Matching-adjusted Indirect Comparison and Cost-utility Analysis of Zorifertinib versus Osimertinib in Treating Newly Diagnosed EGFR-mutant NSCLC with CNS Metastases in China

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BACKGROUND

- **The central nervous system (CNS)** is a major metastatic site in epidermal growth factor receptor mutations (EGFRm+) non-small cell lung cancer (NSCLC) patients, with the detection rate of 25% to 40% among EGFRm+ NSCLC patients at initial diagnosis, and increasing to 50% during disease progression.
- **EGFR-tyrosine kinase inhibitors (EGFR-TKIs)** are currently the standard systemic therapy for EGFRm+ NSCLC patients.
  - Third-generation EGFR-TKIs was recommended as first-line treatment in guidelines worldwide. In China, **osimertinib**, an oral irreversible third-generation EGFR-TKI targeting sensitizing mutations and T790M resistance, is reported to have the highest market share in the clinical application for patients with CNS metastases.
  - Approved for marketing in China in November 2024, **zorifertinib** is the first EGFR-TKI specifically designed for EGFRm+ NSCLC patients with CNS metastases.
- The comparative efficacy and cost-effectiveness of these two drugs in treating newly diagnosed EGFRm+ NSCLC with CNS metastases in China are still unclear.

OBJECTIVES

- To **generate comparative efficacy evidence** via matching-adjusted indirect comparison (MAIC) and **assess the cost-effectiveness** of first-line zorifertinib versus osimertinib for newly diagnosed EGFRm+ NSCLC patients with CNS metastases from the perspective of the Chinese healthcare system.

METHODS

Matching-adjusted indirect comparison (MAIC) and cost-utility analysis methods were used to simulate the medical costs and health outcomes of zorifertinib and osimertinib.

Model Structure and settings

- **Four state partitioned-survival structure** (Figure 1):
  - PFS, CNS PD, Non-CNS PD, death
- Perspective: China's healthcare system.
- Corrected by half-cycle correction.
- A 30-day cycle length and a lifetime horizon.
- Incremental cost-effectiveness ratios (ICERs) were expressed in CNY (¥) per QALY gained, with all costs and utilities discounted at 4.5% annually.
- Willingness to pay (WTP) threshold: one time China's per capita GDP (**CNY 95,700/QALY**, 2024).

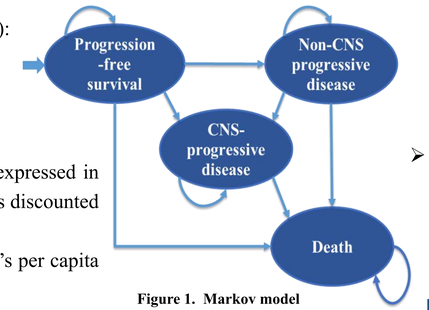


Figure 1. Markov model

Patient population and efficacy data sources

- The target population in this study was newly diagnosed EGFRm+ NSCLC patients with CNS metastases in China.
- The efficacy data of zorifertinib was the individual patient data (IPD) from **the EVEREST trial** (NCT03653546; full analysis set, N=439).
- The efficacy data source of osimertinib included the aggregated data (AgD) from the CNS subgroup of **the FLAURA trial** (NCT02296125; CNS full-analysis set, N=128) and **one retrospective cohort study** (N=83).

Indirect comparison of efficacy and safety

- We adopted **an anchored MAIC**, which involves weighting the IPD from the EVEREST trial to align the baseline characteristics of the weighted patient populations with those of the FLAURA trial (iPFS) and the retrospective study (PFS and OS), respectively.
- **A weighted Cox proportional hazards model** was used to estimate the hazard ratios (HRs) for time-to-event outcomes (OS, PFS, and iPFS) comparing zorifertinib with first-generation EGFR-TKIs.
- **The bucher indirect comparison method** was applied to estimate the relative efficacy between zorifertinib versus osimertinib, using equation (1): $\mathbf{HR_{ZO} = HR_{ZC} / HR_{OC}}$.

Model Parameters

- **Clinical Inputs**
  - Under the proportional hazards (PH) assumption, **the fitted and extrapolated curves of osimertinib** were chosen to fit the survival data of zorifertinib using MAIC adjusted HR_{ZO}.
  - Survival data of osimertinib from the literature were fitted to six parametric distribution functions: exponential, Weibull, Gompertz, loglogistic, lognormal, and generalized gamma.
  - The optimal distribution for each survival was determined through visual inspection, the Akaike Information Criterion (AIC), and Bayesian Information Criterion (BIC).
  - Zorifertinib survival curves were derived by applying the indirectly estimated HR_{ZO} to the osimertinib curves using the following equation (2):

    Zorifertinib survival probability = Osimertinib survival probability^{HR}
- **Utility Inputs (Table 1)**
  - The utility values of PFS and non-CNS PD were derived from a Chinese study.
  - The relative utility decrement proportion associated with CNS PD states (0.69) relative to the PFS state (0.8) was calculated from a Canadian study, which was then applied to estimate the utility value of the CNS PD state.

Table 1. Utility Parameters of Partitioned Survival Model

Utility	Value (range)	Distribution
PFS state	0.856 (0.59, 1.00)	Beta
CNS PD state	0.738 (0.59, 0.88)	Beta
Non-CNS PD state	0.781 (0.52, 1.00)	Beta
Death	0	NA

- **Cost Inputs (Table 2)**
  - All drug prices were obtained from the 2025 NRDL reimbursement standards or the annual weighted average prices in the publicly available pharmaceutical database.
  - Healthcare resource utilization and unit cost data were collected through clinical expert consultations or published literature.

Table 2. Cost Parameters of Partitioned Survival Model

Costs (CNY)	Value (range)
Costs of zorifertinib (daily)	134.26 (120.84, 134.26)
Costs of osimertinib (daily)	165.54 (149.00, 165.54)
Local intracranial treatment costs in CNS PD (one-off)	34393 (27514, 41272)
Relief treatments for intracranial symptoms in CNS PD (per cycle)	1380 (1104, 1656)
Subsequent treatment costs of zorifertinib in non-CNS PD (per cycle)	6065 (4852, 7279)
Subsequent treatment costs of osimertinib in non-CNS PD (per cycle)	15775 (12620, 18930)
Routine follow-up costs in PFS (per cycle)	968 (775, 1162)
Routine follow-up costs in CNS PD (per cycle)	1697 (1357, 2036)
Routine follow-up costs of zorifertinib in non-CNS PD (per cycle)	1310 (1048, 1572)
Routine follow-up costs of osimertinib in non-CNS PD (per cycle)	1855 (1484, 2226)
Genetic testing of zorifertinib (one-off)	6274 (5019, 7529)
Genetic testing of osimertinib (one-off)	8600 (6880, 10320)
Terminal care costs (one-off)	11328 (9062, 13594)

RESULTS

- **Indirect comparison results (Table 3)**
  - Zorifertinib exhibited a numerical advantage over osimertinib in terms of median point estimate survival of iPFS, PFS, and OS; however, none of these differences reached statistical significance.

Table 3. Relative efficacy estimate of survival outcomes with MAIC and bucher method

Survival outcome	Before population matching of zorifertinib group	After population matching of zorifertinib group	Osimertinib group	Bucher method
iPFS	0.47 (0.35-0.62)	0.39 (0.25-0.60)	0.48 (0.26-0.86)	**0.81 (0.39-1.71)**
PFS	0.72 (0.58-0.89)	0.57 (0.39-0.83)	0.69 (0.36-1.31)	**0.83 (0.39-1.75)**
OS	0.90 (0.67-1.20)	0.70 (0.41-1.17)	0.81 (0.40-1.63)	**0.86 (0.36-2.08)**

- **Base case results**
  - The incremental cost per QALY gained showed that zorifertinib was **dominant** (Table 4).

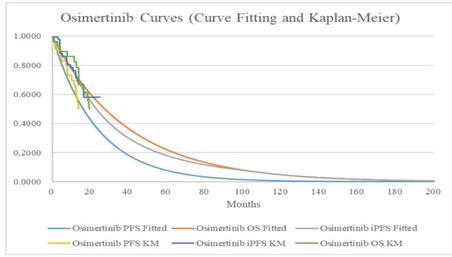


Figure 2. Osimertinib iPFS, PFS, and OS Kaplan-Meier and Parametric Survival Curves

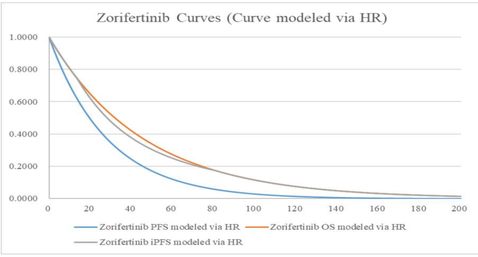


Figure 3. Zorifertinib iPFS, PFS, and OS Parametric Survival Curves modeled via HR based on the Osimertinib curves

- **Sensitivity analysis results**
  - ΔQALY-OWSA (Figure 4).
  - Probabilistic sensitivity analysis (Figure 5).

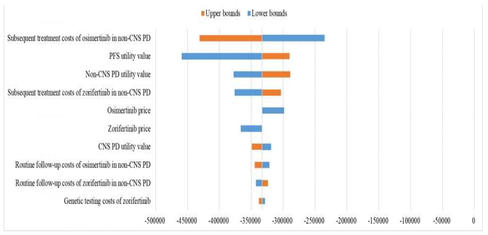
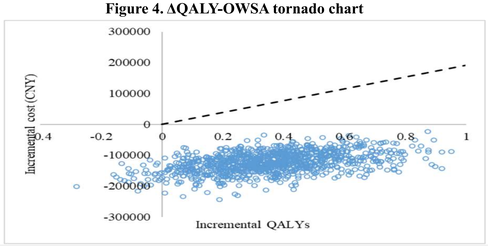


Figure 4. ΔQALY-OWSA tornado chart

Table 4. Base Case Results (discounted)

Outcomes	Zorifertinib	Osimertinib	Increment
Total costs (CNY)	281,173	393,610	**-112,437**
First-line treatment costs	106,184	114,090	-7,906
Routine follow-up costs	45,580	46,973	-1,394
AE management costs	386	15	370
Subsequent treatment costs	113,431	214,461	-101,030
Genetic testing costs	5,782	8,058	-2,276
Terminal care costs	9,811	10,013	-202
Total LYs	3.41	3.02	0.39
Total QALYs	2.83	2.49	**0.34**
ICER (CNY/QALY)		**dominant**	



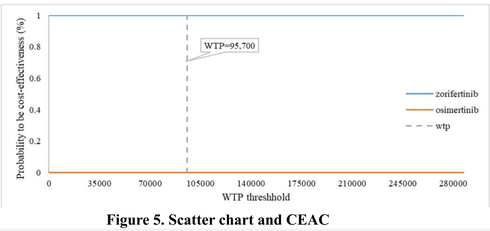


Figure 5. Scatter chart and CEAC

CONCLUSIONS

- From the perspective of the Chinese healthcare system, zorifertinib is a clinically effective and economically dominant first-line treatment option for newly diagnosed EGFRm+ NSCLC patients with CNS metastases.

References:

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[3] Tatineni V, O'Shea PJ, Ozair A, Khosla AA, Saxena S, Rauf Y, et al. First- versus Third-Generation EGFR Tyrosine Kinase Inhibitors in EGFR-Mutated Non-Small Cell Lung Cancer Patients with Brain Metastases. Cancers. 2023 Apr 20;15(8):2382.

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