original contributions

Clinical Benefit and Expedited Approval of Cancer Drugs in the United States, European Union, Switzerland, Japan, Canada, and Australia

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QUESTION ASKED: What are regulatory review times, delays in the approval process, and the association between review times and clinical benefit for new cancer medicines in the United States, European Union, Switzerland, Japan, Canada, and Australia?

SUMMARY ANSWER: Most new cancer therapies were first approved by the US Food and Drug Administration (FDA), and delays in submission of regulatory applications accounted for between 20% and 84% of the time to subsequent approval. There was no evidence of an association between high clinical benefit and faster regulatory review.

WHAT WE DID: We studied new cancer drugs approved by the FDA (United States), European Medicines Agency (EMA; European Union), Swissmedic (Switzerland), Pharmaceuticals and Medical Devices Agency (PMDA; Japan), Health Canada (Canada), and Therapeutic Goods Administration (Australia) from January 2007 to May 2020 using publicly available registers of drug approvals available for each regulatory agency. We extracted all applicable expedited programs, regulatory review times, and, for drugs first approved by the FDA, times to subsequent regulatory approval. We assessed clinical benefit using validated and widely used value frameworks: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale and the ASCO's Cancer Research Committee targets.

WHAT WE FOUND: There were 128 drugs that received initial approval in at least one of the six included jurisdictions. Most drugs approved by the FDA (91%) and Health Canada (59%) qualified for at least one expedited program within those jurisdictions, compared with 46% of EMA approvals and 18% of PMDA approvals. The FDA was the first regulator to approve 102 (80%) drugs. Delays in submission accounted for a median of 20.2% (EMA) to 83.8% (PMDA) of the time to subsequent approval.

BIAS, CONFOUNDING FACTORS, REAL-LIFE IMPLICATIONS: Consistent with prior studies, regulatory review time was defined as the total time between drug application submission and date of approval, and may include time that is not directly within regulators' control. In addition, clinical benefit was assessed on the basis of the data available at approval, since this represents the data used to justify inclusion in expedited programs. Assessments of clinical benefit could change as more evidence becomes available after approval. Delays in regulatory submission account for a substantial fraction of delays in approving new cancer drugs in other countries. Review times were fastest in the United States, mainly because virtually all cancer drugs approved by the FDA qualified for one or more expedited programs. Drugs with high clinical benefit should be prioritized for faster regulatory review and availability globally.

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ASSOCIATED CONTENT

Appendix

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HEALTH POLICY

original contributions

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abstract

PURPOSE Regulatory agencies have sought to speed up the review of new cancer medicines and reduce delays in approval between countries. We examined trends in regulatory review times and association with clinical benefit for new cancer medicines in six jurisdictions: United States (Food and Drug Administration [FDA]), European Union (European Medicines Agency [EMA]), Switzerland (Swissmedic), Japan (Pharmaceuticals and Medical Devices Agency [PMDA]), Canada (Health Canada), and Australia (Therapeutic Goods Administration).

METHODS We studied all new cancer drugs approved in the six aforementioned jurisdictions from 2007 to 2020. We extracted all applicable expedited programs, total regulatory review times, and, for drugs first approved by the FDA, times to subsequent regulatory approval. Clinical benefit was assessed using the European Society for Medical Oncology-Magnitude of Clinical Benefit Scale value framework and ASCO-Cancer Research Committee's targets. Nonparametric Kruskal-Wallis test was used to compare total review times for high versus low clinical benefit drugs.

RESULTS One hundred and twenty eight drugs received initial approval in at least one of the six included jurisdictions. Most drugs approved by the FDA (91%) and Health Canada (59%) qualified for at least one expedited program within those jurisdictions, compared with 46% of EMA approvals and 18% of PMDA approvals. The FDA was the first regulator to approve 102 (80%) drugs. Delays in submission accounted for a median of 20.2% (EMA) to 83.8% (PMDA) of the time to subsequent approval. There was no association between high clinical benefit and shorter total review times.

CONCLUSION Most new cancer therapies were approved first by the FDA, and delays in submission of regulatory applications accounted for substantial delays in approving cancer drugs in other countries. Regulators should prioritize faster review for drugs with high clinical benefit.

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INTRODUCTION

Regulatory agencies around the world have increasingly sought to speed up the development and approval of new medicines. Notably, since 2012, regulators in the United States (Food and Drug Administration [FDA]), Europe (European Medicines Agency [EMA]), Japan (Pharmaceuticals and Medical Devices Agency [PMDA]), Switzerland (Swissmedic), and Australia (Therapeutic Goods Administration [TGA]) have established new expedited programs. These expedited programs, as well as existing regulatory pathways, are frequently used to facilitate the approval of cancer therapies.[1,2] For example, in 2019, all cancer drugs approved by the FDA qualified for at least one expedited program.[3]

Nevertheless, regulatory agencies continue to face pressure to accelerate new drug approvals[4-6] and reduce delays in approval when drugs are approved first in a comparable country.[7] In 2019, the FDA announced plans (Project Orbis) for concurrent submission and review of oncology products with regulators in Canada and Australia; this initiative was expanded in 2020 to include Switzerland and Singapore.[8] In October 2020, the United Kingdom announced plans to join a consortium of drug regulatory agencies to jointly review certain new medicines with its exit from the European Union (EU).[9] Ideally, both international initiatives and individual regulators' expedited programs would prioritize cancer therapies providing clinically meaningful benefits. Widely used value frameworks include the

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European Society for Medical Oncology (ESMO)-Magnitude of Clinical Benefit Scale (MCBS)[10] and the ASCO's Cancer Research Committee (ASCO-CRC) targets.[11]

Given substantial changes in the regulatory landscape in recent years, we aimed to assess trends in total regulatory review times for new cancer medicines in six jurisdictions: United States (FDA), EU (EMA), Switzerland (Swissmedic), Japan (PMDA), Canada (Health Canada), and Australia (TGA). We also evaluated the association between clinical benefit and times to approval and use of expedited programs.

METHODS

We identified new cancer drugs approved by the FDA (United States), EMA (EU), Swissmedic (Switzerland), PMDA (Japan), Health Canada (Canada), and TGA (Australia) from January 2007 to May 2020 using publicly available registers of drug approvals available for each regulatory agency. The study period was chosen to include key expedited programs that have been established by regulators, including EMA's conditional marketing authorization in 2006 and the FDA's breakthrough therapy designation in 2012. For each drug, we used the ingredient (generic) name to determine whether it had been approved by any of the other regulators. We included drugs for solid tumors and hematologic malignancies, and focused on the first approved indication, which corresponds to initial market availability of these therapies.

Data Extraction

To assess the regulatory characteristics of the included drug approvals, for each drug, we extracted the dates of regulatory application submission and approval, indication, cancer type, and expedited program. Dates of regulatory approval were available from all six regulators; dates of regulatory application submission were available for the FDA, EMA, PMDA, and Health Canada for the entire study period and for TGA after 2014, but not for Swissmedic. Information on expedited program and approval type (Appendix Table A1, online only) were publicly available from FDA (priority review, accelerated approval fast track, breakthrough therapy designation, and real-time oncology review pilot), EMA (accelerated assessment, conditional marketing authorization, and priority medicines scheme), PMDA (priority review, conditional approval, and sakigake designation), Swissmedic (temporary authorization), Health Canada (priority review and Notice of Compliance with Conditions), and TGA (priority review and provisional approval). Among these, the expedited programs with shorter targets for regulatory review times were FDA's priority review (6 months), EMA's accelerated assessment (150 days), PMDA's priority review (9 months) and sakigake (6 months), Health Canada's priority review (180 days), and TGA's priority review (150 days). All data for the study period were updated in December 2021.

We reviewed regulatory review dossiers or, if unavailable, product labeling for data on the pivotal trials supporting approval of the included drugs. For solid tumor drugs, clinical benefit was assessed using the ESMO-MCBS version 1.1 scale[10] and targets for clinically meaningful benefit developed by working groups of ASCO-CRC (limited to randomized controlled trials).[11] Consistent with prior studies[1,12-16] as well as developers of these frameworks,[17] high clinical benefit was defined as ESMO-MCBS scores of 4-5 (in palliative settings) or A-B (in adjuvant or neoadjuvant therapy settings), and overall survival gains $>$ 2.5 months or progression-free survival gain $>$ 3 months.[11,18]

Statistical Analysis

For jurisdictions with available data (all except Swissmedic), we calculated total regulatory review times, defined as the time from submission to regulatory approval. We assessed differences in total review times and submission dates between jurisdictions. For drugs first approved by the FDA, we evaluated times to subsequent regulatory approval by one of the other included regulators and the proportion of these times accounted for by later submission to other regulators (ie, delays in submission of regulatory applications).

To evaluate the association between regulatory review times and clinical benefit, we used the nonparametric Kruskal-Wallis test to compare total review times for high versus low benefit drugs. We then fit separate Cox regression models to assess the association between clinical benefit and times to subsequent regulatory approval for drugs first approved by the FDA.

Statistical analyses were performed using Stata version 12.0 (Stata Corp, College Station, TX). Two-tailed P values $<$ .05 were considered statistically significant. Institutional review board approval was not required because all data were publicly available.

RESULTS

Between January 2007 and May 2020, 128 cancer drugs received initial regulatory approval in at least one of the six included jurisdictions (Table 1, Appendix Table A2, online only). Seventy-seven (60%) of the 128 included drugs were approved for solid tumors. As of May 2020, 58 (45%) drugs were approved by all six regulators; 26 (20%) were approved in only one jurisdiction. The FDA approved 117 (91%) drugs, the EMA 94 (73%), Swissmedic 84 (66%), PMDA 75 (59%), Health Canada 88 (69%), and the TGA 84 (66%). The FDA was the first regulator to approve 102 (80%) drugs, compared with 10 (8%) drugs approved first by EMA, three (2%) by Swissmedic, 11 (9%) by PMDA, and two (2%) by TGA; no drugs were first approved by Health Canada.

Regulatory Review and Expedited Programs

Overall, most cancer drugs approved by the FDA (91%) and Health Canada (59%) qualified for at least one expedited program within those jurisdictions (Table 2). By contrast, only 46% of EMA approvals and 18% of PMDA

TABLE 1. Characteristics of New Cancer Drugs Approved by the FDA, EMA, Swissmedic, PMDA, Health Canada, and TGA, January 2007-May 2020

Study Cohort (N = 128)	No. (%)
Cancer type	
Solid tumors	77 (60)
Hematologic malignancies	51 (40)
Initial approval year	
2007-2009	16 (13)
2010-2012	24 (19)
2013-2015	31 (24)
2016-2018	38 (30)
2019-2020	19 (15)
Approval jurisdiction	
FDA	117 (91)
EMA	94 (73)
Swissmedic	84 (66)
PMDA	75 (59)
Health Canada	88 (69)
TGA	84 (66)
No. of approved jurisdictions	
1	26 (20)
2	10 (8)
3	6 (5)
4	11 (9)
5	17 (13)
6	58 (45)
First regulatory approval	
FDA	102 (80)
EMA	10 (8)
Swissmedic	3 (2)
PMDA	11 (9)
Health Canada	0 (0)
TGA	2 (2)

NOTE. Sums may not total to 100% because of rounding.

Abbreviations: EMA, European Medicines Agency; FDA, US Food and Drug Administration; PMDA, Pharmaceuticals and Medical Devices Agency; TGA, Therapeutic Goods Administration.

approvals qualified for an expedited program within those jurisdictions. Most (82%) cancer drugs approved by the FDA received priority review, compared with 17% of EMA approvals (accelerated assessment), 16% of PMDA approvals (priority review and sakigake), 28% of Health Canada approvals, and 12% of TGA approvals (after creation of the program in July 2017).

Time to Subsequent Regulatory Approval

As of May 2020, among the 102 drugs first approved by FDA, the median time to subsequent approval by EMA was 9.7 months (95% CI, 7.9 to 11.7), 15.7 months (95% CI, 13.6 to 18.0) for Swissmedic, 37.4 months for PMDA (95% CI, 31.2 to 42.7), 12.2 months for Health Canada (95% CI, 10.2 to 15.7), and 17.1 months for TGA (95% CI, 13.7 to 21.8; Fig 1).

Delays in submission accounted for a median of 20.2% (interquartile range [IQR], 4.3%-32.9%) of the time to subsequent approval by EMA, 44.2% (IQR, 29.7%-77.9%) of time to approval by TGA, 60.9% (IQR, 44.9%-81.4%) of time to approval by Health Canada, and 83.8% of time to approval by PMDA (IQR, 65.8%-96.4%).

Association With Clinical Benefit

Sixteen of 74 (22%) solid tumor drugs were rated as high clinical benefit as assessed with ESMO-MCBS. Drugs considered high clinical benefit according to ESMO-MCBS were associated with shorter total regulatory review times for Health Canada (–1.90 months; 95% CI, –0.18 to –3.61 months; $P = .03$). However, there was no association between clinical benefit and total review times for FDA ($P = .90$), EMA ($P = .32$), PMDA ($P = .83$), and TGA ($P = .57$).

In Cox regression models for each jurisdiction, high-benefit drugs were associated with decreased times to subsequent approval by EMA (6.0 *v* 10.4 months; hazard ratio, 2.61; 95% CI, 1.32 to 5.17; $P = .006$) and Swissmedic (6.7 *v* 15.9 months; hazard ratio, 2.18; 95% CI, 1.12 to 4.23; $P = .02$; Fig 2, Appendix Table A3, online only). The association between clinical benefit and time to subsequent approval was not significant for PMDA (18.7 *v* 31.7 months; $P = .21$), Health Canada (6.9 *v* 10.8 months; $P = .05$), and TGA (8.8 *v* 17.0 months; $P = .09$).

Only 38 drugs could be assessed with ASCO-CRC (randomized controlled trials), of which 28 (74%) were categorized as providing high clinical benefit. No expedited programs were associated with high clinical benefit according to ASCO-CRC. There was no association between clinical benefit according to ASCO-CRC and total review times or time to subsequent approval by any regulatory agency.

DISCUSSION

In this analysis of regulatory review times and clinical benefit for cancer drugs approved by six major regulatory agencies since 2007, we found that most new cancer therapies were approved first by the FDA and qualified for one of FDA's expedited programs. For drugs approved first by the FDA, the median time to subsequent approval ranged from 9.7 months for Europe (EMA) to 37.4 months for Japan (PMDA). Delays in submission of regulatory applications accounted for 20% (EMA), 44% (TGA), 61% (Health Canada), and 84% (PMDA) of these times to subsequent approval.

Our findings that delays in regulatory submission to regulators other than the FDA and EMA account for a substantial fraction of delays in approving new cancer drugs in

TABLE 2. Expedited Programs and Total Regulatory Review Times by Jurisdiction[a]

Characteristic	No. (%)	Median Regulatory Review Time, Months (IQR)
FDA		
None	11 (9)	10.0 (9.7-11.9)
Priority review	96 (82)	6.1 (5.0-7.9)
Accelerated approval	43 (37)	6.0 (4.9-8.0)
Fast track	51 (44)	6.9 (5.0-9.1)
Breakthrough therapy designation	43 (37)	6.2 (4.8-7.8)
Real-time oncology review pilot	1 (1)	NA
EMA		
None	61 (64)	14.4 (13.4-16.5)
Accelerated assessment	16 (17)	9.7 (9.0-10.8)
Conditional marketing authorization	19 (20)	14.9 (11.7-16.8)
Priority medicines scheme	3 (3)	12.8 (9.6-12.9)
PMDA		
None	61 (82)	10.0 (8.8-11.0)
Priority review	10 (14)	10.5 (7.8-11.7)
Conditional approval	1 (1)	NA
Sakigake	2 (3)	6.0 (NA)
Health Canada		
None	35 (41)	11.5 (11.4-13.3)
Priority review	24 (28)	7.3 (7.0-8.3)
NOC/c	30 (35)	9.7 (9.1-13.0)
TGA[a]		
None	79 (94)	11.5 (9.9-12.5)
Priority review	3 (4)	6.2 (3.9-7.3)
Provisional approval	2 (2)	12.0 (NA)

NOTE. Regulatory review times were not available from Swissmedic. Sums may not total to 100% because of rounding.

EMA, European Medicines Agency; FDA, Food and Drug Administration; IQR, interquartile range; NA, not available; NOC/c, notice of compliance with conditions; PMDA, Pharmaceuticals and Medical Devices Agency; TGA, Therapeutic Goods Administration.

[a]Expedited programs for TGA came into effect from 2017.

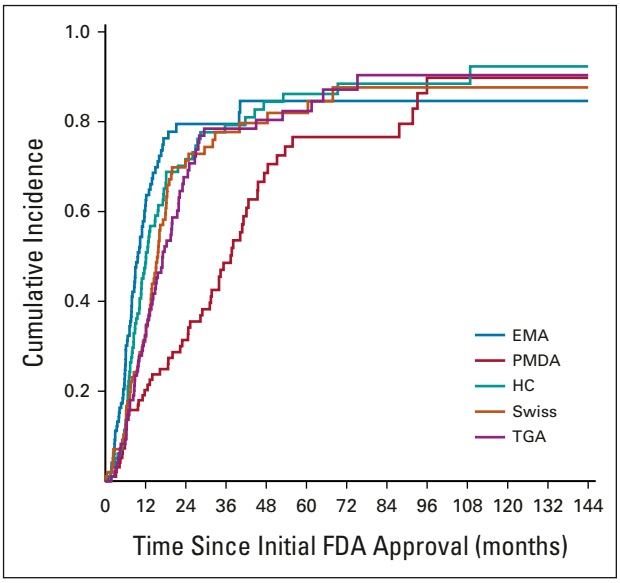

FIG 1. Time to subsequent regulatory approval for cancer drugs in other countries first approved by the FDA. EMA, European Medicines Agency (European Union); FDA, US Food and Drug Administration; HC, Health Canada (Canada); PMDA, Pharmaceuticals and Medical Devices Agency (Japan); Swiss, Swissmedic; TGA, Therapeutic Goods Administration (Australia).

those countries provide support for coordinating joint submission and review of new drug applications. Such initiatives are currently underway. In 2018, Australia, Canada, Switzerland, and Singapore announced plans to jointly review and approve new medicines through a New Chemical Entities Work Sharing Initiative.[19] The first products approved by this consortium were cancer therapies, namely, apalutamide (prostate cancer), abemaciclib (breast cancer), and niraparib (ovarian, fallopian tube, or peritoneal cancers). In 2019, Switzerland established a pathway for temporary approval of drugs already approved in comparable countries[20]; this pathway was used to accelerate the availability of larotrectinib (tumors with NTRK gene fusion) and cemiplimab (cutaneous squamous cell carcinoma). In 2020, tucatinib, indicated for human epidermal growth factor receptor 2–positive breast cancer, was the first new drug approved through Project Orbis[21]: FDA approval was granted in April 2020, with subsequent approval by Swissmedic issued in 19 days (May 2020) and by Health Canada in 49 days (June 2020).

In addition to international regulatory collaboration, regulatory agencies have established expedited programs, which have resulted in shorter regulatory review times for qualifying products. We found that the application of these expedited programs varied between countries. Although the FDA granted priority review to 82% of cancer drugs, only 12%-28% of drugs approved by EMA, PMDA, Health Canada, or TGA qualified for faster regulatory review through comparable programs. We also found little evidence that expedited programs successfully prioritized drugs with high clinical benefit, including notably the breakthrough therapy program in the United States. These findings may reflect uncertainty or lack of systematic definition of the level of benefit expected for drugs qualifying for faster clinical development or regulatory review. Aligning reviews with health technology assessment agencies, such as in Canada and in the EU, and using a validated value framework, such as ESMO's MCBS, may help raise the bar for expedited programs in general so that regulators can deploy limited time and resources most efficiently. Strengthening the standards for expedited programs is also important for patients and clinicians, given the signaling effect that such programs may have,[22] the need for patient-relevant outcomes data to guide treatment decisions, and the possible safety risks associated with drugs approved through expedited programs in general.[23-25]

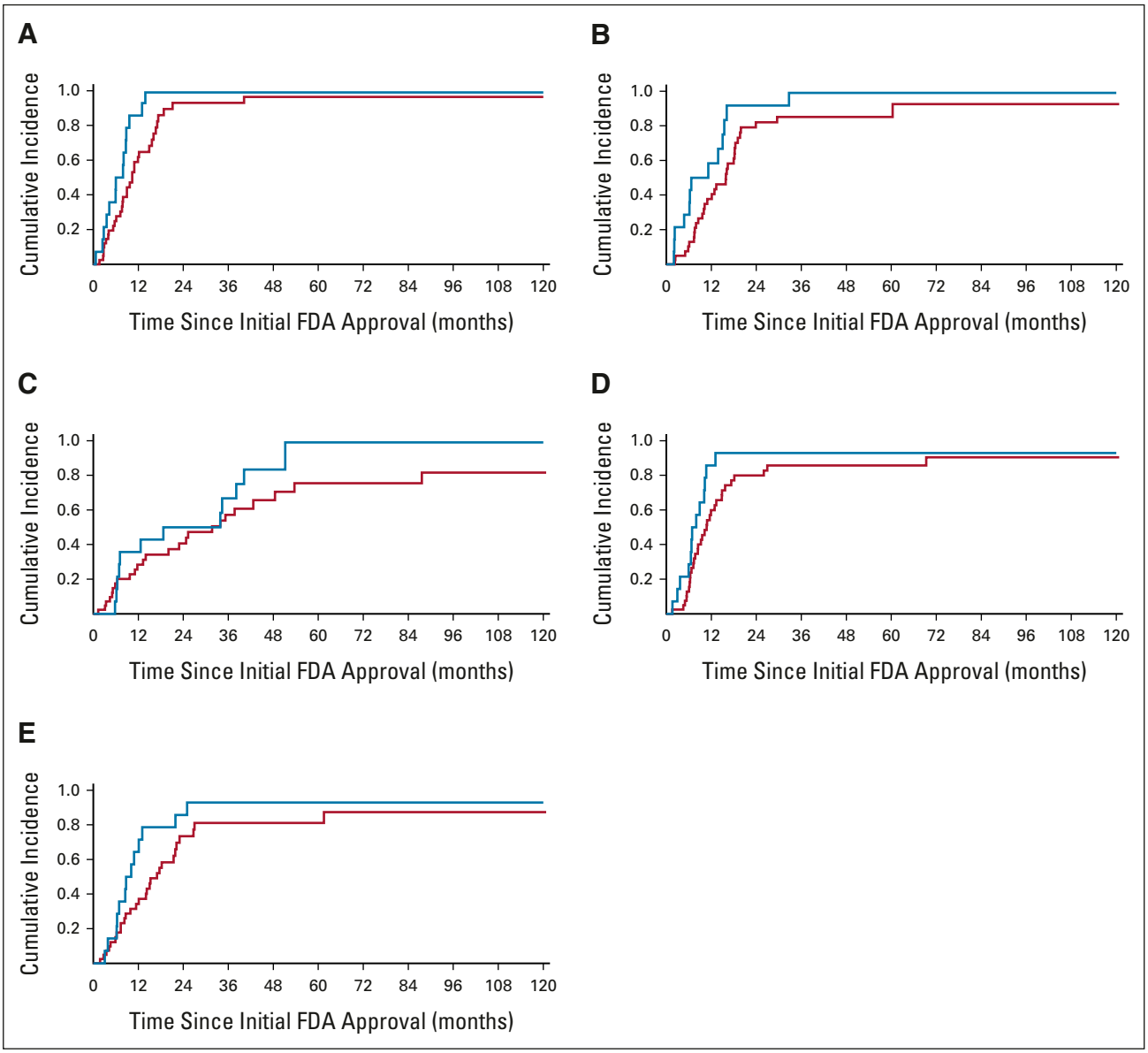

FIG 2. Association between time to subsequent regulatory approval and clinical benefit according to ESMO-MCBS: (A) EMA, (B) Swissmedic, (C) PMDA, (D) Health Canada, and (E) TGA. High clinical benefit is shown in blue; low clinical benefit is shown in red. EMA, European Medicines Agency; ESMO-MCBS, European Society for Medical Oncology Magnitude of Clinical Benefit Scale; FDA, US Food and Drug Administration; PMDA, Pharmaceuticals and Medical Devices Agency; TGA, Therapeutic Goods Administration.

This study has limitations. First, we focused on approved products and assessed differences in regulatory review times between jurisdictions. Some variation in times to approval may be accounted for by factors other than application submission or regulatory review alone. For example, manufacturers may need to conduct additional trials enrolling local participants. Second, there were limited data for several expedited programs, such as PMDA's sakigake program and TGA's priority review, which were only recently established. Third, consistent with prior studies,[26-29] total regulatory review time was defined as the total time between drug application submission and date of approval. This period includes time elapsed (including regulatory clock-stops) as the manufacturer submits updated data or application amendments, responds to questions from the regulator, or corrects other components of the overall application (eg, manufacturing issues)—which may not be directly within the regulator's control. Finally, clinical benefit was assessed on the basis of the data available at approval, since this represents the data used to justify inclusion in expedited programs. It is possible that assessments of clinical benefit could change as more evidence becomes available after approval.

In conclusion, this study found substantial variation in regulatory review times for cancer drugs by major regulatory agencies around the world. Review times were fastest in the

United States, mainly because virtually all cancer drugs approved by the FDA qualified for one or more expedited programs. For regulators other than the FDA and EMA, delays in submission of regulatory applications by manufacturers accounted for a significant portion of the time to subsequent approval. Although some drugs with expedited approval provided substantial clinical benefit, regulators could use value frameworks such as ESMO-MCBS to better prioritize faster review for drugs with high clinical benefit.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Clinical Benefit and Expedited Approval of Cancer Drugs in the United States, European Union, Switzerland, Japan, Canada, and Australia

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. List of Key Expedited Programs and Approval Pathways

Regulatory Agency	Year	Qualifying Criteria
FDA (United States)		
Priority review	1992	Drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness
Accelerated approval	1992	Drug that treats a serious condition; and generally provides a meaningful advantage over available therapies; and demonstrates an effect on a surrogate end point that is reasonably likely to predict clinical benefit or on a clinical end point that can be measured earlier than IMM that is reasonably likely to predict an effect on IMM or other clinical benefit (ie, an intermediate clinical end point)
Fast track	1997	Drug that is intended to treat a serious condition and nonclinical or clinical data demonstrate the potential to address unmet medical need
Breakthrough therapy designation	2012	Drug that is intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant end point(s) over available therapies
Real-time oncology review pilot program	2018	Drug that is likely to demonstrate substantial improvements over available therapy; straightforward study design; and end points that can be easily interpreted, including overall survival or progression-free survival
EMA (EU)		
Accelerated assessment	2006	Drug is expected to be of major interest for public health and therapeutic innovation
Conditional marketing authorization	2006	Drug is aimed at treating, preventing, or diagnosing seriously debilitating or life-threatening diseases and the following criteria are met: risk-benefit balance of the medicinal product is positive; it is likely that the applicant will be in a position to provide the comprehensive clinical data; unmet medical needs will be fulfilled; and the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required
PRIME	2016	Fulfill criteria for accelerated assessment; and may offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options
PMDA (Japan)		
Priority review	1993	Drug intended to treat a serious disease; and no standard therapy exists or substantial improvement compared with existing products in efficacy, safety, or quality of life
Sakigake designation	2015	Innovative medical product intended to treat a serious disease; prominent effectiveness expected on nonclinical and early-phase clinical studies; and intent to develop and file new drug application first in Japan or simultaneously with other countries
Conditional approval	2017	Fulfill criteria for priority review; and confirmatory clinical trials are time-consuming or impracticable because of reasons such as a small subject population
Fast track procedure	1998	Drug indicated for treatment or prevention of severe, disabling or life-threatening disease; treatment using currently authorized medicinal products is either unavailable or unsatisfactory; and a high therapeutic benefit is expected
Temporary authorization (Article 9 TPA)	2019	Drug indicated for life-threatening or debilitating diseases if compatible with the protection of health; its use is expected to have a major therapeutic benefit; and no authorized, alternative, or equivalent medicinal product is available in Switzerland
Health Canada (Canada)		
Priority review	1996	Drug intended for treatment, prevention, or diagnosis of serious, life-threatening or severely debilitating illnesses or conditions where there is no existing drug on the Canadian market with the same profile or where the new product represents a significant improvement in the benefit/risk profile over existing products
NOC/c	1998	Eligibility for priority review; and promising clinical effectiveness in clinical trials through surrogate or clinical end point that is reasonably likely to predict clinical benefit; must also be of high quality and possess an acceptable benefit/risk profile
TGA (Australia)		
Priority review	2017	Drug is indicated for treatment, prevention or diagnosis of a life-threatening or seriously debilitating condition; compared against registered therapeutic goods; and substantial evidence demonstrating that the medicine provides a major therapeutic advance
Provisional approval	2018	Drug is indicated for treatment, prevention, or diagnosis of a life-threatening or seriously debilitating condition; compared against registered therapeutic goods; preliminary clinical data demonstrating that the medicine is likely to provide a major therapeutic advance; and evidence of a plan to submit comprehensive clinical data

NOTE. Swissmedic additionally has a prior notification procedure and pathway for approval of products already approved in a country with comparable medicinal product control (Article 13 TPA).

Abbreviations: EMA, European Medicines Agency; EU, European Union; FDA, US Food and Drug Administration; IMM, irreversible morbidity or mortality; NOC/c, Notice of Compliance with Conditions; PMDA, Pharmaceuticals and Medical Devices Agency; PRIME, Priority Medicines scheme; TGA, Therapeutic Goods Administration; TPA, Therapeutic Products Act.

TABLE A2. List of Cancer Drugs Approved by FDA, EMA, Swissmedic, PMDA, Health Canada, and TGA, 2007-May 2020

Drug	FDA	EMA	PMDA	Health Canada	Swissmedic	TGA
Lapatinib	●	●	●	●	●	●
Temsirolimus	●	●	●	●	●	●
Ixabepilone	●				●	
Nilotinib	●	●	●	●	●	●
Trabectedin	●	●	●	●	●	
Tegafur/ gimeracil/ oteracil		●	●			
Bendamustine	●		●	●	●	●
Plerixafor	●	●	●	●	●	●
Degarelix	●	●	●	●	●	●
Everolimus	●	●	●	●	●	●
Pralatrexate	●		●	●	●	●
Pazopanib	●	●	●	●	●	●
Ofatumumab	●	●	●	●	●	●
Romidepsin	●		●	●		●
Vinflunine		●				●
Miriplatin			●			
Mifamurtide		●			●	
Cabazitaxel	●	●	●	●	●	●
Eribulin	●	●	●	●	●	●
Sipuleucel-T	●	●				
Ipilimumab	●	●	●	●	●	●
Vandetanib	●	●	●	●	●	●
Abiraterone	●	●	●	●	●	●
Vemurafenib	●	●	●	●	●	●
Brentuximab	●	●	●	●	●	●
Crizotinib	●	●	●	●	●	●
Ruxolitinib	●	●	●	●	●	●
Axitinib	●	●	●	●	●	●
Vismodegib	●	●		●	●	●
Pertuzumab	●	●	●	●	●	●
Carfilzomib	●	●	●	●	●	●
Ziv-aflibercept	●	●	●	●	●	●
Enzalutamide	●	●	●	●	●	●
Bosutinib	●	●	●	●	●	●
Regorafenib	●	●	●	●	●	●
Omacetaxine	●					
Cabozantinib	●	●	●	●	●	●
Ponatinib	●	●	●	●	●	●
Mogamulizumab	●	●	●			
Pixantrone		●				
Pomalidomide	●	●	●	●	●	●

(continued in next column)

TABLE A2. List of Cancer Drugs Approved by FDA, EMA, Swissmedic, PMDA, Health Canada, and TGA, 2007-May 2020 (continued)

Drug	FDA	EMA	PMDA	Health Canada	Swissmedic	TGA
Ado-trastuzumab emtansine	●	●	●	●	●	●
Radium-223	●	●	●	●	●	●
Trametinib	●	●	●	●	●	●
Dabrafenib	●	●	●	●	●	●
Afatinib	●	●	●	●	●	●
Obinutuzumab	●	●	●	●	●	●
Ibrutinib	●	●	●	●	●	●
Ramucirumab	●	●	●	●	●	●
Ceritinib	●	●	●	●	●	●
Belinostat	●					
Idelalisib	●	●		●	●	●
Pembrolizumab	●	●	●	●	●	●
Blinatumomab	●	●	●	●	●	●
Olaparib	●	●	●	●	●	●
Nivolumab	●	●	●	●	●	●
Trifluridine/tipiracil	●	●	●	●	●	●
Alectinib	●	●	●	●	●	●
Nintedanib		●				●
Palbociclib	●	●	●	●	●	●
Lenvatinib	●	●	●	●	●	●
Panobinostat	●	●	●		●	●
Dinutuximab	●	●		●		
Sonidegib	●	●			●	●
Cobimetinib	●	●		●	●	●
Osimertinib	●	●	●	●	●	●
Daratumumab	●	●	●	●	●	●
Ixazomib	●	●	●	●	●	●
Necitumumab	●	●	●	●		
Elotuzumab	●	●	●	●	●	●
Talimogene laherparepvec	●	●			●	●
Venetoclax	●	●	●	●	●	●
Atezolizumab	●	●	●	●	●	●
Olaratumab	●	●		●	●	
Rucaparib	●	●				
Ribociclib	●	●		●	●	●
Avelumab	●	●	●	●	●	●
Niraparib	●	●		●	●	●
Brigatinib	●	●		●		●
Midostaurin	●	●		●	●	●
Durvalumab	●	●	●	●	●	●
Neratinib	●	●		●	●	●

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TABLE A2. List of Cancer Drugs Approved by FDA, EMA, Swissmedic, PMDA, Health Canada, and TGA, 2007-May 2020 (continued)

Drug	FDA	EMA	PMDA	Health Canada	Swissmedic	TGA
Enasidenib	●			●		●
Inotuzumab	●	●	●	●	●	●
Copanlisib	●					
Abemaciclib	●	●	●	●	●	●
Acalabrutinib	●			●		●
Lutetium Lu177	●	●		●	●	
Tisagenlecleucel	●	●	●	●	●	●
Padeliporfin		●				
Axicabtagene ciloleucel	●	●		●	●	●
Tivozanib		●				
Forodesine			●			
Apalutamide	●	●	●	●	●	●
Binimetinib	●	●	●		●	●
Encorafenib	●	●	●	●	●	●
Ivosidenib	●					
Moxetumomab	●					
Duvelisib	●					
Dacomitinib	●	●	●	●	●	
Cemiplimab	●	●		●	●	
Talazoparib	●	●		●	●	●
Lorlatinib	●	●	●	●	●	●
Glasdegib	●			●		
Larotrectinib	●	●		●	●	
Gilteritinib	●	●	●	●		●
Calaspargase	●					
Tagraxofusp	●					
Plitidepsin						●
Erdafitinib	●			●		
Alpelisib	●			●	●	●
Polatuzumab	●	●				●
Selinexor	●					
Darolutamide	●	●	●	●		●
Pexidartinib	●					
Entrectinib	●		●	●		
Fedratinib	●					
Zanubrutinib	●					
Enfortumab	●					
Fam-trastuzumab	●		●			
Quizartinib			●			
Avapritinib	●					
Tazemetostat	●					

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TABLE A2. List of Cancer Drugs Approved by FDA, EMA, Swissmedic, PMDA, Health Canada, and TGA, 2007-May 2020 (continued)

Drug	FDA	EMA	PMDA	Health Canada	Swissmedic	TGA
Isatuximab	●	●		●	●	
Selumetinib	●					
Tucatinib	●				●	
Pemigatinib	●					
Sacituzumab govitecan	●					

Abbreviations: EMA, European Medicines Agency; FDA, US Food and Drug Administration; PMDA, Pharmaceuticals and Medical Devices Agency; TGA, Therapeutic Goods Administration.

TABLE A3. Cox Regressions of Clinical Benefit and Time to Subsequent Approval

Regulatory Agency	HR (95% CI)	*P*
EMA	2.61 (1.32 to 5.17)	.006
Swissmedic	2.18 (1.12 to 4.23)	.02
PMDA	1.57 (0.77 to 3.17)	.21
Health Canada	1.94 (0.98 to 3.81)	.05
TGA	1.80 (0.92 to 3.52)	.09

Abbreviations: EMA, European Medicines Agency; FDA, US Food and Drug Administration; HR, hazard ratio; PMDA, Pharmaceuticals and Medical Devices Agency; TGA, Therapeutic Goods Administration.