Original Article

Clinical Benefit and Cost of Breakthrough Cancer Drugs Approved by the US Food and Drug Administration

Consolación Molto, MD[1]; Thomas J. Hwang, AB[2]; Maria Borrell, MD[1]; Marta Andres, MD[1]; Ignasi Gich, MD, PhD[3]; Agustí Barnadas, MD, PhD[1]; Eitan Amir, MD, PhD[4]; Aaron S. Kesselheim, MD, JD, MPH[2]; and Ariadna Tibau, MD, PhD[1]

BACKGROUND: The clinical benefit and pricing of breakthrough-designated cancer drugs are uncertain. This study compares the magnitude of the clinical benefit and monthly price of new and supplemental breakthrough-designated and non–breakthrough-designated cancer drug approvals. **METHODS:** A cross-sectional cohort comprised approvals of cancer drugs for solid tumors from July 2012 to December 2017. For each indication, the clinical benefit from the pivotal trials was scored via validated frameworks: the American Society of Clinical Oncology Value Framework (ASCO-VF), the American Society of Clinical Oncology Cancer Research Committee (ASCO-CRC), the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS), and the National Comprehensive Cancer Network (NCCN) Evidence Blocks. A high clinical benefit was defined as scores ≥ 45 for the ASCO-VF, overall survival gains ≥ 2.5 months or progression-free survival gains ≥ 3 months for all cancer types for the ASCO-CRC criteria, a grade of A or B for trials of curative intent and a grade of 4 or 5 for trials of noncurative intent for the ESMO-MCBS, and scores of 4 and 5 and a combined score ≥ 16 for the NCCN Evidence Blocks. Monthly Medicare drug prices were calculated with Medicare prices and DrugAbacus. **RESULTS:** This study identified 106 trials supporting approval of 52 drugs for 96 indications. Forty percent of these indications received the breakthrough designation. Among the included trials, 33 (43%), 46 (73%), 35 (34%), and 67 (69%) met the thresholds established by the ASCO-VF, ASCO-CRC, ESMO-MCBS, and NCCN, respectively. In the metastatic setting, there were higher odds of clinically meaningful grades in trials supporting breakthrough drugs with the ASCO-VF (odds ratio [OR], 3.69; $P = .022$) and the NCCN Evidence Blocks (OR, 5.80; $P = .003$) but not with the ASCO-CRC (OR, 3.54; $P = .11$) or version 1.1 (v1.1) of the ESMO-MCBS (OR, 1.22; $P = .70$). The median costs of breakthrough therapy drugs were significantly higher than those of nonbreakthrough therapies ($P = .001$). **CONCLUSIONS:** In advanced solid cancers, drugs that received the breakthrough therapy designation were more likely than nonbreakthrough therapy drugs to be scored as providing a high clinical benefit with the ASCO-VF and the NCCN Evidence Blocks but not with the ESMO-MCBS v1.1 or the ASCO-CRC scale. ***Cancer* 2020;126:4390-4399**. © *2020 American Cancer Society*.

KEYWORDS: American Society of Clinical Oncology (ASCO), breakthrough therapy designation, clinical benefit, cost, European Society for Medical Oncology (ESMO), value frameworks.

INTRODUCTION

Improved understanding of the molecular basis of cancer has led to the discovery of several new therapies, which, in some cases, have demonstrated substantial antitumor activity in early phase trials[1,2] and subsequently improved overall survival (OS).[3,4] In 2012, the breakthrough therapy designation was established to expedite the development of US Food and Drug Administration (FDA) approval of such therapies as well as promising new medications intended to treat other serious or life-threatening conditions.[5] A drug may receive this designation if preliminary clinical evidence suggests a substantial improvement in a clinically significant endpoint over available treatments; a clinically significant endpoint may include not only survival but also surrogate endpoints or biomarkers likely to predict a clinical benefit.[6] This designation provides many benefits to sponsors, such as intensive guidance from the FDA throughout the drug development process, which results in significantly faster development and regulatory review times.[7] Since its creation in 2012, the breakthrough therapy designation program has grown rapidly, with more than 30 cancer drug approvals receiving designations to date.[8,9] However, the clinical benefit and cost of breakthrough-designated cancer drugs are uncertain.

Corresponding Author: Ariadna Tibau, MD, PhD, Oncology Department, Hospital de la Santa Creu i Sant Pau, Institut d'Investigació Biomèdica Sant Pau, and Universitat Autònoma de Barcelona, Carrer de Sant Quintí, 89, 08041, Barcelona, Spain (atibau@santpau.cat).

[1]Oncology Department, Hospital de la Santa Creu i Sant Pau, Institut d'Investigació Biomèdica Sant Pau, and Universitat Autònoma de Barcelona, Barcelona, Spain; [2]Program on Regulation, Therapeutics, and Law, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; [3]Department of Epidemiology, Hospital de la Santa Creu i Sant Pau and Universitat Autònoma de Barcelona, Barcelona, Spain; [4]Division of Medical Oncology and Hematology, Department of Medicine, Princess Margaret Cancer Centre and University of Toronto, Toronto, Ontario, Canada

The first 2 authors contributed equally to this article.

This study was presented at the 2019 American Society of Clinical Oncology Annual Meeting; May 31 to June 4, 2019; Chicago, Illinois.

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.33095, **Received:** January 22, 2020; **Revised:** June 17, 2020; **Accepted:** June 22, 2020, **Published online** July 22, 2020 in Wiley Online Library (wileyonlinelibrary.com)

The prices of cancer drugs at market entry have grown substantially over the years.[10] At the same time, regulatory approval of cancer drugs has relied increasingly on surrogate endpoints.[11] A prior study, which focused on new drug approvals, found no statistically significant advantage in efficacy or safety for breakthrough-designated cancer therapies versus non–breakthrough-designated cancer therapies.[12]

Here, we present an analysis of the clinical benefit, drug prices, and clinical trial characteristics of new and supplemental cancer drug approvals in the 5-year period from 2012 to 2017. Clinical benefit was defined with the value frameworks developed by the American Society of Clinical Oncology (ASCO),[13,14] the European Society for Medical Oncology (ESMO),[15] and the National Comprehensive Cancer Network (NCCN).[16] We hypothesized that compared with non–breakthrough-designated drugs, those with the breakthrough designation would be more likely to be scored as providing high benefit according to these value frameworks. In addition, we aimed to assess individual drugs' molecular targets by using a recently published framework to rank the clinical evidence supporting targets for precision cancer medicines (the ESMO Scale of Clinical Actionability for Molecular Targets [ESCAT]).[17]

MATERIALS AND METHODS

Data Sources

We searched the Drugs@FDA database[18] to identify new and supplemental approvals of cancer drugs and biologics for solid tumors from July 9, 2012 (the date of the creation of the breakthrough therapy program by the US Congress),[5] to December 31, 2017. We excluded drugs approved for hematologic malignancies, supportive care agents, diagnostic or contrast agents and supplemental approvals for new dosing regimens, manufacturing changes, and other non–clinical label updates. The remaining drug approvals were then categorized as breakthrough-designated or non–breakthrough-designated according to a publicly available list of breakthrough therapy designations maintained by the FDA.[8]

Data Extraction

Data on drug characteristics and clinical benefit were extracted by 2 authors (C.M. and M.B.) using predesigned electronic forms that have been described previously.[19,20] The following drug characteristics were collected for each application: approval type (initial vs supplemental indications), date of approval, type of application (New Drug Application or Biologic Licensing Application), regulatory designations (priority or standard review[21,22] and orphan or nonorphan designation),[23] and type of approval (accelerated or regular approval).[24] We also collected data on whether a companion diagnostic test was available, as determined by the FDA.[25] Disagreements were resolved by consensus with a third author (A.T.).

The FDA's drug review dossiers and labeling[26] were reviewed to obtain data on the primary, or pivotal, trials supporting approval. When more than 1 pivotal study supported a single approval, each trial was considered separately. For each trial, we extracted information on the following characteristics: number of pivotal trials, trial phase (phase 1/2 vs 3), sample size, study design (randomized vs single-arm), blinding (blinded vs open-label), treatment intent ([neo]adjuvant vs palliative), and primary efficacy endpoints (OS vs intermediate endpoints). For studies with coprimary endpoints, we identified the most definitive primary endpoint chosen by the FDA to support approval (ie, OS prioritized over intermediate endpoints). For trials performed in the palliative setting, we collected data on the line of therapy (first line vs other). Given that quality of life (QOL) information is often not reported in drug labeling and that toxicity information is commonly reported in a summary format based on data derived from multiple trials, we supplemented this review of regulatory documents with safety and QOL data from peer-reviewed publications of the pivotal trials.

The monthly Medicare price for each drug was obtained from DrugAbacus (Memorial Sloan Kettering Cancer Center).[27] For drugs without cost information on DrugAbacus, we applied a similar methodology to estimate monthly drug costs as of May 2018 by using Medicare's Average Sales Price Drug Pricing Files, the Medicare Plan Finder tool, and the Red Book (Truven Health Analytics).[28,29]

Data Synthesis and Scoring

For each indication, 3 investigators (C.M., M.B., and M.A.) scored the clinical benefit from the pivotal trial(s) by using the value frameworks developed by ASCO,[13,14] ESMO,[15] and the NCCN.[16] These included version 2 of the American Society of Clinical Oncology Value Framework—Net Health Benefit Score (ASCO-NHB),[14] version 1.1 (v1.1) of the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS),[15] and the NCCN Evidence Blocks[16] as well as targets for clinically meaningful benefit developed by the American Society of Clinical Oncology Cancer Research Committee (ASCO-CRC).[13] Discordant scores were

resolved by a fourth investigator (A.T.). Greater interobserver discordance was seen with American Society of Clinical Oncology Value Framework (ASCO-VF) grading (22 of 76 [29%]) than ESMO-MCBS (9 of 103 [9%]), ASCO-CRC (1 of 63 [2%]), or NCCN grading (4 of 97 [4%]), although for the ASCO-VF, this discordance resulted in changes to the threshold for a substantial clinical benefit in only 2 of 76 cases (3%).

For all value frameworks, if more than 1 trial supported an indication, the highest score was used. We analyzed drugs approved in the metastatic setting. Because there were insufficient (neo)adjuvant studies, formal statistical analysis was not performed for those therapies.

ASCO-NHB scores were assigned via the revised ASCO-VF, which combines information on clinical benefit, toxicity, and symptom palliation from randomized controlled trials (RCTs) into an NHB score.[14] The ASCO-CRC published targets for clinically meaningful benefit using a single cutoff in clinical trials for 4 cancer types (pancreatic cancer, lung cancer, triple-negative breast cancer, and colon cancer): OS improvements ranging from 2.5 to 6 months and progression-free survival (PFS) improvements ranging from 3 to 5 months.[13] Consistent with prior studies, we expanded the definition of meaningful clinical benefit as an OS gain greater than 2.5 months and a PFS gain greater than 3 months for all solid cancers.[12] For the ESMO-MCBS, grades based on efficacy were adjusted only when statistically significant changes in toxicity or QOL were reported. Finally, NCCN categories of evidence (category 1 vs categories 2A and 2B) as well as NCCN Evidence Block scores (efficacy, safety, quality of evidence, consistency of evidence, and affordability of regimen/agent) were collected from the most recent versions of those guidelines as of May 2018.[30]

On the basis of published recommendations, high clinical benefit was defined as follows: 1) ASCO-VF pragmatic threshold scores of 45 or higher,[31] 2) ASCO criteria OS gains of 2.5 or more months and PFS gains of 3 or more months,[12] 3) an ESMO-MCBS grade of A or B for trials of curative intent and a grade of 4 or 5 for trials of noncurative intent,[15] and 4) NCCN Evidence Blocks scores of 4 and 5 and a combined score for the 5 categories (efficacy, safety, quality of evidence, consistency of evidence, and affordability of regimen/agent) of 16 or higher.[16]

For targeted therapies, we also used the ESCAT framework[17] to evaluate the level of clinical evidence for drugs indicated for genomic alterations detected (or evaluable) by next-generation sequencing as an approved companion diagnostic test. Level 1 evidence was attributed to targets ready for implementation in routine clinical decisions and was considered high; level 2 evidence defined a patient population that benefitted from a targeted drug but for which additional data were needed.[17]

Statistical Analysis

Data were reported descriptively as proportions, medians, and ranges as appropriate. Comparisons between trial characteristics and the breakthrough therapy designation were assessed with the Mann-Whitney U test and chi-square tests for continuous and categorical variables, respectively. Associations between characteristics of trials, approval pathways, and clinically significant benefit thresholds were evaluated via logistic regression in univariate and multivariate settings and were reported as odds ratios (ORs) and respective 95% confidence intervals (CIs). Associations between clinically significant benefit thresholds and breakthrough therapy–designated drugs were evaluated for trials in the noncurative setting only. To avoid model overfitting, a maximum of 1 variable for every 10 events was chosen for multivariable analysis on the basis of previous findings and statistical significance. Two sensitivity analyses were performed. First, we excluded trials supporting accelerated-approval indications that were converted to regular approval during the study period to avoid duplicate indications. Second, we repeated our analysis in the subgroup of trials that could be evaluated with both ASCO-VF and ESMO-MCBS frameworks. Comparisons of median monthly prices between drugs that met and drugs that did not meet high clinical benefit according to the ESMO-MCBS, ASCO-VF, ASCO-CRC, and NCCN Evidence Blocks frameworks were evaluated with the nonparametric Mann-Whitney U test. All analyses were conducted with SPSS (version 21; IBM Corp, Armonk, New York). Statistical tests were 2-sided, and statistical significance was defined as a 2-tailed P value $<.05$. No corrections were applied for multiple significance testing.

RESULTS

Study Cohort

Between July 2012 and December 2017, the FDA approved 52 drugs for 96 solid tumor indications (Table 1). Of the 96 applications, 38 (40%) received the breakthrough therapy designation, 78 (81%) were granted priority review, and 50 (52%) were given Orphan Drug Act designation. Twenty-seven (28%) were approved under the accelerated-approval pathway, and 9 of these (33%) were subsequently converted to regular approval.

TABLE 1. Application Characteristics

Comparison of Breakthrough Therapies and Nonbreakthrough Therapies

Variable	Total Applications (n = 96)	Breakthrough Therapy (n = 38 [40%])	Nonbreakthrough Therapy (n = 58 [60%])	P^a
Approval pathway, No. (%)				
Regular	69 (72)	23 (60)	46 (79)	.045
Accelerated	27 (28)	15 (40)	12 (21)	
Orphan drug designation, No. (%)	50 (52)	19 (50)	31 (53)	.74
Priority review, No. (%)	78 (81)	36 (95)	42 (72)	.006
Approval type, No. (%)				
Initial	41 (43)	17 (45)	24 (41)	.74
Supplemental	55 (57)	21 (55)	34 (59)	
No. of trials supporting approval, No. (%)				
1	81 (84)	29 (76)	52 (90)	.078
≥2	15 (16)	9 (24)	6 (10)	

Association With Breakthrough Therapies and Nonbreakthrough Therapies: Univariable Analysis

Variable	OR (95% CI)	P^b
Accelerated approval (vs regular approval)	2.50 (1.01-6.21)	.048
Orphan drug designation (vs not)	0.87 (0.38-1.98)	.74
Priority review designation (vs not)	6.86 (1.48-31.86)	.014
Initial approval (vs supplemental)	1.15 (0.50-2.62)	.74
Multiple trials supporting approval (vs 1 trial)	2.69 (0.87-8.31)	.086

Abbreviations: CI, confidence interval; OR, odds ratio.
This analysis included 96 applications.
[a]Based on the Mann-Whitney U test and chi-square tests. All *P* values are 2-sided.
[b]Based on logistic regression. All *P* values are 2-sided.

In the univariable analysis, compared with nonbreakthrough therapy drugs, applications supporting breakthrough designation drugs were more frequently granted priority review designation and approved through the accelerated-approval pathway (Table 1).

Pivotal Trial Characteristics

The 96 cancer drug approvals were supported by 104 pivotal trials, and 2 of these studies included multiple subgroups suitable for grading; this resulted in 106 data points available for scoring. Ninety-one percent of these evaluated a targeted therapy, 74% were RCTs, 62% were phase 3 trials, and 66% were open-label. In addition, 28% were approved on the basis of a subgroup analysis of pivotal trials. Table 2 shows characteristics of pivotal trials for breakthrough and nonbreakthrough drugs.

In multivariable analyses, in comparison with nonbreakthrough drugs, trials supporting breakthrough drug approvals were more often based on subgroup analyses (OR, 2.92; 95% CI, 1.05-8.10; $P = .04$), were more likely to be open-label (OR, 4.19; 95% CI, 1.37-12.89; $P = .01$), and, for drugs tested in the palliative setting, were more likely to evaluate later lines of treatment (OR, 3.59; 95% CI, 1.13-11.42; $P = .03$; Table 2).

Clinical Benefit, Value Framework Scores, and Molecular Targets

The clinical benefit observed in pivotal trials of breakthrough-designated cancer drugs versus non–breakthrough-designated cancer drugs in the noncurative setting is shown in Table 3. Details of the included drugs, their approval pathways, and the clinical benefit of the trials supporting registration are shown in Supporting Table 1.

ASCO-NHB scores were applied to 76 of 78 RCTs that could be evaluated, and this resulted in available data from 72% of all trials (76 of 106). Two RCTs were not evaluable under the ASCO-VF (the primary endpoints were pathologic complete response and cardiac safety, respectively). Seven percent of the trials (5 of 76) supported approvals in the (neo)adjuvant setting, and 93% (71 of 76) did so in the palliative setting. Only 43% (33 of 76) met the ASCO-VF high-benefit threshold (0% of [neo]adjuvant trials and 47% [33 of 71] of palliative trials). Of those trials to which the ASCO-VF could be applied, 33% (25 of 76) concerned breakthrough therapy drugs, and 67% (51 of 76) concerned nonbreakthrough therapy drugs. In the noncurative setting, a majority of the trials supporting breakthrough drugs showed high clinical benefit on the basis of ASCO-VF scores (71% vs 34%; $P = .003$; Table 3).

TABLE 2. Pivotal Trial Characteristics

Comparison of Breakthrough Therapies and Nonbreakthrough Therapies

Variable	Total Trials (n = 106)	Breakthrough Therapy (n = 44 [42%])	Nonbreakthrough Therapy (n = 62 [58%])	P[a]
Sample size, median (range)		373 (50-1033)	612 (74-4804)	.033
Cancer sites, No. (%)				
Lung	31 (29)	20 (45)	11 (17)	.010
Breast	12 (11)	6 (14)	6 (10)	
Colorectal	7 (7)	1 (2)	6 (10)	
Prostate	3 (3)	0 (0)	3 (5)	
Other	53 (50)	17 (39)	36 (58)	
Agent type, No. (%)				
Drug	61 (58)	24 (55)	37 (60)	.60
Biologic	45 (43)	20 (46)	25 (40)	
Drug class, No. (%)				
Standard chemotherapy and hormonal therapy	10 (9)	0 (0)	10 (16)	.005
Targeted therapies	96 (91)	44 (100)	52 (84)	
Companion diagnostic, No. (%)[b]	38 (36)	18 (41)	20 (32)	.36
Study design, No. (%)				
Randomized	78 (74)	25 (57)	53 (86)	.001
Single-arm	28 (26)	19 (43)	9 (15)	
Phase, No. (%)				
1/2	40 (38)	24 (55)	16 (26)	.003
3	66 (62)	20 (46)	46 (74)	
Approval based on subgroup analysis, No. (%)	30 (28)	19 (43)	11 (18)	.004
Blinding, No. (%)				
Open-label	70 (66)	37 (84)	33 (53)	.001
Double-blind	36 (34)	7 (16)	29 (47)	
Intermediate endpoint, No. (%)	72 (68)	33 (75)	39 (63)	.19
Setting, No. (%)				
Palliative intent	98 (93)	43 (98)	55 (89)	.083
Curative intent	8 (7)	1 (2)	7 (11)	
First line, No. (%)	26 (25)	5 (11)	21 (34)	.003
Monthly cost, $				
Median		12,592.5	10,061.5	.001
Mean		12,831.2	10,985.3	
IQR		9240-18,223	1608-50,391	

Association With Breakthrough Therapies and Nonbreakthrough Therapies

Variable	OR (95% CI)	P[c]
Univariable analysis		
Sample size per 100 patients	1.16 (1.02-1.33)	.029
Lung, breast, colorectal, and prostate cancer (vs others)	2.00 (0.91-4.38)	.083
Multiple trials supporting approval (vs 1 trial)	1.95 (0.76-5.03)	.17
Biologic agent type (vs drug agent type)	1.23 (0.57-2.69)	.60
Targeted therapies (vs standard chemotherapy and hormonal therapy)	14.96 (1.90-117.66)	.010
Companion diagnostic (vs none)[b]	1.45 (0.65-3.25)	.36
Single-arm (vs randomized)	4.48 (1.78-11.28)	.001
Phase 1/2 (vs phase 3)	3.45 (1.52-7.85)	.003
Approval based on subgroup analysis (vs not)	3.52 (1.46-8.52)	.005
Open-label (vs double-blind)	4.65 (1.79-12.00)	.002
Intermediate endpoint (vs overall survival)	1.77 (0.75-4.16)	.19
Palliative intent (vs curative intent)	5.47 (0.65-46.19)	.12
Later lines (vs first line)	4.34 (1.47-12.82)	.008
Multivariable analysis		
Sample size per 100 patients	1.12 (0.75-1.06)	.19
Approval based on subgroup analysis (vs not)	2.92 (1.05-8.10)	.040
Open-label (vs double-blind)	4.19 (1.37-12.89)	.012
Later lines (vs first line)	3.59 (1.13-11.42)	.031

Abbreviations: CI, confidence interval; IQR, interquartile range; OR, odds ratio.

This analysis included 104 pivotal trials, and 2 of these studies included multiple subgroups suitable for grading; this resulted in 106 data points available for analysis.

[a]Based on the Mann-Whitney U test and chi-square tests. All *P* values are 2-sided.

[b]Companion diagnostic test as defined by the US Food and Drug Administration framework.[25]

[c]Based on logistic regression. All *P* values are 2-sided.

TABLE 3. Clinical Benefit of Pivotal Trials in the Noncurative Setting

Comparison of Breakthrough Therapies and Nonbreakthrough Therapies

Variable	Total Trials (n = 98)	Breakthrough Therapy (n = 43)	Nonbreakthrough Therapy (n = 55)	P[a]
ASCO-VF v2 clinical benefit, No. (%)[b]	33 (46)	17 (71)	16 (34)	.003
ASCO-CRC clinical benefit, No. (%)[c]	46 (73)	18 (82)	28 (68)	.25
ESMO-MCBS v1.1 clinical benefit No. (%)[d]	30 (31)	14 (33)	16 (30)	.70
Category of NCCN Summary, No. (%)[e]				
Level 1	48 (51)	21 (49)	27 (52)	.76
Level 2A-2B	47 (49)	22 (51)	25 (48)	
NCCN Evidence Blocks score ≥ 16 (vs <16), No. (%)[f]	64 (71)	35 (85)	29 (59)	.006
NCCN Evidence Blocks score ≥ 4 for each block, No. (%)	26 (29)	18 (44)	8 (16)	.004
NCCN Efficacy Box, No. (%)	61 (68)	35 (85)	26 (53)	.001
NCCN Safety Box, No. (%)	30 (33)	20 (49)	10 (20)	.004
NCCN Quality of Evidence Box, No. (%)	71 (79)	34 (83)	37 (76)	.39
NCCN Consistency of Evidence Box, No. (%)	68 (76)	35 (85)	33 (67)	.048
NCCN Affordability Box, No. (%)[g]	—	—	—	—
ESCAT, No. (%)[h]				
Level I	17 (55)	5 (31)	12 (80)	.006
Level II	14 (45)	11 (69)	3 (20)	

Association With Breakthrough Therapies and Nonbreakthrough Therapies

Variable	OR (95% CI)	P[i]
Univariable analysis		
ASCO-VF v2 clinicalbenefit (vs not)[b]	4.71 (1.62-13.68)	.004
ASCO-CRC clinical benefit (vs not)[c]	2.09 (0.59-7.42)	.25
ESMO-MCBS v1.1 clinical benefit (vs not)[d]	1.19 (0.50-2.83)	.70
Category of NCCN Summary level I (vs level II)[e]	1.13 (0.50-2.54)	.76
NCCN Evidence Blocks score ≥ 16 (vs <16)[f]	4.02 (1.43-11.34)	.008
NCCN Efficacy Box	5.16 (1.84-14.48)	.002
NCCN Safety Box	3.71 (1.42-9.38)	.005
NCCN Quality of Evidence Box	1.58 (0.56-4.47)	.39
NCCN Consistency of Evidence Box	2.83 (0.99-8.10)	.053
NCCN Affordability Box[g]	—	—
ESCAT level II (vs level I)[h]	8.80 (1.69-45.76)	.010
Multivariable analysis[j]		
ASCO-VF v2 clinical benefit (vs not)	3.69 (1.20-11.31)	.022
ASCO-CRC clinical benefit (vs not)	3.54 (0.75-16.70)	.11
ESMO-MCBS v1.1 clinical benefit (vs not)	1.22 (0.44-3.40)	.70
NCCN Evidence Blocks score ≥ 16 (vs <16)	5.80 (1.82-18.47)	.003

Abbreviations: ASCO-CRC, American Society of Clinical Oncology Cancer Research Committee; ASCO-VF, American Society of Clinical Oncology Value Framework; CI, confidence interval; ESCAT, ESMO Scale of Clinical Actionability for Molecular Targets; ESMO-MCBS, European Society for Medical Oncology Magnitude of Clinical Benefit Scale; NCCN, National Comprehensive Cancer Network; OR, odds ratio; v1.1, version 1.1; v2, version 2.

This analysis included 98 clinical trials available for analysis.

[a]Based on the Mann-Whitney U test and chi-square tests. All *P* values are 2-sided.

[b]This analysis included 71 trials.

[c]This analysis included 63 trials.

[d]This analysis included 96 trials.

[e]This analysis included 95 trials.

[f]This analysis included 90 trials.

[g]Statistical analysis was not feasible (no cases affordable on the breakthrough-designated drugs part according to the NCCN Guidelines).

[h]This analysis included 31 trials.

[i]Based on logistic regression. All *P* values are 2-sided.

[j]Multivariable analyses were performed with adjustments for clinical trial characteristics showing independent statistical significance with the breakthrough drug designation, as reported in Table 2. Variables included blinding (open-label vs double-blind), approval based on subgroup analysis (yes vs no), and line of treatment (later lines vs first line).

The median ASCO-VF scores were also statistically significant higher for breakthrough drugs (51 vs 37; $P = .02$). In univariable analyses, there were higher odds of substantial clinical benefit in trials supporting breakthrough drugs versus trials supporting nonbreakthrough drugs. Similar results were observed in multivariable analyses adjusted for clinical trial characteristics associated with the breakthrough drug designation (OR, 3.69; 95% CI, 1.20-11.31; $P = .02$; Table 3).

ASCO-CRC grades were applicable to only 63 RCTs, and this resulted in available data from 59% of all trials (63 of 106) in the noncurative setting. Seventy-three

percent (46 of 63) met the ASCO scores for clinically meaningful benefit. Although a numerically greater number of trials supporting breakthrough drugs showed high clinical benefit, this was not statistically significantly different from nonbreakthrough drugs in univariable and multivariable logistic regression (Table 3).

The ESMO-MCBS v1.1 was applied to both RCTs and single-arm trials, and this resulted in data available from 103 of 106 trials (97%). Among those trials to which the ESMO-MCBS could not be applied, in 2 cases, the experimental drug was included in both arms, and in the other, the primary endpoint was not suitable for assessment (cardiac safety outcome). Seven percent of the trials (7 of 103) supported approvals in the (neo)adjuvant setting, and 93% (96 of 103) did so in the palliative setting. Only 34% (35 of 103) met the ESMO-MCBS high-benefit threshold (71% of [neo]adjuvant trials and 31% of palliative trials). Among the trials to which the ESMO-MCBS could be applied, 42% (43 of 103) were breakthrough therapy–designated drugs. In the noncurative setting, similarly low proportions of trials supporting breakthrough and nonbreakthrough drugs showed high clinical benefit when the ESMO-MCBS v1.1 was used (Table 3).

When NCCN categories of evidence and consensus were evaluated, similar proportions of trials supporting breakthrough and nonbreakthrough drugs were designated as providing level 1 evidence as reported in the NCCN Guidelines (Table 3). NCCN Evidence Blocks were applied to 97 of 106 trials (91%). Only 67 of them (69%) showed high clinical benefit. When NCCN Evidence Blocks were analyzed in the palliative setting, there was no significant difference in median scores between breakthrough-designated and non–breakthrough-designated drugs (16.93 vs 16.27; $P = .11$), but breakthrough therapy–designated drugs were associated with higher odds of high clinical benefit than nonbreakthrough drugs in both univariable and multivariable analyses (OR, 5.80; 95% CI, 1.82-18.47; $P = .003$; see Table 3).

Thirty-two percent of the trials (34 of 106) supporting clinical approval of targeted drugs with genomic alterations detectable with a next-generation sequencing test and approved with a companion diagnostic test were scored according to ESCAT (Supporting Table 2). In the palliative setting, 55% (17 of 31) achieved the highest scores of level I evidence, with fewer trials receiving this level for breakthrough therapy drugs than nonbreakthrough therapy drugs (Table 3 and Supporting Table 2).

In a sensitivity analysis that excluded trials in the noncurative setting that supported accelerated approval of drugs that were subsequently converted to regular approval during the study period, similar results were found. The magnitude of association was similar with the ASCO-VF (OR, 5.00; 95% CI, 1.64-15.28), ESMO-MCBS (OR, 1.46; 95% CI, 0.59-3.62), and ASCO-CRC (OR, 1.97; 95% CI, 0.55-7.04). The magnitude of effect was a little smaller for the NCCN (OR, 2.70; 95% CI, 0.95-7.67; $P = .062$) and for the ESCAT scale (OR, 6.60; 95% CI, 0.97-44.93; $P = .054$).

In a second sensitivity analysis of trials in the metastatic setting that could be assessed by both the ASCO-VF and the ESMO-MCBS (69 of 98 trials [70%]), there was a significant difference in grading between breakthrough and nonbreakthrough drugs with the ASCO-VF (OR, 5.37; 95% CI, 1.58-18.20; $P = .001$); meanwhile, there was no significant difference with the ESMO-MCBS (OR, 1.23; 95% CI, 0.37-4.03; $P = .09$).

Drug Costs

The median monthly price of breakthrough drugs was US $2531 per month more than that of nonbreakthrough drugs ($12,592.5 vs $10,061.5; $P = .001$ [Mann-Whitney test]). In bivariate comparisons, there was no statistically significant difference in the median monthly price for drugs that met and drugs that did not meet the high-benefit threshold according to the ASCO-VF ($12,155 vs $10,662; $P = .50$), ASCO-CRC ($11,434 vs $11,063; $P = .69$), ESMO-MCBS ($12,262 vs $11,723; $P = .45$), and NCCN Evidence Blocks ($12,295 vs $12,262.5; $P = .76$).

DISCUSSION

In recent years, given rapidly increasing cancer drug prices,[32] ASCO, ESMO, and the NCCN have released value frameworks to assist clinicians and patients with assessing the relative benefits of new cancer drugs.[13-16] Prior studies showed that breakthrough-designated cancer drugs were not associated with a statistically significant advantage in OS, PFS, or response rates in comparison with non–breakthrough-designated drugs.[33] In addition to relative and absolute differences in efficacy, value frameworks such as the ASCO-VF, ESMO-MCBS, and NCCN Evidence Blocks also consider other factors when comparing cancer drugs, such as toxicity, QOL, and tail-of-the-curve gains. Therefore, the current study focused on identifying differences in clinical value assessed with value frameworks between breakthrough and nonbreakthrough drugs.

When we evaluated the FDA's cancer drug approvals using value frameworks, a greater proportion of breakthrough-designated drugs met the threshold for

high clinical benefit with the ASCO-VF and the NCCN Evidence Blocks; this association retained statistical significance after adjustments for clinical trial characteristics associated with the breakthrough drug designation. However, there was no statistically significant difference according to the ESMO-MCBS v1.1 or the ASCO-CRC. The ASCO-VF, the ASCO-CRC, and the ESMO-MCBS have a shared goal of helping patients and physicians to make informed comparisons between cancer therapies.[31] However, the methodologies of these value frameworks differ.[13-15,34] The discordance in the results could be explained in part by the large number of single-arm trials supporting those approvals (almost 50% of approvals). Although the ASCO-VF[14] and the ASCO-CRC scale[13] cannot be applied to nonrandomized clinical trials, the ESMO-MCBS v1.1 allows scoring of single-arm trials.[15] In addition, the ESMO framework assigns a higher grade of 4 (substantial clinical benefit) to single-arm trials that report an improvement in QOL or have data available from a confirmatory phase 4 postmarketing study. Because many single-arm trials do not report QOL and may not have confirmatory phase 4 data reported yet, it is unlikely that the drugs approved on the basis of single-arm trials would be able to achieve a grade consistent with a high clinical benefit on the basis of the ESMO-MCBS v1.1.

This study of new cancer drug approvals since 2012 reveals several important differences in the preapproval evaluation of drugs assigned with breakthrough status versus nonbreakthrough status. We found that most breakthrough-designated cancer drugs were approved by the FDA on the basis of single-arm, nonrandomized trials that enrolled relatively small numbers of patients. These trials tended to be open-label and relied on surrogate measures of disease response. When the ESCAT framework was applied, the level of evidence for breakthrough therapies was lower than that for nonbreakthrough therapies, with a substantial number of tumor markers constituting category II target-drug pairs; this indicates that the magnitude of benefit associated with an alteration-drug match is unknown.[17] Moreover, in almost 50% of cases, the FDA approved these breakthrough-designated drugs via the accelerated-approval pathway. Although these features point to the flexibility employed by the FDA to speed up approval of new drugs, the relatively high frequency of unblinded, nonrandomized trials among breakthrough-designated agents raises questions about the rigor of data supporting the approval of breakthrough drugs,[33] especially with respect to safety.[35]

Despite the uncertain evidence of clinical benefit, drugs that received the breakthrough designation were marketed at higher prices than nonbreakthrough drugs. These results are consistent with prior studies that have reported no association between drug price and clinical benefit[34,36] and with the widespread understanding that pricing reflects what the market will accept.[36]

This study has limitations. First, because the breakthrough designation was established in 2012, the duration of follow-up was relatively limited. This study builds on prior work by including not only first approvals but also supplemental indications and, therefore, the entire scope of the breakthrough therapy program. Second, 2 of the included frameworks (ASCO-VF and ASCO-CRC) do not consider evidence from single-arm trials and rely exclusively on RCTs as evidence sources. Because more than 40% of trials supporting breakthrough therapy designations were single-arm trials, this limited our ability to apply value frameworks to the drugs in the study cohort. Third, the analysis of clinical benefit can change over time because new information on toxicity[37] or more mature survival data may be reported after the initial approval.[38]

Consequently, assessments of clinical benefits using value frameworks may change with time. Similarly, for drugs approved under the accelerated-approval program, eventual completion of confirmatory trials could clarify the risk-benefit profile.[39] Finally, analyses were not corrected for multiplicity, and the possibility of additional unexplained confounders cannot be excluded.

In conclusion, the promise of breakthrough-designated cancer drugs remains unclear, with discordant results from validated value frameworks. The ESMO-MCBS framework, which allows the evaluation of single-arm trials and, therefore, could be applied to the broadest set of registration studies, did not identify differences in substantial clinical benefit between breakthrough-designated and non–breakthrough-designated drugs. For the other value frameworks, significant differences were observed, but they may be limited to breakthrough drugs approved on the basis of RCTs. Overall, many drugs were approved on the basis of intermediate endpoints, and this underscores the importance of timely completion of randomized confirmatory studies to establish whether breakthrough-designated therapies offer improved OS and QOL.

FUNDING SUPPORT

Aaron S. Kesselheim reports grants from Arnold Ventures and the Harvard-MIT Center for Regulatory Science.

CONFLICT OF INTEREST DISCLOSURES

Thomas J. Hwang received grant support from the Swiss Cancer Foundation and was previously employed by Blackstone and Bain Capital, which have invested in health care companies. Marta Andres reports funding to attend congresses from Pfizer and Roche outside the submitted work. Agustí Barnadas reports grants from Roche, Novartis, Pfizer, Bristol-Myers Squibb, AstraZeneca, and Lilly during the conduct of the study and personal fees from Novartis, Roche, Pfizer, Genomic Health, Pierre Fabre, AstraZeneca, Eisai, and Palex outside the submitted work. Eitan Amir reports expert testimony for Genentech/Roche and consulting for Sandoz, Apobiologix, Agendia, and Myriad Genetics. Ariadna Tibau reports travel grants from Roche, Ipsen, Pfizer, and Lilly and honoraria from Eisai outside the submitted work. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Consolación Molto: Conceptualization, formal analysis, methodology, resources, data curation, validation, and writing–original draft. **Thomas J. Hwang:** Conceptualization, formal analysis, methodology, resources, data curation, validation, and writing–original draft. **Maria Borrell:** Methodology, resources, data curation, and validation. **Marta Andres:** Methodology, resources, data curation, and validation. **Ignasi Gich:** Formal analysis, methodology, resources, data curation, and validation. **Agustí Barnadas:** Conceptualization, methodology, resources, data curation, and validation. **Eitan Amir:** Conceptualization, formal analysis, methodology, resources, data curation, validation, and writing–review and editing. **Aaron S. Kesselheim:** Conceptualization, formal analysis, methodology, resources, data curation, validation, and writing–review and editing. **Ariadna Tibau:** Conceptualization, formal analysis, methodology, resources, data curation, validation, and writing–original draft and editing.

REFERENCES

1. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non–small-cell lung cancer. *N Engl J Med*. 2015;372:2018-2028.
2. Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med*. 2012;367:1694-1703.
3. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. *N Engl J Med*. 2016;375:1823-1833.
4. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med*. 2015;372:30-39.
5. Pub L No. 112-144, §902, 126 Stat 993 (2012).
6. US Food and Drug Administration. Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics. Published May 2014. Accessed July 11, 2020. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf
7. US Food and Drug Administration. Manual of Policies and Procedures—Good Review Practice: Review of Marketing Applications for Breakthrough Therapy-Designated Drugs and Biologics That Are Receiving an Expedited Review. Published March 9, 2015. Accessed July 11, 2020. https://www.fda.gov/media/90933/download
8. US Food and Drug Administration. Breakthrough therapy at FDA. Accessed July 11, 2020. https://www.fda.gov/media/95302/download
9. Darrow JJ, Avorn J, Kesselheim AS. The FDA breakthrough-drug designation—four years of experience. *N Engl J Med*. 2018;378:1444-1453.
10. Bach PB. Limits on Medicare's ability to control rising spending on cancer drugs. *N Engl J Med*. 2009;360:626-633.
11. Mailankody S, Prasad V. Five years of cancer drug approvals: innovation, efficacy, and costs. *JAMA Oncol*. 2015;1:539-540.
12. Hwang TJ, Franklin JM, Chen CT, et al. Efficacy, safety, and regulatory approval of Food and Drug Administration–designated breakthrough and nonbreakthrough cancer medicines. *J Clin Oncol*. 2018;36:1805-1812.
13. Ellis LM, Bernstein DS, Voest EE, et al. American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol*. 2014;32:1277-1280.
14. Schnipper LE, Davidson NE, Wollins DS, et al. Updating the American Society of Clinical Oncology Value Framework: revisions and reflections in response to comments received. *J Clin Oncol*. 2016;34:2925-2934.
15. Cherny NI, Dafni U, Bogaerts J, et al. ESMO–Magnitude of Clinical Benefit Scale version 1.1. *Ann Oncol*. 2017;28:2340-2366.
16. Carlson RW, Jonasch E. NCCN Evidence Blocks. *J Natl Compr Canc Netw*. 2016;14:616-619.
17. Mateo J, Chakravarty D, Dienstmann R, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT). *Ann Oncol*. 2018;29:1895-1902.
18. US Food and Drug Administration. Drugs at Food and Drug Administration. Accessed July 11, 2020. http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm
19. Tibau A, Molto C, Ocana A, et al. Magnitude of clinical benefit of cancer drugs approved by the US Food and Drug Administration. *J Natl Cancer Inst*. 2018;110:486-492.
20. Tibau A, Molto C, Borrell M, et al. Magnitude of clinical benefit of cancer drugs approved by the US Food and Drug Administration based on single-arm trials. *JAMA Oncol*. 2018;4:1610-1611.
21. US Food and Drug Administration. Review classification new drug applications. Accessed July 11, 2020. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/ucm373420.htm
22. US Food and Drug Administration. Review classification supplement drug applications. Accessed July 11, 2020. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/ucm2007013.htm
23. US Food and Drug Administration. Orphan drugs. Accessed July 11, 2020. http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm
24. US Food and Drug Administration. Accelerated drugs. Accessed July 11, 2020. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/ucm373430.htm
25. US Food and Drug Administration. List of cleared or approved companion diagnostic devices (in vitro and imaging tools). Accessed July 11, 2020. https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm
26. US Food and Drug Administration. Drugs@FDA: FDA-approved drugs. Accessed July 11, 2020. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
27. Memorial Sloan Kettering Cancer Center. DrugAbacus. Accessed July 11, 2020. http://abacus.realendpoints.com/abacus-mskcc?ab-eff=1000&ab-tox=0.1&ab-nov=1&ab-rare=1&ab-pop=1&ab-dev=1&ab-prog=1.0&ab-need=1&ab-time=1501410712
28. US Centers for Medicare and Medicaid Services. 2018 ASP Drug Pricing Files. Accessed July 11, 2020. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2018ASPFiles.html
29. US Centers for Medicare and Medicaid Services. Medicare Plan Finder. Accessed July 11, 2020. https://www.medicare.gov/find-a-plan/questions/home.aspx
30. National Comprehensive Cancer Network. NCCN Guidelines. Accessed July 11, 2020. https://www.nccn.org/professionals/physician_gls/default.aspx
31. Cherny NI, de Vries EGE, Dafni U, et al. Comparative assessment of clinical benefit using the ESMO–Magnitude of Clinical Benefit Scale version 1.1 and the ASCO Value Framework Net Health Benefit Score. *J Clin Oncol*. 2019;37:336-349.
32. Monthly and median costs of cancer drugs at the time of FDA approval 1965-2016. *J Natl Cancer Inst*. 2017;109:djx173.
33. Puthumana J, Wallach JD, Ross JS. Clinical trial evidence supporting FDA approval of drugs granted breakthrough therapy designation. *JAMA*. 2018;320:301-303.
34. Del Paggio JC, Sullivan R, Schrag D, et al. Delivery of meaningful cancer care: a retrospective cohort study assessing cost and benefit with the ASCO and ESMO frameworks. *Lancet Oncol*. 2017;18:887-894.
35. Shepshelovich D, Tibau A, Goldvaser H, et al. Postmarketing modifications of drug labels for cancer drugs approved by the US Food and Drug

Administration between 2006 and 2016 with and without supporting randomized controlled trials. *J Clin Oncol*. 2018;36:1798-1804.
36. Vokinger KN, Hwang TJ, Grischott T, et al. Prices and clinical benefit of cancer drugs in the USA and Europe: a cost-benefit analysis. *Lancet Oncol*. 2020;21:664-670.
37. Seruga B, Templeton AJ, Badillo FE, et al. Under-reporting of harm in clinical trials. *Lancet Oncol*. 2016;17:e209-e219.
38. Davis C, Naci H, Gurpinar E, et al. Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009-13. *BMJ*. 2017;359:j4530.
39. Beaver JA, Howie LJ, Pelosof L, 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;4:849-856.