Table S1 :PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 3-4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 4-5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	NA
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	NA
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 5 Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Page 6 Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 5 Table S3,S4
Results of	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its	NA

Section and Topic	Item #	Checklist item	Location where item is reported
individual studies		precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 7-8
	23b	Discuss any limitations of the evidence included in the review.	Page 8
	23c	Discuss any limitations of the review processes used.	Page 8
	23d	Discuss implications of the results for practice, policy, and future research.	Page 8
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	NA
Competing interests	26	Declare any competing interests of review authors.	NA
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Table S4

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Table S2: Search performed on 7 October 2024

Database	No	Search Query	Results
PubMed/ OVID-Medline	**#1**	((((((((((((((((((((("Costs and Cost Analyses"[Title/Abstract]) OR ("Costs, Cost Analysis"[Title/Abstract])) OR ("Cost, Cost Analysis"[Title/Abstract])) OR ("Cost Measures"[Title/Abstract])) OR ("Cost Measure"[Title/Abstract])) OR ("Measure, Cost"[Title/Abstract])) OR ("Measures, Cost"[Title/Abstract])) OR ("Cost"[Title/Abstract])) OR ("Costs"[Title/Abstract])) OR ("Pricing"[Title/Abstract])) OR ("Cost Comparison"[Title/Abstract])) OR ("Comparison, Cost"[Title/Abstract])) OR ("Comparisons, Cost"[Title/Abstract])) OR ("Cost Comparisons"[Title/Abstract])) OR ("Cost-Minimization Analysis"[Title/Abstract])) OR ("Analyses, Cost-Minimization"[Title/Abstract])) OR ("Analysis, Cost-Minimization"[Title/Abstract])) OR ("Cost-Minimization Analyses"[Title/Abstract])) OR ("Cost Minimization Analysis"[Title/Abstract])) OR ("Cost Analysis"[Title/Abstract])) OR ("Analysis, Cost"[Title/Abstract])) OR ("Analyses, Cost"[Title/Abstract])) OR ("Cost Analyses"[Title/Abstract])) OR ("Affordability"[Title/Abstract])) OR ("Affordabilities"[Title/Abstract])	7,92,972
	#2	(((((("Analysis, Cost-Effectiveness"[Title/Abstract]) OR ("Cost Effectiveness Analysis"[Title/Abstract])) OR ("Cost Effectiveness"[Title/Abstract])) OR ("Effectiveness, Cost"[Title/Abstract])) OR ("Cost Effectiveness Ratio"[Title/Abstract])) OR ("Cost Effectiveness Ratios"[Title/Abstract])) OR ("Effectiveness Ratio, Cost"[Title/Abstract])) OR ("Ratio, Cost Effectiveness"[Title/Abstract])	83,491
	#3	((((((((((((((((((((("Analysis, Cost-Benefit"[Title/Abstract]) OR ("Cost-Benefit Analyses"[Title/Abstract])) OR ("Cost Benefit Analysis"[Title/Abstract])) OR ("Analyses, Cost Benefit"[Title/Abstract])) OR ("Analysis, Cost Benefit"[Title/Abstract])) OR ("Cost Benefit Analyses"[Title/Abstract])) OR ("Cost Benefit"[Title/Abstract])) OR ("Cost and Benefit"[Title/Abstract])) OR ("Benefit and Cost"[Title/Abstract])) OR ("Benefits and Costs"[Title/Abstract])) OR ("Costs and Benefits"[Title/Abstract])) OR ("Cost-Benefit Data"[Title/Abstract])) OR ("Cost Benefit Data"[Title/Abstract])) OR ("Data, Cost-Benefit"[Title/Abstract])) OR ("Cost-Utility	42,020

		Analysis"[Title/Abstract])) OR ("Analysis, Cost-Utility"[Title/Abstract])) OR ("Cost-Utility Analyses"[Title/Abstract])) OR ("Cost Utility Analysis"[Title/Abstract])) OR ("Marginal Analysis"[Title/Abstract])) OR ("Analysis, Marginal"[Title/Abstract])) OR ("Marginal Analyses"[Title/Abstract])) OR ("Economic Evaluation"[Title/Abstract])) OR ("Economic Evaluations"[Title/Abstract])) OR ("Evaluation, Economic"[Title/Abstract])	
	#4	(((#1)) OR (#2)) OR (#3)	7,96,842
	#5	fruquintinib	143
	#6	((((((((((((Colorectal Neoplasm) OR (Neoplasm, Colorectal)) OR (Colorectal Tumors)) OR (Colorectal Tumor)) OR (Tumor, Colorectal)) OR (Tumors, Colorectal)) OR (Neoplasms, Colorectal)) OR (Colorectal Cancer)) OR (Cancer, Colorectal)) OR (Cancers, Colorectal)) OR (Colorectal Cancers)) OR (Colorectal Carcinoma)) OR (Carcinoma, Colorectal)) OR (Carcinomas, Colorectal)) OR (Colorectal Carcinomas)	3,15,894
	#7	((#4) AND (#5)) AND (#6)	8
EMBASE	**#1**	'economic evaluation'/exp OR 'economic evaluation' OR 'cost effectiveness analysis'/exp OR 'cost effectiveness analysis' OR 'cost utility analysis'/exp OR 'cost utility analysis'	**379,143**
	#2	'fruquintinib'/exp OR 'fruquintinib'	**443**
	#3	'colorectal cancer'/exp OR 'colorectal cancer'	**454,470**
	#4	**#1 AND #2 AND #3**	**24**
WOS advanced	**#1**	((ALL=(Economic Evaluation)) OR ALL=(Cost Effectiveness)) OR ALL=(Cost Utility)	**301,001**
	#2	ALL=(fruquintinib)	**259**
	#3	(ALL=(Colorectal Neoplasm)) OR ALL=(Colorectal Cancer)	**282,837**
	#4	#1 AND #2 AND #3	**7**
Scopus	**#1**	(TITLE-ABS-KEY ("economic evaluation ") OR TITLE-ABS-KEY ("cost effectiveness analysis") OR TITLE-ABS-KEY ("cost utility analysis"))	**203,107**
	#2	(TITLE-ABS-KEY ("colorectal cancer ") OR TITLE-ABS-KEY ("colorectal neoplasm"))	**248,267**
	#3	TITLE-ABS-KEY ("fruquintinib")	**308**

	#4	((TITLE-ABS-KEY ("economic evaluation ") OR TITLE-ABS-KEY ("cost effectiveness analysis") OR TITLE-ABS-KEY ("cost utility analysis"))) AND ((TITLE-ABS-KEY ("colorectal cancer ") OR TITLE-ABS-KEY ("colorectal neoplasm"))) AND (TITLE-ABS-KEY ("fruquintinib"))	**10**

Table S3: CHEQUE Tool for Quality Assessment

		Yao et al 2019		Peng et al 2020		Zhang et al 2020		Guan et al 2021		Obeng-Kusi et al 2023		Huang et al 2024		Cho et al 2024	
CHEQUE Tool	**Rounded Importance Score**	**Scoring Weight Assessment**	**Final Score**	**Scoring Weight Assessment**	**Final Score**	**Scoring Weight Assessment**	**Final Score**	**Scoring Weight Assessment**	**Final Score**	**Scoring Weight Assessment**	**Final Score**	**Scoring Weight Assessment**	**Final Score**	**Scoring Weight Assessment**	**Final Score**
Decision Problem and Scope															
M1. The analysis answers an important question for decision-making.	**5**	Yes	5	Yes	5	Yes	5	Yes	5	Yes	5	Yes	5	Yes	5
M2. The study objective (decision problem) is measurable.	**6**	Yes	6	Yes	6	Yes	6	Yes	6	Yes	6	Yes	6	Yes	6
Intervention and Comparator(s)															
M3. Comparator is the best possible option that appropriately measures the opportunity cost of using the new treatment.	**4**	Yes	4	Yes	4	Yes	4	Yes	4	Yes	4	Yes	4	Yes	4
Perspective															
M4. Analytic perspective is appropriate to answer the research question posed.	**4**	Yes	4	Yes	4	Yes	4	Yes	4	Yes	4	Yes	4	Yes	4
Population															
M5. The scope of the study encompasses all populations affected by the intervention.	**1**	Yes	1	Yes	1	Yes	1	Yes	1	Yes	1	Yes	1	Yes	1
Outcome Measures															

M6. Health outcomes are measured in health metrics that aggregate survival and healthrelated quality-of-life or disability (e.g., QALY or DALY).															
	3	Yes	3	Yes	3	Yes	3	Yes	3	Yes	3	Yes	3	Yes	3
Time Horizon															
M7. Time horizon is sufficient to reflect all important differences between intervention(s) and comparator(s), analytic time horizon	**4**	Yes	4	Yes	4	Yes	4	Yes	4	Yes	4	Yes	4	Yes	4
Discounting															
M8. Costs and health effects that occur in the future are discounted to their present value using a recommended discount rate.	**2**	Yes	2	Yes	2	Yes	2	Yes	2	Yes	2	Yes	2	Yes	2
Modeling	**30**		30		30		30		30		30		30		30
M9. The chosen model type is appropriate to address study questions.		Yes		Yes		Yes		Yes		Yes		Yes		Yes	
M10. Structure of the model reflects the underlying health condition and the impact of interventions.		Yes		Yes		Yes		Yes		Yes		Yes		Yes	
M11. Modeling assumptions are reasonable given the underlying data.		Yes		Yes		Yes		Yes		Yes		Yes		Yes	
M12. Need for extrapolation and/or need to integrate multiple data sources are considered.		Yes		Yes		Yes		Yes		Yes		Yes		Yes	
M13. Model validation - including an assessment of the model structure, assumptions, data, and results - is conducted.		Yes		Yes		Yes		Yes		Yes		Yes		Yes	

Data Inputs and Evidence Synthesis	**17**		17		17		17		17		17		17		17
M14. A "best available evidence" approach is used to select data sources for model parameters (e.g., conducted or references systematic reviews/metaanalysis).		Yes		Yes		Yes		Yes		Yes		Yes		Yes	
M15. Data inputs are generated by appropriate statistical and epidemiological techniques.		Yes		Yes		Yes		Yes		Yes		Yes		Yes	
M16. Quality of the data (e.g. sources of bias) are assessed appropriately.		Yes		Yes		Yes		Yes		Yes		Yes		Yes	
Consequences															
M17. Major consequences affected by the choice of interventions being compared are identified.	**5**	Yes	5	Yes	5	Yes	5	Yes	5	Yes	5	Yes	5	Yes	5
Utilities (Preference Measures)															
M18. Health preferences reflect those of the jurisdiction(s) of interest (as specified in the decision problem).	**2**	Yes	2	Yes	2	Yes	2	Yes	2	Yes	2	Yes	2	Yes	2
Costs and Resource Use															
M19. Resource use that is non-trivial in magnitude are included in the Reference Case analysis.	**2**	Yes	2	Yes	2	Yes	2	Yes	2	Yes	2	Yes	2	Yes	2
Analysis	**14**		14		14		14		14		14		14		14

M20. Incremental analyses are conducted (i.e., the additional costs generated by one alternative over another are compared to the additional effects generated).	Yes		Yes		Yes		Yes		Yes		Yes		Yes	
M21. ICERs are obtained by comparing each intervention to the next most effective option, after eliminating dominated options.	Yes		Yes		Yes		Yes		Yes		Yes		Yes	
M22. Probabilistic sensitivity analysis is conducted to account for uncertainty in input parameters simultaneously.	Yes		Yes		Yes		Yes		Yes		Yes		Yes	
M23. Alternative modeling choices and assumptions (structural uncertainty) are explored through additional sensitivity analysis (i.e., scenario analysis).	Yes		Yes		Yes		Yes		Yes		Yes		Yes	
Equity Considerations														
M24. Relevant equity or distributional considerations are taken into account.	Yes		Yes		Yes		Yes		Yes		Yes		Yes	
Total	**1**	**100**	1	**100**	1	**100**	1	**100**	1	**100**	1	**100**	1	**100**

Table S4: Economic Evaluation Methods and Outcomes in Fruquintinib Studies

Study, Year	Evaluation Framework	Analysis Perspective	Costs	Outcome (QALY)	Willingness to Pay (WTP)	Incremental Cost-Effective Ration	Insights
Yao et al, 2019(19)	CEA, Markov Model	Chinese Payer	Fruquintinib: $33536 Regorafenib: $35607	Fruquintinib:0.274, Regorafenib:0.246	$26508/QALY	NR	Fruquintinib is cost-effective

Peng et al,2020(18)	CEA, Markov Model	Chinese payers	Fruquintinib: $20,750.9 Placebo: $12,042.2	Fruquintinib:0.640 Placebo: 0.478	$27,130/QALY	$53508.7/QALY, ICER is 25% lower than the one calculated before the price drop ($70952.6/QALY).	Despite a price reduction for fruquintinib, its cost-effectiveness remains below the accepted threshold of three times the GDP in China, hence it's still considered not economically viable for treating metastatic colorectal cancer.
Zhang et al,2020(20)	CEA, Markov Model	Chinese societal	Fruquintinib+BSC:15,404.57, BSC: $9603.94	Fruquintinib+BSC:0.54 BSC: 0.38	$28,988.40/QALY	$36,253.94/QALY	Combining Fruquinitinib with BSC does not meet CEA
Guan et al, 2021(15)	CEA, Markov Model	Chinese healthcare system	Fruquintinib:CNY 151,058 ($22,888), Regorafenib CNY 226,657 ($34,342)	Fruquintinib:0.74 Regorafenib:0.75	CNY 212,676) ($ 32,224)/QALY	CNY 1529196.84/QALY ($231,676/QALY)	Fruquintinib is cost-effective
Kusi et al,2023(17)	CEA, Partitioned-Survival Model	NR	FRU: $355,796 Placebo: $278,877 ATE: $316,170 ATE+COB:342,976 REG: $353604 TAS: $334000 TAS+BEV: $417,495 TAS+BEV_Biosimilar: $405,002	FRU:0.62 PBO:0.44 ATE: 0.50 ATE+COB:0.57 REG:0.61 TAS:0.58 TAS+BEV:0.85 TAS+BEV Biosimilar:0.85	NR	FRU:352,422 ATE: $522,602 ATE+COB: $369,374 REG: $325,797 TAS: $290,850 TAS+BEV: $261,421 TAS+BEV Biosimilar: $237,860	In later-line treatments for metastatic colorectal cancer, TAS+BEV is the most economical option, whereas atezolizumab ranks as the least economical.
Huang et al,2024(16)	CEA, Partitioned-Survival Model	Chinese healthcare system	Fruquintinib: $11,089.05, Placebo: $ 5,374.48	Fruquintinib:0.61 QALY Placebo:0.43	$35,974.31 /QALY	$31,747.67/QALY	Fruquintinib is a viable treatment for refractory metastatic colorectal cancer, with its cost-effectiveness contingent on the specific willingness-to-pay threshold adopted
Cho et al,2024(14)	CEA, Markov Model	US payer	Redo: $86,694 TAS-BEV: $17,684,	ReDO:0.571,	NR	ReDO, resulting in an ICER of	ReDO was cost-effective

			FRUQ: $108,927	TAS-BEV:0.571, FRUQ:0.524		$790,988 per QALY	compared with TAS-BEV and FRUQ

Abbreviation:ATE: Atezolizumab, BEV: Bevacizumab, BSC: Best Supportive Care, CEA: Cost-Effectiveness Analysis, COB: Cobimetinib, FRU: Fruquintinib, ICER: Incremental Cost-Effectiveness Ratio, NR: Not Reported, PBO: Placebo, QALY: Quality Adjusted Life Year ReDO: Regorafenib Dose Optimization, REG: Regorafenib, TAS: TAS-102, TAS-BEV: Combination of TAS-102 and Bevacizumab, WTP: Willingness to Pay