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Efficacy and toxicity of anti-vascular endothelial growth receptor tyrosine kinase inhibitors in patients with neuroendocrine tumours — A systematic review and meta-analysis

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Abstract

Aim: Although anti-vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitors (RTKIs) have been tested in patients with neuroendocrine tumours (NETs) over the last two decades, no study to date has benchmarked efficacy and toxicity of these drugs in this patient population.

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Author contribution form

Satya Das and Arvind Dasari: Conceptualisation; Satya Das, Heather LaFerriere and Cody Lebeck Lee: Data curation; Sharon Phillips: Formal analysis; NA: Funding acquisition; All Authors: Investigation; Satya Das, Arvind Dasari and Sharon Phillips: Methodology; NA: Project administration; Heather LaFerriere: Resources; Sharon Phillips: Software; Satya Das and Arvind Dasari: Supervision; NA: Validation; NA: Visualisation; All Authors: Roles/Writing – original draft; All Authors: Writing – review and editing.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Das reported receiving personal fees from Novartis, Ipsen, TerSera and Cancer Expert Now outside the submitted work. Dr. Chan reported receiving personal fees from Advanced Accelerator Applications, Ipsen, Lexicon, Crinetics and Novartis, and owning stock in Merck outside the submitted work. Dr Berlin reported receiving personal fees from IPsen, LSK, Bayer, SeaGen, QED, Clovis, Mirati, Novocure and AstraZeneca, and grants from Immunomedics, Karyopharm, Symphogen, Pfizer, AbbVie, Merck, Array, Pharmacyclics, Lilly, Loxo, Bayer, I-Mab, Atreca and Dragonfly outside the submitted work. Dr. Dasari reported receiving grants from Novartis, Merck, Eisai and Hutchison Pharma, and personal fees from Novartis, Hutchison Pharma and Eisai outside the submitted work. No other disclosures were reported. Dr. Ramirez reported receiving personal fees from Amgen, Ipsen Biopharmaceuticals, Novartis, Advanced Accelerator Applications, Curium Pharma, EMD Serono, Astra-Zeneca and Ter-Sera. No other disclosures were reported.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.12.031.

Methods: All phase II and phase III studies of anti-VEGF RTKIs in patients with NETs, published between January 1, 2000 andJuly 31, 2021, across major trial databases, were searched in August 2021 for relevant studies. The primary objectives of the meta-analysis were to compare objective response rate (ORR) and progression-free survival (PFS) between patients with pancreatic NETs (pNETs) and extra-pancreatic NETs (epNETs), and the incidence rate ratio (IRR) of adverse events between patients receiving anti-VEGF RTKIs and control.

Results: 1611 patients were available for the meta-analysis; 1194 received anti-VEGF RTKIs. ORR in pNETs was 18% (95% confidence interval (CI) 13–25%), while ORR in epNETs was 8% (95% CI 5–12%); test for differences between pNETs and epNETs ($x12 = 8.38$, $p < .01$). Median PFS in pNETs was 13.9 months (95% CI 11.43–16.38 months), while median PFS in epNETs was 12.71 months (95% CI 9.37–16.05 months); test for differences between pNETs and epNETs ($x12 = .35$, $p = .55$). With regards to common grade 3/4 adverse events , patients who received anti-VEGF RTKIs were more likely to experience hypertension (IRR 3.04, 95% CI 1.63–5.65) and proteinuria (IRR 5.79, 95% CI 1.09–30.74) in comparison to those who received control.

Conclusions: Anti-VEGF RTKIs demonstrate anti-tumour effect in both pNETs and epNETs, supporting their development in both populations. These agents also appear to be safe in patients with NETs.

Keywords

Anti-vascular endothelial growth factor; Receptor tyrosine kinase inhibitors; Neuroendocrine tumours; Toxicity; Objective response rate; Progression-free survival; Systematic review & meta-analysis

1. Introduction

Well differentiated neuroendocrine tumours (NETs) are highly vascular malignancies; this characteristic prompted the initial exploration of angiogenesis inhibition in NETs [1]. Vascular endothelial growth factor (VEGF)-mediated signalling is central to well differentiated NETs, with multiple studies suggesting the overexpression of VEGF and VEGF receptor subtypes in both pancreatic NETs (pNETs) and extra-pancreatic NETs (epNETs) [2–5]. As such, anti-VEGF receptor tyrosine kinase inhibitors (RTKIs) have been tested in patients with NETs over the last two decades, mostly in small phase II studies. While only sunitinib has garnered regulatory licensure for patients with advanced pNETs [6], several other anti-VEGF RTKIs (e.g. surufatinib, lenvatinib, cabozantinib, axitinib, pazopanib, nintedanib and motesanib) have been tested clinically in patients with pNETs and epNETs, with mixed results [7–9]. Despite the clinical promise of these drugs, their toxicity profile is a concern to many treating oncologists. In addition to well-chronicled common adverse events (AEs), rare serious AEs (e.g. cerebrovascular accident, non-myocardial infarction (nMI) cardiac dysfunction, non-central nervous system (nCNS) emboli, nCNS bleeding, gastrointestinal perforation and MI) have also been documented in patients with other malignancies, receiving treatment with anti-VEGF RTKIs [10–12]. The objectives of our systematic review and meta-analysis were to benchmark the efficacy and safety of anti-VEGF RTKIs in patients with NETs.

2. Methods

2.1. Search strategy

A literature search was performed by a biomedical librarian to identify all phase II and phase III studies of anti-VEGF RTKIs in patients with NETs, published between January 1, 2000 andJuly 31, 2021. Medline (via PubMed), EMBASE (OvidSP), Cumulative Index of Nursing and Allied Health Literature (EBSCOhost), Web of Science (Clarivate), Cochrane Database of Systematic Reviews (Wiley), Cochrane CENTRAL Register of Controlled Trials (Wiley), ClinicalTrials.gov (National Institutes of Health), World Health Organisation International Clinical Trials Registry Platform, EU Clinical Trials Register and National Cancer Institute Clinical Trials were searched in August 2021 for relevant studies.

The search strategy was composed of a combination of keywords and database-specific subject headings, including the following search terms and variations of each term: neuroendocrine, tumours, tumours, malignancies, carcinoma, carcinoid, cancer, neoplasms, adenomas, sunitinib, sorafenib, cabozantinib, lenvatinib, nintedanib, pazopanib, surufatinib, sulfatinib, tyrosine kinase, tyrosine protein kinase, tyrosine phosphokinase, tyrosyl kinase, tyrosylprotein kinase, tyrosine receptors, PTK receptors, receptor tyrosine, src family, src kinase, inhibitors, clinical trials, randomised trials, controlled trials, drug trials, phase II and phase III. Search results were imported into EndNote 20 for removal of duplicate citations.

2.2 Data abstraction

A data abstraction spreadsheet was generated by two authors (S.D. and A.D.). One author (C.L.) performed the data abstraction on all 17 studies, while a second co-author (S.D.) reviewed these data. Any data disagreements were resolved after consensus was achieved through discussions with the abstracting author. Details of data abstraction are described in the eMethods.

2.3. Statistical analysis

We performed a meta-analysis using a random effects model to reduce the impact of heterogeneity between the included studies. Objective response rate (ORR) and progression free survival (PFS) used all 17 studies. Using the median and 95% confidence intervals (CIs) for PFS, a standard error was computed for the meta-analysis. ORR used the proportion of patients for each study. Incidence rate ratio (IRR) was adjusted for duration of treatment, and only included studies with controls to compare AEs. In IRR analyses, using I^2, we found no significant heterogeneity between the studies. Chi-squared tests were used for the rates of dose interruption, dose reduction, drug discontinuation and progressive disease. A statistical analysis was performed using R version 4.1.2 (2021–11-01).

3. Results

Our search yielded a total of 92 potentially relevant studies with anti-VEGF RTKIs. After excluding studies which were redundant and possessed insufficient data, 17 studies with 8 distinct RTKIs were included in the meta-analysis (Fig. 1). The baseline characteristics of each trial are presented in Table 1. A total of 12 (70.59%) studies allowed concomitant

somatostatin analogue administration; 5 studies were randomised trials, although only 4 could be included in aIRR analysis. Of the included studies, 8 (47.06%) were conducted in North America, 8 (47.06%) were conducted outside North America and 1 (5.88%) was conducted globally. A total of 1611 patients (853 men, 758 women) were available for the meta-analysis. Of these patients, 1194 received anti-VEGF RTKIs.

ORR in pNETs was 18% (95% CI 13–25%), while ORR in epNETs was 8% (95% CI 5–12%); test for differences between pNETs and epNETs (x_1^2, $p < .01$) ($I^2 = 66\%$, $p < .01$) (Fig. 2). Median PFS in pNETs was 13.9 months (95% CI 11.43–16.38 months), while median PFS in epNETs was 12.71 months (95% CI 9.37–16.05 months); test for differences between pNETs and epNETs (x_1^2, $p = .55$) ($I^2 = 73\%$, $p < .01$) (Fig. 3).

There was no difference in IRR for rare serious AEs between patients who received anti-VEGF RTKIs and those who received control. However, with regards to common grade 3/4 AEs, patients who received anti-VEGF RTKIs were more likely to experience all AEs (IRR 1.58, 95% CI 1.23–2.02), hypertension (IRR 3.04, 95% CI 1.63–5.65) and proteinuria (IRR 5.79, 95% CI 1.09–30.74) compared to those who received control. Regarding common all grade AEs, patients who received anti-VEGF RTKIs were more likely to experience hypertension (IRR 1.87, 95% CI 1.39–2.50) and diarrhoea(IRR 1.33, 95% CI 1.03–1.73) compared to patients who received control (Table 2).

The incidence of AEs in patients who received anti-VEGF RTKIs is described in Table 3. Notably, the incidence of cerebrovascular accident, non-myocardial infarction cardiac dysfunction, nCNS emboli, nCNS bleeding, gastrointestinal perforation, MI and treatment-related death were .4%, 6.4%, .3%, 8.7%, 0%, .4% and 1%, respectively. Patients treated with anti-VEGF RTKIs were more likely to experience dose interruptions (39.2% versus 19.9%, $p < .001$), dose reductions (30.1% versus 5.9%, $p < .001$) and drug discontinuation (19.7% versus 7.2%, $p < .001$) due to AEs compared to patients who received control. Patients treated with anti-VEGF RTKIs were less likely to discontinue therapy due to progressive disease compared to patients who received control (31.3% versus 62.2%, $p < .001$).

4. Discussion

The results of our meta-analysis lead to the following insights. First, while ORR was greater with anti-VEGF RTKIs in patients with pNETs compared to patients with epNETs, there were similar PFS durations between the patient populations. PFS is more useful clinically than ORR as an end-point for patients with well differentiated NETs, and it is possible that the development of sunitinib solely for pNETs on the basis of this end-point may have missed a patient population (e.g. epNETs), in whom the drug would have demonstrated anti-tumour activity [13,14]. The measure of anti-VEGF RTKI efficacy, however, likely depends on the tested patient population in a clinical trial as much as it does on the specific drug being tested; trials including patients with more aggressive baseline disease (e.g. higher tumour grade, pNETs) will demonstrate greater benefit from the drugs in the experimental arms given poorer relative outcomes in the control arms, whereas trials including patients with more indolent disease (e.g. lower tumour grade, midgut predominant

NETs) may not demonstrate the same magnitude of difference due to improved outcomes in the control arms (eFig. 1). This likely explains why randomized anti-VEGF RTKI studies in patients with epNETs have demonstrated mixed outcomes, with some studies demonstrating benefit (e.g. surufatinib in NCT02588170; 83.2% of patients possessed grade 2 NETs) and others demonstrating a lack of benefit (e.g. axitinib in NCT01744249; unknown NET grade distribution amongst patients). Second, given the differences in ORR, it is possible that AEs vary among patients, based upon primary tumour origin. Only two of nine studies included in the analysis, which included patients with both pNETs and epNETs, reported AEs separately for each of these patient populations. We believe this should become a standardised expectation for future NET trial reporting given the intrinsic differences in patients with each of these tumour types. Third, although progressive disease was the most common reason for study discontinuation in patients treated with anti-VEGF RTKIs, compared to drug discontinuation due to AEs, 19.7% of patents still discontinued the drugs due to AEs. In the context of relatively few grade 3/4 AEs (e.g. the only grade 3/4 AE with >10% incidence was grade 3/4 hypertension) experienced by patients, this suggests that lower grade chronic AEs (e.g. diarrhoea, nausea/vomiting, fatigue, asthenia, hand-foot syndrome) may contribute to poor tolerance of anti-VEGF RTKIs over time. Fourth, although rare serious AEs are cited as reasons for concern to avoid anti-VEGF RTKIs in patients, we found no difference in the occurrence of these AEs, by IRR, between anti-VEGF RTKI- and placebo-treated patients. However, it should be noted that this finding was in a highly selected pool of clinical trial patients, who are generally not representatives of real-world patients. Real-world patients possess more co-morbidities (e.g cardiovascular) and worse performance statuses, which may increase the risk of rare serious AEs with anti-VEGF RTKIs in the daily clinical practice setting. Fifth, to contextualise AEs observed with anti-VEGF RTKIs in patients with NETs, AEs in patients with renal cell carcinoma (RCC) may be the ideal comparator given the number of shared drugs in both diseases. The incidence of grade 3/4 hand-foot syndrome (5–16%) in patients with RCC treated with anti-VEGF RTKIs was higher than the incidence of grade 3/4 hand-foot syndrome in our analysis (1.3%) [15]. Conversely, the incidence of grade 3/4 hypertension in patients in our analysis (22.4%) was higher than reported in patients with RCC (8–16%). The rates of drug discontinuation, dose interruption and dose reduction were similar in our analysis compared to rates reported in RCC [15]. Treatment-related deaths due to anti-VEGF RTKIs were lower in patients in our meta-analysis (1%) compared to rates of treatment-related deaths cited in RCC (3.68%) [16].

4.1. Limitations

A primary limitation of this analysis is that there was significant heterogeneity between studies when pooling efficacy outcomes; this is an inherent limitation of NET trials, which are mostly small phase II studies in diverse patient populations. We believe the three following factors contributed most profoundly to the differences in patient population amongst the included studies: difference in tumour grade, difference in study location where trials were conducted and difference in NET disease status at time of study enrolment. With regards to difference in tumour grade, 8 of 17 studies did not report distribution of tumour grade amongst patients. Even amongst studies which reported tumour grade distribution, significant interstudy differences were observed (e.g. 80.2% of patients treated

with surufatinib in NCT02267967 possessed grade 2 NETs, while 26.9% of patients treated with pazopanib in NCT00454363 possessed grade 2 NETs). These interstudy differences could lead to observed differences in ORR and PFS, given that patients with higher grade NETs tend to demonstrate greater ORR but shorter PFS with any systemic therapy compared to patients with lower grade NETs. With regards to difference in study location where trials were conducted, eight were conducted in North America only, five were conducted in Asia only, three were conducted in Spain only and one was globally conducted. It is plausible that population pharmacogenomics could influence differential treatment outcomes with anti-VEGF RTKIs, given that regional differences in treatment outcomes have been observed with other types of systemic therapies studied globally such as immunotherapy [17]. With regards to difference between NET disease status at study enrolment, five studies did not mandate progressive disease at study entry while even amongst the 12 studies which did, seven did not mandate response evaluation criteria in solid tumours-defined progression. As such, there were significant differences in disease status (e.g. patients starting with stable disease versus progressive disease versus response evaluation criteria in solid tumours-defined progressive disease) between patients starting treatment with anti-VEGF RTKIs in the studies, which could significantly impact ORR and PFS outcomes. Another limitation of this analysis is the paucity of studies with control arms, which limited the number of studies (N = 4) from which IRR data was calculated as well as limited our ability to compare hazard ratios for PFS across trials; this is also a by-product of the few randomised trials conducted in NETs to date.

5. Conclusions

Anti-VEGF RTKIs demonstrate anti-tumour activity in both pNETs and epNETs, supporting future development of this agent class in both patient populations. Significant heterogeneity was identified between the trials included in the meta-analysis, suggesting that more randomised global studies of anti-VEGF RTKIs are needed to better compare the anti-tumour activity of anti-VEGF RTKIs across studies. No difference in rare serious AEs, and only few differences in common grade 3/4 AEs (e.g. hypertension and proteinuria) were observed between patients with NETs receiving anti-VEGF RTKIs and those receiving control, suggesting the overall safety of this agent class in the tested patient population. Still, the relatively high rates of discontinuation of anti-VEGF RTKIs in study patients suggest that the health-related quality of life burden of chronic lower grade AEs from the agent class in patients are underappreciated. How to optimally manage these chronic lower grade AEs, thereby allowing patients to remain on anti-VEGF RTKIs for long periods of time, is an area of active research need in the field.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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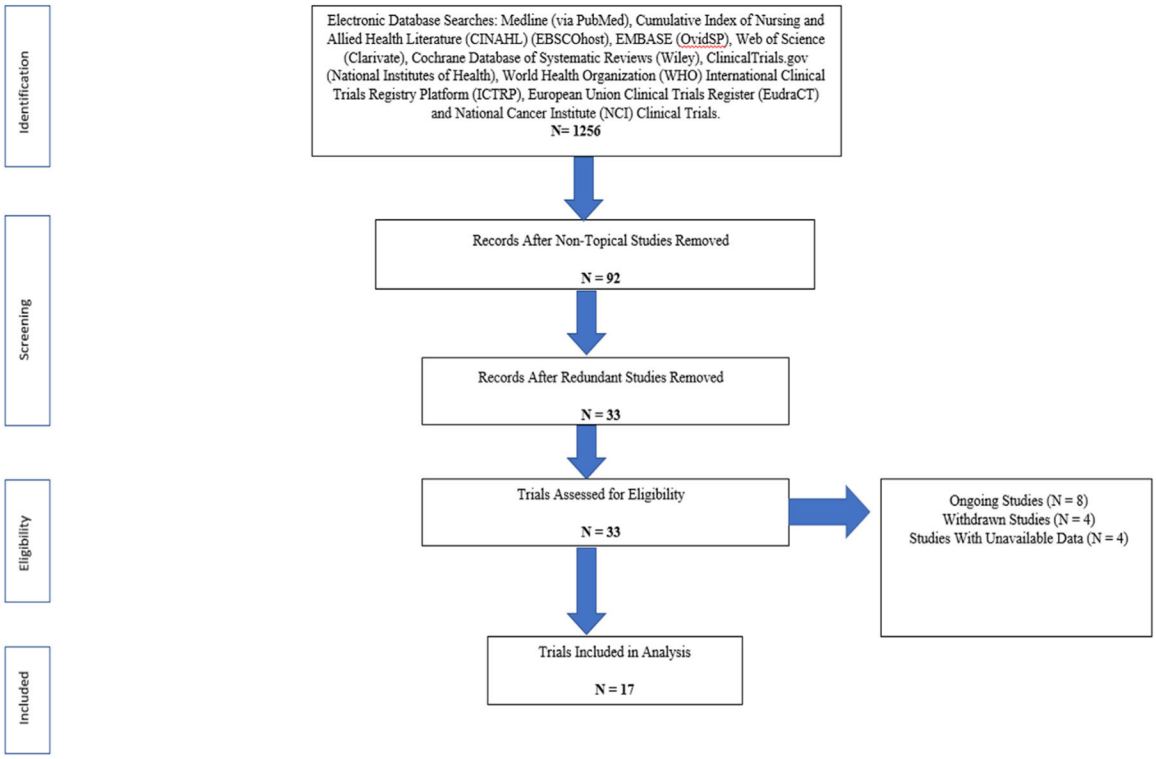

Fig. 1. PRISMA diagram depicting how the studies included in the analysis were chosen.

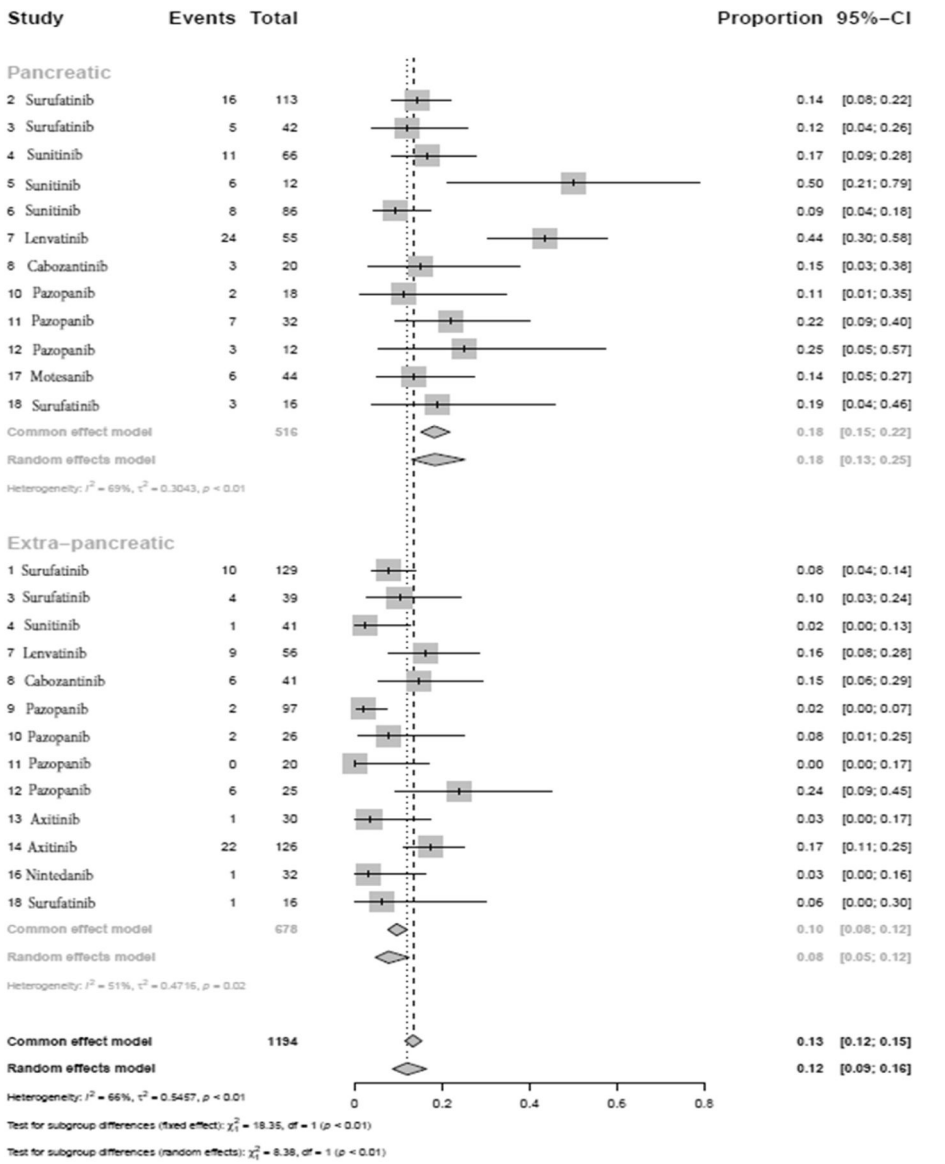

Fig. 2. Pooled objective response rates for patients treated with anti-VEGF RTKIs, separated by primary tumour type (pancreatic and extra-pancreatic).

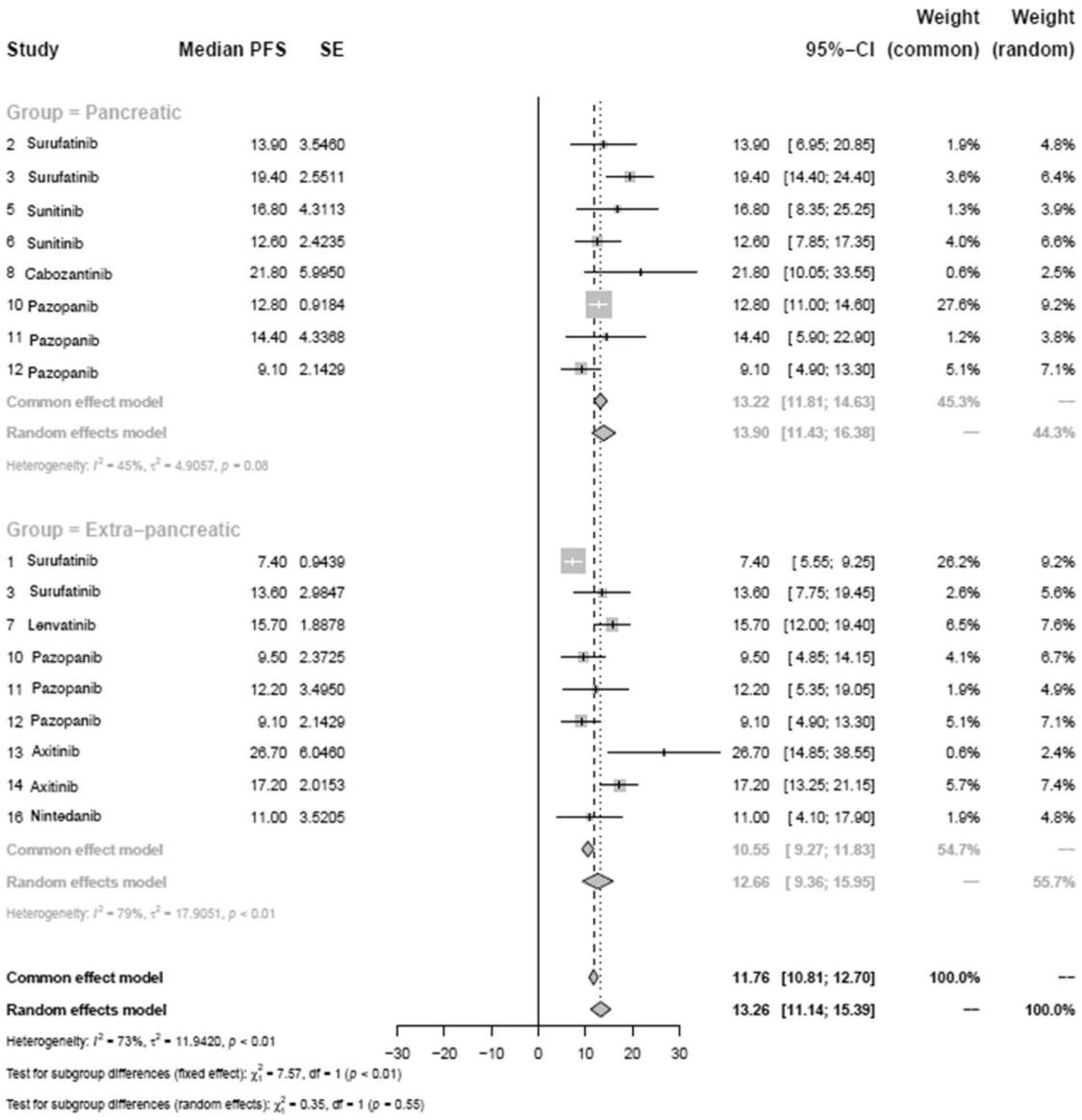

Fig. 3. Pooled median progression-free survival (months) for patients treated with anti-VEGF RTKIs, separated by primary tumour type (pancreatic and extra-pancreatic).

Table 1

Baseline characteristics of the studies included in the meta-analysis.

Trial Identifier and First Author of Publication	Anti-VEGF RTKI (Primary Receptor Targets)	Study Phase	Study Design	NETs Included	PD Req	Prior LOT Req	Ki-67 Index Specified in IC	Total Sample Size (% of Patients With Tumour Grade Specified)	# Treated ith RTKI	# Men	# Women	Median Patient Age	Study Location	Year of Trial Start
NCT02588170 (1) Jianming Xu	Surufatinib (VEGFR 1–3, FGFR1 and CSF1R)	III	RCT	EP	Y (not by RECIST, within 12 months of enrolment)	N	≤20%	198 (16.2% Grade 1, 83.8% Grade 2)	129	108	90	52	Outside North America (China)	2015
NCT02589821 (2) Jianming Xu	Surufatinib	III	RCT	P	Y (not by RECIST, within 12 months of enrolment)	N	≤20%	172 (13.4% Grade 1, 86.6% Grade 2)	113	88	84	51	Outside North America (China)	2016
NCT02267967 (3) Jianming Xu	Surufatinib	II	SA	EP and P	N	Y	≤20%	81 (19.8% Grade 1, 80.2% Grade 2)	81	44	37	49	Outside North America (China)	2014
NCT02549937 (18) Andrew Scott Paulson	Surufatinib	II	SA	EP and P	Y (not by RECIST and no timeframe specified)	Y	NS	32 (NET grade distribution not specified)	32	22	10	NA (overall) EP – 62.2 P – 64.4	North America	2015
NCT01121562 (5) Tetsuhide Ito	Sunitinib (VEGFR 1–3, PDGFR α and β)	II	SA	P	Y (by RECIST, within 12 months of enrolment)	N	NS	12 (NET grade distribution not specified)	12	8	4	54	Outside North America (Japan)	2010
PMID:18612155 (4) Matthew Kulke	Sunitinib	II	MCP	EP and P	N	N	NS	107 (NET grade distribution not specified)	107	64	43	NA (overall) EP – 58 P – 56	North America	2003
NCT00428597 (6) Eric Raymond	Sunitinib	III	RCT	P	Y (by RECIST, within 12 months of enrolment)	N	NS	171 (NET grade distribution not specified)	86	82	89	56	Global	2007
NCT03290079 (7) Jaume Capdevila	Lenvatinib (VEGFR 1–3 and FGFR 1–4)	II	MCP	EP and P	Y (by RECIST, within 12 months of enrolment)	Y	≤20%	111 (29.7% Grade 1 and 68.5% Grade 2)	111	57	54	NA (overall) EP – 61 P – 58	Outside North America (Spain)	2015

Trial Identifier and First Author of Publication	Anti-VEGF RTKI (Primary Receptor Targets)	Study Phase	Study Design	NETs Included	PD Req	Prior LOT Req	Ki-67 Index Specified in IC	Total Sample Size (% of Patients With Tumour Grade Specified)	# Treated ith RTKI	# Men	# Women	Median Patient Age	Study Location	Year of Trial Start
NCT01466036 (8) Jennifer Chan	Cabozantinib (VEGFR2, MET and RET)	II	MCP	EP and P	Y (not by RECIST, within 12 months of enrolment)	Y	≤20%	61 (NET grade distribution not specified)	61	30	31	NA (overall) EP – 63 P – 55	North America	2012
NCT01280201 (10) Enrique Grande	Pazopanib (VEGFR 1–3, FGFR 1,3,4 and PDGFR α and β)	II	SA	EP and P	Y (by RECIST, within 12 months of enrolment)	Y	≤20%	44 (NET grade distribution not specified)	44	24	20	60.2	Outside North America (Spain)	2011
NCT00454363 (11) Alexandria Phan	Pazopanib	II	MCP	EP and P	N	Y	≤20%	52 (73.1% Grade 1 and 26.9% Grade 2)	52	34	18	60	North America	2007
PMID: 23989950 (12) H K Ahn	Pazopanib	II	MCP	EP and P	N	N	NS	37 (22% Grade 1, 43% Grade 2 and 35% Grade 3)	37	25	12	55	Outside North America (Korea)	2010
NCT01841736 (9) Emily Bergsland	Pazopanib	II	RCT	EP	Y (not by RECIST, within 12 months of enrolment)	Y	≤20%	171 (NET grade distribution not specified)	97	75	96	62	North America	2013
NCT02399215 (16) Renuka Iyer	Nintedanib (VEGFR 1–3, FGFR 1–3 and PDGFR α and β)	II	SA	EP	N	N	≤20%	32 (NET grade distribution not specified)	32	17	15	65	North America	2015
NCT01435122 (13) Jonathan Strosberg	Axitinib (VEGFR 1–3)	II	SA	EP	Y (not by RECIST, within 12 months of enrolment)	Y	≤20%	30 (70% Grade 1 and 30% Grade 2)	30	13	17	64	North America	2011
NCT01744249 (14) Rocio Garcia-Carbonero	Axitinib	II/III	RCT	EP	Y (not by RECIST, within 12 months of study enrolment)	N	≤20%	256 (NET grade distribution not specified)	126	138	118	62	Outside North America (Spain)	2011
NCT00427349 (17) Sam Lubner	Motesanib (VEGFR 1–3, PDGFR α and β and RET)	II	SA	EP and P	Y (by RECIST, no specified	N	≤2%	45 (100% Grade 1)	44	24	20	65	North America	2008

Trial Identifier and First Author of Publication	Anti-VEGF RTKI (Primary Receptor Targets)	Study Phase	Study Design	NETs Included	PD Req	Prior LOT Req	Ki-67 Index Specified in IC	Total Sample Size (% of Patients With Tumour Grade Specified)	# Treated ith RTKI	# Men	# Women	Median Patient Age	Study Location	Year of Trial Start
					timeframe for progression)									

Abbreviations: VEGF, vascular endothelial growth factor; RTKI, receptor tyrosine kinase inhibitor; EP, extra-pancreatic; p, pancreatic; RTKI, receptor tyrosine kinase inhibitor; PD Req, progressive disease required at inclusion; Y, yes; N, no; LOT Req, prior lines of therapy required; NA, not available; IC, inclusion criteria; NS, not specified; RCT, randomised controlled trial; SA, single arm; MCP, multi-cohort parallel; #, number; FGFR, fibroblast growth factor receptor; PDGFR, platelet derived growth factor receptor; CSF1R, colony stimulating factor 1 receptor; RECIST, response evaluation criteria in solid tumours.

* Please note numbers listed in parentheses in the trial identifier category correspond to the trial designations in Figs. 2 and 3 and eFig. 1.

Table 2

Incidence rate ratio for select common and rare adverse events in patients treated with anti-VEGF RTKIs compared to patients treated with control.

Adverse Event	IRR (95% CI)	Total N of Patients From Representative Studies	Heterogeneity of Representative Studies
Rare			
Myocardial Infarction	NA	NA	NA
Non-Myocardial Infarction Cardiac Dysfunction	1.55 (.73–3.28)	413	I^2 = 0% (p = .64)
Non-Central Nervous System Bleeding	1.31 (.81–2.12)	585	I^2 = 0% (p = .71)
Non-Central Nervous System Emboli	NA	NA	NA
Cerebrovascular Accident	.82 (.1–6.63)	343	I^2 = 0% (p = .98)
Perforation	NA	NA	NA
Treatment-Related Death	1.05 (.19–5.92)	541	I^2 = 0% (p = .91)
Common			
Grade 3/4 Adverse Events	**1.58 (1.23–2.02)**	712	I^2 = 34% (p = .21)
Grade 3/4 Hypertension	**3.04 (1.63–5.65)**	712	I^2 = 12% (p = .33)
All Grade Hypertension	**1.87 (1.39–2.50)**	712	I^2 = 0% (p = .44)
Grade 3/4 Diarrhoea	1.32 (.51–3.39)	712	I^2 = 0% (p = .98)
All Grade Diarrhoea	**1.33 (1.03–1.73)**	712	I^2 = 0% (p = .68)
Grade 3/4 Hand-Foot Syndrome	NA	NA	NA
All Grade Hand-Foot Syndrome	NA	NA	NA
Grade 3/4 Proteinuria	**5.79 (1.09–30.74)**	370	I^2 = 2% (p = .026)
All Grade Proteinuria	.85 (.63–1.14)	370	I^2 = 0% (p = .37)
Grade 3/4 Nausea and Vomiting	.98 (.32–3.01)	514	I^2 = 2% (p = .31)
All Grade Nausea and Vomiting	1.15 (.71–1.85)	514	I^2 = 72% (p = .01)
All Grade Asthenia	1.10 (.71–1.72)	541	I^2 = 0% (p = .65)
All Grade Anorexia	1.77 (.28–11.14)	541	I^2 = 67% (p = .05)
All Grade Headaches	1.2 (.66–2.16)	541	I^2 = 0% (p = .4)

Abbreviations: NA, not available (too few studies documenting event of interest); VEGF, vascular endothelial growth factor; RTKI, receptor tyrosine kinase inhibitor.

Table 3

Incidence of common and rare adverse events experienced by patients treated with anti-VEGF RTKIs from the meta-analysis

AE	Incidence of All Grade AEs	Incidence of Grade 3/4 AEs
Rare		
Myocardial Infarction	.3%	
Non-Myocardial Infarction Cardiac Dysfunction	6.4%	
Non-Central Nervous System Bleeding	8.7%	
Non-Central Nervous System Emboli	.3%	
Cerebrovascular Accident	.4%	
Perforation	0%	
Treatment-Related Death	1%	
Common		
Hypertension	52.01%	22.4%
Proteinuria	22.9%	4.6%
Diarrhoea	55.8%	6.4%
Hand-Foot Syndrome	11%	1.3%
Nausea/Vomiting	49.9%	3.4%
Fatigue	32.2%	4.1%
Asthenia	22.2%	3.1%
Arthralgias	5.4%	.2%
Stomatitis	11.4%	.8%
Anaemia	16.6%	1.5%
Neutropenia	17%	5.2%
Thrombocytopaenia	16.4%	1.8%
Headaches	11.8%	.3%
Anorexia	14.8%	1%

Abbreviations: VEGF, vascular endothelial growth factor; RTKI, receptor tyrosine kinase inhibitor; AEs, adverse events.