



Hypertension Induced by Combination Therapy of Cancer: A Systematic Review and Meta-Analysis of Global Clinical Trials

Xiaodan Guo^{1†}, Xiaoyu Qian^{1†}, Ying Jin², Xiangyi Kong³, Zhihong Qi⁴, Tie Cai⁵, Lin Zhang^{6,7}*, Caisheng Wu¹* and Weihua Li²*

¹Fujian Provincial Key Laboratory of Innovative Drug Target Research and State Key Laboratory of Cellular Stress Biology, School of Pharmaceutical Sciences, Xiamen University, Xiamen, China, ²Department of Cardiology, Xiamen Key Laboratory of Cardiac Electrophysiology, Xiamen Institute of Cardiovascular Diseases, The First Affiliated Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen, China, ³Department of Breast Surgical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, ⁴Clinical Laboratory, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical and Environmental Engineering, China, ⁵State Key Laboratory of Coal Resources and Safe Mining, School of Population Medicine and Public Health, Chinese Academy of Medical College, Beijing, China, ⁷Melbourne School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia

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*Correspondence:

Lin Zhang tony1982110@gmail.com Caisheng Wu wucsh@xmu.edu.cn Weihua Li liweihua@xmu.edu.cn

[†]These authors have contributed equally to this article.

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Guo X, Qian X, Jin Y, Kong X, Qi Z, Cai T, Zhang L, Wu C and Li W (2021) Hypertension Induced by Combination Therapy of Cancer: A Systematic Review and Meta-Analysis of Global Clinical Trials. Front. Pharmacol. 12:712995. doi: 10.3389/fphar.2021.712995 **Background:** Nowadays, due to the limitation of single therapy, combination therapy for cancer treatments has become important strategy. With the advancement of research on cardiotoxicities induced by anti-cancer treatment, among which cancer treatment-induced hypertension is the most frequent case. However, due to the small sample size and the absence of comparison (single-arm study alone), these studies have limitations to produce a feasible conclusion. Therefore, it is necessary to carry out a meta-analysis focusing on hypertension caused by cancer combination therapy.

Methods: We systematically searched PubMed, Embase, Cochrane Library, Web of Science, and CNKI, from database inception to November 31, 2020, with randomized controlled trials (RCTs) associated with hypertension induced by cancer combination drugs. The main endpoint of which was to assess the difference in the incidence of hypertension in cancer patients with monotherapy or combination therapy. We calculated the corresponding 95% confidence interval (95% CIs) according to the random effect model and evaluated the heterogeneity between different groups.

Results: According to the preset specific inclusion and exclusion criteria, a total of 23 eligible RCTs have been included in the present meta-analysis, including 6,241 patients (Among them, 2872 patients were the control group and 3369 patients were the experimental group). The results showed that cancer patients with combination therapy led to a higher risk of hypertension (All-grade: RR 2.85, 95% CI 2.52~3.22; 1~2 grade: RR 2.43, 95% CI 2.10~2.81; 3~4 grade: RR 4.37, 95% CI 3.33~5.72). Furthermore, compared with the control group who received or did not receive a placebo, there was a higher risk of grade 3-4 hypertension caused by cancer combination treatment.

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Conclusion: The present meta-analysis carries out a comprehensive analysis on the risk of patients suffering from hypertension in the process of multiple cancer combination therapies. Findings in our study support that the risk of hypertension may increase significantly in cancer patients with multiple cancer combination therapies. The outcomes of this meta-analysis may provide a reference value for clinical practice and may supply insights in reducing the incidence of hypertension caused by cancer combined treatment.

Keywords: hypertension, combination therapy, angiogenesis inhibitors, meta-analysis, randomized controlled trial

INTRODUCTION

Hypertension has been recognized as the most common comorbidity among various types of cancers, which directly affects the prognosis of cancer patients, and is one of the high-risk factors for cancer survivors suffering from the comorbidity of heart diseases (Jain and Townsend, 2007). In the early stage of diagnosis, there is generally a similar probability of developing hypertension. However, with different cancer treatment patterns, patients may experience significantly altered incidence of hypertension, especially those receiving chemotherapy, which can reach 38% (Piccirillo et al., 2004; Maitland et al., 2010). In addition, novel cancer therapies, such as targeted therapy, which is a type of cancer treatment that targets proteins controlling cancer cells' growth, division, and spreading, are also associated with the incidence of hypertension. Cardio-Oncology is an evolving discipline which aims to analyze the relationship between cancer treatment and cardiotoxicity (Lenneman et al., 2016; Barac, 2020). Cardiovascular toxicity in cancer treatment refers to the occurrence of cardiovascular disease during the disturbance or elimination of cancer cells in patients in vivo. Significantly, cardiovascular disease is the second leading cause of the morbidity and mortality of cancer survivors. According to previous studies, the probability of all-grade hypertension is between 15 and 67% during the treatment by using small molecule vascular endothelial growth factor tyrosinase inhibitors (e.g., sunitinib, sorafenib, pazopanib, etc.), and the rate would be higher with the use of inhibitors with higher efficiency (e.g., axitinib) (Brinda et al., 2016). The incidence of hypertension induced by tyrosinase inhibitors ranges from 5 to 80% in a dose-dependent manner (Agarwal et al., 2018). In addition, some patients may have a history of hypertension before the diagnosis of cancer. However, some patients develop hypertension due to anti-cancer treatment, and hypertension may be the direct result of cancer treatment under this circumstance.

The progress of cancer treatment has promoted the development of multiple new treatment strategies. Combination therapies means combining two or more therapies for cancer patients and the effectiveness may be excellent than single therapy. However, most programs will be accompanied by a series of cardiovascular adverse reactions, especially the existed high correlation of some new drugs with hypertension. In addition, the use of some chemotherapy drugs can also induce hypertension.

Generally, angiogenesis is a necessary process of tumorigenesis, growth, and metastasis. Vascular endothelial growth factor (VEGF) is an angiogenic growth factor. Angiogenesis inhibitor is a classic drug highly associated with the occurrence of hypertension (Hamnvik et al., 2015), primarily including monoclonal antibodies and small-molecule drugs. It has been documented that the proposed highly specific drugs are important inhibitors of angiogenesis, which play a role by blocking the signaling pathways necessary for angiogenesis, such as blocking Vascular Endothelial Growth Factor Receptor (VEGFR), Epidermal Growth Factor Receptor (EGFR), basic Fibroblast Growth Factor (bFGF), Platelet-derived Growth Factor Receptor (PDGFR), etc. (Folkman, 2007). To be specific, VEGF is the main growth factor that controls angiogenesis. Epidermal growth factor (EGF) is responsible for differentiation and apoptosis. bFGF can regulate the proliferation and differentiation of specific types of cells and has an effective effect on angiogenesis. Platelet-derived growth factor (PDGF) involves significantly cell growth, cell division, and angiogenesis (Wilkins et al., 2014; Agarwal et al., 2018).

With the emergence of various novel approaches to cancer treatment, the survival of cancer patients is becoming higher, which, however, is accompanied by an increasingly more obvious change in cardiotoxicity. Given the differences in cancer tissue types, therapeutic drugs, and drug doses, a systematic review and meta-analysis were carried out on hypertension caused by cancer treatment (Said et al., 2017), which aimed to clarify the incidence and risk of hypertension in cancer patients treated with combination therapy. At present, there is incomplete knowledge of hypertension caused by cancer combination therapy. Besides, there is few systematic reviews or metaanalyses in this aspect based on the comprehensive analysis of previous literature. Accordingly, through comprehensive literature analysis, it is expected to analyze and elaborate the risk factors of hypertension caused by cancer combination therapy, to provide a certain reference value for clinical treatment.

METHODS

The present systematic review and meta-analysis were conducted following PRISMA guidelines (Moher et al., 2009). The protocol

has been registered in PROSPERO with the registration number CRD42021220923.

Data Sources and Searches

A comprehensive literature search was made in databases [PubMed, embase, Cochrane Library, Web of Science, and CNKI] since November 31, 2020, to identify all articles related to the subject. In addition to the above databases, the clinical trial registration website (https://clinicaltrials.gov/) was searched to obtain information about registered prospective trials.

The keywords used in PubMed were listed as follows:

- 1) randomized controlled trial [pt]
- 2) controlled clinical trial [pt]
- 3) randomized [tiab]
- 4) placebo [tiab]
- 5) clinical trials as topic [mesh: noexp]
- 6) randomly [tiab]
- 7) trial [ti]
- 8) (1) OR (2) OR (3) OR (4) OR (5) OR (6) OR (7)
- 9) animals [mh] NOT humans [mh]
- 10) (8) NOT (9)

The final selected literatures were checked and reviewed separately to include the latest and most complete clinical trial reports in the case of repeated publications. All the search results were incorporated into the management tool of Endnote.

Study Selection and Data Extraction

The major objective of our study was to determine the incidence of hypertension associated with combination therapy for cancer and to establish a relationship between combination therapy and the risk of hypertension. Therefore, eligible studies were those evaluating the combination of drugs with hypertension induced in cancer patients. Phase I trial was excluded considering the multi-dose level and limited sample size. In addition, phase II, III, and IV randomized controlled trials (RCTs) in combination therapy were enrolled in the analysis compared with those without combination therapy.

The eligible studies met the inclusion criteria:

- 1) Phase II, III, and IV trials involving cancer patients;
- 2) RCTs for cancer treatment;
- 3) Intervention group: combination therapy (including targeted therapy and chemotherapy);
- 4) Control group: monotherapy or placebo treatment;
- 5) Studies with available data on hypertension events or incidence and sample size.

The exclusion criteria:

- 1) Review articles
- 2) Not randomized control trial
- 3) Reports from same study sample
- 4) Not report associate with hypertension
- 5) Not report associate with cancer combination therapy
- 6) No usable data

- 7) No comparable trial
- 8) Republished literature

Two investigators (G.X and Q.X) extracted data independently, and any disagreements between the two reviewers were resolved by consensus. Online studies before publication were also eligible, but not including reviews, Conference reviews, studies published only in abstract form, quality of life research, non-randomized trials, and studies that could not determine the toxicity of combination therapy. Data extraction covered author, year of publication, research institution, journal name, trial phase, cancer tissue type, combination therapy, number of patients, age of patients, administration schedule and drug dose, size of control group, number of patients with hypertension, with the data of hypertension at all grades extracted.

Data Synthesis and Analysis

Statistical analysis of this study was performed by using the Cochrane Review Manager (RevMan 5.3) software provided by the Cochrane Library Collaboration Network.

The proportion of patients with hypertension in each study was calculated by dividing the number of patients with hypertension caused by combination therapy extracted from eligible clinical trials by the total number of patients receiving combination therapy in each study. We refer to all levels of hypertension events as "All-grade," "1–2 grade" is combined the grade of 1 or 2 hypertension events, and "3–4 grade" which is the sum of the level of 3 or 4 hypertension events.

For each study enrolled in this analysis, the relative risk (RR) and 95% confidence interval (95% CI) of the incidence of events between the intervention group and the control group were calculated according to the number of reported events and sample size. The I2 index and Q-statistics were used to evaluate the heterogeneity among studies, among which the Q-test is widely used at present (Zintzaras and Ioannidis, 2005). p < 0.05 of the Q-test indicated the existence of heterogeneity (Zhang et al., 2019), and p < 0.05 meant the existence of statistical significance. If p > 0.05, the results of the independent studies might be homogeneous, suggesting the use of the fixed-effect model; On the contrary, the random-effect model should be used and/or consider the clinical suitability of combination therapy when there was heterogeneity with p < 0.05. I^2 can quantify the heterogeneity among studies, which is calculated generally based on χ^2 test. It describes the percentage of variation among studies in total variation, which may indicate a higher heterogeneity with the increase of the value of I^2 (Huedo-Medina et al., 2006). $I^2 > 25$, 50, and 75% suggest that there may be low, moderate, and high heterogeneity among studies. Besides, it is generally believed that there is substantial heterogeneity when $I^2 > 50\%$.

RESULTS

Search Results

A total of 3,915 articles were identified by literature search and reference list review. After screening and qualification evaluation,



23 clinical trials involving 6,241 patients were finally included after excluding review articles, case reports, and meta-analysis articles, with the flow chart of literature selection shown in **Figure 1**. Of the 23 studies, there were 12 phase II, 11 phase III, and 1 phase IV trials, with the year of publication ranging from 2005 to 2020 (**Table 1**) (Miller et al., 2005; Heymach et al., 2008; Goss et al., 2010; Mok et al., 2011; Rugo et al., 2011; Baselga et al., 2012; Kato et al., 2012; Johnston et al., 2013; Laurie et al., 2014; Liu et al., 2014; Mackey et al., 2015; Rini et al., 2016; Baselga et al., 2017; Kubota et al., 2017; Yan et al., 2017; Dummer et al.,

2018; Lu et al., 2018; Liu et al., 2019; Nakagawa et al., 2019; Cortot et al., 2020; Guo et al., 2020; Sinn et al., 2020; Tao et al., 2020). According to the published Common Terminology Criteria for Adverse Events (CTCAE) by the National Cancer Institute (NCI), hypertension caused by anti-cancer treatment includes 5 grades of grade 1–5 (**Table 2**) (National Cancer Institute, 2017). Among them, grade 5 hypertension includes fatal elevated blood pressure. There were no patients with grade 5 hypertension in the included literatures. Consequently, only grade 1–4 hypertension was enrolled in the data extraction. After research, there is no

Ref			9	17	ά	0	20	5
tion	Regimen		Orally Capecitabine (2,500 mg/m ² /d) twoe daily for 14 days followed by a 7-days rest period. Patients continued therapy for a maximum of 35 cycles	Orally Placebo + Pacilitaxel (200 mg/m ²) and Carboplatin (area under the concentration-time curve at steady-state, 6 mg/m ⁴ mi) once every 3 weeks for a maximum of six cycles	Pacifiaxel 200 mg/m ² by intravenous 3-h infusion and carbopistin dosed to an area under the serum concentration-time curve of 6 every 3 weeks for 6 to 8 cycles, placebo was administered orally once daily concurrently with chemotherapy	Placebo + Cisplatin was administered i.v. at 80 mg/ m ² on day 1 and gemctlabine was administered i.v. at 1,250 mg/m ² on days 1 and 8. Chemotherapy and 8. Chemotherapy every 3 weeks for up to sky cycles	Docetaxel 80 mg/m² once every 3 weeks plus placebo twice per day	Capecitabine 1,000 mg/ m ² orally twice a day for days 1-14 of every 21- days cycle with placebo orally twice a day
n informa	nsion	Grade 3-4	. -	0	N	0	0	N
Control arn	Hyperte Eve	Grade 1-2	4	N	ω	a	0	9
	Age (Range)		27-08	42-83	80 8-	29-75	34-71	54(mean)
	Patient number		530	22	125	e e	20	1 4
mation	Regimen		Orally Capecitabrie (2,500 mg/m ² /d) twice daily for 14 days followed by a 7-days rest period, by a 7-days rest period, hitravenously on day 1 of aech 3-weeks cycle Patients continued therapy for a maximum of 35 cycles	Orally vandetantb (300 mg) + Paclitaxel (200 mg/m ³) and Carboptetin (area under the concentration- time curve at steady-state, 6 mg/m ³ mil) once every 3 weeks for a maximum of six cycles	Pacifitavel 200 mg/m ² by intravenous 3-h infusion and carbotahi dosed to an area under the serum concentration-time curve of 6 every 3 weeks for 6 to 8 soycies, cardiaraib 30 mg was administered orally orice daily concurrently with chemotherapy	Bevaczumab 15 mg/kg plus Cisplatin was administered Lv. at 80 mg/ m°on day 1 and gendiabine was administered Lv. at 1.250 mg/m° on days 1 and 8. Chemotherapy every 3 weeks for up to six cycles	Docetaxel 80 mg/m² once every 3 weeks plus axitinib 5 mg twice per day	Capecitabine 1,000 mg/ m² orally twice a day for days 1-14 of every 21- days cycle with sorafenib 400 mg orally twice a day
arm infor	nsion nt	Grade 3-4	4	4	φ.	n	۵	-
ervention a	Hyperte Evei	Grade 1-2	ő	4	0	6	26	7
<u>n</u>	Age (Range)		29-78	36-79	22-92	0 29 29	30-79	55 (mean)
	Patient number		33 73	20	126	34	112	- 15
Combination	therapy		Capecitabine + bevacizumab vs Capecitabine	Vandetanib + Pacifiaxel and Carboptin vs Placebo + Pacebo + Pacifiaxel and Carboplatin	Cediranib + Pacifiaxel and Carboptatin vs Placebo + Pacifiaxel and Carboptatin	Bevacizumab + Cisplatin and Gemcitabine vs Placebo + Cisplatin and Gemcitabine	Docetaxel + axitinib vs Docetaxel + Placebo	Capecitabine + Sorafenib vsCapecitabine + Placebo
Cancer	type		Breast Cancer	Non-Small- Cell Lung Cancer	Non-Smal- Cell Lung Cancer	Non-Smal- Cell Lung Cancer	Breast Cancer	Breast Cancer
Study	phase		=	=	E	=	=	=
Journal			Journal of Clinical Oncology	Journal of Clinical Oncology	Journal of Clinical Oncology	Asia- Asia- Journal of Clinical Oncology	Journal of Clinical Oncology	Journal of Clinical Oncology
Institution			University	Dana-Farber Cancer Institute	The Ottawa Hospital Cancer Centre	Prince of Wales Hospital	University of California	Massachusetts General Hospital Cancer Center
Country			United States	United States	Canada	China	United States	United States
Year			2005	2008	2010	2011	2011	2012
Author			Miller et al.(2005)	Heymach et al.(2008)	Goss et al.(2010)	Mok et al.(2011)	Rugo et al.(2011)	Baselga et al.(2012)
Entry			-	N	σ	4	a	ω

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TABLE 1 | Characteristics of the studies included in this meta-analysis.

Ref			1-days 22 titin m² N, m² N sn uous	1-days 22 titin m² N, m² N sn uous	0 mg	m ²) 24 a a a fricon construction from the construction of the co	00 mg 25	² plus 26
ttion	Regimen		Once-daily placebo combination with 14 treatment cycles of mFOLFCX6 (oxelipk 85 mg/m [*] V, day 1, the leucovorin 200 mg/r day 1; 5-FU 400 mg bolus, day 1 and th 2.400 mg/m ² continh 2.400 mg/m ² continh	Once-daily placebo combination with 14 treatment cycles of m mFOLFOX6 (oxalipk 85 mg/m ² / day 1 leucovorin 200 mg/n day 1; 5-FU 400 mg bolus, day 1 and th 2,400 mg/m ² contith 2 valot mg/m ² contith	Daily lapatinib 1,500	Pacifizsel (200 mg/i and carboplatin (are under the concentra time cuve 6) intrave every 3 weeks. Dain placebo was comm day 1 of cycle 1 and day 1 of cycle 1 and day 1 of cycle 3 and other completion of the cycles of chemother	Olaparib capsules 4 twice daily	Docetaxel 75 mg/m placebo once every 3 weeks
n informa	ension nt	Grade 3-4	-	-	0	e	0	~
Control an	Hyperte Eve	Grade 1-2	4	4	ო	÷	0	37
	Age (Range)		8- 8- 8:	00 00 00 00	29-80	36-77	42-86	29-81
	Patient number		8 S	ő	72	5 2	46	385
mation	Regimen		Once-daily ceditanib 20 mg combination with 14-days reament cycles of mFOLFCK (exalptatin 85 mg/m ² N, day 1; leucovorin 200 mg/m ² N, day 1; 5-FU J40 mg/m ² N, bolus, day 1 and then 2400 mg/m ² controuots N infusion over 46 h)	Once-daily ceditanih 30 mg combination with 14-days reament cycles of mFCLFCK6 (oxalptatin 85 mg/m ² N, day 1; leucovorin 200 mg/m ² N, day 1; 5-FU 400 mg/m ² N, bolus, day 1 and then 2.400 mg/m ² combuous N infusion over 46 h)	Daily lapatinib 1,500 mg plus pazopanib 800 mg	Pacifizsel (200 mg/m ²) and carboplatin (area under the concentration time curve 6) intra-erously every 3 weeks. Daily oral cedirarib 20 mg was commenced day 1 of cycle 1 and continued as montherapy after completion of 4–6 cycles of chemotherapy	Cediranib 30 mg daily and olaparib capsules 200 mg twice daily	Docetaxel 75 mg/m ² plus ramucirumab 10 mg/kg once every 3 weeks
arm infor	ension ent	Grade 3-4	4	Q	0	μ	18	51
tervention	Hyperte Eve	Grade 1-2	43	42	5	ê	17	152
5	Age (Range)		33-179	40-82	3382	23-85	32-82	24-82
	Patient number		œ	ß	æ	5 20	44	759
Combination	therapy		Cediranb + mFOLFOX6 vs Placebo + mFOLFOX6	Cediranb + mFOLFOX6 vs Placebo + mFOLFOX6	Lapatinib + pazopanib vs Lapatinib	Cedirantb + Pacifizxel and Carboptatin vs Pacifizzebo + Pacifizzela and Carboptatin	Cediranib + Olaparib vs Olaparib	Ramucirumab + Docetaxel vs Placebo + Docetaxel
Cancer	type		Cancer Cancer	Colorectal	Breast Cancer	Non-Small- Cell Lung Cancer	Ovarian Cancer	Breast Cancer
Study	phase		=	=	=	Ē	=	=
Journal			Annals of Oncology	Annals of Oncology	Breast Cancer Research and Treatment	European Journal of Cancer	Lancet Oncol	Journal of Clinical Oncology
Institution			National Hospital Organization Osaka National Hospital	National Hospital Organization Osaka National Hospital	Institute of Cancer Research	University of Ottawa	Dana-Farber Cancer Institute	Cross Cancer Institute
Country			Japan	Japan	United Kingdom	Canada	United States	Canada
Year			2012	2012	2013	2014	2014	2015
Author			Kato et al.(2012)	Kato et al.(2012)	Johnston et al.(2013)	et al.(2014)	Liu et al.(2014)	Mackey et al.(2015)
Entry			~	ω	o		=	5

Ref			5	28	29	8	31	32
Ition	Regimen		Suntitruib (50 mg) was given orally once daily, with each vycid defined as 4 weeks on treatment followed by 2 weeks off treatment	Capecitabine (1,000 mg/ m ² bid on days 1–14 of each 21-days cycle) plus placebo	Once daily oral placebo and received pacifitaxel 200 mg/m ² IV and carboption area under the concentration-time curve 6 mg/minmin IV on day 1 of each 3-weeks cycle for up to six cycles	Oxaliplatin (130 mg/m ² bic on 1 day of each 21-days cycle) IV. Tiggio depends on the body surface area (c.1.25m ² take 40 mg, 1.25m ² -1.50m ² take 60 mg, twice a day) 60 mg, twice a day)	Encoratenib 300 mg once daily orally	Oral placebo was given in 4-weeks cycles of 3 weeks of treatment followed by 1 week off, and combination with best supportive care
informa	nsion 1t	Grade 3-4	~	Q	4	0	ω	-
control arn	Hyperte Evel	Grade 1-2	24	o	25	0	ى	0
	Age (Range)		54 - 66 - 6	55 (Median)	89 85		23-88	55 (Median)
	Patient number		5 6	271	204	75	194	00
mation	Regimen		Suntimb (50 mg) was given orally once daily with each cycle defined as a weeks on treatment followed by 2 weeks off treatment, plus up to ten intradement pus vaccinations of IMA901 (4.13 mg) and granudoyte macrophage colony-stimulating factor (75 kg) and granudoyte macrophage colony-stimulating factor (75 kg) solve (75 kg) and granuboyte macrophage (75 kg) and granuboyte macrop	Capecitabine (1,000 mg/ m ² bid on days 1–14 of each 21-days cycle) plus soratenib (600 mg/day)	Once daily oral molesantb 125 mg and received pacitaxel 200 mg/m ² IV and carboptatin area under the concentration-time curve 6 mg/m imin IV on day 1 of each 3-weeks cycle for up to six cycles	Apatinib 850 mg/d, 0.5 h after meal begin oral administration, from the first day of chemotherapy and each 4-weeks cycle. Oxalipistin (130 mg/m ^b bid on 1 day of each 21-days cycle ¹ IV. Tiggio depends on the body surface area do mg, 1.28m ² take 40 mg, 1.28m ² take 60 mg, twice a day)	Encoratientib 450 mg once daily orally plus binimetintib 45 mg twice daily orally	Oral fruquintinib (5 mg once daily) was given in 4- weeks cycles of 3 weeks of treatment followed by 1 week off, and combination with best
	nt	Grade 3-4	24	æ	3	0	5	a
ervention	Hyperte Eve	Grade 1-2	27	32	5 4	4	16	თ
	Age (Range)		50 - 03	53 (Median)	59-70	34-75	20-89	54 (Median)
	Patient number		204	266	197	22	192	6
Combination			IMA601 + suntinib vs Suntinib	Sorafenib + Capecitabine vs Placebo + Capecitabine	Motesanib + Paciltaxel and Carboptatin vs Placebo + Paciltaxel and Carboptatin	Apapathib + Cxalptin and Tiggio vs Cxalptin and Tiggio	Encorafenib + binimetinib vs Encorafenib	Fruquintinib + Best supportive care vs Placebo + Best supportive care
type	-		Renal Cell Carcinoma	Breast Cancer	Non-Small- Cell Lung Cancer	Gastric Canoar	Melanoma	Non-Small- Cell Lung Cancer
phase			=	=	=	2	=	=
Journal			Oncology 0	Clin Breast Cancer	Journal of Clinical Oncology	Cancer Research and Clinic	Lancet Oncol	Journal of Clinical Oncology
Institution			Cleveland Clinic Tauesig Cancer Institute	Memorial Sloan Kettering Cancer Center	Graduate School of Medicine	Baoji Central Hospital	University Hospital Zürich Skin Cancer Center	Jiao Tong University
Country			States	United States	Japan	China	Switzerland	China
Year			2016	2017	2017	2017	2018	2018
Author			Rini et al.(2016)	Baselga et al.(2017)	Kubota et al.(2017)	Yan et al.(2017)	Dummer et al.(2018)	Lu et al.(2018)
Entry			ő	14	<u>م</u>	6 0	17	œ

Ref			33	34	35	ő	37	38
tion	Regimen		Olaparib capsules 400 mg twice daily	Oral entotinib (150 mg/day) plus placebo once every 2 weeks	Docetaxel (75 mg/m2) every 21 days	135–175 mg/m ² pacitaxel (alkuted in 500 ml of 0.9% sailre and intursed intravenously over 3 h) on day 1 and carboptain AUC 5 (diuted in 500 ml or (0.9% sailre solution and inturse intravenously over 30 min) on day 2 every 3 weeks, for 6 cycles	The average weekly dose of gemcitabine was 690 mg/m² and placebo	Intravenous 175 mg/m ² paciltaxel (Taxol: Bristol- Myers Squibb) and Intravenous 6 mg/mL/min area under the curve earboptain (Paraplatin; Bristol-Myers Squibb) even's sweeks
i informa	1sion It	Grade 3-4	0	12	0	0		ى ا
Control arm	Hyperter Ever	Grade 1–2	0	- 1	0	N		÷
	Age (Range)		T	56-70	35-78	69 - 08	43-80	30-70
	Patient number		46	225	55	ත N	9	161
mation	Regimen		Cediranib 30 mg datiy and olaparib capsules 200 mg twice daily	Oral erlotinib (150 mg/day) plus intravenous ramucirumab (10 mg/kg) once every 2 weeks	90 mg/m2of pacitaxel/[D1, D8, D15) plus 10 mg/kg of bevacizumab (D1,D15) every 28 days	500 mg apatingh mesylate orally in between arally in between 1356–175 mg/m² pacifiaxel (altuded in 500 ml of 0.9% sailne and infused day 1 and carboptin AUC 5 (altuded in 500 ml of 0.9% sailne solution and infused intravenously over 30 min) on day 2 every 3 weeks, for 6 cycles	The average weekly dose of gemcitabine was 690 mg/m ² , the average daily dose of soratenib in the GamSoratenib arm was 650 mg (plenned 800 mg daily)	Intravenous 175 mg/m ² pacitraxel, intravenous 6 mg/m1/m area under the cure carboptinh, and intravenous 15 mg/m ² Devactumab (Roche, Holding AG) every 3 weeks
arm infor	nsion nt	Grade 3-4	8	52	ω	N	<i>с</i> у	÷
tervention a	Hyperte Evel	Grade 1-2	16	48	14	0		2
Ē	Age (Range)			57-71	18-81	28-62	38-78	30-70
	Patient number		44	224	111	R	57	127
Combination	therapy		Cediranib + Olaparib vs Olaparib	Ramucirumab + erlotinib vs Placebo + erlotinib	Paclitaxel + bevacizumab vs	Apatinib + Pacifiaxel and Carboplatin vs Pacifiaxel and Carboplatin	Soratenib + Gemotabine Vs Placebo + Gemotabine	Paclitaxel + Carboplatin + bewacizumab vs Paclitaxel + Carboplatin
Cancer	type		Ovarian Cancer	Non-Small- Cell Lung Cancer	Non-Small- Cell Lung Cancer	Canver	Pancreatic Cancer	Cancer
Study	phase		=	=	=	=	=	=
Journal			Annals of Oncology	The Lancet Oncology	European Journal of Cancer	Medicine (Battimore)	European Journal of Cancer	Dose- Response
Institution			Dana-Farber Cancer Institute	Kindai University Faculty of Medicine	Thoracic Oncology Department	Shandong Provincial Heispital Affiliated to Shandong University	Department of Medical Oncology and Hematology	Medicine School of University of Electronic Science and Technology
Country			United States	Japan	France	China	Germany	China
Year			2019	2019	2020	2020	2020	2020
Author			Liu et al.(2019)	Nakagawa et al.(2019)	Cortot et al.(2020) Docetaxel	Guo et al.(2020)	Sinn et al(2020)	Tao et al.(2020)
Entry			19	20	21	20	33	2

TABLE 1 | (Continued) Characteristics of the studies included in this meta-analysis.

TABLE 2 | Characterized of hypertension in CTCAE.

		Hypertension		
Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Adult: Systolic BP 120–139 mm Hg or diastolic BP 80–89 mm Hg	Adult: Systolic BP 140–159 mm Hg or diastolic BP 90–99 mm Hg if previously WNL; change in baseline medical intervention indicated; recurrent or persistent (≥24 h); symptomatic increase by > 20 mm Hg (diastolic) or to >140/ 90 mm Hg; monotherapy indicated initiated	Adult: Systolic BP≥160 mm Hg or diastolic BP≥100 mm Hg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated	Adult and Pediatric: Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Death
Pediatric: Systolic/diastolic BP > 90th percentile but< 95th percentile	Pediatric and adolescent: Recurrent or persistent (≥24 h) BP > ULN; monotherapy indicated; systolic and/or diastolic BP between the 95th percentile and 5 mmHg above the 99th percentile	Pediatric and adolescent: Systolic and/ or diastolic >5 mmHg above the 99th percentile		
Adolescent: $BP \ge 120/80$ even if < 95th percentile	Adolescent: Systolic between 130 and 139 or diastolic between 80 and 89 even if < 95th percentile			

Author (Year)	Randomization	Concealment of allocation	Double blinding	Withdrawals and dropouts	Score
Baselga et al. (2012)	2	2	2	1	7
Baselga et al. (2017)	1	1	2	1	5
Cortot et al. (2020)	2	1	1	1	5
Dummer et al. (2018)	2	2	2	1	7
Goss et al. (2010)	2	2	0	1	5
Guo et al. (2020)	1	1	0	1	3
Heymach et al. (2008)	1	1	2	1	5
Johnston et al. (2013)	0	2	1	1	4
Kato et al. (2012)	2	2	2	1	7
Kato et al. (2012)	2	2	2	1	7
Kubota et al. (2017)	2	2	2	1	7
Laurie et al. (2014)	1	2	0	1	4
Liu et al. (2014)	2	2	2	1	7
Liu et al. (2019)	2	2	2	1	7
Lu et al. (2018)	2	2	2	1	7
Mackey et al. (2015)	2	2	2	1	7
Miller et al. (2005)	2	2	2	1	7
Mok et al. (2011)	1	1	2	1	5
Nakagawa et al. (2019)	2	2	2	1	7
Rini et al. (2016)	2	2	2	1	7
Rugo et al. (2011)	2	2	2	1	7
Sinn et al. (2020)	2	2	2	1	7
Tao et al. (2020)	2	2	2	1	7
Yan et al. (2017)	1	1	1	1	4

discovery showing that the patients enrolled in the reviewed RCTs were taking anti-hypertensive drugs.

In this study, cancer types were Breast Cancer (n = 6), Cervical Cancer (n = 2), Colorectal Cancer (n = 1), Gastric Cancer (n = 1), Melanoma (n = 1), Non-Small-Cell Lung Cancer (n = 8), Ovarian Cancer (n = 2), Pancreatic Cancer (n = 1), and Renal Cell Carcinoma (n = 1). As for cancer combination therapy regimens, there was the combination of 2 drugs (n = 14), 3 drugs (n = 8), and >3 drugs (n = 1). Among the 23 therapeutic regimens, there were targeted therapy combined with chemotherapy (n = 17), two targeted therapies combined with

chemotherapy (n = 5), and targeted therapy combined with other treatments (n = 1). In the control group, 10 studies adopted monotherapy, and 13 studies used placebo combined with monotherapy.

In all eligible studies, the average age of patients ranged from 18 to 89 years old. Among the eligible research articles, papers published in the United States accounted for the majority, with 8 articles, followed by China with 5 articles, Canada with 3 articles, Japan with 3 articles, Britain with 1 article, France with 1 article, Germany with 1 article and Switzerland with 1 article. Meanwhile, 8 articles were published in "Journal of Clinical

Bereige et al 2012 Provide al 2012 Provide al 2012 Provide al 2012 Provide al 2012 Provide al 2012 Provide al 2013 Provide al 2013 Pro	Study or Subaroup	Intervention Events	Arm Total	Control Events	Arm Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Beselge at 2017 22 28 09 0 27 40 09 220 17 7.44 14 09 09 220 17 7.74 14 14 09 09 14 00 00 09 14 00 00 09 10 00 00 00 00 00 00 00 00 00 00 00 00	Baselga et al.2012	17	115	10	114	3.9%	1.69 [0.81, 3.52]	IV. FIXEU, 35% CI
Candid et al. 2020 Control et	Baselga et al.2017	32	266	9	271	4.0%	3.62 [1.76, 7.44]	
$ \frac{1}{120} = \frac{1}{120} + 1$	Cortot et al.2020	14	111	0	55	0.3%	14.50 [0.88, 238.66]	
Discrete 12020 Discret	Jummer et al. 2018 Soccet al 2010	16	192	5	194	2.2%	3.23 [1.21, 8.65]	
Hemscher 14.2006 Missen et 42.2017 Missen et 42.2018 Missen et 42.2017 Missen et 42.2017 Missen et 42.2017 Missen et 42.2017 Missen et 42.2017 Missen et 42.2018 Missen et 42.2	3uo et al.2020	10	30	2	29	1.0%	4.83 [1.16, 20.19]	
Jonustan et J2013 12 36 3 72 15% 800 pt 1, 26 57 Kuoba et J2017 14 10 17 56 17 56 175 52 175 325 175 325 185 182 57 175 325 175 325 185 182 182 52 175 325 175 325 185 183 182 185 <	Heymach et al.2008	14	56	2	52	1.0%	6.50 [1.55, 27.24]	
Sale at 2012 2 36 11 58 256 1158 256 1158 256 1158 256 1158 256 1158 256 1158 256 1158 256 1158 256 1158 256 1158 256 1158 256 327 1158 256 1156 1	Johnston et al.2013	12	36	3	72	1.5%	8.00 [2.41, 26.57]	
$\begin{aligned} \frac{\log \log n}{\log 1} \frac{\log 1}{\log 1} $	(ato et al.2012 (ato et al.2012	43	56	17	58	11.4%	2.55 [1.65, 3.66]	
Lauis et al. 2014 36 153 11 153 5.2% 3.27 (1.7, 6, 16) Luis et al. 2014 17 44 0 44 0.3% 34.67 (2.7, 86.87) Luis et al. 2013 16 44 0 44 0.3% 34.77 (2.1, 36.75 0) Luis et al. 2013 16 44 0 44 0.3% 34.77 (2.1, 37.75 0) Miller et al. 2005 13 2.22 4 220 1.7% 3221 (1.0, 4.30 7) Miller et al. 2005 13 2.22 4 15 2.25 6.3% 321 (1.8, 5.57) Rule at al. 2013 16 42 2.27 15 2.25 6.3% 321 (1.8, 5.57) Rule at al. 2013 17 17 7.5 0 7.5 0.3% 25.00 (2.1, 5.71 0) Total (16% C) 3.369 2.27 100.0% 2.33 (2.1, 6.8, 30.71 0) Total (16% C) 3.369 2.27 100.0% 2.33 (2.1, 6.8, 30.71 0) Total (16% C) 3.369 2.27 100.0% 2.33 (2.1, 6.8, 30.71 0) Total (16% C) 3.369 2.27 100.0% 2.33 (2.1, 6.8, 30.71 0) Total (16% C) 3.369 2.27 100.0% 2.33 (2.1, 6.8, 30.71 0) Total (16% C) 3.369 2.27 100.0% 2.33 (2.1, 6.8, 30.71 0) Total (16% C) 3.369 2.27 100.0% 2.33 (2.1, 6.8, 30.71 0) Total (16% C) 3.369 2.27 100.0% 2.33 (2.1, 6.8, 30.71 0) Total (16% C) 3.369 2.27 100.0% 2.33 (2.1, 6.8, 30.71 0) Total (16% C) 3.369 2.27 100.0% 2.33 (2.1, 6.8, 30.71 0) Total (16% C) 1.376 2.6 6 2.71 10.1% 6.11 (2.2, 1.4.27 1) Total (16% C) 1.376 2.6 6 2.71 10.1% 6.11 (2.2, 1.4.27 1) Total (16% C) 1.376 2.6 6 0.21 0.3% 8.50 (0.0, 5.39 0) Total (16% C) 1.38 2.6 0.72 0.9% 8.50 (0.0, 5.39 0) Total (16% C) 1.32 0.5 0.72 0.9% 8.50 (0.0, 5.39 0) Total (16% C) 1.32 0.5 0.72 0.9% 8.50 (0.0, 5.39 0) Total (16% C) 2.38 11 0.55 0.50 0, 5.39 0, 5	<ubota al.2017<="" et="" td=""><td>54</td><td>197</td><td>25</td><td>204</td><td>11.2%</td><td>2.24 [1.45, 3.44]</td><td></td></ubota>	54	197	25	204	11.2%	2.24 [1.45, 3.44]	
Lue et al. 2014 1 17 4 44 0 44 0.3% 33.65 (E. 27, 598 97) Hardwey et al. 2015 152 759 37 385 12.3% 2.08 (1.42, 2.23) Hardwey et al. 2015 152 759 37 385 12.3% 2.08 (1.42, 2.23) Hardwey et al. 2016 12 22 4 123 2 4 123 12 4 123 4 123 1 4 1 123 4 123 1 123 1 123 4 123 1 123 1 123 4 123 1 123 1 123 4 123 1 123 1 123 4 123 1 123 1 123 4 123 1 123 1 123 1 123 4 123 1 123 1 123 1 123 1 123 1 123 1 123 1 123 1 123 1 123 1 123 1 123 1 123 1 123 1 1	aurie et al.2014	36	153	11	153	5.2%	3.27 [1.73, 6.19]	-
$\begin{aligned} \begin{array}{c} \text{List} u = 10^{-1} & \text{Control} Arm \\ \text{Miller et al. 2016} & \text{1} & \text{1} & \text{2} & \text{2} & \text{1} & \text{2} & \text{2} & \text{2} & \text{1} & \text{2} & $	iu et al.2014	17	44	0	46	0.3%	36.56 [2.27, 589.97]	
$\frac{1}{1280} = \frac{1}{12016} = \frac{1}{12} = \frac{1}{129} = \frac{1}{19} = \frac{1}{19$	u et al.2019 u et al.2018	10	44 61	0	40	0.3%	34.47 [2.13, 557.59] 9.50 [0.57, 157.94]	
$\begin{aligned} \begin{array}{c} \text{Miler et al. 2005} & 11 & 222 & 4 & 230 & 1.7\% & 3.22 [10.7, 7.3] \\ \text{Margawa et al. 2019} & 40 & 224 & 15 & 222 & 6.5\% & 3.21 [1.86, 5.5] \\ \text{Margawa et al. 2019} & 40 & 224 & 15 & 222 & 6.5\% & 3.21 [1.86, 5.5] \\ \text{Margawa et al. 2019} & 40 & 224 & 15 & 222 & 6.5\% & 3.21 [1.86, 5.5] \\ \text{Margawa et al. 2010} & 21 & 210 & 24 & 138 & 2.2\% & 0.21 [1.86, 5.2] \\ \text{Margawa et al. 2017} & 17 & 75 & 0.75 & 0.3\% & 35.00 [2.14, 571.60] \\ \text{Margawa et al. 2017} & 17 & 75 & 0.75 & 0.3\% & 35.00 [2.14, 571.60] \\ \text{Margawa et al. 2017} & 17 & 75 & 0.75 & 0.3\% & 35.00 [2.14, 571.60] \\ \text{Margawa et al. 2017} & 17 & 75 & 0.75 & 0.3\% & 35.00 [2.14, 571.60] \\ \text{Margawa et al. 2017} & 17 & 75 & 0.75 & 0.3\% & 35.00 [2.14, 571.60] \\ \text{Margawa et al. 2017} & 10 & 150 & 227 & 10.00\% \\ \text{Test for ownal effect. 2-12.20; 0+ 0.00007)} & 255 & 10.75 & 0.3\% & 35.00 [2.14, 571.60] \\ \text{Margawa et al. 2017} & 30 & 266 & 6 & 271 & 10.1\% & 6.11 [2.62, 1.427] \\ \text{Margawa et al. 2010} & 12 & 192 & 6 & 194 & 7.5\% & 0.2\% & 5.03\% & 5.00 (55.14.462) \\ \text{Dummer et al. 2010} & 12 & 192 & 6 & 194 & 7.5\% & 0.205 & 1.44.52 & 2.22 & 3.061 \\ \text{Margawa et al. 2017} & 23 & 0.02 & 0.0\% & 4.24 & 0.24 & 9.6\% & 3.24 & 0.24 & 3.6\% & 0.5\% $	dackey et al.2015	152	759	37	385	18.3%	2.08 [1.49, 2.92]	-
Maket al. 2011 1 19 2, 751 1 128	diller et al.2005	13	232	4	230	1.7%	3.22 [1.07, 9.73]	
$\begin{aligned} \begin{array}{c} \begin{array}{c} \begin{array}{c} \mbox{transmin} \\ \mbox{transmin} \\\mbox{transmin} \\\mbox{transmin} \\ \mbox{transmin} \\ transmi$	Nok et al.2011	16	34	5	33	2.7%	3.11 [1.28, 7.51]	
Rupp et al. 2011 2 0 11 2 0 15 0 55 0 35 227 21 (65, 43.72) Tao et al. 2020 2 1 122 11 161 44.8 242 [12, 14, 83] Tao et al. 2020 2 1 122 11 161 44.8 242 [12, 14, 83] Total remote and the second	Rini et al 2016	27	204	24	135	8.2%	0.74 [0.45 1.23]	
Sim et al 2020 0 57 0 65 Not estimate Total al 2020 1 7 7 75 0 78 0.38 35.0 [214, 571.60] Total services of the service of	Rugo et al.2011	26	112	0	56	0.3%	26.73 [1.66, 430.79]	
Take et al. 2020 Take et al. 2021 Take et al. 2020 Take et al. 2020 Take et al. 2021 Take et al. 2020 Take et al. 2021 Take et al. 2020 Take et al. 2021 Take et al.	Sinn et al.2020	0	57	0	65		Not estimable	
Internation 10	Fao et al.2020	21	127	11	161	4.4%	2.42 [1.21, 4.83]	
Total effect 0 Total events 671 205 Test for overall effect 2 = 12.03 (P + 0.0007), P = 558 Test for overall effect 2 = 12.03 (P + 0.0007) Test 572 (P + 0.	an et al.2017	17	75	0	75	0.3%	35.00 [2.14, 571.00]	
Total events $p_{11} = 225$ Test for overall effect 2 = 12.03 (P + 0.0007); E = 56%. Test for overall effect 2 = 12.03 (P + 0.0007); Exercise 12.03 (P + 0.0007); E = 56%. Test for overall effect 2 = 12.03 (P + 0.0007); Exercise 12.000 (P + 0.0007); Exercise 12.000 (P +	Fotal (95% CI)		3369		2872	100.0%	2.43 [2.10, 2.81]	•
Heterogenery: Ch ⁺ = 4.8.4.01 = 22 (ℓ = 0.0007); // = 0.5% Test for overall effect Z = 12.03 (ℓ = 0.0007); // = 0.5% Subject of the control Arm Control Arm Risk Res 55% (ℓ = 0.0007, // Except 55\% (ℓ = 0.0007	Fotal events	671		205				
Number Number 2 = 1,200 + 5000001 Facurs experimental Facurs control Arm Risk Ratio Nike Ratio Starty or Subaroun Feents Total Feents Total Veents Nike Ratio V. Fixed, 95% CI Baseiga et al. 2017 36 266 6 271 10.1% 6.11 (2.6, 14.27) Control et al. 2000 12 12 12 6 145 7.5% 2.02 (0.7, 5.27) Jonnan et al. 2010 12 12 0 0.52 0.9% 8.27 (0.4, 17.2, 27) Jonnan et al. 2010 12 136 0 7.2 0.9% 8.86 (14.0, 22.36) Jonnan et al. 2011 4 56 0 2.2 0.9% 8.86 (14.0, 22.2.8) Jonand et al. 2017 32 167 4 2.04 7.0% 8.28 (2.8, 22.8) Luet et al. 2014 18 44 0 46 0.9% 3.86 (14.0, 62.2.30) Luet et al. 2015 51 17.3 51.1% 3.2.2.9% 3.0.1% 5.2.2.9% June et al. 2016 51 12.0%	Heterogeneity: Chi ² = 4 Fest for overall effect 7	9.40, df = 22 (P - 12.02 /P = 0	= 0.000	07); I* = 5	5%			0.01 0.1 1 10 100
Intervention Arm Control Arm Risk Ratio Risk Ratio Strekt or standard Freents Total 113 6 111 125 125 111 125 <	1631101 0161411 611601. 2.	= 12.05 (1 = 0.					F	avours experimental Favours control
Intervention Arm Risk Ratio Risk Ratio Risk Ratio Breedge et al. 2012 1 1 19 0.00 (Do. 5, 2.9) Ontot et al. 2020 3 116 0.27 10.18 0.00 (Do. 5, 2.9) Ontot et al. 2020 3 112 0.5 0.98 8.60 (Do. 144.62) Ourmare et al. 2020 12 3.08 1.06 52 0.99 9.42 (2.24, 39.61) Oce et al. 2020 2 3.0 1.28 0.89 9.42 (2.24, 39.61) Joinston et al. 2013 2 0.89 8.37 (D.46, 151.74) 1.44 (0.24, 98.61) Joinston et al. 2014 1.53 3.15 4.98 0.098, 3.82 (1.40, 62.2.38) Lue et al. 2013 2 3.6 1.53 4.00 (0.46, 3.47.11) Lue et al. 2014 15 1.3 1.64 0.098, 3.84 (1.40, 62.2.38) Lue et al. 2014 15 1.63 3.154 4.98 0.014.8, 16.82 Lue et al. 2014 15 2.34 1.233 1.03 1.04 0.039 2.064 (1.02.2.30)								
Sindy or Subaroon Formation Freeds Total Weight N. (Fieed, 95% CI N. Fieed, 95% CI Need, 95% CI		Intervention	Arm	Control	Arm		Risk Ratio	Risk Ratio
Baselga et al. 2012 1 115 2 114 1.3% 0.50 (005, 5.39) Descing et al. 2017 36 226 6 5 271 10.1% 8.50 (5.6, 112 (5.2, 1.4, 6.2) Dummer et al. 2018 12 192 6 114 6 1.3% 0.50 (0.95, 5.39) does et al. 2010 19 126 2 125 3.5% 9.42 (2.4, 3.861) Out et al. 2020 2 3 30 0 29 0.8% 4.48 (0.24, 96.66) Hermach et al. 2008 4 56 0 52 0.9% 8.37 (0.46, 151.74) Joinston et al. 2013 2 36 0 72 0.9% 8.25 (0.46, 151.74) Joinston et al. 2011 4 58 1.7% 6.26 (2.4, 3.9.67) Kado et al. 2012 6 56 1 58 1.7% 6.26 (2.4, 3.9.67) Kado et al. 2012 6 56 1 58 1.7% 6.26 (2.4, 3.9.77) Kado et al. 2011 6 56 1 58 1.7% 6.26 (2.4, 3.9.77) Kado et al. 2011 6 56 1 51 39 17% 6.26 (2.4, 3.9.77) Kado et al. 2011 6 51 759 7 385 (1.2.0% 4.2.9 (2.3.9) Lue et al. 2016 5 1 759 7 385 (1.2.0% 4.2.9 (2.3.9) Lue et al. 2016 5 1 759 7 385 (1.2.0% 5.55 (0.3, 19.68, 0.07) Makey et al. 2015 51 759 7 385 (1.2.0% 5.55 (0.3, 19.68, 0.07) Makey et al. 2015 51 759 7 385 (1.2.0% 5.55 (0.3, 19.68, 0.07) Makey et al. 2015 51 759 7 1 65 1.5% 3.42 (0.37, 3.1.98) Total (2.50 11 5 112 0 56 0.9% 5.55 (0.3, 19.68, 0.07) Find et al. 2010 7 75 0 75 Not estimable Total (2.50 11 5 112 0 13 24 0 224 1 12 225 20.28% 1.49 (7.5, 2.94) Baselga et al. 2011 5 112 0 156 0.2% 2.27 (1.0.1, 5.1.2) King et al. 2016 30 122 (P = 0.39); P = 5% Total (2.50 11 5 112 0 12 7 15 116 6.8% 3.77 (1.9.7, 5.2.94) Heterogenehy: ChF = 23.21, dF = 2.2 (P = 0.39); P = 5% Total (2.50 11 5 112 0 12 7 15 118 4 3.3% 1.49 (0.75, 2.94) Baselga et al. 2017 6 8 129 2 11 1 1 44 3.3% 1.49 (0.75, 2.94) Baselga et al. 2017 6 2 2.0 (1.1) 1 127 5 1 116 6.3% 3.77 (1.9.7, 7.2.9) Control et al. 2010 3 12 20 11 35 12 23 1.9.8 3.77 (1.9.7, 7.2.9) Control et al. 2010 3 12 20 1 125 3.3% 3.77 (1.9.7, 7.2.9) Control et al. 2017 6 3 120 1 125 3.3% 3.77 (1.9.7, 7.2.9) Control et al. 2017 6 3 120 1 125 3.5% 3.77 (1.9.7, 7.2.9) Control et al. 2017 6 3 120 1 125 3.8% 3.77 (1.9.7, 7.2.9) Control et al. 2017 6 1 2.0% 0.20001); P = 6.8% Text for overall effect Z = 16.73 (P < 0.00001); P = 6.8% Text ore oreall effe	Study or Subgroup	Events	Total	Events	Total	Weight	IV, Fixed, 95% CI	IV. Fixed, 95% CI
$ \frac{1}{1000} = \frac{1}{1000} + \frac{1}{10000} + \frac{1}{100000} + \frac{1}{10000000000000000000000000000000000$	Baselga et al.2012	1	115	2	114	1.3%	0.50 [0.05, 5.39]	
$ \frac{1}{1000} = \frac{1}{10000} = \frac{1}{10000} = \frac{1}{100000} = \frac{1}{10000000000000000000000000000000000$	baselga et ál.2017 Cortot et al.2020	36	266	6	2/1	10.1%	0.11 [2.62, 14.27] 8.50 [0.50 144 62]	
Cose et al 2010 19 126 2 125 35% 9 42 [24] 39.61] Heymach et al 2006 4 66 0 52 0.9% 8.37 [0.46, 151.74] Joinston et al 2013 4 59 1 58 1.7% 4 40 [0.46, 56] 10 72 0.6% 9 86 [0.49, 200.23] 4 59 1 58 1.7% 4 0.00 [0.45, 34.71] 4 59 1 58 1.7% 5 0.01 1.48, 16.92] Lue et al 2014 1 53 3 153 4.9% 5 0.01 1.48, 16.92] Lue et al 2014 1 53 3 153 4.9% 5 0.01 1.48, 16.92] Lue et al 2019 1 8 44 0 4 6 0.9% 38.84 [2.40, 622.38] Lue et al 2019 1 8 44 0 4 6 0.9% 38.84 [2.40, 622.38] Lue et al 2019 1 8 44 0 4 6 0.9% 38.84 [2.40, 622.38] Lue et al 2019 1 8 44 0 4 6 0.9% 38.84 [2.40, 622.38] Lue et al 2019 1 8 44 0 4 6 0.9% 38.84 [2.40, 622.38] Lue et al 2010 1 9 18 4 4 0 4 8 0.9% 38.84 [2.40, 622.38] Lue et al 2010 1 1 30 1.16% 2 24 (0.62) 1 1 30 1.16% 2 4 (0.66, 1.38).027 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Dummer et al.2018	12	192	6	194	7.9%	2.02 [0.77, 5.27]	+
Gue et al 2020 2 30 0 22 0.8% 44 84 [0.24, 96.66] Johnston et al 2013 2 36 0 72 0.8% 9.26 [0.4, 920.23] Johnston et al 2013 2 36 0 72 0.9% 9.26 [0.4, 920.23] Kado et al 2012 4 56 1 58 1.7% 6.21 [0.77, 49.99] Values at al 2014 1 5 153 1 58 1.5% 1.62 [1.07, 49.99] Values at al 2014 1 5 153 1 59 157 59 7 39 8.46 [2.40, 922.38] Lu et al 2019 1 5 44 0 46 0.9% 3364 [2.40, 922.38] Lu et al 2019 1 5 44 0 46 0.9% 3364 [2.40, 922.38] Lu et al 2019 1 5 44 0 46 0.9% 3364 [2.40, 922.38] Lu et al 2019 1 52 224 1 22 25 20.2% 4.35 [2.39, 7.93] Miller et al 2005 41 222 1 220 1 9.9% 1.06 56.56 [0.31, 98.60] Sine et al 2020 3 57 1 68 0.9% 2.479 [0.99, 7.82] Nakagawa et al 2015 51 72 59 7 36 1.0% 2.479 [0.99, 7.82] Nakagawa et al 2019 52 224 12 225 202% 4.35 [2.39, 7.93] Teal et al 2020 3 57 1 1 68 0.9% 2.479 [0.99, 7.82] Nakagawa et al 2017 5 161 6 3.9% 2.279 [0.99, 7.82] Nate standard to 2017 5 10 7 50 7 7 50 7 10.9% 4.37 [3.33, 5.72] Heterogeneity: Chrl= 23.21, df = 22.02 = 0.39, F = 5% Teat for overall effect Z = 10.70 (P < 0.00001) Teal events 327 59 7 20 8% 3.877 [1.97, 7.23] Constrat al 2020 2 21 11 0 55 0.2% 2.26 (0.13, 38.61.4] Dummer et al 2018 28 192 21 11 42 3.5% 4.49 [0.75, 2.94] Hesengeneity: Chrl= 23.21, df = 22.02 = 0.39, F = 5% Teat for overall effect Z = 10.70 (P < 0.00001) Teal events 327 2 59 8 3.377 [1.97, 7.23] Constrat al 2020 2 21 11 0 55 0.2% 2.26 [1.33, 36.14] Dummer et al 2018 28 192 21 11 42 3.4% 3.277 [1.97, 7.23] Constrat al 2020 2 21 11 0 55 0.2% 2.26 [1.74, 3.91] Kabo et al 2017 88 156 2 52 0.9% 8.38 [2.44, 34.27] Johnston et al 2020 3 57 1 65 0.2% 3.276 [1.8, 38.414] Dummer et al 2018 18 55 2 52 0.9% 8.38 [1.44, 34.27] Heymach et al 2017 44 58 11 25 14 4 38 3 2.26% 3.377 [1.97, 7.23] Constrat al 2020 32 127 18 14 38 3 2.0% 3.372 [1.24, 4.64] Heymach et al 2017 45 197 2 204 1.0% 3.377 [1.97, 7.23] Heymach et al 2017 45 197 2 204 1.0% 2.377 [1.97, 7.23] Heymach et al 2017 45 197 2 204 1.0% 2.377 [1.97, 7.23] Heymach et al 2017 44 56 197 2.26 [1.74, 3.91] Heymach	Goss et al.2010	19	126	2	125	3.5%	9.42 [2.24, 39.61]	
Hermather at 2008 4 956 0 22 04% 627 (14, 15) 74 Hermather at 2013 2 36 0 72 06% 626 (14, 15) 74 Hermather at 2013 2 36 0 72 06% 626 (14, 15) 74 Hermather at 2013 2 36 0 72 06% 626 (14, 15) 74 Hermather at 2014 1 5 153 3 153 49% 500 [14, 16, 16, 22] Lauris et 12014 1 5 153 3 153 49% 500 [14, 16, 16, 22] Lauris et 12014 1 5 144 0 46 09% 3364 [24, 06, 22] Lauris et 12019 1 5 44 0 46 09% 3364 [24, 06, 22] Lauris et 12019 1 5 44 0 46 09% 3364 [24, 06, 22] Hermather at 2015 51 759 7 365 [20% 3.70 [16, 9, 007] Mackey et 12015 51 759 7 365 [20% 3.70 [16, 9, 007] Mackey et 12015 51 759 7 365 [20% 3.70 [16, 9, 007] Mackey et 12015 51 729 7 165 510 31, 96, 800] Mackey et 12015 51 729 7 165 510 31, 96, 800] Mackey et 12015 52 724 122 722 720 72% A 35 [23, 7, 31] Hier et 12016 7 12 20 11 1 12 7 5 16 86.09 7 Notestimable Tool 12020 11 1 77 5 10 75 Notestimable Tool 12020 12 10 115 12 114 32% 14.00, 75, 249 Heterogenety: ChF 23 21, 07 20 (20, 300); P = 5% Tool 12017 68 0 266 15 27 3.250 Vistor 4.37 [3.3, 5, 72] Heterogenety: ChF 23 21, 07 20 (20, 300); P = 5% Tool 12017 63 122 10 15 12 114 32% 14.00, 75, 249 Baselga et 12017 63 122 10 125 38% 3.77 [1.97, 7.23] Heterogenety: ChF 23 2.1, 07 20 (20, 300); P = 5% Tool 12020 13 16 12 21 13 14 32% 14.00, 75, 249 Heterogenety: ChF 23 2.1, 07 20 (20, 300); P = 5% Tool 12020 13 16 120 12 12 13 14 32% 14.00, 75, 249 Heterogenety: ChF 23 2.1, 17, 287 Control et 12020 13 16 120 12 15 38% 3.77 [1.97, 7.23] Heterogenety: ChF 23 2.1, 17, 287 Heterogenety: ChF 23 2.2, 11% 63 12 27 15, 38% 3.77 [1.97, 7.23] Heterogenety: ChF 23 2.2, 01, 39, 304 [4] Herogenety: ChF 23 2.2, 01, 39, 304 [4] Herogenety: ChF 23 2.2, 01, 39, 304 [21, 1, 30] Heterogenety: ChF 23 2.2, 01, 39, 31 [21, 20, 60, 98, 93] Heterogenety: ChF 23 2.2, 01, 39, 31 [21, 20, 60, 98, 93] Heterogenety: ChF 27 0.4, 47 (20, 000001); P = 68% Herogenetic: ChF 27 0.4, 47 (20, 00	Buo et al.2020	2	30	0	29	0.8%	4.84 [0.24, 96.66]	
$\begin{aligned} \begin{aligned} \frac{1}{12} \det 2 \det$	Heymach et al.2008	4	36	0	52	0.9%	9.86 ID 49, 200 231	
Kalo et al.2017 32 197 4 204 7.0% 8.21 [26,72,49.9] Laurie et al.2014 15 153 3 153 4.9% 5.00 [1.48, 16.92] Lue et al.2014 15 44 0 48 0.9% 38.84 [2.40, 622.38] Lue et al.2018 5 61 1 30 1.6% 2.46 [0.30, 2012] Lue et al.2018 5 61 1 30 1.6% 2.46 [0.30, 2012] Mackey et al.2015 51 759 7 386 12.0% 3.70 [1.69, 6.07] Mackey et al.2015 51 759 7 386 12.0% 3.70 [1.69, 6.07] Mackey et al.2015 51 759 7 386 12.0% 3.70 [1.69, 5.07] Mackey et al.2015 51 729 7 386 12.0% 3.70 [1.69, 5.07] Mackey et al.2016 22 42 12 22 12 22 22 20 22 4 (3.55 [1.3, 16.9] Sime et al.2016 24 204 7 138 11.0% 2.27 [1.0, 5.12] Knog et al.2011 5 11 2 0 5 60 0.9% 5.56 [0.3] et al.00 Sime et al.2020 3 57 1 65 1.5% 3.42 [0.3, 3.1.69] To et al.2020 11 1 27 5 161 6.6% 7.71 [3.63, 0.73] To et al.2020 11 1 27 5 161 6.6% 7.71 [3.63, 0.73] To et al.2020 11 1 27 5 161 6.6% 7.71 [3.63, 0.73] To et al.2020 11 1 27 5 10 75 Not estimable To et al.2010 12 22 (2.0 - 0.39); F = 5% To et al.2010 13 12 0 52 22 (1.0, 5.12] To all events 70 2 7 10 (1.5, 12] To all events 70 2 7 10 (1.5, 12] To all events 70 2 7 1 164 1.5% 3.77 [1.3, 5.72] To all events 10 12 2 2 2 2 2 0 2.0% 4.37 [3.33, 5.72] To all events 10 20 2 2 2 11 0 5 2 0 5% 2.07 [1.5, 2.67] Consert et al.2012 1 1 15 12 11 4 3.2% 14.49 [7.5, 2.49] Consert et al.2012 2 10 1 15 12 126 3.3% 2.27 [1.1, 2.60] Consert et al.2012 1 2 30 2 2 29 0.5% 5.00 [1.42, 22.60] To all effect Z = 10.70 (P < 0.00001) Extend et al.2012 44 56 18 58 9.5% 2.26 [1.4, 3.04 [1.4, 3.04] Hermache et al.2014 51 153 14 153 5.0% 3.84 [2.1, 4.30 [1.4, 2.44 [1.4, 3.04] Hermache et al.2014 51 153 14 153 5.0% 3.84 [2.1, 4.30 [1.4, 2.44 [1.4, 3.04] Hermache et al.2014 51 153 14 153 5.0% 3.84 [2.1, 4.30 [1.4, 2.44 [1.4, 3.44 [1.4, 3.44 [1.4, 3.44 [1.4, 3.44 [1.4, 3.43 [1.4, 3.43 [1.4, 4.4] [1.44 [1.44 [1.44 [1.45 [1.5, 3.44 [1.5, 3.44 [1.5, 3.44 [1.44 [1.44 [1.45 [1.5, 3.44 [1.5, 3.44 [1.44 [1.44 [1.45 [1.5, 3.44 [1.5, 3.44 [1.5, 3.44 [1.5, 3.44 [1.5, 3.44 [1.5, 3.44 [1.5, 3.44 [1.5, 3.44 [1.44 [1.44 [1.45 [1.5, 3.44 [1.5,	<ato al.2012<="" et="" td=""><td>4</td><td>58</td><td>1</td><td>58</td><td>1.6%</td><td>4.00 [0.46, 34.71]</td><td></td></ato>	4	58	1	58	1.6%	4.00 [0.46, 34.71]	
Ranche at 12017 32 197 4 204 7.0% 8.28 [28, 22.99] Lue et 12014 15 153 3 154 4.9% 5.00 [1.48, 16.2] Lue et 12014 15 153 3 154 4.9% 5.00 [1.48, 16.2] Lue et 12014 15 153 3 154 4.9% 5.00 [1.48, 16.2] Lue et 12019 18 44 0 46 0.9% 38.64 [2.40, 622.38] Lue et 12018 5 61 1 30 1.6% 2.46 [0.30, 20.12] Miller et 12016 51 759 7 7 168 120% 4.35 [2.38, 7.6] Rink et 2016 51 724 724 12 225 20.2% 4.35 [2.37, 7.8] Rink et 2016 52 224 12 225 20.2% 4.35 [2.37, 7.8] Rink et 2016 52 224 12 225 20.2% 4.35 [2.37, 7.8] Rink et 2016 51 75 0 75 8 7 1 655 [0.31, 9.60] Sinn et a12016 72 50 75 8 Not estimable Total (95% C) 3269 2872 100.0% 4.37 [3.3, 5.72] Total events 372 59 Heterogeneity: Chf = 23.21, df = 22 (P = 0.39); F = 5% Total events 372 59 Heterogeneity: Chf = 23.21, df = 22 (P = 0.39); F = 5% Total events 372 59 Heterogeneity: Chf = 23.21, df = 22 (P = 0.39); F = 5% Total events 372 59 Heterogeneity: Chf = 23.21, df = 22 (P = 0.39); F = 5% Total events 372 59 Heterogeneity: Chf = 23.21, df = 22 (P = 0.39); F = 5% Total events 372 59 Heterogeneity: Chf = 23.21, df = 22 (P = 0.39); F = 5% Total events 372 59 Heterogeneity: Chf = 23.21, df = 22 (P = 0.39); F = 5% Total events 372 59 Heterogeneity: Chf = 23.21, df = 22 (P = 0.39); F = 5% Heterogeneity: Chf = 23.21, df = 22 (P = 0.39); F = 5% Total events 372 50 Total events 41.2016 51 Total events 41.2017 60 Total events 41.2017 60 Total events 41.2017 70 Total e	<ato al.2012<="" et="" td=""><td>6</td><td>56</td><td>1</td><td>58</td><td>1.7%</td><td>6.21 [0.77, 49.99]</td><td></td></ato>	6	56	1	58	1.7%	6.21 [0.77, 49.99]	
Latifies at 2014 19 15 15 3 3 15 4 98 300 [140, 152] Latifies at 2014 19 16 15 16 4 4 0 6 6 0.98 356 [140, 022] Lue stat 2015 51 759 7 398 1208 246 [030, 2012] Miller et al.2015 51 759 7 398 1208 246 [030, 2012] Miller et al.2015 41 222 1 230 198 40.65 [64, 293.02] Miller et al.2015 41 222 1 225 202% 4.35 [239.7.93] Nakagawa et al.2019 52 224 12 225 202% 4.35 [239.7.93] Total events 51 759 7 7 198 1108 227 [10, 15, 12] Total events 51 759 7 7 198 1108 227 [10, 15, 12] Total events 51 72 75 161 6.98 27 [0, 09, 7.82] Total events 372 75 161 6.98 27 [0, 09, 7.82] Total events 372 75 161 6.98 27 [0, 09, 7.82] Total events 372 75 9 Total events 372 75 9 Total events 372 75 9 Total events 372 75 9 Hermach et al.2017 0 75 0 75 Notestimable Total (95% Cl) 3369 2872 100.0% 4.37 [3.33, 5.72] Total events 372 75 9 Hermach et al.2020 11 127 5 161 6.98 2.79 [0.99, 7.82] Total events 372 75 9 Hermach et al.2020 12 10 125 1018 Keato Total (95% Cl) 3269 2872 100.0% 4.37 [3.33, 5.72] Total events 372 75 9 Hermach et al.2020 12 10 125 36% 3.77 [1.97, 7.23] Control et al.2020 12 20 P = 0.39, P = 5% Total events 372 75 9 Hermach et al.2020 12 20 P = 0.39, Y = 5% Total events 372 75 9 Hermach et al.2020 12 10 125 36% 3.77 [1.97, 7.23] Control et al.2020 12 30 22 9 0.8% 3.77 [1.97, 7.23] Control et al.2020 12 30 22 9 0.8% 3.77 [1.97, 7.23] Control et al.2020 12 30 12 9 0.8% 3.77 [1.97, 7.23] Control et al.2020 12 30 12 9 0.8% 3.77 [1.97, 7.23] Control et al.2020 12 30 12 9 0.8% 3.77 [1.97, 7.23] Control et al.2020 12 30 12 9 0.8% 3.77 [1.97, 7.23] Control et al.2020 12 30 12 9 0.9% 3.37 [1.94, 6.31] Hermach et al.2017 61 97 72 204 10.3% 3.37 [1.94, 6.41] Hermach et al.2017 71 75 0 75 0.2% 3.36 01 [1.4, 57, 10] Total events 1043 5 14 4 0 46 0.2% 7.416 [468, 1173.01] Lue et al.2011 31 112 0 66 0.2% 7.416 [468, 1173.01] Lue et al.2011 31 12 0 66 0.2% 3.37 [1.94, 6.41] Hermach et al.2017 71 75 0 75 0.2% 3.500 [1.41, 57, 10] Hermach et al.2017 71 75 0 75 0.2% 3.500 [2.44,	<ubota al.2017<="" et="" td=""><td>32</td><td>197</td><td>4</td><td>204</td><td>7.0%</td><td>8.28 [2.98, 22.99]</td><td></td></ubota>	32	197	4	204	7.0%	8.28 [2.98, 22.99]	
Lu et al 2019 Lu et al 2019 Lu et al 2016 51 759 7 385 12083201 [169, 607] Mackey et al 2015 51 759 7 385 12083201 [169, 607] Mok et al 2015 51 759 7 385 12083201 [169, 607] Mok et al 2011 51 222 1228 2028 3270 [169, 607] Mok et al 2015 51 722 224 122 222 522 2228 2028 4.35 [23, 78] Hill et al 2016 24 204 7 135 11.0% 2.277 [107, 512] Too et al 2020 11 127 5 161 6.689 2.277 [107, 512] 728 Not estimable 100 0.1 1 $10Favours experimental100$ 0.1 1 101010 10 1 10	_aune et al.2014	15	153	3	153	4.9%	5.00 [1.48, 16.92] 38 64 [2 40, 622 36]	
Lue et al. 2018 5 61 1 30 16% 2.46 [0.30, 20.12] Miller et al. 2005 41 232 1 230 1.9% 40.65 [5.64, 293.02] Miller et al. 2015 51 759 7 398 12.0% 4.35 [1.39, 7.9] Nakagawa et al. 2019 52 224 12 225 202% 4.35 [1.39, 7.9] Rug et al. 2011 5 122 0 56 0.9% 555 [0.31, 96.60] Sinn et al. 2020 3 57 1 58 1.5% 2.27 [0.10, 97, 82] Tao et al. 2020 11 127 5 181 6.9% 2.78 [0.90, 7.8] Tao et al. 2020 11 127 5 181 6.9% 2.78 [0.90, 7.8] Tao et al. 2020 11 127 5 181 6.9% 2.78 [0.90, 7.8] Tao et al. 2020 12 11 127 5 181 6.9% 2.78 [0.90, 7.8] Tao et al. 2020 13 57 1 15 12 144 3.3% 14.90 75, 2.94 Heterogeneity: Chr ² = 23 21, dr = 22 (P = 0.39); P = 5% Test for overall effect Z = 10.70 (P < 0.00001) Fereits and tailor 2020 12 19 11 5 12 114 3.2% 14.9 [D.75, 2.94] Baselga et al. 2017 69 226 115 221 527 15.3% Control tail 2020 22 111 0 56 0.2% 2.250 [1.3, 364.14] Dummer et al. 2018 18 52 22 19 2.0 8% 8.38 [2.04, 34.27] Johnshon et al. 2019 18 52 22 0.8% 8.38 [2.04, 34.27] Johnshon et al. 2019 18 56 2 52 0.8% 8.38 [2.04, 34.27] Johnshon et al. 2011 43 34 37 21 11, 49 33 [2.87, 30.41] Kato et al. 2012 47 58 18 58 0.3% 2.77 [1.97, 7.23] Meremach et al. 2012 48 58 19 22 11 0.9% 3.07 [1.7, 7.3] Kato et al. 2012 48 58 19 22 11 0.9% 3.07 [1.7, 7.3] Kato et al. 2012 49 58 19 22 11 0.9% 3.07 [2.12, 4.48] Kato et al. 2011 45 14 34 40 46 0.3% 7.7 [1.97, 7.23] Meremach et al. 2019 10 224 27 22 0.8% 8.38 [2.04, 34.27] Johnshon et al. 2013 44 0 46 0.3% 7.7 [1.97, 7.23] Mokel et al. 2011 45 14 13 35 0.9% 3.37 [2.12, 4.48] Kato et al. 2011 45 14 13 15 14 13 35 0.9% 3.37 [2.12, 4.48] Heterogeneiny: Chr ² = 70.94, dr = 23 (P < 0.00001) Fervours experimental Fervours Heterologic all 2015 203 759 44 385 16.5% 2.24 [1.74, 3.91] Heterologic 35 7 1 65 0.3% 3.24 [2.14, 53, 0.91] Heterologic 35 7 1 65 0.3% 3.24 [2.14, 53, 0.91] Heterologic 35 7 1 65 0.3% 3.24 [2.14, 53, 0.91] Heterologic 35 7 1 65 0.3% 3.24 [2.14, 53, 0.93] Heterologic 35 7 1 65 0.3% 3.24 [2.14, 53, 0.93] Heterologic 35 7 1 65 0.3% 3.24 [2.14, 53, 0.93]	iu et al.2019	18	44	ō	46	0.9%	38.64 [2.40, 622.36]	
Mackey et al.2015 61 759 7 365 12.0% 3.70 [1.69, 6.07] Mole et al.2011 3 34 0 33 0.9% 6.60 [3.61, 26.76] Mole et al.2011 3 34 0 33 0.9% 6.60 [3.61, 26.76] Mole et al.2016 22 224 12 224 222 22 20 20.% 4.35 [2.37, 7.9] Find et al.2016 24 204 7 135 11.0% 2.27 [1.01, 5.12] Sime et al.2010 11 5 112 0 6 0.9% 5.55 [0.31, 86 60] Sime et al.2020 3 57 1 65 1.5% 3.42 [0.37, 31.69] To et al.2020 11 127 5 161 6.6% 7.79 [0.96, 7.02] To et al.2020 11 127 5 161 6.6% 7.79 [0.96, 7.02] Total events 372 59 Hetrogenetic 2 = 10.70 (P < 0.00001) Total events 722 (J = 2.02, P = 0.39); P = 5% Test for overall effect Z = 10.70 (P < 0.00001) Total events 22 (J = 2.02, P = 0.39); P = 5% Test for overall effect Z = 10.70 (P < 0.00001) Total events 22 (J = 10 15 12 114 3.2% 14.49 [0.75, 2.47] Ourmer et al.2018 18 56 2 20 0.5% 5.07 [1.42, 2.50] Ourmer et al.2010 12 17 15 12 144 3.2% 2.56 [1.42, 2.56] Ourmer et al.2010 12 47 58 165 8 3.377 [1.37, 7.23] Cos et al.2010 13 14 36 3 72 1.1% 9.33 [2.87, 30.41] Hermach et al.2011 46 56 19 59 9.5% 3.377 [1.32, 5.17] Cos et al.2011 36 44 0 46 0.2% 7.27 [1.45, 5, 141, 3.91] Hermach et al.2012 47 58 115 59 3.22 [1.1% 9.33 [2.87, 30.41] Harmoner et al.2013 14 36 3 72 1.1% 9.33 [2.87, 30.41] Harmoner et al.2014 45 16 153 14 153 5.0% 3.342 [1.73, 3.17] Makey et al.2015 203 759 44 365 16.5% 2.34 [1.73, 3.17] Makey et al.2015 44 0 46 0.2% 7.27 [1.45, 5, 141, 6.3] Harmoner et al.2014 51 153 14 153 5.0% 3.372 [1.45, 5, 140, 6.7] Makey et al.2015 12 37 59 44 365 18 5.9% 3.372 [1.56, 5, 4.9] Find et al.2014 35 44 0 46 0.2% 7.207 [4.55, 140, 6.7] Makey et al.2015 203 759 44 365 18 5.9% 3.372 [1.56, 5, 4.9] Find et al.2014 35 11 12 0 56 0.2% 3.372 [1.56, 5, 4.9] Find et al.2015 12 37 7.9 (7.5 0.2% 3.5.00 [1.4, 571, 6.9] Harmoner et al.2014 35 11 12 0.6 0.2% 3.372 [1.56, 5, 4.9] Find et al.2015 12 3.369 2.22 [1.30, 3.372 [1.56, 5, 4.9] Find et al.2016 51 204 31 155 0.2% 3.372 [1.56, 5, 4.9] Harmoner et al.2017 50 7.5 0.2% 3.5.00 [1.4, 571, 6.9] Harmoner et al.2010 3 57 1 65 0.	.u et al.2018	5	61	1	30	1.6%	2.46 [0.30, 20.12]	
$\frac{411}{1000} = \frac{41}{1000} = \frac{223}{1000} = \frac{198}{1000} = \frac{4005}{1000} = \frac{9400}{1000} = \frac{410}{1000} = \frac{410}{10000} = $	dackey et al.2015	51	759	7	385	12.0%	3.70 [1.69, 8.07]	
Nating we at al 2019 52 224 12 225 202% 4 35 (2) 37, 39 (2) (2) (2) (2) (2) (2) (2) (2) (2) (2)	diller et al.2005 dok et al 2011	41	232	1	230	1.9%	40.65 [5.64, 293.02]	
Rine id 2016 24 24 24 24 7 135 110% 2.27 [10], 512] Wing of al 2016 35 512 0 65 0.3% 55[0.3], 86.0] Sinn et al 2020 3 57 1 65 1.5% 3.42 [0.7, 31.98] Total (95% CI) 3289 2872 100.0% 4.37 [3.33, 5.72] Total (95% CI) 3289 2872 100.0% 4.37 [3.33, 5.72] Total (95% CI) 3289 2872 100.0% 4.37 [3.33, 5.72] Test for overall effect Z = 10.70 (P < 0.0001) Risk Ratio Risk Ratio N. Fixed .95% CI Study or Subarous Events Total Weinth N. Fixed .95% CI V. Fixed .95% CI Dummer et al 2012 10 15 12 114 3.2% 1.49 [0.75, 2.4] Baseige et al 2017 68 228 1.49 [0.75, 2.4] Res Ratio V. Fixed .95% CI V. Fixed .95% CI Dummer et al 2018 1.28 1.29 [0.13, 3.6, 1.2] 1.49 [0.75, 2.4] 1.49 [0.75, 2.4] Baseige et al 2017 68 1.28 [3.6, 3.7] 1.49 [0.75, 2.4] 1.49 [0.75, 2.4] Dummer et al 2018<	Vakagawa et al.2019	52	224	12	225	20.2%	4.35 [2.39, 7.93]	
Rugo et al.2011 5 112 0 66 0.9% 5.55 [0.3], 96.60] Tao et al.2020 11 127 5 161 6.9% 2.70 [0.97, 52] Tao et al.2020 11 127 5 161 6.9% 2.77 [0.99, 7.62] Tao et al.2020 11 127 5 161 6.9% 2.77 [0.99, 7.62] Total elevents 372 59 2872 100.0% 4.37 [3.33, 5.72]	Rini et al.2016	24	204	7	135	11.0%	2.27 [1.01, 5.12]	
Simile at 2020 1 1 127 5 18 16.8 342 [0.7], 31.9 [1] Tara et al 2020 1 1 127 5 18 16.8 342 [0.7], 31.9 [1] Tara et al 2020 1 1 127 5 18 16.8 342 [0.7], 31.9 [1] Tara et al 2017 0 75 0 75 Not estimable Total events 372 59 Test for overall effect Z = 10.70 (P < 0.0001) Test for overall effect Z = 10.70 (P < 0.0001) Test for overall effect Z = 10.70 (P < 0.0001) Test for overall effect Z = 10.70 (P < 0.0001) Test for overall effect Z = 10.70 (P < 0.0001) Test for overall effect Z = 10.70 (P < 0.0001) Test for overall effect Z = 10.71 (P < 0.0001) Test for overall effect Z = 10.71 (P < 0.0001) Test for overall effect Z = 10.71 (P < 0.0001) Test for overall effect Z = 10.71 (P < 0.0001) Test for overall effect Z = 10.71 (P < 0.0001) Test for overall effect Z = 10.71 (P < 0.0001) Test for overall effect Z = 10.71 (P < 0.0001) Test for overall effect Z = 10.71 (P < 0.0001) Test for overall effect Z = 10.71 (P < 0.0001) Test for overall effect Z = 10.71 (P < 0.0001) Test for overall effect Z = 10.71 (P < 0.0001) Test for overall effect Z = 10.71 (P < 0.0001) Test for overall effect Z = 10.71 (P < 0.0001) Test for overall effect Z = 10.73 (P < 0.0001) Test for overall effect Z = 10.73 (P < 0.0001) Test for overall effect Z = 10.73 (P < 0.0001) Test for overall effect Z = 10.73 (P < 0.0001) Test for overall effect Z = 10.73 (P < 0.0001) Test for overall effect Z = 10.73 (P < 0.0001) Test for overall effect Z = 10.73 (P < 0.00001) Test for overall effect Z = 10.73 (P < 0.00001) Test for overall effect Z = 10.73 (P < 0.00001) Test for overall effect Z = 10.73 (P < 0.00001) Test for overall effect Z = 10.73 (P < 0.00001) Test for overall effect Z = 10.73 (P < 0.00001) Test for overall effect Z = 10.73 (P < 0.00001) Test for overall effect Z = 10.73 (P < 0.00001) Test for overall effect Z = 10.73 (P < 0.00001) Test for overall effect Z = 10.73 (P < 0.00001) Test for overall effect Z = 10.73 (P < 0.00001) Test for overall effect Z = 10.73 (P < 0.00001) Test for overall effect Z = 10.7	Rugo et al.2011	5	112	0	56	0.9%	5.55 [0.31, 98.60]	
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Total (95% CI) 3389 2872 100.0% 4.37 (3.33, 5.72) Total events 372 59 Hetrogenetic, Ch* 23.21, df = 24 (P = 0.39); F = 5% 101 101 10 Test for overall effect Z = 10.70 (P < 0.00001)	/an et al.2017	0	75	0	75		Not estimable	
$\begin{array}{c} \text{Start sprace}{(372)} & 303 \\ \text{Heterogeneity: Chir = 23.21, df = 22 (P = 0.39); P = 5\% \\ \text{Heterogeneity: Chir = 23.21, df = 22 (P = 0.39); P = 5\% \\ \text{Test for overall effect Z = 10.70 (P < 0.0001)} \\ \hline \\ $	Fotal (05% CP		3300		2070	100.04	4 37 19 39 5 70	▲
$\begin{array}{c} \label{eq:product} \mbox{Here} 23.21, \mbox{displays} p = 5\% \\ \mbox{Test for overall effect } Z = 10.70 \mbox{(P = 0.00001)} \\ \mbox{Test for overall effect } Z = 10.70 \mbox{(P < 0.00001)} \\ \mbox{Test for overall effect } Z = 10.70 \mbox{(P < 0.00001)} \\ \mbox{Test for overall effect } Z = 10.70 \mbox{(P < 0.00001)} \\ \mbox{Test for overall effect } Z = 10.70 \mbox{(P < 0.00001)} \\ \mbox{Test for overall effect } Z = 10.70 \mbox{(P < 0.00001)} \\ \mbox{Test for overall effect } Z = 10.70 \mbox{(P < 0.00001)} \\ \mbox{Test for overall effect } Z = 10.70 \mbox{(P < 0.00001)} \\ \mbox{Test for overall effect } Z = 10.70 \mbox{(P < 0.00001)} \\ \mbox{Test for overall effect } Z = 10.70 \mbox{(P < 0.00001)} \\ \mbox{Test for overall effect } Z = 10.70 \mbox{Test for overall Comparison of Hymeertension} \\ \mbox{Test for overall effect } Z = 10.70 \mbox{Test for the Overall Comparison of Hymeertension} \\ \mbox{Test for overall effect } Z = 10.73 \mbox{Test for the Overall Comparison of Hymeertension} \\ \mbox{Test for overall effect } Z = 10.73 \mbox{Test for the Overall Comparison of Hymeertension} \\ \mbox{Test for overall effect } Z = 10.73 \mbox{Test for the Overall Comparison of Hymeertension} \\ \mbox{Test for overall effect } Z = 10.73 \mbox{Test for the Overall Comparison of Hymeertension} \\ \mbox{Test for overall effect } Z = 10.73 \mbox{Test for the Overall Comparison of Hymeertension} \\ \mbox{Test for overall effect } Z = 10.73 \mbox{Test for the Overall Comparison of Hymeertension} \\ \mbox{Test for overall effect } Z = 10.73 Test for the Overall Comparison of Hymeert$	Total (95% CI) Fotal events	372	3309	59	2812	100.0%	4.37 [3.33, 5.72]	•
Test for overall effect Z = 10.70 (P < 0.0001) Discrete Stream Stre	Heterogeneity: Chi ² = 2	3.21, df = 22 (F	= 0.39)	; I² = 5%				
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Fest for overall effect: Z	= 10.70 (P < 0	.00001)				F	avours experimental Favours control
Intervention Arm Control Arm Risk Ratio Risk Ratio Study or Subgroup Fvents Total Vents Total Weight V. Fixed, 95% CI V. Fixed, 95% CI Baseiga et al. 2012 10 115 12 114 32.4% CI V. Fixed, 95% CI Baseiga et al. 2012 10 115 127 5.3% 4.89 (D7.5, 2.94) + Dummer et al.2018 20 122 111 0.65 0.5% 3.77 (19.7, 7.23) + + Goes et al.2010 12 10 2.2 2.08 8.83 (2.04, 3.2.7) + + Heymach et al.2013 14 3.6 7 7.1 1.4% 9.3% 2.01 1.4%								
Reservation Arm Reservation Study or Subarou Reservation Baselga et al. 2012 10 11 11 11 Reservation Reservatin Reservation							0.10	
Baselga et al. 2012 18 116 12 114 3.2% 1.49 [D.75, 2.94] Baselga et al. 2017 68 256 152 71 5.3% 4.42 [D.71, 78 /7] Contor tal. 2020 22 111 0 65 0.2% 22.66 [1.39, 364.14] Dummer et al. 2018 28 192 11 144 3.4% 2.57 [1.37, 7.23] Goes et al. 2010 38 128 10 125 3.8% 3.77 [1.97, 7.23] Johnston et al. 2018 18 65 2 22 0.8% 8.38 [2.04, 34.27] Johnston et al. 2013 14 36 3 72 1.1% 9.33 [2.87, 30.41] Kato et al. 2012 48 58 16 58 9.5% 2.76 [1.65, 4.11] Kato et al. 2014 46 58 16 58 3.64 [2.1, 7.3, 30.41]	Study or Subgroup	Events	n Arm Tota	L Events	Tota	Weigh	t IV Fixed 95%	CI IV Fixed 95% CI
Basegia et al.2017 68 266 15 271 5.3% 4.62 [2.71, 7.87] Dummer et al.2018 20 21 111 0 550 226 [13, 3, 60.2] Dummer et al.2018 28 192 11 194 3.4% 2.57 [13, 2, 60.2] Goss et al.2010 38 126 10 125 3.6% 3.77 [19, 7, 7.2] Guo et al.2020 12 30 2 29 0.8% 5.80 [1.42, 23.69] Heymach et al.2018 14 36 3 7.2 11.% 9.33 [2.67, 30.41] Kab et al.2012 47 58 16 59 3.5% 2.76 [1.85, 4.11] Kab et al.2014 41 56 19 2.92 111 9.30 [2.12, 4.46] Laurie et al.2014 51 157 14 135 5.6% 3.44 [2.11, 6.30] Lue et al.2014 54 40 60 2.72 / 1.65 (9.117.20.1] 14.12 (1.65 (1.10.62) Lue et al.2014 51 143 30 1.6.8 (3.90.26.49.	Baselga et al.2012	18	115	5 12	11	4 3.2%	1.49 [0.75, 2.9	941 +
Contot et al. 2020 22 111 0 65 0.2% 22.50(1.39, 364.14) Ourse et al. 2018 20 11 24 13 44 34 4 25.71 (1.3, 25.02) Oue et al. 2020 12 20 2.9 0.8% 3.77 (1.9.7, 7.23) Heymach et al. 2010 12 30 2 29 0.8% 8.30 (2.4, 32.26) Heymach et al. 2010 12 40 25 0.8% 8.30 (2.4, 32.26) Heymach et al. 2012 47 58 18 56 9 3.5% 2.76 (1.6, 4.11) Kato et al. 2012 46 59 15 99 25% 2.76 (1.6, 5, 4.11) Kato et al. 2014 55 14 0 46 0.2% 7.20 74.55, 114 0.82) Hue rata. 2015 203 759 44 385 16.5% 2.34 (1.7.4, 3.9.1) Hadagave et al. 2015 203 759 44 385 16.5% 2.34 (1.7.4, 3.9.1) Mackay et al. 2015 203 759 44 385 16.5% 2.34 (1.7.4, 3.9.1) Mackay et al. 2015 203 759 44 385 16.5% 2.34 (1.7.4, 3.9.1) Mackay et al. 2015 203 759 44 385 16.5% 2.34 (1.7.4, 3.9.1) Mackay et al. 2015 203 759 44 385 16.5% 2.34 (1.7.4, 3.9.1) Mackay et al. 2015 203 759 44 385 16.5% 3.37 (2.1.5, 4.54) Mackay et al. 2015 203 759 44 385 16.5% 3.37 (2.1.5, 4.54) Mackay et al. 2015 203 759 44 385 16.5% 3.37 (2.1.5, 4.54) Mackay et al. 2015 203 759 44 385 16.5% 3.37 (2.1.5, 4.54) Mackay et al. 2015 203 759 45 33 2.0% 3.37 (2.1.5, 4.54) Mackay et al. 2015 203 759 45 33 2.0% 3.37 (2.1.5, 4.54) Mackay et al. 2015 203 759 45 33 2.0% 3.37 (2.1.5, 4.54) Mackay et al. 2015 203 759 45 33 2.0% 3.37 (2.1.5, 4.54) Mackay et al. 2015 203 759 45 33 2.0% 3.37 (2.1.5, 4.54) Mackay et al. 2015 203 759 45 33 2.0% 3.37 (2.1.5, 4.54) Mackay et al. 2015 203 759 45 33 2.0% 3.37 (2.1.5, 4.54) Hay et al. 2016 51 204 31 135 9.3% 1.09 (1.7.4, 1.61) Mackay et al. 2017 17 75 0 75 0.2% 3.50 (2.1.4, 57.1.60) Total (9.5% (1) 3.369 247 100.0% 2.45 (2.5.2, 3.22) Mackay et al. 2017 10 3 26 27 (2.0.00001)) P = 68% Heterogenetily Chil [#] = 70.44, df = 23 (P < 0.00001) P = 68% Heterogenetily Chil [#] = 70.44, df = 23 (P < 0.00001) P = 68% Heterogenetily Chil [#] = 70.44, df = 23 (P < 0.00001) P = 68% Heterogenetily Chil [#] = 70.44, df = 23 (P < 0.00001) P = 68% Heterogenetily Chil [#] = 70.44, df = 23 (P < 0.00001) P = 68% Heterogenetily Chil [#] = 70.44, df = 23 (P < 0.00001) P = 68%	Baselga et al.2017	68	266	5 15	27	1 5.3%	4.62 [2.71, 7.8	37]
$\begin{array}{c} \text{Lumthare is a Lote} & \text{zo} & 192 & 11 & 194 & 34\% & 250 (132, 502) \\ \text{Goss et al. 2010} & 32 & 126 & 10 & 22 & 29 & 0.8\% & 500 (142, 22.69) \\ \text{Heymach et al. 2003} & 18 & 56 & 22 & 0.8\% & 580 (142, 22.69) \\ \text{Heymach et al. 2003} & 18 & 56 & 25 & 0.8\% & 580 (142, 22.69) \\ \text{Heymach et al. 2013} & 14 & 36 & 37 & 22 & 11\% & 9.33 (287, 30.41) \\ \text{Kate et al. 2012} & 47 & 58 & 18 & 69 & 9.5\% & 276 (185, 4.11) \\ \text{Kate et al. 2012} & 47 & 58 & 18 & 69 & 9.5\% & 276 (185, 4.11) \\ \text{Laurie et al. 2014} & 155 & 14 & 153 & 50\% & 336 (2.14, 3.91) \\ \text{Laurie et al. 2014} & 51 & 155 & 14 & 153 & 50\% & 336 (2.14, 5.14) \\ \text{Laurie et al. 2014} & 51 & 44 & 0 & 46 & 0.2\% & 72.07 (4.55, 11406, 5.49) \\ \text{Lu et al. 2013} & 14 & 65 & 13 & 50\% & 336 (2.14, 5.14) \\ \text{Lu et al. 2013} & 14 & 65 & 13 & 0.04\% & 6.29 (0.55, 4.92) \\ \text{Mackey et al. 2015} & 14 & 51 & 125 & 10.5\% & 2.34 (1.73, 3.17) \\ \text{Mackey et al. 2015} & 14 & 65 & 123 & 55\% & 3.37 (156, 6.76) \\ \text{Mackey et al. 2015} & 10 & 244 & 52 & 220 & 1.5\% & 3.17 (156, 5.49) \\ \text{Mackey et al. 2015} & 10 & 244 & 52 & 220 & 1.5\% & 3.17 (156, 6.27) \\ \text{Mine et al. 2015} & 10 & 244 & 52 & 220 & 1.5\% & 3.17 (156, 5.42) \\ \text{Mackey et al. 2015} & 10 & 244 & 52 & 220 & 1.5\% & 3.17 (156, 6.27) \\ \text{Mackey et al. 2015} & 10 & 244 & 52 & 220 & 1.5\% & 3.17 (156, 6.27) \\ \text{Mackey et al. 2015} & 10 & 244 & 52 & 220 & 1.5\% & 3.17 (156, 6.27) \\ \text{Total (events} & 10.3 & 2.244 & 3.25 & 10.3\% & 3.24 (12.37, 3.18) \\ \text{Total (events} & 10.43 & 2.64 & 327 & 10.00\% & 2.85 (2.52, 3.22) \\ \text{Total events} & 10.43 & 2.64 & 3.27 & 0.00001) \\ \text{Test for overall effect Z = 16.73 (P < 0.00001) } \\ \text{Test for overall effect Z = 16.73 (P < 0.00001) \\ \end{array}$	Cortot et al.2020	22	111		5	5 0.2%	22.50 [1.39, 364.1	14]
Gut entropy 100 <th< td=""><td>Goss et al 2010</td><td>28</td><td>192</td><td>: 11 ; 10</td><td>19</td><td>4 3.4% 5 3.6%</td><td>2.57 [1.32, 5.0</td><td>231</td></th<>	Goss et al 2010	28	192	: 11 ; 10	19	4 3.4% 5 3.6%	2.57 [1.32, 5.0	231
Heymach et al. 2008 18 56 2 52 02% 8 33 [20, 34:27] Johnston et al. 2013 14 36 37 21 11% 93 12 87 30 41] Kato et al. 2011 47 58 18 58 9.3% 2.61 [1.7.4, 3.91] Kato et al. 2012 48 55 18 58 9.3% 2.761 [1.6.5, 11] Kubot et al. 2017 86 197 29 204 10.9% 307 [21.2, 4.46] Lux et al. 2014 51 153 14 135 50% 3.64 [21, 16, 30] Lux et al. 2014 51 153 14 61 1 30 0.4% 6.89 [0.95, 49.92] Makeky et al. 2015 203 759 44 085 138 2.24 [1.7.3, 317] Miller et al. 2015 54 232 5 230 1.9% 10.74 [1.6.30] Makeky et al. 2011 91 12 0 56 0.2% 31.761 [1.8, 57.2] Makeky et al. 2011 91 12 0 56 0.2% 31.72 [1.8, 50.96 9] Sim et al. 2020 32 127 16 161 4.9% 2.54 [1.4, 6.1] Total (95% Ch) 326 21 127 15 0.3% 324 [21.3, 31.98] Total (95% Ch) 326 2872 10.0% 2.54 [1.4, 57.160] Total (95% Ch) 326 2872 10.00% 2.54 [1.4, 57.160] Total (95% Ch) 3369 2872 10.00% 2.54 [1.4, 57.160] Total (95% Ch) 3369 2872 10.00% 2.54 [1.4, 57.160] Total (95% Ch) 356 2872 10.00% 3.20 [1.4, 57.160] Total (95% Ch) 35	Guo et al.2020	12	30		2	9 0.8%	5.80 [1.42, 23.6	
Jonnson et al.2013 14 36 3 72 11% 9.33[287,30.41] Kato et al.2012 47 59 16 59 9.5% 226[17,4,90] Kato et al.2014 49 56 19 59 9.5% 276[185,411] Laurie et al.2014 51 153 14 153 50% 3.07 [21,2,46] Laurie et al.2014 51 153 14 153 50% 3.07 [21,2,46] Laurie et al.2014 51 153 14 153 50% 3.07 [21,2,46] Laurie et al.2014 51 153 14 153 50% 3.07 [21,2,46] Laurie et al.2014 35 44 0 46 0.2% 72.07 [455,1140.62] Laurie et al.2015 14 61 130 0.4% 6.89 [0.95,40.92] Mackey et al.2015 203 759 44 395 15.5% 2.34 [1.73,317] Mackey et al.2015 54 222 520 1.9% 10.71 [4.36, 22.89] Mok et al.2019 10 24 27 225 10.3% 3.72 [25,45] Fini et al.2010 31 12 56 0.2% 31.72 [1.96,03.99] Sime et al.2010 32 127 16 151 45% 2.34 [1.46,54] Yan et al.2010 32 127 16 151 45% 2.34 [1.46,54] Total (etworks 1043 264 0.00001); P= 68% Test for overall effect Z = 16.73 (P < 0.00001); P= 68% Test for overall effect Z = 16.73 (P < 0.00001); P= 68% Test for overall effect Z = 16.73 (P < 0.00001); P= 68%	Heymach et al.2008	18	56	3 2	5	2 0.8%	8.36 [2.04, 34.2	27]
new servacy: +7 >0 10 >0 9.3.78 2.01 1.74 3.91 Kab et al.2012 48 56 15 50 9.5% 2.76 16.5, 4.11 Kab et al.2014 51 154 14 19.5% 3.07 17.17, 4.49 Lue at al.2014 51 154 14 16 56.5% 3.57 17.17, 4.49 Lue at al.2014 51 154 14 0 46 0.2% 7.207, 14.55, 1140, 621	Johnston et al.2013	14	36	5 5	7	2 1.1%	9.33 [2.87, 30.4	1) <u> </u>
Function et al. 2017 68 197 29 204 10.9% 307/12.12, 446 Luis et al.2014 51 153 14 153 50, 93 344 [211, 30]	Koto at al 2012	4/	56	, 18 3 19	5	0 9.3% 8 9.5%	2.01 [1./4, 3.9	
Laurie et al. 2014 51 153 14 153 50% 3.84 [2:1, 6:30] Liu et al. 2014 55 44 0 46 0.2% 7.16 [4:6, 117.01] Liu et al. 2019 34 44 0 46 0.2% 7.2.07 [4:5, 114.06.2] Liu et al. 2019 34 44 0 46 0.2% 7.2.07 [4:5, 114.06.2] Mackey et al. 2015 203 759 44 305 16.5% 2.34 [1.73, 317] Mackey et al. 2015 203 759 44 305 16.5% 2.34 [1.73, 317] Mackey et al. 2015 203 759 44 305 16.5% 2.34 [1.73, 317] Mackey et al. 2015 203 759 44 305 16.5% 2.34 [1.73, 317] Mackey et al. 2015 203 759 44 305 16.5% 2.34 [1.73, 317] Mackey et al. 2015 54 203 759 44 305 16.5% 2.34 [1.73, 317] Mackey et al. 2015 54 204 31 155 9.8% 10.0 [0.74, 1.61] Fining et al. 2016 51 204 31 155 9.8% 10.0 [0.74, 1.61] Sim et al. 2020 32 127 16 161 4.9% 2.54 [1.46, 4.41] Yan et al. 2020 32 127 16 161 4.9% 2.54 [1.46, 4.41] Yan et al. 2017 3369 2672 100.0% 2.65 [2.52, 3.22] Total events Heterogeneity: chi = 20.64, die -22 (P < 0.00001); P = 68% Heterogeneity: chi = 20.64, die -22 (P < 0.00001); P = 68% Heterogeneity: chi = 20.64, die -22 (P < 0.00001); P = 68% Heterogeneity: chi = 21.673 (P < 0.00001); P = 68% Heterogeneity: chi = 21.673 (P < 0.00001); P = 68% Heterogeneity: chi = 21.673 (P < 0.00001); P = 68% Heterogeneity: chi = 21.673 (P < 0.00001); P = 68% Heterogeneity: chi = 21.673 (P < 0.00001); P = 68% Heterogeneity: chi = 21.673 (P < 0.00001); P = 68% Heterogeneity: chi = 21.673 (P < 0.00001); P = 68% Heterogeneity: chi = 21.673 (P < 0.00001); P = 68% Heterogeneity: chi = 21.673 (P < 0.00001); P = 68% Heterogeneity: chi = 21.673 (P < 0.00001); P = 68% Heterogeneity: chi = 21.673 (P < 0.00001); P = 68% Heterogeneity: chi = 21.673 (P < 0.00001); P = 68% Heterogeneity: chi = 21.673 (P < 0.00001); P = 68% Heterogeneity: chi = 21.673 (P < 0.00001); P = 68% Heterogeneity: chi = 21.673 (P < 0.00001); P = 68% Heterogeneity: chi = 21.673 (P < 0.00001); P = 68% Heterogeneity: chi = 21.673 (P < 0.00001); P = 68% Heterogeneity: chi = 21.673 (P < 0.00001); P = 68% Heterogeneity: chi = 21.673 (P < 0.00001); P = 68% Heterogeneity: chi =	Kato et al.2012 Kato et al.2012	86	197	29	20	4 10.9%	3.07 [2.12, 4.4	46]
Lu et al.2014 35 44 0 46 0.2% 74.16 (48, 1173.01) Lu et al.2019 34 44 0 46 0.2% 72.07 (4.5, 114.06.2) Lu et al.2019 14 61 1 30 0.4% 6.89 (0.95, 49.92) Makeky et al.2015 203 759 44 385 16.5% 234 (17.3, 377) Miller et al.2005 54 232 5 230 1.9% 10.71 (4.3, 26.28) Makegawa et al.2019 100 224 27 225 10.3% 372 [2.54, 5.45] Rui et al.2016 51 204 31 125 9.9% 3.98 (1.56, 8.72) Fini et al.2010 3 57 1 65 0.3% 3.72 [2.54, 5.45] Tao et al.2020 3 27 127 16 161 4.9% 2.54 (1.46, 4.41) Total (95% C) 3369 2872 10.0.0% 2.85 [2.52, 3.22] Total events 1043 264 Heterogeneity: ChP = 70.94, df = 23 (P < 0.00001); P = 68% Testfor overall effect Z = 16.73 (P < 0.00001); P = 68% Testfor overall effect Z = 16.73 (P < 0.00001); P = 68%	Kato et al.2012 Kato et al.2012 Kubota et al.2017		153	3 14	15	3 5.0%	3.64 [2.11, 6.3	30]
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IGURE 2 (A) Forest Plots for the Overall Comparison of Hypertension	Kato et al.2012 Kubot at al.2017 Kubot at al.2017 Luurie at al.2014 Luurie at al.2014 Luu et al.2014 Luu et al.2019 Luu et al.2019 Miller et al.2015 Miller et al.2005 Miller et al.2005 Miller et al.2005 Miller et al.2007 Van et al.2020 Van et al.2020 Van et al.2020 Total events Heterogeneity: Chiller Test for overall effect:	51 35 34 14 203 54 19 100 51 31 3 32 17 1043 70.94, df = 23 Z = 18.73 (P <	44 61 758 233 34 224 112 57 123 75 3368 (P < 0.0 0.0000	1 1 9 44 2 5 4 6 4 27 1 31 2 0 7 1 7 16 5 0 9 264 00001); P	38 23 22 13 5 6 16 16 7 287 5 68%	0 1.9% 3 2.0% 5 10.3% 5 9.9% 6 0.2% 5 0.3% 1 4.9% 5 0.2% 2 100.0%	10.71 [4.36, 26.] 3.69 [1.56, 8.3 3.69 [1.56, 8.3 3.72 [2.54, 5.4 5 3.72 [2.54, 5.4 5 1.09 [0.74, 1.6 5 3.1.78 [1.89, 509.5 5 3.42 [0.37, 31.6 2.54 [1.46, 4.4 5 35.00 [2.14, 571.6 6 2.85 [2.52, 3.2	28]
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aused by cancer combination therapy. (B) Summary Relative Risks for	Kato et al.2012 Kubota et al.2017 Kubota et al.2017 Luuri et al.2014 Luu et al.2014 Luu et al.2014 Luu et al.2019 Malkey et al.2015 Miller et al.2005 Miller et al.2005 Miller et al.2005 Miller et al.2020 Tao et al.2021 Tao et al.2020 Tao et al.2021 Tao et al.2020 Tao et al.2021 Tao et al.2020 Tao et al.2021 Tao et al.2020 Tao et al.2021 Costa (SeS CI) Total events Heterogenety: Chill = GURE 2 (A	51 35 34 14 203 54 19 100 51 31 32 27 17 1043 70.94, df = 23 Z = 18.73 (P <	44 61 759 232 34 204 112 51 121 75 3369 (P < 0.0 0.0000	1 3 4 4 4 5 1 7 1 1 1 1 1 1 1 1 1 1 1 1 1	38 23 3 22 13 5 6 16 16 17 287 = 68%	0 1.99 3 2.09 5 10.39 5 9.99 6 0.29 5 0.39 1 4.99 5 0.29 2 100.09 Overal	 10.71 (4.38; 28: 3.369) (1.56; 8: 3.372 (2:45; 5: 1.09) (0.74; 1:6; 5: 3.72 (2:45; 5: 1.09) (0.74; 1:6; 5: 31.72 (1:19; 5: 003; 3: 42) (0.37; 3: 1:5; 3: 42; 0:37; 3: 1:5; 3: 42; 0:37; 3: 1:5; 3: 42; 0:37; 3: 1:5; 3: 42; 0:37; 3: 1:5; 3: 42; 0:37; 3: 1:5; 3: 42; 0:37; 3: 1:5; 3: 42; 0:37; 3: 1:5; 3: 42; 0:37; 3: 1:5; 3: 42; 0:37; 3: 1:5; 3: 42; 0:37; 3: 1:5; 3: 42; 0:37; 3: 1:5; 3: 42; 0:37; 3: 1:5; 3: 42; 0:37; 3: 1:5; 3: 42; 0:37; 3: 1:5; 3: 42; 0:37; 3: 1:5; 3: 42; 0:37; 3: 1:5; 3: 42; 0:37; 3: 1:5; 0:37; 3: 1:5; 0:37; 3: 1:5; 0:37; 3: 1:5; 0:37; 3: 1:5; 0:37; 3: 1:5; 0:37; 3: 1:5; 0:37; 1:1; 0:37; 0:	Reg 12 15 15 15 15 15 15 15 15 15 15

Oncology,", 4 in "The Lancet Oncology,", and 3 in "European Journal of Cancer."

Evaluation of Included Studies

The Modified Jadad Scores scale (Jadad et al., 1996) was used to evaluate the quality of the 23 eligible articles. Following the evaluation based on the Randomization, Concealment of Allocation, Double Blinding, Withdrawals, and Dropouts, etc., there were 15 articles in 7 points, 5 articles in 5 points, 3 articles in 4 points, and 1 article in 3 points, as shown in **Table 3**.

Relative Risk of Hypertension

A total of 3,369 patients received cancer combination therapy, as well as 2,872 patients received cancer single therapy and/or placebo, which was available for comparative analysis. The incidence of grade 1-2 hypertension events ranged from 0 to 75%, and cediranib combined with mFOLFOX6 for the treatment of Colorectal Cancer had the highest probability of inducing hypertension (Kato et al., 2012). However, no events were observed in grade 1-2 hypertension in one trial (Sinn et al., 2020). Using the random-effect model, the RR in all patients developing grade 1-2 hypertension was 2.43 [95% CI 2.10-2.81, p < 0.001, Figure 2A]. Furthermore, the probability of grade 3–4 hypertension in all patients ranged from 0 to 40.9%, among which cediranib combined with Olaparib in treating Ovarian Cancer showed the highest probability of developing hypertension events (Liu et al., 2014; Liu et al., 2019). However, no grade 3-4 hypertension events were observed in the use of Oxaliplatin combined with oxaliplatin and Tiggio in the treatment of Gastric Cancer (Yan et al., 2017). Based on the random-effect model, the RR in all patients developing grade 3-4 hypertension was 4.37 [95% CI 3.33–5.72, *p* < 0.001, Figure 2B]. In addition, the incidence of all-grade hypertension ranged from 5.26 to 85.71%, and the highest incidence of hypertension was observed in the use of cediranib combined with mFOLFOX6 for the treatment of Colorectal Cancer (Kato et al., 2012). In the random-effect model, the RR in all patients developing grade 3-4 hypertension was 2.85 [95% CI 2.52–3.22, *p* < 0.001, Figure 2C].

Overall Comparison of Hypertension

For all grades of hypertension, cancer patients receiving combination therapy had a relatively higher probability of developing hypertension (All-grade: RR 2.85, 95% CI 2.52–3.22; 1–2 grade: RR 2.43, 95% CI 2.10–2.81; 3–4 grade: RR 4.37, 95% CI 3.33–5.72) (**Figure 2**). In terms of all grades of hypertension caused by targeted drugs combined with chemotherapy, schemes with a relatively higher risk of developing hypertension included Paclitaxel combined with bevacizumab (RR 22.50, 95%CI 1.39–364.14) (Cortot et al., 2020), cediranib combined with Olaparib (RR 74.16, 95%CI 4.69–1,173.01; RR 72.07, 95%CI 4.55–1,140.62) (Liu et al., 2014; Liu et al., 2019), Docetaxel combined with axitinib (RR 31.78, 95%CI 1.98–509.95) (Johnston et al., 2013), as well as apapatinib combined with Oxaliplatin and Tiggio (RR 35.00, 95% CI 2.14–571.60) (Yan et al., 2017).

In six RCTs on the treatment of breast cancer, combination therapies included Capecitabine combined with bevacizumab (All-grade: RR 10.71, 95% CI 4.36–26.28; 1–2 grade: RR 3.22, 95% CI 1.07–9.73; 3–4 grade: RR 40.65, 95% CI 5.64–293.02) (Miller et al., 2005), Docetaxel combined with axitinib (All-grade: RR 31.78, 95% CI 1.98–509.95; 1–2 grade: RR 26.73, 95% CI 1.66–430.79; 3–4 grade: RR 5.55, 95% CI 0.31–98.60) (Rugo et al., 2011), Capecitabine combined with Sorafenib (All-grade: RR 1.49, 95% CI 0.75–2.94; 1–2 grade: RR 1.69, 95% CI 0.81–3.52;





3-4 grade: RR 0.50, 95% CI 0.05-5.39) (Baselga et al., 2012), lapatinib combined with pazopanib (All-grade: RR 9.33, 95% CI 2.87-30.41; 1-2 grade: RR 8.00, 95% CI 2.41-26.57; 3-4 grade: RR 9.86, 95% CI 0.49-200.23) (Johnston et al., 2013), ramucirumab combined with Docetaxel (All-grade: RR 2.34, 95% CI 1.73-3.17; 1-2 grade: RR 2.08, 95% CI 1.49-2.92; 3-4 grade: RR 3.70, 95% CI 1.69-8.07) (Mackey et al., 2015), Sorafenib combined with Capecitabine (All-grade: RR 4.62, 95% CI 2.71-7.87; 1-2 grade: RR 3.62, 95% CI 1.76-7.44; 3-4 grade: RR 6.11, 95% CI 2.62-14.27) (Baselga et al., 2017). According to the treatment of breast cancer, the RR of combination therapies induced hypertension is different, and the RR of Docetaxel combined with axitinib is higher than that of other treatments. In the combined treatment of breast cancer patients, Figure 3, it is not difficult to see that the RR of hypertension caused by ramucirumab combined with Docetaxel is small when the number of patients is gradually increasing, which indicates that ramucirumab combined with Docetaxel is the best

treatment for low risk of hypertension caused by breast cancer in 6 RCTs of this research.

In eight RCTs on the treatment of non-small cell lung cancer, combination therapies included vandetanib combined with Paclitaxel and Carboplatin (All-grade: RR 8.36, 95% CI 2.04-32.27; 1-2 grade: RR 6.50, 95% CI 1.55-27.24; 3-4 grade: RR 8.37, 95% CI 0.46–151.74) (Heymach et al., 2008), cediranib combined with Paclitaxel and Carboplatin (All-grade: RR 3.77, 95% CI 1.97-7.23; 1-2 grade: RR 2.36, 95% CI 1.07-5.18; 3-4 grade: RR 9.42, 95% CI 2.24-39.61) (Goss et al., 2010), bevacizumab combined with Cisplatin and Gemcitabine (Allgrade: RR 3.69, 95% CI 1.56-8.72; 1-2 grade: RR 3.11, 95% CI 1.28-7.51; 3-4 grade: RR 6.80, 95% CI 0.36-126.76) (Mok et al., 2011), cediranib combined with Paclitaxel and Carboplatin (Allgrade: RR 3.64, 95% CI 2.11-6.30; 1-2 grade: RR 3.27, 95% CI 1.73-6.19; 3-4 grade: RR 5.00, 95% CI 1.48-16.92) (Laurie et al., 2014), motesanib combined with Paclitaxel and Carboplatin (Allgrade: RR 3.07, 95% CI 2.12-4.46; 1-2 grade: RR 2.24, 95% CI



1.45–3.44; 3–4 grade: RR 8.28, 95% CI 2.98–22.99) (Kubota et al., 2017), fruquintinib combined with Best supportive care (All-grade: RR 6.89, 95% CI 0.95–49.92; 1–2 grade: RR 9.50, 95% CI 0.57–157.94; 3–4 grade: RR 2.46, 95% CI 0.30–20.12) (Lu et al., 2018), ramucirumab combined with erlotinib (All-grade: RR 3.72, 95% CI 2.54–5.45; 1–2 grade: RR 3.21, 95% CI 1.86–5.57; 3–4

grade: RR 4.35, 95% CI 2.39–7.93) (Nakagawa et al., 2019), Paclitaxel combined with bevacizumab (All-grade: RR 22.50, 95% CI 1.39–364.14; 1–2 grade: RR 14.50, 95% CI 0.88–238.66; 3–4 grade: RR 8.50, 95% CI 0.50–144.62) (Cortot et al., 2020). Depending on the above data, **Figure 4**, in 8 RCTs of non-small cell lung cancer, the highest RR of hypertension caused



TABLE 4 | Risk of bias of included randomized controlled trials.

Author (Year)	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Baselga et al. (2012)	Low	Low	Low	Unclear	Low	Low	Low
Baselga et al. (2017)	Unclear	Unclear	Low	Low	Low	Low	Low
Cortot et al. (2020)	Low	Unclear	Unclear	Low	Low	Low	Low
Dummer et al. (2018)	Low	Low	Low	Low	Low	Low	Low
Goss et al. (2010)	Low	Low	High	Low	Low	Low	Low
Guo et al. (2020)	Unclear	Unclear	High	Unclear	Low	Low	Low
Heymach et al. (2008)	Unclear	Unclear	Low	Low	Low	Low	Low
Johnston et al. (2013)	High	Low	Unclear	Low	Low	Low	Low
Kato et al. (2012)	Low	Low	Low	Low	Low	Low	Low
Kato et al. (2012)	Low	Low	Low	Low	Low	Low	Low
Kubota et al. (2017)	Low	Low	Low	Low	Low	Low	Low
Laurie et al. (2014)	Unclear	Low	High	Low	Low	Low	Low
Liu et al. (2014)	Low	Low	Low	Low	Low	Low	Low
Liu et al. (2019)	Low	Low	Low	Low	Low	Low	Low
Lu et al. (2018)	Low	Low	Low	Low	Low	Low	Low
Mackey et al. (2015)	Low	Low	Low	Low	Low	Low	Low
Miller et al. (2005)	Low	Low	Low	Low	Low	Low	Low
Mok et al. (2011)	Unclear	Unclear	Low	Low	Low	Low	Low
Nakagawa et al. (2019)	Low	Low	Low	Low	Low	Low	Low
Rini et al. (2016)	Low	Low	Low	Low	Low	Low	Low
Rugo et al. (2011)	Low	Low	Low	Low	Low	Low	Low
Sinn et al. (2020)	Low	Low	Low	Low	Low	Low	Low
Tao et al. (2020)	Low	Low	Low	Low	Low	Low	Low
Yan et al. (2017)	Unclear	Unclear	Unclear	Low	Low	Low	Low

by Paclitaxel combined with bevacizumab, With the increase of the number of patients, ramucirumab combined with erlotinib has a relatively small and better chance of inducing hypertension in the treatment of non-small cell lung cancer.

From an intuitive point of view, the incidence of hypertension caused by combination therapy of cancer is higher than that of single therapy, whether it is at all-grade, 1–2 grade or 3–4 grade

hypertension, the results shown in **Figure 5A–C**. As cancer combination therapy regimens, **Figure 6**, the result of analyze show that the RR of hypertension caused by two drugs combination therapy is higher than three drugs combination therapy, because there are very few plans of multi-drug (n > 3) combination therapy, it is not included as a comparison. For more details of the other schemes, please refer to **Table 1**.





Heterogeneity and Bias of Included Studies

As presented in **Figure 2**, there was moderate heterogeneity in grade 1–2 hypertension ($I^2 = 55\%$, p < 0.001), low heterogeneity in grade 3–4 hypertension ($I^2 = 5\%$, p = 0.39), and moderate heterogeneity in all grades of hypertension ($I^2 = 68\%$, p < 0.001) caused by cancer combination therapy, with the presence of statistical significance. Using the risk-of-bias assessment tool (Higgins et al., 2011), the results of the Cochrane risk-of-bias assessment of the enrolled 23 RCTs are shown in **Table 4** and **Figures 7–9** showed that the funnel plot indicated evidence of heterogeneities and publication bias in the studies included in the

meta-analysis with scatters beyond 95% CI and asymmetry display (p < 0.00001).

DISCUSSION

To our knowledge, the present meta-analysis for the first time evaluated the potential risk of hypertension in cancer patients treated with combination therapy. As a "silent killer,", hypertension has been reported to have a doubled prevalence in the past 40 years, with 7.6 million people dying of

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bia	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Baselga et al.2012	•	•	•	?	•	•	•
Baselga et al.2017	?	?	•	•	•	•	•
Cortot et al.2020	•	?	?	+	•	•	•
Dummer et al.2018	•	•	•	•	•	•	•
Goss et al.2010	•	•	•	•	•	•	•
Guo et al.2020	?	?	•	?	•	•	•
Heymach et al.2008	?	?	•	•	•	•	•
Johnston et al.2013	•	•	?	•	•	?	•
Kato et al.2012	•	•	•	•	•	•	•
Kubota et al.2017	•	•	•	•	•	•	•
Laurie et al.2014	?	•	•	•	•	•	•
Liu et al.2014	•	•	•	•	•	•	•
Liu et al.2019	•	•	•	+	•	•	•
Lu et al.2018	•	•	•	•	•	•	•
Mackey et al.2015	•	•	•	•	•	•	•
Miller et al.2005	•	•	•	•	•	•	•
Mok et al.2011	?	?	•	•	•	•	•
Nakagawa et al.2019	•	•	•	•	•	•	•
Rini et al.2016	•	•	•	•	•	•	•
Rugo et al.2011	•	•	•	•	•	•	•
Sinn et al.2020	•	•	•	•	•	•	•
Tao et al.2020	•	•	•	•	•	•	•
Yan et al.2017	?	?	?	•	•	•	•

hypertension annually in the world (Arima et al., 2011). Despite no significant direct influence, long-term hypertension may result in damage of the heart and blood vessels, and cerebral artery vasospasm as well.

In the field of Cardio-Oncology, cancer combination therapy may produce the effective outcome in killing cancer cells and controlling the deterioration of cancer. Nevertheless, there is an inevitable adverse effect of heart disease, especially the occurrence of hypertension. In this regard, there is an urgent need for medical staff to adjust the therapeutic schemes of patients, timely prevent and alleviate side effects during and after cancer treatment, to ensure the life safety of patients.

Current anti-hypertensive therapeutics included Selective $\alpha 1$ adrenoceptor antagonist, non-selective $\alpha 1$ and $\alpha 2$ -antagonists, β -adrenoceptor antagonists, angiotensin II receptor blockers, calcium channel blockers, ACE inhibitors, renin inhibitors, direct vasodilators, loop diuretics (Kumar et al., 2020). However, we should pay more attention to the related complications which they are accompanied, such as organ damage, hypotension and so on (Kumar et al., 2020).

In our meta-analysis, based on the collection of all relevant data from retrospective clinical trials, the final objects of study were a total of 23 clinical trials involving 6,241 patients. The combination therapy of cancer patients resulted in a higher risk of developing hypertension (All-grade: RR 2.85, 95% CI 2.52–3.22; 1–2 grade: RR 2.43, 95% CI 2.10–2.81; 3–4 grade: RR 4.37, 95% CI 3.33–5.72). According to the results, the risk of grade 3–4 hypertension induced by cancer combination therapy was higher than that of the control group with or without placebo therapy.

There may exist different mechanisms of increase in blood pressure under different anti-cancer therapeutic schemes. The mechanism of elevated blood pressure by using anti-cancer drugs may exhibit a direct association with its anti-cancer mechanism. The mechanism of hypertension induced by cancer combination therapy may be explained by the following reasons. To be specific, monoclonal antibodies (for example, bevacizumab) may reduce the number of capillaries in microcirculation, competitively inhibit the binding of EGFR with other ligands, and block the interaction between VEGF and endothelial cell surface receptors, resulting in inhibit the signal pathway of VEGF, reduce the activity of endothelial nitric oxide synthase and the production of NO and PGI₂ by vascular endothelial cells, decrease vascular permeability and vasodilation, increased peripheral vascular resistance and blood flow, and finally lead to hypertension (Chen et al., 2011; Mayer et al., 2011; Mourad and Levy, 2011; Campia et al., 2019). Besides, it has been reported that reducing the activity of eNOS will lead to expression of uncoupling protein of eNOS, produces a large amount of reactive oxygen species and then decrease the level of NO (Kumar et al., 2020). Meanwhile, NO is involved in maintaining the steady state of sodium ions and participating in tubuloglomerular feedback to regulate renal blood flow and glomerular filtration, which can increase systemic blood pressure (Lankhorst et al., 2017). Another possible mechanism of hypertension caused by inhibiting other VEGF pathways is that angiogenesis inhibitors may reduce the number of blood vessels and lead to hypertension owing to the thinning of peripheral microvessels



(Aparicio-Gallego et al., 2011). In addition, additional research also reveals that the increase in blood pressure may be related to the inhibition of VEGFR-2 (Kamba and McDonald, 2007). Also, Small molecular targeted drugs (such as sunitinib) can upregulate endothelin-1, increase salt sensitivity, and further increase in blood pressure owing to thrombotic glomerular injury (Kidoguchi et al., 2021). In addition, some novel targeted drugs (e.g., brutinib) may increase the risk of hypertension by inhibiting PI3K/Akt or reducing the level of NO (Dickerson et al., 2019). (Figure 10)

With respect to the above, there is necessary to adopt targeted treatment of hypertension. Before the treatment of cancer patients, it is recommended to adopt a comprehensive risk assessment, including blood pressure measurement and examination of known risk factors. For cancer patients with existed cardiovascular diseases, it is necessary to consider carefully whether to use anti-cancer drugs that may lead to cardiotoxicity or not. In the field of Cardio-Oncology, further consideration of the overall health status of patients is required for doctors to make a prudent decision in patients with a high risk of hypertension and those with hypertension prior to the use of anti-cancer drugs. Moreover, in case of poor control of cancer development by monotherapy, the better therapeutic outcome may be produced by combination therapy, However, it should be noted that combination therapy may also lead to a higher risk of hypertension.

So far, there is still no systematic analysis of hypertension caused by cancer combination therapy. Data in our study fully supports that cancer combination therapy has a high risk of inducing hypertension. Findings in this meta-analysis suggest that much attention shall be paid constantly to the adverse reactions of combined use of drugs, with in-time prevention required simultaneously. However, there are limitations in this study. For example, due to the absence of experimental data, relevant experiments are needed in the future to fully clarify the pathophysiological basis of hypertension caused by the combination of drugs and to increase the credibility of the results of our study.

CONCLUSION

The accuracy of meta-analysis research is high, but there is also a certain degree of publication bias, and risk of bias is low. It is worth mentioned that the reliability of meta-analysis results as well as the suitability in clinical practice might still requires critical thinking and objective judgments.

To sum up, the present meta-analysis carries out a comprehensive analysis on the risk of patients suffering from hypertension in the process of multiple cancer combination therapies. Findings in our study support that the risk of hypertension may increase significantly in cancer patients with multiple cancer combination therapies. The outcomes of this meta-analysis may provide a reference value for clinical practice and may supply insights in reducing the incidence of hypertension caused by cancer combined treatment.

AUTHOR CONTRIBUTIONS

XG, XQ, YJ, XK, ZQ, TC, LZ, CW, WL: Study concept and design; acquisition of data; statistical analysis; interpretation of data; drafting and critical review of the manuscript for important intellectual content; approval of the final version of the manuscript.

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