Efficacy and Safety of targeted therapy Inhibitors for RET-driven Solid Cancer: A Systematic Review and Meta-analysis

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Abstract

Advanced and metastatic RET-driven solid cancer is not susceptible to chemotherapy or radiotherapy. The development of targeted therapy has led to a new therapeutic model. Nevertheless, no systematic evaluation of their efficacy and safety has been carried out in RET-driven solid cancer. Systematic review and single-arm meta-analysis were performed. Four electronic databases were searched (PubMed, Embase, Cochrane Library, and Web of Science) from each database's inception date until February 27, 2022. Study inclusion criteria focused on peer-reviewed published articles that reported the efficacy and safety of targeted therapy Inhibitors for RET-driven Solid Cancer, excluding case reports/series, review papers, meta-analyses, organizational guidelines, editorial letters, expert opinions, and conference abstracts. 15 randomized, locally advanced or metastatic RET-driven solid cancer assays (n=1835) were included. Previously untreated with RET-Specific Tyrosine Kinase Inhibitors(TKI) group showed the highest objective remission rate(ORR) (0.75,95%CI=0.68-0.82) or disease control rate(DCR) (0.96,95%CI=0.92-0.99), and lower dose reduction(34.8%) or discontinuation(3.4%), but the performance of general adverse reactions (Grade1-5 96.8%, Grade3-5 69.2%) were not as good as Multi-Target Tyrosine Kinase Inhibitors (MKI) group, followed by previously treated/untreated with MKI/TKI group (MIX group). Targeted therapy inhibitors have significant efficacy in RET-driven solid cancer therapy. The ORR, DCR parameters and adverse reaction of TKI are better than those of MKI. It was also related to the patient's previous treatment status. The ORR/DCR of the patients who received no targeted therapy was superior to those who received Vandetanib or Cabozantinib as first-line therapy.

Review Article

Title Page: 21 Title: Efficacy and Safety of targeted therapy Inhibitors for RET-driven Solid Cancer: A Systematic Review and Meta-analysis Authors' names: Guoli Li,Yufan Chen,Keyang Wei,Honghao Deng,Yanfeng Chen. Authors' affiliations: Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, CHINA. Corresponding author: Yanfeng Chen, 651 Dongfeng East Rd, Guangzhou 510060, P.R. China(Sun Yat-sen University Cancer Center).*chenyf@sysucc.org.cn.* +86-20-87343303. Keywords: RET-driven Solid Cancer,Multikinase inhibitors,Tyrosine kinase inhibitors,Targeted therapy, Meta-analysis Word count:4525 Number of Figures: 4 Number of Tables: 2 Number of Supporting Information: 4

Abstract

Advanced and metastatic RET-driven solid cancer is not susceptible to chemotherapy or radiotherapy. The development of targeted therapy has led to a new therapeutic model. Nevertheless, no systematic evaluation of their efficacy and safety has been carried out in RET-driven solid cancer. Systematic review and single-arm meta-analysis were performed. Four electronic databases were searched (PubMed, Embase, Cochrane Library, and Web of Science) from each database's inception date until February 27, 2022. Study inclusion criteria focused on peer-reviewed published articles that reported the efficacy and safety of targeted therapy Inhibitors for RET-driven Solid Cancer, excluding case reports/series, review papers, meta-analyses, organizational guidelines, editorial letters, expert opinions, and conference abstracts. 15 ran-

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Text :Introduction

RET mutations or fusions are carcinogenic to multiple tumor types. The medullary thyroid carcinoma with point mutations, small deletions, and/or RET insertions has been reported in 50% sporadic MTC and 100% familial MTC comprising the MEN2 syndrome germline[1]. The most commonly reported mutation is M918T[2]. RET rearrangements occur in up to 10%-20% of PTC and 1-2% of patients with unselected NSCLCs, particularly in younger, non-smoking patients with adenocarcinoma histology[3]. It is rare in ovarian epithelial cancer, pancreatic cancer, breast cancer, colorectal cancer, and bile duct cancer [4-6]. Patients with locally advanced or metastatic MTC are hard to cure, and chemotherapy and radiation therapy have been largely ineffective. Therefore, the ability to substantially prolong the time for disease progression will benefit such patients. Mutations in the RET proto-oncogene are central to the development of MTC in virtually all patients with hereditary MTC and approximately half of the patients with sporadic MTC. Various chemotherapeutic regimens are inappropriate in MTC therapy due to the results of several studies[7, 8]. Outcomes with immunotherapies in patients with RET fusion-positive NSCLC are poor[9-11]. Standard therapies provide limited benefit for patients with RET fusion-positive tumors[12-16]. In recent years, selective RET inhibitors have been developed to achieve higher potency and less toxicity. Several multikinase inhibitors and RET-specific inhibitors with activity against RET have been explored in clinical practice. The superior efficacy of targeted therapy with these agents has been observed in patients with RET rearranged lung cancers or RET mutant thyroid cancers[17, 18]. RET-driven solid cancer has been hitherto studied with multikinase inhibitors (MKI) having anti-RET activities, but they inhibit other kinase targets more potently and show limited clinical benefits. The lack of target specificity and increased side effects responsible for dose reduction and drug discontinuation are critical limitations of MKIs in practice[19]. Therefore, the appropriate use of the inhibitors is the challenge of RET-driven cancer therapy.

Recent selective RET inhibitors, selpercatinib and pralsetinib, show promising activities, improved response rates, and more favorable toxicity profiles in early clinical trials, which open up new options for treatment. MKIs cabozantinib, vandetanib, lenvatinib, and RXDX-105 have been evaluated in phase II studies in RET-rearranged NSCLC patients who received chemotherapy[20-24]. These drugs showed modest clinical activities with ORR, median progression-free survival (mPFS), and median overall survival (mOS) ranging from 16%-47%, 4.5-7.3 months, and 9.9-11.6 months respectively. These results are better than those observed with single-drug chemotherapy administered in unselected(RET unknow) patients with advanced NSCLC after failure from initial platinum-based doublet therapy[25]. Cabozantinib and vandetanib are approved for first-line treatment in MTC based on the results of EXAM[26, 27] and ZETA[28] trials; although the drug approval was independent from RET alteration status. In the EXAM trial, cabozantinib increased the ORR (28% vs. 0%; $P < 0.001$) and mPFS compared with placebo (11.2 vs 4.0months; HR=0.28;95%CI=0.19–0.40; P<0.001) with a nonsignificant increase in overall survival (OS=26.6vs21.1 months; HR=0.98; 95%CI=0.63-1.52). ZETA[28] trial demonstrated that vandetanib prolonged the mPFS compared with placebo (30.5 vs19.3 months; $P = 0.001$) and also demonstrated a statistically significant improvement in ORR (45% vs13%; $P < 0.001$). Other MKIs with anti-RET activities like sorafenib, lenvatinib, sunitinib, dovitinib, and motesanib have also been tested in phase II clinical trials in MTC[29-33]. Regardless of the RET alteration status in the global population, ORR and mPFS ranged from 2% to 36% and 5.4 to 17.9 months. Some of these studies did perform post hoc RET subgroup analyses, but no significant correlation with tumor response was found

in these subgroups of patients[29, 30, 33].

In conclusion, cabozantinib and vandetanib seem to give better results for some specific RET+ cases in thyroid cancer, but this hypothesis needs to be verified in prospective trials in RET+ selected patients. It is also noteworthy that the side effects recorded with these drugs are not negligible and are similar to NSCLC trials. The treatment discontinuation rate was 12% with vandetanib and 16% with cabozantinib, while 35% treated with vandetanib and 79% treated with cabozantinib required dose reduction because of adverse events. The limited activities and increased toxicities of MKIs in RET-driven solid cancer, responsible for dose reduction or treatment discontinuation, are partly explained by their off-target activities. New generation RET inhibitors are being designed both to overcome the acquired resistances and inhibit RET more potently and selectively. Selpercatinib and pralsetinib might solve off-target toxicity problems as they more potently and selectively inhibit both wild-type RET and RET-driven cancer cell lines in biochemical assays [19]. These data formed the basis for the first-inhuman phase I/II trial of these drugs in RET+ tumors. The present meta-analysis investigates the efficacy and safety of Tyrosine kinase inhibitors in the treatment of RET-driven solid cancer patients by systematically analyzing the ORR, DCR, and adverse, providing a reference for clinicians to make the best choice in clinical practice.

Methods

A single arm meta-analysis was conducted, and the English-language literature published from PubMed, Embase, Cochrane Library, and Web of Science before February 27 2022 were systematically retrieved. Quality assessment is carried out in accordance with a 12 items checklist form prepared by the Methodological Index for Nonrandomized Studies (MINORS). To stabilize the variance of the original ratio, a Freeman-tukey double arcsine conversion transformation is carried out. In the case of I2$>$ 50%, the random effect model is used to calculate the pooled parameters; otherwise, the fixed effect model will be used. Subgroup analysis was performed according to prior treatment and medication.

Data sources and searches

We searched the PubMed, Embase, Cochrane Library, and Web of Science databases to include relevant studies published in English from their inception to February 27, 2022. Search terms and their combinations used in the search strategy included proto-oncogene proteins c-ret, neoplasms, cancer, carcinoma, multikinase inhibitors, tyrosine kinase inhibitor and specific targeted therapy drugs names (Vandetanib, Cabozantinib, Sunitinib, LOXO-292, BLU-667). Details of the search strategy are provided in the Supplementary Materials (Doc.S1). After screening titles or abstracts in advance, two independent reviewers (L-GL and W-KY) assessed the full text and reference lists of relevant publications for final inclusion; articles cited as references that were deemed potentially relevant were also retrieved and evaluated in their entirety. Any disagreements were resolved by discussion with a third investigator (C-YF).

Study selection

Only randomized controlled trials with locally advanced or metastatic RET-driven solid cancer or single arm trials including a targeted therapy drug (i.e., one targeted therapy medication, two targeted therapy medications, and one targeted treatment medication with conventional therapy) were eligible for enrollment. Studies that is prospective or retrospective cross-sectional cohort studies and case-control studies were excluded. We excluded abstracts, posters, and presentations of ongoing randomized controlled trials from conferences because these brief reports lacked detailed data.

Data extraction

We evaluated the main text, supplementary materials, and all possible information available at ClinicalTrials.gov to implement an extensive and detailed data extraction. If both original and updated studies derived from one trial were included in this meta-analysis, we extracted treatment-related data from the study with the most detailed report; the remained data were used to supplement basic information. Data extraction and summarization were performed independently using a standardized form by two reviewers (L-GL and W-KY): first author, year of publication, study ID, cancer type, study design, total patient number, tumor

response parameters, treatment regimens, adverse events.Clinical responses included objective response rate (ORR), disease control rate (DCR), and adverse events. All adverse reactions are classified into grades 1–5 and 3–5, including dose reduction and discontinuation.

Quality assessment

Risk of bias was assessed by two reviewers (L-GL and W-KY) based on the original study, the possible updated study, and the supplementary materials using the tool recommended by the Cochrane Collaboration Manual. The methodological quality of the included studies was assessed using the Methodological Index for Nonrandomized Studies (MINORS)[9], which is a valid tool for assessing the quality of both randomized controlled trials and nonrandomized studies. The highest score of MINORS was 24. Any disagreements regarding study selection, data extraction, and quality assessment were resolved through discussion to reach consensus.

Statistical analysis

This article uses the R language for data analysis. See Doc.S2 for code. For the original data that do not conform to the normal distribution, Freeman-tukey double arcsine conversion is performed to stabilize the variance of the original ratio. Heterogeneity assessment included chi-square test and I2 value. $P < 0.1$ indicated a statistically significant difference. For I2 values above 50%, the combined proportion and 95% confidence interval are calculated by the random effects model. Otherwise, a fixed effect model is used. Considering the limited statistical efficiency of the chi-square test and the limited number of studies included in our research, P value of 0.10 was adopted as the significance level rather than the conventional level of 0.05 to increase the test efficiency. Potential sources of heterogeneity were investigated by subgroup.

Results

Study identification

Fig.1 shows a flowchart of the study selection procedure. A total of 1351 potentially relevant studies were identified through electronic searches, with 256 potentially eligible articles evaluated. A total of 1095 studies remained after exclusion of repetitive trials. After screening the titles and abstracts, we excluded 893 irrelevant studies. 251 studies that could not extract RET detailed data were eliminated by reading the full text (*Fig.1*). Finally, a total of 15 studies involving 1180 patients with RET-driven solid cancer were finally included in this meta-analysis.

Systematic review and characteristics

Patient characteristics and quality assessment

All 15 eligible studies were selected, including 13 single-arm trials and 2 phase III clinical trials. All patients had advanced or metastasis RET-driven solid cancer were treated with MKIs or Selective RET inhibitor drugs. As shown in Table.S1, all of the studies included scored 14 or higher on quality assessments. Details of all studies and the characteristics of the patients with advanced RET-driven thyroid cancer and non-small cell lung cancer are shown in Table.S2. Table.S2 shows the baseline characteristics of the 15 studies (13single-arm trials and 2 randomised controlled trials). The15 trials (n=1835) evaluating 8 treatments with different drugs (Sorafenib 400mg BID;Vandetanib 100/300mg QD;Cabozantinib 140mgQD;Sunitinib;Lenvatinib 24mgQD;Alectinib 450 mg BID;LOXO-292 160mg BID;BLU-667 400mg QD) were included in the single-arm meta-analysis.

Therapeutic efficacy assessments

ORR

The pooled objective remission rate (ORR) of RET-driven positive thyroid cancer and non-small cell lung cancer treated by MKI and TKI was 0.45 (95%CI = 0.33-0.58), with high inter-study heterogeneity (I2 = 88%, p¡0.01) (*Fig.2A*). Based on the previous treatment, ORR of previous untreated group was the highest (0.65, 95%CI = 0.40-0.86) and the heterogeneity level was high (I2 = 80.0%, p¡0.01), ORR of mix group

was the lowest (0.30, 95%CI = 0.17–0.44) and the heterogeneity was still high (I2 = 78.0%, p¡0.01), ORR of previous treated group was 0.63(95%CI = 0.58-0.69) and the heterogeneity level was low (I2 = 0.0%, p = 0.74) (*Fig.2A*). After the exclusion of a study of Lam2010 and 2 studies of TKI in mix group, the pooled ORR was recalculated to 0.75(95%CI = 0.68-0.82, I2 = 0%, p = 0.43) of previous untreated group and 0.22(95%CI = 0.13-0.31, I2 = 48.0%, p = 0.04) of mix group, indicating a significant decrease in heterogeneity. According to MKI and TKI grouping, ORR of MKI group was the lowest (0.21, 95%CI = 0.13-0.29) and the heterogeneity level was low (I2 = 44.0%, p = 0.06), ORR of TKI group was the highest (0.68, 95%CI = 0.64-0.73) and the heterogeneity was low (I2 = 24.0%, p = 0.22) (*Fig.2B*).

DCR

A total of 21 subgroups included DCR parameters, with a pooled value of 0.89 (95%CI = 0.81-0.94, I2 = 77.0%, p¡ 0.01) (*Fig.2C*). DCR of age groups were similar to ORR, the MKI group (0.81, 95%CI = 065-0.92) was lower than that TKI group (0.94, 95%CI = 0.92-0.96, I2 = 10.0%, p= 0.35). DCR was highest in the previous untreated group (0.96, 95%CI = 0.92-0.99, I2 = 23.0%, p= 0.27), followed by the previous treated group (0.92, 95%CI = 0.89-0.95, I2 = 0.0%, p= 0.91) and the mix group (0.81, 95%CI = 0.67-0.92, I2 = 81.0%, p¡0.01) (*Fig.2D*).

mPFS and mOS

Due to the lack of mPFS and mOS data, this paper selects the representative research description. In the EXAM trial, cabozantinib increased the ORR(28% vs. 0%; P<0.001) and mPFS compared with placebo (11.2 vs 4.0 months; HR=0.28; 95%CI=0.19–0.40; P<0.001) with a nonsignificant increase in over all survival (OS=26.6 vs 21.1 months; HR=0.98; 95%CI=0.63-1.52). ZETA trial demonstrated that vandetanib prolonged the mPFS compared with placebo (30.5vs19.3months;P=0.001) and also demonstrated a statistically significant improvement in ORR (45%vs13%; P<0.001). However, relevant data of mPFS and mOS have not been reported in the study of TKI including LIBRETTO-001 (NCT03157128) and ARROW trial (NCT03037385), and follow-up data are required(Table.S1).

Adverse events

Additionally, this study evaluated the incidence of adverse events in RET-driven solid cancer patients treated with MKI and TKI, with all adverse events classified as grade 1-5 or grade 3-5 AE. The number of studies included in the subgroup analysis was 12-15 (593 to 1835 patients) based on grade 1-5 adverse events and dose reduction or discontinuation. Calculated by weighted average method, the incidence of grade 1-5 adverse events in MKI group was 94.8%, grade 3-5 was 35.9%, 55.7% drug reduction and 14.3% drug withdrawal due to adverse events. In the TKI group, the incidence of grade 1-5 adverse events was 96.8%, grade 3-5 was 69.2%. Moreover, the dose reduction was 34.8% and the drug withdrawal was 3.4% because of adverse effects. Integrated evidence implied that the incidence of general adverse events was slightly higher in the TKI group than in the MKI group, but the incidence of drug reduction and withdrawal due to adverse events was significantly lower in the TKI group than in the MKI group (*Table.1*).

Assessment of reporting biases

We create a funnel plot to assess possible publication bias or small-study effects. The symmetrical distribution of funnel plot may have publication bias. Based on Peters test, P = 0.0193 < 0.1 indicates publication bias. We further analyzed whether publication bias would affect the results of the comprehensive effect size with the shear-complement method. From the results of the analysis, the raw data still have some deviation. At this point, K =27, six hollow circles were added to the right side of the funnel plot after the shear-complement method analysis, representing the effect size added. A new comprehensive effect size of 0.6028 (95%CI=0.4544-0.7428) was obtained after the algorithm was automatically completed. The significance of P < 0.0001 was unchanged from that before the shear-complement method. Therefore, it can be shown that the comprehensive effect size is not affected by publication bias to a certain extent (*Fig.3A/B*).

subgroup analysis

A subgroup analysis was performed to explore the sources of heterogeneity in MKI or TKI and patient previous treatment. The heterogeneity of the TKI group was significantly reduced (I^2 = 24, p=0.22). TKI group showed higher ORR or DCR and lower dose reduction or discontinuation, but the performance of general adverse reactions were not as good as MKI group. Previous treatment subgroup analysis showed that the heterogeneity of ORR and DCR in previous untreated with TKI group was significantly reduced. The ORR and DCR of the previous untreated with TKI group were optimal, followed by mix group (In fact, almost all of the PATIENTS in the MIX group were previously treated), at while the previous treated with MKI group were performed the worst. Results of the subgroup analysis are depicted in *Table.2*.

Sensitivity analysis

We conducted sensitivity analyses to confirm the robustness of analysis results when appropriate. If sufficient studies were eligible for the analysis, we would select studies with low risk of bias for the majority of risk of bias domains. We also performed sensitivity analysis on the primary outcomes by utilising a random-effects model and comparing results to our default fixed-effect model. Through sensitivity analysis, we found that the significance of the combined effect size did not change significantly when the included studies were removed one by one, indicating that there was no extreme phenomenon in the included studies (*Fig.4*).

Discussion

Our meta-analysis showed that objective response rates and disease control rates were better in patients of previous untreated patients received TKI, but grage1-5 adverse reactions were not as good as MKI group. A variety of multikinase inhibitors (MKI), which exhibit anti-RET activities, but more potently inhibit other kinase targets such as VEGFR2 KIT, PDGFR, EGFR, MET, and BRAF, have also been tested in RET-driven solid cancer, especially in NSCLC and thyroid cancers in this study. And based on the pooled analysis, the incidence of adverse events in the MKI group is low, mostly grade 3-5 adverse reactions, but the frequency of drug dosage reduction and drug withdrawal due to adverse reactions is high, indicating that patients' tolerability to MKI related adverse reaction is poor. Drug safety is the top priority in treatment. Although the incidence of adverse reactions in the TKI group is high, the frequency of drug dosage reduction and drug withdrawal is significantly reduced, which shows great advantages in tolerability and long-term drug delivery. In addition, the ORR of MKI compared to TKI is relatively low, only about 20%. It is rather difficult to identify whether their anti-tumor activity was mainly induced by the inhibition of RET gene or by inhibition of other kinase targets due to their multi-target inhibition. Collectively, MKIs demonstrate less clinical benefit in RET-driven solid cancer. In addition, a lack of targeted specificity is probably responsible for increased toxicity leading to dose reduction or even treatment interruption. A novel selective RET inhibitor, selpercatinib and pralsetinib, may resolve off-target toxicity issues as it potently and selectively inhibits RET wild-type and RET-driven cancer cell lines in biochemical assays[19]. Therefore, the clinical benefits of MKIS remains confused when compared with TKIs, further studies of molecular mechanism and clinical trials are necessary.

We also conducted subgroup analysis and explored the source of heterogeneity. A significant reduction in heterogeneity was found after grouping by MKI or TKI and prior treatment status, indicating that the heterogeneity was primarily from the mix of treatment status and MKI treatment. The subgroup analysis of prior treatment status showed a significant reduction in the heterogeneity of objective response rates and a higher rate of objective response and disease control in newly treated patients. The subgroup analysis of MKI and TKI in both treated and untreated patients showed a significant reduction in heterogeneity of ORR and DCR, especially in the TKI group. The limited reduction in heterogeneity in the MKI group may be due to the a smaller sample size in the MKI group. Therefore, prior treatment status and MKI treatment are main sources of heterogeneity in this study. Several limitations in this study may restrict the dissemination of our conclusions. Firstly, there have been few phase III randomized controlled trials of RET-driven solid cancer. Case series is the main source of evidence, and most studies included were phase II, single-arm without a control group. However, more and more small sample size studies need meta-analysis to improve the quality of evidence, corresponding analysis methods need to be developed. Considering a lack of randomized controlled trials , we will continue to follow relevant studies in the future and update

our analysis, hoping that this study can provide a reference for future clinical trials. Secondly, studies with drug combination may bias the results. At last, heterogeneity between the included studies manifested the difference of follow-up time, cancer type, drug, previous treatment status and so on.

Conclusion

Targeted therapy inhibitors have significant efficacy in the treatment of RET-driven solid cancer. The ORR and DCR of TKI are better than MKI, and TKI has a relatively better safety compared to MKI. And prior untreated patients benefit more than those treated with Vandetanib or Cabozantinib.

Disclosure:

Conflict of Interest

The authors have no conflicts of interest to declare. None of the authors are current editors or editorial board members of *Cancer Science* .

Ethics Statement Approval of the research protocol by an Institutional Reviewer Board: N/A Informed Consent: N/A Registry and the Registration No. of the study/trial: N/A Animal Studies: N/A

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Figure legends:

Fig.1. Flow diagram of the selection process. (We did not use the PRISMA flow diagram, just a collaborative process of sorting papers by three persons.)

Fig.2. Forest plots of studies. The ORR of targeted therapy Inhibitors in the treatment of RET-mutation Solid Cancer according prior treatment status(A) or treatments(B). The treatment status was divided into three subgroups: previous untreated, previous treated and a mixture of both(MIX). The treatment was divided into treatment with multikinase inhibitors (MKI) and treatment with tyrosine kinase inhibitors (TKI) subgroups. The DCR of targeted therapy Inhibitors in the treatment of RET-driven solid cancer according prior treatment status(C) or treatments(D). The treatment status was divided into three subgroups: previous untreated, previous treated and a mixture of both(MIX). The treatment was divided into treatment with multikinase inhibitors (MKI) and treatment with tyrosine kinase inhibitors (TKI) subgroups. We analyze the data ORR and DCR with the help of R language version 4.2.0, using the command metaprop() into provides five estimation methods of the sample rate, according to the distribution of the sample rate to decide which merging method to use, the five estimation methods are as follows: "PRAW" (original rate without transformation), "PLN" (logit transformation), "PLOGIT" (logit transformation), "PAS" (inverse sine transformation), " PFT" (Freeman-Tukey double inverse sine transformation), Before Meta-analysis, the original rates and the rates after transformation according to the four estimation methods were tested for normality, and the method closest to the normal distribution was selected according to the test results, i.e. "PFT" (Freeman-Tukey double inverse sine transformation). The merging of the effects was performed by the command metaprop(), and the merging of the rates was performed to obtain the merged rates and 95% confidence intervals.

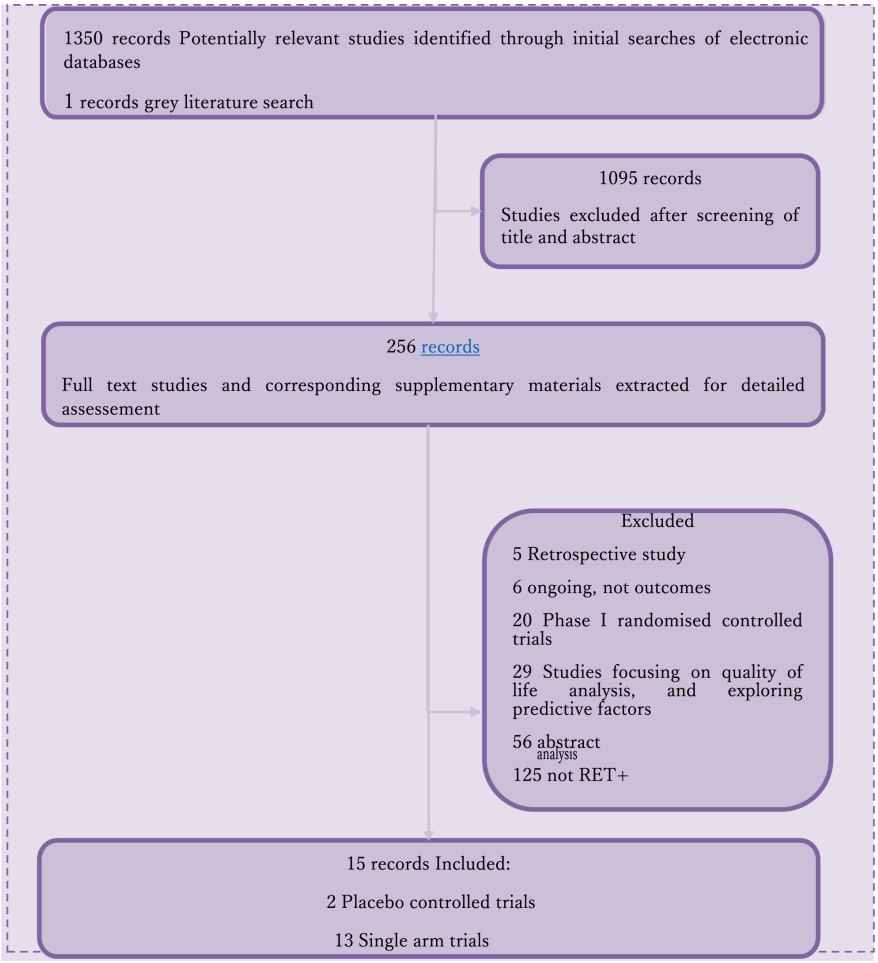
CI: confidence interval; ORR: objective remission rate; DCR: disease control rate; TKI: tyrosine kinase inhibitors; MKI: multikinase inhibitors; MIX: a mixture of previous untreated and previous treated.

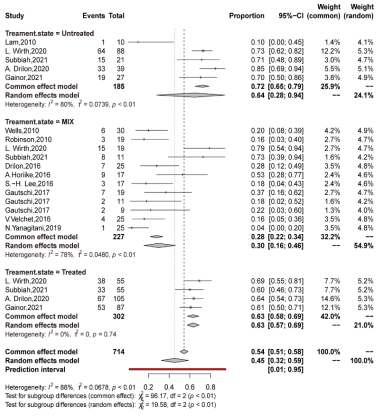
Fig.3. Funnel plot(A), the funnel plot evaluated by shear-complement method(B) and sensitive analysis diagram(C). We applied funnel drawing funnel plot (A) to identify publication bias or other bias methods, and judged the presence or absence of bias in Meta-analysis based on the degree of asymmetry of the graphs and detection of publication bias with the peters test of the command metabias() of publication bias. Finally, the cut-and-patch method of evaluation (B) was applied to evaluate whether publication bias had an effect on the results.

Fig.4 Sensitivity analysis was performed using metainf to calculate the combined OR and 95% confidence interval after excluding each enrolled study separately.

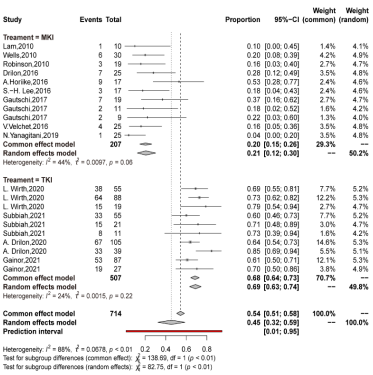
We would like to use the Fig.2 for the graphical table of contents and for the publication cover. Thank you very much.

List of Supporting Information: Doc.S1 Search term details**Doc.S2** R language statistical analysis code**Table.S1** Quality assessment results of included studies by MINORS assessment tool**Table.S2** Clinical outcomes with targeted therapy Inhibitors therapy in RET-driven solid cancer

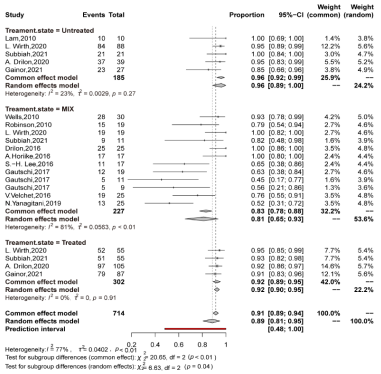




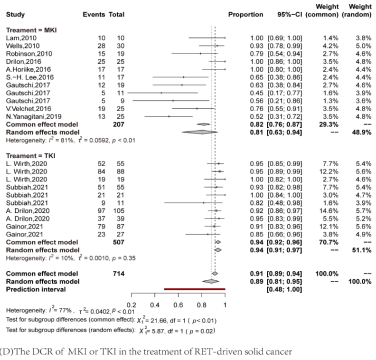
(A)The ORR of targeted therapy Inhibitors in the treatment of RET-mutation Solid Cancer according prior treatment status



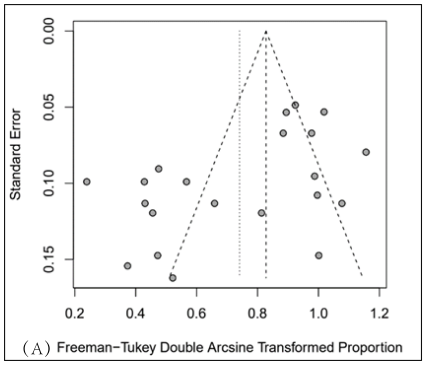
(B) The ORR of MKI or TKI in the treatment of RET-mutation Solid Cancer

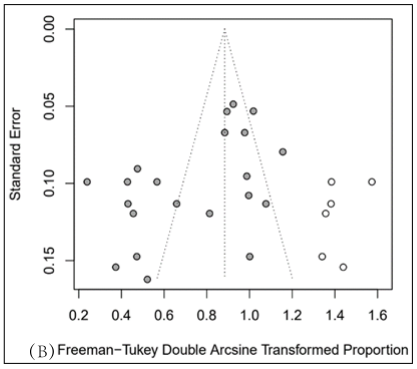


(C)The DCR of targeted therapy Inhibitors in the treatment of RET-driven solid cancer according prior treatment status



(D)The DCR of MKI or TKI in the treatment of RET-driven solid cancer





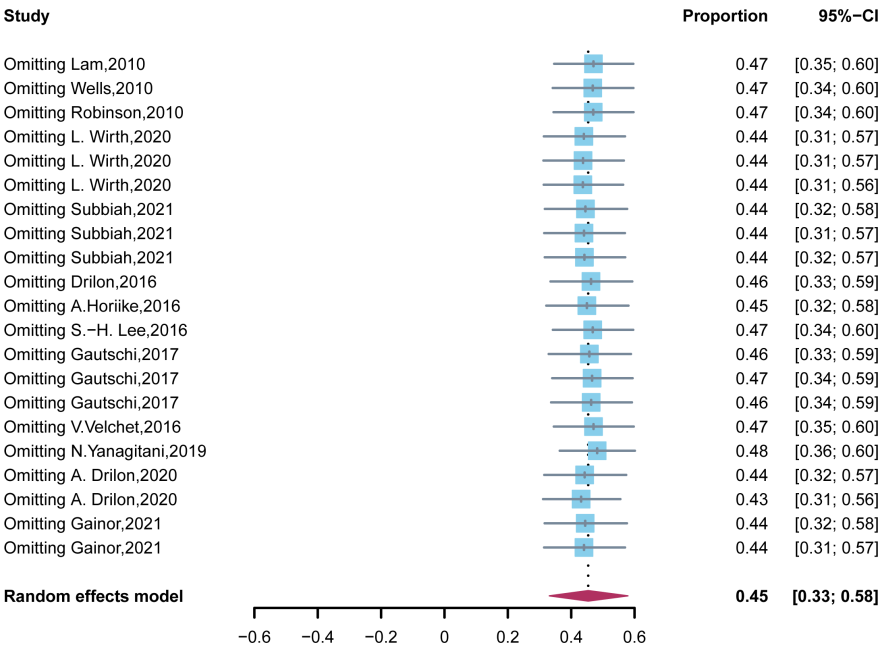


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Table.2._ORR,_DCR_and_adverse_reactions_in_the_targeted_therapy_Inhibitors_of_RET-driven_solid_cancer.d available at https://authorea.com/users/557694/articles/607250-efficacy-and-safety-of-targeted-therapy-inhibitors-for-ret-driven-solid-cancer-a-systematic-review-and-meta-analysis