Efficacy and Safety of Multi-Kinase Inhibitors for Patients with Advanced or Metastatic Radioiodine Refractory Differentiated Thyroid Cancer: A Systematic Review and Meta-Analysis

Jaekyoung Yoo

The Graduate School
Yonsei University
Department of Pharmaceutical Medicine
and Regulatory Science

Efficacy and Safety of Multi-Kinase Inhibitors for Patients with Advanced or Metastatic Radioiodine Refractory Differentiated Thyroid Cancer: A Systematic Review and Meta-Analysis

A Master's Thesis
Submitted to the Department of Pharmaceutical Medicine
and Regulatory Science
and the Graduate School of Yonsei University
in partial fulfillment of the
requirements for the degree of
M.S. in Pharmacy

Jaekyoung Yoo

December 2022

This certifies that the master's thesis

of Jaekyoung Yoo is approved.

_____

Thesis Supervisor: Min Jung Chang

_____

Thesis Committee Member #1: Yun Mi Yu

_____

Thesis Committee Member #2: Jun Jeong Choi

The Graduate School

Yonsei University

December 2022

Acknowledgement

I would like to thank various people for their help and supports during the production of this thesis. My most profound appreciation goes to my supervisor, Professor Min Jung Chang, for her invaluable patience, endless encouragement, support, and guidance throughout my master's course. I am extremely grateful that she had took me on as her student and for the times she had spent for me late at nights and even during the weekends.

I would also like to express my gratitude to Professors Jun Jeong Choi and Yun Mi Yu for their times to review my research, and providing me with encouraging words, thoughtful, and detailed feedbacks.

Very special thanks to Jieun Lee, Mirim Kim, Yeonsook Seo, Chiyoung Lee, and Yeonmi Lee for their kind supports and advice during my course. Also, I extend my thanks to all my friends and colleagues at Celltrion, especially Goeun Yang, Hana Ju, Suji Jung, and Juree Hwang for their continuous encouragements and tremendous supports.

Last, but not least, I would like to thank my family for their endless love and support throughout my life.

Contents

List of Figures

List of Tables

List of Abbreviations

AE	Adverse event
CBR	Clinical benefit rate
CI	Confidence interval
CrI	Credible interval
DCR	Disease control rate
DTC	Differentiated thyroid cancer
HR	Hazard ratio
MKI	Multi-kinase inhibitor
NCCN	National comprehensive cancer network
NMA	Network meta-analysis
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PFS	Progression free survival
RCT	Randomized controlled trial
SAE	Serious adverse event
VEGF(R)	Vascular endothelial growth factor (receptor)

ABSTRACT

Efficacy and Safety of Multi-Kinase Inhibitors for Patients with Advanced or Metastatic Radioiodine Refractory Differentiated Thyroid Cancer: A Systematic Review and Meta-Analysis

Yoo, Jaekyoung
Dept. of Pharmaceutical Medicine and Regulatory Science
The Graduate School
Yonsei University

Background

Differentiated thyroid cancer (DTC) type represents over 90% of thyroid cancers, and often present as an indolent disease with an excellent prognosis following thyroid surgery and radioiodine therapy. However, recurrence of locally advanced or distant metastases occur up to approximately 15% of patients and systemic therapy with multi-kinase inhibitor is important for treatment of these patients.

The aim of the study is to provide comparative overview to assist with selecting optimal MKIs in clinical practice due to lack of information on the comparison with multiple MKIs.

Method

The PubMed, Embase, and Cochrane library databases were searched for randomized controlled trials (RCTs) in patients with locally advanced or metastatic,

radioiodine refractory differentiated thyroid cancer. Studies reported on medullary or anaplastic histologic subtypes, retrospective or prospective observational cohort studies were excluded. The primary efficacy outcome was progression-free survival (PFS). The secondary outcomes included overall survival (OS), objective response rate (ORR), disease control rate (DCR), clinical benefit rate (CBR), and additional safety outcomes of adverse events (AEs). A traditional pairwise meta-analyses and Bayesian network meta-analyses were performed on the reported outcomes.

Result

A total of 9 RCTs were included in the meta-analyses. Based on the network meta-analyses, PFS improvement was shown in the order of lenvatinib, anlotinib, cabozantinib, and apatinib. There was no statistically significant improvement for OS in the MKIs. For other efficacy outcomes, cabozantinib ranked 1st for ORR, apatinib ranked 1st for DCR, and lenvatinib ranked 1st for CBR. Higher toxicities were also shown with lenvatinib and apatinib. Lenvatinib ranked 1st for AEs and SAEs, apatinib ranked 1st for AEs related to study drug and AEs of ≥ grade 3.

Conclusion

Lenvatinib was associated with best improvement in PFS and CBR, and highly effective in lung metastasis patients. Based on the finding of this study, lenvatinib is mostly recommended in patients with tolerable toxicities. Anlotinib, cabozantinib, or apatinib can be recommended for patients with intolerable toxicities with lenvatinib. Safety profiles were generally comparable between treatments, but higher toxicity was shown with drugs with higher efficacy, therefore, a close safety monitoring will be required during MKI treatment.

KEYWORDS: differentiated thyroid cancer, multi-kinase inhibitor, protein kinase inhibitor, efficacy, safety, meta-analysis

1. Introduction

Thyroid cancer accounts for approximately 3% of all cancers and is the most common endocrine cancer, with a higher global incidence rate in women (10.1 per 100,000) than in men (3.1 per 100,000) (Sung et al. 2021). Differentiated thyroid cancer (DTC) type represents over 90% of thyroid cancers, which major histologic subtypes comprises of papillary and follicular cancers (Miranda-Filho et al. 2021; Rossi et al. 2021). DTC arises from the follicular cells of the thyroid and follicular cells express a sodium iodide symporter for iodine entry (Puliafito et al. 2022).

In general, DTC often presents as an indolent disease with an excellent prognosis following thyroid surgery and radioiodine therapy (Haugen et al. 2016). However, recurrence of locally advanced or distant metastases occur up to approximately 15% of patients with DTC (Wang et al. 2016) and 60-70% accompanies radioiodine refractoriness (Fugazzola et al. 2019). Overall survival rate at 10 years in patients with radioiodine refractory was less than 30% (Durante et al. 2006).

Systemic therapy with multi-kinase inhibitor is a candidate for patients with recurrent, locally advanced, or metastatic radioiodine refractory DTCs and recommended treatments by the National Comprehensive Cancer Network (NCCN) are as follows: lenvatinib as a preferred regimen, sorafenib as other recommended regimen, cabozantinib if progression after lenvatinib and/or sorafenib, and other commercially available MKIs such as axitinib, pazopanib, and vandetanib if considered appropriate (Cabanillas et al. 2019; Haddad et al. 2022; National Comprehensive Cancer Network 2022). These drugs target multiple kinase receptors such as VEGFR, RET, c-KIT, etc. VEGF over expression is highly shown in the DTC type and for poorly differentiated thyroid cancer as described in Table 1 (Puliafito et al. 2022).

Table 1 Molecular alterations in thyroid cancer histologic types

Histologic type	Major genetic alterations	Frequency
Papillary	VEGF over expression	79%
	RET/PTC rearrangements	Variable depending on geographic region
Follicular	VEGF over expression	50%
	RAS mutations	40-50%
	PAX8/PPARg	35%
Medullary	RET point mutations	100% of hereditary form
	RET M918T	50% of sporadic cases
	RAS (HRAS, KRAS or NRAS)	85% of RET-mutated sporadic cases 18-80% of RET-negative sporadic form
Anaplastic	$BRAF^{V600E}$	45%
	RAS mutations	24%
	PIK3CA	18%
	PTEN	10-15%
	Genes in PI3K/AKT/mTOR pathway	39%
	TP53	50-80%
	NTRK fusion	rare
Poorly differentiated	VEGF over expression	37%
	BRAF mutations	81%
	$BRAF^{V600E}$	33%
	RAS mutations	28%
	Genes in PI3K/AKT/mTOR pathway	11%
	TP53	8-35%

Abbreviations: AKT, alpha serine/threonine-protein kinase; ALK, anaplastic lymphoma kinase; BRAF, rapidly accelerated fibrosarcoma kinase; NTRK, neurotrophic tyrosine receptor kinase; PAX8/PPARg, paired box gene 8 / peroxisome proliferator-activated receptor g; PTEN, phosphatase and tensin homologous; RAS, rat sarcoma; RET, rearranged during transfection receptor; TP53, tumor protein P53; VEGF, vascular endothelial growth factor.

Several clinical trials involving the use of MKIs in locally advanced, or metastatic

radioiodine refractory DTC patients were conducted and revealed the use of MKI treatments had confirmatory efficacy but was also associated with severe adverse effects leading to discontinuation of treatment such as hand-foot syndrome (Belum et al. 2016; Klein Hesselink et al. 2015), hypertension (Fleeman et al. 2019; Yang et al. 2017), QTc prolongation (Zang et al. 2012), and thromboembolic events (Bai et al. 2019).

The use of MKI treatments has substantially increased since the advent of these therapies. According to the recent report of treatment patterns in radioactive iodine refractory DTC patients, up to 32% of the patients received MKI treatment, whereas 21% of the patients continued with disease monitoring (Gianoukakis et al. 2016). Innovate medicines, such as MKI treatments are often very expensive due to market exclusivity and most of the MKIs will only expire after more than a decade (Venkatesan et al. 2017). For instance, the average payment per 30-day supply of a MKI was from 9,000 to 10,000 US dollars in the chronic myelogenous leukemia indication (Talon et al. 2021). The decision to initiate MKI treatment in recurrent, locally advanced, or metastatic DTC patients will be based on overall tumor burden, symptoms, location of distant metastasis, refractoriness to radioiodine, etc. Many patients may be candidates for active surveillance, however, use of MKI treatments is increasing and to reduce patient's economic burden of the MKI treatment, it is important to note the differences between the available MKI treatments in order to select optimal treatment. Therefore, the study to evaluate the appropriate MKI to treat recurrent, locally advanced, or metastatic radioiodine refractory DTC is crucial.

Due to the lack of head-to-head comparative trial of MKIs in locally advanced, or metastatic radioiodine refractory DTC patients, there was a need to compare the differences of these multiple MKIs in terms of efficacy and safety. Several meta-analyses of the randomized control trials conducted in locally advanced, or metastatic radioiodine refractory DTC patients were performed (Fleeman et al. 2019; Liu et al. 2018; Su et al. 2022; Tsoli et al. 2020; Yimaer et al. 2016). However not

all up-to-date available results were included in these meta-analyses. We conducted a systematic review and meta-analysis of the RCTs with all available result of either published or unpublished clinical data to provide comparative overview to assist with selecting optimal MKIs in clinical practice.

2. Method

The systematic review was conducted following the Preferred Report Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al. 2021). The study was registered on PROSPERO (CRD42022349978).

2.1. Search strategy

The PubMed, Embase, and Cochrane library databases were searched by two independent reviewers (JKY and MJC) for studies published up to 28 May 2022. The research question in PICOS is provided in Table 2. The main search keywords included “thyroid cancer”, “differentiated thyroid cancer”, “kinase inhibitor”, and generic names of kinase inhibitors approved for the use of locally advanced, or metastatic radioiodine refractory DTC. Detailed search strategies used for each database are presented in Appendix 1. The two authors independently reviewed the literatures for inclusion by screening titles and abstracts, followed by full text review of potential literatures. Any discrepancies were resolved by consensus through discussion between the two reviewers.

Table 2 PICOS

Elements	Contents
Population (P)	Advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer (DTC)
Intervention (I)	Multi-kinase inhibitor
Comparator (C)	Not applicable
Outcome (O)	Efficacy and safety
Study design (S)	Randomized clinical trial

2.2. Inclusion and Exclusion criteria

Inclusion criteria were: (i) published or unpublished randomized controlled trials, (ii) patients with locally advanced or metastatic, radioiodine-refractory differentiated

thyroid cancer, (iii) treated with multi-kinase inhibitors irrespective of duration, and (iv) at least one efficacy or safety outcomes. Exclusion criteria were: (i) studies with medullary thyroid cancer or anaplastic thyroid cancer, (ii) retrospective or prospective observational cohort studies, or (iii) case report, letters, reviews, or meta-analysis.

2.3. Outcomes

The primary efficacy outcome was progression-free survival (PFS), defined as time from randomization to the occurrence of disease progression or death. The secondary outcomes included overall survival (OS, defined as time from randomization to death from any cause), objective response rate (ORR, defined as complete or partial response), disease control rate (DCR, defined as complete or partial response, or stable disease), and clinical benefit rate (CBR, defined as complete or partial response, or durable stable disease), and additional safety outcomes of adverse events.

2.4. Data extraction and risk of bias assessment

For the eligible trials, the following data were extracted into a spreadsheet: study information (first author, year of publication, number of patients, duration of treatment, and duration of follow-up), patient characteristics (country, age, histology type, metastatic site, and prior treatment), efficacy outcomes (hazard ratios and confidence intervals for PFS and OS, number of patients with ORR, DCR, and CBR), and safety outcomes (number of patients with adverse events).

The Cochrane Risk of Bias 2 (RoB 2) Tool was used to assess the risk of bias for each study. Two independent reviewers (JKY and MJC) evaluated the domains of randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result and scored each as low, some concerns, or high risk of bias. Any discrepancies were resolved

by consensus between the two independent reviewers.

2.5. Statistical analysis

A traditional pairwise meta-analyses were performed for MKIs versus placebos. Data were entered and analyzed using Review Manager (version 5.4.1, the Cochrane Collaboration, 2020). Pooled hazard ratio (HR) along with the 95% confidence interval (CI) was analyzed for PFS and OS using the inverse variance technique. For other dichotomous outcomes, odds ratio (OR) and 95% CI were analyzed using the Mantel-Haenszel method. Statistical significance was defined as $p < 0.05$. Meta-analyses results were presented by pooling the whole MKI treatment group and by individual treatment group, to provide a comparative overview of treatment effects between treatments.

Statistical heterogeneity was assessed using the Cochran's Q test and I^2 statistic. A random-effects model was applied if significant heterogeneity was observed (defined as $p < 0.10$ or $I^2 > 50\%$). Otherwise, a fixed-effects model was applied.

Subgroup analyses were also performed in different histologic type of DTC (papillary or follicular), by prior MKI use (MKI naïve, 1 prior MKI, or 2 prior MKIs), by age (≤ 65 or > 65), by gender (male or female), by metastatic site (bone or lung), and by MKI treatment duration (< 6 months, ≥ 6 to < 12 months, or ≥ 12 to < 24 months), to explore the impact of baseline characteristics in PFS. Meta-regression was performed to evaluate the effect for prior MKI use on the log of the hazard ratio for the progression free survival using the R meta package version 4.2.1.

We also conducted a Bayesian network meta-analysis, using the R gemtc package version 4.2.1. Analyses were based on the Markov Chain Monte Carlo model with the setting of 5,000 burn-ins, 50,000 sample iterations, and a thinning interval of 1. The convergence of the model was assessed by the Brooks-Rubin diagnosis plot, trace plot, and density plot. For PFS and OS, contract-based analyses were performed

using the log HR and standard error, which were calculated from the reported HR and confidence intervals. The results were presented as HRs and 95% credible intervals (CrI). For other dichotomous outcomes, arm-based analyses were performed using the available raw data from the studies and the results were presented as ORs and 95% CrIs. Network plots illustrated the connectivity of treatment network, and a forest plot with ranking probabilities were presented to estimate relative effects in comparison of the network model.

In addition to the above analyses, a sensitivity analysis was performed to assess the robustness and reliability of the progression free survival, by excluding trials that had enrolled previous MKI failure patients only (Schlumberger et al. 2018 and Brose et al. 2021).

3. Results

3.1. Literature search and study characteristics

Following the literature search, a total of 4,597 articles were retrieved. A total of 9 randomized control trials were selected from the screening process (Figure 1). This included a total of 1,830 patient data from 7 MKIs; a single study each from anlotinib, apatinib, cabozantinib, nintedanib, and sorafenib and two studies each from lenvatinib and vandetanib. The molecular targets of the 7 MKIs and its approval status for recurrent, locally advanced, or metastatic radioiodine refractory DTC in US and EMA are described in Table 3 (Dimitroulis 2014; Puliafito et al. 2022; Shen et al. 2018; Zhang 2015).

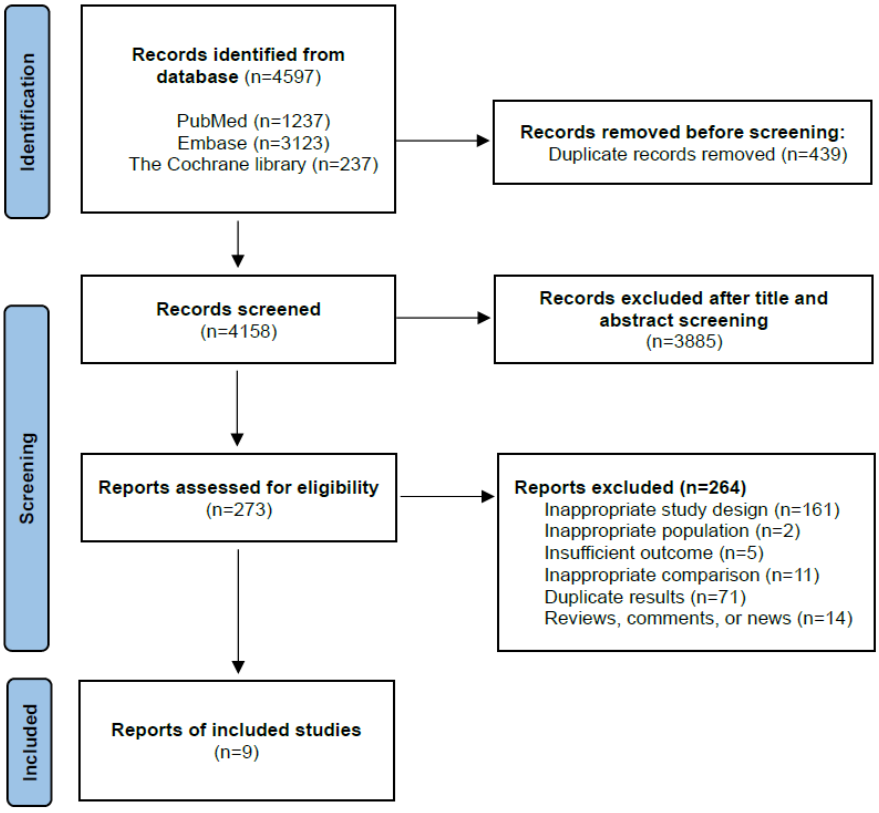


Figure 1 PRISMA flow diagram of study selection

Table 3 Molecular targets of multi-kinase inhibitors included in the study and its approval date for recurrent, locally advanced, or metastatic radioiodine refractory DTC

MKI	Targets	FDA approval	EMA approval
Apatinib	VEGFR 2, c-KIT, c-Src	Not approved	Not approved
Anlotinib[1)]	c-KIT, PDGFR, FGFR, VEGFR 1-3	Not approved	Not approved
Cabozantinib	RET, MET, c-KIT, VEGFR 1-3	2021.09.17	2022.03.24
Lenvatinib	RET, c-KIT, VEGFR 1-3, PDGFR, FGFR	2015.02.13	2015.05.28
Nintedanib	VEGFR 1-3, PDGFR, FGFR	Not approved	Not approved
Sorafenib	RET, c-KIT, VEGFR 1-3, PDGFR, BRAF	2013.11.22	2014.04.25
Vandetanib	RET, c-KIT, EGFR, VEGFR 2	Not approved	Not approved

Abbreviations: BRAF, rapidly accelerated fibrosarcoma kinase; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; c-KIT, stem cell factor receptor; MET, hepatocyte growth factor receptor; PDGFR, platelet derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor.

1) Approved for recurrent, locally advanced, or metastatic radioiodine refractory DTC in China in 2022.04

All studies were phase 2 or 3 placebo-controlled RCTs, conducted in patients with locally advanced or metastatic radioiodine-refractory DTCs, including poorly differentiated thyroid cancers. Patients with evidence of progression per RECIST were enrolled in all studies. Three studies (Chi et al. 2020; Zheng et al. 2021; Lin et al. 2022) were conducted in a single country of China, whereas other studies were conducted in multiple countries.

The Brose et al. 2014 (sorafenib vs. placebo), NCT01876784 (vandetanib vs.

placebo), and Chi et al. 2020 (anlotinib vs. placebo) trials enrolled MKI naïve patients only. The rest of the trials allowed patients who have previously received MKIs, however, the Schlumberger et al. 2018 (nintedanib vs. placebo) and Brose et al. 2021 (cabozantinib vs. placebo) trials enrolled patients only who had failed previous MKI therapy and therefore, allowed patients with up to 2 previous MKI treatments. Details of the study characteristics including median treatment duration and follow up duration with reported outcomes are presented in Table 4.

The histologic types of DTC in the studies included both papillary and follicular thyroid cancers, and Hürthle cell carcinoma, a variant of follicular thyroid carcinoma. All studies where the histologic subtypes were reported, included both papillary and follicular thyroid cancer patients. In addition to this, the trials (Brose et al. 2014; Leboulleux et al. 2012; Lin et al. 2022; Schlumberger et al. 2015) also enrolled poorly differentiated thyroid cancers ranging from 0 to 40% of the enrolled patients (Table 5). Zheng et al. 2021 did not report the proportion of the population, but had also included poorly differentiated thyroid cancer types as a variant of the papillary thyroid cancer type in their inclusion criteria of the study protocol (NCT02966093).

The metastatic lesion reported in each study are included in Table 6. Most of the patients were reported with lung metastasis.

Table 4 Baseline characteristics of studies included in the meta-analysis

Study (Phase, Country)	Intervention	N (% male)	Median age (range)	Prior MKI therapy (%)	Median treatment duration	Median follow-up duration
Leboulleux 2012	Vandetanib 300mg QD	72 (54.2)	63 (29-81)	4.2[1)]	192 d	18.9 m
(II, Europe)	Placebo	73 (53.4)	64 (23-87)	4.1[1)]	175.5 d	19.5 m
Schlumberger 2015	Lenvatinib 24mg QD	261 (47.9)	64	25.3	13.8 m	17.1 m
(III, International)	Placebo	131 (57.3)	61	20.6	3.9 m	17.4 m
Brose 2014	Sorafenib 400mg BID	207 (50.2)	63 (24-82)	MKI-naïve	10.6 m	NR
(III, International)	Placebo	210 (45.2)	63 (30-87)	MKI-naïve	6.5 m	NR
NCT01876784	Vandetanib 300mg QD	119 (41.2)	64.2[2)]	MKI-naïve	NR	NR
(III, International)	Placebo	119 (46.2)	63.2[2)]	MKI-naïve	NR	NR
Schlumberger 2018	Nintedanib 400mg QD	NR	NR	100.0	17.7 w	NR
(II, Europe)	Placebo	NR	NR	100.0	10.4 w	NR
Chi 2020	Anlotinib 12mg QD	NR	NR	MKI-naïve	NR	NR
(II, China)	Placebo	NR	NR	MKI-naïve	NR	NR
Brose 2021	Cabozantinib 60mg QD	125 (45.6)	65 (56-72)	100.0	4.4 m	6.2 m
(III, International)	Placebo	62 (45.2)	66 (56-72)	100.0	2.3 m	
Zheng 2021	Lenvatinib 24mg QD	103 (55.3)	61 (28-80)	25.2	9.26 m	NR
(III, China)	Placebo	48 (43.8)	60 (22-80)	25.0	6.26 m	NR
Lin 2022	Apatinib 500mg QD	46 (41.3)	56 (31-75)	10.9[1)]	7.8 m	18.1 m
(III, China)	Placebo	46 (37.0)	59.5 (18-79)	6.5[1)]	2.6 m	

Abbreviations: BID, twice a day; d, day; m, months; NR, not reported; QD, once a day; w, week.

1) Reported as prior targeted therapy.
2) Mean value reported.

Table 5 Histologic subtypes of differentiated thyroid cancer of studies included in the meta-analysis

Study (Phase, Country)	Intervention	Papillary	Follicular	Hürthle cell	Poorly differentiated	Other
Leboulleux 2012[1)]	Vandetanib 300mg QD	25 (34.7)	8 (11.1)	0	29 (40.3)	NR
(II, Europe)	Placebo	24 (32.9)	10 (13.7)	2 (2.7)	28 (38.4)	NR
Schlumberger 2015	Lenvatinib 24mg QD	132 (50.6)	53 (20.3)	48 (18.4)	28 (10.7)	NR
(III, International)	Placebo	68 (51.9)	22 (16.8)	22 (16.8)	19 (14.5)	NR
Brose 2014[2)]	Sorafenib 400mg BID	118 (57.0)	13 (6.3)	37 (17.9)	24 (11.6)	17 (8.2)[3)]
(III, International)	Placebo	119 (56.7)	19 (9.0)	37 (17.6)	16 (7.6)	20 (9.5)[4)]
NCT01876784	Vandetanib 300mg QD	NR	NR	NR	NR	NR
(III, International)	Placebo	NR	NR	NR	NR	NR
Schlumberger 2018	Nintedanib 400mg QD	NR	NR	NR	NR	NR
(II, Europe)	Placebo	NR	NR	NR	NR	NR
Chi 2020	Anlotinib 12mg QD	NR	NR	NR	NR	NR
(II, China)	Placebo	NR	NR	NR	NR	NR
Brose 2021[5)]	Cabozantinib 60mg QD	67 (53.6)	62 (49.6)	NR	NR	NR
(III, International)	Placebo	35 (56.5)	28 (45.2)	NR	NR	NR
Zheng 2021	Lenvatinib 24mg QD	83 (80.6)	20 (19.4)	NR	NR	NR
(III, China)	Placebo	40 (83.3)	8 (16.7)	NR	NR	NR
Lin 2022	Apatinib 500mg QD	37 (80.4)	9 (19.6)	NR	0	0
(III, China)	Placebo	35 (76.1)	8 (17.4)	NR	2 (4.3)	1 (2.2)[6)]

Abbreviations: BID, twice a day; NR, not reported; QD, once a day.

1) Histological status was not reported for 19 patients because archived tissue samples were not available.
2) Two patients in the sorafenib group and one in the placebo group were assigned two different histologies on the basis of multiple samples.

3) Included 2 well differentiated, 2 oncocytic carcinoma, and 13 missing or nondiagnostic subtypes per central review (All patients had DTC according to investigator assessment).
4) Included 1 well differentiated, 1 medullary, 3 carcinomas, not otherwise specified, and 14 missing or nondiagnostic per central review (All patients had DTC according to investigator assessment).
5) Five patients had both papillary and follicular histology.
6) Mixed papillary-poorly differentiated type.

Table 6 Metastatic lesions of thyroid cancer of studies included in the meta-analysis

Study (Phase, Country)	Intervention	Distant meta	Lung	Bone	Lymph nodes	Pleura	Head or neck	Liver	Other
Leboulleux 2012 (II, Europe)	Vandetanib 300mg QD	71 (98.6)	NR	NR	NR	NR	NR	NR	NR
	Placebo	71 (97.3)	NR	NR	NR	NR	NR	NR	NR
Schlumberger 2015 (III, International)	Lenvatinib 24mg QD	NR	226 (86.6)	104 (39.8)	NR	NR	NR	NR	NR
	Placebo	NR	124 (94.7)	48 (36.6)	NR	NR	NR	NR	NR
Brose 2014 (III, International)	Sorafenib 400mg BID	NR	178 (86.0)	57 (27.5)	113 (54.6)	40 (19.3)	33 (15.9)	28 (13.5)	NR
	Placebo	NR	181 (86.2)	56 (26.7)	101 (48.1)	24 (11.4)	34 (16.2)	30 (14.3)	NR
NCT01876784 (III, International)	Vandetanib 300mg QD	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	NR	NR	NR	NR	NR	NR	NR	NR
Schlumberger 2018 (II, Europe)	Nintedanib 400mg QD	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	NR	NR	NR	NR	NR	NR	NR	NR
Chi 2020 (II, China)	Anlotinib 12mg QD	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	NR	NR	NR	NR	NR	NR	NR	NR
Brose 2021 (III, International)	Cabozantinib 60mg QD	117 (93.6)	88 (70.4)	62 (49.6)	NR	NR	NR	27 (21.6)	104 (83.2)
	Placebo	60 (96.8)	49 (79.0)	24 (38.7)	NR	NR	NR	6 (9.8)	56 (90.3)
Zheng 2021 (III, China)	Lenvatinib 24mg QD	NR	91 (88.3)	36 (35.0)	72 (69.9)	NR	NR	91 (88.3)	43 (41.7)
	Placebo	NR	38 (79.2)	13 (27.1)	35 (72.9)	NR	NR	38 (79.2)	23 (47.9)
Lin 2022 (III, China)	Apatinib 500mg QD	NR	38 (82.6)	NR	NR	NR	4 (8.7)	NR	4 (8.7)
	Placebo	NR	37 (80.4)	NR	NR	NR	3 (6.5)	NR	6 (13.0)

Abbreviations: BID, twice a day; meta, metastasis; NR, not reported; QD, once a day.

3.2. Efficacy Outcomes

Reported efficacy outcomes that have been included in the meta-analyses in each study are provided in Table 7.

Table 7 Reported efficacy outcomes

Study	Intervention	PFS	OS	ORR	DCR	CBR
Leboulleux 2012	Vandetanib	✓	✓	✓	✓	
Schlumberger 2015	Lenvatinib	✓	✓	✓	✓	✓
Brose 2014	Sorafenib	✓	✓	✓		✓
NCT01876784	Vandetanib	✓				
Schlumberger 2018	Nintedanib	✓				
Chi 2020	Anlotinib	✓		✓	✓	
Brose 2021	Cabozantinib	✓	✓	✓	✓	✓
Zheng 2021	Lenvatinib	✓	✓	✓	✓	✓
Lin 2022	Apatinib	✓	✓	✓	✓	

Abbreviations: CBR, clinical benefit rate; DCR, disease control rate; ORR, objective response rate; OS, overall survival; PFS, progression free survival.

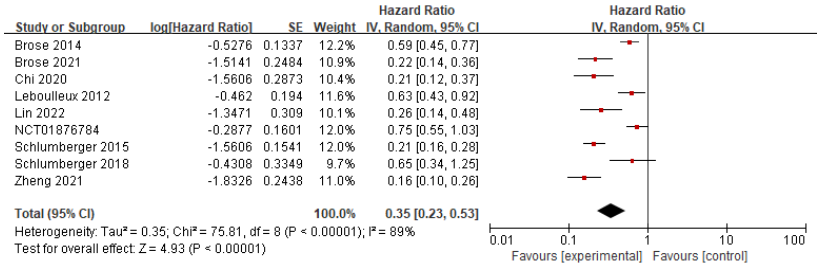
3.2.1. Progression free survival

Meta-analysis result revealed pooled MKIs, compared to placebo, significantly improved PFS (HR: 0.35, 95% CI: 0.23–0.53, P<0.00001) (Figure 2A).

PFS by treatment also revealed significantly improved PFS in all the MKIs, with the exception of nintedanib, for which the upper CI lies above 1.0 (HR: 0.65, 95% CI: 0.34–1.25) (Figure 2B).

The Bayesian network meta-analysis supported evidence of MKIs compared to placebo in improvement of PFS: statistically significant PFS improvement was shown in lenvatinib (HR: 0.19, 95% CrI: 0.08–0.41), anlotinib (HR: 021, 95% CrI: 0.07–0.68), cabozantinib (HR: 0.22, 95% CrI: 0.07–0.69), and apatinib (HR: 0.26, 95% CrI: 0.08–0.85). The consistency test was not available. The 1st rank treatment for a better PFS was lenvatinib (Table 8).

A



B

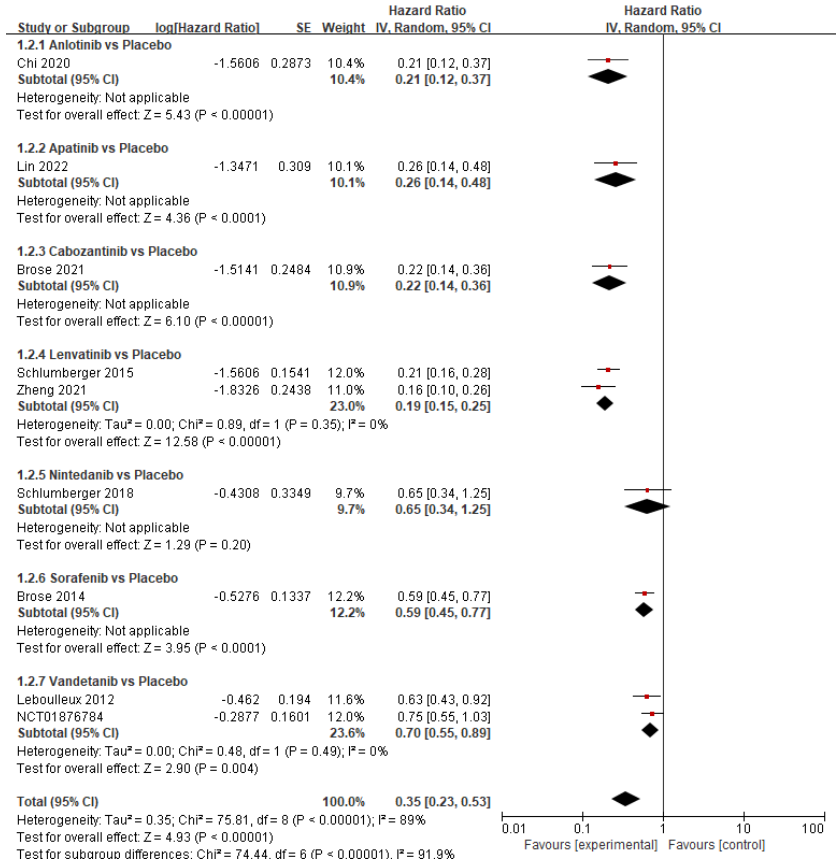
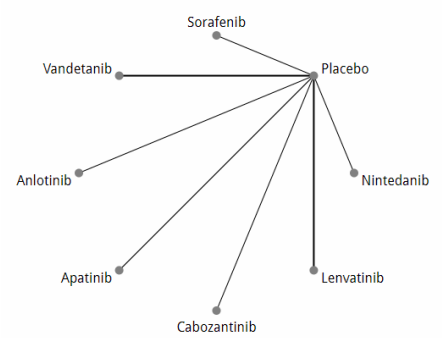


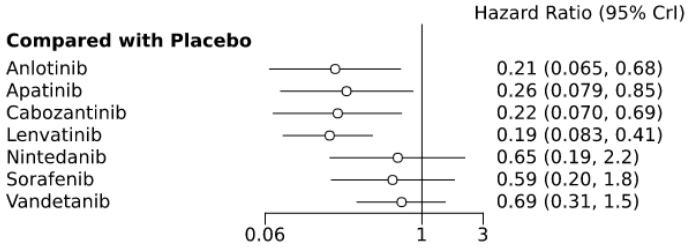
Figure 2 Comparison of progression free survivals in multi-kinase inhibitors (MKI) vs. placebo: (A) in all MKIs and (B) by treatment

Table 8 **Network meta-analysis result of progression free survival**

Network plot



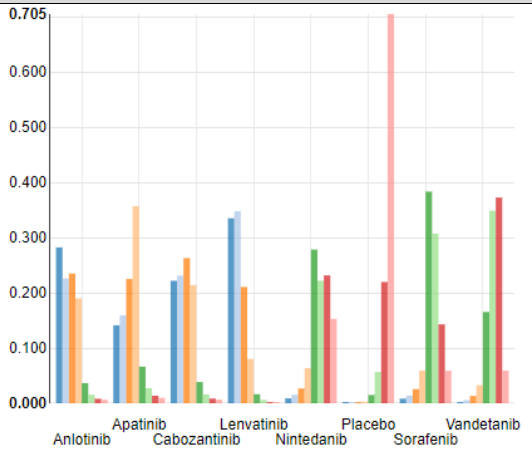
Forest plot



Ranking probability table

	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7	Rank 8
Anlotinib	0.279	0.230	0.233	0.189	0.038	0.015	0.009	0.007
Apatinib	0.141	0.159	0.226	0.353	0.067	0.028	0.014	0.011
Cabozantinib	0.221	0.232	0.263	0.212	0.039	0.017	0.009	0.007
Lenvatinib	0.339	0.341	0.209	0.083	0.018	0.007	0.003	0.001
Nintedanib	0.009	0.017	0.029	0.065	0.274	0.219	0.232	0.156
Placebo	0.000	0.000	0.000	0.003	0.016	0.060	0.225	0.696
Sorafenib	0.009	0.015	0.026	0.061	0.382	0.302	0.144	0.061
Vandetanib	0.002	0.006	0.014	0.034	0.166	0.352	0.365	0.061

Ranking probability plot



3.2.1.1.Subgroup analysis of PFS

Both papillary and follicular histology types had improvement in PFS (HR 0.32, 95% CI: 0.24–0.42, p<0.00001 and HR: 0.13, 95% CI: 0.04–0.40, p=0.00004, respectively). When divided by treatment, vandetanib in the papillary histology type showed no statistically significant improvement in PFS (Appendix Figure 16).

All three subgroups of MKI naïve, 1 prior MKI, and 2 prior MKIs had improvement in PFS (HR: 0.20, 95% CI: 0.14–0.28, p <0.00001, HR: 0.23, 95% CI: 0.15–0.34, p<0.00001, HR: 0.24, 95% CI: 0.09–0.61, p=0.003, respectively) (Appendix Figure 17). Figure 3 shows the meta-regression plot for the effect of the proportion of prior MKI use on progression free survival. Each bubble on the plot shows the value of the predictor measurement for each study on the horizontal axis and the effect measure “log hazard ratio” on the vertical axis. The result did not show any influence of proportion of patients with prior MKI use on the HR for PFS (p=0.749).

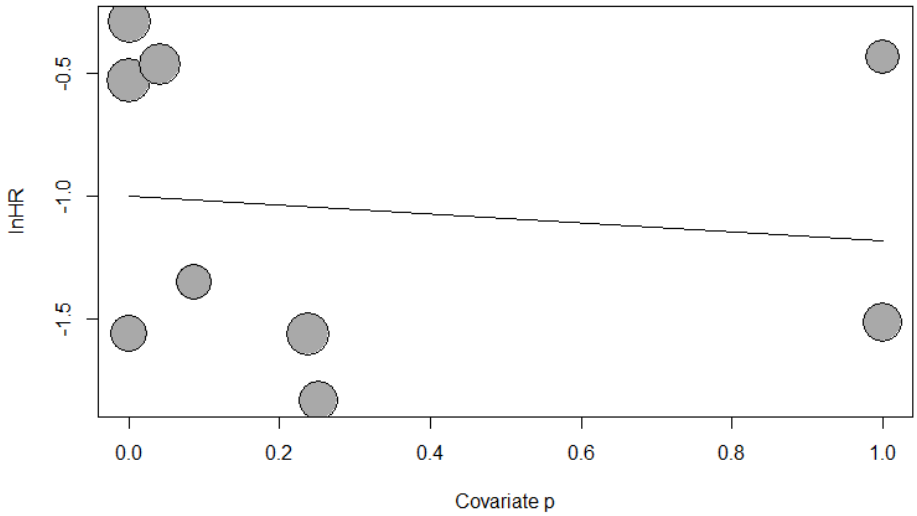


Figure 3 Meta-regression analysis of the log hazard ratio of progression free survival based on the proportion of patients with prior MKI use

Both ≤65 years age group and >65 years age group had improvement in PFS (HR: 0.20, 95% CI: 0.15–0.27, p<0.00001 and HR: 0.28, 95% CI: 0.19–0.40, p<0.00001, respectively) (Appendix Figure 18). Both male and female had improvement in PFS (HR: 0.21, 95% CI: 0.15–0.29, p<0.00001 and HR: 0.26, 95% CI: 0.19–0.37, p<0.00001, respectively) (Appendix Figure 19). Both patient groups who had metastatic site of bone and lung had improvement in PFS (HR: 0.28, 95% CI: 0.19–0.41, p<0.00001 and HR: 0.22, 95% CI: 0.17–0.29, p<0.00001, respectively) (Appendix Figure 20). Treatment duration reported of ≥6 to <12 month and ≥12 to <24 months had improvement in PFS (HR: 0.36, 95% CI: 0.19–0.68, p=0.001 and HR: 0.21, 95% CI: 0.16–0.28, p<0.00001, respectively). There was no statistically significant difference between the placebo in the <6 months group and studies where the treatment duration was not reported (Appendix Figure 21).

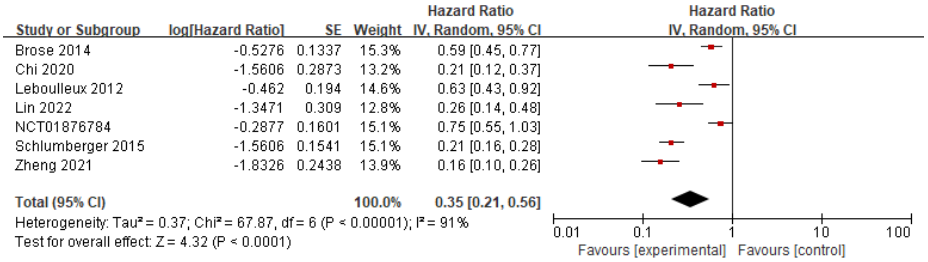
3.2.1.2.Sensitivity analysis of PFS

Two trials (one each from cabozantinib and nintedanib) that enrolled patients with previous MKI failure were excluded from the progression free analysis.

The result of the sensitivity analysis revealed the pooled HR did not change when we excluded the two studies. Pooled MKIs, compared to placebo, significantly improved PFS (HR: 0.35, 95% CI: 0.21–0.56, P<0.00001) (Figure 4A).

PFS by treatment also revealed significantly improved PFS in all the MKIs (Figure 4B).

A



B

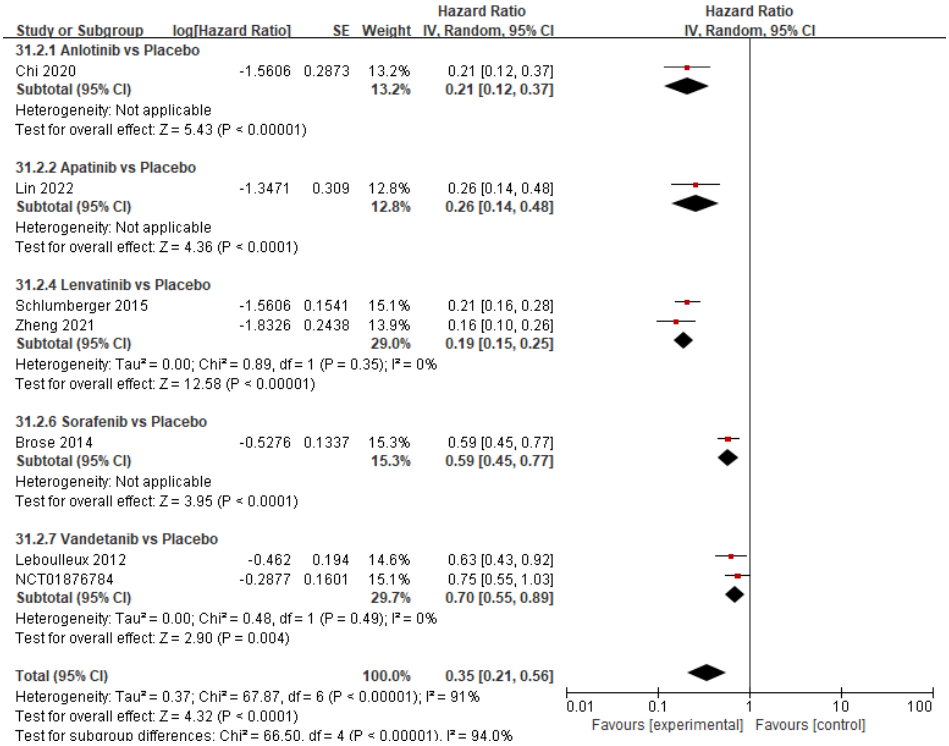


Figure 4 Sensitivity analysis: comparison of progression free survivals in multi-kinase inhibitors (MKI) vs. placebo: (A) in all MKIs and (B) by treatment

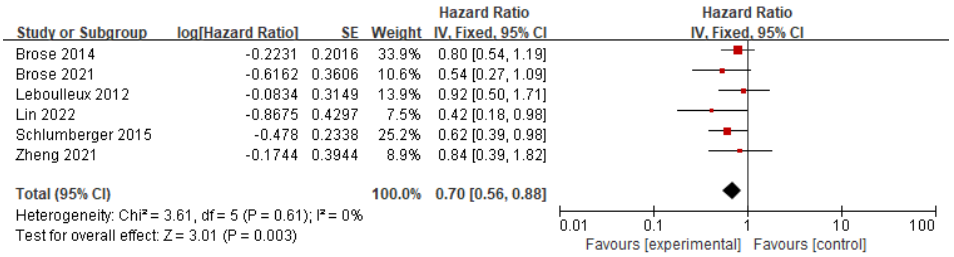
3.2.2. Overall survival

Meta-analysis result revealed pooled MKIs, compared to placebo, significantly improved OS (HR: 0.70, 95% CI: 0.56–0.88, p=0.003) (Figure 5A).

However, OS by treatment had not demonstrated significant improvement in cabozantinib, lenvatinib, sorafenib, and vandetanib, except for apatinib (HR: 0.42, 95% CI: 0.18–0.98, P=0.04) (Figure 5B).

The Bayesian network meta-analysis revealed no statistically significant improvement in all individual MKIs; apatinib, cabozantinib, lenvatinib, sorafenib, and vandetanib. The consistency test was not available. The 1st rank treatment for a better OS was apatinib (Table 9).

A



B

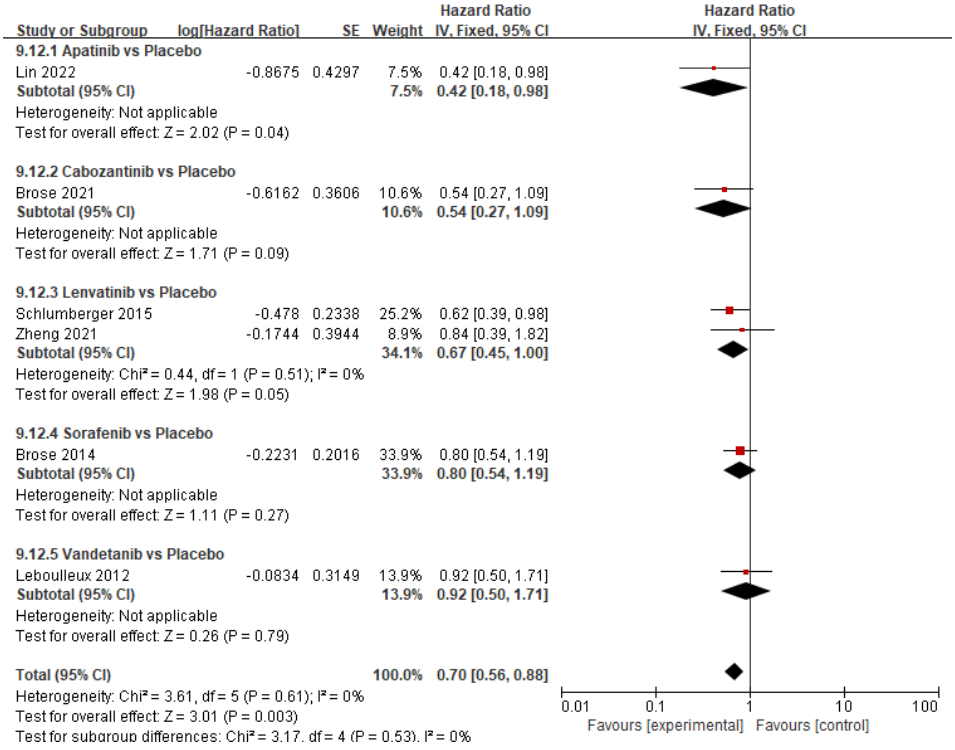
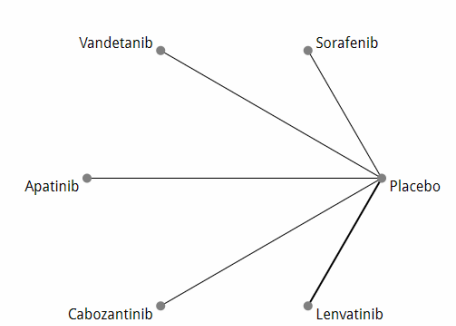


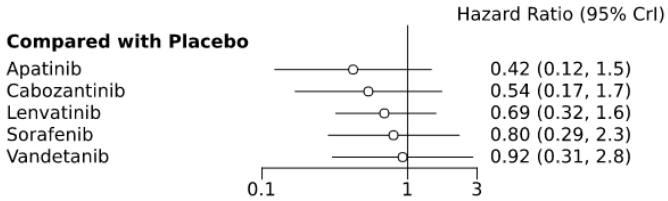
Figure 5 Comparison of overall survival in multi-kinase inhibitors (MKI) vs. placebo: (A) in all MKIs and (B) by treatment

Table 9 **Network meta-analysis result of overall survival**

Network plot



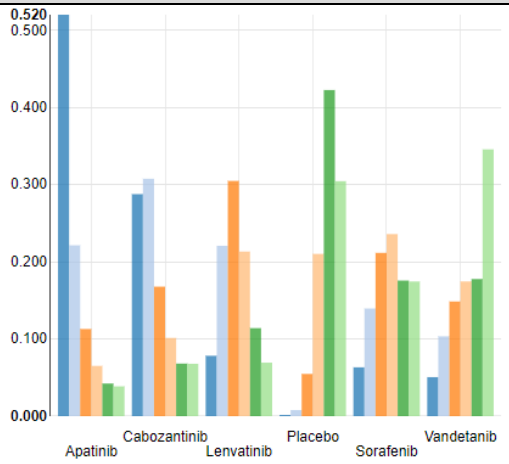
Forest plot



Ranking probability table

	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6
Apatinib	0.523	0.223	0.110	0.064	0.041	0.039
Cabozantinib	0.281	0.304	0.168	0.109	0.070	0.069
Lenvatinib	0.078	0.220	0.303	0.212	0.116	0.071
Placebo	0.000	0.008	0.056	0.209	0.418	0.309
Sorafenib	0.063	0.138	0.213	0.235	0.177	0.173
Vandetanib	0.054	0.106	0.150	0.171	0.178	0.340

Ranking probability plot



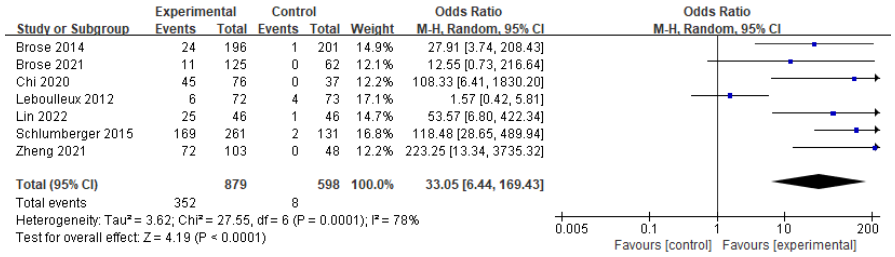
3.2.3. Objective response rate

Meta-analysis result revealed pooled MKIs, compared to placebo, had significantly higher ORR (OR: 33.05, 95% CI: 6.44–169.43, P=0.0001) (Figure 6A).

ORR by treatment had shown lenvatinib, anlotinib, apatinib, and sorafenib showed significantly higher ORR, while cabozantinib and vandetanib had not demonstrated statistically significant higher ORR compared to placebo (Figure 6B).

The Bayesian network meta-analysis revealed statistically significant improvement ORR in anlotinib, cabozantinib, and lenvatinib, but not in apatinib, sorafenib, and vandetanib. The consistency test was not available. The 1st rank treatment for a better ORR was cabozantinib (Table 10).

A



B

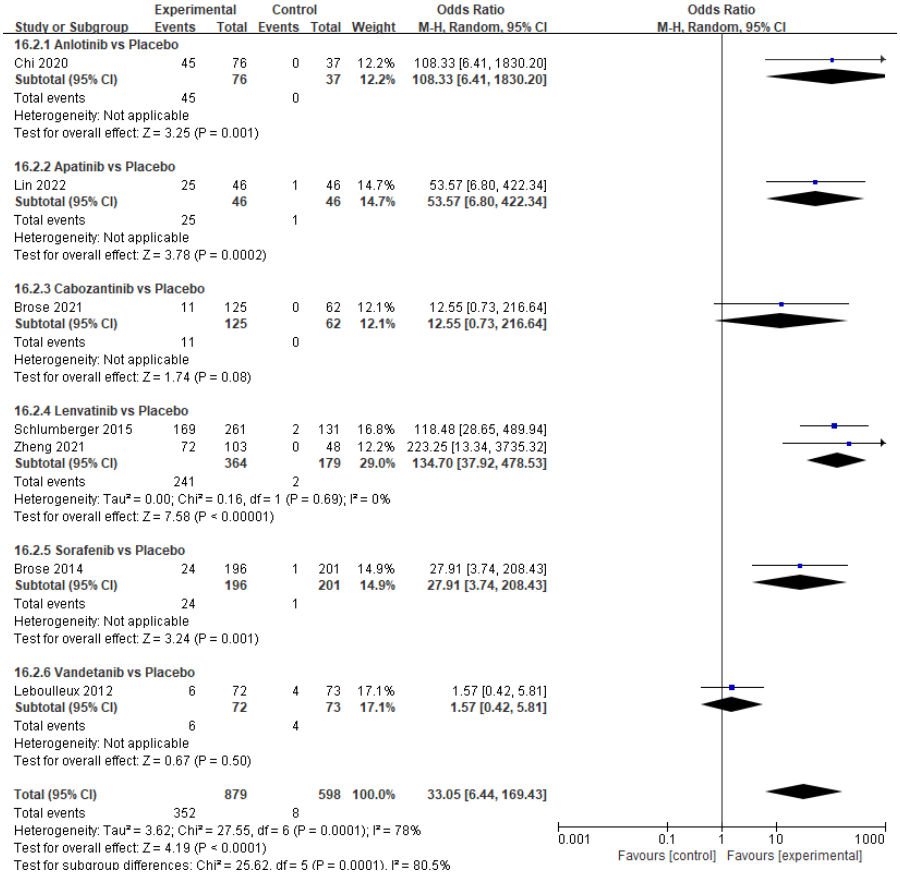
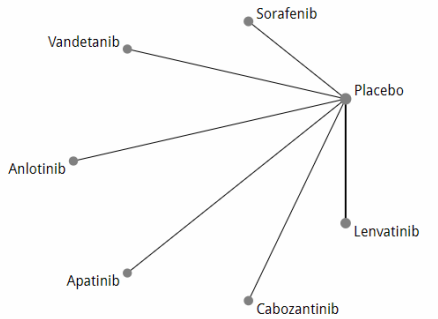


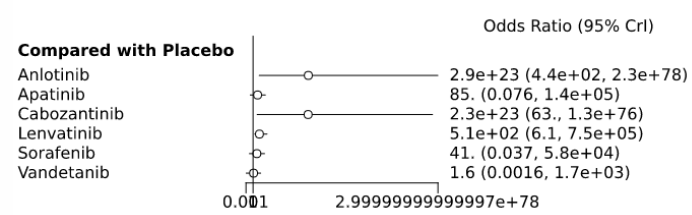
Figure 6 Comparison of objective response rates in multi-kinase inhibitors (MKIs) vs. placebo: (A) in all MKIs and (B) by treatment

Table 10 **Network meta-analysis result of objective response rate**

Network plot



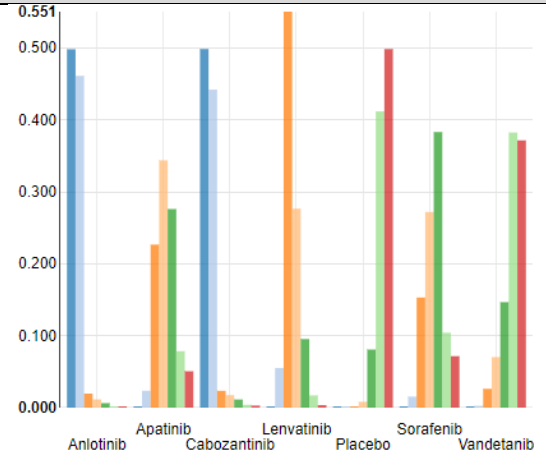
Forest plot



Ranking probability table

	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7
Anlotinib	0.498	0.462	0.020	0.011	0.006	0.002	0.001
Apatinib	0.001	0.023	0.227	0.344	0.276	0.078	0.051
Cabozantinib	0.499	0.442	0.023	0.017	0.011	0.004	0.003
Lenvatinib	0.002	0.055	0.551	0.277	0.095	0.017	0.003
Placebo	0.000	0.000	0.000	0.008	0.081	0.412	0.499
Sorafenib	0.000	0.015	0.153	0.272	0.383	0.104	0.072
Vandetanib	0.000	0.002	0.026	0.070	0.147	0.383	0.372

Ranking probability plot



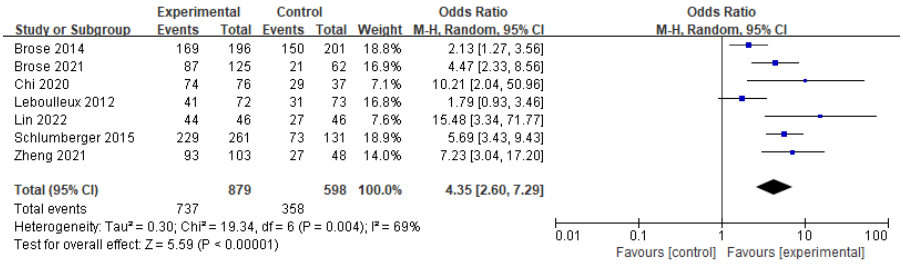
3.2.4. Disease control rate

Meta-analysis result revealed pooled MKIs, compared to placebo, had significantly higher DCR (OR: 5.08, 95% CI: 2.95–8.75, P<0.00001) (Figure 7A).

DCR by treatment had shown that compared to placebo, apatinib, anlotinib, lenvatinib, and cabozantinib showed significantly higher DCR. Vandetanib had not demonstrated statistically significant higher DCR (Figure 7B).

The Bayesian network meta-analysis revealed statistically significant improvement DCR in apatinib and lenvatinib, but not in anlotinib, cabozantinib, sorafenib, and vandetanib. The consistency test was not available. The 1st rank treatment for a better DCR was apatinib (Table 11).

A



B

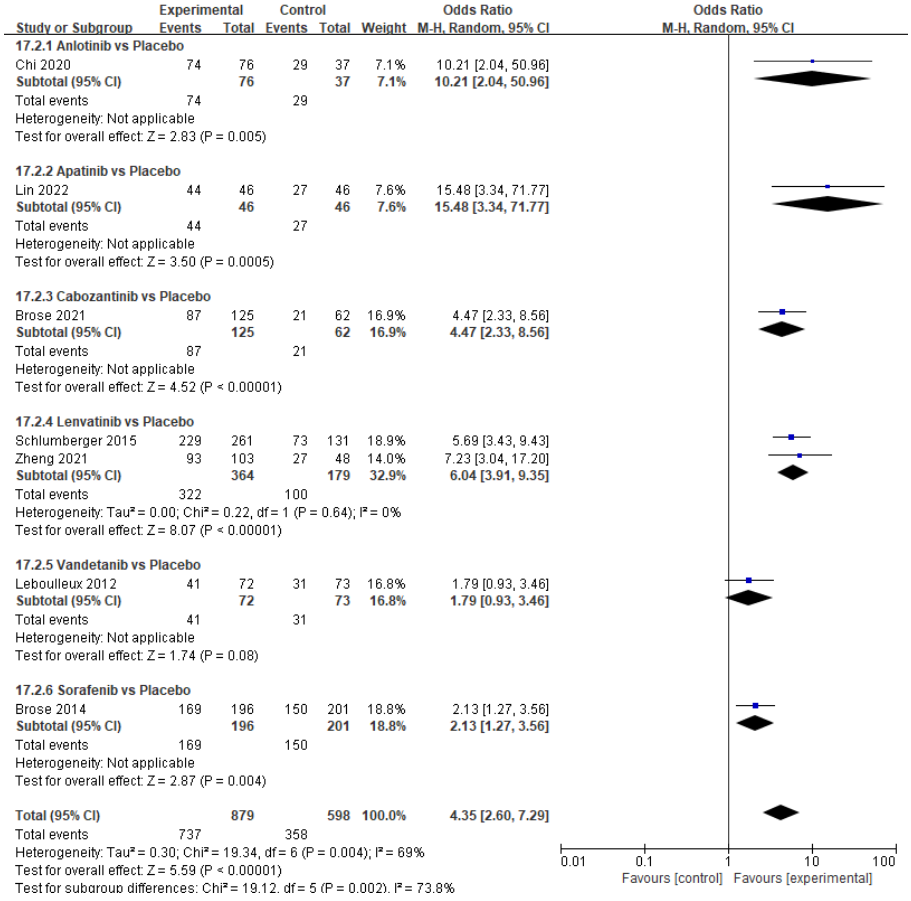
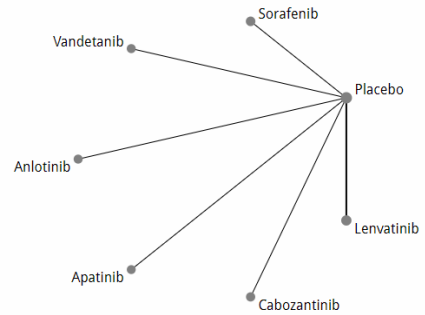


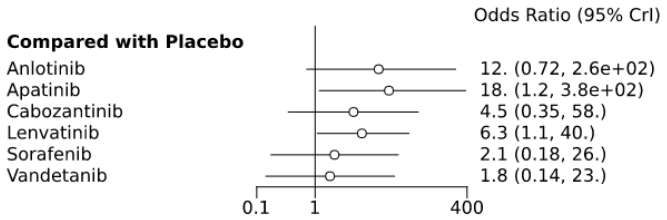
Figure 7 Comparison of disease control rates in multi-kinase inhibitors (MKIs) vs. placebo: (A) in all MKIs and (B) by treatment

Table 11 **Network meta-analysis result of disease control rate**

Network plot



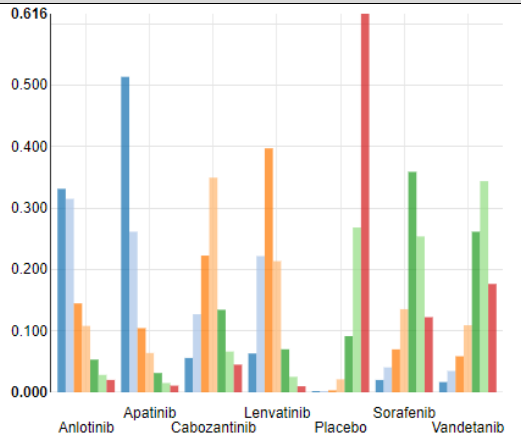
Forest plot



Ranking probability table

	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7
Anlotinib	0.331	0.315	0.145	0.108	0.053	0.028	0.020
Apatinib	0.513	0.261	0.104	0.064	0.031	0.015	0.011
Cabozantinib	0.056	0.127	0.222	0.349	0.134	0.066	0.045
Lenvatinib	0.063	0.222	0.397	0.213	0.070	0.025	0.010
Placebo	0.000	0.000	0.003	0.021	0.091	0.268	0.616
Sorafenib	0.020	0.040	0.070	0.135	0.359	0.254	0.122
Vandetanib	0.017	0.035	0.059	0.109	0.261	0.344	0.176

Ranking probability plot



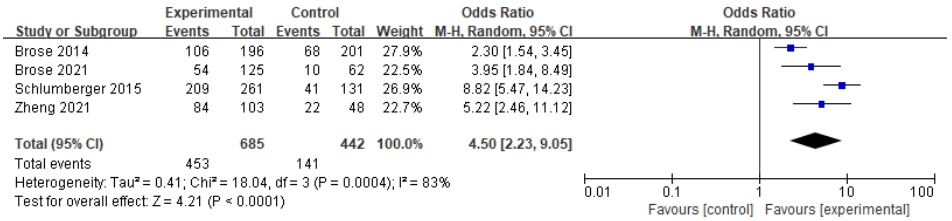
3.2.5. Clinical benefit rate

Meta-analysis result revealed pooled MKIs, compared to placebo, had significantly higher CBR (OR: 3.98, 95% CI: 1.53–10.34, P=0.005) (Figure 8A).

CBR by treatment had shown that compared to placebo, lenvatinib and cabozantinib showed significantly higher CBR. Sorafenib had not demonstrated statistically significant higher CBR (Figure 8B).

The Bayesian network meta-analysis revealed statistically significant improvement CBR in lenvatinib only, but not in cabozantinib and sorafenib. The consistency test was not available. The 1st rank treatment for a better CBR was lenvatinib (Table 12).

A



B

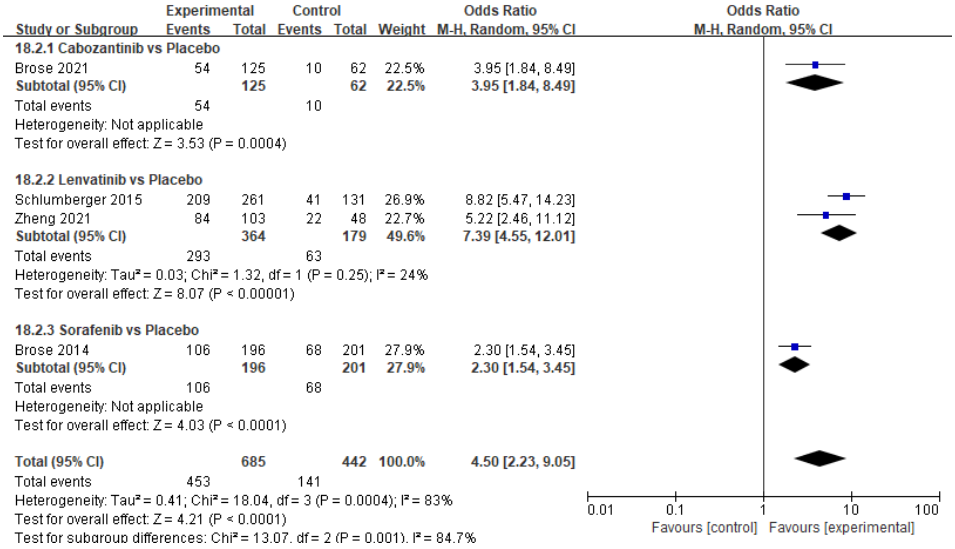
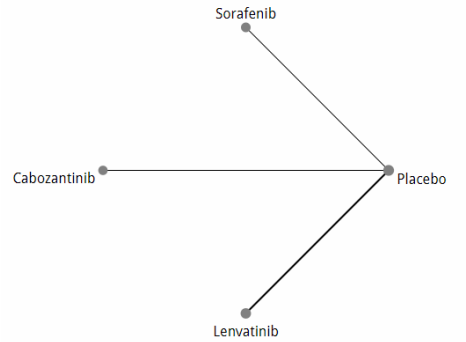


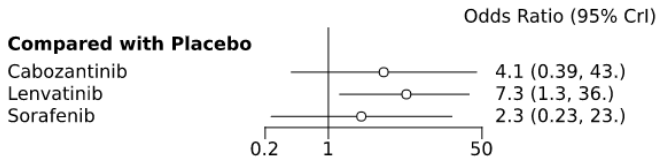
Figure 8 Comparison of clinical benefit rates in multi-kinase inhibitors (MKIs) vs. placebo: (A) in all MKIs and (B) by treatment

Table 12 **Network meta-analysis result of clinical benefit rate**

Network plot



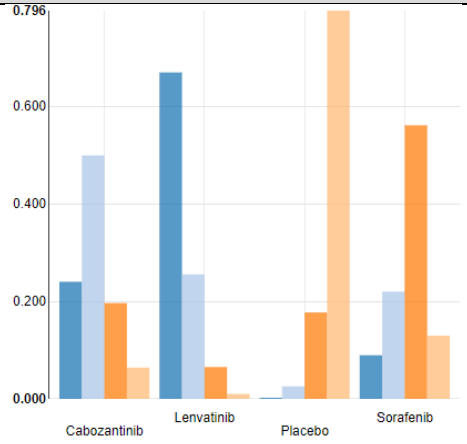
Forest plot



Ranking probability table

	Rank 1	Rank 2	Rank 3	Rank 4
Cabozantinib	0.240	0.499	0.196	0.064
Lenvatinib	0.669	0.255	0.065	0.010
Placebo	0.001	0.026	0.177	0.796
Sorafenib	0.089	0.220	0.561	0.130

Ranking probability plot



3.3. Safety Outcomes

Reported safety outcomes that have been included in the meta-analyses in each study are provided in Table 13.

Table 13 Reported safety outcomes

Study	Intervention	AE	Related AE	AE ≥G3	SAE	Fatal AE	Discont. AE
Leboulleux 2012	Vandetanib			✓		✓	✓
Schlumberger 2015	Lenvatinib	✓	✓		✓	✓	✓
Brose 2014	Sorafenib	✓			✓	✓	✓
NCT01876784	Vandetanib				✓		
Schlumberger 2018	Nintedanib			✓			
Chi 2020	Anlotinib		✓				
Brose 2021	Cabozantinib	✓		✓		✓	✓
Zheng 2021	Lenvatinib	✓	✓	✓	✓	✓	✓
Lin 2022	Apatinib	✓	✓	✓			✓

Study	Intervention	HTN	Diarrhea	HFS	Proteinuria	QTc prolong	Hypocalcemia
Leboulleux 2012	Vandetanib	✓	✓			✓	
Schlumberger 2015	Lenvatinib	✓	✓	✓	✓	✓	
Brose 2014	Sorafenib	✓	✓	✓			✓
NCT01876784	Vandetanib						
Schlumberger 2018	Nintedanib						
Chi 2020	Anlotinib						
Brose 2021	Cabozantinib	✓	✓	✓	✓		✓
Zheng 2021	Lenvatinib	✓	✓	✓	✓		✓
Lin 2022	Apatinib		✓	✓	✓	✓	✓

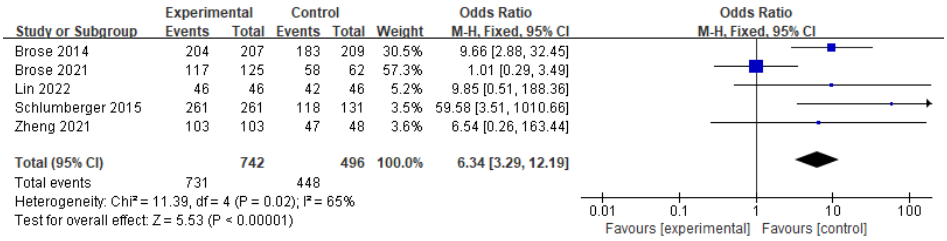
Abbreviations: AE, adverse event; Discont, Discontinued; HFS, hand foot syndrome; HTN, hypertension; SAE, serious adverse event.

3.3.1. Adverse event

In comparison with placebo, proportion of patients who experienced adverse events were significantly higher in the lenvatinib (OR: 32.64, 95% CI: 4.30–247.77, p=0.0008) and sorafenib (OR: 9.66, 95% CI: 2.88–32.45, p=0.0002). There was no statistically significant difference in apatinib and cabozantinib compared to placebo (Figure 9).

The Bayesian network meta-analysis revealed that in comparison with placebo, apatinib and lenvatinib was associated with significantly higher adverse events. Cabozantinib and sorafenib were not significantly different from placebo. The consistency test was not available. The 1st rank treatment for highest toxicity of AE was lenvatinib (Table 14).

A



B

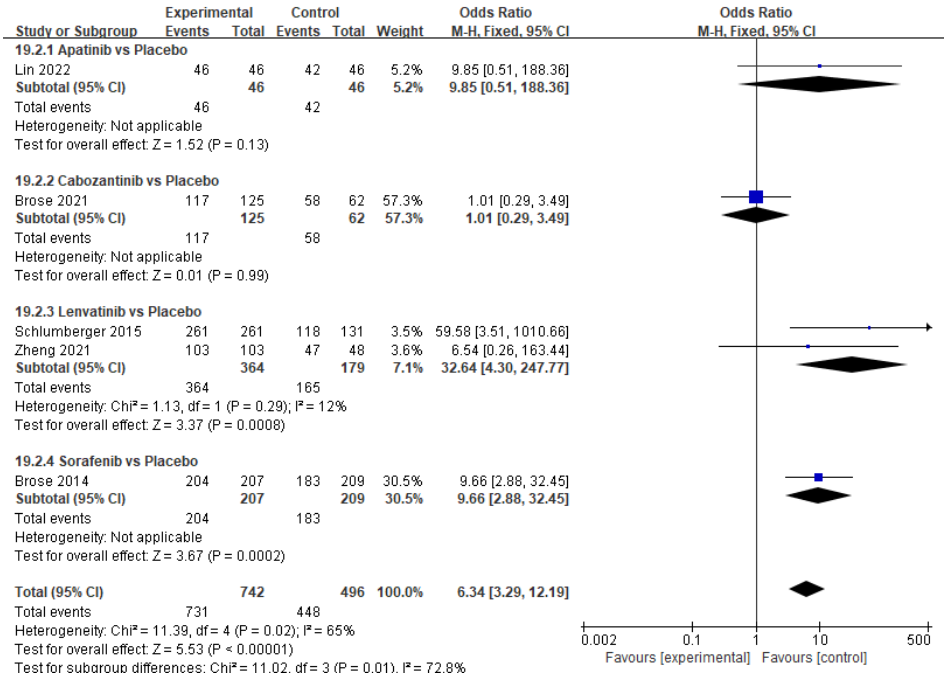
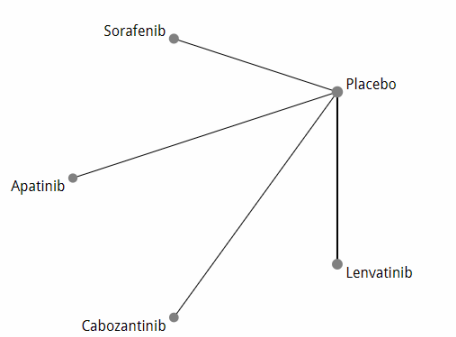


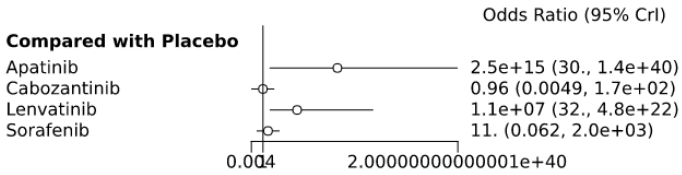
Figure 9 Comparison of adverse events in multi-kinase inhibitors (MKIs) vs. placebo: (A) in all MKIs and (B) by treatment

Table 14 **Network meta-analysis result of adverse event**

Network plot



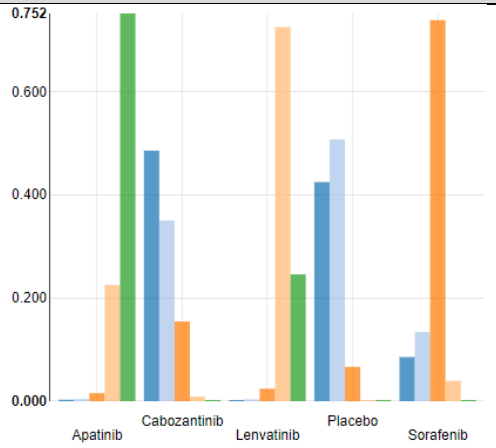
Forest plot



Ranking probability table

	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5
Apatinib	0.003	0.004	0.015	0.225	0.752
Cabozantinib	0.486	0.350	0.155	0.009	0.000
Lenvatinib	0.001	0.003	0.024	0.726	0.246
Placebo	0.425	0.508	0.067	0.001	0.000
Sorafenib	0.086	0.134	0.739	0.040	0.002

Ranking probability plot

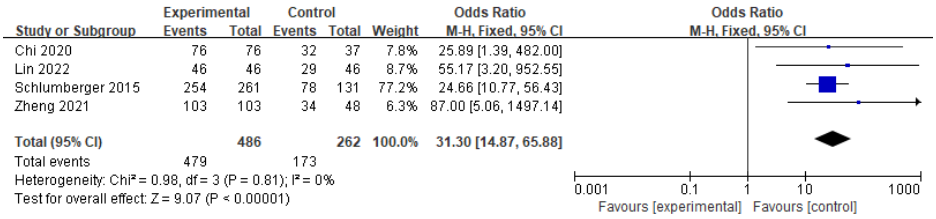


3.3.2. Adverse event related to study drug

In comparison with placebo, proportion of patients who experienced adverse events related to study drug were significantly higher in the apatinib (OR: 55.17, 95% CI: 3.20–952.55, p=0.006) and lenvatinib (OR: 29.32, 95% CI: 13.29–64.68, p<0.00001). There was no statistically significant difference in anlotinib compared to placebo (Figure 10).

The Bayesian network meta-analysis revealed that in comparison with placebo, all anlotinib, apatinib and lenvatinib was associated with significantly higher adverse events related to study drug. The consistency test was not available. The 1st rank treatment for highest toxicity of AE related to study drug was apatinib (Table 15).

A



B

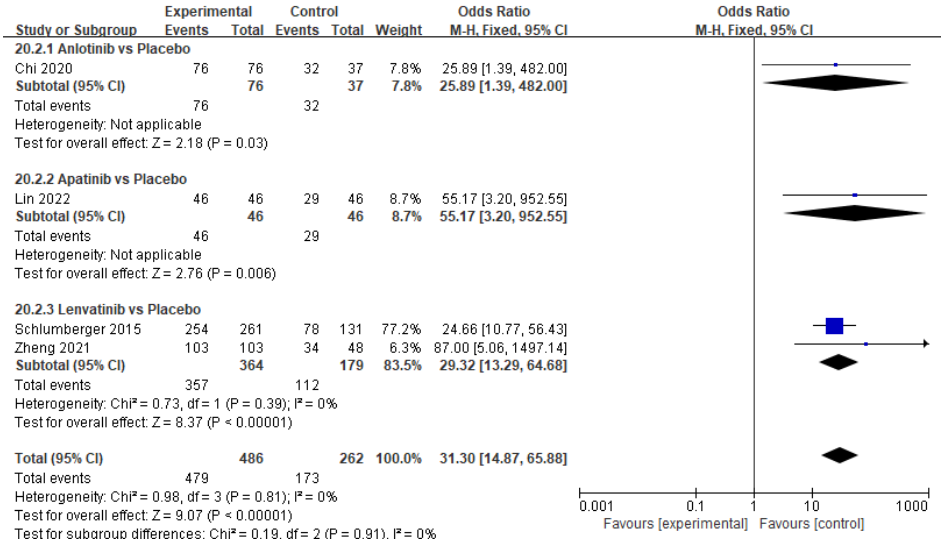
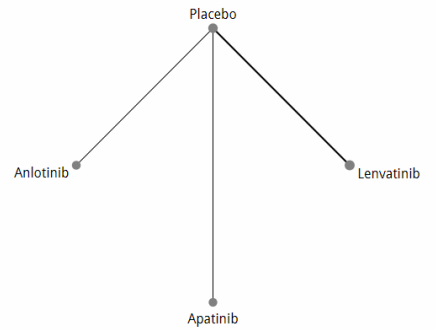


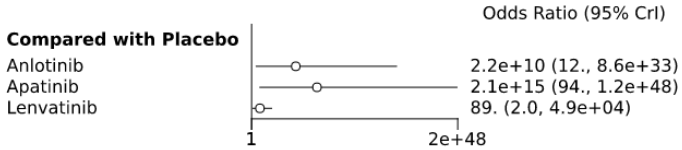
Figure 10 Comparison of adverse events related to study drug in multi-kinase inhibitors (MKIs) vs. placebo: (A) in all MKIs and (B) by treatment

Table 15 **Network meta-analysis result of adverse event related to study drug**

Network plot



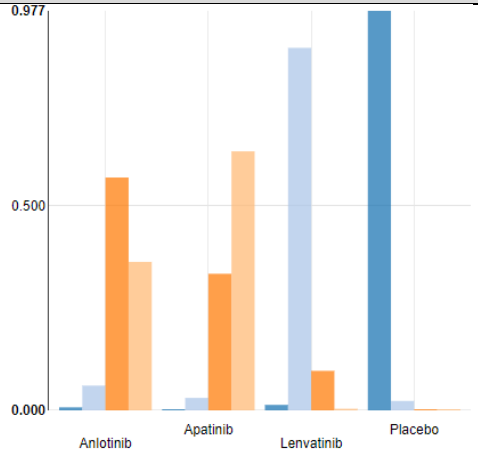
Forest plot



Ranking probability table

	Rank 1	Rank 2	Rank 3	Rank 4
Anlotinib	0.007	0.060	0.569	0.363
Apatinib	0.003	0.030	0.334	0.633
Lenvatinib	0.013	0.886	0.097	0.004
Placebo	0.977	0.023	0.000	0.000

Ranking probability plot

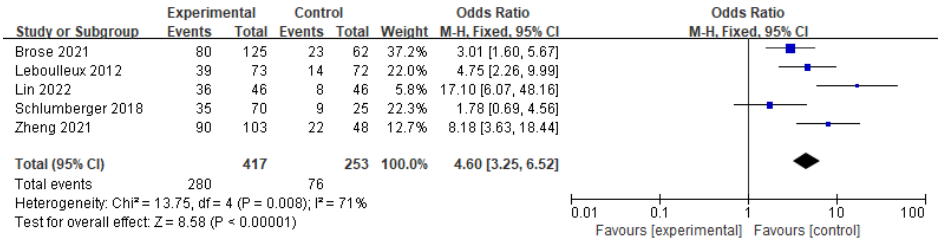


3.3.3. Adverse event ≥ grade 3

In comparison with placebo, proportion of patients who experienced adverse events ≥ grade 3 were significantly higher in the apatinib (OR: 17.10, 95% CI: 6.07–48.16, p<0.00001), lenvatinib (OR: 8.18, 95% CI: 3.63–18.44, p<0.00001), vandetanib (OR: 4.75, 95% CI: 2.26–9.99, p<0.0001), and cabozantinib (OR: 3.01, 95% CI: 1.60–5.67, p=0.0006) treatments. There was no statistically significant difference in nintedanib compared to placebo (Figure 11).

The Bayesian network meta-analysis revealed that in comparison with placebo, all apatinib, lenvatinib, vandetanib, cabozantinib, and nintedanib treatments were not associated with significantly higher adverse events ≥ grade 3. The consistency test was not available. The 1st rank treatment for highest toxicity of AE ≥ grade 3 was apatinib (Table 16).

A



B

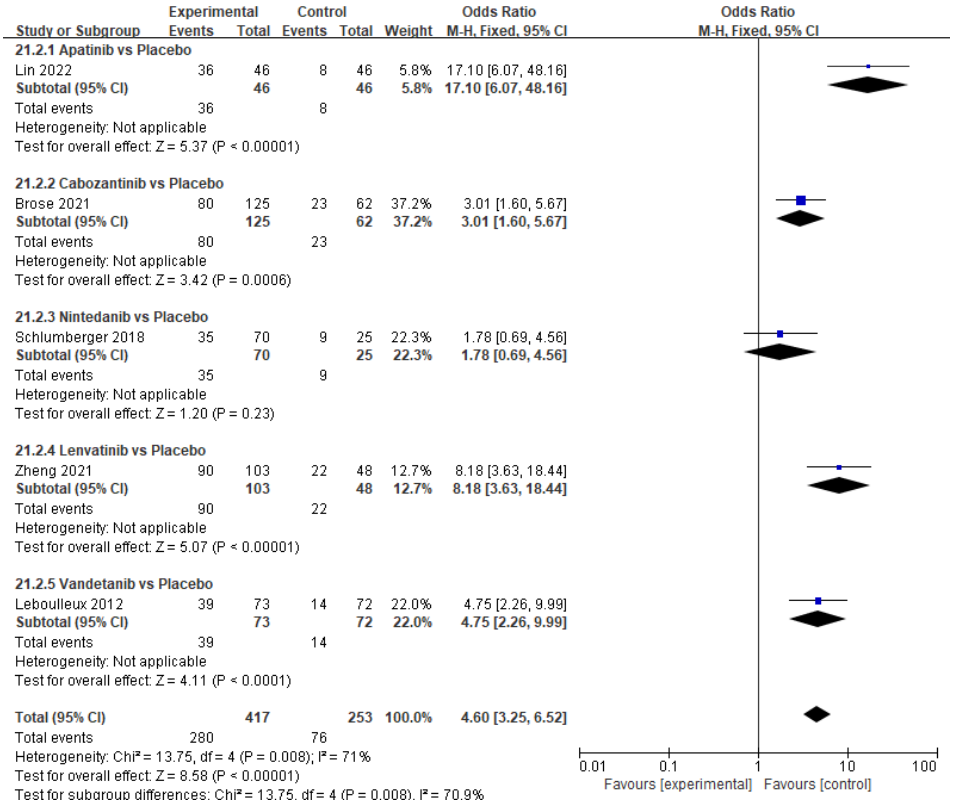
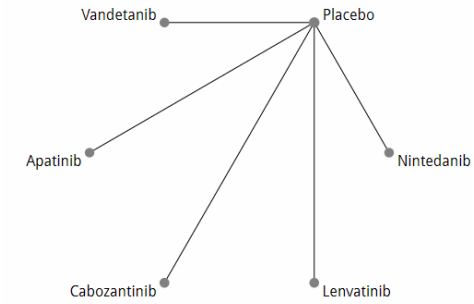


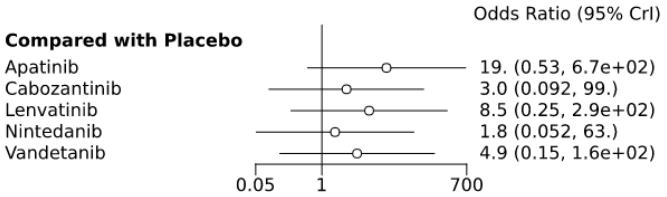
Figure 11 Comparison of adverse events ≥ grade 3 in multi-kinase inhibitors (MKIs) vs. placebo: (A) in all MKIs and (B) by treatment

Table 16 **Network meta-analysis result of adverse event ≥ grade 3**

Network plot



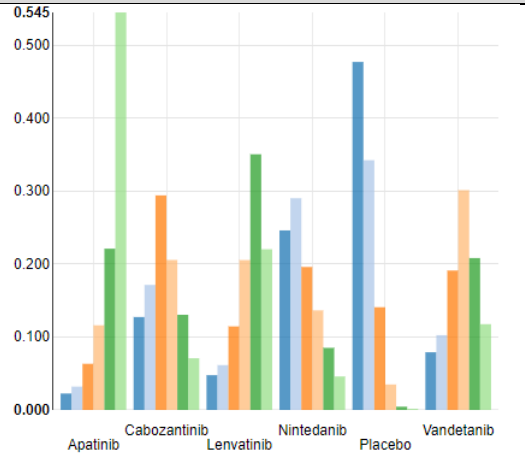
Forest plot



Ranking probability table

	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6
Apatinib	0.023	0.032	0.063	0.116	0.221	0.545
Cabozantinib	0.127	0.171	0.294	0.206	0.130	0.071
Lenvatinib	0.048	0.061	0.115	0.205	0.351	0.220
Nintedanib	0.246	0.290	0.196	0.137	0.085	0.046
Placebo	0.477	0.342	0.141	0.035	0.004	0.000
Vandetanib	0.079	0.103	0.191	0.301	0.208	0.118

Ranking probability plot

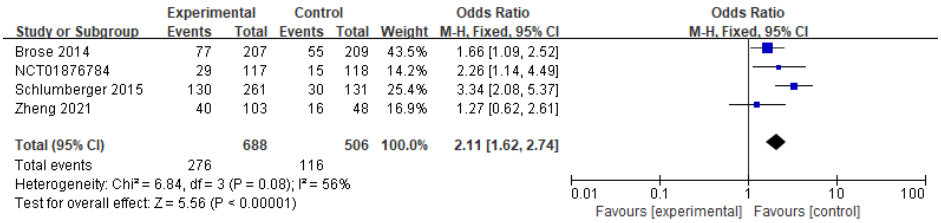


3.3.4. Serious adverse event

In comparison with placebo, proportion of patients who experienced serious adverse events were significantly higher in the lenvatinib (OR: 2.51, 95% CI: 1.70–3.72, p<0.00001), vandetanib (OR: 2.26, 95% CI: 1.14–4.49, p=0.02), and sorafenib (OR: 1.66, 95% CI: 1.09–2.52, p=0.02) treatments (Figure 12).

The Bayesian network meta-analysis revealed that in comparison with placebo, all lenvatinib, sorafenib, and vandetanib treatments were not associated with significantly higher serious adverse events. The consistency test was not available. The 1st rank treatment for highest toxicity of SAE was lenvatinib (Table 17).

A



B

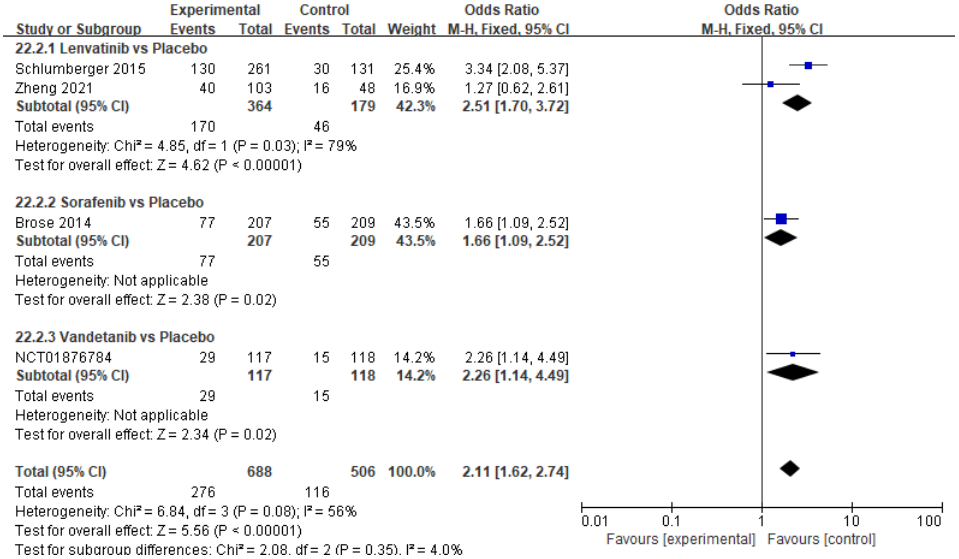
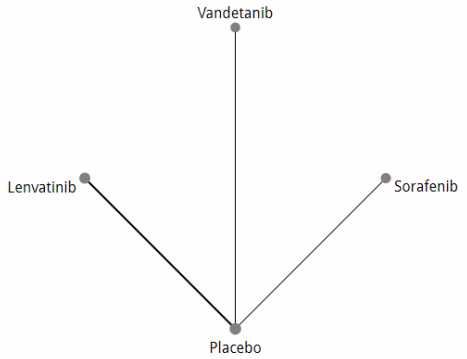


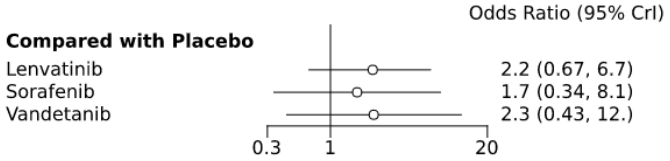
Figure 12 Comparison of serious adverse events in multi-kinase inhibitors (MKIs) vs. placebo: (A) in all MKIs and (B) by treatment

Table 17 **Network meta-analysis result of serious adverse event**

Network plot



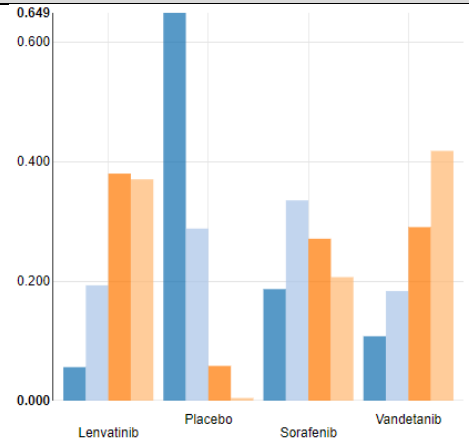
Forest plot



Ranking probability table

	Rank 1	Rank 2	Rank 3	Rank 4
Lenvatinib	0.056	0.193	0.380	0.371
Placebo	0.649	0.288	0.058	0.004
Sorafenib	0.187	0.335	0.271	0.207
Vandetanib	0.108	0.183	0.291	0.418

Ranking probability plot

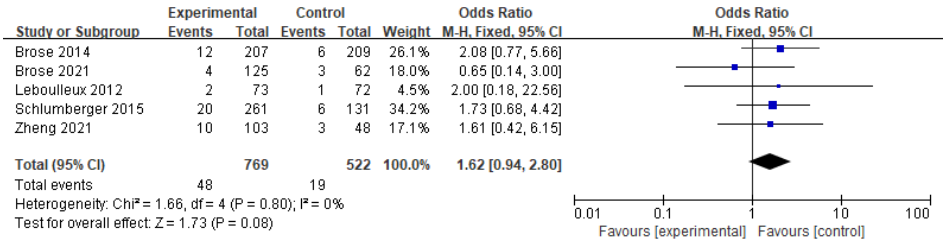


3.3.5. Fatal adverse event

In comparison with placebo, all cabozantinib, lenvatinib, sorafenib, and vandetanib treatments were not associated with significantly higher fatal adverse events (Figure 13).

The Bayesian network meta-analysis also revealed that in comparison with placebo, all cabozantinib, lenvatinib, sorafenib, and vandetanib treatments were not associated with significantly higher fatal adverse events. The consistency test was not available. The 1st rank treatment for highest toxicity of fatal AE was lenvatinib (Table 18).

A



B

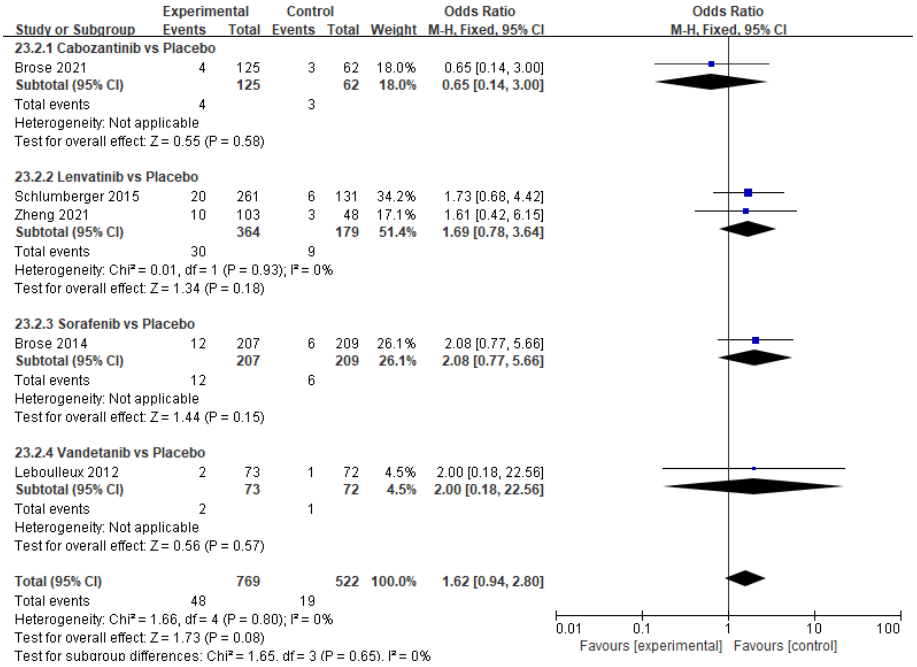
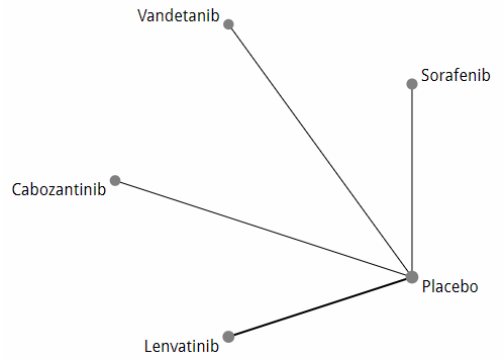


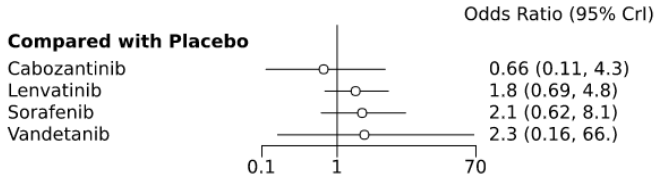
Figure 13 Comparison of fatal adverse events in multi-kinase inhibitors (MKIs) vs. placebo: (A) in all MKIs and (B) by treatment

Table 18 **Network meta-analysis result of fatal adverse event**

Network plot



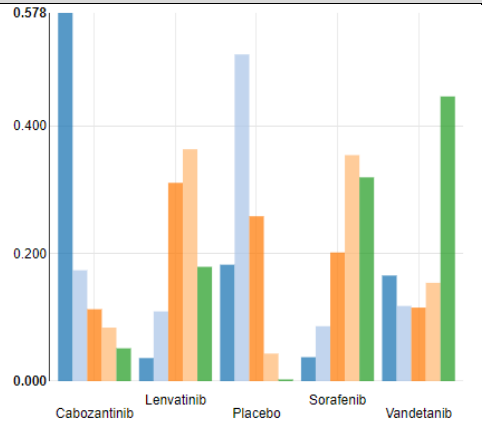
Forest plot



Ranking probability table

	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5
Cabozantinib	0.578	0.174	0.113	0.084	0.051
Lenvatinib	0.036	0.109	0.311	0.364	0.179
Placebo	0.183	0.513	0.259	0.043	0.003
Sorafenib	0.038	0.086	0.202	0.355	0.320
Vandetanib	0.166	0.118	0.115	0.154	0.447

Ranking probability plot

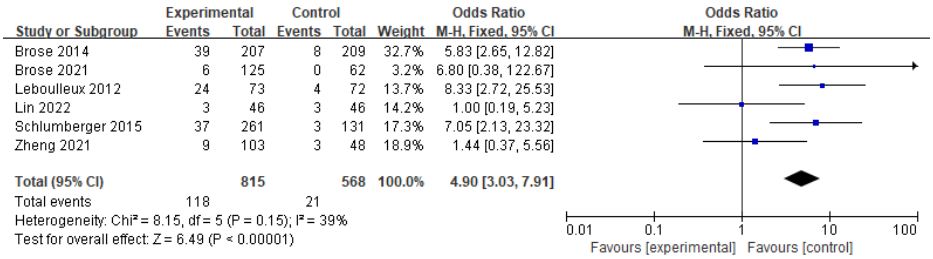


3.3.6. Adverse event leading to study discontinuation

In comparison with placebo, proportion of patients who experienced adverse events leading to study discontinuation were significantly higher in the vandetanib (OR: 8.33, 95% CI: 2.72–25.53, p=0.0002), sorafenib (OR: 5.83, 95% CI: 2.65–12.82, p<0.0001), and lenvatinib (OR: 4.12, 95% CI: 1.74–9.79, p=0.001) treatments (Figure 12). There were no statistically significant differences in cabozantinib and apatinib compared to placebo (Figure 14).

The Bayesian network meta-analysis revealed that in comparison with placebo, only cabozantinib was associated with significantly higher adverse events leading to study discontinuation. Rest of the treatments (apatinib, lenvatinib, sorafenib, and vandetanib) were not associated with significantly higher adverse events leading to study discontinuation. The consistency test was not available. The 1st rank treatment for highest toxicity of adverse events leading to study discontinuation was cabozantinib (Table 19).

A



B

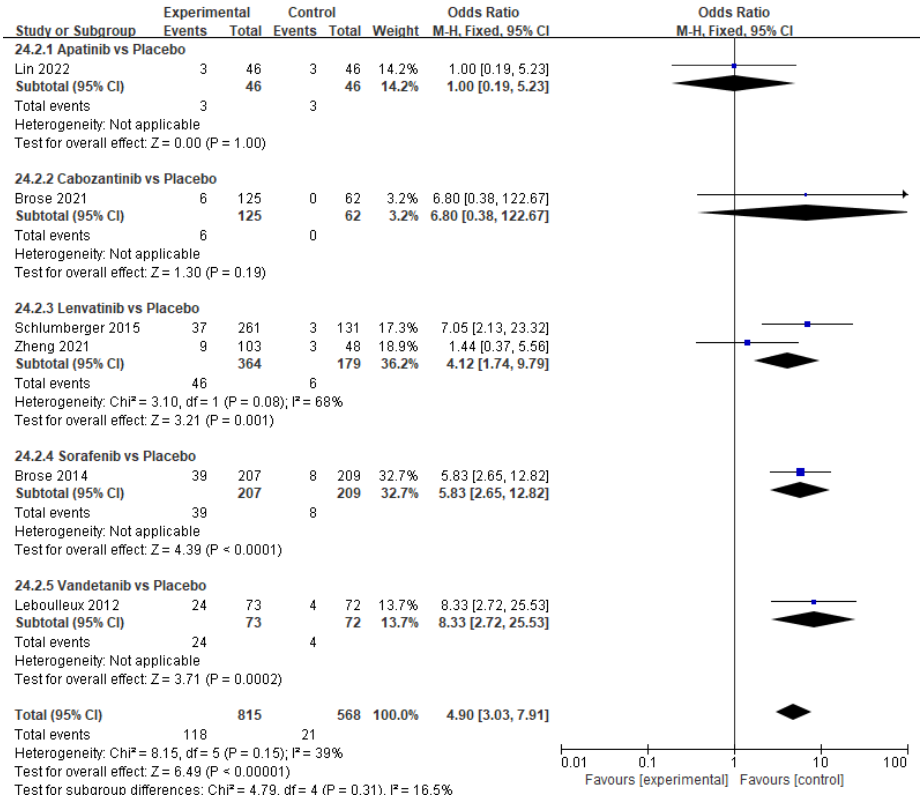
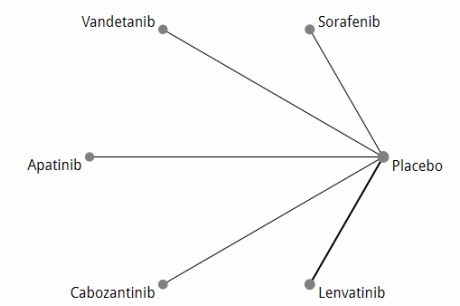


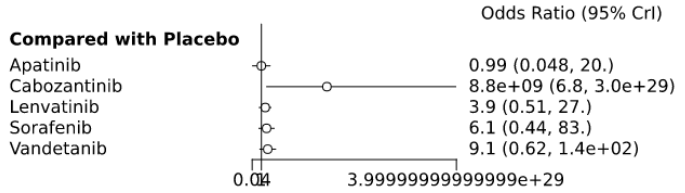
Figure 14 Comparison of adverse events leading to study drug discontinuation in multi-kinase inhibitors (MKIs) vs. placebo: (A) in all MKIs and (B) by treatment

Table 19 **Network meta-analysis result of adverse event leading to study discontinuation**

Network plot



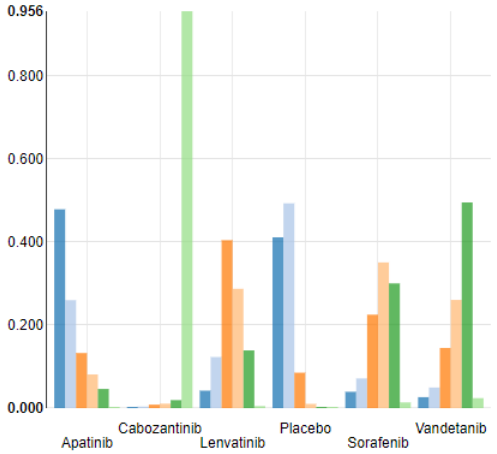
Forest plot



Ranking probability table

	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6
Apatinib	0.479	0.260	0.133	0.081	0.046	0.002
Cabozantinib	0.003	0.004	0.008	0.011	0.019	0.956
Lenvatinib	0.042	0.123	0.404	0.287	0.139	0.005
Placebo	0.411	0.493	0.085	0.010	0.001	0.000
Sorafenib	0.039	0.071	0.225	0.351	0.300	0.014
Vandetanib	0.026	0.049	0.145	0.260	0.495	0.024

Ranking probability plot



3.3.7. Adverse event of special interest

In comparison with placebo, proportion of patients who experienced hypertension were significantly higher in the lenvatinib (OR: 13.56, 95% CI: 8.55–21.48, p<0.00001), vandetanib (OR: 8.85, 95% CI: 2.89–27.09, p=0.0001), and sorafenib (OR: 4.81, 95% CI: 2.93-7.89, p<0.00001) treatments, respectively. There was no statistically significant difference in cabozantinib compared to placebo (Appendix Figure 22).

In comparison with placebo, proportion of patients who experienced diarrhea were significantly higher in the cabozantinib (OR: 31.48, 95% CI: 7.37–134.43, p<0.00001), vandetanib (OR: 14.21, 95% CI: 6.32–31.97, p<0.00001), sorafenib (OR: 12.08, 95% CI: 7.50–19.48, p<0.00001), lenvatinib (OR: 11.81, 95% CI: 7.20–19.38, p<0.00001), and apatinib (OR: 6.63, 95% CI: 2.46–17.88, p=0.0002) treatments, respectively (Appendix Figure 23).

In comparison with placebo, proportion of patients who experienced hand-foot syndrome were significantly higher in the apatinib (OR: 146.67, 95% CI: 27.98–768.75, p<0.00001), cabozantinib (OR: 104.93, 95% CI: 6.35–1733.90, p=0.001), lenvatinib (OR: 45.18, 95% CI: 13.39–152.51, p<0.00001), and sorafenib (OR: 30.47, 95% CI: 17.38–53.42, p<0.00001) (Appendix Figure 24).

In comparison with placebo, proportion of patients who experienced proteinuria were significantly higher in the apatinib (OR: 33.71, 95% CI: 10.36–709.72, p<0.00001), lenvatinib (OR: 22.96, 95% CI: 10.35–50.91, p<0.00001), and cabozantinib (OR: 5.38, 95% CI: 1.21–23.88, p=0.03) (Appendix Figure 25).

In comparison with placebo, proportion of patients who experienced QTc prolongation were significantly higher in the vandetanib (OR: 44.91, 95% CI: 2.64–763.00, p=0.008), and lenvatinib (OR: 6.23, 95% CI: 1.45–26.86, p=0.01). There was no statistically significant difference in apatinib compared to placebo (Appendix

Figure 26).

In comparison with placebo, proportion of patients who experienced hypocalcemia were significantly higher in the apatinib (OR: 21.77, 95% CI: 2.73–173.47, p=0.004), cabozantinib (OR: 18.43, 95% CI: 2.45–138.79, p=0.005), and sorafenib (OR: 4.62, 95% CI: 2.24–9.53, p<0.001). There was no statistically significant difference in lenvatinib compared to placebo (Appendix Figure 27).

3.4. Risk of bias assessment

The risk of bias assessment result is presented in Figure 15. The domain for selection of the reported results for the three studies (NCT01876784, Schlumberger et al. 2018, and Chi et al. 2020) were evaluated to have some concerns on bias due to absence of information on the pre-specified analysis plan which was to be finalized before unblinding data outcome for analysis. NCT01876784 trial result was not published and only reported through the clinicaltrial.gov website and the other two studies were conference abstract which lack detailed information on the statistical methods described above. All other studies were evaluated to have low risk of bias.

Study ID	Experimental	Comparator	D1	D2	D3	D4	D5	Overall
Leboulleux 2012	Vandetanib	Placebo	+	+	+	+	+	+
Schlumberger 2015	Lenvatinib	Placebo	+	+	+	+	+	+
Brose 2014	Sorafenib	Placebo	+	+	+	+	+	+
NCT01876784	Vandetanib	Placebo	+	+	+	+	!	!
Schlumberger 2018	Nintedanib	Placebo	+	+	+	+	!	!
Chi 2020	Anlotinib	Placebo	+	+	+	+	!	!
Brose 2021	Cabozantinib	Placebo	+	+	+	+	+	+
Zheng 2021	Lenvatinib	Placebo	+	+	+	+	+	+
Lin 2022	Apatinib	Placebo	+	+	+	+	+	+

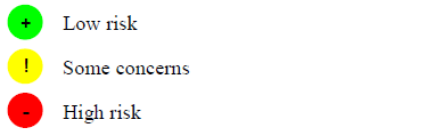


Figure 15 Risk of bias 2 assessment result

4. Discussion

4.1. Key findings

This study comprehensively compared the efficacy and safety outcomes of many MKIs for locally advanced or metastatic radioiodine refractory DTC patients. Even though most patients with DTC are at low risk, with a slow progression of disease and or most recurrences can be cured, there are about 5-10% of DTC patients who are at high-risk of persistent or recurrent disease. These patients are cured less frequently resulting in higher mortality, and they require more aggressive treatment and follow-up than those with the low-risk (Schlumberger and Leboulleux 2021). Ten-year survival rate in these high-risk patients is less than 30%, which is why finding optimal treatment is critical in managing the disease. Recently, two studies were published which presented the meta-analyses of effectiveness and safety of the MKI treatments in radioiodine refractory DTC. One study only presented the pooled analyses of traditional meta-analyses with MKI treatments (Su et al. 2022) and the other study reported a network meta-analyses of the efficacy and a single safety outcome of adverse events ≥ grade 3 (Ji et al. 2022). This is the first study to present network meta-analyses with extensive safety profile involving various adverse event classifications.

MKIs that have shown significant improvement in PFS compared to placebo were in the order of lenvatinib, anlotinib, cabozantinib, and apatinib. Nintedanib, sorafenib, and vandetanib had not shown significant improvement in PFS. In the papillary histologic subgroup, vandetanib had not shown significant improvement in PFS. To note, currently approved MKIs for recurrent, locally advanced, or metastatic radioiodine refractory DTC are lenvatinib, sorafenib, cabozantinib, and anlotinib (in China only). Vandetanib, nintedanib, and apatinib are not approved for the use in DTC patients yet, but this study supported that apatinib can be the candidate for treating recurrent, locally advanced, or metastatic radioiodine refractory DTC.

Because the result of apatinib was published in 2022, more clinical experience is necessary to confirm the efficacy.

In the network meta-analysis of OS, no treatment showed significant improvement compared to placebo. The meta-analysis by individual treatment also revealed that only apatinib was shown to be effective in OS, however improvement in OS is not as evident as in PFS since the upper limit of the 95% CI lied slightly below 1.0 (HR: 0.42, 95% CI: 0.18–0.98).

As such, MKI treatment is associated with improvement in PFS, but not in OS. In other words, MKI will aid recurrent, locally advanced, or metastatic radioiodine refractory DTC patients from disease progression but will hardly benefit patients from survival. We should also consider that DTC is relatively an indolent disease and all the OS data collected from the studies were immature and have not reached the median OS at the time of the report. The final analysis of the Brose et al. 2021 study (cabozantinib vs. placebo) had shown no significant improvement in OS compared to placebo as well (HR: 0.76, 95% CI: 0.45–1.31) (Capdevila et al. 2021). Other drug class approved for DTC, pembrolizumab, was also studied in advanced or metastatic radioiodine refractory DTC and the study data with a median follow up of 31 months also showed immature OS data with median OS not reached (Mehnert et al. 2019).

In the subgroup analysis of PFS, lenvatinib was effective in both MKI naïve and 1 prior MKI groups. Lenvatinib is currently a single preferred regimen according to the NCCN treatment guideline and is widely used as the first line MKI therapy, and the study results support this recommendation and suggest lenvatinib may also be used after initial MKI failure. Cabozantinib was effective in both patient groups who used 1 prior MKI and 2 prior MKIs, which is in line with the cabozantinib label to be used for patients who progressed after lenvatinib and/or sorafenib.

In addition, lenvatinib was most effective in patients with lung metastasis, and this

supports that lenvatinib may be the best treatment option for metastatic DTC patients as lung being the most common metastatic site in this disease. Distant metastases of DTC present with lung metastasis in 50%, bone metastasis in 26% and both lung and bone metastasis in 18.5% of the DTC patients (Durante et al. 2006).

Lenvatinib was also effective when used for both 6 ~ 12 months and 12 ~ 24 months, meaning that treatment duration will not affect the overall effect of the treatment. Patients who received lenvatinib may continue to receive for up to at least 2 years when shown adequate response. All other treatments were classified in only one of the period classifications, so the interpretation is limited for other MKIs.

In the network meta-analysis of ORR, cabozantinib, anlotinib, and lenvatinib had showed significantly higher ORR compared to placebo, but not in the apatinib, sorafenib, and vandetanib groups. To note, cabozantinib trial enrolled patients who failed previous lenvatinib or sorafenib treatment and were allowed to enroll after 2 weeks or 5 half-lives. The relatively low ORR in this study might have been affected by the amount of time that has passed following progression from the most recent VEGFR TKI, with longer periods resulting in new vessel growth, which is more likely to respond to reintroduction of VEGFR and other kinase inhibition (Brose et al. 2021).

In the safety analyses, all MKI treatments were associated with significantly higher adverse events related to the study drug compared to the placebo group. Apatinib was ranked 1st for higher adverse events related to the study drug and also for adverse events ≥ grade 3. Lenvatinib was ranked 1st for higher serious adverse events and fatal adverse events, however these were not considered to be statistically different from the placebo group. Cabozantinib was the 1st to rank for the higher adverse events leading to study discontinuation, and also the only treatment that was considered to be significantly higher than the placebo group.

Most of the MKI treatments were associated with higher adverse events of

hypertension, diarrhea, hand-foot syndrome, and proteinuria compared to the placebo group. These are well known toxicities associated with the use of VEGF targeting agents and are usually manageable with supportive pharmacologic treatment (Eskens and Verweij 2006). Treatment interruption or discontinuation may be indicated in case of failure of toxicities, so monitoring of the safety events are crucial to patients receiving MKI treatments.

In general, drugs with higher efficacy were related with higher toxicities; lenvatinib, apatinib, and cabozantinib, for instance, showed higher adverse events related to the drug or adverse events leading to study discontinuation. This indicates that understanding the benefit risk ratio of the MKI will be important in the clinical settings to select optimal treatment for the high-risk DTC patients.

4.2. Limitations

This study has several limitations. First, most of the studies included locally advanced or metastatic radioiodine refractory DTC patients with papillary and follicular histology. However, some studies also included the poorly differentiated thyroid cancer type since having the same kinase targets as the DTCs; VEGF over expression being the most dominant genetic alteration. This may have negative impact on the outcome (Ibrahimpasic et al. 2014) and result in bias in interpretation. Second, all the 6 studies included in OS data analyses were immature, so the result may be biased. Third, apatanib and anlotinib trials were conducted in a single country (China), therefore the result may not apply to other races. Fourth, cabozantinib and nintedanib was studied in patients with previous MKI failure, therefore the result may be biased by including more severe patients. In contrast, anlotinib, sorafenib, and vandetanib trials were studied in MKI naïve patients. Lastly, test for inconsistency was not performed for the network meta-analyses as all the included studies were two-arm placebo controlled RCTs and there were no head-to-head comparison trials.

5. Conclusion

DTC often presents as an indolent disease and many patients may be asymptomatic from progressive disease. It is a lifelong disease and the main treatment goal for these patients will be to improve quality of life with or without aggressive treatments. Less than 5-10% of DTC patients are candidates for MKI treatments. However, due to the limited treatment option, high expense of treatment, and low survival rate in high-risk patients, understanding the optimal MKIs to treat recurrent, locally advanced, or metastatic radioiodine refractory DTC is very important.

MKIs will benefit recurrent, locally advanced, or metastatic radioiodine refractory DTC patients in PFS in the order of lenvatinib, anlotinib, cabozantinib, and apatinib. Lenvatinib and apatanib was also associated with best DCR and CBR. Cabozantinib was associated with the best ORR. Lenvatinib was also very effective in lung metastasis patients. Therefore, lenvatinib is mostly recommended in patients with tolerable toxicities. This is also in line with the NCCN guideline, recommending lenvatinib as the preferred regimen for recurrent, locally advanced, or metastatic radioiodine refractory DTC patients. If lenvatinib is not tolerable, anlotinib, cabozantinib, or apatinib can be recommended based on the finding of this study. Safety profiles were generally comparable between treatments, but higher toxicity was shown with drugs with higher efficacy, therefore, a close safety monitoring will be required during MKI treatment.

References

Bai Y, JY Li, J Li, B Zhang, YH Liu, BY Zhang and J Jing. 2019. Risk of venous and arterial thromboembolic events associated with tyrosine kinase inhibitors in advanced thyroid cancer: a meta-analysis and systematic review. Oncotarget, 10(41):4205-12.

Belum VR, C Serna-Tamayo, S Wu and ME Lacouture. 2016. Incidence and risk of hand-foot skin reaction with cabozantinib, a novel multikinase inhibitor: a meta-analysis. Clin Exp Dermatol, 41(1):8-15.

Brose MS, CM Nutting, B Jarzab, R Elisei, S Siena, L Bastholt, C de la Fouchardiere, F Pacini, R Paschke, YK Shong and et al. 2014. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet (london, england), 384(9940):319-28.

Brose MS, B Robinson, SI Sherman, J Krajewska, CC Lin, F Vaisman, AO Hoff, E Hitre, DW Bowles, J Hernando, L Faoro, K Banerjee, JW Oliver, B Keam and J Capdevila. 2021. Cabozantinib for radioiodine-refractory differentiated thyroid cancer (COSMIC-311): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol, 22(8):1126-38.

Cabanillas ME, M Ryder and C Jimenez. 2019. Targeted Therapy for Advanced Thyroid Cancer: Kinase Inhibitors and Beyond. Endocr Rev, 40(6):1573-604.

Capdevila J, B Robinson, SI Sherman, B Jarzab, CC Lin, F Vaisman, AO Hoff, E Hitre, DW Bowles, S Sen, P Patel, J Oliver, B Keam and MS Brose. 2021. LBA67 Cabozantinib versus placebo in patients with radioiodine-refractory differentiated thyroid cancer who have progressed after prior VEGFR-targeted therapy: Updated results from the phase III COSMIC-311 trial and prespecified subgroup analyses by prior therapy. Annals of Oncology, 32:S1343.

Dimitroulis IA. 2014. Nintedanib: a novel therapeutic approach for idiopathic pulmonary fibrosis. Respir Care, 59(9):1450-5.

Durante C, N Haddy, E Baudin, S Leboulleux, D Hartl, JP Travagli, B Caillou, M Ricard, JD Lumbroso, F De Vathaire and M Schlumberger. 2006. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J Clin Endocrinol Metab, 91(8):2892-9.

Eskens FA and J Verweij. 2006. The clinical toxicity profile of vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor (VEGFR) targeting angiogenesis inhibitors; a review. Eur J Cancer, 42(18):3127-39.

Fleeman N, R Houten, M Chaplin, S Beale, A Boland, Y Dundar, J Greenhalgh, R Duarte and A Shenoy. 2019. A systematic review of lenvatinib and sorafenib for treating progressive, locally advanced or metastatic, differentiated thyroid cancer after treatment with radioactive iodine. BMC Cancer, 19(1):1209.

Fugazzola L, R Elisei, D Fuhrer, B Jarzab, S Leboulleux, K Newbold and J Smit. 2019. 2019 European Thyroid Association Guidelines for the Treatment and Follow-Up of Advanced Radioiodine-Refractory Thyroid Cancer. Eur Thyroid J, 8(5):227-45.

Gianoukakis AG, NM Flores, CL Pelletier, A Forsythe, GR Wolfe and MH Taylor. 2016. Treatment patterns, health state, and health care resource utilization of patients with radioactive iodine refractory differentiated thyroid cancer. Cancer Manag Res, 8:67-76.

Haddad RI, L Bischoff, D Ball, V Bernet, E Blomain, NL Busaidy, M Campbell, P Dickson, QY Duh, H Ehya, WS Goldner, T Guo, M Haymart, S Holt, JP Hunt, A Iagaru, F Kandeel, DM Lamonica, S Mandel, S Markovina, B McIver, CD Raeburn, R Rezaee, JA Ridge, MY Roth, RP Scheri, JP Shah, JA Sipos, R Sippel, C Sturgeon,

TN Wang, LJ Wirth, RJ Wong, M Yeh, CJ Cassara and S Darlow. 2022. Thyroid Carcinoma, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw, 20(8):925-51.

Haugen BR, EK Alexander, KC Bible, GM Doherty, SJ Mandel, YE Nikiforov, F Pacini, GW Randolph, AM Sawka, M Schlumberger, KG Schuff, SI Sherman, JA Sosa, DL Steward, RM Tuttle and L Wartofsky. 2016. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid, 26(1):1-133.

Ibrahimpasic T, R Ghossein, DL Carlson, I Nixon, FL Palmer, AR Shaha, SG Patel, RM Tuttle, JP Shah and I Ganly. 2014. Outcomes in patients with poorly differentiated thyroid carcinoma. J Clin Endocrinol Metab, 99(4):1245-52.

Ito Y, N Onoda, T Kudo, H Masuoka, T Higashiyama, M Kihara, A Miya and A Miyauchi. 2021. Sorafenib and lenvatinib treatment for metastasis/recurrence of radioactive iodine-refractory differentiated thyroid carcinoma. In Vivo, 35(2):1057-64.

Ji X, W Liang, G Lv, C Ding, H Lai, L Li, Q Zeng, B Lv and L Sheng. 2022. Efficacy and safety of targeted therapeutics for patients with radioiodine-refractory differentiated thyroid cancer: Systematic review and network meta-analysis. Front Pharmacol, 13:933648.

Klein Hesselink EN, D Steenvoorden, E Kapiteijn, EP Corssmit, AN van der Horst-Schrivers, JD Lefrandt, TP Links and OM Dekkers. 2015. Therapy of endocrine disease: response and toxicity of small-molecule tyrosine kinase inhibitors in patients with thyroid carcinoma: a systematic review and meta-analysis. Eur J Endocrinol, 172(5):R215-25.

Leboulleux S, L Bastholt, T Krause, C de la Fouchardiere, J Tennvall, A Awada,

JM Gómez, F Bonichon, L Leenhardt, C Soufflet, M Licour and MJ Schlumberger. 2012. Vandetanib in locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 2 trial. Lancet Oncol, 13(9):897-905.

Li L, L Cheng, R Sa, X Qiu and L Chen. 2022. Real-world insights into the efficacy and safety of tyrosine kinase inhibitors against thyroid cancers. Crit Rev Oncol Hematol, 172:103624.

Lin Y, S Qin, Z Li, H Yang, W Fu, S Li, W Chen, Z Gao, W Miao, H Xu, Q Zhang, X Zhao, J Bao, L Li, Y Ren, C Lin, S Jing, Q Ma, J Liang, G Chen, H Zhang, Y Zhang, X Zhou, Y Sang and Z Hou. 2022. Apatinib vs Placebo in Patients With Locally Advanced or Metastatic, Radioactive Iodine-Refractory Differentiated Thyroid Cancer: The REALITY Randomized Clinical Trial. JAMA Oncol, 8(2):242-50.

Liu JW, C Chen, EW Loh, CC Chu, MY Wang, HJ Ouyang, YT Chang, WZ Zhuang, CW Chou, DJ Huang, CH Lee, Y Yen and KW Tam. 2018. Tyrosine kinase inhibitors for advanced or metastatic thyroid cancer: a meta-analysis of randomized controlled trials. Curr Med Res Opin, 34(5):795-803.

Mehnert JM, A Varga, MS Brose, RR Aggarwal, CC Lin, A Prawira, F de Braud, K Tamura, T Doi, SA Piha-Paul, J Gilbert, S Saraf, P Thanigaimani, JD Cheng and B Keam. 2019. Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with advanced, PD-L1-positive papillary or follicular thyroid cancer. BMC Cancer, 19(1):196.

Miranda-Filho A, J Lortet-Tieulent, F Bray, B Cao, S Franceschi, S Vaccarella and L Dal Maso. 2021. Thyroid cancer incidence trends by histology in 25 countries: a population-based study. The Lancet Diabetes & Endocrinology, 9(4):225-34.

National Comprehensive Cancer Network. 2022. Thyroid Carcinoma (Version 1.2022).

NCT02966093.

Page MJ, JE McKenzie, PM Bossuyt, I Boutron, TC Hoffmann, CD Mulrow, L Shamseer, JM Tetzlaff, EA Akl, SE Brennan, R Chou, J Glanville, JM Grimshaw, A Hrobjartsson, MM Lalu, T Li, EW Loder, E Mayo-Wilson, S McDonald, LA McGuinness, LA Stewart, J Thomas, AC Tricco, VA Welch, P Whiting and D Moher. 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Rev Esp Cardiol (Engl Ed), 74(9):790-9.

Puliafito I, F Esposito, A Prestifilippo, S Marchisotta, D Sciacca, MP Vitale and D Giuffrida. 2022. Target Therapy in Thyroid Cancer: Current Challenge in Clinical Use of Tyrosine Kinase Inhibitors and Management of Side Effects. Front Endocrinol (Lausanne), 13:860671.

Rossi ED, L Pantanowitz and JL Hornick. 2021. A worldwide journey of thyroid cancer incidence centred on tumour histology. The Lancet Diabetes & Endocrinology, 9(4):193-4.

Schlumberger M and S Leboulleux. 2021. Current practice in patients with differentiated thyroid cancer. Nat Rev Endocrinol, 17(3):176-88.

Schlumberger M, M Tahara, LJ Wirth, B Robinson, MS Brose, R Elisei, MA Habra, K Newbold, MH Shah, AO Hoff, AG Gianoukakis, N Kiyota, MH Taylor, SB Kim, MK Krzyzanowska, CE Dutcus, B de las Heras, J Zhu and SI Sherman. 2015. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med, 372(7):621-30.

Shen G, F Zheng, D Ren, F Du, Q Dong, Z Wang, F Zhao, R Ahmad and J Zhao. 2018. Anlotinib: a novel multi-targeting tyrosine kinase inhibitor in clinical development. J Hematol Oncol, 11(1):120.

Su J, M Wang, Y Fu, J Yan, Y Shen, J Jiang, J Wang, J Lu, Y Zhong, X Lin, Z Lin

and S Lin. 2022. Efficacy and safety of multi-kinase inhibitors in patients with radioiodine-refractory differentiated thyroid cancer: a systematic review and meta-analysis of clinical trials. Expert Rev Anticancer Ther:1-10.

Sung H, J Ferlay, RL Siegel, M Laversanne, I Soerjomataram, A Jemal and F Bray. 2021. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: A Cancer Journal for Clinicians, 71(3):209-49.

Talon B, GS Calip, TA Lee, LK Sharp, P Patel and DR Touchette. 2021. Trend in Tyrosine Kinase Inhibitor Utilization, Price, and Out-of-Pocket Costs in Patients With Chronic Myelogenous Leukemia. JCO Oncol Pract, 17(11):e1811-e20.

Tsoli M, KI Alexandraki, ME Spei, GA Kaltsas and K Daskalakis. 2020. Anti-Tumor Activity and Safety of Multikinase Inhibitors in Advanced and/or Metastatic Thyroid Cancer: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials. Horm Metab Res, 52(1):25-31.

Venkatesan S, M Lamfers, S Leenstra and A Vulto. 2017. Overview of the patent expiry of (non-)tyrosine kinase inhibitors approved for clinical use in the EU and the US. GaBI Journal, 6(2):89-96.

Wang LY, IJ Nixon, SG Patel, FL Palmer, RM Tuttle, A Shaha, JP Shah and I Ganly. 2016. Operative management of locally advanced, differentiated thyroid cancer. Surgery, 160(3):738-46.

Yang X, X Pan, X Cheng, Y Kuang and Y Cheng. 2017. Risk of Hypertension With Sorafenib Use in Patients With Cancer: A Meta-Analysis From 20,494 Patients. Am J Ther, 24(1):e81-e101.

Yimaer W, A Abudouyimu, Y Tian, S Magaoweiya, D Bagedati and H Wen. 2016. Efficacy and safety of vascular endothelial growth factor receptor tyrosine kinase

inhibitors in the treatment of advanced thyroid cancer: a meta-analysis of randomized controlled trials. Onco Targets Ther, 9:1167-73.

Zang J, S Wu, L Tang, X Xu, J Bai, C Ding, Y Chang, L Yue, E Kang and J He. 2012. Incidence and risk of QTc interval prolongation among cancer patients treated with vandetanib: a systematic review and meta-analysis. PLoS One, 7(2):e30353.

Zhang H. 2015. Apatinib for molecular targeted therapy in tumor. Drug Des Devel Ther, 9:6075-81.

Appendix 1. Search strategies

PubMed	
1	Thyroid Neoplasm [Mesh Terms]
2	"Protein Kinase Inhibitors" [Mesh Terms] OR "Inhibitors, Protein Kinase" [All Fields] OR "Kinase Inhibitors, Protein" [All Fields] OR "Protein Kinase Inhibitor*" [All Fields] OR "Inhibitor, Protein Kinase" [All Fields] OR "Kinase Inhibitor, Protein" [All Fields] OR "Tyrosine kinase inhibitor*" [All Fields] OR TKI [All Fields] OR TKIs [All Fields] OR "Multikinase Inhibitor*" [All Fields] OR "Lenvatinib" [All Fields] OR "E7080" [All Fields] OR "Sorafenib" [All Fields] OR "BAY43-9006" [All Fields] OR "Cabozantinib" [All Fields] OR "XL184" [All Fields] OR "Larotrectinib" [All Fields] OR "BAY2757556" [All Fields] OR "Entrectinib" [All Fields] OR "RXDX-101" [All Fields] OR "Selpercatinib" [All Fields] OR "LOXO-292" [All Fields] OR "Pralsetinib" [All Fields] OR "BLU-667" [All Fields] OR "Axitinib" [All Fields] OR "AG-013736" [All Fields] OR "Pazopanib" [All Fields] OR "GW786034" [All Fields] OR "Sunitinib" [All Fields] OR "SU011248" [All Fields] OR "Vandetanib" [All Fields] OR "ZD6474" [All Fields] OR "Vemurafenib" [All Fields] OR "RO5185426" [All Fields] OR "Dabrafenib" [All Fields] OR "GSK2118436" [All Fields] OR "Apatinib" [All Fields] OR "YN968D1"
3	"clinical study" [All Fields] OR "study" [All Fields] OR "clinical trial" [All Fields] OR "trial" [All Fields]
4	#1 AND #2 AND #3
EMBASE	
1	'thyroid tumor'/exp OR 'thyroid gland tumor' OR 'thyroid gland tumour' OR 'thyroid neoplasm' OR 'thyroid neoplasms' OR 'thyroid tumor' OR 'thyroid tumour' OR 'thyroidal tumor' OR 'thyroidal tumour' OR 'tumor, thyroid gland' OR 'tumour, thyroid gland'
2	'protein kinase inhibitor'/exp OR 'protein kinase inhibitor' OR 'protein kinase inhibitors' OR 'Lenvatinib'/exp OR '1 [4 [(6 carbamoyl 7 methoxy 4 quinolinyl) oxy] 2 chlorophenyl] 3 cyclopropylurea' OR '4 [3 chloro 4 (3 cyclopropylureido) phenoxy] 7 methoxyquinoline 6 carboxamide' OR '4 [3 chloro 4 [(cyclopropylcarbamoyl) amino] phenoxy] 7 methoxyquinoline 6 carboxamide' OR '4 [3 chloro 4 [[(cyclopropylamino) carbonyl] amino]

	phenoxy] 7 methoxy 6 quinolinecarboxamide' OR 'aiv 007' OR 'aiv007' OR 'e 7080' OR 'e7080' OR 'er 203492-00' OR 'er203492-00' OR 'kisplyx' OR 'Lenvatinib' OR 'Lenvatinib mesilate' OR 'Lenvatinib mesylate' OR 'Lenvatinib methanesulfonate' OR 'lenvima' OR 'mk 7902' OR 'mk7902' OR 'n [4 [(6 carbamoyl 7 methoxyquinolin 4 yl) oxy] 2 chlorophenyl] n` cyclopropylurea' OR 'Sorafenib'/exp OR '4 [4 [3 [4 chloro 3 (trifluoromethyl) phenyl] ureido] phenoxy] n methyl 2 pyridinecarboxamide' OR 'bay 43 9006' OR 'bay 43-9006' OR 'bay 439006' OR 'bay43 9006' OR 'bay43-9006' OR 'bay439006' OR 'nexavar' OR 'Sorafenib' OR 'Sorafenib tosylate' OR 'Cabozantinib'/exp OR 'bms 907351' OR 'bms907351' OR 'cabometyx' OR 'Cabozantinib' OR 'Cabozantinib malate' OR 'Cabozantinib s malate' OR 'Cabozantinib s-malate' OR 'cometriq' OR 'cyclopropane 1, 1 dicarboxylic acid [4 (6, 7 dimethoxyquinolin 4 yloxy) phenyl] amide (4 fluorophenyl) amide' OR 'n [4 (6, 7 dimethoxy 4 quinolinyloxy) phenyl] n` (4 fluorophenyl) 1, 1 cyclopropanedicarboxamide' OR 'n [4 [ (6, 7 dimethoxyquinolin 4 yl) oxy] phenyl] n` (4 fluorophenyl) cyclopropane 1, 1 dicarboxamide' OR 'xl 184' OR 'xl184' OR 'larotrectinib'/exp OR 'arry 470' OR 'arry470' OR 'larotrectinib' OR 'larotrectinib sulfate' OR 'loxo 101' OR 'loxo101' OR 'n [5 [2 (2, 5 difluorophenyl) 1 pyrrolidinyl] pyrazolo [1, 5 a] pyrimidin 3 yl] 3 hydroxy 1 pyrrolidinecarboxamide' OR 'n [5 [2 (2, 5 difluorophenyl) 1 pyrrolidinyl] pyrazolo [1, 5 a] pyrimidin 3 yl] 3 hydroxy 1 pyrrolidinecarboxamide sulfate' OR 'n [5 [2 (2, 5 difluorophenyl) pyrrolidin 1 yl] pyrazolo [1, 5 a] pyrimidin 3 yl] 3 hydroxypyrrolidine 1 carboxamide' OR 'n [5 [2 (2, 5 difluorophenyl) pyrrolidin 1 yl] pyrazolo [1, 5 a] pyrimidin 3 yl] 3 hydroxypyrrolidine 1 carboxamide hydrogen sulfate' OR 'n [5 [2 (2, 5 difluorophenyl) pyrrolidin 1 yl] pyrazolo [1, 5 a] pyrimidin 3 yl] 3 hydroxypyrrolidine 1 carboxamide sulfate' OR 'vitrakvi' OR 'entrectinib'/exp OR 'entrectinib' OR 'n [5 (3, 5 difluorobenzyl) 1h indazol 3 yl] 4 (4 methyl 1 piperazinyl) 2 [(tetrahydropyran 4 yl) amino] benzamide' OR 'n [5 (3, 5 difluorobenzyl) 1h indazol 3 yl] 4 (4 methylpiperazin 1 yl) 2 (tetrahydro 2h pyran 4 ylamino) benzamide' OR 'n [5 (3, 5 difluorobenzyl) 1h indazol 3 yl] 4 (4 methylpiperazin 1 yl) 2 [(tetrahydro 2h pyran 4 yl) amino] benzamide' OR 'n [5 [(3, 5 difluorophenyl) methyl] 1h indazol 3 yl] 4 (4 methyl 1 piperazinyl) 2 [(tetrahydro 2h pyran 4 yl) amino] benzamide' OR 'n [5 [(3, 5 difluorophenyl) methyl] 1h indazol 3 yl] 4 (4 methylpiperazin 1 yl) 2

	[(oxan 4 yl) amino] benzamide' OR 'nms e 628' OR 'nms e628' OR 'rg 6268' OR 'rg6268' OR 'rozlytrek' OR 'rxdx 101' OR 'rxdx101' OR 'selpercatinib'/exp OR '6 (2 hydroxy 2 methylpropoxy) 4 [6 [6 [(6 methoxy 3 pyridinyl) methyl] 3, 6 diazabicyclo [3.1.1] hept 3 yl] 3 pyridinyl] pyrazolo [1, 5 a] pyridine 3 carbonitrile' OR '6 (2 hydroxy 2 methylpropoxy) 4 [6 [6 [(6 methoxy 3 pyridinyl) methyl] 3, 6 diazabicyclo [3.1.1] heptan 3 yl] 3 pyridinyl] pyrazolo [1, 5 a] pyridine 3 carbonitrile' OR '6 (2 hydroxy 2 methylpropoxy) 4 [6 [6 [(6 methoxypyridin 3 yl) methyl] 3, 6 diazabicyclo [3.1.1] hept 3 yl] pyridin 3 yl] pyrazolo [1, 5 a] pyridine 3 carbonitrile' OR '6 (2 hydroxy 2 methylpropoxy) 4 [6 [6 [(6 methoxypyridin 3 yl) methyl] 3, 6 diazabicyclo [3.1.1] heptan 3 yl] pyridin 3 yl] pyrazolo [1, 5 a] pyridine 3 carbonitrile' OR 'loxo 292' OR 'loxo292' OR 'ly 3527723' OR 'ly3527723' OR 'retevmo' OR 'retsevmo' OR 'selpercatinib' OR 'pralsetinib'/exp OR 'blu 123244' OR 'blu 3244' OR 'blu 667' OR 'blu123244' OR 'blu3244' OR 'blu667' OR 'c 683' OR 'c683' OR 'cs 3009' OR 'cs3009' OR 'gavreto' OR 'n [1 [6 (4 fluoro 1 (1h) pyrazolyl) 3 pyridinyl] ethyl] 1 methoxy 4 [4 methyl 6 [(5 methyl 3 (1h) pyrazolyl) amino] 2 pyrimidinyl] 1 cyclohexanecarbonylamine' OR 'n [1 [6 (4 fluoro 1 (1h) pyrazolyl) 3 pyridinyl] ethyl] 1 methoxy 4 [4 methyl 6 [(5 methyl 3 (1h) pyrazolyl) amino] 2 pyrimidinyl] cyclohexanecarbonylamine' OR 'n [1 [6 (4 fluoro 1 pyrazolyl) 3 pyridinyl] ethyl] 1 methoxy 4 [4 methyl 6 [(5 methyl 3 (1h) pyrazolyl) amino] 2 pyrimidinyl] 1 cyclohexanecarbonylamine' OR 'n [1 [6 (4 fluoro 1 pyrazolyl) 3 pyridinyl] ethyl] 1 methoxy 4 [4 methyl 6 [(5 methyl 3 (1h) pyrazolyl) amino] 2 pyrimidinyl] 1 cyclohexanecarboxamide' OR 'n [1 [6 (4 fluoro 1 pyrazolyl) 3 pyridinyl] ethyl] 1 methoxy 4 [4 methyl 6 [(5 methyl 3 (1h) pyrazolyl) amino] 2 pyrimidinyl] cyclohexanecarbonylamine' OR 'n [1 [6 (4 fluoro 1 pyrazolyl) 3 pyridinyl] ethyl] 1 methoxy 4 [4 methyl 6 [(5 methyl 3 (1h) pyrazolyl) amino] 2 pyrimidinyl] cyclohexanecarboxamide' OR 'n [1 [6 (4 fluoro 1h pyrazol 1 yl) 3 pyridinyl] ethyl] 1 methoxy 4 [4 methyl 6 [(5 methyl 1h pyrazol 3 yl) amino] 2 pyrimidinyl] cyclohexanecarboxamide' OR 'n [1 [6 (4 fluoro 1h pyrazol 1 yl) pyridin 3 yl] ethyl] 1 methoxy 4 [4 methyl 6 [(5 methyl 1h pyrazol 3 yl) amino] pyrimidin 2 yl] cyclohexane 1 carbonylamine' OR 'n [1 [6 (4 fluoro 1h pyrazol 1 yl) pyridin 3 yl] ethyl] 1 methoxy 4 [4 methyl 6 [(5 methyl 1h pyrazol 3 yl) amino] pyrimidin 2 yl] cyclohexane 1 carboxamide' OR 'n [1 [6 (4 fluoro 1h pyrazol 1 yl) pyridin 3 yl] ethyl] 1 methoxy 4 [4 methyl 6 [(5 methyl 1h pyrazol 3 yl)

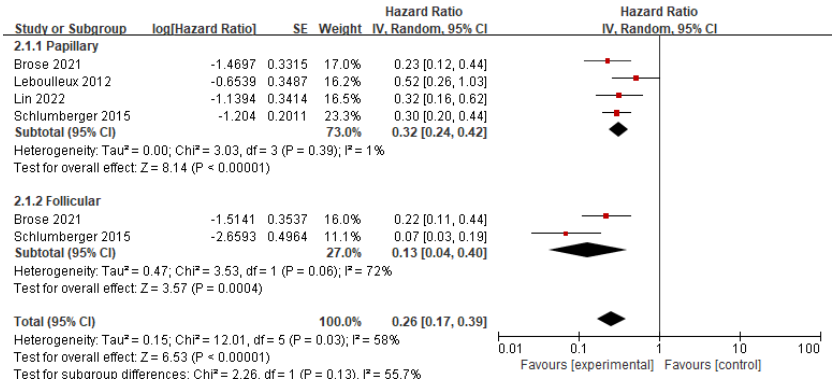
	amino] pyrimidin 2 yl] cyclohexanecarbonylamine' OR 'n [1 [6 (4 fluoro 1h pyrazol 1 yl) pyridin 3 yl] ethyl] 1 methoxy 4 [4 methyl 6 [(5 methyl 1h pyrazol 3 yl) amino] pyrimidin 2 yl] cyclohexanecarboxamide' OR 'n [1 [6 (4 fluoropyrazol 1 yl) pyridin 3 yl] ethyl] 1 methoxy 4 [4 methyl 6 [(5 methyl 1h pyrazol 3 yl) amino] pyrimidin 2 yl] cyclohexane 1 carbonylamine' OR 'n [1 [6 (4 fluoropyrazol 1 yl) pyridin 3 yl] ethyl] 1 methoxy 4 [4 methyl 6 [(5 methyl 1h pyrazol 3 yl) amino] pyrimidin 2 yl] cyclohexanecarbonylamine' OR 'pralsetinib' OR 'rg 6396' OR 'rg6396' OR 'ro 7499790' OR 'ro7499790' OR 'x 581238' OR 'x581238' OR 'axitinib'/exp OR 'ag 013736' OR 'ag 13736' OR 'ag013736' OR 'ag13736' OR 'ar 14034' OR 'ar14034' OR 'axitinib' OR 'inlyta' OR 'n methyl 2 [[3 [2 (2 pyridinyl) ethenyl] 1h indazol 6 yl] thio] benzamide' OR 'n methyl 2 [[3 [2 (pyridin 2 yl) ethenyl] 1h indazol 6 yl] sulfanyl] benzamide' OR 'n methyl 2 [3 [2 (2 pyridyl) vinyl] 1h indazol 6 ylsulfanyl] benzamide' OR 'pazopanib'/exp OR '5 [[4 [(2, 3 dimethyl 2h indazol 6 yl) methylamino] 2 pyrimidinyl] amino] 2 methylbenzenesulfonamide' OR '5 [[4 [(2, 3 dimethylindazol 6 yl) methylamino] pyrimidin 2 yl] amino] 2 methylbenzenesulfonamide' OR 'armala' OR 'gw 786034' OR 'gw 786034b' OR 'gw 786034x' OR 'gw786034' OR 'gw786034b' OR 'gw786034x' OR 'pazopanib' OR 'pazopanib hydrochloride' OR 'sb 710468' OR 'sb 710468a' OR 'sb710468' OR 'sb710468a' OR 'votrient' OR 'sunitinib'/exp OR '5 (5 fluoro 1, 2 dihydro 2 oxo 3 indolylidenemethyl) 2, 4 dimethyl 1h pyrrole 3 carboxylic acid (2 diethylaminoethyl) amide' OR '5 (5 fluoro 2 oxo 1, 2 dihydroindol 3 ylidenemethyl) 2, 4 dimethyl 1h pyrrole 3 carboxylic acid (2 diethylaminoethyl) amide' OR 'gb 102' OR 'gb102' OR 'n [2 (diethylamino) ethyl] 5 [(5 fluoro 1, 2 dihydro 2 oxo 3h indol 3 ylidene) methyl] 2, 4 dimethyl 1h pyrrole 3 carboxamide' OR 'pha 2909040ad' OR 'pha 290940ad' OR 'pha2909040ad' OR 'pha290940ad' OR 'pno 290940' OR 'pnu290940' OR 'su 010398' OR 'su 011248' OR 'su 10398' OR 'su 11248' OR 'su010398' OR 'su011248' OR 'su10398' OR 'su11248' OR 'sunitinib' OR 'sunitinib cyclamate' OR 'sunitinib malate' OR 'suo 11248' OR 'suo11248' OR 'sutent' OR 'Vandetanib'/exp OR '4 (4 bromo 2 fluoroanilino) 6 methoxy 7 [(1 methylpiperidin 4 yl) methoxy] quinazoline' OR '4 [(4 bromo 2 fluorophenyl) amino] 6 methoxy 7 [(1 methyl 4 piperidinyl) methoxy] quinazoline' OR 'azd 6474' OR 'azd6474' OR 'caprelsa' OR 'n (4 bromo 2 fluorophenyl) 6 methoxy 7 (1 methyl 4 piperidinylmethoxy) 4 quinazolinamine' OR 'n (4 bromo 2 fluorophenyl) 6

	methoxy 7 (1 methylpiperidin 4 ylmethoxy) quinazolin 4 amine' OR 'sar 390530' OR 'sar390530' OR 'Vandetanib' OR 'vandetinib' OR 'zactima' OR 'zd 6474' OR 'zd6474' OR 'zictifa' OR 'vemurafenib'/exp OR 'n [3 [[5 (4 chlorophenyl) 1h pyrrolo [2, 3 b] pyridin 3 yl] carbonyl] 2, 4 difluorophenyl] 1 propanesulfonamide' OR 'n [3 [5 (4 chlorophenyl) 1h pyrrolo [2, 3 b] pyridine 3 carbonyl] 2, 4 difluorophenyl] propane 1 sulfonamide' OR 'n [3 [5 (4 chlorophenyl) 1h pyrrolo [2, 3 b] pyridine 3 carbonyl] 2, 4 difluorophenyl] propanesulfonamide' OR 'plx 4032' OR 'plx4032' OR 'r 7204' OR 'r7204' OR 'rg 7204' OR 'rg7204' OR 'ro 5185426' OR 'ro5185426' OR 'vemurafenib' OR 'zelboraf' OR 'dabrafenib'/exp OR 'dabrafenib' OR 'dabrafenib mesilate' OR 'dabrafenib mesylate' OR 'drb 436' OR 'drb436' OR 'gsk 2118436' OR 'gsk 2118436a' OR 'gsk 2118436b' OR 'gsk2118436' OR 'gsk2118436a' OR 'gsk2118436b' OR 'n [3 [5 (2 amino 4 pyrimidinyl) 2 (1, 1 dimethylethyl) 1, 3 thiazol 4 yl] 2 fluorophenyl] 2, 6 difluorobenzenesulfonamide' OR 'n [3 [5 (2 amino 4 pyrimidinyl) 2 (1, 1 dimethylethyl) 4 thiazolyl] 2 fluorophenyl] 2, 6 difluorobenzenesulfonamide' OR 'n [3 [5 (2 amino 4 pyrimidinyl) 2 tert butyl 4 thiazolyl] 2 fluorophenyl] 2, 6 difluorobenzenesulfonamide' OR 'n [3 [5 (2 aminopyrimidin 4 yl) 2 tert butyl 1, 3 thiazol 4 yl] 2 fluorophenyl] 2, 6 difluorobenzenesulfonamide' OR 'tafinlar' OR 'rivoceranib'/exp OR 'aitan' OR 'Apatinib' OR 'Apatinib mesilate' OR 'Apatinib mesylate' OR 'Apatinib methanesulfonate' OR 'n [4 (1 cyanocyclopentyl) phenyl] 2 (4 pyridinylmethyl) amino 3 pyridinecarboxamide' OR 'n [4 (1 cyanocyclopentyl) phenyl] 2 [(4 pyridinylmethyl) amino] nicotinamide' OR 'n [4 (1 cyanocyclopentyl) phenyl] 2 [(pyridin 4 ylmethyl) amino] nicotinamide' OR 'n [4 (1 cyanocyclopentyl) phenyl] 2 [[(4 pyridinyl) methyl] amino] 3 pyridinecarboxamide' OR 'n [4 (1 cyanocyclopentyl) phenyl] 2 [[(pyridin 4 yl) methyl] amino] pyridine 3 carboxamide' OR 'rivoceranib' OR 'rivoceranib mesilate' OR 'rivoceranib mesylate' OR 'rivoceranib methanesulfonate' OR 'yn 968d1' OR 'yn968d1'
3	'clinical study'/exp OR 'clinical data' OR 'clinical studies as topic' OR 'clinical study' OR 'medical trial'
4	#1 AND #2 AND #3
Cochrane	
1	(thyroid tumor) OR (thyroid gland tumor) OR (thyroid gland tumour) OR (thyroid neoplasm) OR (thyroid neoplasms) OR (thyroid tumor) OR (thyroid tumour) OR (thyroidal tumor) OR (thyroidal tumour) OR (tumor,

	thyroid gland) OR (tumour, thyroid gland)
2	(Protein Kinase Inhibitor*) OR (Inhibitors, Protein Kinase) OR (Kinase Inhibitors, Protein) OR (Inhibitor, Protein Kinase) OR (Kinase Inhibitor, Protein) OR (Tyrosine kinase inhibitor*) OR (TKI) OR (TKIs) OR (Multikinase Inhibitor*) OR (Lenvatinib) OR (E7080) OR (Sorafenib) OR (BAY43 9006) OR (Cabozantinib) OR (XL184) OR (Larotrectinib) OR (BAY2757556) OR (Entrectinib) OR (RXDX-101) OR (Selpercatinib) OR (LOXO-292) OR (Pralsetinib) OR (BLU-667) OR (Axitinib) OR (AG-013736) OR (Pazopanib) OR (GW786034) OR (Sunitinib) OR (SU011248) OR (Vandetanib) OR (ZD6474) OR (Vemurafenib) OR (RO5185426) OR (Dabrafenib) OR (GSK2118436) OR (Apatinib) OR (YN968D1)
3	(clinical study) OR (study) OR (clinical trial) OR (trial)
4	#1 AND #2 AND #3

Appendix 2. Progression free survival subgroup analysis

A



B

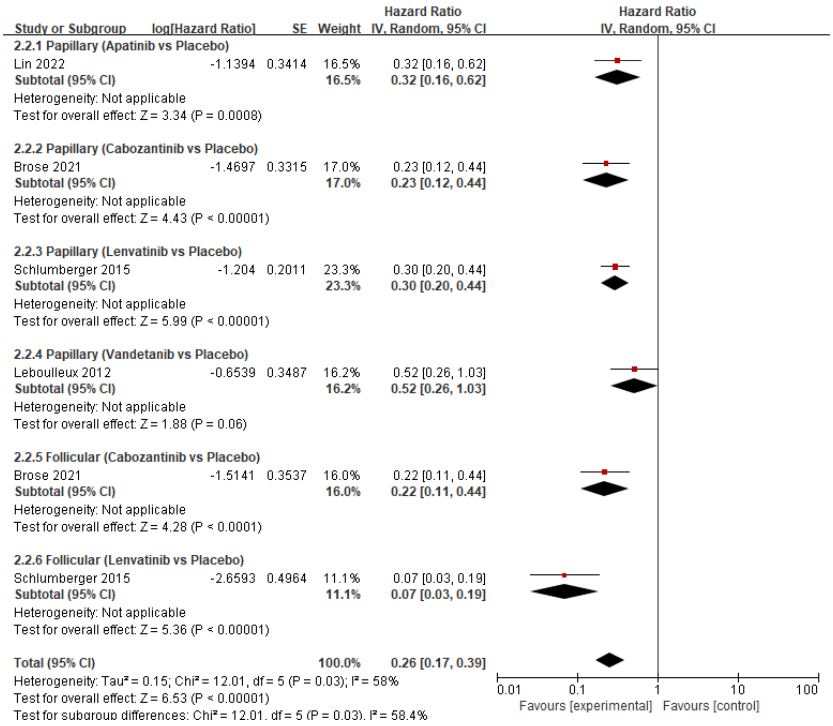
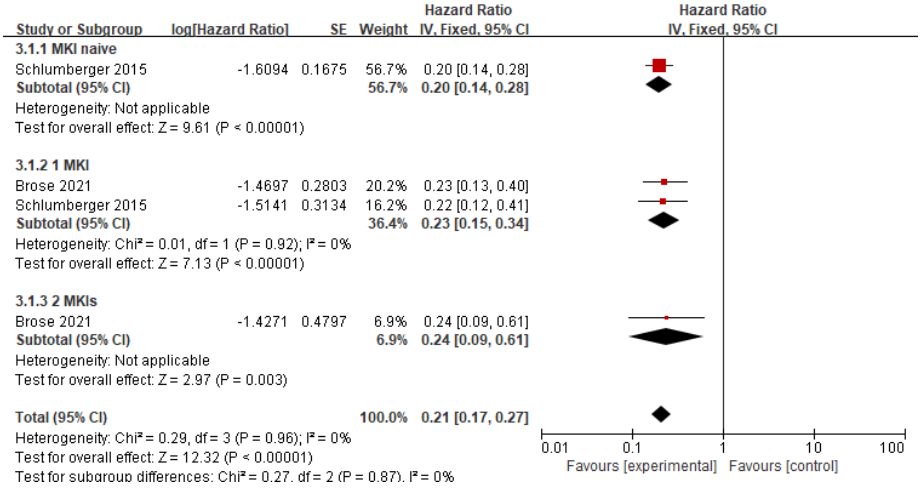


Figure 16 Subgroup analysis of progression free survivals by histology type: (A) in all MKIs and (B) by treatment

A



B

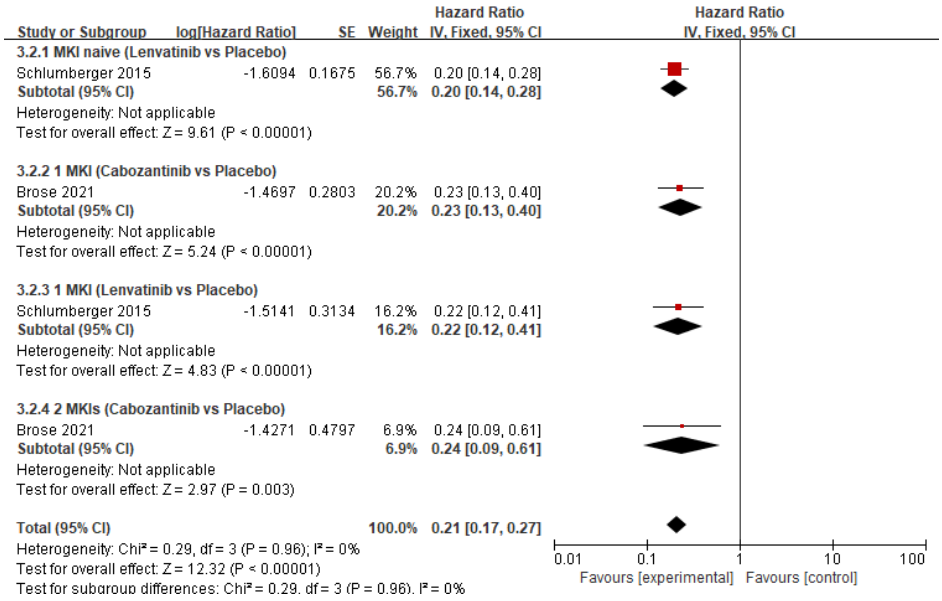
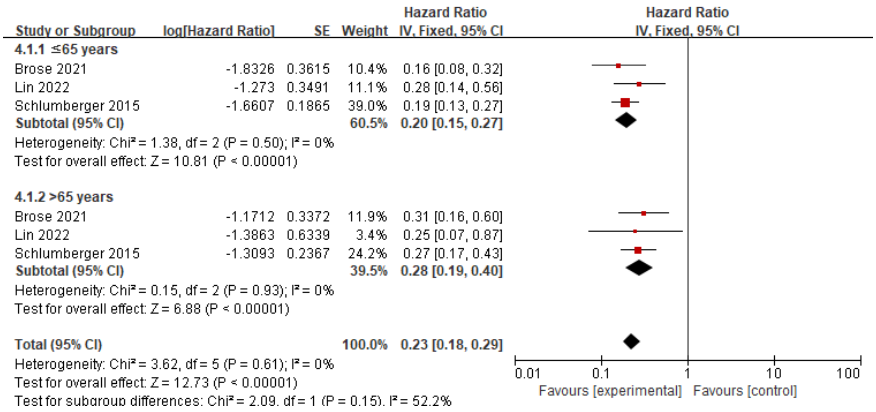


Figure 17 Subgroup analysis of progression free survivals by prior multi-kinase inhibitor (MKI) use: (A) in all MKIs and (B) by treatment

A



B

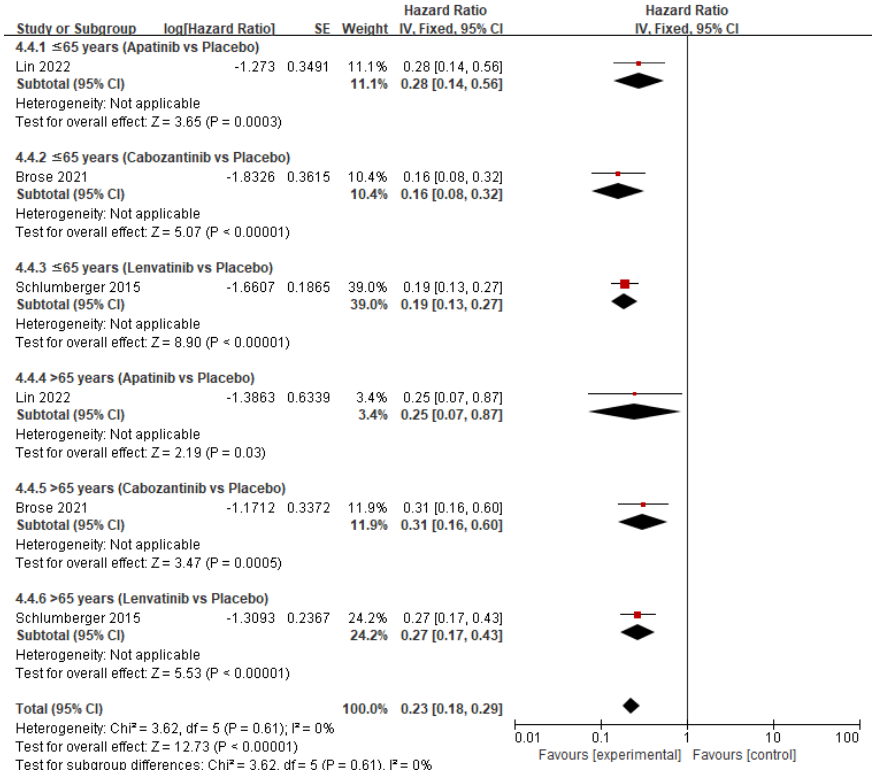
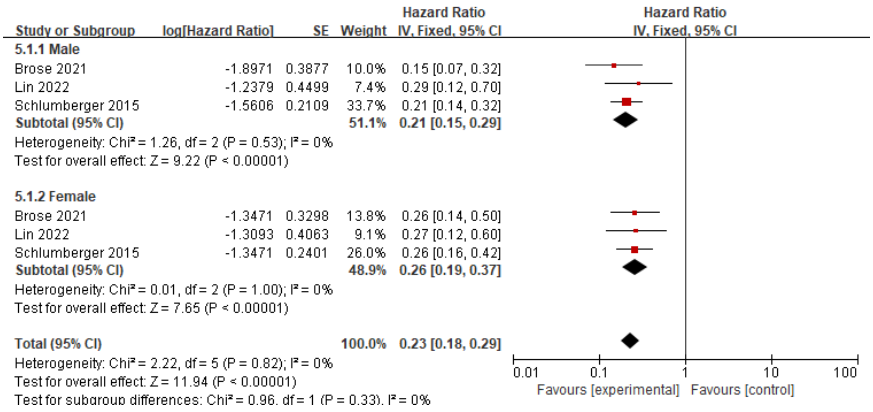


Figure 18 **Subgroup analysis of progression free survivals by age: (A) in all MKIs and (B) by treatment**

A



B

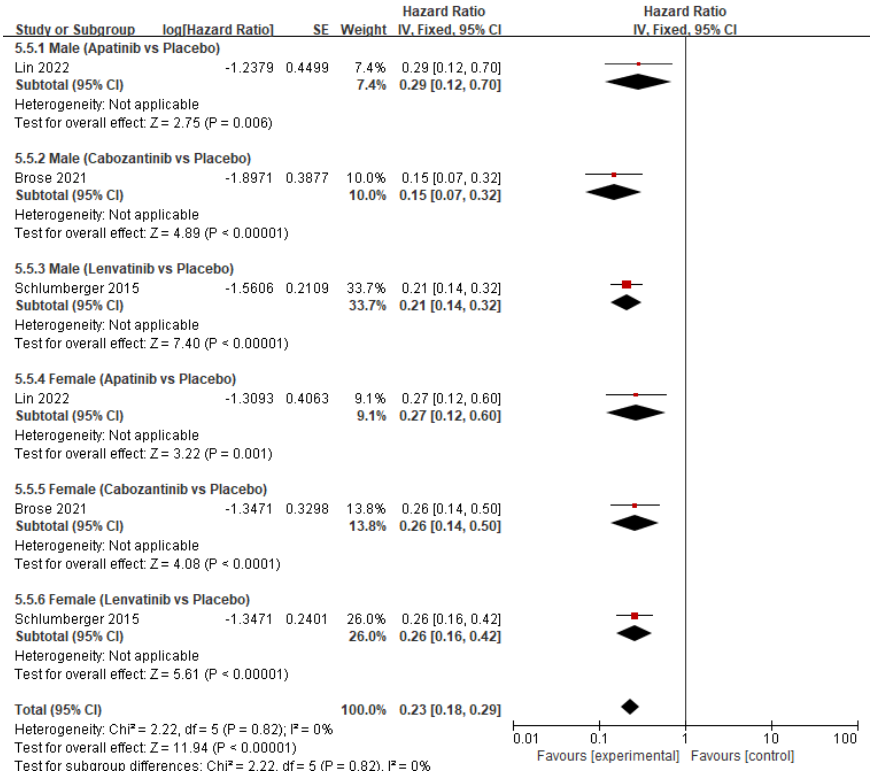
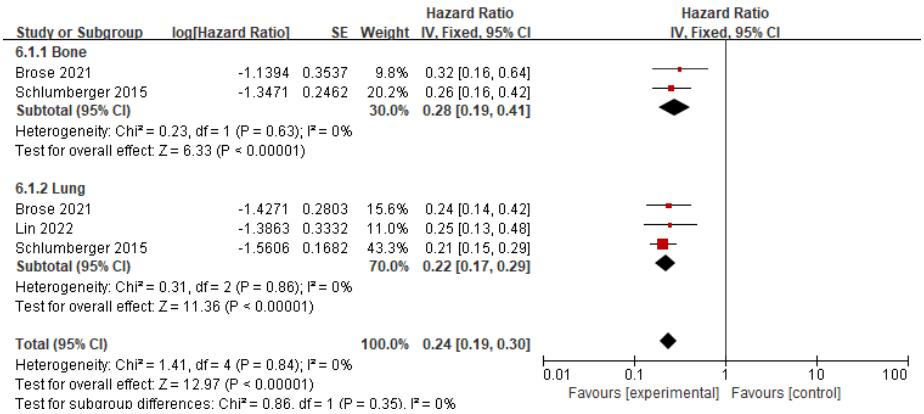


Figure 19 **Subgroup analysis of progression free survivals by gender: (A) in all MKIs and (B) by treatment**

A



B

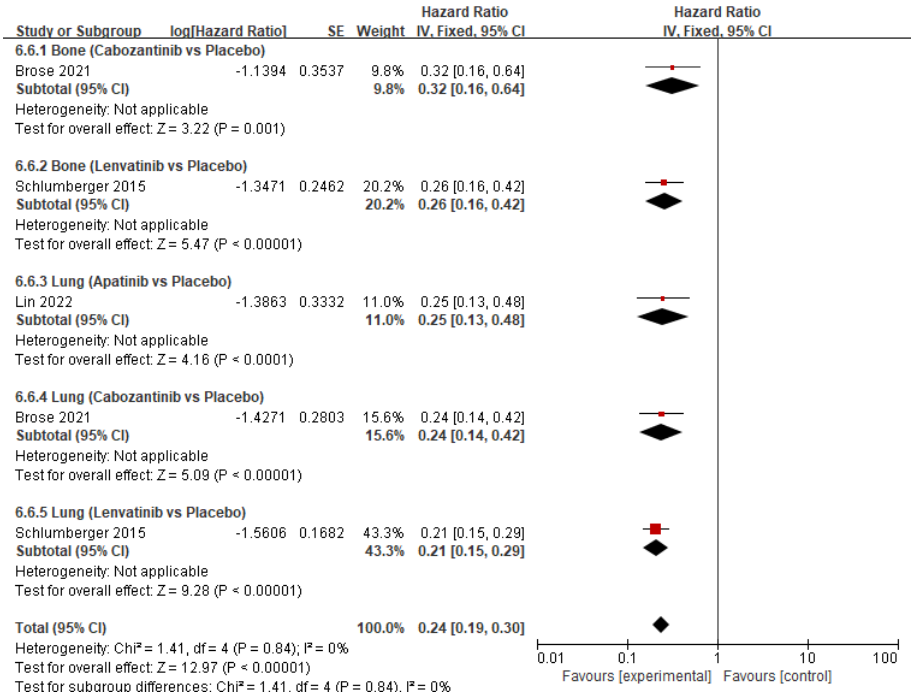
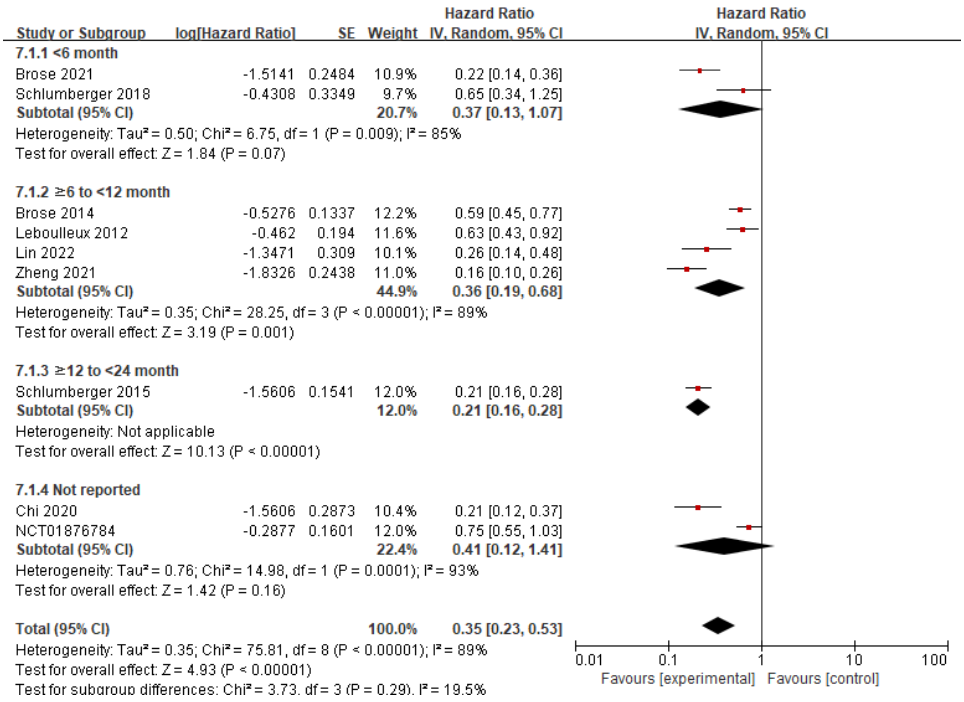


Figure 20 **Subgroup analysis of progression free survivals by metastatic site: (A) in all MKIs and (B) by treatment**

A



B

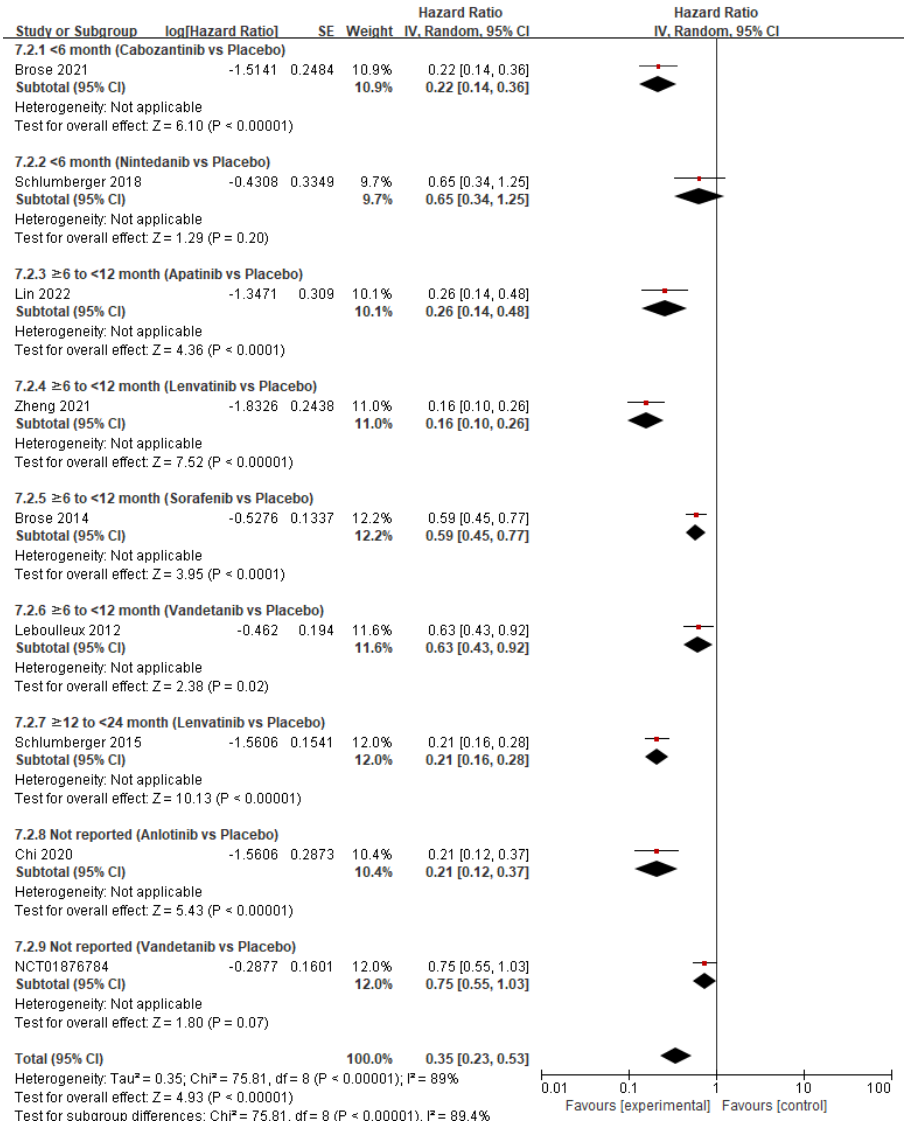
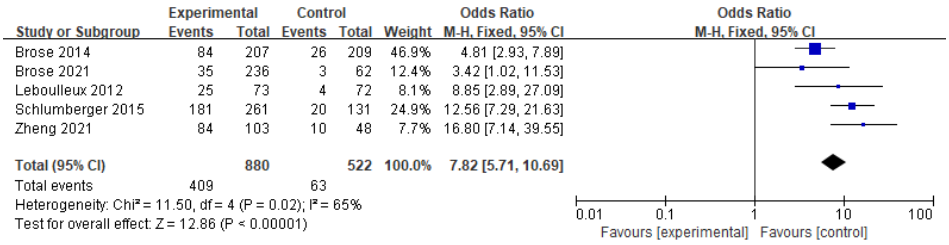


Figure 21 Subgroup analysis of progression free survivals by treatment duration in the multi-kinase (MKI) arm: (A) in all MKIs and (B) by treatment

Appendix 3. Adverse events of special interest meta-analyses

A



B

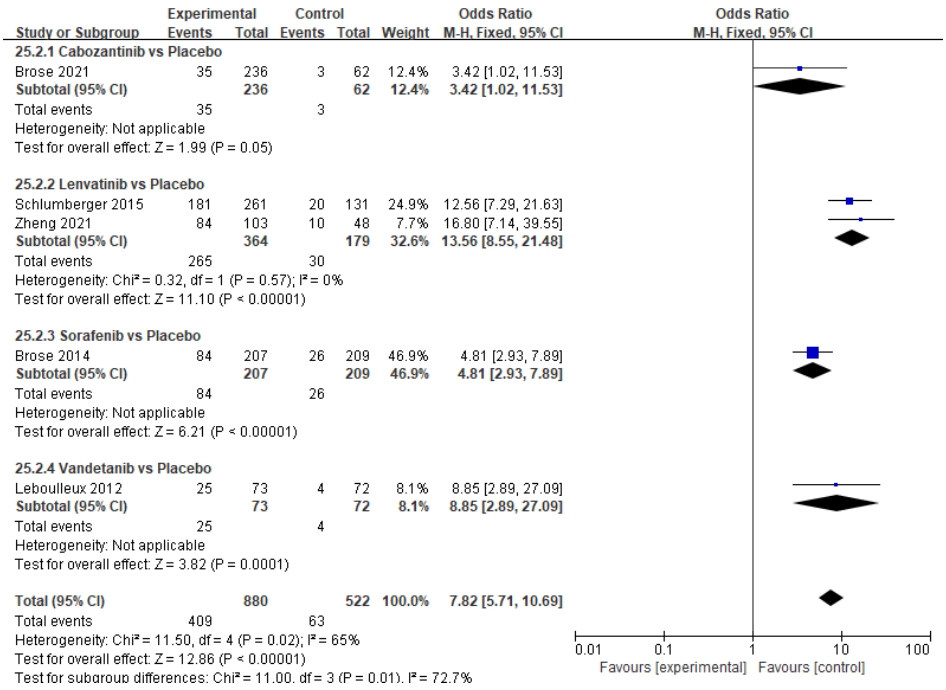
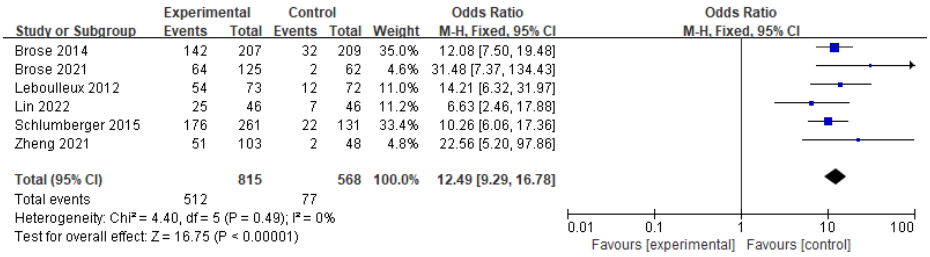


Figure 22 Comparison of hypertension adverse events in multi-kinase inhibitors (MKIs) vs. placebo: (A) in all MKIs and (B) by treatment

A



B

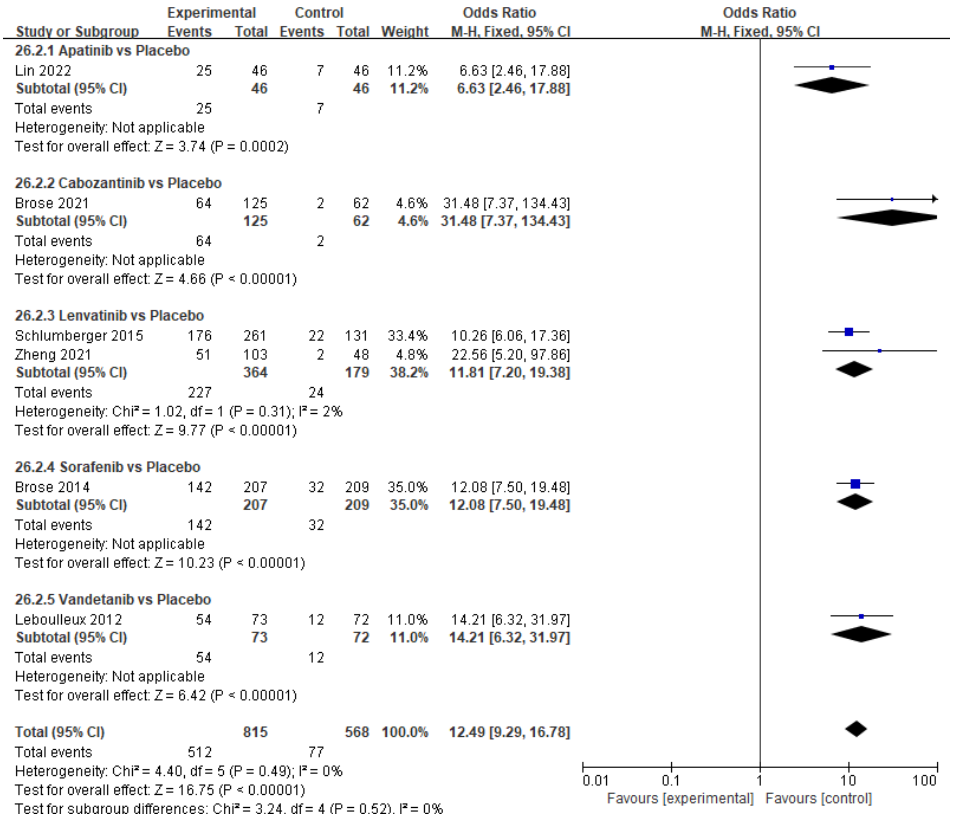
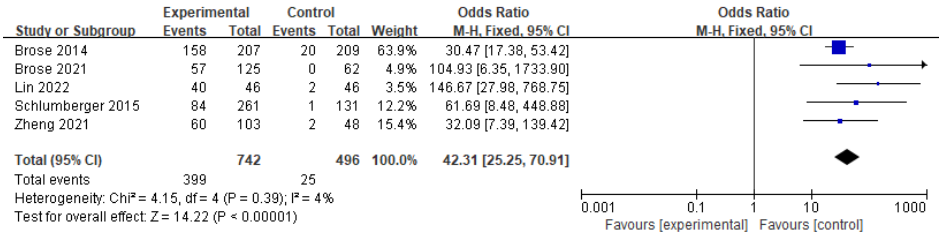


Figure 23 Comparison of diarrhea adverse events in multi-kinase inhibitors (MKIs) vs. placebo: (A) in all MKIs and (B) by treatment

A



B

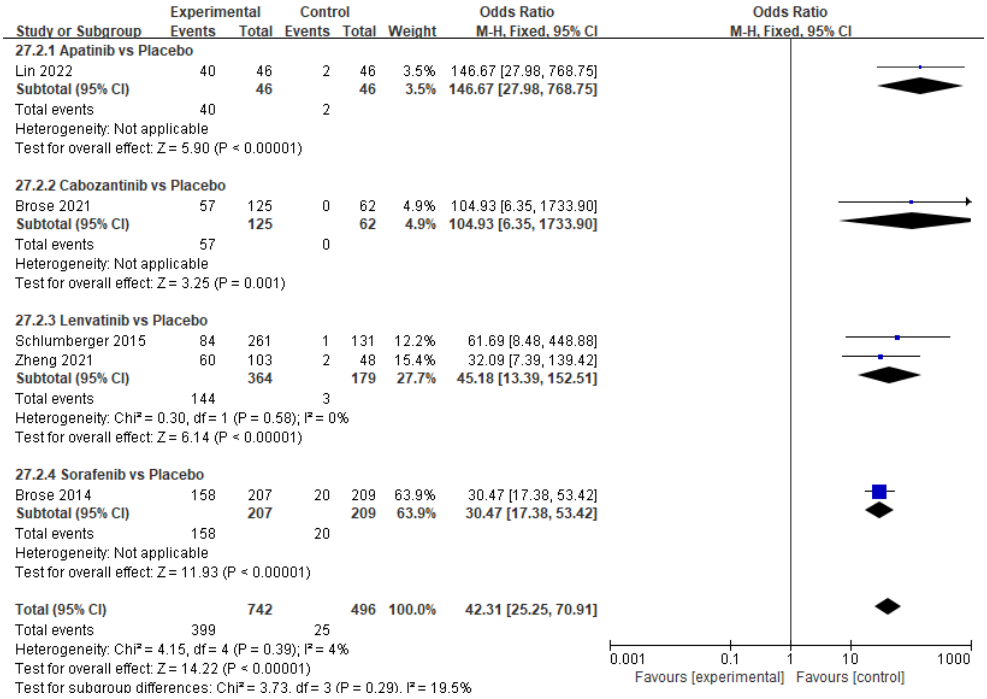
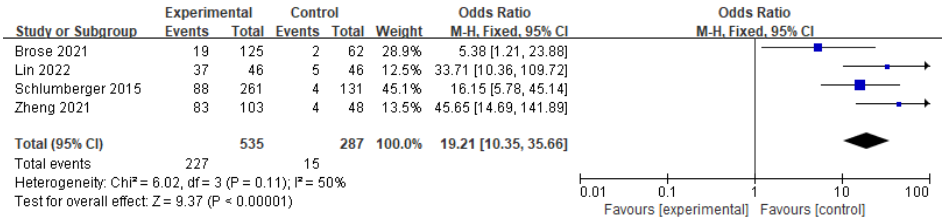


Figure 24 Comparison of hand-foot syndrome adverse events in multi-kinase inhibitors (MKIs) vs. placebo: (A) in all MKIs and (B) by treatment

A



B

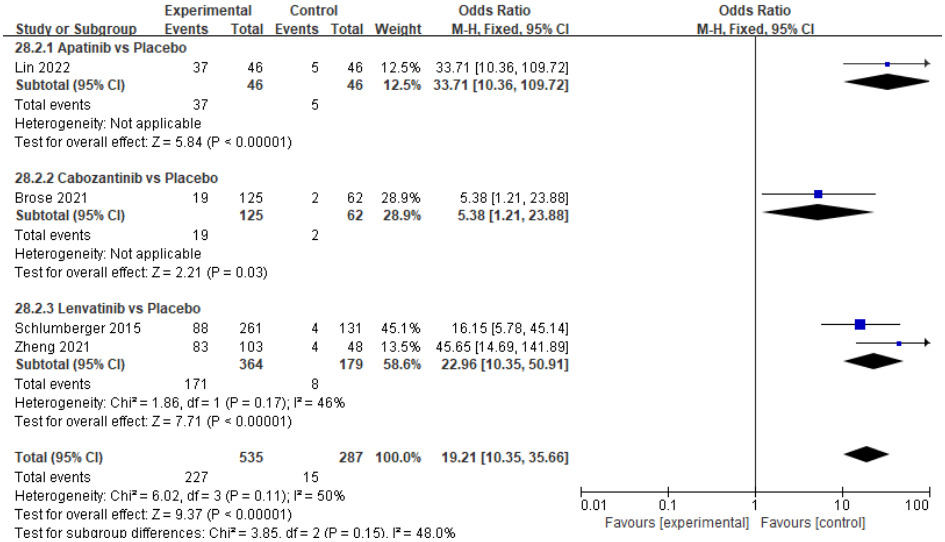
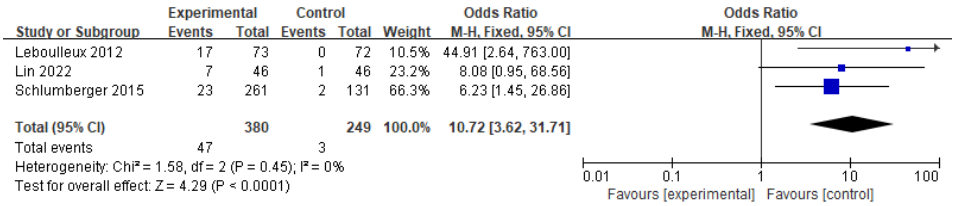


Figure 25 Comparison of proteinuria adverse events in multi-kinase inhibitors (MKIs) vs. placebo: (A) in all MKIs and (B) by treatment

A



B

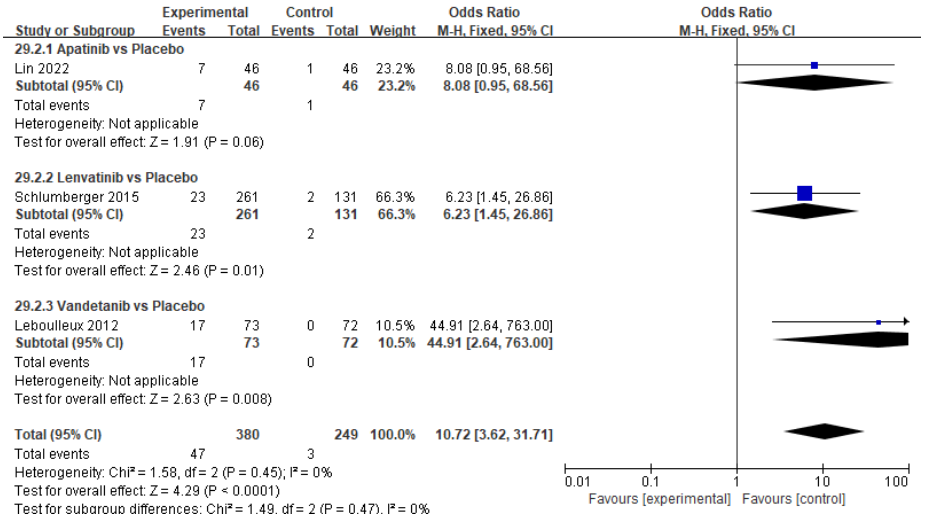
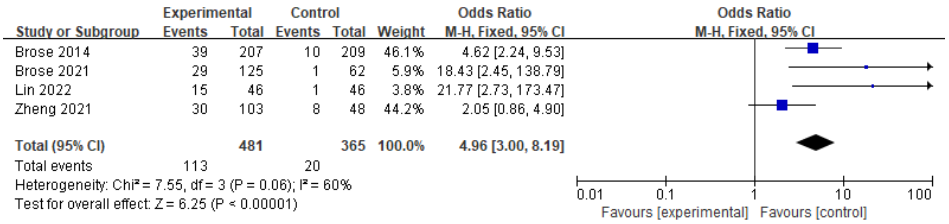


Figure 26 Comparison of QTc prolongation adverse events in multi-kinase inhibitors (MKIs) vs. placebo: (A) in all MKIs and (B) by treatment

A



B

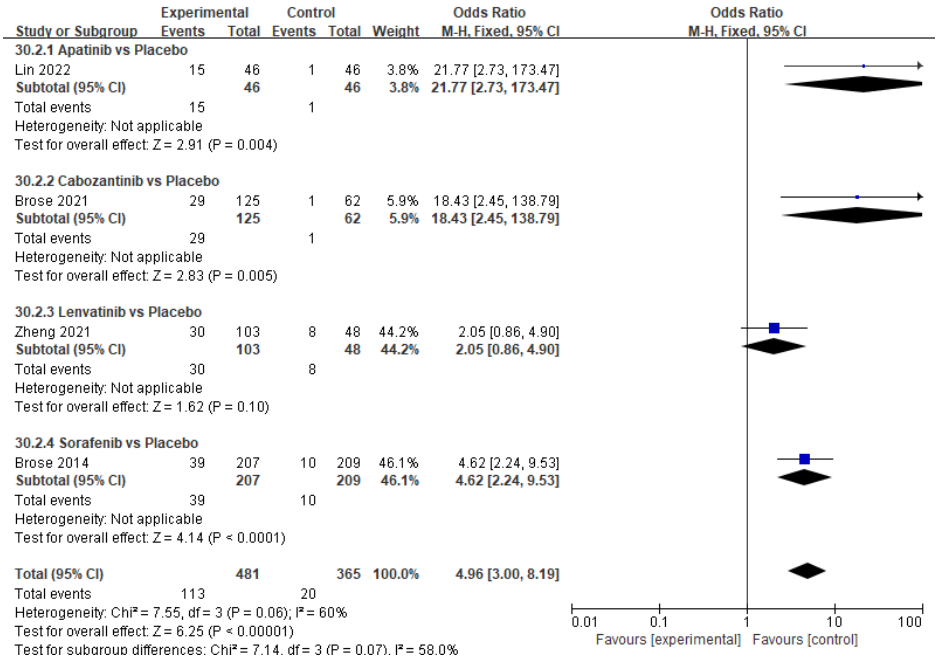


Figure 27 Comparison of hypocalcemia adverse events in multi-kinase inhibitors (MKIs) vs. placebo: (A) in all MKIs and (B) by treatment

ABSTRACT (Korean)

진행성, 전이성, 방사성요오드 불응성 갑상선 분화암 환자에서 Multi-kinase Inhibitor의 유효성과 안전성에 대한 체계적 문헌고찰과 메타분석

연세대학교
일반대학원
제약의료규제과학협동과정
유재경

I. 연구 배경

갑상선 분화암 유형은 갑상선암의 90% 이상을 차지하며, 흔히 갑상선 수술 및 방사성 요오드 요법 이후 우수한 예후를 보이는 질병이다. 그러나 환자의 15%에서 국소 진행성 또는 원격 전이의 재발이 발생하며 이러한 환자의 치료에는 multi-kinase inhibitor(MKI)를 이용한 전신적인 치료요법이 중요하다. 이 연구의 목적은 여러 MKI간 비교 정보를 제공하여 임상에서 환자에게 최적의 MKI를 선택할 수 있도록 근거를 제공하고자 한다.

II. 연구 내용 및 방법

PubMed, Embase, 및 Cochrane library 데이터베이스에서 국소 진행성, 전이성, 방사성요오드 불응성 갑상선 분화암 환자를 대상으로 한 무작위 배정 임상시험을 검색하였다. 수질 또는 역형성 조직학적 하위 유형에 대해 보고된 연구, 후향적 또는 전향적 관찰 코호트 연구는 제외되었다.

1차 유효성 평가변수는 무진행 생존(PFS)으로 설정하였다. 2차 평가변수에는 전체 생존(OS), 객관적 반응률(ORR), 질병 통제율(DCR), 임상적 이득률(CBR), 그리고 이상반응들과 관련된 안전성 결과를 포함하였다. 보고된 결과들을 이용하여 전통적인 메타분석과 베이지안 네트워크 메타분석을 수행하였다.

III. 연구 결과

메타분석에 총 9개의 무작위배정 임상시험이 포함되었다. 네트워크 메타분석 결과, 무진행생존(PFS)의 개선은 lenvatinib, anlotinib, cabozantinib, apatinib 순으로 나타났다. MKI에서 전체 생존(OS)에 대한 통계적으로 유의미한 개선은 보이지 않았다. 다른 유효성 변수의 경우, cabozantinib이 객관적 반응률(ORR) 1위, apatinib이 질병 통제율(DCR) 1위, lenvatinib이 임상적 이득률(CBR) 1위로 확인되었다. Lenvatinib 과 apatinib의 경우 독성도 더 높게 나타났다. Lenvatinib 은 AE와 SAE에서 1위, apatinib은 약물과 관련성이 있는 AE 및 grade 3 이상의 AE에서 1위로 확인되었다.

IV. 결론

Lenvatinib은 무진행생존(PFS) 및 임상적 이득률(CBR)에서 가장 좋은 개선을 보였고 폐 전이 환자에게도 매우 효과적이었다. 결과에 따르면, 환자에게 lenvatinib이 가장 권고된다. 만약 lenvatinib으로 인한 약물이상반응으로 인해 치료약을 변경해야할 경우, anlotinib, cabozantinib, 또는 apatinib을 권고할 수 있다. 안전성 결과는 일반적으로 치료간 비슷한 수준이었지만, 대체로 높은 효과를 보이는 약물에서 더 높은 독성을 보였기 때문에 MKI 치료 중에 면밀한 안전성 모니터링이 요구된다.

핵심 용어: 갑상선 분화암, multi-kinase inhibitor, protein kinase inhibitor, 유효성, 안전성, 메타분석