Correlation between clinical trial endpoints of marketed cancer drugs and reimbursement decisions in China

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Objective: This study aimed to assess whether different clinical trial endpoints in pivotal trials of cancer drugs were associated with reimbursement decisions in China.

Materials and methods: Cancer drugs marketed before June 30th, 2021 with publicly available technical review reports for application of drug registration on Center for Drug Evaluation (CDE) website were reviewed. The trial design characteristics and relevant clinical outcomes [e.g., overall survival (OS), progression-free survival (PFS) and objective response rate (ORR)] were extracted from the technical review reports, while the reimbursement decisions were reviewed from National Healthcare Security Administration (NHSA) website. The differences in trial characteristics and clinical outcomes between drugs with positive reimbursement decisions and negative ones were compared by hypothesis test (Pearson’s chi-squared test, Fisher’s exact test, independent samples t-test and Mann-Whitney U test). The correlation between different clinical trial endpoints and reimbursement decisions was analyzed by multivariate logistic regression.

Results: There were 112 cancer drug indications included in this study. Among these indications, 76 received a positive reimbursement decision, and the most common primary endpoints of them were PFS (42.1%) and ORR (30.3%). Taking PFS (OR = 7.333) and ORR (OR = 5.271) as the primary endpoints were more likely to receive a positive reimbursement decision compared with OS (P = 0.003). The proportion of drugs marketed with phase I (75.0%) and phase II (85.7%) clinical trials receiving positive reimbursement decisions are significantly higher than those marketed with phase III clinical trials (61.3%, P = 0.043). The magnitude of clinical benefit only had subtle influences (P_{risk benefit−OS} = 0.627, P_{risk benefit−PFS} = 0.087, P_{survival benefit−OS} = 0.545, P_{survival benefit−PFS} = 0.189) on the drug reimbursement decisions, however, the drug prices and clinical needs also made a difference on that.

Conclusion: This study found that, in Chinese drug price negotiations from 2017 to 2021, policymakers have focused more on meeting clinical needs and filling therapeutical gaps in National Reimbursement Drug List (NRDL), while requirements for the selection of primary endpoints, clinical trial phases, and
Introduction

Cancer is the main leading cause of death globally, with nearly 10 million people dying of cancer worldwide in 2020 (1). In China, cancer is also a serious health problem (2), and the latest statistics released by the National Cancer Center of China showed that there were about 4,064,000 new cancer cases (3) and 2,413,500 new cancer deaths in China in 2016 (4). The annual medical expenditure on cancer in China exceeded 220 billion yuan, and the average inpatient expenditure for lung and gastric cancer alone reached 25,000 yuan in 2020 according to China Health Statistics Yearbook 2021, imposing a heavy financial burden on patients (5).

Drug therapy is the primary means of cancer treatment (6). To promote the accessibility of cancer drugs, the Chinese government has launched five rounds of drug price negotiations from 2017 to 2021, and has released five editions of National Reimbursement Drug List (NRDL) since the first edition introduced in 2000 (7), including many clinically necessary but expensive exclusive cancer drugs into NRDL at reduced prices to expand drug coverage (8).

According to the concept of value-based strategic purchase of medical insurance (9), policymakers focus on assessing the clinical value of drugs, of which the core indicators are outcome and cost (10, 11). For outcomes, clinical trial endpoints are commonly used to measure clinical benefit, and are classified into clinical endpoint and surrogate endpoint based on whether they directly measure clinical benefit (12). Since overall survival (OS, defined as the time from randomization until death from any cause) can directly measure the survival outcome of patients, it is often used as the clinical endpoint for cancer drugs (12, 13). To shorten the duration of clinical trials and accelerate drug launch, investigators may choose surrogate endpoints related to survival benefit as clinical trial endpoints, such as progression-free survival (PFS, defined as the time from randomization until objective tumor progression or death, whichever occurs first) and objective response rate (ORR, defined as the proportion of patients with tumor size reduction of a predefined amount and for a minimum time period, equal to partial responses plus complete response) (12–14). On July 1st, 2020, China National Medical Products Administration (NMPA) permitted the application for drug marketing with surrogate endpoints through a conditional approval process (15, 16).

However, evidence shows unclear correlations between surrogate endpoints and OS, which means such surrogate endpoints may not accurately predict clinical benefit (17–20). Scholars are divided on drugs of uncertain clinical benefit, with some opposing the positive reimbursement decisions of drugs with unclear clinical benefits (21) and others advocating that a new standard for drugs with surrogate endpoints should be established (22). Previous studies have analyzed the relevance between reimbursement decisions and clinical trial endpoints (23–28), the situation is not consistent across countries, while few studies have focused on the situation in China.

This study systematically reviewed the clinical evidence of all marketed cancer drugs in China, explored whether the use of surrogate endpoints had an impact on reimbursement decisions, and further identified the correlation between clinical trial design, the clinical benefits and reimbursement decisions in China.

Materials and methods

Sample

All of our analysis were based on drug indications for the following reasons: firstly, drug registration evaluation was based on indications; secondly, although NRDL was managed based on drugs, not all indications of a drug could be reimbursed, one was that some drugs were only accessed part of indications due to payment restrictions, another was that some intra-list drugs had approved new indications after NRDL admissions. The above practice was more common for cancer drugs, usually with multiple indications, compared with other drugs.

Cancer drug indications included in this study were marketed before June 30th, 2021 and had publicly available technical review reports for application of drug registration (hereinafter referred to as “technical review reports”), including drugs treating solid tumors and hematologic malignancies. Data were collected until May 10th, 2022.

All the marketed drug information was exported from the Center for Drug Evaluation (CDE) website (29), and a total of 659 pieces of drug registration information with technical review reports were collected. We excluded registration information of non-cancer drugs, generic cancer drugs and cancer drugs marketed after June 30th, 2021, and got a total of 174 pieces...
of drug registration information (specific selection process was shown in Figure 1), which are corresponding to 70 drugs' 112 indications and 107 technical review reports.

In general, a drug indication corresponds to a technical review report. However, among the 107 technical review reports, 5 reports each included 2 indications, so the numbers of reports and indications were 107 and 112, respectively.

In addition, as some indications had multiple specifications, each specification corresponded to a piece of registration information, so the number of registered information was far more than the number of drug indications.

Variables

A Microsoft Excel data form was created to extract the following variables: reimbursement decision, indication, tumor type, trial design characteristics (primary endpoint, phase, randomization, blinded trial, control group), and relevant clinical outcomes such as the hazard ratios (HRs) and the median OS or PFS. The clinical outcomes were used to describe clinical benefits. For the HRs, we defined “risk benefit” as HR<1.0, which was equal to the value of 1 minus HR times 100%, meant drugs in the experimental group reduced the risk of death or disease progression. For the median survival time, we defined “survival benefit” as the difference in the median survival time in OS and PFS between the experiment and control groups, and calculated the median of the survival benefits in PFS and OS of drugs that received positive and negative reimbursement decisions separately. The definitions of variables were shown in Table 1.

Data sources

The study extracted drug indications, corresponding tumor types, and time to market from the drug basic information module of the technical review reports, extracted clinical study design and clinical trial result data from the pivotal clinical trials of the technical review reports, extracted the reimbursement decisions from NRDL (2021 edition), extracted drugs failing the NRDL admission but applying for reimbursement from the List of Drugs Passing the Preliminary Formal Review for Reimbursement Application in 2020 and 2021; and extracted the time when drug indications first entered NRDL (2017 edition-2021 edition).

The inclusion criteria of the pivotal trial were: the clinical trial data of the Chinese population were preferentially used; if there was no clinical trial data of the Chinese population, the clinical trial results of the Asian population would be used; if there was none, the global clinical trial data would be used.
| Categories                  | Variables          | Specific indicators | Definition                                                                 |
|-----------------------------|--------------------|--------------------|-----------------------------------------------------------------------------|
| Basic information           | Indication         | /                  | /                                                                           |
| Tumor type                  |                    |                    |                                                                             |
| Marketing time              |                    |                    |                                                                             |
| Medical insurance access    |                    |                    |                                                                             |
| Medical insurance access    |                    |                    |                                                                             |
| Medical insurance access    |                    |                    |                                                                             |
| Trial design characteristics| Primary endpoint   | Only OS            | Only taking one of OS, PFS and ORR as primary endpoint                      |
|                             |                    | Only PFS           |                                                                             |
|                             |                    | Only ORR           |                                                                             |
|                             |                    | Other              | Not taking any of the endpoints of OS, PFS, ORR as primary endpoint        |
|                             |                    | Two endpoints      | Two endpoints in OS, PFS, and ORR are used simultaneously as primary endpoints |
| Phase                       |                    | Phase I            | Phase of the pivotal clinical trials included in this study                |
|                             |                    | Phase II           |                                                                             |
|                             |                    | Phase III          |                                                                             |
| Blinded trial               |                    | Yes/No             | Whether the pivotal clinical trials included in the study were blinded     |
| Control group               |                    | Yes/No             | Whether the pivotal clinical trials included in the study had a control group |
| Randomization               |                    | Yes/No             | Whether the pivotal clinical trials included in the study were randomized  |
| Clinical outcomes           | Risk benefit       | HR<sub>OS</sub> data available (Yes/No) | Whether HR<sub>OS</sub>, HR<sub>PFS</sub> data of the drug are provided |
|                             |                    | HR<sub>PFS</sub> data available (Yes/No) |                                                                             |
|                             |                    | Risk benefit in OS (Yes/No) | "Benefit" means an HR of <1. "No benefit" refers to HR \( \geq 1 \) or \( P \geq 0.05 \). Risk benefit = \( (1-HR) \times 100\% \) |
|                             |                    | Risk benefit in PFS (Yes/No) | Comparing HR values for drugs with risk benefit, the smaller the HR, the greater the risk of disease progression or death reduced by the drug, and the greater the risk benefit. |
|                             |                    | Magnitude of Risk<sub>OS</sub> benefit |                                                                             |
|                             |                    | Magnitude of Risk<sub>PFS</sub> benefit |                                                                             |
| Survival benefit            |                    | Survival benefit for mOS | The difference in median survival time between the experimental and control groups |
|                             |                    | Survival benefit for mPFS |                                                                             |
| Reimbursement decisions     |                    | Positive/negative  | Whether the drug indications are included in the NRDL (2021 edition)       |

**Statistical analysis**

Descriptive statistical analysis was conducted to describe tumor type, marketing time, and reimbursement time. Different methods were adapted based on the types of data to compare differences between groups of intra-NRDL drugs and extra-NRDL drugs in clinical trial design characteristics and clinical outcomes. For the count data, Pearson’s chi-squared test and Fisher’s exact test were used based on the sample size, to compare the trial design characteristics and clinical benefits with positive and negative reimbursement decisions. For the measurement data, independent samples t-test and Mann-Whitney U test were used according to whether they met normal distribution and homogeneity of variance, to test the difference in the magnitude of risk benefit and survival benefit with positive and negative decisions separately. Statistically significant variables \( (P < 0.05) \) were included in the multivariate logistic regression analysis, and variables were selected by the maximum likelihood ratio-based forward stepwise method \( (\alpha_{in} = 0.05, \alpha_{out} = 0.1) \), with OR values and 95% confidence interval (CI) describing the degree of influence of the factors.
Data collecting and graphing were performed by Excel, and data analyzing was completed by SPSS, version 26.0.

Results

Characteristics of sample

Totally, 112 indications of 70 drugs approved from December 2014 to June 2021 with corresponding 107 technical review reports (among them, five reports containing two drug indications, respectively) were identified, among which 64 were new drug applications and 48 were new indication applications. Seventy-six received a positive reimbursement decision and 36 received a negative reimbursement decision. Of the relevant 112 indications, 59 had HR_{OS} data available at the time of review. Of which 35 had showed risk_{OS} benefit, but only 17 received a positive reimbursement decision. 22.4% of drugs in NRDL showed risk benefit in OS while this proportion for drugs out of NRDL was 50.0%, which was a significant difference in risk_{OS} benefit between drugs in and out of NRDL (P = 0.011). Thirteen drugs without evidence of risk_{OS} benefit and 46 with no HR_{OS} data available also received a positive recommendation, which demonstrated clinical benefits in surrogate endpoints like PFS and ORR. The results shown that clinical benefit evidence was available for both drugs in and out of NRDL. Of the 112 drug indications, 59 had HS_{PFS} data available at the time of review. No significant differences were found in the distribution of drugs with evidence of risk_{PFS} benefit (P = 1.000) based on reimbursement decisions.

As for the magnitude of clinical benefit, no significant difference was observed, no matter risk benefit (P_{riskbenefit−OS} = 0.627, P_{riskbenefit−PFS} = 0.087) or survival benefit (P_{survivalbenefit−OS} = 0.545, P_{survivalbenefit−PFS} = 0.189).

About OS benefit, the drugs that received positive reimbursement decisions reduced the risk of death by 32.0% on average [HR_{median} = 0.680 (0.530–0.747)], while the proportion for drugs that received negative reimbursement decisions is 37.5% [HR_{median} = 0.625 (0.428–0.743)]. Similarly, the median survival benefit of drugs out of NRDL was higher than the proportion for drugs in NRDL [4.95 (1.430–6.680) vs. 2.60 (1.875–5.875)]. About PFS benefit, the drugs in NRDL and out of NRDL reduced the risk of death by 62.3% [HR_{median} = 0.377 (0.280–0.563)] and 41.2% [HR_{median} = 0.588 (0.280–0.735)], respectively, and the median survival benefit of drugs with positive vs. negative decisions was 5.00 (2.075–6.975) vs. 2.10 (0.080–8.075) (Table 2, Figures 2, 3).

Differences in clinical benefits of drugs with positive vs. negative decisions

Of the 112 drug indications, only 49 had HR_{OS} data available at the time of review. Of which 35 showed risk_{OS} benefit, but only 17 received a positive reimbursement decision. 22.4% of drugs in NRDL showed risk benefit in OS while this proportion for drugs out of NRDL was 50.0%, which was a significant difference in risk_{OS} benefit between drugs in and out of NRDL (P = 0.011). Thirteen drugs without evidence of risk_{OS} benefit and 46 with no HR_{OS} data available also received a positive recommendation, which demonstrated clinical benefits in surrogate endpoints like PFS and ORR. The results shown that clinical benefit evidence was available for both drugs in and out of NRDL. Of the 112 drug indications, 59 had HS_{PFS} data available at the time of review. No significant differences were found in the distribution of drugs with evidence of risk_{PFS} benefit (P = 1.000) based on reimbursement decisions.

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Discussion

Impact of the primary endpoints selection on reimbursement decisions

The result showed that the primary endpoint selection was related to reimbursement decisions in China (Pearson’s chi-squared test P = 0.001, multivariate logistic regression P = 0.003). The most common primary endpoints of drugs in NRDL were PFS (42.1%) and ORR (30.3%). Compared with OS, it was more likely to receive a positive reimbursement decision for drugs taking PFS (OR = 7.333) and ORR (OR = 5.271) as the primary endpoints.

Similar studies in other countries were examined to facilitate a qualitative comparison (24, 25), which showed that OS (92.6%) was the most common endpoint of drug that received a positive
### TABLE 2  Results of hypothesis testing.

| Categories | Variables | Options | Reimbursement decisions, No. (%) | Test          | P-value |
|------------|-----------|---------|----------------------------------|---------------|---------|
|            |           |         | Positive (n = 76) | Negative(n = 36) |          |
| Trial design characteristics | Primary endpoint | Only OS | 8 (10.5) | 11 (30.6) | Pearson's chi-squared test | 0.001 |
|            |           | Only PFS | 32 (42.1) | 6 (16.7) |              |      |
|            |           | Only ORR | 23 (30.3) | 6 (16.7) |              |      |
|            |           | Other    | 10 (13.2) | 7 (19.4) |              |      |
|            |           | Two endpoints | 3 (3.9) | 6 (16.7) |              |      |
| Phases     | I         |         | 3 (3.9) | 1 (2.8) | Fisher's exact test | 0.043 |
|            | II        |         | 24 (31.6) | 4 (11.1) |              |      |
|            | III       |         | 49 (64.5) | 31 (86.1) |              |      |
| Blinded experiment | Yes |         | 28 (36.8) | 16 (44.4) | Pearson's chi-squared test | 0.442 |
|            | No        |         | 48 (63.2) | 20 (55.6) |              |      |
| Control group | Yes |         | 53 (69.7) | 28 (77.8) | Pearson's chi-squared test | 0.374 |
|            | No        |         | 23 (30.3) | 8 (22.2) |              |      |
| Randomization | Yes |         | 54 (71.1) | 28 (77.8) | Pearson's chi-squared test | 0.453 |
|            | No        |         | 22 (28.9) | 8 (22.2) |              |      |
| Clinical outcomes | HR\textsubscript{OS}, data availability | Yes | 30 (39.5) | 19 (52.8) | Pearson's chi-squared test | 0.185 |
|            | No |         | 46 (60.5) | 17 (47.2) |              |      |
| Risk benefit in OS | Yes |         | 17 (22.4) | 18 (50.0) | Pearson's chi-squared test | 0.011 |
|            | No |         | 13 (17.1) | 1 (2.8) |              |      |
|            | Missing |         | 46 (60.5) | 17 (47.2) |              |      |
| Magnitude of risk benefit in OS | HR\textsubscript{OS}, median | (interquartile range) | 0.680 [0.530–0.747] | 0.625 [0.428–0.743] | Two-sample t test | 0.627 |
| HR\textsubscript{PFS}, data availability | Yes |         | 41 (53.9) | 18 (50.0) | Pearson's chi-squared test | 0.696 |
|            | No |         | 35 (46.1) | 18 (50.0) |              |      |
| Risk benefit in PFS | Yes |         | 37 (48.7) | 16 (44.4) | Pearson's chi-squared test | 1.000 |
|            | No |         | 4 (5.3) | 2 (5.6) |              |      |
|            | Missing |         | 35 (46.1) | 18 (50.0) |              |      |
| Magnitude of risk benefit in PFS | HR\textsubscript{PFS}, median | (interquartile range) | 0.377 [0.280–0.563] | 0.588 [0.280–0.735] | Two-sample t test | 0.087 |
| Magnitude of survival benefit | Survival benefit for mOS, median | 2.6 [1.875–5.875] | 4.95 [1.430–6.680] | Mann-Whitney U Test | 0.545 |
|            | Survival benefit for mPFS, median | 5.00 [2.075–6.975] | 2.10 [0.080–8.075] | Mann-Whitney U Test | 0.189 |

### TABLE 3  Results of multi-factor logistic analysis.

| Variables | B     | S.E.  | Wald  | df  | Sig.  | Exp (B) | 95% CI of EXP (B) |
|-----------|-------|-------|-------|-----|-------|---------|------------------|
|           |       |       |       |     |       |         | Lower          | Upper          |
| Only OS   | 1.992 | 0.643 | 9.593 | 1   | 0.002 | 7.333   | 2.078           | 25.875         |
| Only PFS  | 1.662 | 0.653 | 6.485 | 1   | 0.011 | 5.271   | 1.466           | 18.944         |
| Only ORR  | 0.675 | 0.677 | 0.994 | 1   | 0.319 | 1.964   | 0.521           | 7.409          |
| Other     | −0.375| 0.846 | 0.196 | 1   | 0.658 | 0.687   | 0.131           | 3.610          |
| Two endpoints | −0.318| 0.465 | 0.470 | 1   | 0.493 | 0.727   |                 |                 |
reimbursement decision, while only 7.4% of drug chose PFS in England and France. While in Canada, the most common primary endpoints with the positive reimbursement decisions were PFS (53.9%) and OS (32.1%), and the most frequently used endpoint for drugs with negative reimbursement decisions was ORR (38.5%) (Table 4).

By sorting out the number of drugs and the tumor types included in the annual NRDL from 2017 to 2021 (7, 8, 30–36), the study found that the selection of primary endpoints associated with reimbursement decisions may be related to the China’s drug reimbursement reform pace in recent years. Since 2017, China has conducted five rounds of price negotiations and adjustments of NRDL, and many cancer drugs successfully have gotten accessed to NRDL at significantly reduced prices. Of the 76 drugs included in this study, which comprised a total of 21 tumor types, 77.6% entered NRDL within 1 year of marketing, and only 3.9% entered NRDL 3 years after marketing.

The speed of incorporating cancer drugs in NRDL has been accelerating in recent years, and policymakers may focus more on filling treatment gaps in the list and meeting clinical needs, while slightly reduced the quality of clinical evidence. In this context, as OS usually requires a long follow-up
TABLE 4 Study results of different nations.

| Indicators                  | China                              | Canada                               | England, France                    |
|-----------------------------|------------------------------------|--------------------------------------|------------------------------------|
| Drugs with positive         | OS:8 (10.5%);                      | OS:25 (32.1%);                       | OS:25 (92.6%);                     |
| reimbursement decision      | PFS:32 (42.1%);                    | PFS:42 (53.9%);                      | PFS:2 (7.4%);                      |
|                            | ORR:23 (30.3%);                    | ORR:5 (6.4%);                        | Other 0 (0%);                      |
| Selection of efficacy       | Two endpoints:3 (3.9%);            | Other 6 (7.7%);                      |                                    |
| endpoints                   | Other:13 (13.2%);                  |                                      |                                    |
| Drugs with negative         | OS:11 (30.6%);                     | OS:6 (23.1%);                        | OS:31 (83.8%);                     |
| reimbursement decision      | PFS:6 (16.7%);                     | PFS:6 (23.1%);                       | PFS:0 (0%);                        |
|                            | ORR:6 (16.7%);                     | ORR:10 (38.5%);                      | Other:6 (16.2%);                   |
|                            | Two endpoints:6 (16.7%);           | Other:4 (15.4%);                     |                                    |
|                            | Other:7 (19.4%);                   |                                      |                                    |

Association between endpoints selections and reimbursement decisions

 Associated (P = 0.001)  Associated (P = 0.01)  No-associated (P = 0.991)

TABLE 5 List of drugs failed the NRDL admission by using OS as the primary endpoint.

| Generic name                          | Company                           | Indication                                           | Date of marketing |
|---------------------------------------|------------------------------------|------------------------------------------------------|-------------------|
| Gilteritinib fumarate tablets         | Astellas Pharma Inc.              | Acute myeloid leukemia                               | Jan. 30th, 2021   |
| Radium [{superscript 223}Ra] chloride | Bayer AG                           | Castration-resistant prostate cancer                 | Aug. 26th, 2020   |
| tablets                               | Tiiho Pharmaceutical Co., Ltd.    | Metastatic colorectal cancer                         | Aug. 29th, 2019   |
| Trifluridine and tipiracil hydrochloride tablets | Abbvie Ireland NL BV | Acute myelogenous leukaemia                         | Dec. 25th, 2020   |
| Venetoclax tablets                    | Ristol-Myers Squibb Holdings Pharma | Non-small-cell lung cancer                          | June 15th, 2018   |
| Nivolumab injection                   | Ristol-Myers Squibb Holdings Pharma | Squamous cell carcinoma of the head and neck        | Sept. 29th, 2019  |
| Nivolumab injection                   | Ristol-Myers Squibb Holdings Pharma | Gastric cancer and adenocarcinoma of Esophagealgastric junction | Mar. 12th, 2020   |
| Nivolumab injection                   | Ristol-Myers Squibb Holdings Pharma | Malignant pleural mesothelioma                      | June 8th, 2021    |
| Pembrolizumab injection               | Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. | Non-small-cell lung cancer                          | Sept. 29th, 2019  |
| Pembrolizumab injection               | Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. | Esophageal squamous cell carcinoma                  | June 17th, 2020   |
| Ipilimumab injection                  | Bristol-Myers Squibb Pharma EElG | Malignant pleural mesothelioma                      | June 8th, 2021    |

Time, pharmaceutical companies may prefer to take surrogate endpoints with shorter follow-up periods such as PFS to accelerate the launch and access of drugs in case of missing the policy window.

In addition, among the 11 drug indications taking OS as the primary endpoint but were not included in NRDL, two drugs (each corresponding to one indication), Gilteritinib and Radium Chloride [{superscript 223}Ra], were not included in the List of Drugs Passing the Preliminary Formal Review for Reimbursement Application and it was uncertain whether they applied for reimbursement [37]; the seven indications corresponding to Nivolumab, Pembrolizumab and Ipilimumab, all of which were qualified for negotiation, were ultimately not included in NRDL due to high prices [38]. It can be seen that taking OS as an endpoint was not the reason for their failure in NRDL admission, though it to some extent also influenced the results of the study (Table 5).

Impact of clinical trial phases on reimbursement decisions in China

Results of Fisher’s exact showed that different phases of pivotal clinical trials were one of the influencing factors in drug reimbursement decisions (P = 0.043). The study found that the proportion of drugs having evidence from phase I (75.0%, 3/4) or II (85.7%, 24/28) studies entering NRDL is significantly higher than that of drugs with phase III (61.3%, 49/80). However, pan-Canadian Oncology Drug Review (pCODR) in Canada preferred to give positive reimbursement recommendations to
drugs with phase III studies. If a phase III trial was deemed possible in later period, the drugs with phase II evidence was less likely to receive a positive recommendation from pCODR \((P = 0.024)\) (26).

In order to explain the phenomenon mentioned above, we analyzed 31 drug indications that were marketed in Phase III clinical trials but were not in NRDL, but only found the reasons why 20 of them were not in NRDL (Table 6), and the remaining 11 drug indications did not find any disclosed news or information. It was found that the clinical needs of drugs marketed in Phase I and Phase II and those in Phase III are different, which may lead to a difference in the focus of policymakers when evaluating the drugs and ultimately affect the reimbursement decisions.

Most of the drugs with Phase I and Phase II marketing were for diseases that did not have effective treatments and were in urgent clinical need. To meet clinical demand, policymakers may loosen the restrictions on clinical trial evidence to make the drugs enter NRDL as soon as possible. Besides, among the 31 indications with evidence from phase III clinical trials but out of NRDL, 35.5\% (11/31) of them already have the same indication treatment drugs in NRDL. In this case, policymakers will place more emphasis on the cost-effectiveness of the drugs instead of the quality of evidence, making NRDL access more difficult.

In addition, 7 out of 31 drug indications, corresponding to 3 drugs, Nivolumab, Pembrolizumab and Ipilimumab, all failed to negotiate because of the disagreement on the price reduction; another four drugs (each corresponding to one indication), Olaparib, Osimertinib, Lenvatinib and Pertuzumab, has already been in NRDL, but adding the indications need to reduce prices again, which may affect the willingness of drug companies to negotiate (Table 6).

### Impact of clinical benefit on reimbursement decisions

The study shown that the difference in the magnitude of clinical benefits between drugs received positive and negative reimbursement decisions did not reach statistical significance \((P_{\text{riskbenefit-OS}} = 0.627, P_{\text{riskbenefit-PFS}} = 0.087, P_{\text{survivalbenefit-OS}} = 0.545, P_{\text{survivalbenefit-PFS}} = 0.189)\). The clinical benefit of PFS was generally better than that of OS whether intra-list drugs or extra-list drugs. Furthermore, there is even a higher level of OS clinical benefit for drugs outside of NRDL than for drugs within NRDL.

One explanation for this was the sample drugs were greatly influenced by price. Drugs such as Olaparib, Lenvatinib and Patuximab mentioned above, despite having OS clinical benefit, failed to negotiate due to the need for another price reduction for new indications. Some drugs, like Atelizumab, Ipilimumab, Palivizumab and Nabrituzumab, were out of NDRL for their high prices. Another explanation was that more than 90\% of drugs with clinical benefits had evidence from phase III clinical trials, which meant it may not be clinically urgent. Under this situation, policymakers may pay more attention to cost-effectiveness ratio when making reimbursement decisions. It was shown that clinical benefit only has a weak impact on reimbursement decisions which needed to be considered in combination with the cost-effectiveness ratio of drugs and clinical needs.

### Limitations

This study had several limitations. First, we only included drugs with publicly available technical review reports, which resulted in small sample size. Second, since nearly 60\% of the OS benefit data were missing, the results may be different from the total sample. Third, among the 36 drugs out of NRDL, 8 drugs weren’t in the List of Drugs Passing the Preliminary Formal Review for Reimbursement Application, so we couldn’t know whether they applied for reimbursement or not. Finally, drug reimbursement policy is a complex decision-making process, which should evaluate the effectiveness, safety, cost-effectiveness ratio, innovation, equity and other dimensions of drugs. While this study focused on the selection and improvement of efficacy endpoints, neglected indicators related to other drug evaluation dimensions and only included factors related to clinical trial design to minimize interference. So the impact of different drug evaluation dimensions on drug reimbursement policy will need to be further discussed in future studies.

### Conclusion

In Chinese drug price negotiations from 2017 to 2021, policymakers have focused more on meeting clinical needs and filling the therapeutic area gaps in NRDL, while requirements for the quality of clinical evidence (such as the selection of primary endpoints and clinical trial phases) and clinical benefits have been relaxed. It requires more attention to surrogate endpoints and clinical benefits of drugs.

For drugs with urgent clinical needs, the government should allow them apply for NRDL with surrogate endpoints and phase I or II clinical trials, however, it is necessary to continuously pay attention to the benefit of patients in the real world, and remove drugs that don’t achieve the expected therapeutic effect promptly out of NRDL. For drugs that are not clinically urgent or there are other drugs with the same indications in NRDL, enterprises are encouraged to use OS endpoints and Phase III clinical studies for NRDL application. For intra-list drugs with poor clinical outcomes and having extra-list competitors with better therapeutic effects, reevaluation should be adopted to include drugs with better efficacy in NRDL. Finally, a procedure
| Generic name             | Indication                                                                 | Date of marketing | Whether in the formal review list | The main reasons for negative reimbursement decision                                                                 |
|-------------------------|-----------------------------------------------------------------------------|-------------------|-----------------------------------|---------------------------------------------------------------------------------------------------------------------|
| Olaparib tablets        | Metastatic castration-resistant prostate cancer                             | Jun. 16th, 2021   | Yes (2021)                        | Already in NRDL, applying for another indication, need to reduce price again                                         |
| Osimertinib mesylate    | Non-small-cell lung cancer                                                  | Apr. 7th, 2021    | No                                | Already in NRDL, applying for another indication, need to reduce price again                                         |
| Lenvatinib mesilate      | Thyroid carcinoma                                                          | Nov. 4th, 2020    | No                                | Already in NRDL, applying for another indication, need to reduce price again                                         |
| Pertuzumab injection    | Unresectable or metastatic HER2-low breast cancer                           | Dec. 6th, 2019    | Yes (2021)                        | Competing products with the same indication in NRDL, such as Trastuzumab Emtansine for Injection; Already in NRDL, applying for another indication, need to reduce price again |
| Atezolizumab injection  | Hepatocellular carcinoma                                                   | Oct. 28th, 2020   | No                                | Competing products, Donafenib Toslate Tablets and Lenvatinib Mesilate Capsules with the same indication in NRDL,     |
| Enzalutamide soft       | Non-Metastatic Castration-Resistant Prostate Cancer                        | Nov. 2nd, 2020    | No                                | Competing products, Apalutamide Tablets and Darolutamide Tablets with the same indication in NRDL;                   |
| Gilteritinib fumarate   | Acute myeloid leukemia                                                     | Jan. 30th, 2021   | No                                | Competing product, Azacitidine for Injection, with the same indication in NRDL                                         |
| Pralatrexate injection  | Peripheral T cell lymphoma                                                 | Aug. 26th, 2020   | Yes (2020, 2021)                  | Competing product, Trastuzumab Emtansine for Injection, with the same indication in NRDL                              |
| Venetoclax tablets      | Acute myeloid leukemia                                                     | Dec. 2nd, 2020    | Yes (2021)                        | Competing product, Azacitidine for Injection, with the same indication in NRDL                                         |
| Trastuzumab emtansine   | HER2-positive early breast cancer                                           | Jan. 21st, 2020   | Yes (2020)                        | Competing product, Azacitidine for Injection, with the same indication in NRDL                                         |
| Palbociclib capsules    | Receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer | Jul. 31st, 2018   | Yes (2020, 2021)                  | Competing product, Abemaciclib Tablets, with the same indication in NRDL                                              |

(Continued)
| Generic name | Indication | Date of marketing | Whether in the formal review list | The main reasons for negative reimbursement decision |
|--------------|------------|-------------------|-----------------------------------|-----------------------------------------------------|
| Trifluridine and tipiracil hydrochloride tablets | Metastatic colorectal cancer | Aug. 29th, 2019 | Yes (2020, 2021) | Competing products, Fruquintinib Capsules and Regorafenib Tablets, with the same indication in NRDL |
| Nivolumab injection | Gastric cancer and adenocarcinoma of esophagogastric junction | Mar. 12th, 2020 | Yes (2020, 2021) | Competing product, Regorafenib Tablets, with the same indication in NRDL |
| Pembrolizumab injection | Squamous cell carcinoma of the head and neck | Dec. 8th, 2020 | Yes (2021) | Competing product, Regorafenib Tablets, with the same indication in NRDL; Negotiations failed due to high price |
| Nivolumab injection | Malignant pleural mesothelioma | Jun. 8th, 2021 | Yes (2021) | Negotiations failed due to high price |
| Pembrolizumab injection | Non-small-cell lung cancer\(^a\) | Mar. 28th, 2019 | Yes (2021) | Negotiations failed due to high price |
| Pembrolizumab injection | Non-small-cell lung cancer\(^b\) | Sept. 29th, 2019 | Yes (2021) | Negotiations failed due to high price |
| Pembrolizumab injection | Non-small-cell lung cancer\(^c\) | Nov. 22nd, 2019 | Yes (2021) | Negotiations failed due to high price |
| Pembrolizumab injection | Esophageal squamous cell carcinoma | Jun. 17th, 2020 | Yes (2021) | Negotiations failed due to high price |
| Ipilimumab injection | Malignant pleural mesothelioma | Jun. 8th, 2021 | Yes (2021) | Negotiations failed due to high price |
| Atezolizumab injection | Small cell lung cancer | Feb. 13th, 2020 | Yes (2020) | Reasons not disclosed |
| Durvalumab injection | Non-small-cell lung cancer | Dec. 6th, 2019 | Yes (2020, 2021) | Reasons not disclosed |
| Lenalidomide capsules | Multiple myeloma | Dec. 20th, 2017 | No | Reasons not disclosed |
| Lenalidomide capsules | Lymphoma | Nov. 17th, 2020 | No | Reasons not disclosed |
| Nivolumab injection | Non-small cell lung cancer | Jun. 15th, 2018 | Yes (2020, 2021) | Reasons not disclosed |
| Nivolumab injection | Squamous cell carcinoma of neck | Sept. 29th, 2019 | Yes (2020, 2021) | Reasons not disclosed |
| Plerixafor injection | Lymphoma | Nov. 30th, 2018 | Yes (2020) | Reasons not disclosed |
| Plerixafor injection | Multiple myeloma | Aug. 26th, 2020 | Yes (2020) | Reasons not disclosed |
| Brentuximab vedotin for injection | Lymphoma | Apr. 15th, 2021 | Yes (2020, 2021) | Reasons not disclosed |
| Radium chloride [223Ra] | Prostatic cancer | Aug. 26th, 2020 | No | Reasons not disclosed |
| Blinatumomab for injection | Leukemia | Dec. 2nd, 2020 | Yes (2021) | Reasons not disclosed |

\(^a\) Pembrolizumab in combination with pemetrexed and platinum chemotherapy, is indicated for first-line treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations.

\(^b\) Pembrolizumab is indicated as a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) \(\geq 1\%\)] as determined by an NMPA-approved test, with no EGFR or ALK genomic tumor aberrations.

\(^c\) Pembrolizumab in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with metastatic squamous NSCLC.
for identifying surrogate endpoints should also be established, listing available surrogate endpoints for each disease type is necessary to regulate the use of surrogate endpoints in drug marketing and drug reimbursement policy.

Data availability statement

The original contributions presented in the study are included in the article supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

KL contributed to study design and conception, data collection, data analysis, and manuscript drafting. WL and JD guided this study, including the design of the study, and the interpretation of data and the original draft preparation. HQ participated in the paper structure design, data verification, the manuscript drafting and modification. YF provided valuable suggestions for the thesis. HC provided great helps with figures depiction and revision. All authors contributed to the article and approved the submitted version.

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