in the subgroups of drugs and indications receiving standard and accelerated approval. Supplementary Figure S4B shows that in the subgroup of drugs with accelerated approval, breakthrough drugs had shorter clinical development times (median, 5.4 vs 8.3 years; \( P = .009 \)). Supplementary Figure S4A shows that this association was not significant in the sample of drugs with standard approval because of a limited sample size (median, 6.6 vs 8.9 years; \( P = .362 \)). Across both subgroups, most drug characteristics did not significantly differ because of the small sample sizes (Supplementary Table S4). In the standard approval subgroup, there was a trend for breakthrough drugs to more frequently be first-in-class (50% vs 24%; \( P = .053 \)) and for breakthrough indications to be first-in-indication (34% vs 24%; \( P = .001 \)). These associations were not significant for the accelerated approval subgroup. In the accelerated approval subgroup, a higher rate of biomarker-directed therapies was observed for breakthrough than for nonbreakthrough indications (53% vs 29%; \( P = .012 \)). In the accelerated approval subgroup, pivotal trial characteristics did not differ between the breakthrough and nonbreakthrough indications (Supplementary Table S5). However, for the standard approval subgroup, breakthrough indications were more often supported by single-arm (26% vs 13%; \( P = .012 \)) phase I or II trials (34% vs 14%; \( P = .002 \)) evaluating tumor response (88% vs 82%; \( P = .008 \)) instead of OS (13% vs 25%; \( P = .042 \)) as the primary endpoint. Results of the meta-analysis were robust under sensitivity analysis stratified by FDA approval type (standard approval vs accelerated approval) and supporting confirmatory trial (normal vs confirmatory) (Supplementary Table S6).

Discussion

In this study of 355 FDA-approved cancer indications (2012–2022), we identified significant differences in the FDA approval, efficacy, clinical trial design, and pricing of breakthrough and nonbreakthrough cancer indications. However,
and more robust clinical trials for breakthrough indications and are more often supported by larger
the observation that supplemental approvals are less frequently
breakthrough cancer drugs. These results could be explained by
et al,11 who evaluated the same timeframe, found signi-
that the underlying clinical trials.22
be partially caused by differences in the design characteristics of
approvals, offers the largest assessment of clinical bene-
beings receiving the BTD in late clinical development could not
In contrast to previous studies,11,12 our analyses revealed a sub-
breakthrough and nonbreakthrough drugs did not differ significantly.
Clinical Benefit
In contrast to previous studies,11,12 our analyses revealed a sub-
breakthrough cancer indications in 5 of 8 evaluated benefit
Most importantly, breakthrough indications were asso-
with a greater efficacy in OS in terms of HRs (0.69 vs 0.74; 
P =.031) and median improvement in OS (4.8 vs 3.2 months; 
P =.002). The studies from Molto et al11 and Hwang et al12 are lim-
limited in their sample size, methodology used, and analyzed time
More specifically, these studies were not able to evaluate the full breadth of the BTD, given their focus on the first 5 years af-
eter the program was signed into law—many of the analyzed ther-
peutics receiving the BTD in late clinical development could not
benefit from all the advantages of the program. Furthermore, 
Hwang et al12 focused only on original drug approvals because supplemental approvals were neglected. Therefore, Hwang et al,12 who examined 58 original FDA drug approvals from 2012 to 2017, found no significant difference in PFS and tumor response benefit 
between breakthrough and nonbreakthrough cancer drugs. Molto et al,11 who evaluated the same timeframe, found significant dif-
fferences in benefit between breakthrough and nonbreakthrough 
drugs in only 2 of 4 evaluated value scores. Our study, which com-
prises data from 355 original and supplemental FDA indication 
approvals, offers the largest assessment of clinical benefits of 
breakthrough cancer drugs. These results could be explained by 
the observation that supplemental approvals are less frequently 
breakthrough indications and are more often supported by larger 
and more robust clinical trials for first-line treatments,14 which re-
results in lower efficacy estimates for nonbreakthrough indications.
In conclusion, breakthrough indications offered a greater clinical 
efficacy in 5 of 8 evaluated measures compared with nonbreak-
breakthrough indications. However, this greater clinical benefit could 
be partially caused by differences in the design characteristics of 
the underlying clinical trials.22

With our new comprehensive findings on the clinical bene-
fit of breakthrough cancer drugs, patients and physicians can 
adequately manage their optimistic expectations for drugs mar-
kedet as innovative promising “breakthroughs.”8–10 Nonetheless, US Congress could consider renaming the “breakthrough” 
designation as “high potential” to avoid invoking misleading 
hopes among patients. The European Union and Japan have 
arguably found more neutral wordings for their analogous 
expedited development programs, naming them Priority 
Medicines (PRIME) and Sakigake (Japanese for “pioneer” or “pathfinder”), respectively.23,24

Figure 3. Association of BTD with tumor response in single-arm trials. A logistic regression quantifies the association between the probability of indications receiving BTD and tumor response in single-arm trials for monotherapies. Odds ratio of the logistic regression was 4.29 (95% CI, 1.85–6.74; P =.001).

Figure 4. (A) Monthly prices of drugs with and without a BTD for the original FDA indication compared in the year 2023. Black bars represent means with 95% confidence intervals. (B) Monthly prices for breakthrough versus nonbreakthrough therapy cancer drugs compared from 2015 to 2023. (C) Mean price change of breakthrough versus nonbreakthrough therapy drugs compared from 2015 to 2023. Lines illustrate price indices with the baseline set in the year 2015. Inflation was measured by the CPI.

Abbreviations: BTD, breakthrough therapy designation; CPI, Consumer Price Index.
Expedited Clinical Development Timelines

US Congress introduced the BTD to facilitate and accelerate the FDA’s premarking approval process for promising drugs that treat serious diseases. Consistent with previous studies,12,25 our study found that the BTD expedites drug development. These faster clinical development timelines were also observed for drugs that received accelerated approval. This observation suggests that the BTD is nonredundant to the existing FDA’s accelerated approval program. However, we also found that the BTD facilitated FDA approval via smaller single-arm trials. For patients, this flexibility in clinical trial design may represent a trade-off between earlier access to innovative medicines versus robust evidence for safety and efficacy. Smaller and shorter trials were shown to be not only more frequently associated with unobserved adverse effects but also a source of bias for efficacy outcomes measured in RCTs and single-arm trials.26–28

Balancing these competing goals, the FDA should encourage sponsors and investigators of breakthrough drugs to conduct high-quality trials with sufficient enrollment and randomization whenever possible. For indications with an uncertain safety and efficacy profile, postmarketing requirements and commitments that encourage additional data collection should be mandated as time-dependent conditions to keep the breakthrough designation.

Innovation

Over the past 2 decades, biotechnological advances resulted in the discovery and development of new classes of medicinal products. Particularly the rise of personalized therapies, immune therapies, and gene and cell therapeutics opened new therapeutic options for otherwise fatal conditions. These targeted therapies are often developed for biomarker-defined patient subgroups of the larger disease population, and their benefit is frequently already apparent in early phase I or II trials. The BTD was intended to expedite patient access and encourage the development of these promising and innovative new treatments. This study confirms that the BTD was especially granted to innovative cancer drug indications. Breakthrough drugs more frequently affected a novel target (first-in-class) using a novel mechanism of action to treat a novel disease (first-in-indication) and also displayed a tendency to be of a novel product class (antibody–drug conjugates, gene and cell therapies, or radionuclides). In contrast to prior studies,12 we therefore conclude that the BTD did fulfill its intention and probably allowed US drug development to keep pace with and facilitate the biopharmaceutical innovations of the 21st century.

The BTD introduced more flexibility in the conduct of clinical trials for these novel therapeutics. To account for genomically homogeneous patient populations across diseases, the BTD specifically accommodates novel trial designs, such as master protocols, umbrella trials, or basket trials. For instance, vemurafenib, a target breakthrough therapy, was approved for BRAF V600–positive Erdheim-Chester disease, an ultra-rare multisystem disorder, based on a basket study that enrolled 24 patients with different forms of glioma.29 The BTD also paved the way for the approval of tumor-agnostic treatments. For instance, pembrolizumab was the first treatment approved for metastatic solid tumors with mismatch-repair deficiency based on a basket study that enrolled 41 patients with colorectal and noncolorectal cancer.30 However, companion diagnostics for these biomarker-directed therapies currently need to be approved by the FDA through a separate review process.31 Legislative action is necessary to combine and harmonize the expedited approval of biomarker therapies and their companion diagnostics to ensure early access for patients.

Treatment and Epidemiologic Characteristics

Over the past 4 decades, the US Congress provided the FDA with a vast set of special designations and approval pathways to expedite the development and approval of new medicines.6,32 For instance, the orphan designation financially incentivizes drug development for treating rare diseases.33,34 The accelerated approval program permits early marketing authorization based on surrogate endpoints for medicines that treat serious conditions and fill unmet medical needs. Similarly, the BTD is supposed to expedite the development of medicines that treat serious conditions and have a preliminary large clinical benefit. Yet, in our study, we could not confirm that the BTD is more frequently granted to treatments for serious diseases, given that there was no significant difference in DALYs and 5-year survival rates for BTD and non-BTD indications. Furthermore, there was no evidence that the BTD is more often granted to treatments for advanced-line patients (ie, patients with serious diseases that have progressed or who are ineligible for standard first-line therapy regimens). Combined with the aforementioned results, these findings suggest that the FDA’s decision to grant the BTD is based mainly on biotechnological innovativeness, clinical novelty, and clinical efficacy rather than disease epidemiology. In other words, this study shows that the FDA seeks out the most innovative and promising drugs within each disease for the breakthrough designation.

Limitations

There are certain limitations inherent in our analyses. First, we included only successful trials that led to the FDA approval of new cancer drug indications. Second, drug price data were assessed for patients covered under Medicare Parts B and D. Although Medicare and Medicaid are the leading health insurers in the United States, drug prices, rebates, copayments, and deductibles may vary for patients covered by private insurance schemes. Third, to compare breakthrough and nonbreakthrough indications, we meta-analyzed the efficacy outcomes of clinical trials for multiple tumor entities, which may be a source of high heterogeneity in calculated effect sizes.35–38 Fourth, in our meta-analyses, Cochran’s Q tests were used to compare differences in efficacy outcomes for breakthrough and nonbreakthrough indications. Cochran’s Q tests are used to examine sources of heterogeneity across subgroups, yet these tests are limited in statistical power and risk increasing alpha errors.39 Nonetheless, our findings were consistent in magnitude and statistical significance for the comparison of median improvements in OS and PFS. Fifth, only 9% of breakthrough and 20% of nonbreakthrough indications were supported by trials measuring OS as the primary endpoint. Therefore, the meta-analysis of OS data is limited to a subset of the overall cohort of cancer drugs. Sixth, although we observed significantly greater RRs in RCTs and ORRs in single-arm trials for breakthrough relative to nonbreakthrough indications, the clinical benefit of these tumor responses must be confirmed in well-designed, robust postmarketing trials that assess OS. Finally, we evaluated only cancer drug indications in our
analysis; the results and policy implications of this study should be confirmed for other therapeutic areas.

Conclusions
The BTD encouraged the development of >1,100 indications. Over the past 10 years, breakthrough cancer drugs have been associated with faster development and approval timelines. Compared with their peers, breakthrough drugs more often affected a novel target using a novel mechanism of action to treat a new disease. Breakthrough indications displayed a substantially higher clinical benefit in 5 of 8 evaluated efficacy measures. Most importantly, breakthrough indications were associated with a greater benefit in OS in terms of HRs (0.69 vs 0.74; \( P = .031 \)) and median improvement in OS (4.8 vs 3.2 months; \( P = .002 \)). However, breakthrough indications were more frequently supported by small, nonrobust single-arm trials that could partly explain the observed greater efficacy. No difference in treatment and epidemiologic characteristics was observed. In brief, the FDA primarily grants the breakthrough designation based on biotechnological innovativeness, clinical novelty, and clinical efficacy rather than disease epidemiology. In contrast to previous criticism, we therefore conclude that the BTD expedites patient access to innovative and effective, but also expensive, new medicines.

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Correspondence: Daniel Tobias Michaeli, MSc, MSc, National Center for Tumor Diseases, Heidelberg University, Im Neuenheimer Feld 460, 69120 Heidelberg, Germany. Email: danielmichaeli@yahoo.com

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