ABSTRACT

Objective Neratinib plus capecitabine (Ner+Cap) were proved to be clinically beneficial as a third-line treatment for women with human epidermal growth factor receptor-2 (HER2) positive metastatic breast cancer (MBC). The objective of this study was to evaluate the cost-effectiveness of Ner+Cap from the Chinese healthcare perspective.

Design A three-state Markov simulation model was performed based on the results of NALA trial. The utilities of health state and disutilities of adverse events were derived from the published literature. Direct costs of anticancer agents, drug administration, routine follow-up and serious adverse events management were calculated in the model. Uncertainty was evaluated through univariate and probability sensitivity analysis.

Participants Patients with confirmed HER2-positive MBC who previously received at least two HER2-targeted treatments and were aged ≥18 years with an Eastern Cooperative Oncology Group performance status 0 or 1. A total of 621 patients were enrolled in the NALA trial.

Interventions Third-line treatment with Ner+Cap or lapatinib plus capecitabine (Lap+Cap).

Main outcome measures The primary health outcomes of the model were costs, expected life-years (LYs), quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs).

Results When compared with Lap+Cap, Ner+Cap provided an additional 0.431 LYs and 0.339 QALYs, and increased the cost by $4299.2. The corresponding ICERs were $9970.1/LY and $12 670.2/QALY. Univariate sensitivity analyses suggested that the results were generally robust. Besides, Ner+Cap had a 100% probability of being cost-effective according to probabilistic sensitivity analysis.

Conclusions Ner+Cap was likely to be a cost-effective regimen as the third-line treatment for women with HER2-positive MBC at the willingness-to-pay threshold of $37 653.0/QALY in China.

INTRODUCTION

Breast cancer remains the most common cancer and the leading cause of cancer deaths in females. It was estimated that there were approximately 2.3 million patients with newly diagnosed breast cancer, accounting for 11.7% of all new cancer cases, and more than 680 000 deaths worldwide in 2020.1 In China, 304 000 women were newly diagnosed with breast cancer and an estimated 70,000 deaths occurred in 2015.2 Approximately 3%–10% of breast cancers were metastatic at the time of diagnosis, and 20%–30% of early breast cancers will eventually metastasise.

Overexpression and/or amplification of human epidermal growth factor receptor2 (HER2) occurred in 20%–30% of all breast cancer.4 5 HER2-positive is a clinically aggressive subtype with a poorer prognosis and shorter survival life, especially for advanced breast cancer.6 Fortunately, the survival rate of patients with this disease has been significantly improved due to the development of HER2-targeted therapy over the last two decades.7

The Chinese Society of Clinical Oncology guideline for breast cancer currently recommended taxane-trastuzumab-pertuzumab as the first-line therapy for HER2-positive metastatic breast cancer (MBC).8 For non-first-line treatment, trastuzumab-emtansine (TDM1)
and tyrosine kinase inhibitor (TKI) contained regimens were recommended.\textsuperscript{8} Neratinib is an oral small molecule irreversible TKI that targets HER1, HER2 and HER4.\textsuperscript{4} It has been approved for the extended adjuvant treatment of early-stage HER2-positive breast cancer by the National Medical Products Administration (NMPA) of China in April 2020. Furthermore, neratinib was also active in combination with capecitabine as non-first-line systemic therapy for MBC. NALA trial was an open-label, multicentre randomised, phase III clinical trial to evaluate the efficacy and safety of neratinib plus capecitabine (Ner+Cap) versus lapatinib plus capecitabine (Lap+Cap) in 621 patients with HER2-positive MBC who had received at least two HER2-directed regimens.\textsuperscript{10} It showed that the risk of disease progression or death in the Ner+Cap arm was reduced by 24\% compared with the Lap+Cap arm. Overall response rate was significantly higher for patients treated with Ner+Cap than those with Lap+Cap (32.8\% vs 26.7\%; p=0.1201). However, there was a similar improvement in progression-free survival (PFS) between two arms (median 5.6 vs 5.5 months) as well as a non-significant improvement in overall survival (OS) (mean 24.0 vs 22.2 months, HR=0.88, 95\% CI 0.72 to 1.07). Based on these results, the Ner+Cap regimen was approved by U.S. Food and Drug Administration for the treatment of patients with HER2-positive MBC who received ≥2 prior anti-HER2 based regimens and also recommended by the guideline of the National Comprehensive Cancer Network.\textsuperscript{11, 12}

 Novel targeted therapies provide more clinical benefits and increase the financial burden on patients with cancer. In 2015, the total inpatient cost for breast cancer treatment in China was 9.7 billion RMB, ranking fifth among all malignant tumours.\textsuperscript{13} The medical cost of breast cancer treatment has increased year by year, with an average annual increase rate of 14.87\% in China.\textsuperscript{14} Hence, we conducted an economic model to evaluate the cost-effectiveness of Ner+Cap with Lap+Cap as the third-line or later treatment for patients with HER2-positive MBC based on the NALA trial from the Chinese healthcare perspective.

**METHODS**

**Patient and treatment**

The target population for our economic analysis was clinically similar to the patients enrolled in the NALA trial. The hypothetical patients were women with confirmed HER2-positive MBC who previously received at least two HER2-targeted treatments and were aged ≥18 years with an Eastern Cooperative Oncology Group performance status 0 or 1. Patients were randomly assigned to receive either neratinib 240 mg orally once a day continuously plus capecitabine 750 mg/m\textsuperscript{2} two times a day for 14 days every 3 weeks, or lapatinib 1250 mg orally once daily continuously plus capecitabine 1000 mg/m\textsuperscript{2} two times a day daily for 14 days every 3 weeks. The dosage of capecitabine was calculated according to the average body surface area of Chinese women.\textsuperscript{15} Furthermore, patients in the Ner+Cap arm received loperamide (initial dose, 4 mg) with the first dose of neratinib, followed by 2 mg every 4 hours for the first 3 days. Thereafter, loperamide 2 mg was administered every 8 hours until the end of the first cycle. Patients continued with their respective regimens until progression, unmanageable toxicity or death was observed.

**Model structure and assumption**

A decision-analytic Markov model was developed using TreeAge Pro Suit 2011 to simulate the process of Ner+Cap or Lap+Cap treatment for HER2-positive MBC. As shown in figure 1, the cost-effectiveness model consisted of three mutually exclusive health states: PFS, progressive disease (PD) and death. According to the disease development process and the clinical practice, the PFS state was assumed to be the initial state and death the terminal state. After a cycle of treatment, patients in the PFS state would remain in the PFS state, move to the PD state or die based on the transition probabilities. Patients in the PD state could either remain in the PD state or transition to death. Each model cycle duration represented 3 weeks. The time horizon of our model was 10 years when more than 99\% of patients transitioned to the terminal state in both intervention arms.

The cost-effectiveness was evaluated by the incremental cost-effectiveness ratio (ICER), which was calculated based on the total cost, expected life-years (LYs) and quality-adjusted life years (QALYs). The Chinese guidelines for phar-macoeconomic evaluations recommended that the willingness-to-pay (WTP) threshold should be set at 1–3 times per-capita gross domestic product (GDP).\textsuperscript{16} In our model, $37 653.0/QALY, which was three times the per-capita GDP of China in 2021, was selected as the WTP. If ICER was less than the WTP threshold, the Ner+Cap was considered as a dominant option compared with the Lap+Cap. Otherwise, the Ner+Cap was not cost-effective.
Transition probabilities
Clinical efficacy data were obtained from the NALA trial to estimate the cycle-specific transition probabilities. Kaplan-Meier survival curves for PFS and OS were read by Engauge Digitizer software for reconstructing individual patient data (IPD). Several parametric models, including Exponential, Weibull, Gompertz, Log-logistic and Log-normal, were considered to fit the reconstructed IPD with R statistical software. Based on the Akaike information criterion and the Schwarz Bayesian criterion (see online supplemental file 1), we found that the Log-normal distribution was most suitable for the PFS curve of Ner+Cap, and the Log-logistic distribution was the fittest to OS curve of Ner+cap, PFS curve of LAP+Cap and OS curve of LAP+Cap (figure 2). All the estimated parameters of the models and adjusted R² are described in table 1. Time-dependent probabilities of transition from PFS to PFS were calculated based on the parametric models of PFS curves by the following formulation: \( p(t) = \frac{s(t)}{s(t-1)} \), where \( t \) stands for the current treatment cycle in the Markov model. The mortality rate from PFS to death was assumed to be equal to 7.14‰, which was the natural mortality of China in 2020. The declining exponential approximation of life expectancy method was used to calculate the constant transition probability from PFS to death based on the natural mortality. The parametric models of OS curves were used to measure the overall mortality of each cycle. Then, the transition probabilities from PD state to PD state were calculated based on the natural mortality and overall mortality.

Cost and utility
In our model, only direct costs of medications, monitoring and serious adverse events (SAEs) management were calculated from the perspective of Chinese healthcare (table 1). According to the protocol of NALA trial and clinical practice, it was assumed that patients were evaluated with laboratory tests, CT, MRI and echocardiography during follow-up. CT was performed every 6 weeks, and brain MRI was performed every 12 weeks. Echocardiography was performed at cycle 3 and cycle 6, and every six cycles thereafter. The unit prices of medications and tests were obtained from the local hospital and Yaozhi platform (https://yaozhi.com/). The most common treatment-related grade 3/4 AEs, including diarrhoea, nausea, palmar-plantar erythrodysesthesia syndrome and vomiting, were estimated. The unit costs of AEs management were derived from the published literature. These costs were only applied once to the first cycle. Patients were assumed to receive the best supportive care (BSC) in the PD state, owing to the subsequent treatment for post-progression was unavailable from the NALA trial. The cost of BSC was derived from a previously published study.

The health utilities of different states were adopted from a previously published study, where the PFS state was 0.850 and the PD state was 0.685. Disutilities for treatment-related SAEs were also considered in our analysis and were derived from a published study by Lloyd et al.

An annual discount rate of 3% was applied to both cost and health utilities to reflect net current values.

Sensitivity analyses
Univariate sensitivity analyses were performed to determine the impact of each independent variable on the result, within a specific range. Due to the lack of CI, the costs were assumed to vary by ±20%, and the utilities were assumed to vary by ±10%, based on their baseline values. The tornado diagram was applied to show the results of univariate sensitivity analyses.

Probabilistic sensitivity analysis (PSA) using a Monte Carlo simulation of 10000 random individuals was carried out to further test the robustness of the result. Costs were assumed to fit the gamma distribution, and utilities were assumed to fit the beta distribution. Furthermore, in order to obtain the price of lapatinib when the acceptable probability of Ner+Cap is greater than 50%, PSA was run repeatedly by adjusting the price of lapatinib. Meanwhile, we took a further exploration with WTP at 1× or 2× per capita GDP. The results of PSA were presented in WTP acceptability curves and scatter plots.

Starting from 1 January 2022, the price of neratinib has dropped from the original $14.25/tablet to $5.74/tablet, so we conducted a scenario analysis at the original price of $14.25/tablet.

Patient and public involvement
There was no direct involvement of patients or the public in this study.

RESULTS
Base case analysis
The Markov model predicted that the total costs of a 10-year horizon incurred with the Ner+Cap arm and Lap+Cap arm were $38698.3 and $54 399.1, respectively. The total life expectancy was estimated to be improved by 0.431 years with Ner+Cap versus Lap+Cap.
Moreover, Ner+Cap gained an additional 0.339 QALYs compared with Lap+Cap. As a result, the ICERs between Ner+Cap and Lap+Cap were $9,970.1/QALY and $12,670.2/QALY. Both of them were less than the WTP threshold of $37,653.0/QALY, demonstrating that Ner+Cap was cost-effective when compared with Lap+Cap. The results of the base case analysis are shown in table 2.

### Sensitivity analysis

The results of univariate sensitivity analyses were summarised in a tornado diagram (figure 3). The price of lapatinib had the greatest influence on the ICERs, which ranged from $5,509.9/QALY to $19,795.9/QALY with the price of lapatinib changing. The second greatest impact on ICER was the price of neratinib. Cost of PD,
utility of PFS, utility of PD and price of capecitabine had moderate influences on the cost-effectiveness results. The influences of other parameters on the results were almost negligible. None of the parameters could make the ICERs greater than the WTP thresholds, and Ner+Cap was always dominant compared with Lap+Cap in all deterministic sensitivity analyses.

The scatter plot (figure 4B) of probabilistic sensitivity analyses showed that ICERs of 10,000 Monte Carlo simulations were all below the WTP threshold, which demonstrated that treatment with Ner+Cap was overwhelmingly cost-effective compared with Lap+Cap. If WTP was set at double per-capita GDP, the probability of Ner+Cap as a cost-effective regimen was 99.2%. If WTP was set at per-capita GDP, the probability of Ner+Cap as a cost-effective option was 49.5%. The cost-effectiveness acceptability curves (figure 4A) showed that when the price of lapatinib was reduced by 70%, Ner+Cap would become a dominated option.

In the scenario analysis, when the price of neratinib was assumed to be the original $14.25/tablet, the ICER was $63,163.6/QALY which was greater than the WTP threshold of $37,653.0/QALY.

### DISCUSSION

In this study, we performed a model-based cost-effectiveness analysis of neratinib plus capecitabine versus lapatinib plus capecitabine as the third-line therapy for HER2-positive MBC in China, using the available efficacy data from the NALA trial and local costs data. According to the results of our base-case analysis, patients who received Ner+Cap treatment would achieve an additional 0.431 LYs and 0.339 QALYs, and spent an extra $4299.2, leading to the ICERs of $9,970.1/LY and $12,670.2/QALY, both of them were below the threshold of WTP. In the univariate sensitivity analyses, ICERs of all scenarios were less than the WTP threshold. The PSA of our study showed that Ner+Cap was preferred in 100% of simulations with the WTP threshold of $37,653.0/QALY. Thus, Ner+Cap

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**Table 2** Results of base case analysis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost ($)</th>
<th>LYs</th>
<th>QALYs</th>
<th>ICER ($/LY)</th>
<th>ICER ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lap+Cap</td>
<td>54,399.1</td>
<td>2.136</td>
<td>1.569</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ner+Cap</td>
<td>58,698.3</td>
<td>2.567</td>
<td>1.908</td>
<td>9,970.1</td>
<td>12,670.2</td>
</tr>
</tbody>
</table>

Cap, capecitabine; ICER, incremental cost-effectiveness ratio; Lap, lapatinib; LY, life-year; Ner, neratinib; QALY, quality-adjusted life year.
was found to be a cost-effective regimen compared with Lap+Cap as the third-line therapy for HER2-positive MBC.

Different WTP thresholds for medical cost-effectiveness analysis were used in different countries. In the UK, a cost-effectiveness threshold range of £20000 to £30000 per QALY was adopted by the National Institute for Health and Clinical Excellence. A range of $50000 to 200000 per QALY was recommended in the USA. The Chinese guidelines for pharmacoeconomic evaluations recommended that if the ICER was lower than per-capita GDP, the additional cost of the novel therapy was worthwhile; if the ICER was between per-capita GDP and triple per-capita GDP, the additional cost of the novel therapy was acceptable; if the ICER was greater than triple per-capita GDP, the additional cost of the novel therapy was not worth it. Triplet per-capita GDP was the most widely used cost-effectiveness threshold when evaluating new treatments in China. In our analysis, the ICER of Ner+Cap versus Lap+Cap was $12 670.2/QALY which was slightly greater than per-capita GDP and well less than triple per-capita GDP. Therefore, Ner+Cap was acceptable as a third-line treatment for HER2-positive MBC based on the view of the Chinese guidelines for pharmacoeconomic. In China, the medical insurance catalogue was uniformly formulated by the national medical security administration (NHSA) of China. Medical insurance costs were managed and paid by the provincial medical security administration. The per-capita GDP of 31 provinces in the Chinese mainland ranged from $6334.0 in Gansu to $28506.3 in Beijing in 2021, of which 11 provinces had a per capita GDP of more than $12 670.2. It means that Ner+Lap as a third-line therapy for HER2-positive MBC was completely worthwhile in these 11 provinces.

Ner was initially approved for patients with early-stage HER2-positive breast cancer within 2 years of trastuzumab therapy. Schwartz et al constructed a three-state Markov model to evaluate the cost-effectiveness of adjuvant neratinib following trastuzumab in early-stage HER2-positive breast cancer from the U.S. healthcare payer perspective. This study found that the estimated ICER was $416106 per QALY gained, and neratinib would need an 85% reduction in price to be cost-effective at a WTP threshold of $150000. In Canada, an economic guidance report associated with neratinib for early breast cancer from Canadian Agency for Drugs and Technologies in Health revealed that neratinib needs an extra cost of approximately $60000 over the assumed lifetime time horizon, resulting in an ICER of $82 326/QALY when compared with BSC. Both the above studies proved that the marginal survival benefit of neratinib did not match its high price.

Neratinib was approved by NMPA in April 2020 in China and was available in early 2021. The high cost of neratinib impeded its use. In just over a year, the price of neratinib has changed several times in China. When it was first available, neratinib was priced at $28.5/tablet with a charity programme that required payment for the first three cycles of every six cycles and free for the last three cycles. In June 2021, the price of neratinib was reduced to $14.25/tablet in the absence of a charity programme. The NHSA published the latest national reimbursement drug list on 3 December 2021. Neratinib was added to the national medical insurance negotiation drug list, which included those clinically necessary and effective but very expensive drugs that were reimbursed by medical insurance through national price negotiation. The latest national reimbursement drug list took effect since 1 January 2022, and neratinib was reduced to its current price ($5.74 per tablet) with a reduction of approximately 60%. The scenario analysis showed that Ner+Cap was not cost-effective when the neratinib’s price was set at $14.25/tablet, whereas, according to the results of our base case analysis, Ner+Cap turned to be a cost-effective regimen at the current price of neratinib. The PSA results suggested that neratinib would always have an economic favour unless the price of lapatinib fell below 30% of current levels. The project of national drug price negotiation improved the access and affordability of neratinib.

Our economic model had several limitations caused by data availability and model assumptions. First, the clinical data were derived from the NALA trial, in which 57.2% of the enrolled patients were white, whereas the proportion of Asians was small and unavailable. It might have a slight impact on our results. This limitation cannot be avoided at present, and updated clinical data for patients with MBC in Chinese populations might improve the accuracy in the future. Second, minor AEs were assumed to be self-limiting and not considered in our models. Nonetheless, the univariate sensitivity analysis suggested that all parameters related to AEs had a minor influence on ICER values. Third, dose adjustment was not considered in our model. Adverse events leading to dose reductions occurred in more than 20% of patients in both treatment groups. However, a reduction in dosage can be understood as a reduction in the cost of medicines. The sensitivity analysis showed that unless the cost of lapatinib was reduced by 70%, it was unlikely to change the final result.

CONCLUSION

The results of the present study suggested that neratinib plus capecitabine was a cost-effective regimen when compared with lapatinib plus capecitabine, as a third-line treatment for patients with HER2-positive MBC at a WTP of triple per-capita GDP. Neratinib under the current price may benefit more Chinese women with HER2-positive MBC. We expect that our study will serve as a reference for physicians or patients when making treatment decisions.

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Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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