Cancer drug indication approvals in China and the United States: a comparison of approval times and clinical benefit, 2001–2020

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Summary

Background Perceived delays in cancer drug approvals have been a major concern for policymakers in China. Policies have been implemented to accelerate the launch of new cancer drugs and indications. This study aimed to assess similarities and differences between China and the United States in the approvals, timing, and clinical benefit evidence of cancer drug indications between 2001 and 2020.

Methods This study retrospectively identified all cancer drugs and indications approved in both China and the United States from January 1st, 2001 to December 31, 2020, and described differences in approval times as well as in submission and review times. Information on the availability of overall survival benefit evidence by December 31, 2020, was collected. Univariate and multiple logistic regression analyses were used to assess whether evidence of benefit and other factors affected the propensity and timing of approvals of cancer drug indications in China.

Findings Between 2001 and 2020, 229 indications corresponding to 145 cancer drugs approved in the United States were identified. Of those, 80 indications (34.9%) were also approved in China by the end of 2020. Cancer drug indications were approved in China at a median of 1273.5 days after approval in the United States. The median submission and review time differences for cancer drug indications in China were 1198.0 days and 180.0 days respectively. Submission time differences accounted for most of the approval time differences ($p < 0.001$). Indications supported by overall survival benefit evidence had shorter median review time differences (145.0 days) than those without such evidence (235.0 days, $p = 0.008$). Indications with overall survival benefit evidence were 3.94 times more likely to be approved in China compared to those without such evidence ($p = 0.001$), controlling for approval year, cancer type, and the prevalence of cancer by site.

Interpretation FDA-approved cancer drug indications demonstrating a survival benefit were more likely to receive approvals in China with shorter regulatory review times compared to indications without such evidence. Given that manufacturer submission times were the main driver of cancer drug approval times in China, factors influencing submission timing should be explored.

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Keywords: Drug approval timing; Overall survival; Anticancer drug; Indication; China; United States

Introduction

Cancer is the second leading cause of death worldwide, with major unmet clinical need.[1,2] Over the past two decades, many new cancer drugs, some representing first-in-class therapeutics, have been developed.[3] However, new cancer therapeutics are not simultaneously available globally. During the past two decades, patients with cancers in the United States accessed new cancer drugs earlier than patients in the European Union, Japan and Canada.[4] New cancer drugs were

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Research in context

Evidence before this study

Evidence assessing the approval of cancer drugs with regard to clinical benefit for specific indications is scarce. Currently, comparative analyses are at the drug rather than at the drug indication level. In this study, we conducted a thorough literature review in PubMed of evaluations of differences in cancer drug approvals across countries, with a particular emphasis on those related to China. Previous analysis revealed that China has a comparatively lower number and later times of cancer drug approvals in comparison to the United States and the European Union. To date, no study has been conducted comparing evidence of clinical benefit and approval times at the indication level.

Added value of this study

To the best of our knowledge, this is the first study assessing differences in approval decisions, timing, and clinical benefit evidence of cancer drugs in China and the United States at the indication level. We identified 229 cancer indications approved in the United States and 80 indications approved in both countries between 2001 and 2020. Indications were approved in China nearly 3.5 years after approvals in the United States. Manufacturers' later submission in China was the primary reason for the later approval times, explaining more than 94% of the variation in approval times. Cancer indications supported by evidence of overall survival benefit were more likely to be approved with shorter review duration in China than indications without such evidence.

Implications of all the available evidence

In China, FDA-approved cancer indications were approved later than in the United States and are more likely to have clinical benefit evidence than those not approved in China. There is a need to understand manufacturers' regulatory submission decisions to facilitate simultaneous launch of new cancer drugs with evidence of clinical benefit across markets. These findings highlight the importance of considering clinical benefit evidence and components of approval times when assessing cancer drug approvals across jurisdictions.

approved in the European Union and Japan 9.7 and 37.4 months after approvals in the United States from 2007 to 2020.[5] In 2019, the medium time from application submission to approval of a new drug by the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Pharmaceutical and Medical Devices Agency of Japan (PMDA) was 243, 423, and 304 days respectively.[6]

Compared with the United States, China was considered to be late in approving new cancer drugs. Of 161 cancer drugs launched globally between 2001 and 2020, 152 were approved in the United States while only 11 were available in China by the end of 2018.[7] The delayed availability of cancer drugs could, in certain cases, impede patients' access to effective treatments and might cause loss of life utilities during the waiting period.[8] For instance, nivolumab, the first-in-class anti-programmed cell death receptor-1 (PD-1) antibody, was approved in Japan for the treatment of esophageal cancer and melanoma in 2014, which marked the initial launch of PD-1 therapy globally.[9] Nivolumab was not approved in China until 2018.[10] However, several new cancer drug indications approved with immature clinical evidence or using surrogate endpoints under the FDA's expedited pathways were later found to be ineffective. For example, atezolizumab was approved for the treatment of triple-negative breast cancer through the FDA's accelerated approval pathway in 2019 based on progression-free survival and its overall survival data remained immature at the time of approval. A follow-up study in 2021 showed that atezolizumab did not improve clinical endpoints in triple-negative breast cancer patients.[11,12] Another example is niraparib, a poly (ADP-ribose) polymerase inhibitor (PARP inhibitor) developed by GlaxoSmithKline, which was approved in 2019 by the FDA for the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status.[13] In September 2022, niraparib was voluntarily withdrawn by GlaxoSmithKline following evidence of potentially detrimental effect on overall survival.[14] The delayed availability of cancer indications for which the clinical benefit evidence is unclear may help protect patients from ineffective treatments and prevent wasteful expenditures of limited resources. Research that assesses both clinical efficacy evidence and approval times is therefore needed.

With increasing societal concerns in China about timely access to much-needed and effective treatments, the Chinese government has embarked upon a comprehensive reform of drug regulations and processes since 2015.[15,16] The government introduced three expedited programs to facilitate approvals of new drugs after 2016, including the conditional approval, the breakthrough therapy designation and the priority review (Supplementary Table S1). The Chinese regulatory agency's capacity was also expanded to process the application backlog before the start of this comprehensive reform.[17–19] China's regulatory policy changes have been used in cancer drug approvals: 44 of 52 new cancer drugs approved in China between 2017 and 2020 benefited from at least one expedited program.[17,20]

Previous studies on regulatory approvals compared the availability of drugs, not their various approved

uses.[5,21–26] Oncology drugs commonly have multiple indications and are approved with or without evidence of clinical benefit for specific indications.[27,28] Not all indications approved in other countries are approved in China. For instance, by the end of 2021, pembrolizumab, a PD-1-blocking antibody, had been approved for 19 cancer indications in the United States vs. five in China.[29,30] Drug efficacy and documented clinical benefit differ across approved indications and research at the indication level is therefore needed to understand the landscape of cancer drug approvals in China.[31] Our study systematically identified approval dates and clinical benefit evidence, documented in approved drug labels, for all cancer drug indications approved in China and the United States from 2001 to 2020. We assessed temporal differences in the approval times and regulatory review durations for cancer indications approved in both countries. We also assessed the association between clinical benefit evidence and other drug indication characteristics (approval year, cancer type, and the prevalence of cancers) of FDA-approved cancer drug indications with the likelihood of approvals in China. Finally, we evaluated whether differences in approval times differed by submission and review times, as well as the characteristics of cancer indications.

Methods

Data sources

We searched the publicly available Drugs@FDA,[32] Center for Biologics Evaluation and Research,[33] and Office of Tissues and Advanced Therapies databases[34] to collect all new drug applications and biologic licensing applications approved by the FDA from January 1, 2001, to December 31, 2020. We identified cancer drugs by matching the generic names, standardized using the International Nonproprietary Names (INNs), with the First DataBank database, a proprietary provider of drug information and the "A to Z list of Cancer Drugs" on the National Cancer Institute website.[35] We excluded combination therapies, blood products, preventive vaccines, radiotherapies, supportive therapies, and treatments for palliative indications (Supplementary Figure S1). Using data sources including approval letters, drug labels, and review documents available in the FDA online database, we collected all indication approvals for each drug (see[36] for more detail). We also used the Drugs@FDA database to review the "Clinical Studies" section of the latest FDA-approved labeling at the end of 2020 and extracted information on the design and outcomes of trials and data on overall survival benefit for each cancer drug indication.

Using the website of the Center for Drug Evaluation (CDE),[37] we collected all new cancer drug applications approved by the National Medical Products Administration (NMPA) of China during the same time period and identified drug-specific approved indications. We then compared all cancer drugs and indications approved by the FDA and the NMPA from January 1, 2001, to December 31, 2020, using the generic name to identify whether the FDA-approved cancer drug indications were also approved in China (Supplementary Figure S1). Other public and commercial data sources including YAOZHI Database[38] and MENET Database[39] were used to cross-check information on NMPA-approved indications and approval dates provided by the CDE website. Data on cancer prevalence were collected from the International Agency for Research on Cancer on the World Health Organization website.[40]

Study sample

We classified all approved indications by cancer sites according to the International Statistical Classification of Diseases 10th Revision (ICD-10) and considered indications for different cancer sites as separate cancer drug indications.

We conducted descriptive analyses to compare cancer drug indications approved by the FDA and the NMPA and to identify trends in approval times. We calculated the difference in the number of days between the FDA's and the NMPA's approval dates by indication. Based on previous studies, we also assessed differences in submission and review times as two major components of the approval time differences.[23,26] The submission difference is the difference in the number of days between the new drug application acceptance dates of the FDA and that of the NMPA. The difference in review time refers to the difference in the review duration of the FDA and the NMPA (i.e., the number of days between the dates of application acceptance and drug approval by each regulator).

We assessed overall survival benefit evidence in the FDA-approved label by the end of 2020. Using the same classification criteria as in our previous study,[36] we divided cancer drug indications into two subgroups according to whether the clinical studies reported in FDA-approved labeling demonstrated overall survival benefit or not. Indications were classified as demonstrating survival benefit if the randomized clinical trials supporting approvals reported final or interim data documenting statistically significant overall survival results. Indications for which randomized clinical trials supporting approvals reported no information on or statistically non-significant overall survival benefit were classified as "no evidence on overall survival benefit" (Supplementary Table S4).

Statistical analysis

Data analyses were performed using Excel 2019 (Microsoft Corp) and Stata 17 (Stata Corp). For univariate analysis, the Spearman test was performed to assess the correlation between approval time differences and submission or review time differences. The Wilcoxon

test and the Spearman test were performed to assess differences in approval times, differences in manufacturer submission times, and differences in regulatory agency review times across factors including FDA approval year, cancer type, cancer site, evidence of overall survival benefit, and the prevalence of cancers by sites in China. Multiple logistic regression analysis was performed to assess the association between evidence of benefit as well as other factors and approvals of cancer drug indications in China. The outcome was indication approval by the NMPA. Overall survival benefit evidence in FDA-approved labels was an explanatory variable to indicate whether or not approved cancer drugs had meaningful evidence of clinical efficacy.[27,41,42] Approval year indicates whether an indication was approved by the FDA after 2016 when it might have benefitted from China's newly started expedited programs when applying for marketing authorization in China (Supplementary Table S1). Cancer type indicates whether an indication was classified as treatment for solid tumors or hematological malignancies, and cancer prevalence indicates the 5-year prevalence of cancers by sites in China. Statistical significance in this study was set at 2-tailed $p < 0.05$.

Ethical approval
Not required.

Patient consent for publication
Not required.

Role of the funding source
No funding received.

Results
Characteristics of cancer drug indications
We identified 229 cancer drug indications corresponding to 145 drugs approved by the FDA from January 1, 2001, to December 31, 2020. Of these, 80 (34.9%) cancer drug indications corresponding to 58 drugs were approved by the NMPA by 31 December 2020. We also identified 149 indications corresponding to 87 cancer drugs that were approved only by the FDA and 24 indications corresponding to 21 cancer drugs that were domestically developed in China and were only approved by the NMPA within this period, which were excluded from our approval timing comparative analysis due to the lack of approval dates in both countries (Supplementary Figure S1 & Supplementary Table S2).

Among the 80 cancer drug indications approved by both the FDA and NMPA, NMPA approved 61 (76.3%) for the treatment of solid tumors and 19 (23.8%) for the treatment of hematological malignancies. The cancer types with the most approvals other than hematologic malignancies were lung (n = 14, 17.5%), breast (n = 8, 10.0%), and kidney cancers (n = 5, 6.3%). Of all cancer drug indications approved by both the FDA and NMPA, 30 were approved between 2001 and 2016 (1.9 per year) and 50 were approved between 2017 and 2020 (12.5 per year) (Table 1).

Among 229 cancer drug indications approved by the FDA from 2001 to 2020, 64 (27.9%) had evidence of overall survival benefit, while 165 (72.0%) reported no such evidence. Among 80 cancer drug indications approved by both the FDA and NMPA, 39 (48.7%) had evidence of overall survival benefit, while 41 (51.2%) had no such evidence (Table 1). We also identified the evidence of overall survival benefit for cancer indications that were approved only in China or the United States. Among the 149 indications that were only approved by the FDA, 27 (18.1%) had documented evidence of overall survival benefit, while 122 (81.8%) had no such evidence. Among the 24 indications that were only approved by the NMPA, 4 (16.6%) reported overall survival evidence, while 20 (83.3%) did not (Supplementary Table S2).

Differences in approval times
Seventy-eight cancer drug indications were included in the comparison of approval time differences (NMPA approval times of oxaliplatin for colorectal cancer and imatinib mesylate for leukemia were not available). The median approval time difference for cancer drug indications (n = 78) was 1273.5 days or 3.5 years (interquartile range [IQR], 658.0–2192.0) (Table 1, Supplementary Figure S2).

Univariate analyses were conducted to analyze whether differences in approval times differed by approval year, cancer type and cancer site, evidence of overall survival benefit, and the prevalence of the indications in China. We found that median approval time differences for cancer drug indications approved by the FDA from 2001 to 2016 were 854.0 days or 2.4 years (IQR, 573.0–1683.0), significantly shorter than the median approval time differences of 1397.5 days or 3.8 years (IQR, 1004.0–2394.0) for indications approved by the FDA from 2017 to 2020 ($p = 0.028$). Median approval time differences for liver cancer indications were significantly shorter (186.5 days or 0.5 years (IQR, 85.5–228.5)) than median approval times for other cancer sites (1323.0 days or 3.6 years (IQR, 742.0–2383.0), $p = 0.001$). Approval times did not differ significantly by availability of evidence of overall survival benefit, solid vs. hematological cancer indications, or prevalence of cancers in China by site (Table 1).

Differences in manufacturer submission and regulatory agency review times
We distinguished between manufacturer submission and regulatory agency review time differences. The median submission time difference for cancer drug indications (n = 78) was 1198.0 days or 3.3 years (IQR, 497.0–2144.0), and the median difference in review time

Variables	Approved by FDA	Approved by NMPA	Differences in approval times, days[a]	Differences in submission times, days	Differences in review times, days
	n (%)	n (%)	Median (Interquartile range)	Median (Interquartile range)	Median (Interquartile range)
Cancer drug indications	229 (100.0)	80 (34.9)	1273.5 (658.0–2192.0)	1198.0 (497.0–2144.0)	180.0 (109.0–314.0)
Approval year					
2001–2016	127 (55.4)	30 (37.5)	854.0* (573.0–1683.0)	518.0* (320.5–1388.5)	197.5 (140.0–350.0)
2017–2020	102 (44.5)	50 (49.0)	1397.5 (1004.0–2394.0)	1302.0 (802.0–2331.0)	159.5 (46.0–289.0)
Cancer type					
Solid tumors	166 (72.5)	61 (36.7)	1232.5 (611.5–2155.0)	1131.5 (405.0–1972.5)	163.5* (45.5–251.5)
Hematological malignancies	63 (27.5)	19 (30.2)	1638.5 (828.0–3189.0)	1335.5 (527.0–2981.0)	268.0 (163.0–446.0)
Cancer site					
C15 Esophagus	2 (0.9)	1 (50.0)	325.0	181.0	144.0
C16 Stomach	2 (0.9)	0 (0.0)	–	–	–
C18-21 Colorectum	11 (4.8)	4 (36.4)	1637.0 (687.0–2192.0)	1323.0 (542.0–2004.0)	188.0 (145.0–314.0)
C22 Liver	9 (3.9)	4 (44.4)	186.5* (85.5–228.5)	65.0* (25.0–175.5)	51.0 (–54.5 to 168.0)
C23, 24 Gallbladder	1 (0.4)	0 (0.0)	–	–	–
C25 Pancreas	5 (2.1)	0 (0.0)	–	–	–
C33, 34 Lung	26 (11.4)	14 (53.8)	1087.0 (515.0–1320.0)	1022.0 (497.0–1281.0)	114.0* (8.0–193.0)
C40, 41 Bone	2 (0.9)	1 (50.0)	2168.0	2144.0	24.0
C43 Melanoma of skin	11 (4.8)	4 (36.4)	2213.0 (1723.5–2394.0)	2076.5 (1625.0–2350.0)	44.0 (6.0–136.5)
C50 Female breast	21 (9.2)	8 (38.1)	2262.5 (1231.0–2743.0)	1660.5 (862.5–2527.0)	239.0 (168.0–332.0)
C53 Cervix	2 (0.9)	0 (0.0)	–	–	–
C54, 55 Uterus	2 (0.9)	0 (0.0)	–	–	–
C56 Ovary	4 (1.7)	2 (50.0)	1173.0 (1004.0–1342.0)	1087.0 (777.0–1397.0)	86.0 (–55.0 to 227.0)
C61 Prostate	10 (4.4)	4 (40.0)	2052.0 (1018.5–3091.5)	1744.5 (927.5–2518.0)	307.5 (91.0–573.5)
C64-66, 68 Kidney	13 (5.7)	5 (38.5)	1188.0 (642.0–1394.0)	1159.0 (292.0–1218.0)	235.0 (185.0–350.0)
C67 Bladder	7 (3.1)	0 (0.0)	–	–	–
C70-72 Brain, CNS	3 (1.3)	2 (66.7)	2680.0 (1203.0–4157.0)	2149.0 (509.0–3789.0)	531.0 (368.0–694.0)
C73 Thyroid	8 (3.5)	2 (25.0)	1652.0 (1205.0–2099.0)	1478.5 (1016.0–1941.0)	173.5 (158.0–189.0)
C81-85, 88, 90, 96 Lymphoma	36 (15.7)	8 (22.2)	2690.0 (1104.0–3956.5)	2423.5 (904.5–3524.5)	286.0 (215.0–432.0)
C91-95 Leukemia	27 (11.8)	11 (40.7)	1103.0 (742.0–1941.0)	882.5 (507.0–1652.0)	232.0 (128.0–454.0)
All other sites[b]	27 (11.8)	10 (37.0)	1034.0 (565.0–1486.0)	698.5 (320.0–1453.0)	156.0 (46.0–350.0)
OS benefit in FDA-approved labeling[c]					
Evidence of OS benefit	64 (27.9)	39 (60.9)	1342.0 (659.0–2394.0)	1281.0 (542.0–2217.0)	145.0* (46.0–207.0)
No evidence	165 (72.0)	41 (24.8)	1205.0 (642.0–2142.0)	942.0 (373.0–1941.0)	235.0 (120.0–418.0)

Data inadequate or unavailable to describe the median or interquartile range of approval lag was marked as "-". **Abbreviation:** FDA, the Food and Drug Administration of the United States; NMPA, the National Medical Products Administration of the People's Republic of China; CNS, central nervous system; OS, overall survival. [a]We conducted the Wilcoxon test to assess differences in approval times across variables including approval year, cancer type, cancer site, and evidence of overall survival benefit. Results that featured significant differences between groups at $p < 0.05$ level were marked with "*". The same went for differences in submission times and differences in review times. [b]We selected 20 cancer sites under ICD-10 to be presented in Table 1. We classified indications other than these 20 cancer sites into a general category named "all other sites", which covered non-melanoma skin cancers, soft tissue sarcoma, neuroendocrine and adrenal tumors, malignant pleural mesothelioma high-risk neuroblastoma, head and neck cancers microsatellite instability-high cancer, NTRK gene fusion-positive solid tumors, and tumor mutational burden-high cancer. [c]We classified the OS benefit in FDA-approved labeling at the end of 2020 as "Confirmed or inferred OS benefit" if the RCT supporting approvals reported final or interim data on OS. We classified the OS benefit in FDA-approved labeling as "No evidence" if: 1) the RCT supporting approvals reported no information on OS or used clinical endpoints other than OS. 2) the RCT supporting approvals reported statistically insignificant OS benefits. 3) the reported OS was obtained from non-inferiority studies.

Table 1: **FDA and NMPA approvals and differences in times concerning approvals of cancer drug indications, 2001 to 2020.**

was 180.0 days or 0.5 years (IQR, 109.0–314.0) (Table 1). The median review time in China was 353.5 days or 1.0 years (IQR, 275.0–518.0), longer than 181.0 days or 0.5 years (IQR, 147.0–241.0) in the United States (Supplementary Table S3). Spearman's test showed that submission time differences explained most of the variation in approval time differences (correlation coefficient 0.953, $p < 0.001$) (Fig. 1).

Univariate analysis showed the median manufacturer submission time differences for cancer drug indications approved by the FDA from 2001 to 2016 were 518.0 days (IQR, 320.5–1388.5), significantly shorter than the median 1302.0 days (IQR, 802.0–2331.0) of indications approved by the FDA from 2017 to 2020 ($p = 0.006$). There was no significant difference in regulatory agency review times by approval year. We found

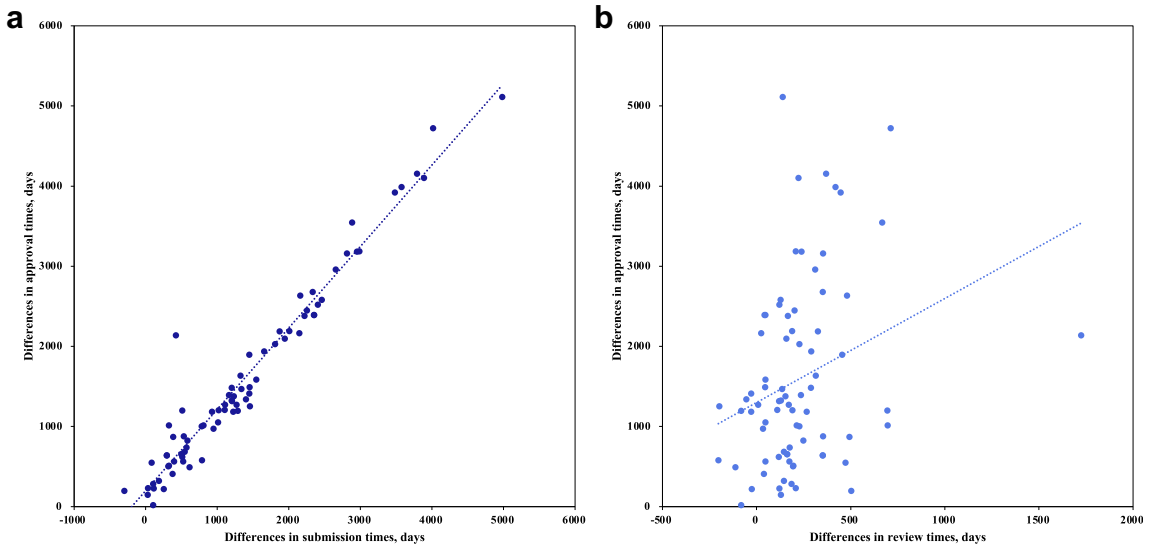

Fig. 1: Approval time differences of cancer drug indications in China, compared with the United States. a. Scatter plot of approval and submission time differences. b. Scatter plot of approval and review time differences.

review time differences varied significantly by cancer type. Indications for solid tumors had median review time differences of 163.5 days (IQR, 45.5–251.5), which was shorter than the 268.0 days (IQR, 163.0–446.0) of indications for hematological malignancies (p = 0.008). Median differences in submission times of liver cancer indications were 65.0 days (IQR, 25.0–175.5), significantly shorter than the median 1209.5 days (IQR, 521.0–2155.0) of indications for other cancer sites (p = 0.002). Median differences in review times of lung cancer indications were 114.0 days (IQR, 8.0–193.0), significantly shorter than the median 198 days (IQR, 127.5–350.5) of indications for other cancer sites (p = 0.004). Median review time differences for indications with overall survival benefit evidence were significantly shorter than those of indications without such evidence (median 145.0 days, IQR, 46.0–207.0 vs. median 235.0 days, IQR, 120.0–418.0, p = 0.008). There was no significant association of manufacturer submission time differences or regulatory agency review time differences with prevalence of cancer sites in China (Table 1).

Multiple logistic regression analysis of impact factors for cancer drug indication approvals in China

Multiple logistic regression analyses showed that approval year and evidence of overall survival benefit were significantly associated with cancer indication approvals in China. Controlling for other variables, cancer indications approved by the FDA from 2001 to 2016 were 6.27 times more likely to be approved by the NMPA compared to those FDA-approved from 2017 to 2020, and indications with overall survival benefit evidence in FDA-approved labeling were 3.94 times more likely to be approved by the NMPA compared to those without such evidence (Table 2).

Discussion

Main findings

To our knowledge, this is the first study assessing differences in approval decisions and timing by clinical benefit evidence of cancer drug indications in China and the United States. Of 229 cancer indications approved in the United States from 2001 to 2020, the Chinese regulatory agency approved 80 (34.9%). Compared with results from a study of approvals by EMA (67% of FDA-approved cancer drug indications between 2009 and 2013 were approved by the EMA), Canada and Australia (53%),[43] our study confirms that fewer FDA-approved cancer drug indications were approved in China than other large markets. There was a median approval time difference of 3.5 years (1273.5 days) for cancer drug indications in China, relative to the United States.

We found that submission time differences of cancer indications accounted for more than 94% (1198.0 days out of 1273.5 days) of the approval time differences between China and the United States, and submission time differences were strongly correlated with approval time differences (0.953, p < 0.001). This finding suggests that manufacturer submission was the primary contributor to differences in cancer indication approvals between China and the United States, which is different from the recent finding of small submission time differences of new drug applications between the European Union and the United States.[44] Submission decisions are likely related to companies' commercial

Variable	Approved by FDA	Approved by NMPA	OR	95% CI	p-value
	n (%)	n (%)			
Cancer drug indications	229 (100.0)	80 (34.9)	–	–	–
Approval year					
2001–2016	127 (55.4)	30 (37.5)	6.27	2.71–14.51	**0.000**
2017–2020	102 (44.5)	50 (49.0)	reference group		
Cancer type					
Solid tumors	166 (72.5)	61 (36.7)	1.46	0.60–3.58	0.405
Hematological malignancies	63 (27.5)	19 (30.2)	reference group		
OS benefit in FDA-approved labeling					
Evidence of OS benefit	64 (27.9)	39 (60.9)	3.94	1.72–9.00	**0.001**
No evidence	165 (72.0)	41 (24.8)	reference group		
5-year prevalence of cancer site in China[a]	–	–	1.00	0.98–1.02	0.807

Abbreviation: FDA, the Food and Drug Administration of the United States; NMPA, the National Medical Products Administration of the People's Republic of China; OR, the odd ratio; 95% CI, 95% confidence interval; OS, overall survival. [a]Data from "World Health Organization, International Agency for Research on Cancer". See Supplementary Figure S3 for details.

Table 2: **Multiple logistics regression results of characteristics related to cancer drug indication approvals in China.**

strategies which influence the order of launches in different countries.[22] It has also been suggested that the pricing strategies of target markets and the epidemiology of cancers were related to pharmaceutical companies' submissions of new drug applications.[2] For example, the estimated age-standardized incidence rate of melanoma was only 0.4 per thousand in China while that in the U.S. was 29.1 per thousand, which might explain why only four of the 11 FDA-approved cancer drug indications for melanoma were available in China.[45]

We found that evidence of overall survival benefit in the FDA-approved labeling was significantly associated with approvals in China and with review time differences between China and the United States. Cancer drug indications with overall survival benefit evidence were 3.94 times more likely to be approved by the NMPA compared than those without such evidence. We applaud this signal of preferential approval by Chinese regulatory authorities of cancer drug indications with evidence of clinical benefit, a finding similar to that of study of cancer drug approvals in Brazil.[46]

Comparison with other studies

In this study, we found the cancer drug indication approval time differences between China and the U.S. were large in 2001–2016 and have since been narrowed in 2017–2020 (30 out of 127 cancer drug indications approved in China in 2001–2016 vs. 50 out of 102 cancer drug indications approved in China in 2017–2020), which is consistent with the trend observed in previous studies.[8,17,26] Cancer indications approved by the NMPA after 2016 might have benefited from the newly established expedited programs in China. The acceptance of the use of surrogate endpoints for new drug applications in China as well as the reduction of standard review durations of the NMPA might be reasons for this observed trend (Supplementary Table S1). Another recent study identified a similar trend among new drug approvals by the FDA and the EMA.[44] However, the overall time difference of cancer drug indication approvals in China has not decreased (median: 854.0 days vs. 1397.5 days). This finding was inconsistent with reports of a shorter median time difference for cancer drug approvals in China in recent years.[8,20,47] We attribute this discrepancy to the difference in our unit of analysis. In contrast to previous studies treating multi-indication drugs as singular entities and determining their earliest approval date, we examined cancer drug indications separately to better understand the time of Chinese patients' access to treatments for specific cancer indications.

Interpretation and policy implication

We used the FDA drug approvals as a benchmark for approvals in China. We suggest, however, that FDA drug approvals should not be considered as the gold standard. As documented in previous research, the FDA has used surrogate endpoints frequently under the accelerated approval process and for traditional approvals, and these endpoints may not indicate clinically meaningful benefit for patients.[48,49] In addition, newly approved drugs are not necessarily better than what is already available. For instance, androgen deprivation therapy (ADT) is a widely used treatment for prostate cancer.[50] Evidence has shown that ADT may increase the risk of cardiovascular disease in prostate cancer patients.[51] Leuprolide, a gonadotropin-releasing hormone (GnRH) agonist was approved for the treatment of prostate cancer by the FDA in 2021. Previous studies argued that leuprolide had shown no significant improvement in reducing the risk of adverse

cardiovascular events than the 2008-approved GnRH antagonist degarelix.[52,53] We believe that drug regulatory agencies should prioritize approvals of new cancer drugs with evidence of clinical benefit.

In addition to evolving its drug regulatory policies, China has made considerable efforts to promote oncology research. There has been an increasing trend of immuno-oncology drug research publications originating in China in the past decade and China has been ranked first globally for 18% of total research outputs in 2021 in this field.[54] It was also suggested that China might prioritize research on cancer with greater unmet clinical need.[54] Studies indicated that between 2012 and 2021, China contributed 32% and 23% of the global research outputs concerning liver cancer and stomach cancer, respectively.[55] These types of cancer pose the most significant burden within China.[55,56] In this study, we found that the approval time differences for liver cancer indications were significantly shorter than those for indications of other cancer sites ($p = 0.001$), and the same for the review time differences of lung cancer indications ($p = 0.004$). These findings may indicate that the Chinese regulatory agency prioritizes approvals for cancer indications with greater clinical burden. In addition, subtypes of the same cancer site may represent different clinical burden and vary in approval timing. For example, triple-negative breast cancer (TNBC) is one subtype of breast cancer with the least favorable outcomes that accounted for 15%–20% of breast cancer diagnoses.[57,58] Pembrolizumab was approved by the FDA on July 26, 2021, for high-risk, early-stage, triple-negative breast cancer in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.[59] After 471.0 days on November 7, 2022, the NMPA approved pembrolizumab for the same indication.[60] We identified a median approval time difference of 2262.5 days for breast cancer in this study (Table 1), which was longer than the approval time difference of 471.0 days among this subtype of TNBC. Studies in the future could consider further refining indications to reflect these potential differences in clinical need and approval timing.

The growth in the development and approvals of "me-too" cancer drugs and indications in China might explain why certain FDA-approved cancer drugs and indications were not approved in China in the past two decades.[61,62] In this study, we identified another 24 cancer indications corresponding to 21 drugs that were developed by pharmaceutical companies based within China (Supplementary Table S2). These cancer drugs were excluded from the comparative analysis because they were approved by the NMPA only. One representative example of these drugs is sintilimab, an anti-PD-1 drug developed by Innovent Biologics in China.[63] Sintilimab was approved for the first time globally by the NMPA in December 2018 for the treatment of classical Hodgkin's lymphoma in patients who have relapsed or are refractory after ≥2 lines of systemic chemotherapy, which was also the first approval of anti-PD-1 antibody treatment for Hodgkin's lymphoma in China.[63,64] This approval might be one reason why NMPA only approved 8 out of 36 FDA-approved lymphoma indications.

Limitations

This study has the following limitations. First, this study did not consider the extension for lines of therapy (e.g., extension from second-line to first-line therapy) or the expansion to pediatric indications as a separate indication for sample cancer drugs. Second, there might be an underestimation of the total drug review duration in this study. The indication application date used in this study was the date of application acceptance by the CDE. Due to limited data availability of the exact application submission date of pharmaceutical companies, we were unable to confirm whether there was still a time difference between application submission by the companies and application acceptance by the CDE. We have used other data sources, including the YAOZHI database and the MENET database, to cross-check the approval dates of the sample oncology drugs due to the limitation of NMPA disclosures. In addition, our study period ended at 2020 and therefore doesn't capture the latest years of data. However, this study used a 20-year timeframe from 2001 to 2020 to address the comparability with previous studies and the consistency with the identification of overall survival benefit in FDA-approved labeling. Third, when analyzing the clinical benefit evidence, we extracted clinical benefit data from FDA-approved labeling by the end of 2020. There may be indications that have evidence of overall survival benefit not documented in FDA-approved labeling. This study did not take into account other clinical benefit evidence based on surrogate endpoints, which might be accepted as clinical benefits in some cases. Moreover, the requirements of regulators, registration pathways, and willingness of manufacturers to submit applications might also affect the timing of drug approval and review of cancer indication as well as the likelihood of approvals in both countries. This study was not able to quantify these factors due to insufficient data. Further studies are needed to understand detailed regulatory requirements across countries and reasons for the relative later application submission of cancer indications in China.

Conclusion

This study confirmed that fewer FDA-approved cancer drug indications were approved in China over the past two decades. We found that Chinese regulators approved more cancer drug indications since 2017 and prioritized approvals of drug indications with evidence of the overall survival benefit. Moreover, we found that the manufacturer submission was the major

determinant of cancer drug indication approval time differences between the two countries.

Contributors

YW, YZ, HN, AKW and XG designed the study and were involved in the interpretation of the results. ZX and GW collected the data. YW and YZ rechecked and organized data set. YW and GW conducted the data analysis. YW drafted the manuscript. HL, HN, AKW and XG provided critical revision of the manuscript. LS supervised the study. All authors provided constructive input and approved the final version for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data sharing statement

All data used in this study were in the public domain. Dr. Guan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

HN has received grants from the Health Foundation, the National Institute for Health and Care Research of the United Kingdom, the Commonwealth Fund and the UK Research and Innovation, outside this submitted work. HN has received consulting fees from the BMJ, the World Health Organization, and the Pharmaceutical Group of the European Union, which are unrelated to this work. He is also an advisor of the BMJ. AKW reports grants to her institution from the American Cancer Society, the Centers for Disease Control of the United States, and the Food and Drug Administration of the United States (Sentinel Initiative), outside this submitted work. AKW has received research grants from the Fulbright Finland Foundation outside this submitted work. AKW has received honorarium and support for attending meetings from the Finnish Medical Association, outside this work.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101055.

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