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Evolution of evidence on overall survival benefits of cancer drugs included on the national reimbursement drug list of China, 2005–2022: an observational study

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Abstract

Objective To assess evidence of overall survival (OS) benefits of cancer drugs listed in China's National Reimbursement Drug List (NRDL), the guiding standard for public insurance coverage of drugs and characterise the evolution of survival evidence after NRDL inclusion.

Design Retrospective observational study.

Setting China's NRDL and journal publications.

Participants Adult cancer drug indications approved in China from 1 January 2005 to 30 June 2022.

Main outcome measures The primary outcome was the availability of OS benefit evidence at the time of initial NRDL listing, defined as a statistically significant survival gain over the control arm in pivotal clinical trials. The secondary outcome was the availability of evidence on clinical benefits after NRDL inclusion as of 31 December 2023, measured by OS and the European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) version 1.1. ESMO-MCBS scores A to B in the curative setting or 4 or 5 in the non-curative setting were considered a substantial clinical benefit.

Results By 30 June 2022, 72.6% (175/241) of cancer indications approved in China were included in the NRDL. The median time interval between marketing authorisation and NRDL inclusion decreased from 9.4 years in 2005–2010 to 4.1 years in 2011–2016, and 1.1 years in 2017–2022. 62 (35.4%) and 4 (2.3%) indications had documented OS benefits at the time of NRDL assessment or after, respectively. The median survival benefit was 3.9 months. Of the 109 indications without documented OS benefits by the end of the observation, 21 (19.3%) had substantial clinical benefits as measured by the ESMO-MCBS.

Conclusions and relevance The time interval from regulatory approval to NRDL listing in China decreased over time. However, more than half of cancer drug indications listed for public insurance reimbursement did not have confirmed survival gain or substantial clinical benefits at the time of NRDL inclusion or after. Payers should give sufficient consideration to clinical benefit evidence when making reimbursement and disinvestment decisions to avoid wasteful spending of public health insurance funds.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The primary goal of cancer treatment is to prolong a patient's life. To steward limited resources wisely, health systems should preferentially pay for drugs with proven survival benefits.

⇒ Cancer drugs increasingly receive regulatory approval in China with uncertain evidence of overall survival benefits. This poses challenges for payers when assessing drugs for reimbursement.

⇒ To date, the evidence of clinical benefits of cancer drugs listed in China's National Reimbursement Drug List has not been adequately characterised.

Introduction

Pharmaceutical policies seek to promote patients' accessibility to and affordability of medicines that have been demonstrated to be safe and effective. For life-threatening diseases like cancers, overall survival (OS), along with quality of life and adverse events, is considered the most patient-relevant outcome. Although OS has been regarded as the gold standard for assessing the therapeutic efficacy of cancer drugs,[1] regulatory agencies in recent years have expedited the approval of new cancer drugs by making decisions based on changes in surrogate endpoints instead of OS gains.[2] This shift poses a challenge to payers (ie, public or private entities that reimburse medical expenses on behalf of patients[3]) when assessing drugs with insufficient evidence of clinical benefits. Tolerance of benefit uncertainty by stakeholders and health technology assessors differs across countries and affects reimbursement decisions.[4 5] For instance, a study comparing reimbursement decisions among

WHAT THIS STUDY ADDS

⇒ Between 2005 and 2022, around three-quarters of cancer drug indications approved in China were included for public payment in the National Reimbursement Drug List. Over half of them had uncertain overall survival benefits at the time of inclusion.

⇒ The median duration between regulatory approval and National Reimbursement Drug List inclusion decreased from 9.4 years in 2005–2010 to 1.1 years in 2017–2022. Following inclusion in the National Reimbursement Drug List, only 4 of 113 indications without evidence of benefit at initial listing had new evidence of survival benefits subsequently.

⇒ Overall, by the end of 2023, less than half of the cancer therapies included in China's National Reimbursement Drug List had documented overall survival benefits.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Given the poor availability of additional efficacy evidence after regulatory and reimbursement decisions, our findings highlight the necessity to improve clinical evidence criteria for cancer drug reimbursement at the time of and after National Reimbursement Drug List inclusion.

8 high-income countries showed that of 18 cancer drug-indication pairs with marginal clinical benefit, the proportion recommended for reimbursement varied from 0 (in New Zealand) to 83% (in Germany), although the countries all considered therapeutic benefit as a key factor.[6]

In China, the National Reimbursement Drug List (NRDL) lists drugs and their indications for reimbursement by the Basic Medical Insurance, which in 2018 enrolled over 95% of Chinese citizens. Pharmaceutical companies seeking drug cost reimbursement through the Basic Medical Insurance must submit applications for review by the agency in charge of NRDL listing (ie, the Ministry of Human Resources and Social Security before 2018 and National Healthcare Security Administration (NHSA) after 2018).[7] Before 2017, experts created the NRDL based on drug safety, efficacy and clinical needs.[8] The 2017 NRDL included all China-approved cancer drugs on the WHO Model List of Essential Medicines, which is intended to include efficacious, safe and cost-effective medicines for priority conditions.[9] Since 2017, China has further mandated national price negotiation as a principal requirement for new drugs to be included in the NRDL, as part of broader efforts to improve coverage of high-cost therapies and ensure the sustainability of the health insurance system.[8] After a clinical expert review, drugs submitted for NRDL inclusion must undergo mandatory price negotiation underpinned by health technology assessment (HTA) if their cost exceeds the payer's willingness to pay.[10] Successfully price-negotiated drugs must be listed on the NRDL and (partially) reimbursed by the Basic Medical Insurance.

The Chinese government reimbursement negotiation promoted the timely inclusion of newly approved cancer drug indications in the NRDL[11] and improved patient availability and affordability of expensive new cancer drugs.[12] In recent years, however, NRDL inclusion decisions have faced an increasing number of new cancer therapies approved for marketing in China with uncertain clinical benefits.[13] Ideally, to steward limited resources wisely, the Basic Medical Insurance should preferentially pay for drugs with proven survival benefits. Cancer drug indications with conditional approval based on surrogate endpoints were less likely to be listed in the NRDL, compared with those that received regular approval.[11] For price-negotiated drugs, the NHSA clarified that changes to their pricing or listing status after the contract has expired will be based on the product's effectiveness, safety, budget impact and cost-effectiveness (see online supplemental eFigure 1 and eTable 1 for more details).[14] However, compared with HTA results, the availability of OS data and estimated OS benefits seems to not have been fully considered in China's drug reimbursement decisions.[15 16] Moreover, for NRDL-listed therapies, the development of clinical evidence over time should, in theory, influence their reassessment and potential delisting. To date, these have not been adequately characterised. We conducted this study to determine the availability of evidence on OS benefits for cancer drug indications at the time of NRDL inclusion, the extent to which evidence was developed after their inclusion, and potential list removals.

Methods

We constructed a dataset of cancer drug-indication pairs (ie, cancer therapies) approved in China by 30 June 2022, the market authorisation cut-off date of new therapies intended to apply for listing in the then-latest NRDL (2022 version). The database was described in detail previously.[13 17 18]

Data sources and sample identification

Using the publicly available National Drug Code Data File obtained from China's National Medical Products Administration (NMPA), we identified all medical products authorised in mainland China between 1 January 2005 and 30 June 2022. We included newly approved chemical and biological antineoplastic agents for malignancies. Drugs indicated only for cancer prevention, diagnosis and supportive care (eg, antiemetics, colony-stimulating factors) were excluded.[19] For 121 eligible cancer drugs, we reviewed their latest product labels and excluded three drugs that did not contain a 'Clinical Trials' section on the label (online supplemental eFigure 2 for more information). We also excluded two cancer drugs for paediatric use only, as OS was rarely used in paediatric cancer trials.[17] Cancer drugs with adult indications were included in the analysis (see online supplemental eFigure 2 for the flowchart of sample identification). For all sample adult cancer drug indications, we identified their initial NRDL inclusion time. As NRDL-listed cancer drug indications with updated trial results could be delisted in subsequent versions of NRDL, we further checked their NRDL status up to 31 December 2023. The end of the observation period allowed for a minimum follow-up duration of 18 months since regulatory approval and NRDL assessment.[20] Each version of the NRDL was obtained from the websites of China's NHSA and the Ministry of Human Resources and Social Security, as reported previously.[18]

Supporting evidence identification and data extraction

For each indication, we identified preapproval pivotal trials supporting regulatory approval and postapproval confirmatory trials required by the regulatory agency for those that received conditional approval. We reviewed the regulatory review documents and the latest labels posted on the NMPA or the manufacturer's official websites to check whether an indication received regular or conditional approval and collected data on the preapproval and postapproval trial(s) supporting specific cancer

indications. We then searched the clinical trial identifiers (eg, National Clinical Trial number) in PubMed and ClinicalTrials.gov to retrieve peer-reviewed publications of included trials published by the end of observation (31 December 2023). When publications were not identified via these approaches, trial names in combination with approved indications were further searched in PubMed and the China National Knowledge Infrastructure database (one of the most commonly used Chinese literature databases), as trial results submitted to the NMPA Registration and Information Disclosure Platform for Drug Clinical Studies are not publicly available.[21] For regular approvals supported by single-arm trials only, we further searched PubMed using the Cochrane Highly Sensitive Search Strategy for identifying non-randomised trials.[22] All peer-reviewed articles reporting preplanned trial results were included for data extraction (see online supplemental eBox 1 for more details).

For each indication, we examined its pivotal trial and postapproval trial design (randomised controlled trial (RCT) or single-arm trial). For indications supported by at least one RCT, we further examined whether OS was measured as a trial endpoint. Survival data (ie, median OS, survival or death rate at a specific time) and statistical analysis results (ie, p value and HR) were extracted for analysis. We also collected the total number of participants and deaths to calculate the percentage of deaths.

Evaluation of OS benefits at the time of and after NRDL assessment

For each eligible cancer therapy, using trial publications and regulatory review documents, we calculated the maturity of survival data (measured by the percentage of death events in clinical trials)[23] and examined its OS benefit over the comparator in pivotal trials before the cut-off date for initial NRDL assessment. OS benefit was classified into five categories: (1) documented statistically significant OS benefit over the control arm; (2) documented lack of statistically significant OS benefit; (3) immature OS data: OS was an endpoint in RCT(s) but the data were not mature; (4) unmeasured OS in randomised trials: OS was not measured as an endpoint in RCT(s); and, for therapies supported by single-arm trials only and (5) OS benefit not evaluable. For indications with immature, unmeasured and not evaluable OS at the time of NRDL assessment (ie, the cut-off date for pharmaceutical companies to submit application materials), we further examined updated results of their preapproval pivotal trials and postapproval trials (see online supplemental eBox 1 for the search strategies) to check whether and when these indications had additional OS results (statistically significant or not significant) after NRDL assessment.

There is no agreed definition of 'immature' OS,[24] and reporting of immature OS information varies (see online supplemental eTable 2 for relevant literature).[25 26] Following previous research and regulatory reports,[23 27] for indications supported by RCTs, OS data was deemed 'mature' if (1) the publication reported results as the 'final OS result' or (2) the maturity of survival data of at least one trial arm exceeded 50% (ie, the median OS was achieved) and 'immature' was not mentioned throughout the main text. This threshold aligns with precedents from the European Medicines Agency,[27] which defines maturity based on whether event distribution allows reliable estimation of treatment effects, and with findings from the English National Institute for Health and Care Excellence appraisals and published studies suggesting that immature data are typically associated with event rates below 50%.[23] When multiple trials were identified, we included the trial with the most comprehensive survival data.

Statistical analysis

Data were analysed at the indication level. The primary outcome was the availability of OS benefit evidence at the time of initial NRDL listing. The secondary outcome was the availability of evidence on clinical benefits after NRDL inclusion as of 31 December 2023, measured by OS and the European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS). Other outcomes include the time interval from regulatory approval to NRDL inclusion. For cancer indications that showed documented OS benefits after NRDL assessment, we calculated the time interval from NRDL assessment to the availability of mature survival data, and the magnitude of OS gain for cancer indications with statistically significant OS benefits. For cancer indications with statistically significant OS benefits, we also documented the magnitude of OS gain.

We descriptively summarised the number of cancer indications by NRDL inclusion status and category of OS benefit. For NRDL-listed cancer indications without evidence of statistically significant OS benefits by the end of the observation period, we used the ESMO-MCBS version 1.1 to assess their clinical benefits.[28 29] ESMO-MCBS, considering OS, progression-free survival, disease-free survival, response rate, quality of life, prognosis of the condition and toxicity, is a validated and reproducible tool to assess the magnitude of clinical benefit from cancer drugs.[30] Scores A to B in the curative setting or 4 or 5 in the non-curative setting are considered a substantial benefit.[28 29] The ESMO-MCBS Scorecards published assessments for solid tumour drugs approved by the European Medicines Agency and the US Food and Drug Administration.[31] If the ESMO-MCBS score for a specific indication was not available in the scorecard, we evaluated it using the efficacy and safety data available by 31 December 2023. Two investigators (YZ and JC) independently extracted information and assessed the ESMO-MCBS score. Disagreements were resolved by consensus.

Patient and public involvement

Patients or members of the public were not involved in the design, conduct, reporting or dissemination plans of this research. No patients or members of the public were asked to advise on the interpretation or writing up of results. We plan to engage patients and the wider public in the dissemination stage by making the study findings available through a publicly accessible website.

Results

Characteristics and NRDL listing of newly approved cancer therapies

From 1 January 2005 to 30 June 2022, a total of 121 new cancer drugs received marketing authorisation in China. Of these, we identified 116 cancer drugs corresponding to 241 adult cancer indications. More than two-thirds (173/241 (71.8%)) of indications received regular approval and 28.2% (68/241) were conditional approvals (table 1). By 30 June 2022, 83 (71.6 %) cancer drugs and 175 (72.6 %) cancer indications were included in the NRDL and the time from regulatory approval to NRDL inclusion decreased from a median of 9.4 years (IQR 7.6–11.0 years) in 2005–2010 to 4.1 years in 2011–2016 (IQR 2.7–6.0 years), and 1.1 years in 2017–2022 (IQR: 0.8–1.6 years, figure 1, see online supplemental eTable 3 for further details).

Table 1 shows the OS benefits of cancer drug indications at the time of regulatory approval. Among 175 NRDL-listed indications, 56 (32.0%) had documented statistically significant OS benefits over the control group in the pivotal trials, 54 (30.9%) indications had immature OS data in their randomised trials, while 18 (10.3%)

Table 1 Characteristics of cancer therapies approved between January 2005 and June 2022, by China's NRDL status

Characteristics	Cancer indication, No. (%)		
	All (n=241, 100%)	Listed in the NRDL (n=175, 72.6%)	Not listed in the NRDL (n=66, 27.4%)
Indication approval pathway			
Regular approval	171 (71.0)	133 (76.0)	38 (57.6)
Conditional approval	70 (29.0)	42 (24.0)	28 (42.4)
Preapproval pivotal trial design			
Randomised controlled trial	183 (75.9)	137 (78.3)	46 (69.7)
Single-arm or dose optimisation trial	58 (24.1)	38 (21.7)	20 (30.3)
Cancer type			
Solid tumour	187 (77.6)	138 (78.9)	49 (74.2)
Haematological malignancy	54 (22.4)	37 (21.1)	17 (25.8)
Line of therapy			
First line	113 (46.9)	82 (46.9)	31 (47.0)
Later line	106 (44.0)	78 (44.6)	28 (42.4)
Neoadjuvant or adjuvant	13 (5.4)	8 (4.6)	5 (7.6)
Maintenance	7 (2.9)	7 (4.0)	0
Consolidation	2 (0.8)	0	2 (3.0)
OS benefit at the time of regulatory approval			
Documented OS benefit	85 (35.3)	56 (32.0)	29 (43.9)
Immature OS data in randomised trial(s)	64 (26.6)	54 (30.9)	10 (15.2)
OS benefit not evaluable in single-arm trial(s)	58 (24.1)	38 (21.7)	20 (30.3)
Documented lack of OS benefit	22 (9.1)	18 (10.3)	4 (6.1)
OS information not reported in randomised trial(s)	12 (5.0)	9 (5.1)	3 (4.5)

NRDL, National Reimbursement Drug List; OS, overall survival.

had demonstrated statistically non-significant OS results. Of indications that had not been listed in the NRDL, 43.9% (n=29/66) had documented OS benefits at the time of marketing authorisation.

OS benefits of cancer indications at the time of NRDL assessment

Among the 175 NRDL-listed indications, 133 (76.0%) were authorised through regular approval; 38 (21.7%) were approved on the basis of single-arm trials only. Most (n=152/175, 86.9%) cancer drug indications entered the NRDL through price negotiation (table 2). At the time of NRDL assessment, compared with the control arm in the pivotal trials, 35.4% (62/175) NRDL-listed cancer therapies had documented OS benefits, with a median of 3.9 months of OS gain (range: 1.0–35.0 months, see online supplemental eTable 4 and eFigure 3 for more details), while 22 (12.6%) demonstrated lack of statistically significant OS benefits. In contrast, the OS data for 46 (26.3%) and 7 (4.0%) therapies were immature and not measured, respectively.

Table 2 shows the annual number of NRDL-listed indications by OS category. The proportion of cancer therapies listed in the NRDL with documented OS benefits declined from 66.7% in 2009 to 39.0% in 2023. Among the 82 NRDL-listed first-line cancer therapies, this number decreased from 100.0% in 2009 to 30.0% in 2021 and then rose to 40.0% in 2023. Regarding the 78 second-line therapies listed in the NRDL, the annual proportion of indication fluctuated, peaking at 40.0% in 2023 (see online supplemental eTable 5). The proportion of cancer therapies supported by RCT with immature OS data fluctuated during the observation period and peaked at 42.5% in 2022.

Evolution of evidence on OS benefits of cancer indications after NRDL inclusion

Figure 2A illustrates the evolution of evidence on OS benefits over time. By the end of our observation period, OS data for 29.9% (n=47/175), 3.4% (n=6/175) and 15.4% (n=27/175) of NRDL-listed

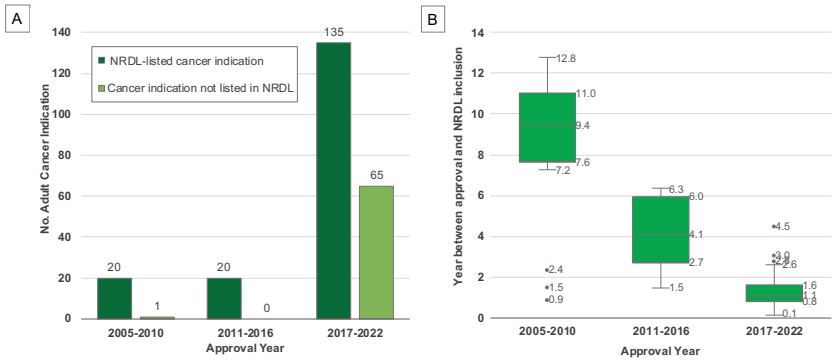

Figure 1 (A) Number of NRDL listings, and (B) time between regulatory authorization and NRDL inclusion of newly-approved adult cancer indications in China, by approval time. Note:The approval date of cancer indications authorized by June 30, 2022). NRDL, National Reimbursement Drug List.

Table 2 Category of OS benefit evidence of cancer therapies listed in the NRDL

Characteristics	All (No. %)	Indications, No. (%)*†‡				
		Documented OS benefit	Documented lack of OS benefit	Immature OS data in randomised trial(s)	OS not measured in randomised trial(s)	OS benefit not evaluable in single-arm trial(s)
Total	175 (100)	62 (35.4)	22 (12.6)	46 (26.3)	7 (4.0)	38 (21.7)
NRDL listing year§						
2009	3 (1.7)	2 (66.7)	1 (33.3)	0	0	0
2017	29 (16.6)	14 (48.3)	8 (27.6)	2 (6.9)	2 (6.9)	3 (10.3)
2018	24 (13.7)	10 (41.7)	5 (20.8)	7 (29.2)	0	2 (8.3)
2020	12 (6.9)	4 (33.3)	2 (16.7)	4 (33.3)	1 (8.3)	1 (8.3)
2021	26 (14.9)	6 (23.1)	2 (7.7)	7 (26.9)	2 (7.7)	9 (34.6)
2022	40 (22.9)	10 (25.0)	1 (2.5)	17 (42.5)	0	12 (30.0)
2023	41 (23.4)	16 (39.0)	3 (7.3)	9 (22.0)	2 (4.9)	11 (26.8)
Approval pathway						
Regular approval	133 (76.0)	56 (42.1)	22 (16.5)	41 (30.8)	6 (4.5)	8 (6.0)
Conditional approval	42 (24.0)	6 (14.3)	0	5 (11.9)	1 (2.4)	30 (71.4)
NRDL initial inclusion pathway						
Regular inclusion	23 (13.1)	12 (52.2)	6 (26.1)	2 (8.7)	1 (4.3)	2 (8.7)
Price negotiation	152 (86.9)	49 (32.2)	16 (10.5)	44 (28.9)	7 (4.6)	36 (23.7)

*By the assessment cutoff date of each version of the NRDL.

†Of indications supported by randomised controlled trials, the OS data were deemed 'mature' if (1) the 'final OS result' was clarified in the publication or (2) the proportions of deaths in at least one trial arm exceeded over 50% (ie, the median OS was achieved) and 'immature' was not mentioned throughout the main text.

‡Calculated as row percentages.

§Data were obtained from the websites of China's National Health Security Administration and the Ministry of Human Resources and Social Security.

NRDL, National Reimbursement Drug List; OS, overall survival.

indications were immature, unmeasured or not evaluable, respectively. Of the 91 indications with uncertain OS data at the time of NRDL assessment, 28 conditional approvals and one regular approval supported by single-arm pivotal trials only had post-approval randomised trials (ie, icotinib for first-line therapy of epidermal growth factor receptor mutation-positive non-small cell lung cancer). After a median follow-up duration of 2.5 years (range: 0.1–6.9 years), 12.1% (n=11/91) had mature OS data later (figure 2B, see online supplemental eTable 6 for detailed information). Four indications had evidence of statistically significant OS gain, and seven cancer therapies had evidence of statistically non-significant OS benefit over the comparator. The median time to the availability of statistically significant and non-significant OS evidence was 0.7 years (range: 0.1–1.4 years) and 1.9 years (range: 0.7–2.4 years) after NRDL assessment, respectively. All these indications remained on the NRDL by 31 December 2023. Only one cancer drug indication with documented lack of OS benefit at the time of 2017 NRDL listing (lapatinib for HER2-positive advanced or metastatic breast cancer) was delisted in 2020.

By the end of our observation period, the median improvement in OS was 3.9 months (range: 1.0–35.0 months) for NRDL-listed indications with documented OS benefits. For cancer drug indications not listed in the NRDL, the improvement in OS was 3.7 months, ranging from 1.0 to 16.3 months (online supplemental eFigure 3).

Cancer indications on the NRDL without evidence of OS benefit

By 31 December 2023, 109 of 175 (62.3%) NRDL-listed cancer drug indications had not been documented to have statistically significant OS benefit over the control arm in pivotal or confirmatory trials. Of those, 21 (19.1%) had ESMO-MCBS ratings of substantial clinical benefits, with 5 indications scored as A in the curative setting, and 16 indications scored as 4 in the non-curative setting (online supplemental eTable 7). By contrast, 80 (72.7%) indications only had moderate or negligible clinical benefits, according to the ESMO-MCBS. Nine (8.2%) indications had no evaluable benefits.

Discussion

Between 2005 and 2022, around three-quarters of cancer indications approved in China had been listed in the NRDL for mandatory reimbursement by China's Basic Medical Insurance. The time interval between the drugs' marketing authorisation and listing for insurance coverage decreased substantially over time. However, over half of the indications had uncertain OS benefits at the time of NRDL listing. Of these, less than one-eighth had subsequent mature OS data. By December 2023, of 175 cancer therapies listed in the NRDL, almost half (n=87/175, 49.7%) had documented OS benefits or substantial clinical benefits, and about half (50.3%) had evidence of lack of statistically significant OS gain or only moderate or negligible clinical benefits.

Comparison with other studies

Our study examined the evolution of evidence on OS benefits of all NRDL-listed cancer drug indications during an 18-year time period when NRDL inclusion was reformed to accelerate the reimbursement of newly approved therapies in China. A previous study showed the time interval between market authorisation and NRDL inclusion decreased from 1.5 years in 2015 to 1.0 year in 2022.[11] We also found that since 2020, a growing proportion of newly approved cancer drug indications have been listed in China's NRDL within 1 year of regulatory approval. Although it is challenging to compare times to reimbursement across different settings and periods, our findings suggest that time to reimbursement in China appears similar to that in Europe (the median time to National Health Authority reimbursement recommendations for advanced therapy medicinal products in eight European countries

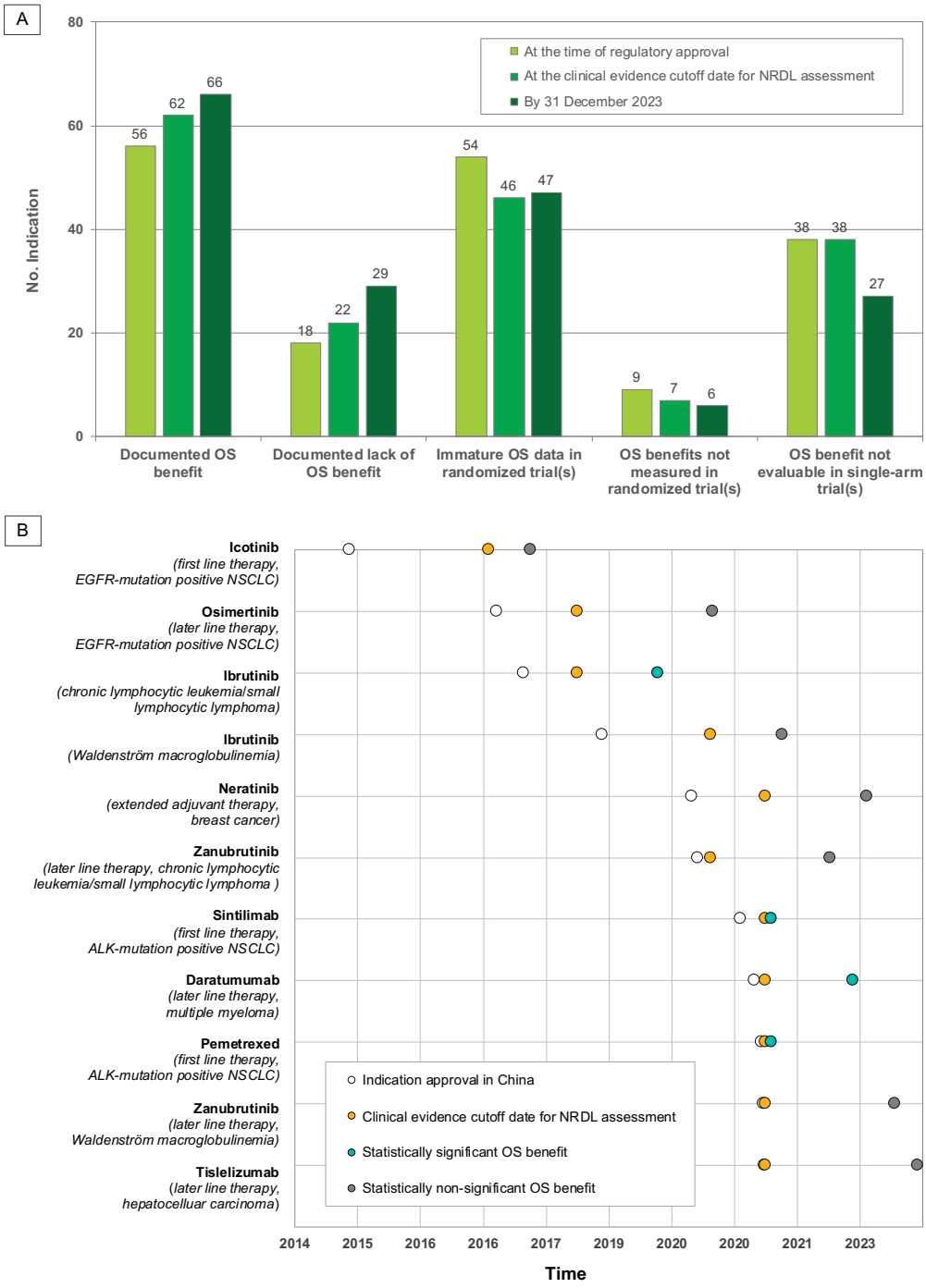

Figure 2 Evolution of overall survival (OS) data of cancer indications with uncertain survival data at the time of National Reimbursement Drug List (NRDL) assessment. (A) Category of OS benefits at the time of approval, NRDL assessment and by 31 December 2023. (B) Time to the publication of mature OS data of NRDL-listed cancer indications (n=11). ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

was 9–17 months) and longer than that in the USA (for 89 cancer drugs approved by the Food and Drug Administration between 2010 and 2019, the median time to coverage determination by 974 pharmacy and therapeutics committees was 4.2 months).[32–34] Nevertheless, it is worth noting that China is often not a first-priority launch country for multinational pharmaceutical companies.[35] Therefore, the time between global first approval (typically by the US FDA[2]) and NRDL listing in China may be significantly longer.

The acceleration of China's reimbursement decision, however, seems not to be accompanied by better evidence of clinical benefit of NRDL-listed indications, as the NRDL-listed therapies had a lower proportion (32.0% vs 43.9%) of documented OS benefits and a similar magnitude of OS gain (3.9 with 3.7 months), compared with those not listed. These findings are consistent with previous research documenting that clinical benefit was not a primary determinant of China's NRDL inclusion.[15 16] In contrast, although studies have shown that regulatory agencies in high-income

countries are increasingly reliant on surrogate endpoints or immature OS data to expedite approvals,[26 36 37] cancer drugs with substantial clinical benefits are still more likely to receive positive reimbursement recommendations in the Group of Seven countries and Oceania.[6 38–41] For instance, recent analyses of Project Orbis approvals found that median OS gains were modest, and HTA bodies in England and Canada often issued conditional or negative reimbursement decisions when clinical benefit was uncertain.[6] Evidence from selected Global South countries shows similar tensions between early approvals and postlisting uncertainties. In Brazil, earlier marketing authorisation of cancer drugs was associated with the availability of RCT evidence and OS benefit at the time of FDA approval.[42] Among cancer drugs that received positive recommendations from the Brazilian HTA agency, manufacturers offered substantial discounts, often driven by clinical uncertainties.[43]

By evaluating the availability and timing of OS data after NRDL listing, our study makes a novel contribution to the existing literature. Although the proportion of NRDL-listed cancer indications with uncertain OS data peaked at 72.5% in 2022, our results showed that most indications have not been confirmed later to prolong patient life. This finding is consistent with data from Sweden, where less than a third of cancer drug indications without clinical benefit at the time of reimbursement showed improvements in OS or quality of life after 6.6 years of follow-up.[44]

Interpretation

The findings must be placed into the context that an increasing number of cancer drugs are approved globally and in China based on immature OS data or surrogate endpoints considered 'reasonably likely' to predict survival gain.[13 45] Our recent study found that over two-thirds of cancer indications approved by the US Food and Drug Administration with immature OS data showed a statistically non-significant OS benefit after approval.[26] Furthermore, reporting of negative OS results took longer than reporting of statistically significant evidence of OS benefits.[26] This poses a challenge to payers as they need to balance facilitating early access to expensive new therapies with insufficient evidence of clinical benefits and potentially wasting scarce resources on those drugs.

The inclusion of cancer therapies without documented OS benefits in the NRDL is partly driven by policy priorities and economic incentives. Since 2017, China's government has managed to shorten the time from a new drug's marketing authorisation to reimbursement by the Basic Medical Insurance.[8] An institutional focus on faster access, combined with limited evidentiary thresholds for NRDL listing and renewal, has lowered the bar for including therapies supported by uncertain evidence. For drugs with high launch prices, HTA-informed value-based and budget-based price negotiations were adopted as a condition for NRDL inclusion.[10] Price negotiations allow reimbursement of cancer drugs with uncertain OS benefits if deemed cost-effective. From a budgetary perspective, negotiated discounts are assumed to reduce financial risk, leading to greater tolerance for uncertainty at the time of inclusion.[8] Nevertheless, the weak correlation between China's negotiated price and surrogate endpoint benefits[18] may reflect the inherent challenges in accurately estimating drug value based on immature OS data.[46 47] For instance, in Study 19 (NCT00753545) of olaparib for the maintenance therapy of platinum-sensitive recurrent ovarian cancer, the cost-effectiveness estimate varied substantially depending on data maturity.[23]

For cancer therapies with uncertain OS benefits at the time of NRDL assessment, health technology reassessment was adopted by the NHSA to support the delisting of the drugs from the NRDL.[14] Yet, our results showed that cancer drug indications with documented lack of OS benefit after NRDL inclusion remained on the list. Clinical evidence may not matter for NRDL-listed therapies whose reimbursement contracts have expired, as documented in recent rules. In June 2022, the NHSA issued the Rules for Contract Renewal of Price-Negotiated Drugs. The rules clarified that the adjustment of negotiated prices will be based on the difference between the actual expenditure of the medical insurance fund during the contract period and the budgeted fund expenditure.[48] The ruling did not mention clinical evidence requirements for continued NRDL listing, which could be an avenue for future reform.

Policy implications

Our findings have important policy implications. Insurers should facilitate affordable access to effective therapies for patients and efficiently allocate limited resources for improving population health. To meet these objectives, payers must weigh the trade-offs of covering cancer drugs quickly and prudently. Drug regulators increasingly rely on surrogate endpoints or immature OS data to make regulatory decisions, intending to provide treatment opportunities to individuals with life-threatening diseases. However, public health insurance must ensure that covered therapies provide meaningful population-level benefits. Paying for expensive cancer therapies without documented clinical benefits can lead to the waste of a finite budget. In most high-income countries, HTA agencies adopted therapeutic impact as a key factor to exclude from reimbursement some therapies with a low magnitude of benefit.[3 6] For certain indications such as rare cancers, RCTs may be infeasible. In such cases, the absence of documented OS benefit does not necessarily imply clinical ineffectiveness. Alternative forms of evidence, including single-arm studies with indirect comparisons, can provide valuable insights. It is imperative for China's NRDL to disclose the rationale behind listing cancer drugs with uncertain clinical benefits and enhance transparency of the standards used.[49] Specifically, the NHSA should clarify how patients would be expected to benefit from using these therapies, possibly based on better safety or other patient-relevant outcomes.

When insurance systems reimburse cancer drugs with uncertain evidence of OS benefit, they need to minimise the money spent on these drugs. Some proposals suggested that large-scale insurance schemes can re-evaluate drug benefits when new evidence becomes available.[50 51] However, concerns are growing that due to the poor availability of OS data after regulatory and reimbursement decisions, they are not often usable in follow-on health technology reassessments.[44 52] Our results revealed the difficulty of delisting following the emergence of additional efficacy data. Given that China's Basic Medical Insurance shoulders the responsibility of ensuring that the essential medical needs of over 1.3 billion citizens are met, our findings highlight the necessity to improve clinical evidence criteria for cancer drug reimbursement at the time of NRDL assessment and ensure adherence to the criteria. For therapies listed in the NRDL based on uncertain clinical benefits, the agency should revise the framework to mandate pharmaceutical companies in collecting and reporting the updated clinical evidence as a condition for further NRDL listing based on demonstrated clinical benefit.

Limitations

Our study has several limitations. First, since HTA dossiers are not publicly available in China, we relied on the peer-reviewed

literature on results of pivotal trials supporting regulatory approval to determine whether cancer drug indications in our sample had documented OS benefits at the time of NRDL listing and after. However, as we noticed that all of the primary clinical evidence was marked as 'preapproval trials' in the application materials submitted by pharmaceutical companies (available since 2021 only),[53 54] this approach is justifiable since the results of pivotal trials were usually the most positive preapproval efficacy evidence. Second, given the difficulty of obtaining the specific approval time of cancer drug indications authorised before 2005, we only included cancer drugs initially approved between 2005–2022 in the analysis. This may lead to an underestimation of the reimbursement rate since most of the previously approved chemotherapies had already been listed in the NRDL by 2005. Third, our criteria for OS benefits are lenient because we adopted the most positive results from the efficacy trials. Fourth, some ESMO-MCBS scores may have been overestimated or underestimated since results on quality of life were not published. Fifth, the ESMO-MCBS scores for haematological malignancies used in this study were based on investigator assessments, as these scores were not available on the ESMO website by the end of the observation. Lastly, our analysis was based on clinical evidence available up to 31 December 2023. While this cut-off ensured adequate follow-up time, more mature OS data may have emerged since then, which could potentially influence the classification of OS category in certain cases.

Conclusions

Around half of cancer drug indications did not have confirmed survival gain or substantial clinical benefits at the time of NRDL inclusion or after. NRDL listing of newly approved drugs in China needs to consider trade-offs of faster listing for mandatory reimbursement and paying from public insurance funds for drugs lacking confirmed clinical benefits.

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