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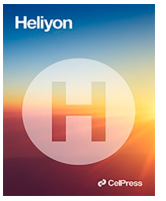

Research article

Efficacy and safety of selpercatinib in treating RET-altered MTC: A single-arm meta-analysis☆

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ABSTRACT

Background: Selpercatinib is effective in the treatment of RET-altered medullary thyroid carcinoma (MTC). This study aimed to evaluate the efficacy and safety of selpercatinib in the treatment of patients with RET-altered MTC.

Methods: PubMed, Embase, the Cochrane Library, and ClinicalTrials.gov were searched from their inception to April 5, 2024. Outcomes included complete response (CR), partial response (PR), stable disease (SD), objective response rate (ORR), disease control rate (DCR), and adverse events (AEs). We carried out a meta-analysis of these studies and exploratory subgroup analyses. The effect sizes for all pooled results were presented as 95% confidence intervals with upper and lower limits.

Results: The pooled CR, PR, and SD rates for all patients were 10%, 59%, and 26%, respectively. The pooled ORR in all patients was 70%, while the pooled ORR in pre-treated and non-pre-treated groups were 67% and 70%, respectively. The pooled DCR in all patients was 95%, while the pooled DCR in pre-treated and non-pre-treated groups were 96% and 95%, respectively. The most common AEs associated with selpercatinib were hypertension, alanine aminotransferase (ALT) increased and aspartate aminotransferase (AST) increased.

Conclusion: Selpercatinib offers significant benefits to patients with RET-altered MTC with assessable CR, PR, SD, ORR, and grade 3–4 AEs; however, treatment-related AEs should be considered.

1. Introduction

Medullary thyroid carcinoma (MTC) arises from the parafollicular C cells of the thyroid, accountings for only 5–10% of all thyroid cancers worldwide, however, despite its rarity, MTC is responsible for 8–13% of thyroid cancer-related deaths [[1,2]]. Approximately 75% of the patients have no family history of MTC, while the rest show a genetic form of the RET mutation [3]. RET mutations are the most common aberrations (37%), followed by fusion (31%) [4]. In MTC, RET mutations are present in more than 90% of hereditary cases and 40–50% of sporadic cases [[5]; 6]. RET fusions often occur in papillary thyroid carcinoma but are less frequent (<10%) [7].

☆ Systematic Review Registration: PROSPERO [https://www.crd.york.ac.uk/PROSPERO/], identifier [CRD42023449288].

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RET mutations are associated with more aggressive features and hence are present in the tumors of most patients with metastatic MTC.

The treatment criteria for recurrent or metastatic MTC include multi-kinase inhibitors (MKIs) that active against multiple kinases [[8,9]]. Among these, vandetanib and cabozantinib have been approved for MTC, while sorafenib and lenvatinib have been approved for radioiodine-refractory differentiated thyroid cancer (DTC) [10–13]. Although MKIs have been shown to be effective in the treatment of MTC, their safety and durability are limited by the toxic effects of non-RET kinase inhibition [14–16]. Selpercatinib is a novel, highly selective RET inhibitor that exerts antitumor activity by targeting RET with lower toxicity than cabozantinib and vandetanib [[10,15,17,18]], and has been approved for the treatment of metastatic RET-altered non-small-cell lung carcinoma or thyroid cancer [7,17,19,20].

To the best of our knowledge, no systematic analyses have been reported on the use of selpercatinib for the treatment of RET-altered MTC. Our study aimed to elucidate the efficacy and safety of selpercatinib in treating RET-altered MTC to obtain greater statistical power for assessing treatment efficacy.

2. Materials and methods

2.1. Protocol and registration

Our protocol was registered with PROSPERO (registration number: CRD42023449288). The checklist, adhering to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement [21], was provided elsewhere (Supplementary Table S1).

2.2. Search strategy

We searched PubMed, Embase, the Cochrane Library, and ClinicalTrials.gov from inception to April 5, 2024. The medical subject headings used were “Selpercatinib,” “Thyroid neoplasms,” and “RET” (Supplementary Table S2). The references of literature reviews and original articles were also scanned to avoid missing any qualified studies.

2.3. Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) patients confirmed to have RET-altered MTC; (2) patients treated with selpercatinib; and (3) studies reporting efficacy and safety endpoints. The exclusion criteria were as follows: (1) article type: case report, review, conference abstract, or cell or animal study; and (2) sample size of less than 10 patients.

2.4. Quality assessment

Two single-arm studies were ultimately included based on the inclusion and exclusion criteria, and evaluated using the methodological index for non-randomized studies [22].

3. Outcomes

The primary endpoints were efficacy according to RECIST criteria, version 1.1 and safety (adverse events (AEs)) according to the CTCAE, version 4.0. Our primary outcome included complete response (CR) was defined as disappearance of all target lesions and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to $<$10 mm. Partial response (PR) was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study. Objective response rate (ORR) was defined as the proportion of patients with a best objective response of CR or PR. Disease control rate (DCR) was defined as the proportion of patients with CR, PR, or SD.

3.1. Data extraction

Two investigators independently conducted the study selection process. In cases of any discrepancies, the third author facilitated a discussion to reach a consensus. The authors, study type, sample size, tumor response [CR, PR, SD, ORR, and DCR], and AEs were recorded.

3.2. Statistical analysis

We divided the efficacy indicators into two subgroups (pre-treated versus non-pre-treated RET-mutant MTC), according to whether they had previously received treatment. R version 4.3.0 was employed to analyze the pooled CR, PR, SD, ORR, and DCR. Heterogeneity between studies was examined using the Cochrane Q chi-square test and I^2 statistic. The fixed-effects model was employed when $I^2 \leq 50\%$; conversely, the random-effects model was utilized when $I^2 > 50\%$. Since the total number of articles included in this study was less than 10, no publication bias test was performed. Effect sizes are presented as 95% confidence intervals (CIs). Statistical significance was set at $P < 0.05$.

4. Results

We included two prospective studies from 403 initially identified studies [[7,23]] (Fig. 1.).
The characteristics of this study are shown in Table 1, and an evaluation of the literature quality is shown in Table 2.

4.1. Tumor response

We extracted efficacy indicators and categorized them into two subgroups (pre-treated versus non-pre-treated RET-mutant MTC), according to prior treatment status (Table 3).

The pooled CR rates for pre-treated and non-pre-treated patients were 9% (2%–16%) and 10% (4%–16%), respectively. The overall pooled CR rate for all patients was 10% (5%–14%) (Fig. 2A).

The pooled PR rates for pre-treated and non-pre-treated patients was 58% (46%–70%) and 60% (51%–69%), respectively. The overall pooled PR rate for all patients was 59% (52%–67%) (Fig. 2B).

The pooled SD rates for pre-treated and non-pre-treated patients was 29% (15%–43%) and 24% (16%–33%), respectively. The overall pooled SD rate for all patients was 26% (19%–32%) (Fig. 2C).

The pooled ORR rates for pre-treated and non-pre-treated patients were 67% (56%–79%) and 70% (59%–81%), respectively. The overall pooled ORR rate for all patients was 70% (63%–76%) (Fig. 2D).

The pooled DCR rates for pre-treated and non-pre-treated patients were 96% (90%–100%) and 95% (91%–99%), respectively. The overall pooled DCR rate for all patients was 95% (92%–99%) (Fig. 2E).

5. Safety

All patients encountered AEs, with most manageable through dose adjustment. The most common AEs observed were hypertension, and increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (Table 4).

Publication Bias: Funnel plots can't be used for reviews of fewer than 10 studies.

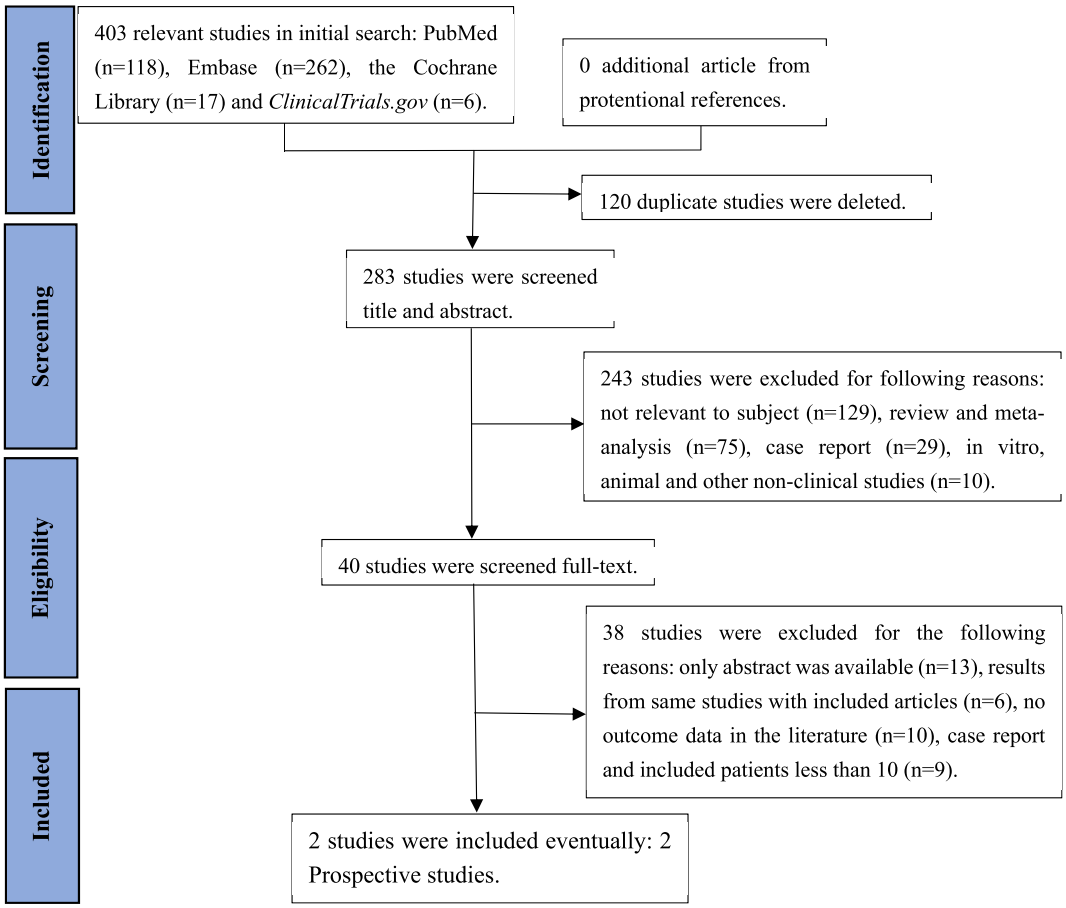


Fig. 1. Flowchart of the studies' selection process.

Table 1
Characteristic of included studies.

Characteristic	Study	
	LIBRETTO-001	LIBRETTO-321
Country	12 countries	China
Study design	open-label, phase I/II	open-label, phase II
Recruitment	May 2017 to June 2019,	March 2020 to March 2021
Number of patients	143	26
Gender, male/ female	94/49	20/6
Key eligibility criteria	Age ≥12 years or ≥18 years RET-mutant medullary thyroid cancer or RET fusion–positive thyroid cancer of any histologic type. An Eastern Cooperative Oncology Group performance-status score of 0–2 Adequate organ function A QT interval corrected for heart rate of 470 msec or less.	Age ≥18 years Confirmed an advanced tumor harboring an RET alteration An Eastern Cooperative Oncology Group performance status of 0–2 Adequate organ function A life expectancy of >3 months.
Primary endpoint	CR PR	ORR
Criteria for response	RECIST version 1.1	RECIST version 1.1

RET: Rearranged during Transfection; CR: complete response; PR: partial response; ORR: objective response rate; RECIST: the Response Evaluation Criteria in Solid Tumors.

Table 2
Quality assessment of included studies.

MINORS index for included non-randomized studies.									
Study	I	II	III	IV	V	VI	VII	VIII	Total
Wirth et al. (2020)	2	2	2	2	2	2	2	2	16
Zheng et al. (2022)	2	2	2	2	2	2	2	2	16

MINORS: Methodological index for non-randomized studies.

Table 3
Efficacy measurement in each study.

Study	No.	CR N (%)	PR N (%)	SD N (%)	PD N (%)	NE N (%)
Pre-treated						
Wirth et al. (2020)	55	5 (9.1)	33 (60.0)	14 (25.5)	1 (1.8)	2 (3.6)
Zheng et al. (2022)	9	1 (11.1)	4 (44.4)	4 (44.4)	0 (0.0)	0 (0.0)
Not Pre-treated						
Wirth et al. (2020)	88	10 (11.4)	54 (61.3)	20 (22.7)	2 (2.3)	2 (2.3)
Zheng et al. (2022)	17	1 (2.1)	9 (52.9)	6 (35.3)	0 (0.0)	1 (5.9)

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NE: not evaluable.

6. Discussion

The incidence of RET mutations in patients with MTC is particularly high [[5,6]], RET mutations are present in almost all patients with hereditary MTC and approximately 60% of sporadic MTC cases [24]. Both vandetinib and cabozantinib have been approved for treating metastatic MTC [[10,11]]. With cabozantinib treatment, the objective response (OR) was 28% with a median progress-free survival (mPFS) of 11.2 months. The OR was 45%, and the mPFS was 30.5 months after treatment with vandetinib. Although both agents proved effective in improving patients' outcomes, AEs led to a 35% dose reduction and 12% permanent discontinuation among patients receiving vandetinib, compared to 79% dose reduction and 16% permanent discontinuation among those receiving cabozantinib. Selpercatinib is a highly selective RET inhibitor that radically alters the therapy for patients with MTC [25]. Our study aimed to assess the efficacy and safety of selpercatinib in the treatment of patients with RET-altered MTC.

LIBRETTO-001 is a phase I/II study of selpercatinib-treated patients with RET-mutant (ClinicalTrials.gov number, NCT03157128) [7]. Patients who had previously received therapy had a response rate of 69% and a 1-year PFS rate of 82%. Patients who had not previously received therapy had a response rate of 73% and a 1-year PFS rate of 92%. This clinical trial demonstrated that selpercatinib exhibited significant antitumor activity in patients with RET-mutated MTC, with and without previous treatment.

LIBRETTO-321 is a phase II study designed to assess the efficacy and safety of selpercatinib in Chinese patients with RET-altered solid tumors (ClinicalTrials.gov number, NCT04280081) [23]. In the RET-altered MTC group (n = 26), the ORR was 57.7%. Within subgroups, the ORR was 55.6% in the pre-treated group and 58.8% in the treatment-naïve group. These findings suggest that selpercatinib exerts significant antitumor activity in Chinese patients with RET-altered MTC.

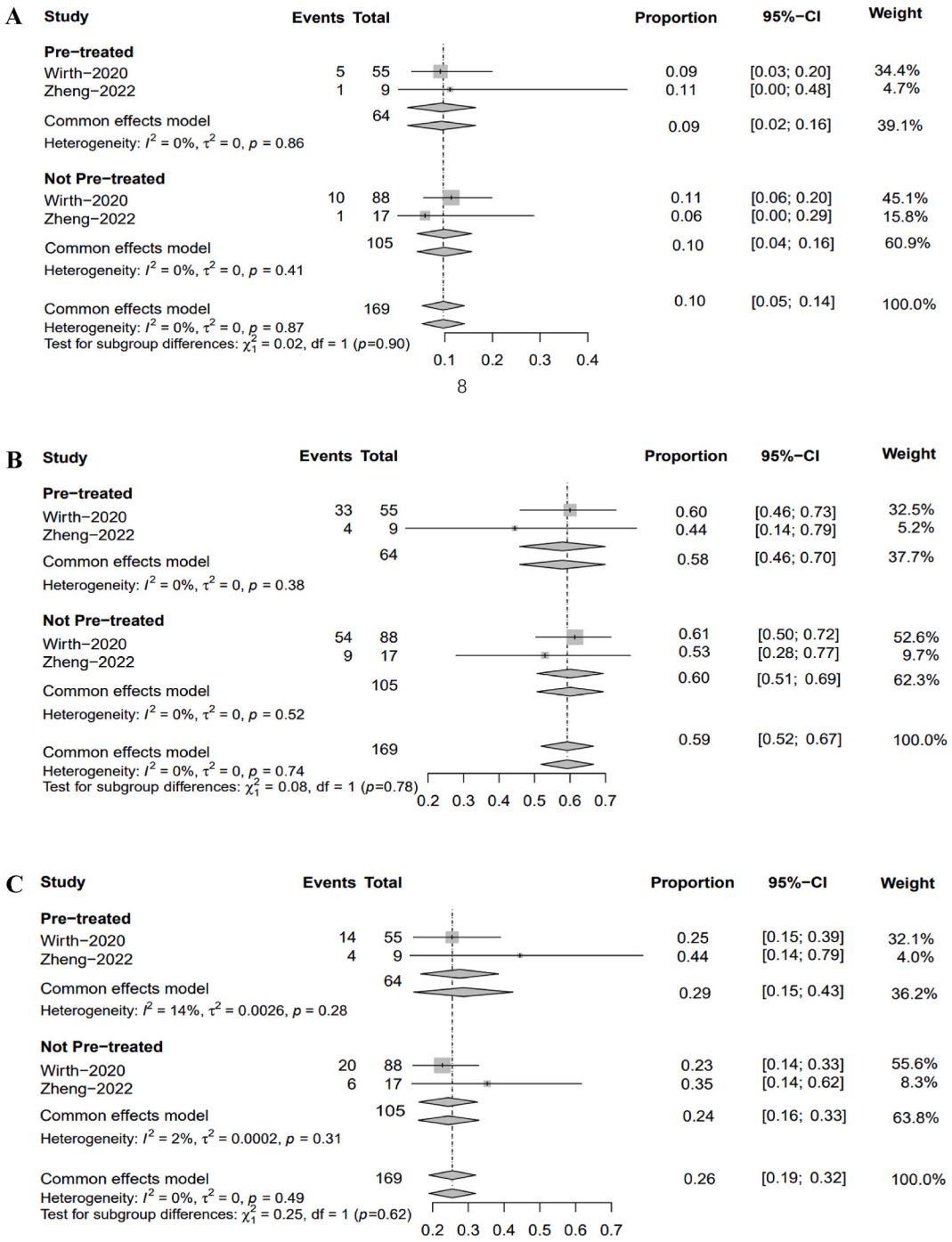
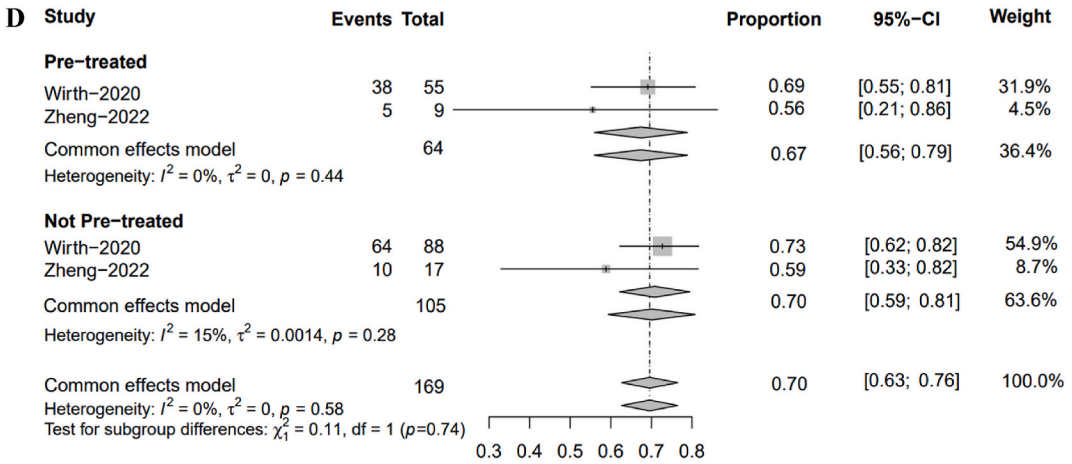


Fig. 2. Pooled results of tumor response by subgroup. (A) Pooled results of CR by subgroup. (B) Pooled results of PR by subgroup. (C) Pooled results of SD by subgroup. (D) Pooled results of ORR by subgroup. (E) Pooled results of DCR by subgroup.

Our study revealed that the pooled CR, PR, SD, ORR, and DCR in all patients were 10%, 59%, 26%, 70%, and 95%, respectively, demonstrating that selpercatinib had robust antitumor activity in patients with RET-altered MTC with or without previous therapy. Moreover, selpercatinib had better anti-tumor activity than vandetinib (45%) and cabozantinib (28%) [[10,11]]. Therefore, effective molecular screening of patients with MTC is essential to identify those who may benefit from RET inhibition.

All patients experienced AEs, the most common of which were hypertension, and ALT and AST increased. The observed AEs were similar to those reported for other MKIs previously [25]; additionally, some new AEs, such as hypertension, diarrhea, and fatigue, were



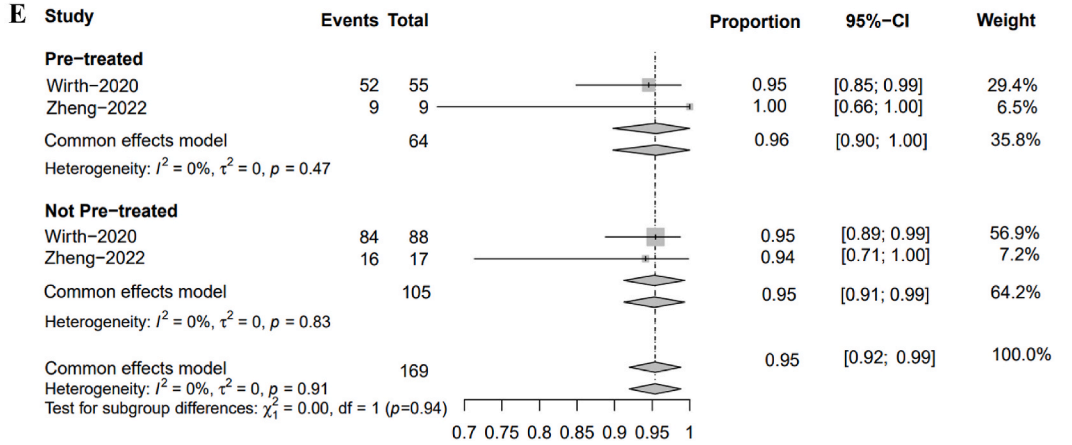


Fig. 2. (*continued*).

Table 4
Safety measurements in each study.

Variable	Study	
	LIBRETTO-001	LIBRETTO-321
Grade 3 or 4 AEs		
Hypertension (%)	21%	15%
ALT increased (%)	11%	12%
AST increased (%)	9%	12%
Diarrhea (%)	6%	1%
Hyponatremia (%)	5%	2%
Abdominal pain (%)	3%	–
Thrombocytopenia*	–	8%
Weight increased (%)	3%	0
Grade 5 AEs	3%	0

AEs: adverse events; ALT: alanine aminotransferase; AST: aspartate aminotransferase; Grade 5 AEs: such as hemoptysis, post-procedure hemorrhage, sepsis, cardiac arrest, and cardiac failure.

also noted [26]. Effusion, particularly chyle, which was also reported by Prete et al., is a novel AE that can be treated with selpercatinib [27]. In the LIBRETTO-001 and the LIBRETTO-321 trials, 30.0% and 32.5% of patients were subjected to dosage reductions, and 2.0% and 3.9% of patients had to discontinue therapy owing to AEs, respectively, but most AEs were manageable, which suggests that the safety profile of selpercatinib is acceptable, and the mechanism may be related to the high selectivity for RET [[7,23]]. Therefore, the careful management and continuous monitoring of this disease are essential.

Selpercatinib effectively controls the progression of thyroid cancer and prolongs patient survival through precise targeting, thereby providing a new direction for the treatment of advanced or refractory thyroid cancer. Although selpercatinib has shown significant

efficacy, we must to be concerned about its safety and potential adverse effects. Therefore, doctors must closely monitor and manage to achieve optimal treatment results.

This study had certain limitations. First, selpercatinib had limited randomized controlled trials on RET-altered MTC owing to reasons such as ethical issues. Consequently, the studies included were observational studies without a control group. Second, the included studies used different doses of selpercatinib, which inevitably caused bias. Finally, although heterogeneity was high, performing a sensitivity analysis was not feasible because of the small number of entries.

7. Conclusion

Selpercatinib is a valuable treatment for patients with RET-altered MTC with assessable CR, PR, SD, ORR, and grade 3–4 AEs; nonetheless, treatment-related AEs should be considered.

Ethics statement: Review and/or approval by an ethics committee was not needed for this study because this Meta-analysis data came from published articles.

Data availability statement

Data included in article/suppmaterial/referenced in article.

CRediT authorship contribution statement

Dongmei Huang: Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Jinming Zhang:** Software, Methodology, Formal analysis, Data curation. **Xiangqian Zheng:** Writing – review & editing, Validation, Supervision, Investigation, Funding acquisition, Conceptualization. **Ming Gao:** Writing – review & editing, Visualization, Validation, Supervision, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e31681.

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