Evidence uncertainty and implementation challenges of conditionally approved cancer drugs in China

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Background

Expedited review and approval of innovative drugs, particularly in oncology, has become a mainstream regulatory strategy worldwide. China National Medical Products Administration (NMPA) officially launched the conditional approval pathway for new drugs in December 2019.

Purpose

To characterize the evidence from pivotal and confirmatory trials supporting conditional approval of cancer indications by NMPA, as well as their regulatory outcomes and magnitude of clinical benefit.

Methods

All cancer drug-indication pairs granted conditional approval in Mainland China between Dec. 1, 2019 and Dec. 31, 2024 were identified from the NMPA review documents, manufacturer press releases, ClinicalTrials.gov, and PubMed.

Results

In total, 90 cancer drugs received conditional approval for 115 indications by NMPA, supported by 146 pivotal trials and 111 confirmatory trials.

Pivotal trials were typically characterized by smaller sample sizes (63.1% enrolled sample ≤100), single-arm design (83.6%), and used response-related rate (85.0%) as the primary endpoint , whereas confirmatory trials were mostly randomized controlled trials (70.3%) and used progression-related survival (54.1%) as the primary endpoint. For 20 of 115 indications (17.4%), a response- related endpoint was the primary endpoint in both the pivotal and the confirmatory stage.

By the end of follow-up, 36 indications (31.3%, 36/115) were converted to regular approval after a median of 1.92 (range: 0, 4.32) years, and 4 (3.5%) had been withdrawn. Of the 36 converted indications, 17 (47.2%) were broadened indications at conversion, only 8 indications (22.2%) were supported by confirmatory trials with overall survival as the primary endpoint, and only 8 (22.2%) for clinical benefit.

Conclusions

The confirmatory stage of China's conditional approval pathway shows persistent limitations, including reliance on surrogate primary endpoints, delayed trial completion, uncertain clinical benefit, and indication expansion at conversion without dedicated evidence. Regulatory agencies should define explicit clinical-benefit criteria for conversion, set standard requirements for indication expansion, and monitor confirmatory trials more closely, thereby protecting patients from long- term exposure to drugs with unconfirmed clinical benefit.

Table. Features of pivotal trials and confirmatory trials

Study Characteristics	Pivotal trials (n =146)	Confirmatory trials (*n* =111)	*P* for difference
Sample size*, median (IQR)	84 (54, 124)	260 (130, 443)	<.001
<50	32 (22.7)	12 (11.0)	
50-100	57 (40.4)	12 (11.0)	
101-200	33 (23.4)	23 (21.1)	
>200	19 (13.5)	62 (56.9)	
Study design			<.001
Single-arm	122 (83.6)	27 (24.3)	
RCT	24 (16.4)	78 (70.3)	
Open label	11 (45.8)	48 (61.5)	.173
Double blinding	13 (54.2)	30 (38.5)	
Placebo	7 (29.2)	6 (7.7)	.005
Active comparator	17 (70.8)	72 (92.3)	
Real-world Study	0	6 (5.4)	
Study phase			<.001
I	14 (9.6)	2 (1.8)	
I/II	14 (9.6)	0	
II	94 (64.4)	19 (17.1)	
III	24 (16.4)	80 (72.1)	
IV	0	10 (9.0)	
Treatment modality			<.001
Monotherapy	123 (84.2)	70 (63.1)	
Combined therapy	23 (15.8)	41 (36.9)	
Primary endpoint			<.001
Response-related rate	124 (85.0)	24 (21.6)	
Overall survival	11 (7.5)	25 (22.5)	
Progression-related survival	11 (7.5)	60 (54.1)	
Pharmacokinetics	0	2 (1.8)	

All data are represented as n (%). IQR: interquartile range; RCT: randomized controlled trial.
*The sample sizes of five pivotal studies and two confirmatory studies were reported together with other studies, so specific sample size data for these seven studies are not available.

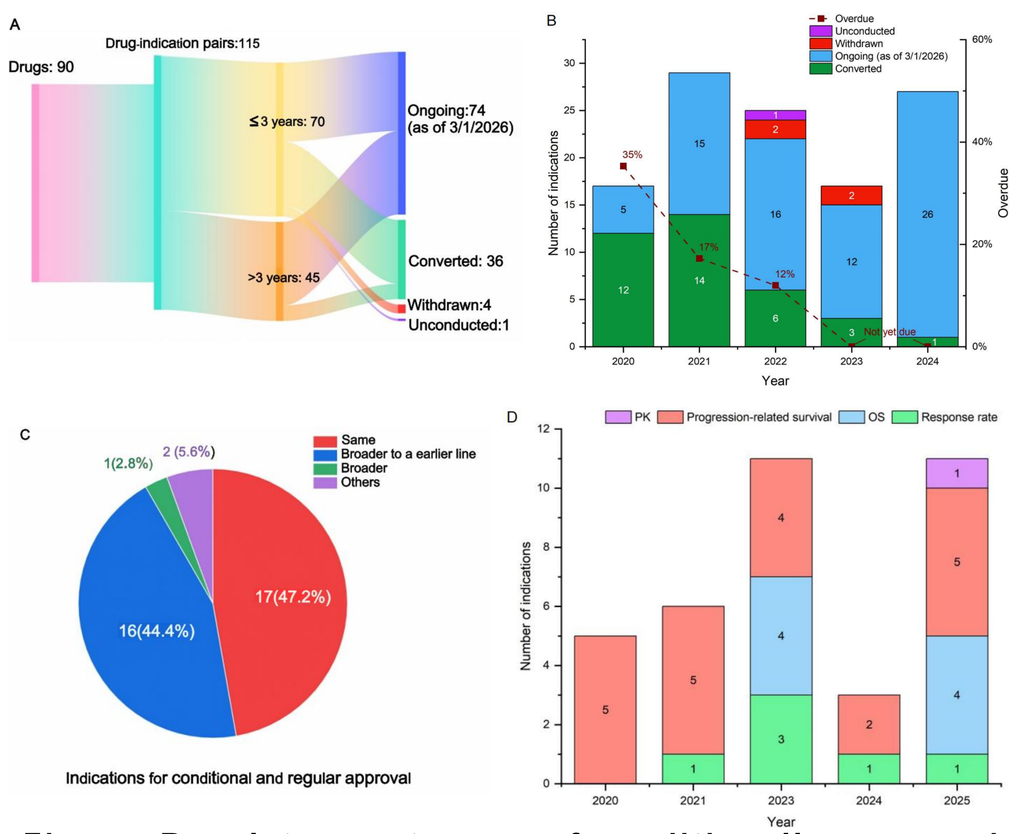


Figure. Regulatory outcomes of conditionally approved cancer drug indications in China

A: the Sankey diagram of conditionally approved drugs and indications stratified by regular status and time duration after conditional approval until Mar. 1, 2026 (≤3 years vs. >3 years)

B: the distribution of indications with regular approval and the overdue proportion of confirmatory trials in each year

C: the changes in indications between conditional approval and regular approval

D: the primary endpoints used in the confirmatory stages for the indications converted to regular approval.

NMPA: National Medical Products Administration; OS: overall survival; PK: Pharmacokinetics; Progression-related survival endpoints included progression-free survival (PFS), event-free survival (EFS), disease-free survival (DFS), and recurrence-free survival (RFS); Response rate comprised objective response rate (ORR), complete response rate (CRR), complete response/ complete remission with partial hematologic recovery (CR/CRh), and overall tumor response rate (OTR), et.al..