Regulatory flexibilities balancing unmet needs, benefits and risks in the approvals of imported cancer drugs in China: a cohort study from 2012 to 2021

Xiangyun Mao,[a,b,j] Jiachen Xu,[c,j] Xiaozhen Liu,[d,j] Shu Kong,[e,j] Yi Li,[f] Xiaoyin Bai,[g] Jiaxuan Yang,[a,b] Aaron S. Kesselheim,[h,i] and Guanqiao Li[a,b,*]

[a]Vanke School of Public Health, Tsinghua University, Beijing, China
[b]Institute for Healthy China, Tsinghua University, Beijing, China
[c]Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
[d]Clinical Development China, Bayer Healthcare Co.Ltd., Research and Development, Beijing, China
[e]School of Basic Medicine, Tsinghua University, Beijing, China
[f]Department of Cancer Medical Center, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China
[g]Department of Gastroenterology, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Science, Beijing, China
[h]Program on Regulation, Therapeutics, and Law, Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA
[i]Harvard Medical School, Boston, MA, USA

The Lancet Regional Health - Western Pacific 2025;55: 101483

Published Online xxx https://doi.org/10.1016/j.lanwpc.2025.101483

Summary

Background China has historically relied on importing new drugs to fulfill domestic clinical needs. However, stringent requirements for local clinical trials for these imported drugs has often delayed their market approval, restricting timely access for patients. To address this issue, China has implemented regulatory flexibility in certain contexts, allowing for expedited approval processes when appropriate. This study aimed to evaluate the characteristics of novel cancer drugs qualifying for flexible approval in China from 2012 to 2021, focusing on pivotal trials features, clinical benefits, safety profiles, and unmet medical needs.

Methods This cohort study identified all newly imported cancer drugs and their indications approved by the China's National Medical Products Administration (NMPA) from 2012 to 2021. Indications meeting standard requirements were categorized as regular approvals, while those supported by limited clinical data from Chinese patients were classified as flexible approvals. Development strategies, pivotal trials characteristics, and clinical outcomes were extracted from publicly available review documents and drug labels. Unmet medical needs were assessed based on two dimensions: the availability of standard-of-care treatments and the novelty of medicines. We compared the pivotal trial characteristics, efficacy end points, safety (serious adverse events) and the extent of unmet clinical needs, between flexible and regular approvals using Chi-square tests. A random-effects meta-regression was conducted to examine the association between flexible status and hazard ratios (HRs) for overall survival (OS) and progression-free survival (PFS).

Findings Among 59 novel cancer drugs approved for importation to China between 2012 and 2021, 56 products with 92 indications were included in this analysis, based on the availability of their review documents. Of these, 48 indications (52%) qualified for flexible approvals, while 44 indications (48%) received regular approvals. The median number of Chinese patients involved in the datasets for flexible approvals was significantly lower than for regular approvals (27 [IQR, 0–62] vs. 165 [IQR, 99–245], $p < 0.001$). Flexible approvals were more frequently supported by early-phase (18/61 vs. 1/60, $p < 0.001$) and single-arm (22/61 vs. 1/60, $p < 0.001$) pivotal trials, with response rates frequently used as the primary endpoint (24/61 vs. 1/60, $p < 0.001$). Meta-regression analysis revealed that flexible approvals were associated with improved OS (HR 0.61 vs. 0.72, $p < 0.01$), and a weaker association for PFS (HR 0.39 vs. 0.51, $p = 0.03$). The rate of serious adverse events was slightly higher, but not significantly, in the flexible approval group than the regular approval group (43% vs. 35%, $p = 0.06$). Flexible approvals were more likely to be indicated for diseases with no available existing drugs (31/48 vs. 10/44, $p < 0.001$) and for first-in-class drugs (21/48 vs. 9/44, $p = 0.03$).

*Corresponding author. Vanke School of Public Health, Tsinghua University, Beijing, China.
E-mail address: guanqiaoli@tsinghua.edu.cn (G. Li).
[j]These authors contributed equally.

Interpretation China's regulatory flexibility in approving imported cancer drugs has enabled access to therapies with limited domestic clinical data. These decisions are largely associated with the potential for greater clinical benefits and the need to address unmet medical needs. The approach offers valuable insights into regulatory considerations for global regulatory practices. By adopting similar regulatory flexibility, other nations could enhance drug accessibility and promote more adaptive regulatory practices.

Funding This work was funded by National Natural Science Foundation of China (72374119, 82102886) Beijing Natural Science Foundation (7242114) and Beijing Nova Program.

Keywords: Cancer drugs; Imported drugs; Regulatory flexibility; Unmet needs; Clinical benefits

Research in context

Evidence before this study

China has traditionally depended on importation of new drugs to meet its domestic clinical needs. To enhance drug accessibility, the country has adopted a flexible regulatory approach, particularly regarding the requirements for clinical data from Chinese populations. However, the characteristic of this flexible regulatory has not been systematically evaluated. In this study, we assessed the features of imported oncology drugs approved in China, comparing drugs under flexible approvals to those approved through regular processes. The aim was to summarize the practices of flexible approvals and inform future regulatory decisions that balance patient access to effective treatments with a substantial body of evidence supporting efficacy, safety, and ethnic relevance.

Added value of this study

To the best of our knowledge, this is the first study to systematically evaluate the evidence requirements supporting approvals of imported oncology drugs in China within the context of regulatory flexibility, focusing on pivotal trial characteristics, clinical benefits, safety profiles, and unmet clinical needs. Our study included 56 novel cancer drugs with 92 indications approved for importation to China between 2012 and 2021, of which 48 indications received flexible approvals and 44 received regular approvals. A significant portion of drugs approved through flexible pathways were supported by early phase, single-arm pivotal studies using response rates as primary endpoints. Medicines with flexible approvals demonstrated relatively higher clinical benefits and a greater degree of unmet medical needs compared to those with regular approvals.

Implications of all the available evidence

Over the past decade, China has successfully address domestic clinical needs by flexibly importing novel drugs. These decisions are largely driven by the potential for greater clinical benefits and the need to address unmet medical needs, allowing for the acceptance of relatively limited clinical evidence from Chinese patients in order to expedite market approval. This approach has proven effective in meeting patient demands and providing valuable therapies in China, offering meaningful insights into regulatory considerations worldwide. Other countries may consider adopting similar regulatory flexibility in their evaluation and approval processes for imported medicines, which could enhance drug accessibility and promote more adaptive and globally harmonized regulatory practices.

Introduction

The Chinese pharmaceutical market has long depended on domestic generics and imported new drugs to meet patients' health care needs.[1,2] Since 2005, for a drug to be considered for inclusion of China in multiregional clinical trials, it must have already been approved internationally or progressed to Phase II/III clinical trials. In 2007, China mandated that drug applications for market entry must include pharmacokinetic studies and local confirmatory randomized controlled trials with over 100 participants.[1] These requirements, combined with lengthy regulatory review time,[3] have created barriers international pharmaceutical companies in entering the Chinese market. Studies have shown that this regulatory framework has led to a drug lag of up to ten years for Chinese patients,[4–6] which is particularly detrimental in the setting of life-threatening diseases such as cancer.

In response to the growing mismatch between review delays and the increasing demand for new treatments, regulatory reforms were initiated starting in 2015. Key initiatives included addressing overdue application backlogs and establishing expedited pathways, such as priority review in 2015, conditional approval in 2017 and breakthrough therapy designation in 2020. At that time, the imported drugs were often developed and tested overseas, with minimal clinical trial data from Chinese patients, posing challenges for drug review and regulation. To address the long-standing issue of insufficient imported innovative

drugs, China issued the "Guidelines for Acceptance of Overseas Clinical Trial Data" in July 2018,[7] providing a framework for classifying the acceptability of foreign clinical trial data while considering ethnic sensitivity. For drugs targeting critical diseases, rare conditions, pediatric use, or those lacking effective treatments, the guidelines adopted a more flexible and conditional approach to accepting clinical data, aiming to improve drug accessibility. Similarly, the expedited approval process for foreign-approved drugs listed under the Urgently Needed Overseas Drugs (UNOD) lists, released between 2018 and 2020, exemplified China's willingness to address unmet needs and drug lag in treating serious or life-threatening diseases. These strategies demonstrated a pragmatic willingness and approach to accepting some level of uncertainty due to the absence or limitation of Chinese-specific data. For example, denosumab (Xgeva) was included on the UNOD List and approved conditionally for the treatment of unresectable giant cell tumor of bone in China in 2018, despite the lack of clinical data from Chinese populations.[8] These expedited pathways, along with the other favorable regulations, have significantly improve the accessibility of medicines.[1,3]

Over the past decade, China has introduced flexible approaches that go beyond a mere set of expedited programs. These approaches embody a broader regulatory philosophy, guiding efforts to address pressing medical needs and promote innovative therapies in a more adaptive and responsive manner. However, limited research has been conducted on the criteria and characteristics associated with these flexible approvals in China, as no clear regulatory framework has been established to define them. To fill this gap, we conducted an evaluation of pivotal trials, clinical benefits, safety, and unmet clinical needs for imported oncology drugs approved in China from 2012 to 2021, comparing drugs falling into the flexible approval category with those undergoing regular approvals. The goal was to inform future policy decisions to balance patient access to effective treatments with sufficient evidence supporting efficacy and safety, taking into account the context of clinical needs. These insights gained could serve as a guide for other countries in evaluating and regulating imported pharmaceuticals, further fostering more adaptive and harmonized regulatory practices, and ultimately improving the accessibility of medicines.

Methods

Data set and selection criteria

In this cohort study, we identified all new approved imported oncology drugs in China between January 1, 2012 and December 31, 2021, using data from the National Medical Products Administration (NMPA) website (https://www.nmpa.gov.cn) and retrieved public review documents and drug labels. Review documents for drugs approved prior to 2012 were not publicly available. For each drug, we identified the first approved indication and all subsequent indication extensions within the study period. Anticancer new therapeutics developed from biopharma companies headquartered outside China were included, excluding nontherapeutic (e.g., diagnostic) cancer care, as well as domestic drugs (discovered and developed by Chinese companies) and generic agents. Drugs developed overseas but in-licensed to Chinese companies were considered imported drugs in this study. In cases of combination regimens involving two novel therapeutic products, each product was considered as a separate entity. Indications for which review documents were unavailable were excluded from further analysis. This retrospective study, utilizing publicly available review reports and not involving protected health information or individual participant data, was exempt from Institutional Review Board approval.

Data extraction

We extracted variables related to drugs, indications, development strategies, characteristics and outcomes of pivotal trials from the review documents and drug labels. Data were independently collected by two reviewers (XL and XM) and cross-checked with clinical trial information from ClinicalTrials.gov and relevant publications. Disagreements between reviewers were resolved by discussions with a third independent reviewer (JX).

Drug and indication characteristics

Drug characteristics included the year of first approval in China, agent type (pharmacologic or biologic), and drug type (targeted, cytotoxic, immunotherapy or others). Time to first approval was defined as the period from the submission of investigational new drug in China to its first approval. For each approved indication, we extracted information on cancer type, line of therapy (neoadjuvant or adjuvant, first-line, second-line or later-line advanced or metastatic), and expedited programs granted by the NMPA (breakthrough therapy designation, conditional approval, priority review or inclusion in the Urgently Needed Overseas Drugs Lists).

Characteristics of clinical development strategies and regulatory flexibilities

With regard to clinical development strategies in China, each indication approval was classified into one of the following categories: a) Multi-regional Clinical Trials (MRCTs): China participating in global or regional (Asian-Pacific) multi-regional clinical trials involving Chinese patients; b) Bridging studies: China conducting bridging studies, including stand-alone randomized controlled trials, single-arm trials, or pharmacokinetic studies; or c) Waiver: China waived the requirement for clinical trials in Chinese populations. Regular approvals

were defined as those with sufficient clinical evidence from other countries, supplemented by substantial clinical data from China. This can include a stand-alone randomized controlled trial conducted in China, or participation in global or regional randomized controlled trials that provided comprehensive data from Chinese patients. Indications that did not meet the above criteria were classified as flexible approvals. Additionally, special cases were considered flexible approvals when China participated in global randomized controlled trials but had limited clinical evidence from Chinese patients. For example, approvals for alectinib (Alecensa) for *ALK*-positive non-small cell lung cancer were granted based on data from only 10 Chinese patients, and regorafenib (Stivarga) for gastrointestinal stromal tumors was approved based on data from 11 Chinese patients. Similarly, in the approval of ibrutinib (Ibrance) for relapsed/refractory mantle cell lymphoma, data from Chinese patients contributed solely to safety evidence.

Pivotal trials, efficacy outcomes, safety and unmet medical needs

Pivotal trials were defined as the clinical trials providing critical evidence of a drug's efficacy that serve as the basis of approval, following a prespecified protocol. Each indication approval may consist of multiple pivotal trials. We extracted key information from these pivotal trials, including study design, participants, clinical trial phase, the begin and end time of clinical trials, from the review documents, labels and clinical trial registries, such as ClinicalTrials.gov and the Chinese Clinical Trial Registry (https://www.chictr.org.cn). The duration of pivotal trials was calculated by subtracting the study start date from the end date. Additional data collected included the number of pivotal trials, the number of pivotal trials involving Chinese patients, the total number of patients across all aggregated pivotal trials, the number of Chinese patients and Asian patients supporting the approval of the intended indication.

The primary efficacy outcomes measured in pivotal trials included overall survival (OS), progression-free survival (PFS), response rate (RR), and other endpoints. We further categorized these endpoints into three types: 1) OS, 2) RR, and 3) time-to-event measures. For trials with co-primary endpoints, we prioritized OS as the most definitive endpoint for approval, over intermediate endpoints such as disease-free or PFS. Hazard ratios (HRs) and their corresponding 95% confidence intervals for OS and PFS were extracted from the review documents or labels. Regarding the safety, we collected information on the overall safety sample size for all relevant trials, along with the proportion of reported serious adverse events.

Finally, unmet medical needs were assessed based on the availability of standard care and the novelty of medicines as described in the review documents. We determined whether standard treatments were available for the indications at that time of review. The novelty of medicines was categorized into four groups: "first-in-class" (the first drug approved globally among candidates with the same target and mechanism of action[9]), "first-in-indication" (the first approved globally for a specific cancer type with a novel target or novel mechanism of action), "advance-in-class" (similar or me-too drugs that offer incremental improvements as recognized by the regulatory authorities), and "addition-to-class" (other me-too drugs with similar mechanisms to existing drugs but without meaningful advancements).

Statistical analysis

Data were descriptively reported as numbers, proportions, medians, and ranges where appropriate. We compared the characteristics of imported drugs between those receiving flexible and regular approvals. Continuous variables were analyzed using the Mann–Whitney test, while categorical variables were assessed with Pearson's chi-square tests. To evaluate the clinical benefits of imported drugs by calculating HRs for OS and PFS, we used random-effects meta-regression to account for both within- and between-study heterogeneity. Sensitivity analyses were performed by approved indication type, cancer type, drug type, and drug innovation. Statistical analyses were performed using IBM SPSS Statistics version 21 and R software version 4.3.0. A two-tailed p-value < 0.05 was considered statistically significant.

Role of the funding source

The funding source had no role in study design, data collection, data analysis, data interpretation, or manuscript preparation. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Characteristics of oncology agents and indications

Between 2012 and 2021, China approved 59 novel imported cancer therapeutic agents, covering 102 indication approvals. Of these, 56 drugs with 92 indications had publicly accessible review documents and were analyzed further in this study (Fig. 1). Among the 56 drugs, 41 (73%) drugs were pharmacologic agents and 15 (27%) were biologics, with targeted therapies representing the highest proportion (40/56, 71%) (Supplementary Table S1). The median time from entering the clinical phase in China to first approval for these drugs was 5.7 years.

In terms of indications, this set of 92 approved indications comprised 59 initial approvals and 33 supplemental approvals. About half (48/92, 52%) were categorized as flexible approvals, which were based on relatively limited data from Chinese populations. The

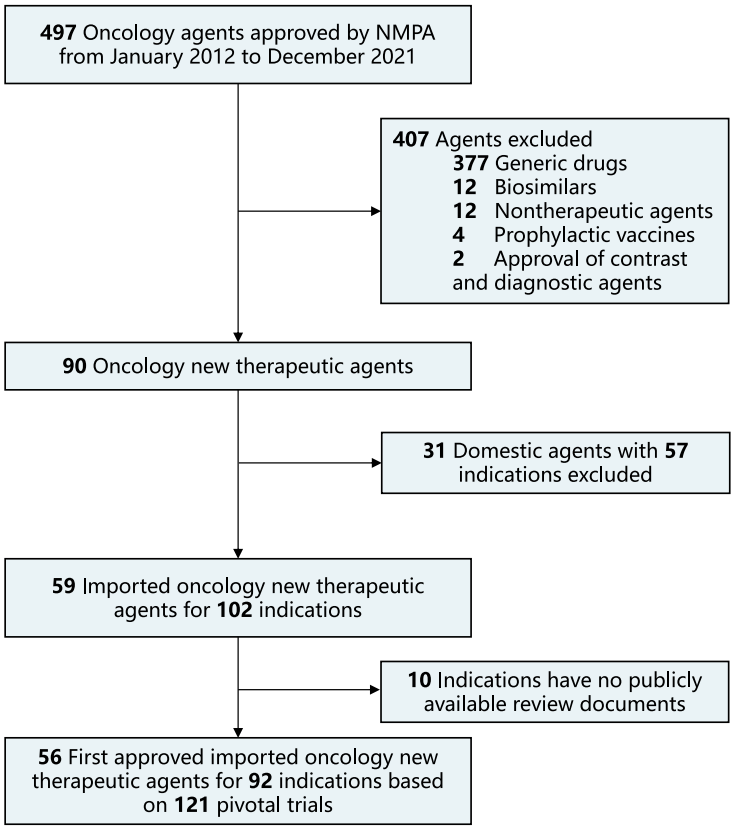

Fig. 1: Flow chart of search results.

remaining 44 (48%) were designated as regular approvals. A growing trend of flexible approvals was observed in recent years (Supplementary Fig. S1). Flexible approvals were associated with a significantly increased likelihood of qualifying for an expedited program ($p < 0.001$, Table 1). Among these, flexible approvals were more likely to be granted conditional approval (23/48 vs. 3/44, $p < 0.001$) and to be approved based on the list of urgently needed overseas drugs (5/48 vs. 0/44, $p = 0.01$).

Features of clinical development strategies

The flexible approvals frequently employed simplified clinical development strategies in China, including pharmacokinetic studies and single-arm studies (Table 1). In some cases, datasets without Chinese participants were also accepted. The median number of Chinese participants in the datasets supporting the intended indication approvals was 27 (IQR, 0–62) for drugs receiving flexible approval, which was significantly lower than for drugs with regular approval (median 165, IQR, 99–245, $p < 0.001$). A similar difference was observed for Asian subjects between the flexible and regular approval groups (81 [39–131] vs. 295 [177–510], $p < 0.001$). As a consequence, drugs granted flexible approvals had a shorter development time in China compared to those receiving regular approval (5.2 [3.4–7.0] vs. 7.9 [5.6–9.8] years, $p = 0.001$, Table 1).

Features of aggregated pivotal trials

The characteristics of pivotal trials supporting flexible approval and regular approval differed, despite both groups having a median of one pivotal trial per indication (Table 1). Pivotal trials assessing response rate (RR) formed the exclusive basis of flexible approvals in 17 indications (35%), while none of regular approvals relied solely on this endpoint. The median number of overall patients and patients within the intervention group in the aggregated pivotal trials were smaller for drugs with flexible approvals, compared to those with regular approvals (total population: 371 [196–668] vs. 817 [573–1369], $p < 0.001$; intervention population: 267 [131–425] vs. 496 [336–764], $p < 0.001$). A similar difference was observed in the total sample size for safety assessment (863 [363–2012] vs. 2595 [1397–3293], $p < 0.001$). The median number of Chinese patients enrolled in pivotal trials was 0 (IQR, 0–4) in the flexible approval group, and 136 (IQR, 78–228) in the regular approval group ($p < 0.001$).

	Total	Flexible Approvals	Regular Approvals	p-value
Indications				
Total Approvals	92	48	44	0.013[a]
Initial approvals	59	37 (77.1%)	22 (50.0%)	
Supplemental approvals	33	11 (22.9%)	22 (50.0%)	
Cancer type				0.228[a]
Solid tumors	69	33 (68.8%)	36 (81.8%)	
Hematological cancers	23	15 (31.3%)	8 (18.2%)	
Line of therapy				0.145[a]
Neoadjuvant or adjuvant	9	4 (8.3%)	5 (11.4%)	
First-line advanced or metastatic	44	19 (39.6%)	25 (56.8%)	
Second-line or later-line advanced or metastatic	39	25 (52.1%)	14 (31.8%)	
Expedited programs[c]				<0.001[a]
Priority review (2015)	70	41 (85.4%)	29 (65.9%)	
Conditional approval (2017)	26	23 (47.9%)	3 (6.8%)	
Urgently needed overseas drugs (UNOD) (2018)	5	5 (10.4%)	0	
Breakthrough therapy designation (2020)	0	0	0	
None	19	5 (10.4%)	14 (31.8%)	
Time to first approval (years)	5.7	5.2	7.9	0.001[b]
Median (IQR)	(4.8–8.3)	(3.4–7.0)	(5.6–9.8)	
Clinical development strategies in China				
Global multiregional clinical trial	31	3 (6.3%)	28 (63.6%)	<0.001[a]
Regional multiregional clinical trial	12	2 (4.2%)	10 (22.7%)	
Stand-alone randomized controlled trial	6	0	6 (13.6%)	
Single-arm clinical trial	19	19 (39.6%)	0	
Pharmacokinetics	6	6 (12.5%)	0	
Waiver	18	18 (37.5%)	0	
Aggregated pivotal trials				
Characteristics				
No. pivotal trials, median (IQR)	1 (1–1)	1 (1–1)	1 (1–2)	0.144[b]
No. Chinese-involved pivotal trials, median (IQR)	1 (0–1)	0 (0–1)	1 (1–1)	<0.001[b]
No. patients (overall) in aggregated pivotal trials, median (IQR)	632 (360–971)	371 (196–668)	817 (573–1369)	<0.001[b]
No. patients (intervention) in aggregated pivotal trials, median (IQR)	357 (200–584)	267 (131–425)	496 (336–764)	<0.001[b]
No. Chinese patient in aggregated pivotal trials, median (IQR)	32 (0–149)	0 (0–4)	136 (78–228)	<0.001[b]
Duration (months)				0.460[b]
Median	37.0	36.0	38.8	
(IQR)	(29.0–47.3)	(28.3–47.3)	(29.8–47.2)	
Endpoints				<0.001[a]
OS (including OS, PFS dual endpoints)	31	13 (27.1%)	18 (40.9%)	
PFS (including PFS, RR dual endpoints)	34	14 (29.2%)	20 (45.5%)	
RR	17	17 (35.4%)	0	
Other (MFS, IDFS, major molecular response rate)	10	4 (8.3%)	6 (13.6%)	
Overall clinical trials for evaluation				
Total Chinese population supporting intended indication approval (IQR)	79 (26–193)	27 (0–62)	165 (99–245)	<0.001[b]
Total Asian population supporting intended indication approval (IQR)	155 (79–342)	81 (39–131)	295 (177–510)	<0.001[b]
Total sample size for safety assessment, median (IQR)	1464 (714–2962)	863 (363–2012)	2595 (1397–3293)	<0.001[b]

IQR, interquartile range; OS, overall survival; PFS, progression-free survival; RR, response rate; MFS, metastasis-free survival; IDFS, invasive disease-free survival. [a]p-values calculated on the basis of Pearson Chi-Square test. [b]p-values calculated on the basis of Mann–Whitney U test (based on the raw values in each study). [c]Approvals for indications may qualify for more than one expedited program.

Table 1: **Characteristics of indications and pivotal trials of imported drug approvals in China between 2012 and 2021.**

Features of individual pivotal trials

A total of 121 pivotal efficacy trials (61 supporting flexible approval and 60 supporting regular approval) were identified for the 92 indications (Table 2). The median trial duration was similar between the two groups (35.0 [22.0–44.0] vs. 35.0 [26.0–44.1] months, p = 0.85). Flexible approvals were primarily supported by early phase (18/61 vs. 1/60, p < 0.001), and single-arm (22/61 vs. 1/

60, p < 0.001) pivotal trials. Among the 60 trials supporting regular approvals, the majority relied on progression-free survival (PFS, 26/60, 43%) and overall survival (OS, 23/60, 38%) as primary outcomes. A total of 39% (24/61) of trials in the flexible approval group used RR as their primary outcome, compared to only one trial (2%) used RR in the regular approval group.

Clinical benefits, safety and unmet clinical needs

The random-effects meta-regression showed greater clinical benefits in the flexible approval group, as indicated by the hazard ratios (HR) for OS (0.61 vs. 0.72, p < 0.01, Fig. 2). Similarly, a significant difference was observed between flexible approvals and regular approvals for PFS (0.39 vs. 0.51, p = 0.03, Fig. 3).

Serious adverse events were reported in 12,482 out of 28,174 treated patients (44%) with drugs receiving flexible approval, compared to 16,422 of 47,681 patients (34%) with drugs receiving regular approval (p = 0.06, Table 3). Sensitivity analyses, stratified by approval type, cancer type, drug type, and drug innovation status, showed consistent trends in OS and PFS (Supplementary Tables S2 and S3). Furthermore, drugs receiving flexible approvals were associated with indications where no existing treatment options were available (31/48 vs. 10/44, p < 0.001) and were more frequently defined as first-in-class therapies (21/48 vs. 9/44, p = 0.03, Table 3).

	Total	Flexible Approvals	Regular Approvals	p-value
Total clinical trials, No.	121	61	60	
Participants, median (IQR)	431 (272–760)	326 (171–616)	580 (390–1006)	<0.001[b]
Clinical trial phase				<0.001[a]
Phase III	102	43 (70.5%)	59 (98.3%)	
Phase I or II	19	18 (29.5%)	1 (1.7%)	
Study design				<0.001[a]
Randomized				
Active[c]	47	22 (36.1%)	25 (41.7%)	
Placebo	51	17 (27.9%)	34 (56.7%)	0.248[a]
No control[d]	23	22 (36.1%)	1 (1.7%)	
Type of blinding (Only for RCT, N = 98)				0.799[a]
Double blind	55	23 (37.7%)	32 (53.3%)	
Open label	43	16 (26.2%)	27 (45.0%)	
Primary endpoint				<0.001[a]
OS (including OS, PFS dual endpoints)	37	14 (23.0%)	23 (38.3%)	
PFS	40	14 (23.0%)	26 (43.3%)	
RR (CR)	25	24 (39.3%)	1 (1.7%)	
Other	19	9 (14.8%)	10 (16.7%)	
Endpoint category				<0.001[a]
OS	37	14 (23.0%)	23 (38.3%)	
RR	27	24 (39.3%)	3 (5.0%)	
Time to event	57	23 (37.7%)	34 (56.7%)	
Trial duration, median (months) (IQR)	35.0 (25.0–44.0)	35.0 (22.0–44.0)	35.0 (26.0–44.1)	0.850[b]

IQR, interquartile range; RCT, randomized clinical trial; OS, overall survival; PFS, progression-free survival; RR, response rate; CR, complete response. [a]p values calculated on the basis of Pearson Chi-Square test. [b]p values calculated on the basis of Mann–Whitney U test (based on the raw values in each study). [c]Includes comparators in which placebo is received in addition to active treatment (i.e., add-on clinical trials). [d]Includes supportive therapy or standard care.

Table 2: **Design of pivotal trials supporting approvals of novel cancer drugs, 2012–2021.**

Discussion

In our analysis of newly approved imported cancer drugs in China between 2012 and 2021, flexible approvals were characterized by fewer Chinese and Asian participants in pivotal trials and in the datasets supporting the approvals. A substantial portion of pivotal trials supporting flexible approvals were early-phase, single-arm studies, with RR as the primary efficacy endpoint. The justification for granting flexible approvals was associated with higher level of unmet clinical needs, often in situations where no existing treatment options were available or with a higher proportion of first-in-class drugs, as well as the potential for substantial clinical benefits, demonstrated by more favorable hazard ratios for OS or PFS.

Regulatory decision-making strategies related to new drugs are complex and multifaceted,[10] requiring a delicate balance between unmet clinical needs and the strength of evidence for efficacy and safety, while acknowledging possible ethnic differences in target populations. In the past, the lack of localized clinical data and lengthy review delays in China made it difficult for imported drugs to enter the market under the previous regulatory framework, leaving many patients without viable treatment options. For instance, mitotane, a critical treatment for adrenocortical carcinoma, was approved in the United States in 1964 but remained unavailable in China for decades, potentially leaving around 2000 Chinese patients without effective treatment.[11,12] In this context, regulatory flexibility became essential to enhance patient access to new medications and broaden treatment options. Particularly in cases of devastating or rare diseases, both regulators and patients would be willing to accept certain levels of evidence uncertainty to expedite access to life-saving medicines.[13] Over the past decade, we observed that nearly half of the oncology indications approved in China have incorporated some degree of regulatory flexibility (Supplementary Fig. S1). Following the regulatory reforms in 2015, China introduced more flexibility through various expedited pathways, such as priority review, conditional approval, breakthrough therapy designation, and accelerated approval for foreign-approved drugs. Based on our findings, the majority of flexible approvals (90%) received at least one of these expedited pathways. A prime example is mitotane, which received marketing approval in China in 2023 with real-world data from in Chinese patients.

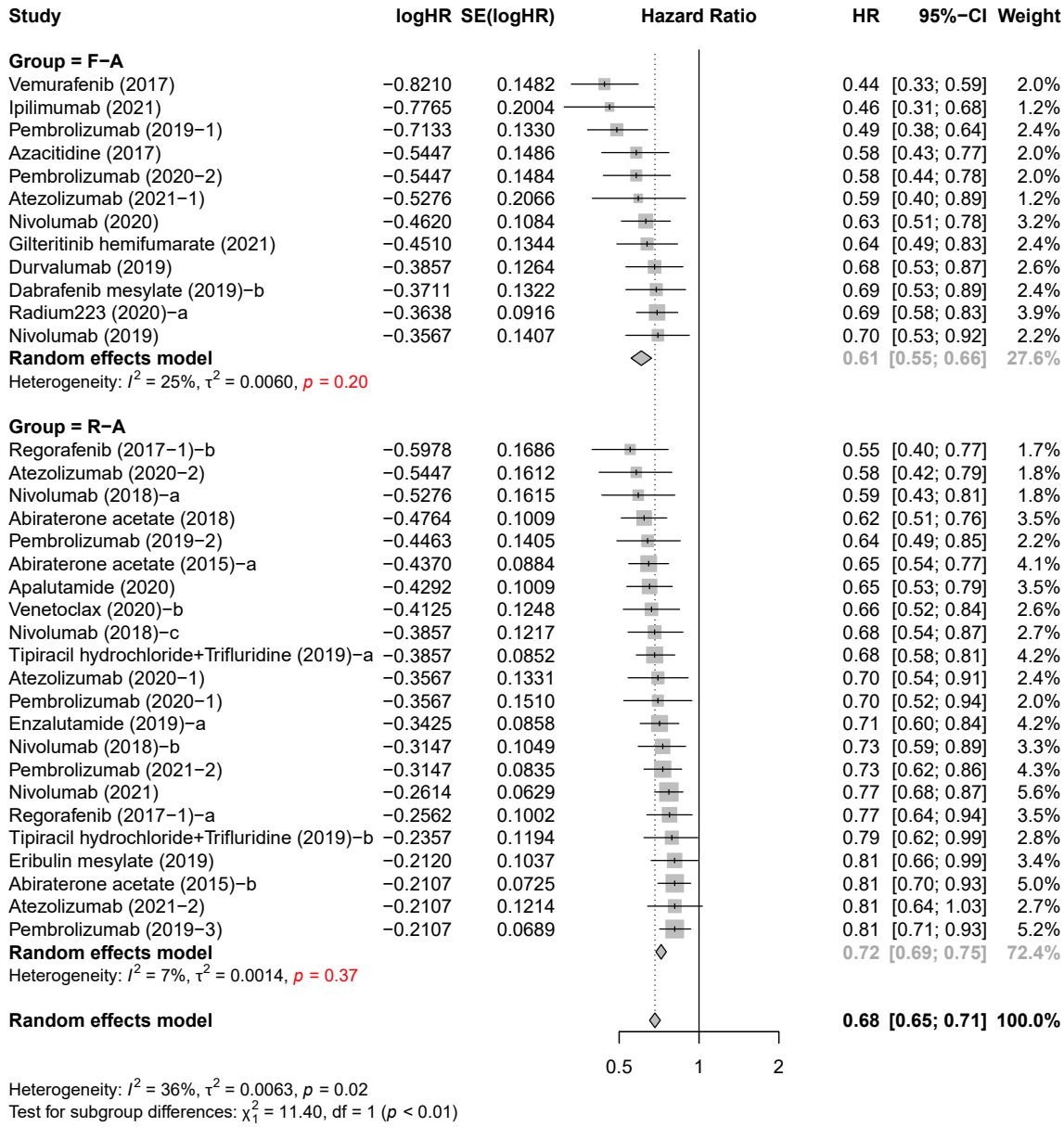

Fig. 2: Forest plot of hazard ratio for OS used for approval of new cancer drugs in China, 2012–2021. Legend: Weights are from random-effects meta-regression analysis, which accounts for between- and within-study heterogeneity. The numbers following the drug names indicate different indications for the same drug, while the letters represent different pivotal trials for the same indication. F–A: Flexible approvals. R–A: Regular approvals.

Despite not being fully aligned with specific regulatory provisions, this study illustrated that such flexibilities were associated with drugs addressing unmet medical needs and demonstrating substantial clinical benefits. Unmet needs in our study were defined by considering both the availability of standard treatments and the novelty of drugs. In the absence of standard treatments, patients face a treatment gap with no available options; while the novelty of drugs often suggests the potential for breakthroughs in therapeutic outcomes. As the treatment landscape evolves, so do clinical needs, which in turn influence the degree of regulatory flexibility. For example, early approvals of kidney cancer treatments like sorafenib and sunitinib (2006 and 2007) in China were based on studies in Asian populations, with little to no data from mainland China.[14,15] These approvals reflected regulatory flexibility, where some risks were

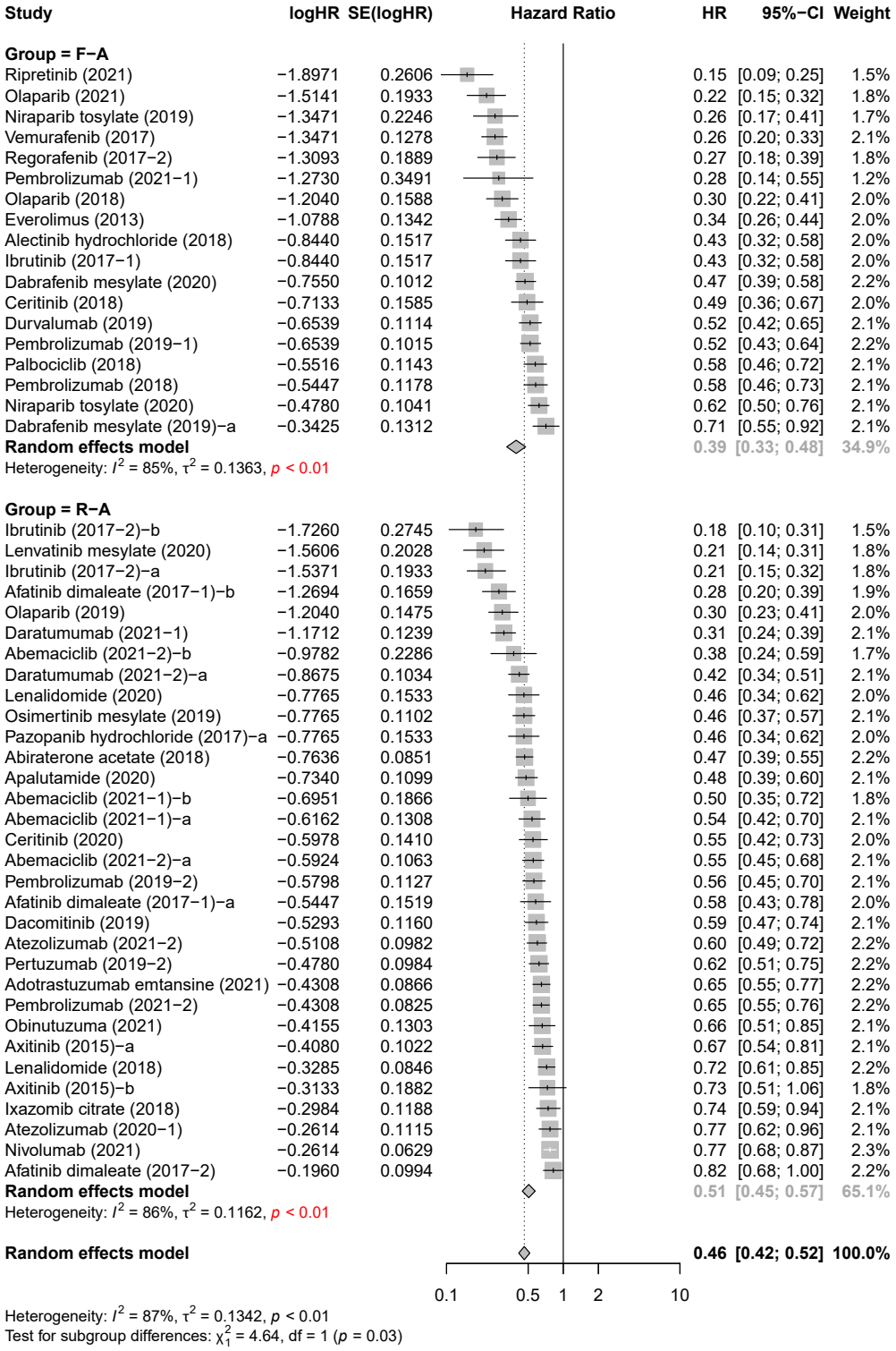

Fig. 3: Forest plot of hazard ratio for PFS used for approval of new cancer drugs in China, 2012–2021. Legend: Weights are from random-effects meta-regression analysis, which accounts for between- and within-study heterogeneity. The numbers following the drug names indicate different indications for the same drug, while the letters represent different pivotal trials for the same indication. F–A: Flexible approvals. R–A: Regular approvals.

	Total	Flexible Approvals	Regular Approvals	p value
Efficacy				
Overall survival				
Pooled Hazard ratio[c] (N = 34)	0.68 (0.65–0.71)	0.61 (0.55–0.66)	0.72 (0.69–0.75)	<0.001[d]
Progress-free survival				
Pooled Hazard ratio[c] (N = 50)	0.46 (0.42–0.52)	0.39 (0.33–0.48)	0.51 (0.45–0.57)	0.03[d]
Safety				
Serious adverse events, No. (%)	28,904 of 75,855 (38.1%)	12,482 of 28,174 (44.3%)	16,422 of 47,681 (34.4%)	0.056[b]
Unmet needs				
Availability of standard care				<0.001[a]
Yes	51	17 (35.4%)	34 (77.3%)	
No	41	31 (64.6%)	10 (22.7%)	
Novelty (Drug innovation)				0.046[a]
First-in-class	30	21 (43.8%)	9 (20.5%)	
First-in-indication	35	16 (33.3%)	19 (43.2%)	
Advance-in-class	8	5 (10.4%)	3 (6.8%)	
Addition-to-class	19	6 (12.5%)	13 (29.5%)	

IQR, interquartile range. [a]p-values calculated on the basis of Pearson Chi-Square test. [b]p-values calculated on the basis of Mann–Whitney U test (based on the raw values in each study). [c]From random-effects meta-regression. [d]p-values calculated on the basis of Cochran's Q test.

Table 3: **Clinical benefits, safety and unmet needs of flexible approvals vs. regular approvals, 2012 to 2021.**

accepted to quickly address urgent clinical needs in kidney cancer. However, as standard treatments became available, the need for stronger evidence grew. Everolimus, which initially sought to skip Chinese trials in 2009, was approved in 2013 after completing a Phase I bridging study in China.[16] Later drugs like axitinib[17] and pegaptanib[18] incorporated China into global or Asia-focused trials, reflecting a decrease in regulatory flexibility as clinical needs became less urgent.

Clinical benefits are a critical consideration in drug review and regulation. Our findings suggest that flexible approvals were associated with drugs showing more favorable clinical outcomes, implying that drugs with greater benefits may be more likely to receive flexible approval despite data uncertainty. However, assessing these benefits and making decisions on regulatory flexibility have to consider ethnic sensitivity. According to the International Council for Harmonization guidelines,[19] disease characteristics can vary across populations due to a range of intrinsic and extrinsic factors including genetics, metabolism, clinical practices, diets, and environments. For instance, while over 90% of melanoma cases in Caucasians are cutaneous non-limbic subtypes, mucosal and limbic melanomas-generally associated with poorer prognosis and fewer BRAF V600 mutations-are more common in China.[20] These differences led China to require comprehensive local trials to verify the efficacy and safety of vemurafenib and the dabrafenib–trametinib combination for BRAF V600+ melanoma before granting approvals.[21,22] This demonstrates how population-specific disease characteristics can influence drug approval requirements. Recently, the FDA has emphasized the need for greater diversity in clinical trials, highlighting the importance of ethnic sensitivity.[23] This ensures that trial outcomes are more applicable to diverse groups. An illustrative case is the FDA's rejection of sintilimab for non-small cell lung cancer, partly due to insufficient diversity in clinical data.[24] Similarly, regulatory bodies in other countries, like Japan, Singapore and Indonesia also consider possible ethnic differences during review, reinforcing the need for population-specific evidence in drug approvals.[25]

Amid the dominance of drug research & development in regions like the US and Europe, China is emerging as a growing player in domestic pharmaceutical research and development.[26] However, many countries still heavily rely on imported drugs due to limited local pharmaceutical markets.[27,28] For these countries, China's flexible regulatory strategy offers a potential model for introducing clinically valuable drugs, balancing data quality with expedited access. For example, countries like Singapore, Malaysia and Indonesia simplify their registration and review processes for drugs already approved in reference countries. Countries adopting similar approach should consider factors such as domestic clinical demand, regulatory capacity, and the ability to conduct local clinical trials, as well as weigh the costs of conducting these trials against the risks of approving drugs based on limited evidence. The insights generated from this study can help guide these countries in developing flexible regulatory strategies, potentially fostering globally aligned regulatory practices while addressing local treatment needs.

Although flexible approvals have enhanced drug accessibility, they often operate on a case-by-case basis without unified and explicit standards. This approach can raise uncertainty regarding clinical benefits and safety for the target population or local patient of approved drugs. For example, it could result in the approval of drugs with limited efficacy or a higher incidence of adverse reactions, which not only delays patients' access to effective treatments but also increases their financial burden. Research has found that the translation of these early benefits into long-term clinical advantages remains uncertain, especially in the setting of drugs receiving accelerated approval from the FDA.[29–31] While China adopted regulatory flexibility in reviewing imported drugs, it is essential to address these uncertainties through post-marketing evidence generation to confirm the clinical benefits and safety of approved drugs. For instance, denosumab (in the UNOD list) was conditionally approved for the Chinese market in 2020. This approval required the applicant to continue conducting clinical research in China and to provide the necessary data within five years to support conversion to standard approval.

Limitations

This study has several limitations. First, the definition of flexible approval used in this study is not explicitly outline in publicly regulatory documents but is derived from the limited data from Chinese participants. Second, while unmet medical needs are frequently referenced by regulatory bodies, there is no universally accepted definition or standardized quantitative criteria for this concept. In this study, we defined unmet clinical needs based on the absence of standard treatments and the innovativeness of drugs. This definition, grounded in extensive literature research and regulatory review experience, reflects practical considerations. Conditions lacking effective medications and highly innovative drugs are typically associated with higher unmet clinical needs, making them strong candidates for "formal" expedited pathways, including accelerated approval, conditional approval, or breakthrough therapy designation. As such, this definition is both practical and reasonable.

Conclusion

Over the past decade, China has heavily depended on imported drugs to address its clinical needs, with many approvals granted through flexible regulatory pathway relying on limited clinical evidence from Chinese patients. A substantial portion of these approvals involved early phase, single-arm pivotal studies using response rate as the primary endpoint. This study demonstrates that these flexible approvals were more likely to encompass drugs targeting significant unmet medical needs and offering greater clinical benefits compared to those approved through regular pathways. These findings offer critical perspectives on the evaluation criteria for imported drugs in China and may provide a valuable framework for other countries to refine their evaluation and approval systems for imported pharmaceuticals, promoting to more adaptive and globally harmonized regulatory practices.

Contributors

XM, JX, XL and SK planned and drafted the paper, and contributed to data quality control, analysis, and interpretation. GL led the overall planning and data interpretation. XB contributed to data quality control and interpretation. JY provided methodological guidance and support with data interpretation. ASK contributed to data interpretation and examination of drafts. All authors reviewed and revised the manuscript. The corresponding author GL verified the data and had access to raw data, with final responsibility for the decision to submit for publication.

Data sharing statement

Data of the research is available upon reasonable request from the corresponding author.

Declaration of interests

GL has received grants from National Natural Science Foundation of China and Beijing Nova Program. JX has received grants from National Natural Science Foundation of China, Beijing Natural Science Foundation and Beijing Nova Program. ASK has received grants from Arnold Ventures and the Commonwealth Fund. All other authors declare no competing interests.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2025.101483.

References

1 Liu Y, Zhang N, Xie C, et al. Evolution of drug regulations and regulatory innovation for anticancer drugs in China. *Acta Pharm Sin B*. 2022;12(12):4365–4377. https://doi.org/10.1016/j.apsb.2022.08.004.
2 Li G, Liu Y, He R, Su L, Chen X. FDA decisions on new oncological drugs. *Lancet Oncol*. 2022;23(5):583–585. https://doi.org/10.1016/S1470-2045(22)00136-X.
3 Xu L, Gao H, Kaitin KI, Shao L. Reforming China's drug regulatory system. *Nat Rev Drug Discov*. 2018;17(12):858–859. https://doi.org/10.1038/nrd.2018.150.
4 Zhou Q, Chen XY, Yang ZM, Wu YL. The changing landscape of clinical trial and approval processes in China. *Nat Rev Clin Oncol*. 2017;14(9):577–583. https://doi.org/10.1038/nrclinonc.2017.10.
5 Huang H, Zhu Q, Ga M, et al. Availability and affordability of oncology drugs in 2012-2021 in China and the United States. *Front Oncol*. 2022;12:930846. https://doi.org/10.3389/fonc.2022.930846.
6 Li X, Yang Y. The drug lag issue: a 20-year review of China. *Invest New Drugs*. 2021;39(5):1389–1398. https://doi.org/10.1007/s10637-021-01117-2.
7 National Medical Product Administration. Guidelines for acceptance of overseas clinical trial data (NMPA [2018] No.52). https://www.nmpa.gov.cn/zhuanti/ypqxgg/ggzhcfg/20180710151401465.html. Accessed September 1, 2024.
8 Palmerini E, Blay JY, Le Cesne A, et al. Long-term efficacy of denosumab in giant cell tumor of bone: results of an open-label phase 2 study. *Ann Oncol*. 2017;28:v645–v646. https://doi.org/10.1093/annonc/mdx440.071.
9 Li G, Qin Y, Xie C, Wu YL, Chen X. Trends in oncology drug innovation in China. *Nat Rev Drug Discov*. 2021;20(1):15–16. https://doi.org/10.1038/d41573-020-00195-w.
10 Cliff ERS, Hilal T, Kesselheim AS. Complicated regulatory decision-making following inconsistent trial results: the issue with ibrutinib for mantle cell lymphoma. *Nat Rev Clin Oncol*. 2024;21(1):1–2. https://doi.org/10.1038/s41571-023-00821-7.

11 Else T, Kim AC, Sabolch A, et al. Adrenocortical carcinoma. *Endocr Rev*. 2014;35(2):282–326. https://doi.org/10.1210/er.2013-1029.
12 Kerkhofs TMA, Verhoeven RHA, Van Der Zwan JM, et al. Adrenocortical carcinoma: a population-based study on incidence and survival in The Netherlands since 1993. *Eur J Cancer*. 2013;49(11):2579–2586. https://doi.org/10.1016/j.ejca.2013.02.034.
13 Farrell AT, Goldberg KB, Pazdur R. Flexibility and innovation in the FDA's novel regulatory approval strategies for hematologic drugs. *Blood*. 2017;130(11):1285–1289. https://doi.org/10.1182/blood-2017-04-742726.
14 Escudier B, Szczylik C, Negrier S, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med*. 2007;356(2):125–134. https://doi.org/10.1056/NEJMoa060655.
15 Goodman VL, Rock EP, Dagher R, et al. Approval summary: sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma. *Clin Cancer Res*. 2007;13(5):1367–1373. https://doi.org/10.1158/1078-0432.CCR-06-2328.
16 Guo J, Huang Y, Zhang X, et al. Safety and efficacy of everolimus in Chinese patients with metastatic renal cell carcinoma resistant to vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy: an open-label phase 1b study. *BMC Cancer*. 2013;13(1):136. https://doi.org/10.1186/1471-2407-13-136.
17 Dror V, Qin S, Bi F, et al. Axitinib versus sorafenib as a second-line therapy in Asian patients with metastatic renal cell carcinoma: results from a randomized registrational study. *OTT*. June 2015:1363. https://doi.org/10.2147/OTT.S83302. Published online.
18 Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med*. 2013;369(8):722–731. https://doi.org/10.1056/NEJMoa1303989.
19 ICH. https://www.ich.org/page/members-observers. Accessed September 1, 2024.
20 Wang Y, Zhao Y, Ma S. Racial differences in six major subtypes of melanoma: descriptive epidemiology. *BMC Cancer*. 2016;16(1):691. https://doi.org/10.1186/s12885-016-2747-6.
21 Robert C, Grob JJ, Stroyakovskiy D, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. *N Engl J Med*. 2019;381(7):626–636. https://doi.org/10.1056/NEJMoa1904059.
22 Mao L, Ding Y, Bai X, et al. Overall survival of patients with unresectable or metastatic BRAF V600-mutant acral/cutaneous melanoma administered dabrafenib plus trametinib: long-term follow-up of a multicenter, single-arm phase IIa trial. *Front Oncol*. 2021;11:720044. https://doi.org/10.3389/fonc.2021.720044.
23 FDA. Considerations for generating clinical evidence from oncology multiregional clinical development programs. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-generating-clinical-evidence-oncology-multiregional-clinical-development-programs. Accessed September 1, 2024.
24 FDA briefing document. Oncologic drugs advisory committee meeting. www.fda.gov/media/156021/download. Accessed September 1, 2024.
25 Singh R, Wang W, Chakravarty A, Wang J, Uyama Y. Simultaneous global drug development and multiregional clinical trials (MRCT): 5 Years after implementation of ICH E17 guidelines. *Ther Innov Regul Sci*. 2024;58(5):845–854. https://doi.org/10.1007/s43441-024-00639-0.
26 Chen Z, Zhong H, Hu H, Kong F, Liang W, Li G. Chinese innovative drug R&D trends in 2024. *Nat Rev Drug Discov*. 2024;23(11):810–811. https://doi.org/10.1038/d41573-024-00120-5.
27 Tawfik EA, Tawfik AF, Alajmi AM, et al. Localizing pharmaceuticals manufacturing and its impact on drug security in Saudi Arabia. *Saudi Pharmaceut J*. 2022;30(1):28–38. https://doi.org/10.1016/j.jsps.2021.12.002.
28 Adebisi YA, Nwogu IB, Alaran AJ, et al. Revisiting the issue of access to medicines in Africa: challenges and recommendations. *Public Health Challenges*. 2022;1(2):e9. https://doi.org/10.1002/puh2.9.
29 Naci H, Zhang Y, Woloshin S, Guan X, Xu Z, Wagner AK. Overall survival benefits of cancer drugs initially approved by the US Food and Drug Administration on the basis of immature survival data: a retrospective analysis. *Lancet Oncol*. 2024;25(6):760–769. https://doi.org/10.1016/S1470-2045(24)00152-9.
30 Liu ITT, Kesselheim AS, Cliff ERS. Clinical benefit and regulatory outcomes of cancer drugs receiving accelerated approval. *JAMA*. 2024. https://doi.org/10.1001/jama.2024.2396. Published online April 7.
31 Mao X, Alexander GC, Li G. Accelerated approvals: early-phase success or premature authorization? *Cancer Cell*. 2024;42(11):1799–1802. https://doi.org/10.1016/j.ccell.2024.09.005.