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Treatment for gastrointestinal and pancreatic neuroendocrine tumours: a network meta-analysis (Review)

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[Intervention Review]

Treatment for gastrointestinal and pancreatic neuroendocrine tumours: a network meta-analysis

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ABSTRACT

Background

Several available therapies for neuroendocrine tumours (NETs) have demonstrated efficacy in randomised controlled trials. However, translation of these results into improved care faces several challenges, as a direct comparison of the most pertinent therapies is incomplete.

Objectives

To evaluate the safety and efficacy of therapies for NETs, to guide clinical decision-making, and to provide estimates of relative efficiency of the different treatment options (including placebo) and rank the treatments according to their efficiency based on a network meta-analysis.

Search methods

We identified studies through systematic searches of the following bibliographic databases: the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library; MEDLINE (Ovid); and Embase from January 1947 to December 2020. In addition, we checked trial registries for ongoing or unpublished eligible trials and manually searched for abstracts from scientific and clinical meetings.

Selection criteria

We evaluated randomised controlled trials (RCTs) comparing two or more therapies in people with NETs (primarily gastrointestinal and pancreatic).

Data collection and analysis

Two review authors independently selected studies and extracted data to a pre-designed data extraction form. Multi-arm studies were included in the network meta-analysis using the R-package netmeta. We separately analysed two different outcomes (disease control and progression-free survival) and two types of NET (gastrointestinal and pancreatic NET) in four network meta-analyses. A frequentist approach was used to compare the efficacy of therapies.

Main results

We identified 55 studies in 90 records in the qualitative analysis, reporting 39 primary RCTs and 16 subgroup analyses. We included 22 RCTs, with 4299 participants, that reported disease control and/or progression-free survival in the network meta-analysis. Precision-of-treatment estimates and estimated heterogeneity were limited, although the risk of bias was predominantly low.

The network meta-analysis of progression-free survival found nine therapies for pancreatic NETs: everolimus (hazard ratio [HR], 0.36 [95% CI, 0.28 to 0.46]), interferon plus somatostatin analogue (HR, 0.34 [95% CI, 0.14 to 0.80]), everolimus plus somatostatin analogue (HR, 0.38 [95% CI, 0.26 to 0.57]), bevacizumab plus somatostatin analogue (HR, 0.36 [95% CI, 0.15 to 0.89]), interferon (HR, 0.41 [95% CI, 0.18 to 0.94]), sunitinib (HR, 0.42 [95% CI, 0.26 to 0.67]), everolimus plus bevacizumab plus somatostatin analogue (HR, 0.48 [95% CI, 0.28 to 0.83]), surufatinib (HR, 0.49 [95% CI, 0.32 to 0.76]), and somatostatin analogue (HR, 0.51 [95% CI, 0.34 to 0.77]); and six therapies for gastrointestinal NETs: 177-Lu-DOTATATE plus somatostatin analogue (HR, 0.07 [95% CI, 0.02 to 0.26]), everolimus plus somatostatin analogue (HR, 0.12 [95%CI, 0.03 to 0.54]), bevacizumab plus somatostatin analogue (HR, 0.18 [95% CI, 0.04 to 0.94]), interferon plus somatostatin analogue (HR, 0.23 [95% CI, 0.06 to 0.93]), surufatinib (HR, 0.33 [95%CI, 0.12 to 0.88]), and somatostatin analogue (HR, 0.34 [95% CI, 0.16 to 0.76]), with higher efficacy than placebo. Besides everolimus for pancreatic NETs, the results suggested an overall superiority of combination therapies, including somatostatin analogues.

The results indicate that NET therapies have a broad range of risk for adverse events and effects on quality of life, but these were reported inconsistently.

Evidence from this network meta-analysis (and underlying RCTs) does not support any particular therapy (or combinations of therapies) with respect to patient-centred outcomes (e.g. overall survival and quality of life).

Authors' conclusions

The findings from this study suggest that a range of efficient therapies with different safety profiles is available for people with NETs.

PLAIN LANGUAGE SUMMARY

Treatment options for neuroendocrine tumours

Review question

We reviewed the evidence on safety and efficacy of therapies for neuroendocrine tumours (NETs) in the gastrointestinal tract and the pancreas to provide a ranking of these treatment options.

Background

NETs are a varied group of rare cancers, which can occur anywhere in the body. However, most neuroendocrine tumours derive from the gastrointestinal tract or the pancreas. There are many types of NETs with different growth rates and symptoms. While some NETs produce excess hormones, others do not release hormones, or not enough to cause symptoms. The treatment options, as well as their combinations and sequencing, depend on the type of tumour, its location, aggressiveness, and whether it produces excess hormones.

Until now, no clear recommendations could be given about which NET therapies were the most effective and caused the fewest adverse events. We used statistical methods to compare all therapies with each other based on the available information.

Study characteristics

We included 22 randomised controlled trials (studies in which participants are randomly assigned to treatment groups), published before 11 December 2020, with a total of 4299 people. There were differences in tumour location (gastrointestinal and pancreatic), tumour type, sample size, treatments, and quality of the research between the studies.

Key results

This analysis suggests, in general, a superiority of combination therapies, including somatostatin-like medications, in both gastrointestinal and pancreatic NETs. However, in pancreatic NETs, everolimus was the most effective therapy with the highest certainty of evidence compared to the other treatments. Furthermore, the results indicate that NET therapies have a broad range of risk for adverse events and effects on quality of life. Because disease is often advanced at presentation and treatment is often given with the intent to control and shrink disease, rather than be ultimately curative, treatment adverse events and quality of life are key considerations.

Quality of evidence

We rated the certainty of the evidence as high to low for the different therapies. An overall ranking of the treatments (and combinations) was not possible. In order to make an informed decision, advantages and disadvantages of each therapy, including its risks for adverse events and effects on quality of life, have to be balanced against each other. Evidence from this network meta-analysis (and underlying

RCTs) does not support any particular therapy (or combinations of therapies) with respect to patient-centred outcomes (e.g. overall survival and quality of life).

Summary of findings 1. Estimates of effects, ranking, and certainty of evidence for different treatment options compared with placebo for disease control in pancreatic neuroendocrine tumours (pNET)

Total studies: 9 Total participants: 1757	Included trials	Median follow-up (months)[1]	Relative effect (95% CI)	Anticipated absolute effects[2]		Certainty of evidence[3]	P-score[4]
				Disease control with intervention	*Disease control without intervention*		
Everolimus (3 RCTs; 632 participants)	Kulke 2017 (1); Salazar 2018; Yao 2011	17	**OR 3.29** (2.21 to 4.90)	80%	55%	Moderate*	0.83
Everolimus + SSA (2 RCTs; 589 participants)	Kulke 2017 (1); Pavel 2011	not reported	**OR 2.89** (1.61 to 5.19)	84%	65%	Moderate‡	0.73
Interferon + SSA (2 RCTs; 171 participants)	Arnold 2005; Faiss 2003	not reported	**OR 2.88** (1.16 to 7.13)	27%	11%	Very low*,‡,¶	0.71
Interferon (1 RCT; 66 participants)	Faiss 2003	not reported	**OR 2.58** (0.75 to 8.81)	35%	17%	Very low**,‡,§§	0.63
SSA (4 RCTs, 804 participants)	Arnold 2005; Caplin 2014; Faiss 2003; Pavel 2011	not reported	**OR 2.36** (1.43 to 3.88)	67%	47%	Moderate‡	0.56
Surufatinib (1 RCT; 172 participants)	Xu 2020 (p)	19	**OR 1.99** (1.02 to 3.88)	74%	59%	High	0.48

Sunitinib (1 RCT; 171 participants)	Raymond 2011 (1)	60	**OR 1.72** (0.91 to 3.27)	72%	60%	Low*,§	0.39
Placebo (4 RCTs; 957 participants)	Caplin 2014; Raymond 2011 (1); Xu 2020 (p); Yao 2011	27	Reference comparator	53%	-	Reference	0.12
Dactolisib (1 RCT; 62 participants)	Salazar 2018	not reported	**OR 0.56** (0.13 to 2.37)	61%	74%	Very low*,§§	0.06

Population: Patients with pNET
Interventions: Everolimus, everolimus + SSA, interferon + SSA, interferon, SSA, surufatinib, sunitinib, dactolisib
Comparator (reference): Placebo
Outcome: Disease control after 12 months
Abbreviation: OR, odds ratio; CI: confidence interval; SSA, somatostatin analogues
[1]Weighted average of trials reporting the median follow-up time
[2]Absolute effects with the intervention were calculated as weighted average over all treatment arms with the intervention. Absolute effects without the intervention were derived using the odds ratio from the network meta-analysis.
[3]Using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach
Downgraded for *risk of bias, †inconsistency, ‡indirectness, §imprecision, ¶intransitivity or #incoherence. Severe limitations are indicated by two symbols.
[4]The P-score measures the probability that a treatment is better than another treatment, averaged over all competing treatments.

Summary of findings 2. Estimates of effects, ranking, and certainty of evidence for different treatment options compared with placebo for progression-free survival in pancreatic neuroendocrine tumours (pNET)

Total studies: 10 **Total participants: 2113**	**Included trials**	**Median follow-up (months)[1]**	**Relative effect (95% CI)**	**Anticipated absolute effect[2]**		**Certainty of evidence[3]**	**P-score[4]**
				Median PFS with intervention (months)	***Median PFS without intervention (months)***		
Everolimus	Kulke 2017 (1); Salazar 2018; Yao 2011	17	**HR 0.36** (0.28 to 0.46)	12	4	Moderate*	0.75

(3 RCT; 632 participants)							
Interferon + SSA (2 RCTs; 468 participants)	Faiss 2003; Yao 2017	not reported	**HR 0.34** (0.14 to 0.80)	15	5	Very low**,‡	0.74
Everolimus + SSA (3 RCTs; 739 participants)	Kulke 2016; Kulke 2017 (1); Pavel 2011	not reported	**HR 0.38** (0.26 to 0.57)	16	6	Low‡	0.68
Bevacizumab + SSA (1 RCT; 402 participants)	Yao 2017	not reported	**HR 0.36** (0.15 to 0.89)	17	6	Very low**,‡,¶	0.65
Interferon (1 RCT; 66 participants)	Faiss 2003	not reported	**HR 0.41** (0.18 to 0.94)	not reported	-	Very low**,‡	0.58
Sunitinib (1 RCT; 171 participants)	Raymond 2011 (1)	60	**HR 0.42** (0.26 to 0.67)	11	5	Moderate*	0.56
Everolimus + bevacizumab + SSA (1 RCT; 150 participants)	Kulke 2016	not reported	**HR 0.48** (0.28 to 0.83)	17	8	Very low**,¶	0.42
Surufatinib (1 RCT; 172 participants)	Xu 2020 (p)	19	**HR 0.49** (0.32 to 0.76)	11	5	High	0.41
Dactolisib (1 RCT; 62 participants)	Salazar 2018	not reported	**HR 0.55** (0.25 to 1.21)	8	4	Low*,§	0.35

SSA (3 RCTs; 586 participants)	Faiss 2003; Pavel 2011; Phan 2015 (2)	not reported	**HR 0.51** (0.34 to 0.77)	11	6	Moderate	0.33
Placebo (4 RCTs; 844 participants)	Phan 2015 (2); Raymond 2011 (1); Xu 2020 (p); Yao 2011	27	Reference comparator	6	-	Reference	0.01

Population: Patients with pNET
Interventions: Bevacizumab + SSA, dactolisib, everolimus, everolimus + SSA, everolimus + bevacizumab + SSA, interferon, interferon + SSA, sunitinib, surufatinib, SSA
Comparator (reference): Placebo
Outcome: Progression-free survival
Abbreviation: HR, hazard ratio; PFS, progression-free survival; CI, confidence interval; SSA, somatostatin analogues.
[1]Weighted average of trials reporting the median follow-up time
[2]Absolute effects with the intervention were calculated as weighted average over all treatment arms with the intervention. Absolute effects without the intervention were derived using the hazard ratio from the network meta-analysis assuming an exponential distribution.
[3]Using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach
Downgraded for *risk of bias, †inconsistency, ‡indirectness, §imprecision, ¶intransitivity or #incoherence. Severe limitations are indicated by two symbols.
[4]The P-score measures the probability that a treatment is better than another treatment, averaged over all competing treatments.

Summary of findings 3. Estimates of effects, ranking, and certainty of evidence for different treatment options compared with placebo for disease control in gastrointestinal neuroendocrine tumours (GI-NET)

Total studies: 11 **Total participants: 1338**	**Included trials**	**Median follow-up (months)[1]**	**Relative effect (95% CI)**	**Anticipated absolute effects[2]**		**Certainty of evidence[3]**	**P-score[4]**
				Disease control with intervention	***Disease control without intervention***		
Bevacizumab + SSA (1 RCT; 44 participants)	Yao 2008 (1)	not reported	**OR 45.0** (3.32 to 609)	95%	32%	Very low*,††,‡,¶¶,§	0.91
177-Lu-DOTATATE + SSA (1 RCT; 229 participants)	Strosberg 2017	14	**OR 30.4** (8.19 to 113)	80%	12%	Very low**,¶,§	0.90

Everolimus + SSA (1 RCT; 39 participants)	Castellano 2013	not reported	**OR 15.1** (2.55 to 88.9)	63%	10%	Very low‡,¶,§	0.78
Interferon + SSA (4 RCTs; 283 participants)	Arnold 2005; Faiss 2003; Kölby 2003; Yao 2008 (1)	76	**OR 5.71** (1.90 to 17.2)	48%	14%	Very low*,††,‡,¶	0.60
Interferon (2 RCTs; 86 participants)	Faiss 2003; Öberg 1989	7	**OR 4.03** (0.86 to 18.8)	55%	23%	Very low**,‡,¶,§§	0.48
Surufatinib (1 RCT; 198 participants)	Xu 2020 (ep)	14	**OR 3.50** (1.21 to 10.1)	84%	61%	Moderate‡	0.45
SSA (7 RCTs; 796 participants)	Arnold 2005; Caplin 2014; Castellano 2013; Faiss 2003; Kölby 2003; Rinke 2009; Strosberg 2017	87	**OR 2.93** (1.36 to 6.32)	43%	21%	Moderate‡	0.37
Everolimus (1 RCT; 302 participants)	Yao 2016	21	**OR 2.53** (0.95 to 6.79)	82%	65%	Very low*,‡,§	0.35
Placebo (4 RCT; 789 participants)	Caplin 2014; Rinke 2009; Xu 2020 (ep); Yao 2016	35	Reference comparator	53%	-	Reference	0.11
Streptozocin + 5-FU (1 RCT; 20 participants)	Öberg 1989	12	**OR 0.13** (0.00 to 4.58)	40%	83%	Very low**,‡,¶,§§	0.04

Population: Patients with GI-NET
Interventions: 177-Lu-DOTATATE + SSA, bevacizumab + SSA, everolimus, everolimus + SSA, interferon, interferon + SSA, SSA, streptozocin + 5-FU, surufatinib
Comparator (reference): Placebo
Outcome: Disease control after 12 months
Abbreviation: OR, odds ratio; CI: confidence interval; SSA, somatostatin analogues
[1]Weighted average of trials reporting the median follow-up time
[2]Absolute effects with the intervention were calculated as weighted average over all treatment arms with the intervention. Absolute effects without the intervention were derived using the odds ratio from the network meta-analysis.
[3]Using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach
Downgraded for *risk of bias, †inconsistency, ‡indirectness, §imprecision, ¶intransitivity or #incoherence. Severe limitations are indicated by two symbols.
[4]The P-score measures the probability that a treatment is better than another treatment, averaged over all competing treatments.

Summary of findings 4. Estimates of effects, ranking, and certainty of evidence for different treatment options compared with placebo for progression-free survival in gastrointestinal neuroendocrine tumours (GI-NET)

Total studies: 9 **Total participants: 1311**	**Included trials**	**Median follow-up (months)[1]**	**Relative effect (95% CI)**	**Anticipated absolute effect[2]**		**Certainty of evidence[3]**	**P-score[4]**
				Median PFS with intervention (months)	***Median PFS without intervention (months)***		
177-Lu-DOTATATE + SSA (1 RCT; 229 participants)	Strosberg 2017	14	**HR 0.07** (0.02 to 0.26)	not reported	-	Very low**,¶,§	0.93
Everolimus + SSA (1 RCT; 39 participants)	Castellano 2013	not reported	**HR 0.12** (0.03 to 0.54)	30	3	Very low‡,¶,§	0.79
Bevacizumab + SSA (2 RCTs; 446 participants)	Yao 2008 (1); Yao 2017	not reported	**HR 0.18** (0.04 to 0.94)	16	3	Very low**,‡,¶¶,§	0.66
Interferon + SSA (3 RCTs; 512 participants)	Faiss 2003; Yao 2008 (1); Yao 2017	not reported	**HR 0.23** (0.06 to 0.93)	15	3	Very low**,‡,¶,§	0.56

Interferon (1 RCT; 66 participants)	Faiss 2003	not reported	**HR 0.27** (0.07 to 1.10)	not reported	-	Very low**,‡,¶,§§	0.49
Surufatinib (1 RCT; 198 participants)	Xu 2020 (ep)	14	**HR 0.33** (0.12 to 0.88)	9	3	Moderate‡	0.43
SSA (5 RCTs; 492 participants)	Castellano 2013; Dasari 2015; Faiss 2003; Rinke 2009; Strosberg 2017	96	**HR 0.34** (0.16 to 0.76)	10	3	High	0.39
Everolimus (1 RCT; 175 participants)	Singh 2018 (1)	21	**HR 0.56** (0.21 to 1.49)	13	7	Low*,§	0.23
Placebo (4 RCTs; 531 participants)	Dasari 2015; Rinke 2009; Singh 2018 (1); Xu 2020 (ep)	38	Reference comparator	8	-	Reference	0.03

Population: Patients with GI-NET
Interventions: 177-Lu-DOTATATE + SSA, bevacizumab + SSA, everolimus, everolimus + SSA, interferon, interferon + SSA, SSA, surufatinib
Comparator (reference): Placebo
Outcome: Progression-free survival
Abbreviation: HR, hazard ratio; CI: confidence interval; SSA, somatostatin analogues
[1]Weighted average of trials reporting the median follow-up time
[2]Absolute effects with the intervention were calculated as weighted average over all treatment arms with the intervention. Absolute effects without the intervention were derived using the hazard ratio from the network meta-analysis assuming an exponential distribution.
[3]Using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach
Downgraded for *risk of bias, †inconsistency, ‡indirectness, §imprecision, ¶intransitivity or #incoherence. Severe limitations are indicated by two symbols.
[4]The P-score measures the probability that a treatment is better than another treatment, averaged over all competing treatments.

BACKGROUND

Description of the condition

Neuroendocrine tumours (NETs), sometimes referred to as carcinoid tumours, are a heterogenous group of malignancies (cancers) that arise from cells of the endocrine (hormonal) and neurological systems. They have an estimated overall 20-year limited-duration prevalence (number of people alive on a certain day who were diagnosed with a NET within the previous 20-year period) of 171,321 and a yearly age-adjusted incidence of 6.98 cases per 100,000 according to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) 18 registry (Dasari 2017). A population-based study found a 6.4-fold increase in incidence between 1973 and 2012 (Dasari 2017). NETs are more common at higher age, with an incidence among people 65 years or older of 25 per 100,000. About 61.0% of NETs derive from the gastrointestinal tract or the pancreas (Lawrence 2011), and accordingly these tumours are called gastroenteropancreatic NET (GEP-NET). Other sites for primary NET include lungs, thyroid, ovaries, cervix, pituitary, and adrenal glands (Hallet 2015).

The relative frequency and annual incidence rate per 100,000 of GEP-NETs differ site by site and, in some cases, change over time and are different between countries and continents (Fraenkel 2014). NETs of the rectum are the most common in east Asia and the USA, while small intestinal NETs are the most common in males, and appendiceal NETs the most common in females in the UK (Fraenkel 2012; Fraenkel 2014). Racial discrepancies have been found in the US SEER registry, with small intestinal NETs being found more often in African-Americans than in the white population (DePalo 2019).

Most GEP-NETs are sporadic, but approximately 5% arise in the context of cancer predisposition syndromes (Clift 2020). Neuroendocrine tumours, especially those of the pancreas (pNET), may be associated with familial syndromes. Multiple endocrine neoplasia type 1 (MEN 1) is the most common familial syndrome associated with NET, while Von Hippel-Lindau syndrome, neurofibromatosis type-1 and tuberous sclerosis are rarer.

Depending on localisation and stage of the disease, they present with a broad clinical spectrum, from asymptomatic people with an incidental discovery on imaging to florid endocrinopathy. Up to 30% to 40% of GEP-NETs may be secretory (i.e. 'functional'), releasing a variety of hormones and hormone-like substances (Clift 2020). Serotonin-secreting small bowel NETs may lead to cardiac valve fibrosis (carcinoid heart disease) as a consequence of hormone hyper-secretion.

The diagnosis of GEP-NETs is usually based on a histopathology that demonstrates neuroendocrine features, such as positive immunohistochemical staining for synaptophysin and chromogranin A. The grading of GEP-NETs, on the other hand, is based on the mitotic index using Ki-67 immunohistochemistry (which estimates how many cells are dividing within a tumour and how quickly it might grow). The World Health Organization (WHO) classification divides NETs according to their proliferative activity into grade 1 (Ki-67 index ≤ 2%) and grade 2 (Ki-67 index 3% to 20%). Based on their morphological characteristics, grade 3 tumours are subdivided into well differentiated NET and poorly differentiated neuroendocrine carcinomas, both with Ki-67 index > 20% (Klimstra 2019). The grading aids in the prognostication of survival: the five-year survival rates of grade 1, 2 and 3 NETs are 96%, 73% and 28%, respectively (Ramage 2012).

Description of the intervention

Tumour growth, treatment and outcome vary considerably with the location of the primary lesions, as well as with their grade, extension, and stage (Lawrence 2011; Modlin 2008; Yao 2008 (2)). A broad spectrum of therapeutic options permits staged disease management with various treatment combinations and sequencing. This approach, however, requires a highly interdisciplinary and dynamic approach, which typically involves physicians of various specialties who work in concert to manage these often-complex cases and select a treatment strategy from an array of available options.

Management strategies depend on primary tumour, locoregional and distant metastases, differentiation, tumour-related symptoms, syndromes and presence of carcinoid heart disease. Depending on primary tumour size and site, NETs are treated surgically whenever feasible, as this is the only potentially curative treatment (Yao 2008 (2)). In metastatic, well differentiated NETs, somatostatin analogues (SSA), and interferon alpha (IFN) as a possible second-line therapy, are a cornerstone in the palliative setting, as effective means of improving quality of life (QoL) and delaying disease progression (Cives 2014; Clift 2020). More recently, molecularly targeted drugs like the mTOR-inhibitor everolimus, the multi-targeted receptor tyrosine kinase inhibitor sunitinib, and the vascular endothelial growth factor (VEGF) antibody bevacizumab have been introduced into the clinical setting following trials demonstrating efficacy in people with progressive NET (Kunz 2013; Pavel 2016; Yao 2017). The radiolabelled somatostatin receptor ligand lutetium-177-DOTATATE also recently demonstrated a benefit over treatment with somatostatin analogues alone in people with progressive NET (Strosberg 2017). Liver-directed therapies further broaden the therapeutic landscape (Pavel 2016). In advanced grade 3 pNET and advanced symptomatic or progressive grade 1 or 2 pNET, systemic chemotherapy with streptozocin- or temozolomide-based regimens is the first choice of treatment. In grade 3 NEC, platinum-based chemotherapy is recommended as a first-line therapy (Pavel 2016).

Why it is important to do this review

Several available therapies have demonstrated efficacy in terms of disease control and/or progression-free survival in randomised controlled trials (RCTs). However, translation of these results into improved care faces several challenges, as several therapies were compared with placebo only and a direct comparison of the most pertinent therapies is incomplete (Kaderli 2019). In a previous systematic review and network meta-analysis on pNETs and neuroendocrine tumours of the gastrointestinal tract (GI-NETs), we found several monotherapies that were superior to placebo, including everolimus, interferon, and sunitinib in pNETs and somatostatin analogues in pNETs and GI-NETs (Kaderli 2019). Furthermore, the results suggested a superiority of combination therapies, especially those including somatostatin analogues. On the other hand, NET therapies have a broad range of risk for adverse events and effects on QoL, which need to be considered while choosing the appropriate treatment. A systematic comparison of benefits and harms of all currently available therapeutic modalities will allow informed clinical decision-making for clinicians, patients and policy makers.

Furthermore, there is ongoing research in the treatment of NETs. Surufatinib has demonstrated a higher progression-free survival in GI-NETs in the SANET-ep trial (Xu 2020 (ep)) and in pNET in the SANET-p trial (Xu 2020 (p)). New results for axitinib and somatostatin analogue are expected in GI-NET (AXINET trial, NCT01744249), for everolimus and streptozocin plus fluorouracil in pNET (SEQTOR trial, NCT02246127), and for lutetium-177 (^{177}Lu)-DOTATATE and everolimus both in GI-NET and pNET (COMPETE trial, NCT03049189). It is, therefore, vital to provide a regularly updated systematic review and network meta-analysis for clinical decision-making based on the best available and most recent evidence.

OBJECTIVES

To evaluate the safety and efficiency of therapies for NETs, to guide clinical decision-making, and to provide estimates of relative efficiency of the different treatment options (including placebo) and rank the treatments according to their efficiency based on a network meta-analysis.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs), including randomised controlled cross-over trials.

If a post hoc subgroup analysis was available and reported disease control after 12 months and/or progression-free survival for either pNET or GEP-NET only, the subgroup analysis was used for the network meta-analysis instead of the main study including more than one type of NETs.

Types of participants

People of any age with any type and any stage of GEP-NETs.

Types of interventions

We included RCTs comparing at least two treatments of any kind (including usual care or placebo) in NETs, administered in any way.

Examples of treatments include the mechanistic target of rapamycin inhibitor everolimus (Yao 2016), the multi-targeted receptor tyrosine kinase inhibitor sunitinib (Raymond 2011), the vascular endothelial growth factor (VEGF) antibody bevacizumab (Yao 2017), the radiolabelled somatostatin analogue lutetium-177 (177Lu)-dotatate (Strosberg 2017), and new combinations of previously established therapies (Pavel 2011). Several therapies were compared only with placebo, while others were directly compared.

Every individual drug or drug combination, as well as placebo, represent individual nodes in the network meta-analysis. Due to the low number of included studies, we grouped together all different somatostatin analogues, as well as all different intervention doses, modalities, and administration frequencies.

Types of outcome measures

Primary outcomes

1. Disease control after 12 months
2. Progression-free survival

Secondary outcomes

1. Overall survival
2. Occurrence of adverse events according to the treatment applied (grades 3 to 4, any grade)
3. Quality of life (QoL)

Disease control is defined as the sum of complete response, partial response and stable disease, or as the total minus the number disease progressions. Progression-free survival is the length of time during and after the treatment, that a patient lives with the disease, but it does not grow. We used unblinded, investigator-assessed progression-free survival outcomes. Adverse events were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI 2010): Grade 1 corresponds to mild, grade 2 to moderate, grade 3 to severe or medically significant, and grade 4 to life-threatening adverse events. Effects on QoL were quantified based on the *QoL Questionnaire C30 of the European Organization for Research and Treatment of Cancer* (EORTC QLQ-30) (Aaronson 1993).

Search methods for identification of studies

Electronic searches

We identified trials through systematic searches of the following bibliographic databases on 11 December 2020:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2020, Issue 12) in the Cochrane Library;
- MEDLINE via Ovid (January 1947 to 11 December 2020);
- Embase.com (January 1947 to 11 December 2020).

In addition, we checked trial registries (ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform Search Portal [apps.who.int/trialsearch/]) for ongoing or unpublished eligible trials and manually searched for abstracts from scientific and clinical meetings related to NETs in 2019 and 2020 (annual ENETS conference and neuroendocrine tumour symposium of the NANETS).

We searched all databases from 1 January 1947, until present, and imposed no restriction on language of publication (Appendix 1; Appendix 2; Appendix 3).

Searching other resources

We scanned the reference lists of the included RCT reports and relevant review articles for additional references.

Data collection and analysis

Selection of studies

With two review authors working in duplicate, we independently screened all abstracts and obtained the full-text report of potentially relevant studies. Subsequently, we screened all potentially relevant studies in the same way. Any discordance was resolved by a third review author.

Data extraction and management

We used a data collection form for study characteristics and outcome data which has been piloted in our previous systematic

review and network meta-analysis on therapeutic options for neuroendocrine tumours (Kaderli 2019). One of the review authors extracted study characteristics from included studies, and a second review author verified the extractions. We extracted the following study characteristics.

1. Characteristics of included trials: first author, year of publication, study origin, type of treatments, median duration and median follow-up of each treatment, percentage of people with complete follow-up, availability of a sample size calculation, and number of participants randomised for each treatment.
2. Participant data: separately for each treatment: primary tumour site, tumour grading, presence of metastases and functional tumours, percentage of female participants and the participants' median/mean age; main primary tumour (pNET and/or GI-NET) for all treatments.
3. Clinical outcomes: complete response, partial response, stable disease, disease control, disease progression, investigator-assessed progression-free survival, median overall survival, occurrence of adverse events (grade 3 to 4, any grade), and QoL.

Any discordance was resolved by a third review author. Data were entered into Review Manager software (RevMan 2014) and checked by a second review author for accuracy.

Due to the well-defined patient characteristics, we did not expect significant effect modifiers and, due to the low number of included studies, we could not systematically analyse effect modifiers.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias for each RCT, using the Cochrane risk of bias tool (Higgins 2011), which utilises the following domains.

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Completeness of outcome data
6. Selectivity of reporting
7. Other bias (including baseline imbalance, protocol deviations, inappropriate influence of funders)

We provided a summary risk of bias assessment for each study using the method outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Each domain was rated as low (bias is unlikely to seriously alter the results), high (bias is likely to seriously weaken confidence in results), or unclear risk of bias. All discordance was resolved by a third review author.

Measures of treatment effect

We used odds ratios as effect measures for disease control after 12 months and hazard ratios as effect measures for progression-free survival, both accompanied by 95% confidence intervals (95% CIs). We applied a continuity correction for studies with a zero cell count by adding 0.5 to all cell frequencies. We summarised all results using forest plots with combined effect estimates and size of squares proportional to the inverse of the standard errors. Due to the low number of included studies and the heterogeneity of secondary outcomes, we presented these outcomes for each intervention (if available) using descriptive statistics — i.e. number and percentage of adverse events, and mean and standard deviation of the change of QoL.

We ranked treatments based on P scores, measuring the extent of certainty that a treatment is better than another one, averaged over all competing treatments (Rücker 2015).

Unit of analysis issues

The analysis was made at the individual allocation level.

Multi-arm trials were included in the network meta-analysis. The correlation of treatment effects on different comparisons was accounted for by re-weighting all comparisons of each multi-arm study (Rücker 2012; Rücker 2014).

We included cross-over trials in the qualitative analysis. However, they were excluded from the network meta-analysis due to the inappropriateness of the study design: including only the first intervention period of a cross-over trial discards more than half of the information in the study.

Dealing with missing data

We contacted authors of included RCT reports for information on unreported outcomes and missing outcome data in their studies.

If a RCT report did not report hazard ratios and further data could not be obtained by contacting authors, we estimated the hazard ratios from reconstructed Kaplan-Meier curves (if available) by using a Cox proportional hazard model.

Assessment of heterogeneity

We assessed heterogeneity using all pairwise comparisons available from more than one trial. We calculated the between-study variance T^2, the within-design component of Cochran's Q (i.e. the weighted sum of squared differences between pairwise comparisons from multiple trials) and the associated I^2 (percentage of variation across studies due to heterogeneity rather than chance). If quantification of heterogeneity was not possible (i.e. if there was no comparison done in more than one trial), we fitted fixed-effect models; otherwise, we used random-effects models.

We assessed homogeneity and transitivity based on the distribution of neuroendocrine tumour types, and the differences in doses and application route, especially for somatostatin analogues.

We assessed inconsistency using closed loops within the network (if any) and calculated the between-design component of Cochran's Q and the associated I^2. In addition, we performed a netsplit analysis and compared direct and indirect estimates via a ratio of odds or hazard ratios.

We calculated the total Cochran's Q as the sum of between- and within-designs component and the associated I^2.

Assessment of reporting biases

To assess the risk for reporting bias, we first searched for a protocol for each of the included studies. For this, we went through the reference lists of corresponding published articles. If there was no reference to a protocol, we searched PubMed, Embase, and the internet for a protocol. If a protocol was available,

we compared the mentioned outcomes and planned statistical analyses in the protocol with those in the published report. If no protocol was available, we used information from a corresponding registry entry of the included study to compare planned outcomes and analyses with those in the published report. If neither a protocol, nor a registry entry was available, we compared the outcomes and described analyses in the methods section of the published report with those reported in the results section. Any unexplained differences between the protocol, registry entry, or methods section and the reported results provided evidence for an increased risk of reporting bias of an included study.

If there were 10 or more included studies for individual pairwise meta-analyses, we created funnel plots for visual inspection to detect potential asymmetry.

Data synthesis

We separately analysed two different outcomes (disease control and progression-free survival) and two types of NET (pNET and GI-NET) in four network meta-analyses. The NET types were distinguished to ensure that the selected studies were similar except for the interventions being compared. If a study included several NET types, we included the respective subgroup analyses (if available): for pNET, one subgroup analysis was included for the analysis of progression-free survival (Phan 2015 (2) instead of Caplin 2014) and, for GI-NET, one subgroup analysis was included for the analysis of disease control and progression-free survival (Castellano 2013 instead of Pavel 2011) and two subgroup analyses were included for the analysis of progression-free survival (Dasari 2015 instead of Caplin 2014 and Singh 2018 (1) instead of Yao 2016). Otherwise, we relied on expert opinion whether or not to include the study and used sensitivity analyses to assess the effect of the decision.

Before including an intervention in the network meta-analysis, we assessed the respective study populations critically in terms of the transitivity assumption. Interventions only given to a subset of participants (i.e. those critically ill) were not included in a sensitivity analysis. However, since the network is currently very sparse, the benefit of additional studies might outweigh a certain risk of violation of the transitivity assumption. The comparison among all interventions (including placebo) were of interest and we would not define a decision and a supplementary set. However, if more data become available, we might focus on a specific set of interventions.

Because the network is sparse, we merged similar interventions, i.e. different doses, administration intervals and routes of application of the same compound. When more data become available, we will consider splitting nodes if the effects are suspected to be different.

We performed the network meta-analyses with a frequentist approach using R-package (R Core 2019) netmeta (Rücker 2021). If quantification of heterogeneity was possible, i.e. if there were pairwise comparisons included in more than one trial, we used random-effects models. Otherwise, we used fixed-effect models. Validity of the network in terms of consistency was assessed quantitatively by comparing direct and indirect estimates for each loop of the network and qualitatively using GRADE (as described in section Assessment of heterogeneity).

Subgroup analysis and investigation of heterogeneity

In view of the small number of RCTs included in this review, we refrained from any subgroup analysis, including subgroup analysis based on tumour grading, since the separate analysis for each treatment included in a RCT was frequently missing.

If there was evidence for heterogeneity, we assessed participant and trial characteristics for a potential source of the heterogeneity.

Sensitivity analysis

Currently, the network is very sparse and we were not able to undertake sensitivity analyses. If sufficient trials would have been identified, we would have considered several sensitivity analyses for the primary outcomes. We would, for example, only use low risk of bias trials (trials without a high risk for selection, performance, detection, attrition, reporting or other biases), exclude trials with a mixture of different types of NETs and use alternative or no merging of nodes. We would have also considered different analytical approaches, such as fixed-effect only, or a Bayesian instead of the specified frequentist approach (e.g. using R package BUGSnet (Béliveau 2019)).

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach to assess confidence in estimates of effect (certainty of evidence) associated with specific comparisons, including estimates from direct, indirect, and final network meta-analysis (Brignardello-Petersen 2018; Puhan 2014; Salanti 2014). Our confidence assessment addressed risk of bias (limitations in study design and execution), inconsistency (heterogeneity of estimates of effects across trials), indirectness (differences in population, interventions, or outcomes to the target of the network meta-analysis) and imprecision (e.g. wide 95% confidence intervals including or close to the null effect). Limitations in any of these domains resulted in a decrease of the certainty of evidence from high to moderate, low, or very low-certainty by -1 (serious concern) or -2 (very serious concern). We based indirect evidence on the most dominant loops (i.e. the shortest path between two treatments) and potentially rated it down for intransitivity (differences in study characteristics that may modify treatment effect in the direct comparisons along the path). We obtained the final network meta-analysis confidence rating from the higher of the direct and indirect rating excluding imprecision and we rated it down for imprecision and incoherence (difference between direct and indirect estimates).

All studies and study arms used for the network meta-analyses had included adult people with advanced GEP-NET that were in need of and eligible for systematic therapies, supporting the transitivity assumption of the network meta-analyses.

In the summary of findings tables, we included estimates of effects, ranking and certainty of evidence for different treatment options compared with placebo for disease control and progression-free survival in pNET and GI-NET.

RESULTS

Description of studies

See: Characteristics of included studies and Characteristics of excluded studies.

Results of the search

In our previous systematic review and network meta-analysis on pNETs and GI-NETs with the same search methods, we included 38 studies in the qualitative synthesis (30 primary studies and 8 subgroup analyses) (Kaderli 2019). The previously published searches on 27 November 2015 and 2 March 2018 led to the identification of 7243 records (Kaderli 2019). Following de-duplication across the databases, the combined total yield of the updated search on 11 December 2020 was 1058 records:

- CENTRAL: 255 records
- MEDLINE (Ovid): 546 records
- Embase: 257 records

Two additional records were added through scanning the reference lists of included RCT reports. After reading the abstracts, we excluded 991 records because they did not match the inclusion criteria. After assessing the full text, we excluded 23 records. In all, we included 55 studies in the qualitative analysis (39 primary RCTs and 16 subgroup analyses). A total of 22 studies reported disease control and/or progression-free survival and were included in the network meta-analyses (see Figure 1).

Figure 1. Study flow diagram.

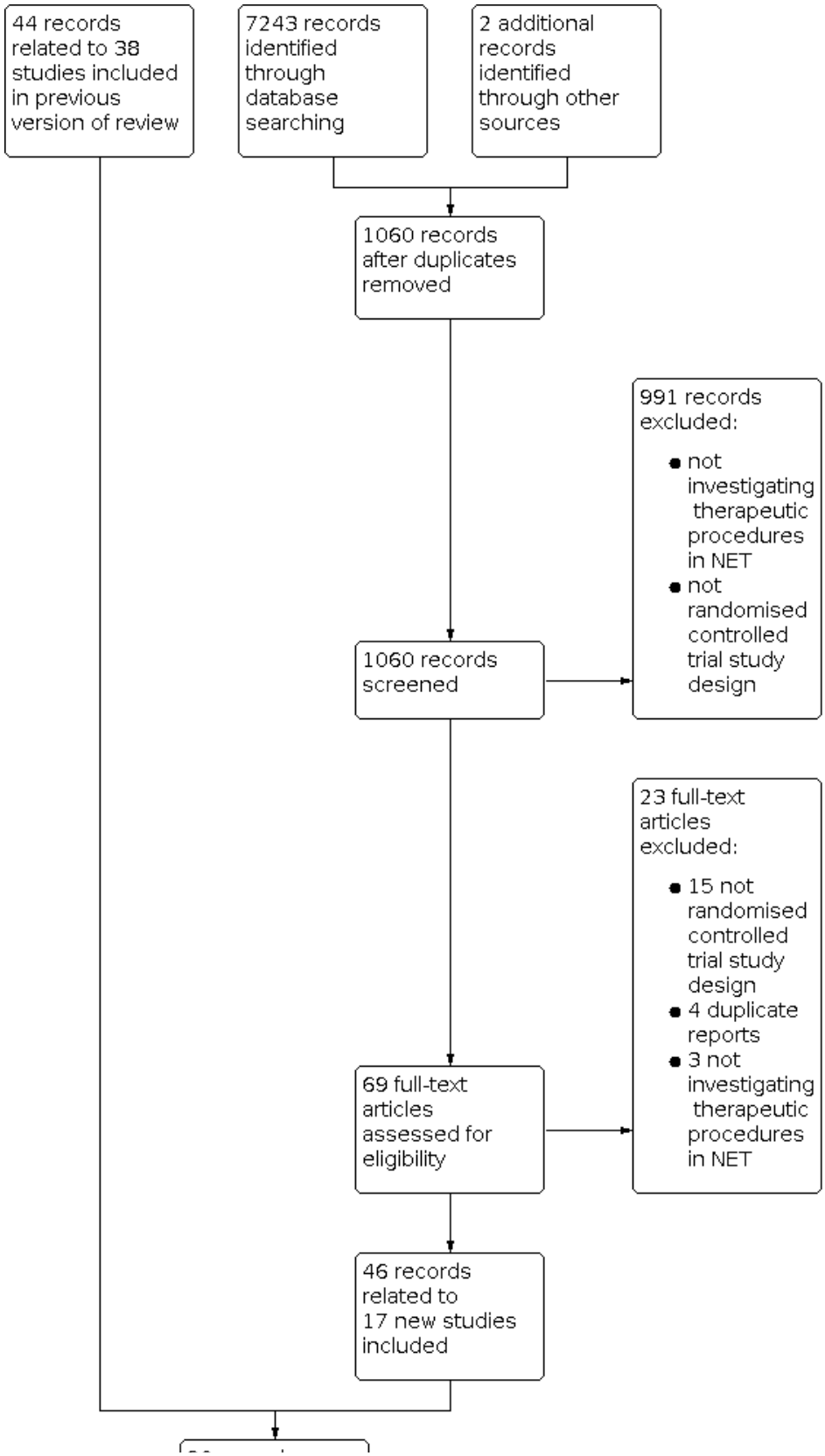
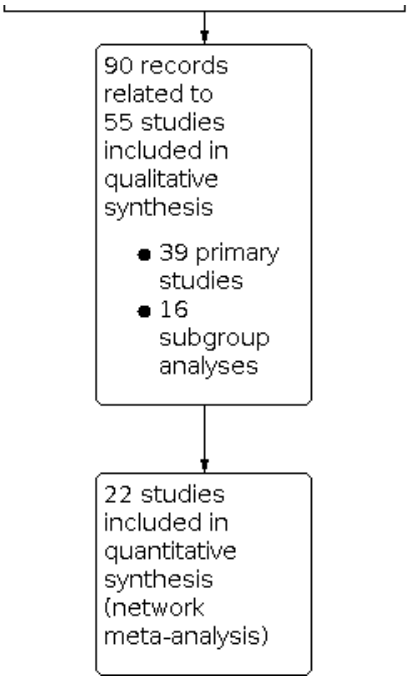


Figure 1. (Continued)



Included studies

We included 55 studies in 90 records in the qualitative analysis, reporting 39 primary RCTs (Arnold 2005; Bergsland 2020; Caplin 2014; Elf 2018; Faiss 2003; Jacobsen 1995; Kölby 2003; Kulke 2016; Kulke 2017 (1); Kulke 2017 (2); Lange 1992; Lepage 2020; Liu 2020; Maire 2012; Meyer 2014; Moertel 1980; Moertel 1992; O'Toole 2000; Öberg 1989; Pavel 2011; Pavel 2018 (1); Pavlakis 2020; Raymond 2011 (1); Rinke 2009; Sakata 2006; Salazar 2018; Saslow 1998; Soulen 2020; Strosberg 2017; Van Der Zwan 2018; Vinik 2016; Wolin 2015; Xu 2020 (ep); Xu 2020 (p); Yao 2008 (1); Yao 2011; Yao 2016; Yao 2017; Zhang 2020) and 16 subgroup analyses (Anthony 2012; Castellano 2013; Dasari 2015; Di Gialleonardo 2020; Fisher 2016; Ito 2012; Lombard-Bohas 2015; Phan 2015 (1); Phan 2015 (2); Pusceddu 2018; Raymond 2011 (2); Singh 2018 (1); Strosberg 2011; Strosberg 2020; Wolin 2016; Yao 2019) (see Characteristics of included studies for details. Overall, 4654 patients were recruited and 26 different therapies were evaluated, including biotherapies, chemotherapies, targeted drugs, locoregional therapies, surgical treatment, and targeted radiopeptide therapy.

A total of 22 RCTs, which included 4299 patients, reported disease control and/or progression-free survival and were included in the network meta-analysis (Arnold 2005; Caplin 2014; Castellano 2013; Dasari 2015; Faiss 2003; Kölby 2003; Kulke 2016; Kulke 2017 (1); Öberg 1989; Pavel 2011; Phan 2015 (2); Raymond 2011 (1); Rinke 2009; Salazar 2018; Singh 2018 (1); Strosberg 2017; Xu 2020 (ep); Xu 2020 (p); Yao 2008 (1); Yao 2011; Yao 2016; Yao 2017).

Eighteen of 22 RCTs included in the network meta-analysis were industry-sponsored (Arnold 2005; Caplin 2014; Castellano 2013; Dasari 2015; Faiss 2003; Kulke 2017 (1); Pavel 2011; Phan 2015 (2); Raymond 2011 (1); Rinke 2009; Salazar 2018; Singh 2018 (1); Strosberg 2017; Xu 2020 (ep); Xu 2020 (p); Yao 2008 (1); Yao 2011; Yao 2016).

Excluded studies

During the first phase of record selection, we screened and excluded 991 records, which were not investigating therapeutic procedures in NET or did not fulfil the criteria of an RCT. Twenty-three of the remaining 69 records were excluded after assessing the full-text articles. They did not fulfil the criteria of an RCT, were duplicate reports or were not investigating therapeutic procedures in NET (see Characteristics of excluded studies for details).

Risk of bias in included studies

Summaries of the risk of bias for each domain and as percentages across all studies are presented in Figure 2 and Figure 3.

Figure 2.

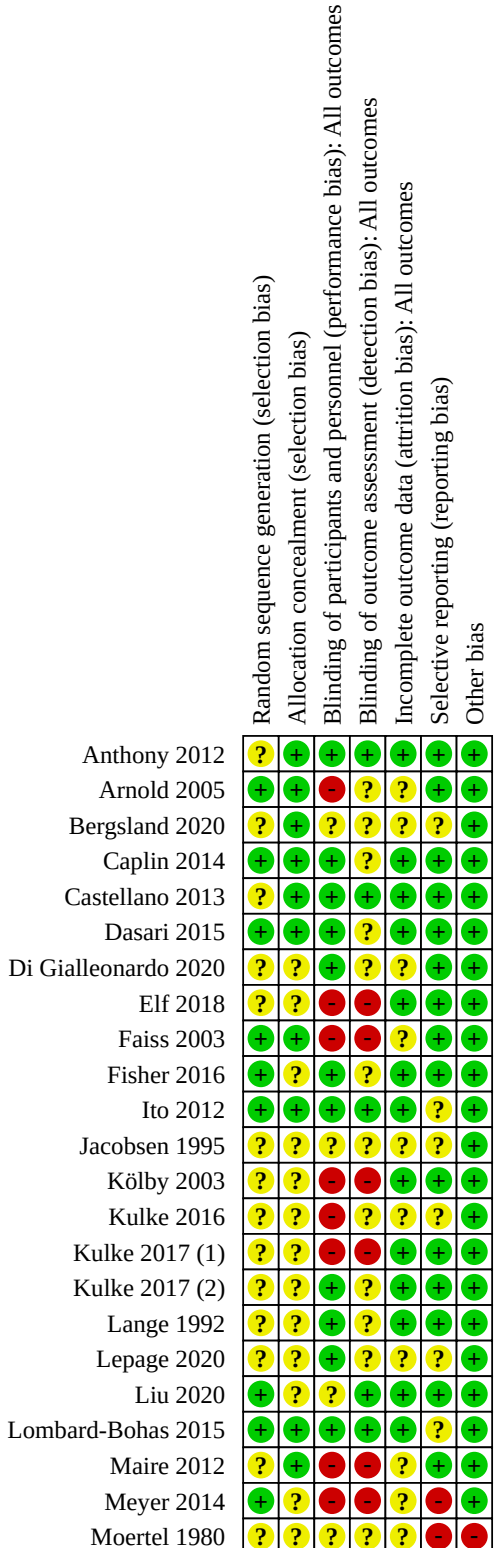


Figure 2. (Continued)

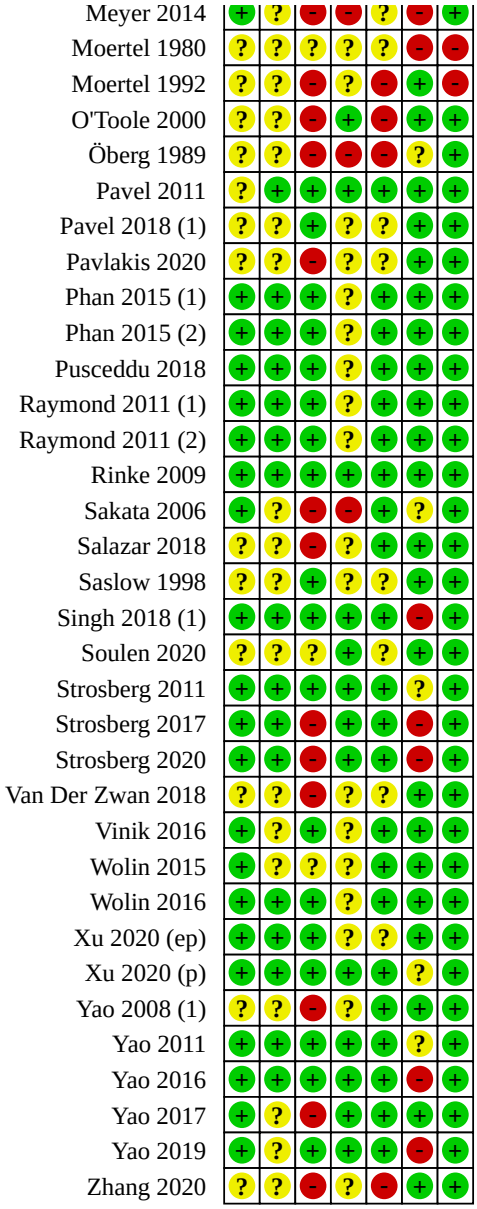
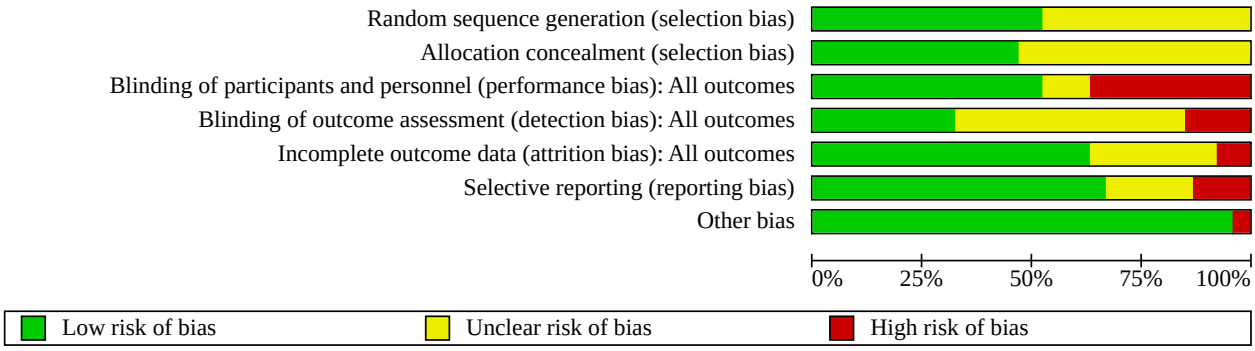


Figure 3.



Allocation

Random sequence generation

Twenty-nine studies described a random component in the sequence generation process and were at low risk of selection bias. The other 26 studies had a randomised controlled trial study design; but in 25 studies there was no further report on the sequence generation process and in one study the randomisation was performed by the study drug supplier (Jacobsen 1995). For these studies, we judged the risk of selection bias as unclear.

Allocation concealment

Twenty-five studies reported on the method to conceal allocation and were at low risk of selection bias. Twenty-eight studies provided no further information addressing allocation concealment and were considered to be at unclear risk of selection bias. Two studies without information on allocation concealment and identical numbers of people in all treatment groups were considered to be at unclear risk of selection bias (Kulke 2017 (2); Yao 2008 (1)).

Blinding

Blinding of participants and personnel (performance bias)

Twenty-nine studies were double-blinded and were at low risk of performance bias. Six studies (Kulke 2017 (1); Pavlakis 2020; Strosberg 2017; Strosberg 2020; Yao 2017; Zhang 2020) were designed as open-label studies and in 14 studies participants and/or personnel were not blinded. They were considered to be at high risk of performance bias. Six studies provided no information and were at unclear risk of performance bias.

Blinding of outcome assessment (detection bias)

Eighteen studies reported blinding of outcome assessors and were at low risk of detection bias. Of the remaining studies, 29 studies were at unclear risk of detection bias due to missing information on the blinding of outcome assessment and eight studies were at high risk of detection bias due to a lack of evidence for a blinding of the outcome assessment.

Incomplete outcome data

Thirty-five studies were at low risk and 16 studies were at unclear risk of attrition bias due to missing information. In three studies, a significant number of people were excluded after randomisation (Moertel 1992; O'Toole 2000; Zhang 2020) and in one study (Öberg 1989) a group cross-over was performed without additional information, whether intention-to-treat or analysis per-protocol was performed. These four studies were considered to be at high risk of attrition bias.

Selective reporting

Thirty-two studies published a study protocol or reported all results of the endpoints stated in the methods section and were at low risk of reporting bias. Sixteen studies provided little information on primary or secondary endpoints and their definition and were judged to be at low or unclear risk for reporting bias, depending on a study-level judgement. In seven studies, not all stated endpoints were reported (Meyer 2014; Moertel 1980; Singh 2018 (1); Strosberg 2017; Strosberg 2020; Yao 2016; Yao 2019). Hence, we judged the risk of reporting bias for these studies as high.

Other potential sources of bias

Two studies were at high risk for other potential sources of bias due to the use of investigator-dependent measurement methods (Moertel 1980; Moertel 1992).

Effects of interventions

See: **Summary of findings 1** Estimates of effects, ranking, and certainty of evidence for different treatment options compared with placebo for disease control in pancreatic neuroendocrine tumours (pNET); **Summary of findings 2** Estimates of effects, ranking, and certainty of evidence for different treatment options compared with placebo for progression-free survival in pancreatic neuroendocrine tumours (pNET); **Summary of findings 3** Estimates of effects, ranking, and certainty of evidence for different treatment options compared with placebo for disease control in gastrointestinal neuroendocrine tumours (GI-NET); **Summary of findings 4** Estimates of effects, ranking, and certainty of evidence for different treatment options compared with placebo for progression-free survival in gastrointestinal neuroendocrine tumours (GI-NET)

Treatment efficacy in pNETs

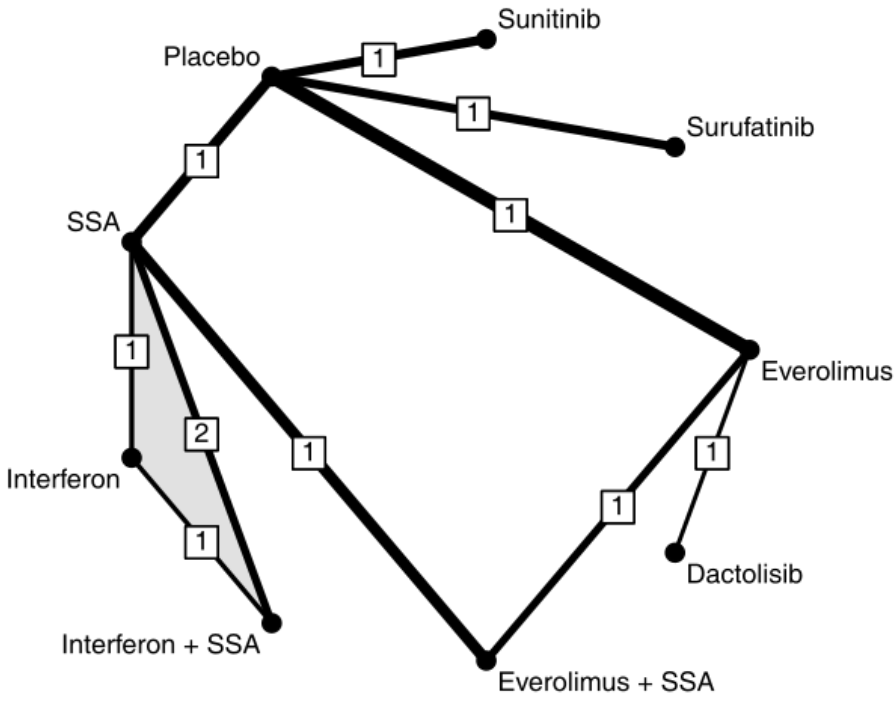
Nine RCTs (Arnold 2005; Caplin 2014; Faiss 2003; Kulke 2017 (1); Pavel 2011; Raymond 2011 (1); Salazar 2018; Xu 2020 (p); Yao 2011) compared disease control rates for nine different therapies in pNETs (Figure 4). The network meta-analysis found that single therapy with everolimus and combination therapies

with a somatostatin analogue were highly effective. Specifically, everolimus (P score, 0.83), everolimus plus a somatostatin analogue (P score, 0.73), and interferon plus a somatostatin analogue (P score, 0.71) achieved the highest disease control rates, followed by single treatment with interferon (P score, 0.63), somatostatin analogues (P score, 0.56), surufatinib (P score, 0.48), sunitinib (P score, 0.39), placebo (P score, 0.12), and dactolisib (P score, 0.06). All therapies except interferon, sunitinib, and dactolisib showed significantly higher disease control rates than placebo (Figure 4, Table 1).

Figure 4. Treatment efficacy in pNET. Network plot (A) and Forest plot (B) for disease control in pNET. The thickness of the edges in the network plots is proportional to the inverse standard errors of the pairwise comparisons, and the numbers indicate the number of studies. One three-arm study is marked by shading. Each section in the Forest plots refers to one treatment (in bold) compared to all others. An odds ratio larger than one indicates increased disease control of the bold treatment. A hazard ratio smaller than one indicates a reduced risk for progression for the bold treatment. All therapies are listed in order of their P-scores, with the most effective therapy on top. Heterogeneity was assessed by the between-study variance tau^2, Cochran's Q with a P value, and I^2. N refers to the total number of patients, and n to the number of patients with disease control. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to rate the quality of evidence of estimates from pairwise

and network meta-analysis. The final network meta-analysis GRADE evidence quality corresponds to *very low, **low, ***moderate, and ****high. SSA refers to somatostatin analogues.

A Network Disease Control in pNET



B Disease Control in pNET

	n/N	Odds ratio (95% CI)	GRADE
Everolimus vs	**256/319**		
Everolimus + SSA	248/295	1.14 (0.63 to 2.04)	*
Interferon + SSA	20/75	1.14 (0.44 to 2.95)	*
Interferon	8/23	1.27 (0.36 to 4.49)	*
SSA	260/387	1.40 (0.79 to 2.46)	**
Surufatinib	84/113	1.65 (0.76 to 3.61)	**
Sunitinib	62/86	1.91 (0.90 to 4.06)	**
Placebo	238/450	3.29 (2.21 to 4.90)	***
Dactolisib	19/31	5.89 (1.46 to 23.7)	**
Everolimus + SSA vs	**248/295**		
Everolimus	256/319	0.88 (0.49 to 1.58)	*
Interferon + SSA	20/75	1.00 (0.41 to 2.46)	*
Interferon	8/23	1.12 (0.33 to 3.79)	*
SSA	260/387	1.23 (0.77 to 1.97)	***
Surufatinib	84/113	1.46 (0.60 to 3.54)	*
Sunitinib	62/86	1.68 (0.71 to 4.00)	*
Placebo	238/450	2.89 (1.61 to 5.19)	***
Dactolisib	19/31	5.18 (1.14 to 23.5)	*
Interferon + SSA vs	**20/75**		
Everolimus	256/319	0.88 (0.34 to 2.26)	*
Everolimus + SSA	248/295	1.00 (0.41 to 2.43)	*
Interferon	8/23	1.12 (0.36 to 3.47)	*
SSA	260/387	1.22 (0.57 to 2.61)	*

Figure 4. (Continued)

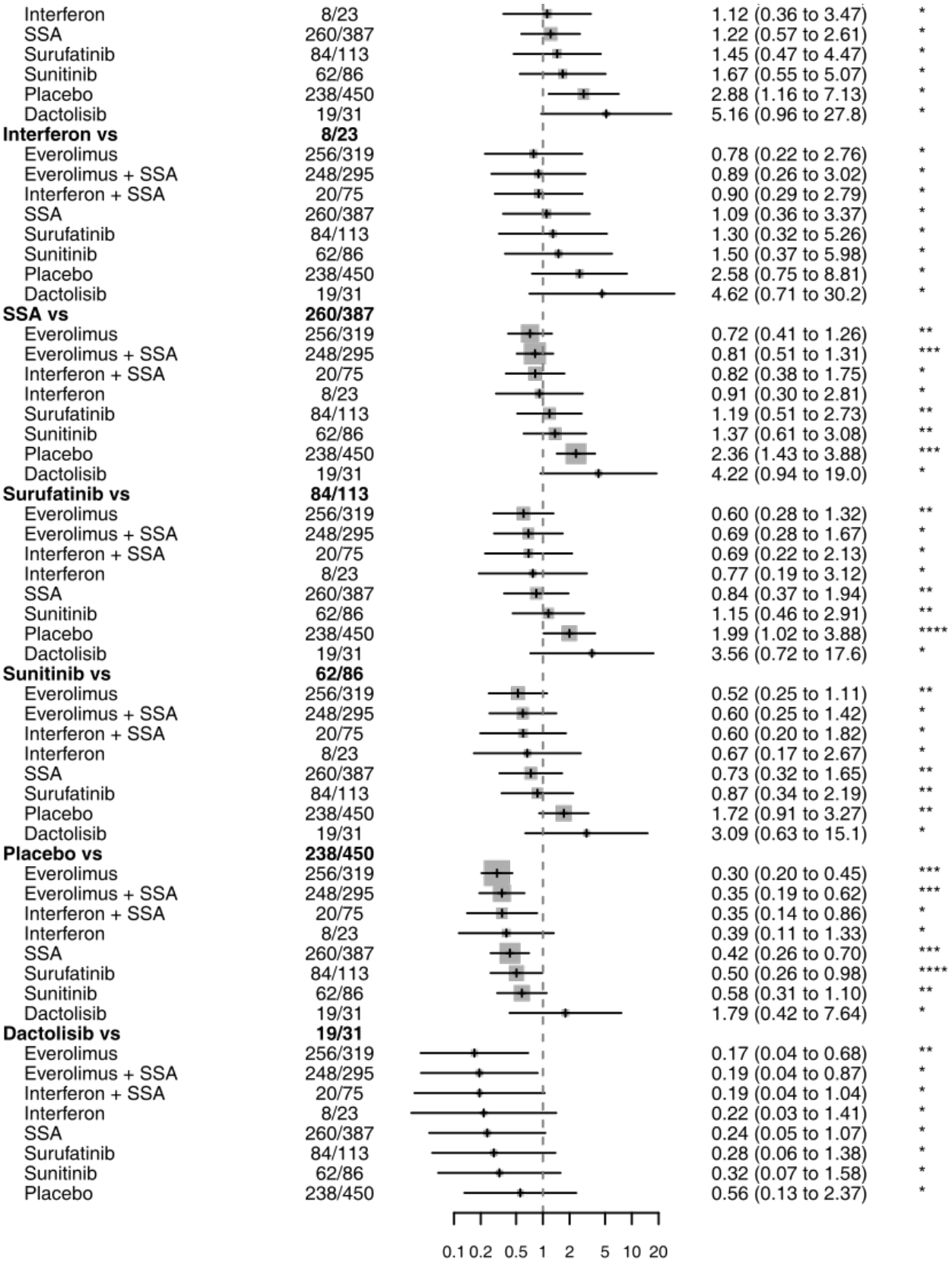
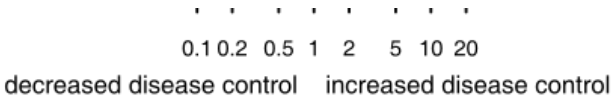


Figure 4. (Continued)



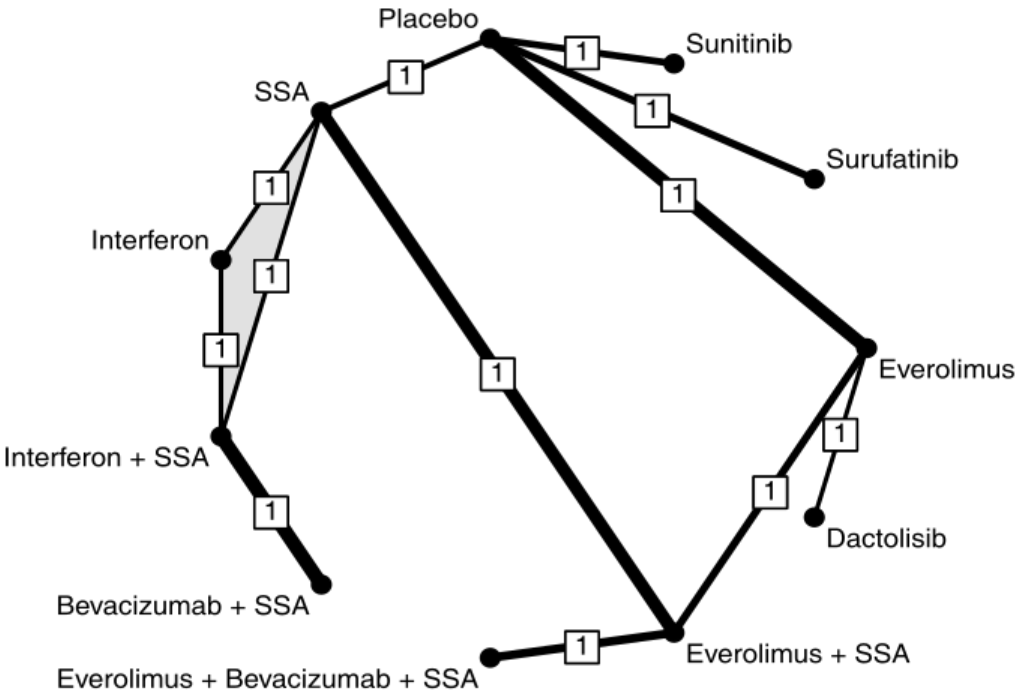
Tau^2 = not estimable
I^2 = not estimable
Cochran's Q = 1.11 (2 df), P = 0.58

Ten RCTs with one 3-arm trial (Faiss 2003; Kulke 2016; Kulke 2017 (1); Pavel 2011; Phan 2015 (2); Raymond 2011 (1); Salazar 2018; Xu 2020 (p); Yao 2011; Yao 2017) assessed progression-free survival for 11 different therapies in pNETs (Figure 5). Again, the network meta-analysis found that single therapy with everolimus and combination therapies with a somatostatin analogue were highly effective, with HRs between 0.34 and 0.38 versus placebo. The lowest hazard for progression was found after treatment with everolimus (P score, 0.75), followed by interferon plus a somatostatin analogue (P score, 0.74), everolimus plus a somatostatin analogue (P score, 0.68), bevacizumab plus a somatostatin analogue (P score, 0.65), interferon (P score, 0.58), sunitinib (P score, 0.56), everolimus plus bevacizumab plus a somatostatin analogue (P score, 0.42), surufatinib (P score, 0.41), dactolisib (P score, 0.35), somatostatin analogues (P score, 0.33), and placebo (P score, 0.01). All therapies but dactolisib significantly reduced the hazard for progression compared with placebo (Figure 5, Table 2).

Figure 5. Treatment efficacy in pNET. Network plot (A) and Forest plot (B) for progression-free survival in pNET. The thickness of the edges in the network plots is proportional to the inverse standard errors of the pairwise comparisons, and the numbers indicate the number of studies. One three-arm study is marked by shading. Each section in the Forest plots refers to one treatment (in bold) compared to all others. An odds ratio larger than one indicates increased disease control of the bold treatment. A hazard ratio smaller than one indicates a reduced risk for progression for the bold treatment. All therapies are listed in order of their P-scores, with the most effective therapy on top. Heterogeneity was assessed by the between study variance tau^2, Cochran's Q with a P value, and I^2. N refers to the total number of patients, and n to the number of patients with disease control. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to rate the quality of

evidence of estimates from pairwise and network meta-analysis. The final network meta-analysis GRADE evidence quality corresponds to *very low, **low, ***moderate, and ****high. SSA refers to somatostatin analogues.

A Network PFS in pNET



B PFS in pNET

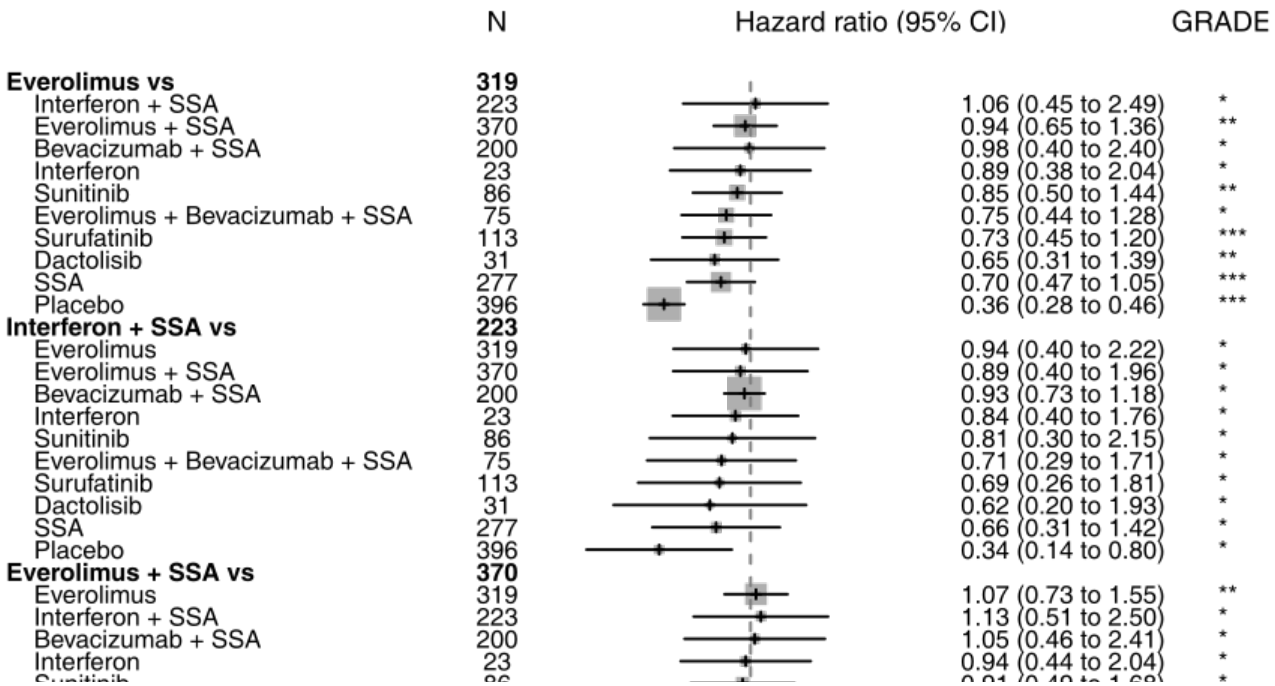


Figure 5. (Continued)

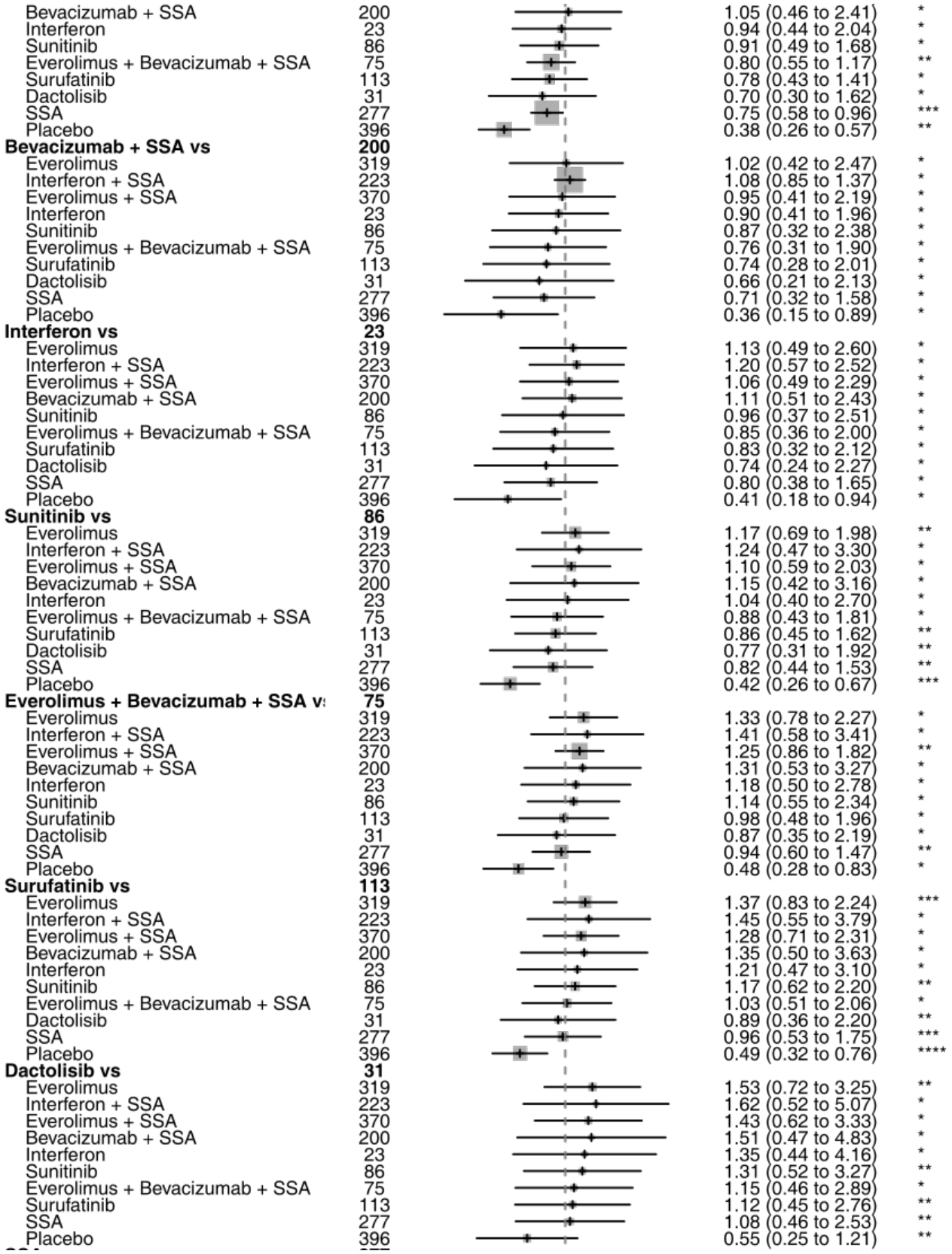
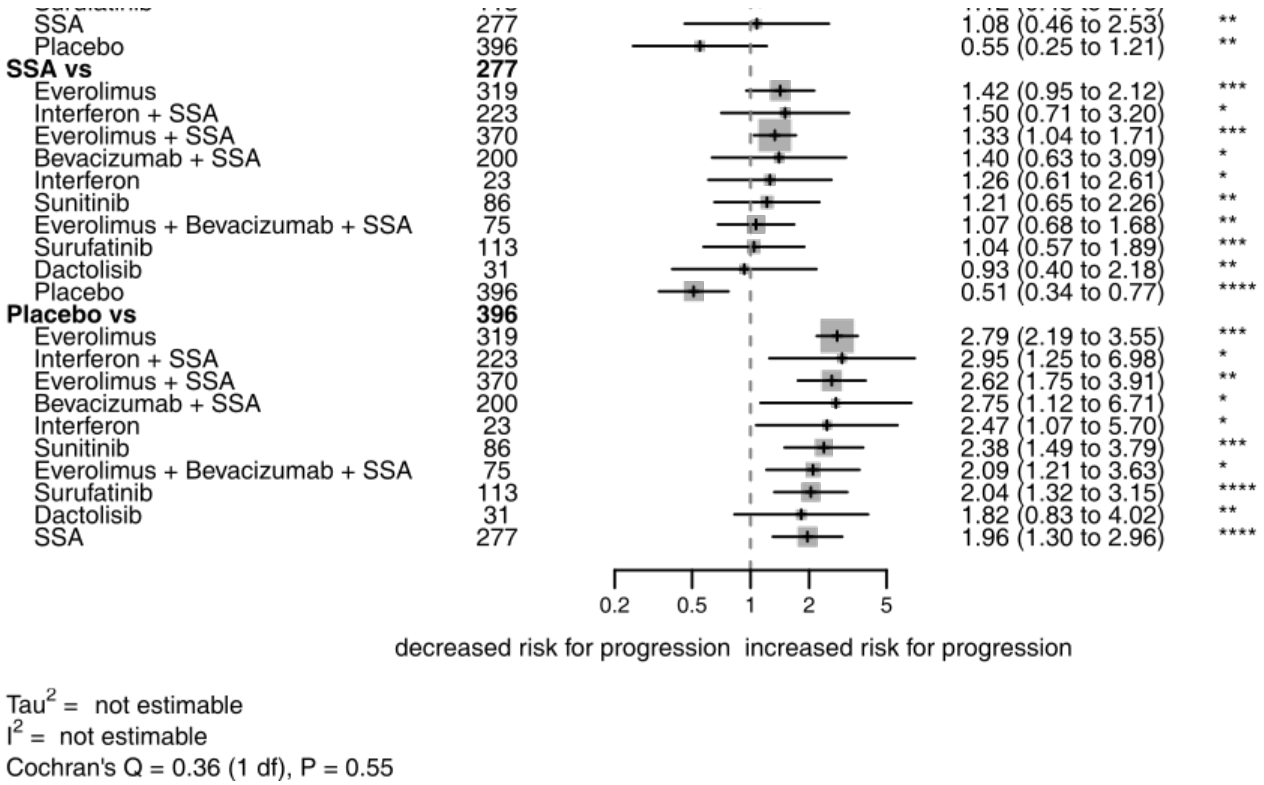


Figure 5. (Continued)



Tau^2 = not estimable
I^2 = not estimable
Cochran's Q = 0.36 (1 df), P = 0.55

The quality of evidence in pNETs was generally the highest for everolimus and surufatinib. The detailed results of the quality assessment are displayed in Table 3 and Table 4.

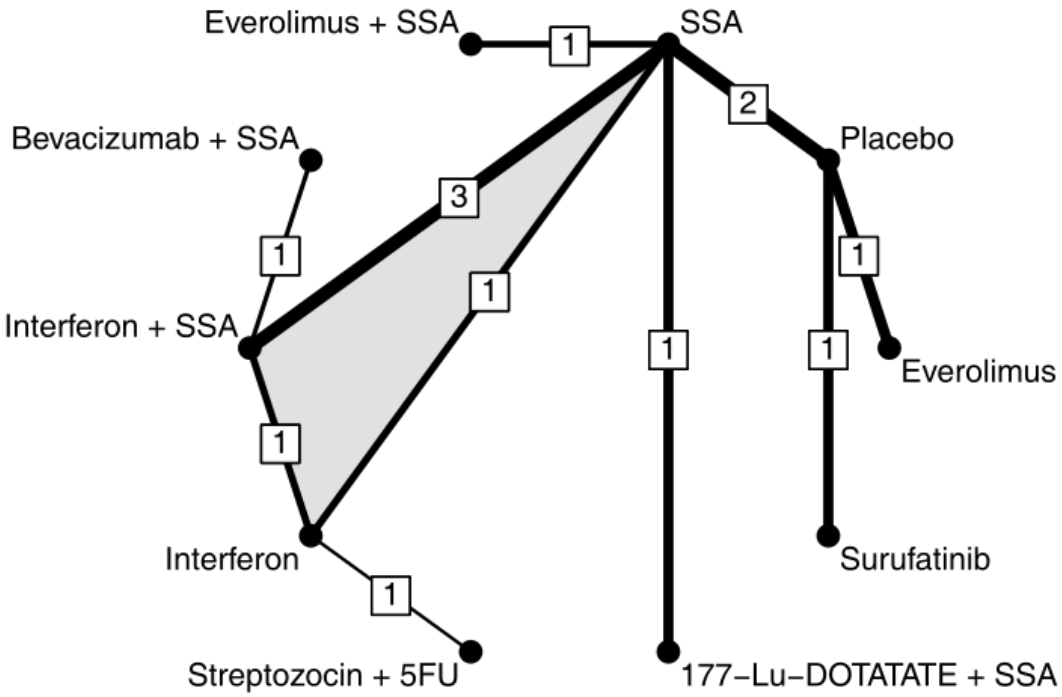
Treatment efficacy in GI-NETs

Eleven RCTs (Arnold 2005; Caplin 2014; Castellano 2013; Faiss 2003; Kölby 2003; Öberg 1989; Rinke 2009; Strosberg 2017; Xu 2020 (ep); Yao 2008 (1); Yao 2016) compared disease control rates for 10 different therapies in GI-NETs (Figure 6). The network meta-analysis found that combination therapies with a somatostatin analogue were highly effective. Bevacizumab plus a somatostatin analogue resulted in the highest disease control rate (P score, 0.91), followed by 177-Lu-DOTATATE plus a somatostatin analogue (P score, 0.90), everolimus plus a somatostatin analogue (P score, 0.78), interferon plus a somatostatin analogue (P score, 0.60), interferon (P score, 0.48), surufatinib (P score, 0.45), somatostatin analogues (P score, 0.37), everolimus (P score, 0.35), placebo (P score, 0.11), and streptozocin plus fluorouracil (P score, 0.04). All therapies but interferon, everolimus, and streptozocin plus fluorouracil showed significantly higher disease control rates than placebo (Figure 6, Table 5).

Figure 6. Treatment efficacy in GI-NET. Network plot (A) and Forest plot (B) for disease control in GI-NET. The thickness of the edges in the network plots is proportional to the inverse standard errors of the pairwise comparisons, and the numbers indicate the number of studies. One three-arm study is marked by shading. Each section in the Forest plots refers to one treatment (in bold) compared to all others. An odds ratio larger than one indicates increased disease control of the bold treatment. A hazard ratio smaller than one indicates a reduced risk for progression for the bold treatment. All therapies are listed in order of their P-scores, with the most effective therapy on top. Heterogeneity was assessed by the between study variance tau^2, Cochran's Q with a P value, and I^2. N refers to the total number of patients, and n to the number of patients with disease control. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to rate the quality of

evidence of estimates from pairwise and network meta-analysis. The final network meta-analysis GRADE evidence quality corresponds to *very low, **low, ***moderate, and ****high. SSA refers to somatostatin analogues.

A Network Disease Control in GI-NET



B Disease Control in GI-NET

	n/N	Odds ratio (95% CI)	GRADE
Bevacizumab + SSA vs	**21/22**		
177–Lu–DOTATATE + SSA	93/116	1.48 (0.10 to 22.1)	*
Everolimus + SSA	12/19	2.99 (0.15 to 57.6)	*
Interferon + SSA	63/130	7.87 (0.74 to 83.5)	*
Interferon	18/33	11.2 (0.74 to 168)	*
Surufatinib	109/129	12.8 (0.77 to 214)	*
SSA	166/384	15.4 (1.28 to 185)	*
Everolimus	169/205	17.8 (1.10 to 288)	*
Placebo	166/312	45.0 (3.32 to 609)	*
Streptozocin + 5FU	4/10	338 (5.14 to 22282)	*
177–Lu–DOTATATE + SSA vs	**93/116**		
Bevacizumab + SSA	21/22	0.68 (0.05 to 10.1)	*
Everolimus + SSA	12/19	2.02 (0.30 to 13.8)	*
Interferon + SSA	63/130	5.33 (1.42 to 20.0)	*
Interferon	18/33	7.55 (1.37 to 41.6)	*
Surufatinib	109/129	8.69 (1.60 to 47.1)	*
SSA	166/384	10.4 (3.59 to 30.1)	**
Everolimus	169/205	12.0 (2.33 to 62.1)	*
Placebo	166/312	30.4 (8.19 to 113)	*
Streptozocin + 5FU	4/10	229 (6.16 to 8512)	*
Everolimus + SSA vs	**12/19**		

Figure 6. (Continued)

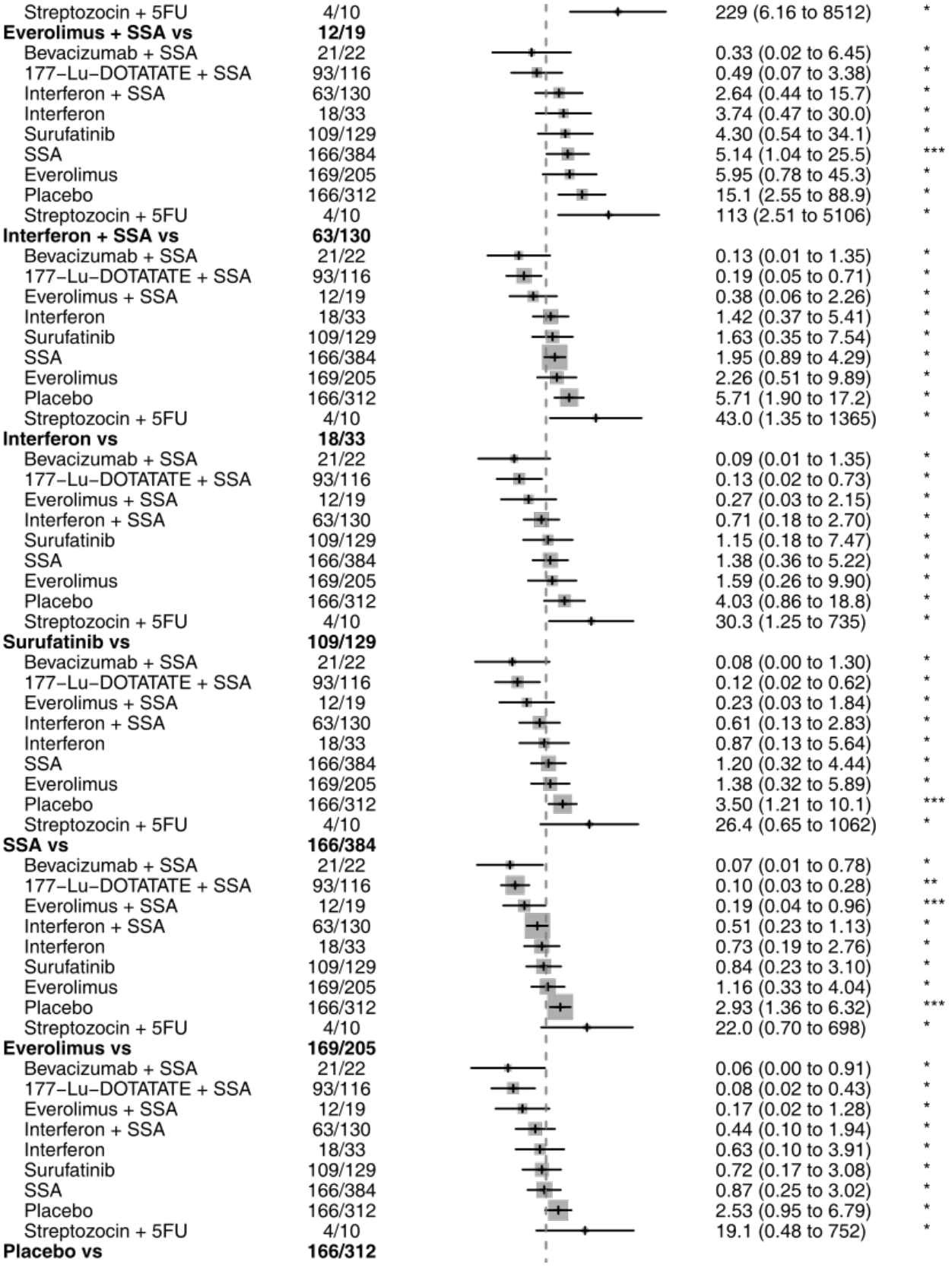
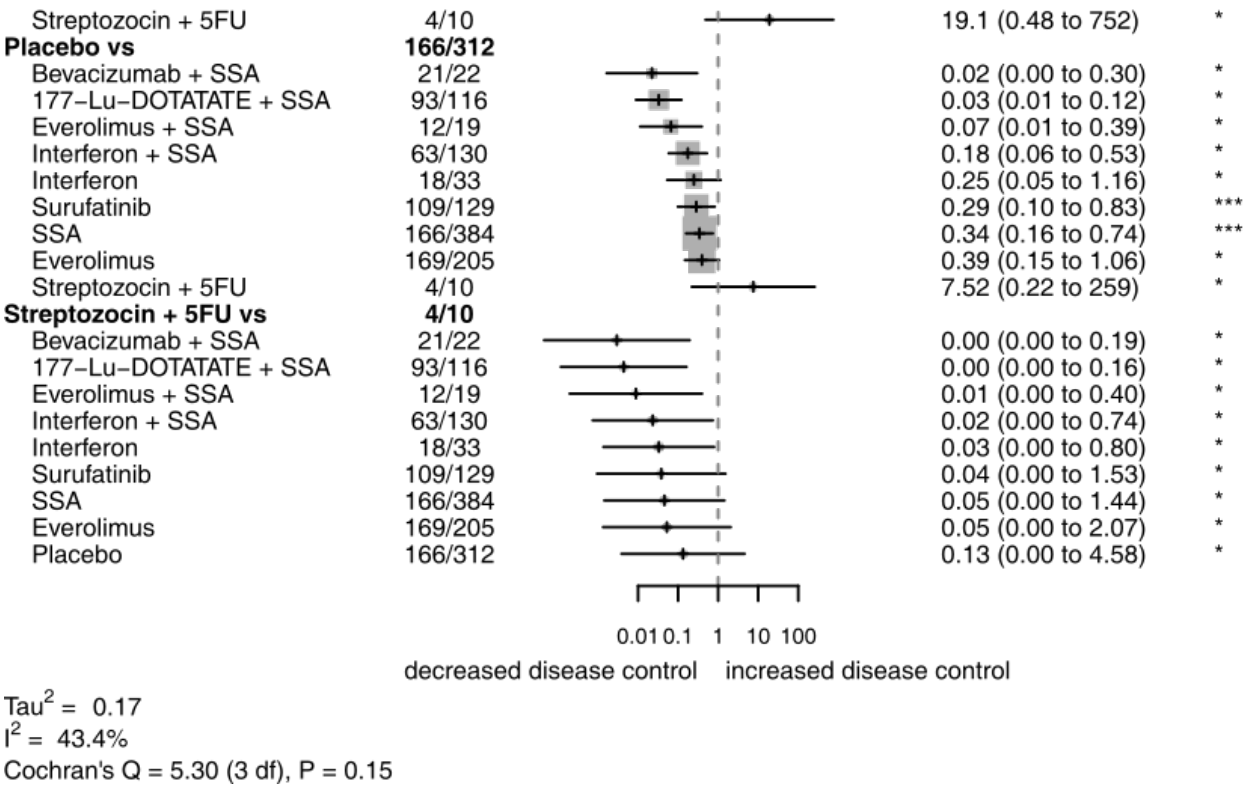


Figure 6. (Continued)

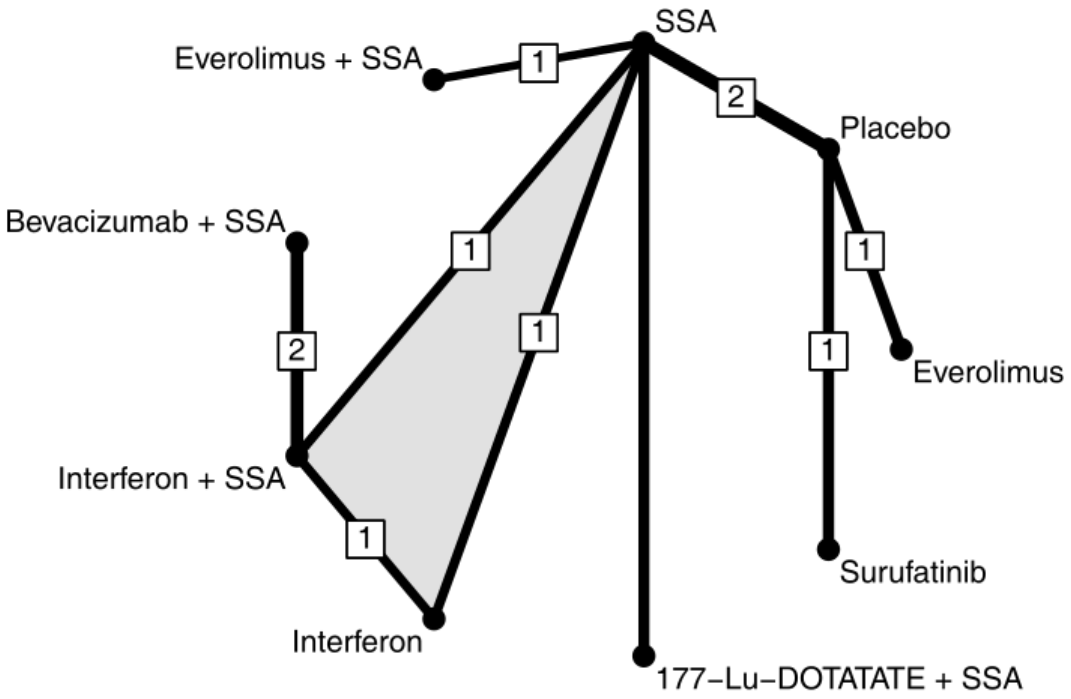


Nine RCTs (Castellano 2013; Dasari 2015; Faiss 2003; Rinke 2009; Singh 2018 (1); Strosberg 2017; Xu 2020 (ep); Yao 2008 (1); Yao 2017) assessed progression-free survival for nine different therapies in GI-NETS (Figure 7). Again, the network meta-analysis found that combination therapies with a somatostatin analogue were highly effective with HRs between 0.07 and 0.23 versus placebo. The lowest hazard for progression was found after treatment with 177-Lu-DOTATATE plus a somatostatin analogue (P score, 0.93), followed by everolimus plus a somatostatin analogue (P score, 0.79), bevacizumab plus a somatostatin analogue (P score, 0.66), interferon plus a somatostatin analogue (P score, 0.56), interferon (P score, 0.49), surufatinib (P score, 0.43), somatostatin analogues (P score, 0.39), everolimus (P score, 0.23), and placebo (P score, 0.03). All therapies but interferon and everolimus significantly reduced the hazard for progression compared with placebo (Figure 7, Table 6).

Figure 7. Treatment efficacy in GI-NET. Network plot (A) and Forest plot (B) for progression-free survival in GI-NET. The thickness of the edges in the network plots is proportional to the inverse standard errors of the pairwise comparisons, and the numbers indicate the number of studies. One three-arm study is marked by shading. Each section in the Forest plots refers to one treatment (in bold) compared to all others. An odds ratio larger than one indicates increased disease control of the bold treatment. A hazard ratio smaller than one indicates a reduced risk for progression for the bold treatment. All therapies are listed in order of their P-scores, with the most effective therapy on top. Heterogeneity was assessed by the between study variance tau^2, Cochran's Q with a P value, and I^2. N refers to the total number of patients, and n to the number of patients with disease control. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to rate the quality of

evidence of estimates from pairwise and network meta-analysis. The final network meta-analysis GRADE evidence quality corresponds to *very low, **low, ***moderate, and ****high. SSA refers to somatostatin analogues.

A Network PFS in GI-NET



B PFS in GI-NET

	N	Hazard ratio (95% CI)	GRADE
177–Lu–DOTATATE + SSA vs	**116**		
Everolimus + SSA	19	0.62 (0.12 to 3.22)	*
Bevacizumab + SSA	222	0.40 (0.07 to 2.32)	*
Interferon + SSA	245	0.32 (0.07 to 1.47)	*
Interferon	23	0.26 (0.06 to 1.22)	*
Surufatinib	129	0.22 (0.04 to 1.09)	*
SSA	230	0.21 (0.08 to 0.57)	**
Everolimus	118	0.13 (0.03 to 0.64)	*
Placebo	209	0.07 (0.02 to 0.26)	*
Everolimus + SSA vs	**19**		
177–Lu–DOTATATE + SSA	116	1.62 (0.31 to 8.43)	*
Bevacizumab + SSA	222	0.64 (0.09 to 4.54)	*
Interferon + SSA	245	0.51 (0.09 to 2.96)	*
Interferon	23	0.43 (0.07 to 2.44)	*
Surufatinib	129	0.35 (0.06 to 2.18)	*
SSA	230	0.34 (0.09 to 1.26)	*
Everolimus	118	0.21 (0.03 to 1.28)	*
Placebo	209	0.12 (0.03 to 0.54)	*
Bevacizumab + SSA vs	**222**		
177–Lu–DOTATATE + SSA	116	2.51 (0.43 to 14.6)	*

Figure 7. (Continued)

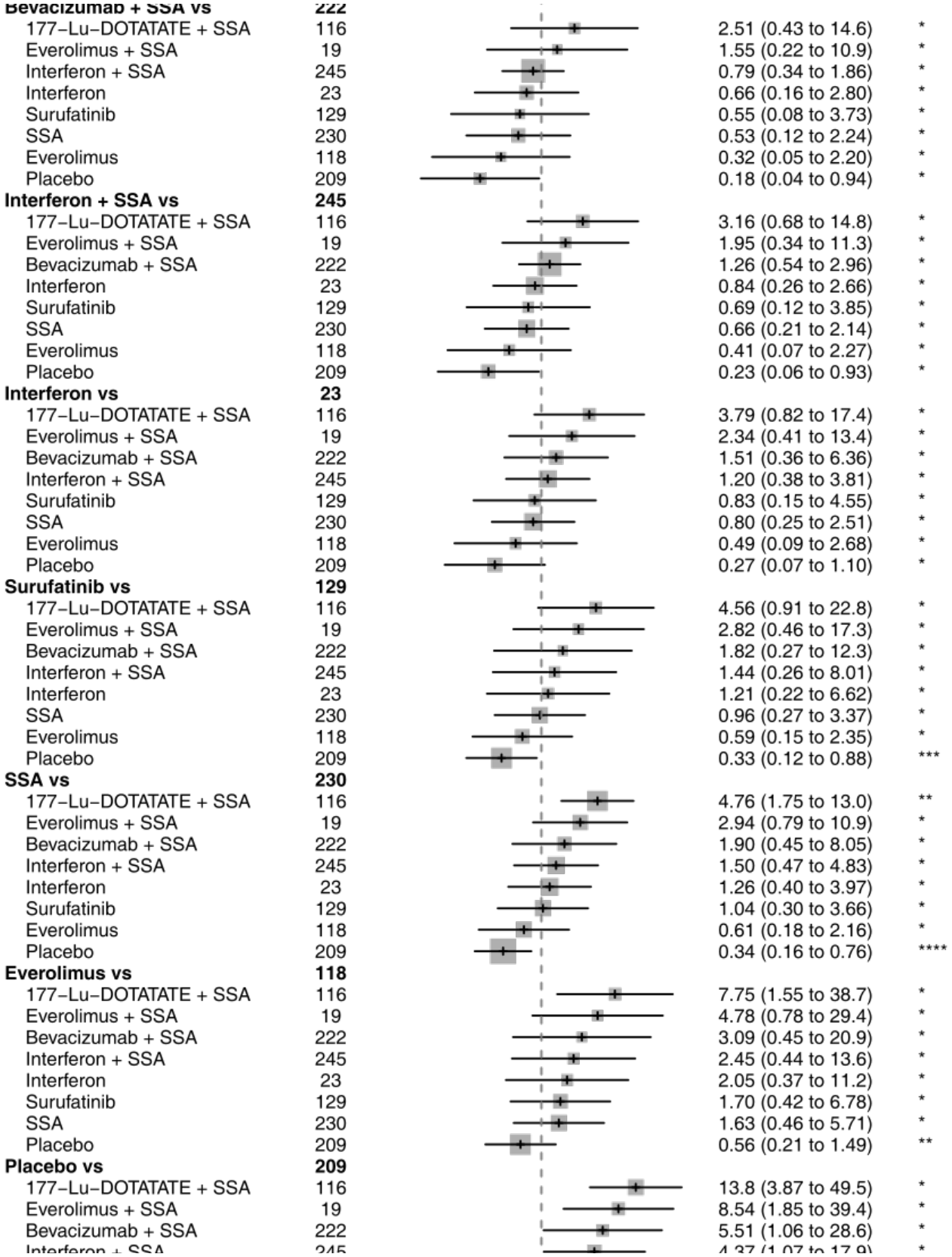
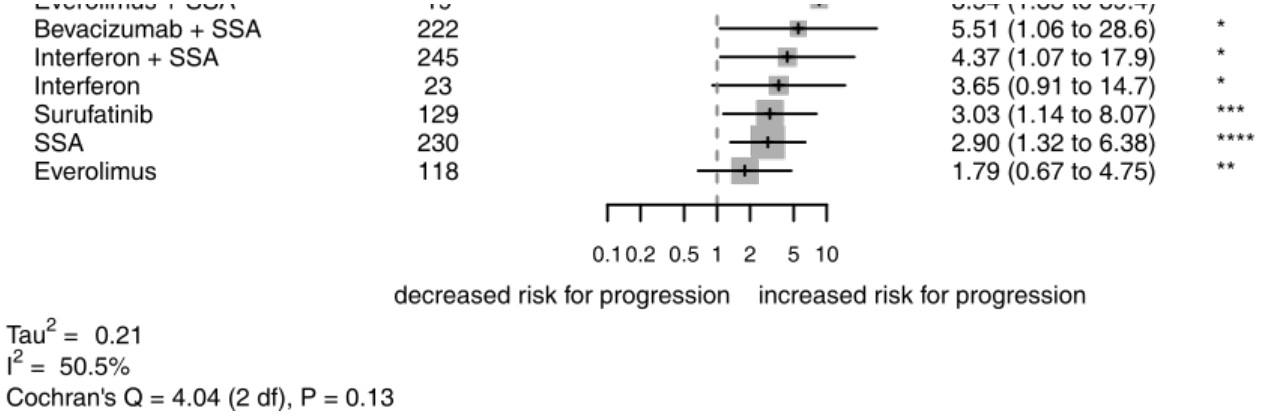


Figure 7. (Continued)

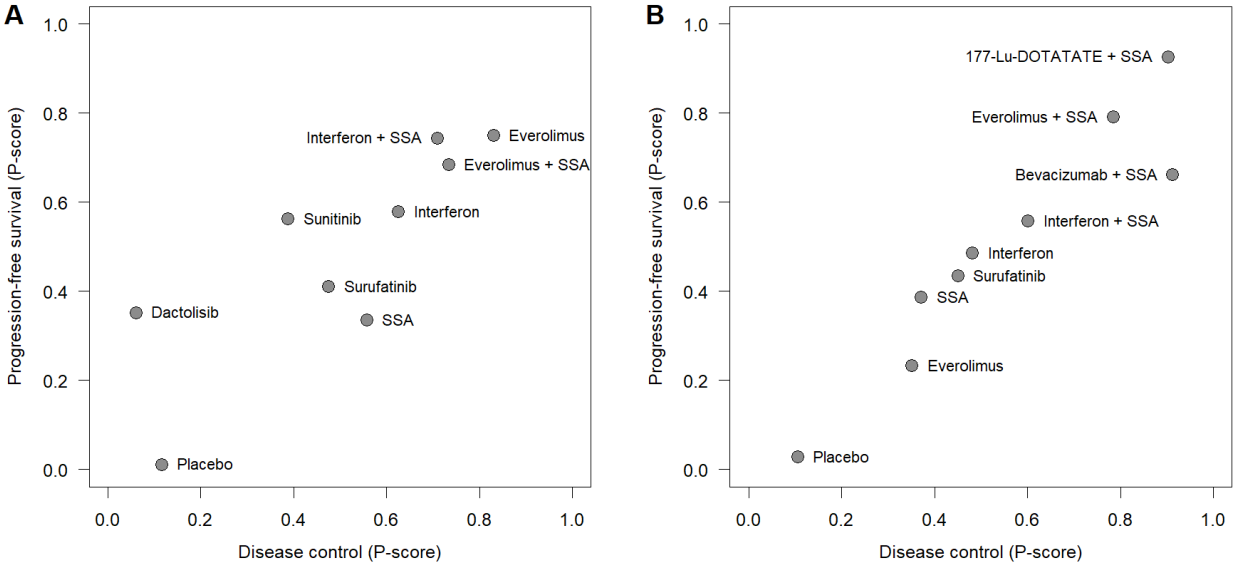


The quality of evidence in GI-NETs was generally the highest for somatostatin analogues. The detailed results of the quality assessment are displayed in Table 7 and Table 8.

Disease control, progression-free survival, and overall survival

Twelve RCTs (Castellano 2013; Faiss 2003; Kulke 2017 (1); Pavel 2011; Raymond 2011 (1); Rinke 2009; Salazar 2018; Strosberg 2017; Xu 2020 (ep); Xu 2020 (p); Yao 2008 (1); Yao 2011) reported data on disease control and progression-free survival (Figure 8). Moreover, 13 RCTs (Arnold 2005; Bergsland 2020; Kulke 2016; Lepage 2020; Meyer 2014; Moertel 1980; Moertel 1992; Raymond 2011 (1); Rinke 2009; Van Der Zwan 2018; Yao 2011; Yao 2017; Zhang 2020) reported data on overall survival (Table 9) and five RCTs reported both progression-free survival and overall survival (Kulke 2016; Raymond 2011 (1); Rinke 2009; Yao 2011; Yao 2017). In each of these RCTs, superiority of a therapy regarding progression-free survival was associated with non-inferiority regarding overall survival.

Figure 8. Ranking of treatment efficacies for disease control and progression-free survival. Plot of treatment efficacies in pancreatic neuroendocrine tumors (pNET, A) and gastrointestinal neuroendocrine tumors (GI-NET, B). Data are expressed as P-scores, measuring the extent of certainty that one therapy is better than another, averaged over all competing therapies. Black nodes are combination therapies with somatostatin analogues (SSA). Due to a lack of P-scores for disease control and progression-free survival, everolimus plus bevacizumab plus somatostatin analogue in pNET and streptozocin plus 5-FU in GI-NET are not depicted.



Quality of life and safety

Nine RCTs (Arnold 2005; Caplin 2014; Kulke 2017 (2); Meyer 2014; Raymond 2011 (1); Rinke 2009; Vinik 2016; Xu 2020 (ep); Xu 2020 (p)) quantified changes for eight different therapies with the Quality of Life Questionnaire C30 of the European Organization for Research and Treatment of Cancer. Of these, telotristat had the greatest effect on improving quality of life, followed by somatostatin analogues (Table 10).

Furthermore, 17 RCTs (Caplin 2014; Kölby 2003; Kulke 2017 (1); Maire 2012; Meyer 2014; Moertel 1992; Pavel 2011; Raymond 2011 (1); Salazar 2018; Strosberg 2017; Vinik 2016; Wolin 2015; Xu 2020 (ep); Xu 2020 (p); Yao 2011; Yao 2016; Zhang 2020) reported frequencies of adverse events for 17 different therapies, of which tyrosine kinase inhibitors showed the highest number of grade 1 to 4 adverse events per patient and streptozocin + 5-FU (fluorouracil) the highest number of serious (grade 3 or 4) adverse events per patient. Interferon plus somatostatin analogues showed the lowest number of grade 1 to 4 and the lowest number of serious adverse events per patient (Table 11).

DISCUSSION

Summary of main results

Everolimus was the most effective therapy in pNET with the highest certainty of evidence compared to the other treatments. Otherwise, the results suggest a superiority of combination therapies including somatostatin analogues. In pNETs, somatostatin analogues plus interferon, everolimus, or bevacizumab were highly efficacious. The certainty of evidence for these therapies was variable and was the highest for somatostatin analogues plus everolimus. In GI-NETs, somatostatin analogues plus 177-Lu-DOTATATE, bevacizumab, everolimus, or interferon were highly efficacious. The certainty of evidence for these therapies was very low.

Furthermore, the results suggest a range of monotherapies that are superior to placebo, including interferon and sunitinib besides everolimus in pNETs, and surufatinib and somatostatin analogues in pNETs and GI-NETs. Conversely, the results did not demonstrate efficacy superior to that of placebo for dactolisib in pNETs or for streptozocin + 5-FU in GI-NETs. The highest quality of evidence was available for everolimus and surufatinib in pNETs.

The results indicate that NET therapies have a broad range of risk for adverse events and effects on quality of life. Because systemic treatment is commonly noncurative for NETs, adverse events and quality of life are priorities.

Overall completeness and applicability of evidence

All relevant drug therapies for neuroendocrine tumours have been considered in this systematic review. However, there is insufficient precision of treatment effects for the following therapies: dactolisib, interferon and sunitinib in pNET, and 177-Lu-DOTATATE + SSA, bevacizumab + SSA, everolimus, everolimus + SSA, interferon, interferon + SSA and streptozocin + 5-FU in GI-NET.

We considered all available patient-relevant outcomes in our review (disease control, progression-free survival, overall survival, occurrence of adverse events and quality of life). However, we did not find a benefit in terms of overall survival for the included therapies, although we found a correlation of overall survival with progression-free survival. Quality of life was rarely and inconsistently reported for included trials, which compromises the evidence-base for decision-making. Therefore, evidence from this network meta-analysis (and underlying RCTs) does not support any particular therapy (or combinations of therapies) with respect to patient-centred outcomes (e.g. overall survival and quality of life). It should be consistently considered as a specified outcome in future trials on the topic.

The people enrolled in included RCTs appeared representative of all people with neuroendocrine tumours treated in high-income countries.

Our search for eligible trials was comprehensive including several electronic databases, trial registries, handsearching of conference proceedings, and contacts with experts in the field. Therefore, we deem it unlikely that we have missed relevant trials.

The results of this review are applicable to people with pNET or GI-NET.

Quality of the evidence

When using the available information for therapeutic decisions in treatment of NETs, we propose to consider the following points regarding indirectness, transitivity, risk of bias, inconsistency, incoherence, and imprecision. First, meta-analyses are based on the assumption of directness, in which populations, therapies, and outcomes of included studies are aligned with population, therapies, and outcomes targeted by the meta-analysis. Our meta-analysis targeted all available therapies and included only studies reporting disease control and/or progression-free survival. Both factors ensured a certain degree of directness. Yet, indirectness was introduced by RCTs including mixed populations of people with pNETs and GI-NETs. We highlight all comparisons that were affected by indirectness (Table 3; Table 4; Table 7; Table 8) to allow incorporation of this fact into clinical decision-making.

Second, network meta-analyses are also based on the assumption of transitivity, in which the included studies are similar enough to build a network. In this study, the moderate differences in study populations and trial methodologies resulted in a network with moderate overall transitivity. The different types of interferons and somatostatin analogues introduced intransitivity for the loop of comparisons of interferon, somatostatin analogues, and their combination, but had no association with the certainty of evidence for the rest of the network.

Third, some RCTs had a high risk of bias due to absent blinding, including an RCT evaluating everolimus (Kulke 2017 (1)), the most efficacious therapy in pNETs, and two others evaluating interferon plus a somatostatin analogue in GI-NETs (Faiss 2003; Kölby 2003). Absent blinding has been shown to be associated with an average exaggeration of estimated therapeutic effects of approximately 9% (Pildal 2008). However, the therapeutic effect for the three aforementioned therapies compared with placebo substantially exceeds 9% and they most likely represent the superior therapies in GI-NETs, although the extent of superiority needs to be interpreted with caution.

Fourth, consistency describes the agreement between estimates of different studies for a specific comparison, while coherence describes agreement between direct and indirect estimates for a specific comparison. Owing to the relatively low number of RCTs, the assessment of incoherence and inconsistency was limited. We identified two comparisons in which indirect and direct estimates differed considerably comparing interferon plus a somatostatin analogue with somatostatin analogues and bevacizumab plus somatostatin analogues, without being statistically significant. Furthermore, we identified two cases of inconsistency comparing interferon with somatostatin analogues and interferon plus somatostatin analogues (Table 3; Table 4; Table 7; Table 8). Likely

owing to different types of somatostatin analogues and interferons, the RCTs found different effects regarding disease control and progression-free survival.

Fifth, the low number of RCTs compared with the number of interventions introduced imprecision to several comparisons, manifesting as wide 95% CIs that included or were close to a null effect. A statistically significant effect does not automatically represent a clinically relevant effect, and the consequence of imprecision is that wide 95% CIs might include significant but clinically irrelevant effects. As clinical relevance often depends on an individual patient's situation, we highlighted all comparisons that were affected by imprecision (Table 3; Table 4; Table 7; Table 8) to allow incorporation of this fact into clinical decision-making. We used the GRADE system to assess the confidence in effect estimates for all comparisons, depending on indirectness, transitivity, risk of bias, inconsistency, incoherence, and imprecision. We incorporated the certainty of evidence in the main results of our analysis to highlight the most robust findings for further use in clinical judgement.

Sixth, we used the endpoints disease control and progression-free survival for all network analyses, instead of overall survival. Although overall survival is arguably the most relevant clinical endpoint, it is used less frequently than disease control and progression-free survival because it requires a larger number of patients and longer follow-up. Cross-over trial design might obscure conclusions about survival by underestimating the overall survival benefit in a intention-to-treat analysis. Overall survival might be confounded by the effect of salvage therapies used after disease progression (Saad 2016). In NETs, progression-free survival has been shown to be well correlated with overall survival (Imaoka 2017), and the RCTs included in the present study revealed the same correlation. Using disease control and progression-free survival instead of overall survival in this study allowed us to include more therapies into the network meta-analyses, which we believe represents the preferred approach.

Furthermore, 18/22 studies included in the network analysis were industry-sponsored, which generally demonstrates exaggerated clinical benefits compared to the clinical benefits observed in real-world populations

Potential biases in the review process

We conducted a comprehensive literature search with a sensitive search algorithm and an extensive manual search of reference lists and conference proceedings. We therefore consider it unlikely that we missed relevant RCTs. However, we could not obtain additional unpublished data and are aware that a substantial amount of information is not available to the public. Thus, we cannot rule out publication bias.

Agreements and disagreements with other studies or reviews

The present study is in agreement with the findings of our previous systematic review and network meta-analysis on therapeutic options for neuroendocrine tumours (Kaderli 2019). Due to the updated literature search, 46 additional records related to 17 new studies were included in the qualitative analysis and six additional RCTs were included in the quantitative analysis. In the updated quantitative analysis, surufatinib was included in the network meta-analysis for disease control and progression-free survival for pNET and GI-NET and bevacizumab plus a somatostatin analogue in the network meta-analysis for progression-free survival in pNET. In the updated quantitative analysis, everolimus was the most effective treatment in pNET with respect to both disease control and progression-free survival.

The present study is also in agreement with clinical practice. Dactolisib ranked lower than placebo regarding disease control in pNET, while streptozocin + 5-FU ranked lower than placebo regarding disease control in GI-NET. The clinical development of dactolisib in neuroendocrine tumours was halted, while streptozocin + 5-FU remains reserved for advanced NET in the clinical setting.

AUTHORS' CONCLUSIONS

Implications for practice

Clinical decisions should be based on the best available evidence. The present results provide a comprehensive overview of the existing evidence on NET therapies as well as the best possible comparison of therapies that have not been directly compared in RCTs. Using this approach, the certainty of evidence is incorporated into the results to assist in decision-making. Safety and efficacy results should both be incorporated into the treatment decision, while in addition the safety results may aid in the decision to establish preventive measures and increase the surveillance for known toxic effects.

However, based on the evidence presented in this review, the results do not allow us to suggest a fixed sequence of therapies or therapy modalities for people with GI-NET and pNET in the course of disease.

Implications for research

The present results may guide future research by highlighting necessary head-to-head comparisons and facilitating their trial design. Specifically, bevacizumab plus a somatostatin analogue, dactolisib, everolimus plus bevacizumab plus a somatostatin analogue, sunitinib and surufatinib have only been compared with one other active therapy in pNET to date, while bevacizumab plus a somatostatin analogue, everolimus, everolimus plus a somatostatin analogue, surufatinib, streptozocin plus fluorouracil and 177-Lu-DOTATATE plus a somatostatin analogue have only been compared with one other active therapy in GI-NETs.

Sunitinib and everolimus have been compared only with placebo in pNETs and GI-NETs respectively and, to our knowledge, head-to-head comparisons with active therapies in RCTs have not yet been performed. When designing such head-to-head comparisons, the estimated associations from our network meta-analysis can help to select the reference therapy and approximate the required patient numbers. Particularly, because the present results identified eight therapies in pNETs and 6 therapies in GI-NETs with higher efficacy than placebo, comparisons with placebo as a reference are discouraged for the future. Because of their proven efficacy and central role in current comparisons, somatostatin analogues represent the logical reference compound for further RCTs. Moreover, the quality assessment of currently available RCTs revealed that further studies should incorporate blinding to avoid overestimation of effects and improve the overall quality of evidence in the field.

In addition, this study demonstrates the need for more research in assessing adverse events and effects on quality of life for NET therapies.

Finally, an important research topic would be a randomised evaluation of different sequences of therapies and therapy modalities in order to determine whether certain therapy modalities (i.e. 177-Lu-DOTATATE) are more efficient early or late in the course of disease .

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REFERENCES

References to studies included in this review

Anthony 2012 *{published data only}*

* Anthony L, Singh N, Passos VQ, Pavel M, Oberg K, Yao JC. Impact of prior somatostatin analog use on PFS in the phase III radiant-2 trial of everolimus + octreotide lar vs placebo + octreotide lar in patients with advanced neuroendocrine tumors. *Pancreas* 2012;**41**:342. [DOI: 10.1097/MPA.0b013e3182433b9f]

Pavel ME, Hainsworth JD, Baudin E, Peeters M, Hörsch D, Winkler RE, Radiant-Study Group. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet* 2012;**378**(9808):2005-12.

Strosberg JR, Yao JC, Bajetta E, Aout M, Hainsworth JD, Bakker B, et al. Efficacy of octreotide long-acting repeatable (OCT) from the phase III RADIANT-2 study in patients with advanced neuroendocrine tumors (NET): A post-hoc analysis of the placebo (PBO) arm with updated survival data. *Pancreas* 2015;**44**:359. [DOI: 10.1097/MPA.0000000000000289]

Arnold 2005 *{published data only}*

* Arnold R, Rinke A, Klose KJ, Muller HH, Wied M, Zamzow K, et al. Octreotide versus octreotide plus interferon-alpha in endocrine gastroenteropancreatic tumors: a randomized trial. *Clinical Gastroenterolology and Hepatolology* 2005;**3**(8):761-71.

Bergsland 2020 *{published data only}*

* Bergsland E, Mahoney M, Asmis T, Hall N, Kumthekar P, Maitland M, et al. Randomized phase II trial of pazopanib versus placebo in patients (Pts) with progressive carcinoid tumors (CARC) (Alliance A021202). *Pancreas* 2020;**49**:464. [DOI: 10.1097/MPA.0000000000001516]

Bergsland EK, Mahoney MR, Asmis TR, Hall N, Kumthekar P, Maitland ML, et al. Prospective randomized phase II trial of pazopanib versus placebo in patients with progressive carcinoid tumors (CARC) (Alliance A021202). *Journal of Clinical Oncology* 2019;**37**(15_suppl):4005. [DOI: 10.1200/JCO.2019.37.15-suppl.4005]

Caplin 2014 *{published data only}*

* Caplin ME, Pavel M, Cwikla JB, Phan AT, Raderer M, Sedlackova E, et al, Clarinet Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *New England Journal of Medicine* 2014;**371**(3):224-33.

Phan A, Caplin M, Pavel M, Cwikła J, Raderer M, Sedláčková E, et al. Relative risk analysis of safety profile of lanreotide autogel/depot vs. placebo in patients with pancreatic and intestinal neuroendocrine tumours. *European Journal of Cancer* 2015;**51**:S460. [EMBASE: 72067952]

Phan AT, Caplin ME, Pavel ME, Cwikla JB, Raderer M, Sedlackova E, et al. Relative risk of adverse events with lanreotide depot/autogel (LAN) vs. Placebo (PBO) in patients with intestinal and pancreatic neuroendocrine tumors (NETs). *Journal of Clinical Oncology* 2015;**33**(15 SUPPL. 1):e15181. [EMBASE: 72012104]

Phan AT, Dasari A, Liyanage N, Cox D, Pitman Lowenthal S, Wolin EM. Tumor response in the CLARINET study of lanreotide depot vs placebo in patients with metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs). *Journal of Clinical Oncology* 2016;**34**(4 suppl):434. [DOI: 10.1200/jco.2016.34.4_ suppl.434]

Regnault A, Ferrer L, Dinet J, Gabriel S, Pavel ME, Ruszniewski PB, et al. Health-related quality of life in CLARINET, a phase III trial of lanreotide autogel 120 mg in patients with non-functioning entero-pancreatic neuroendocrine tumour: Analytical challenges and statistical solutions. *Quality of Life Research* 2015;**24**:75. [EMBASE: 623526027]

Ruszniewski P, Phan AT, Caplin ME, Pavel ME, Ćwikła JB, Raderer M, et al. Quality of life (QoL) with lanreotide autogel/depot (LAN) vs. placebo in patients with enteropancreatic neuroendocrine tumors: results from the CLARINET core study. *2015* Pancreas;**44**:357. [EMBASE: 620121000]

Wolin EM, Caplin ME, Pavel ME, Ćwikla JB, Phan AT, Raderer M, et al. Multivariate analysis of progression-free survival in the CLARINET study of lanreotide autogel/depot vs placebo identifies prognostic factors in neuroendocrine tumors. *Pancreas* 2016;**Conference: 8th Annual Meeting of the North American NeuroEndocrine Tumor Society. United States. 45**(3):486. [EMBASE: 617770785]

Wolin EM, Caplin ME, Pavel ME, Cwikla JB, Phan AT, Raderer M, et al. Prognostic factors for progression-free survival (PFS) in CLARINET study of lanreotide depot/autogel (LAN) vs placebo (PBO) in neuroendocrine tumors (NETs). *Journal of Clinical Oncology* 2015;**33**(15_suppl):e15180.

Castellano 2013 *{published data only}*

* Castellano D, Bajetta E, Panneerselvam A, Saletan S, Kocha W, O'Dorisio T, et al. Everolimus plus octreotide long-acting repeatable in patients with colorectal neuroendocrine tumors: a subgroup analysis of the phase III RADIANT-2 study. *Oncologist* 2013;**18**(1):46-53.

Pavel ME, Hainsworth JD, Baudin E, Peeters M, Hörsch D, Winkler RE, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet* 2011;**378**(9808):2005-12.

Dasari 2015 *{published data only}*

Caplin ME, Pavel M, Cwikla JB, Phan AT, Raderer M, Sedlackova E, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *New England Journal of Medicine* 2014;**371**(3):224-33.

* Dasari A, Phan AT, Caplin ME, Pavel ME, Cwikla JB, Raderer M, et al. Lanreotide depot/autogel (LAN) in patients with neuroendocrine tumors (NETs) aged > 65 vs. >65 years:

subgroup analyses from the CLARINET study. *Journal of Clinical Oncology* 2015;**33**(15_suppl):e15177. [EMBASE: 72012341]

Di Gialleonardo 2020 *{published data only}*

* Di Gialleonardo V, Tesfaye E, Kittur A, Giacalone S, Lapuerta P. Improvement in carcinoid syndrome-related symptoms with telotristat ethyl in patients with 2 or less bowel movements per day. *Pancreas* 2020;**49**:467-68. [DOI: 10.1097/MPA.0000000000001516]

Pavel M, Gross DJ, Benavent M, Perros P, Srirajaskanthan R, Warner RRP, et al. Telotristat ethyl in carcinoid syndrome: safety and efficacy in the TELECAST phase 3 trial. *Endocrine-related Cancer* 2018;**25**(3):309-22.

Elf 2018 *{published data only}*

* Elf AK, Andersson M, Henrikson O, Jalnefjord O, Ljungberg M, Svensson J, et al. Radioembolization versus bland embolization for hepatic metastases from small intestinal neuroendocrine tumors: Short-term results of a randomized clinical trial. *World Journal of Surgery* 2018;**42**(2):506-13.

Faiss 2003 *{published data only}*

* Faiss S, Pape UF, Bohmig M, Dorffel Y, Mansmann U, Golder W, et al. Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors--the International Lanreotide and Interferon Alfa Study Group. *Journal of Clinical Oncology* 2003;**21**(14):2689-96.

Fisher 2016 *{published data only}*

Anselmo L, Shaheen M, Casellini C, Vinik AI, Wolin E, Kunz P, et al. Safety and efficacy of lanreotide depot vs. placebo in neuroendocrine tumor patients with a history of carcinoid syndrome and prior octreotide therapy. *Journal of Oncology Pharmacy Practice* 2016;**22**:19-20.

* Fisher GA, Wolin EM, Kunz P, Liyanage N, Gomez-Panzani E, Lowenthal SP, et al. Efficacy and safety of lanreotide depot vs placebo in patients with neuroendocrine tumor and a history of carcinoid syndrome and prior octreotide therapy. *2016* Pancreas;**45**:475.

Fisher GA, Wolin EM, Kunz P, Liyanage N, Gomez-Panzani E, Lowenthal SP, et al. Safety and efficacy of lanreotide depot versus placebo in neuroendocrine tumor patients with a history of carcinoid syndrome and prior octreotide therapy. *American Journal of Gastroenterology* 2015;**110**:S1007.

Pommier RF, Fisher GA, Wolin EM, Liyanage N, Lowenthal SP, Mirakhur B, et al. Lanreotide depot/autogel for symptomatic control of carcinoid syndrome (CS) in patients with neuroendocrine tumors (NETs) previously responsive to octreotide: subanalysis of patient-reported symptoms from the phase 3 elect study. *Pancreas* 2018;**47**:352.

Vinik AI, Wolin EM, Liyanage N, Gomez-Panzani E, Fisher GA, Elect Study Group. Evaluation of lanreotide depot/autogel efficacy and safety as a carcinoid syndrome treatment (elect): A randomized, double-blind, placebo-controlled trial. *Endocrine Practice* 2016;**22**(9):1068-80.

Ito 2012 *{published data only}*

* Ito T, Okusaka T, Ikeda M, Igarashi H, Morizane C, Nakachi K, et al. Everolimus for advanced pancreatic neuroendocrine tumours: a subgroup analysis evaluating Japanese patients in the RADIANT-3 trial. *Japanese Journal of Clinical Oncology* 2012;**42**(10):903-11.

Yao JC, Shah MH, Ito T, Lombard-Bohas C, Wolin EM, Van Cutsem E, et al, Rad001 in Advanced Neuroendocrine Tumors, Third Trial Study Group. Everolimus for advanced pancreatic neuroendocrine tumors. *New England Journal of Medicine* 2011;**364**(6):514-23.

Jacobsen 1995 *{published data only}*

* Jacobsen MB, Hanssen LE. Clinical effects of octreotide compared to placebo in patients with gastrointestinal neuroendocrine tumours. Report on a double-blind, randomized trial. *Journal of Internal Medicine* 1995;**237**(3):269-75.

Kölby 2003 *{published data only}*

* Kölby L, Persson G, Franzen S, Ahren B. Randomized clinical trial of the effect of interferon alpha on survival in patients with disseminated midgut carcinoid tumours. *British Journal of Surgery* 2003;**90**(6):687-93.

Kulke 2016 *{published data only}*

* Kulke MH, Niedzwiecki D, Foster NR, Fruth B, Kunz PL, Kennecke H, et al. Randomized phase II study of everolimus (E) versus everolimus plus bevacizumab (E+B) in patients (Pts) with locally advanced or metastatic pancreatic neuroendocrine tumors (pNET), CALGB 80701 (alliance). *Pancreas* 2016;**45**(3):477.

Kulke 2017 (1) *{published data only}*

* Kulke MH, Ruszniewski P, Van Cutsem E, Lombard-Bohas C, Valle JW, De Herder WW, et al. A randomized, open-label, phase 2 study of everolimus in combination with pasireotide LAR or everolimus alone in advanced, well-differentiated, progressive pancreatic neuroendocrine tumors: COOPERATE-2 trial. *Annals of Oncology* 2017;**28**(6):1309-15.

Kulke 2017 (2) *{published data only}*

Dillon JS, Kulke MH, Pavel M, Hörsch D, Anthony LB, Warner RRP, et al. Time to sustained improvement in bowel movement frequency with telotristat ethyl: Analysis of the phase 3 telestar study. *Pancreas* 2018;**47**:337-38.

* Kulke MH, Hörsch D, Caplin ME, Anthony LB, Bergsland E, Öberg K, et al. Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. *Journal of Clinical Oncology* 2017;**35**(1):14-23.

Weickert MO, Kaltsas G, Hörsch D, Lapuerta P, Pavel M, Valle JW, et al. Weight change associated with telotristat ethyl in the treatment of carcinoid syndrome. *Pancreas* 2018;**47**:357-58. [DOI: 10.1097/MPA.0000000000000997]

Lange 1992 *{published data only}*

* Lange JR, Steinberg SM, Doherty GM, Langstein HN, White DE, Shawker TH, et al. A randomized, prospective trial of postoperative somatostatin analogue in patients

with neuroendocrine tumors of the pancreas. *Surgery* 1992;**112**(6):1033-7; discussion 1037-8.

Lepage 2020 *{published data only}*

* Lepage C, Phelip JM, Lièvre A, Le Malicot K, Tougeron D, Dahan L, et al. Lanreotide as maintenance therapy after first-line treatment in patients with non-resectable duodeno-pancreatic neuroendocrine tumours (NETs): An international double-blind, placebo-controlled randomized phase II trial. *Annals of Oncology* 2020;**31**:S774. [DOI: 10.1016/j.annonc.2020.08.1376]

Liu 2020 *{published data only}*

* Liu Q, Cheng Y, Zang J, Sui H, Wang H, Jacobson O, et al. Dose escalation of an Evans blue–modified radiolabeled somatostatin analog 177Lu-DOTA-EB-TATE in the treatment of metastatic neuroendocrine tumors. *European Journal of Nuclear Medicine and Molecular Imaging* 2020;**47**(4):947-57. [DOI: 10.1007/s00259-019-04530-1]

Lombard-Bohas 2015 *{published data only}*

* Lombard-Bohas C, Yao JC, Hobday T, Van Cutsem E, Wolin EM, Panneerselvam A, et al. Impact of prior chemotherapy use on the efficacy of everolimus in patients with advanced pancreatic neuroendocrine tumors: a subgroup analysis of the phase III RADIANT-3 trial. *Pancreas* 2015;**44**(2):181-9.

Yao JC, Shah MH, Ito T, Lombard-Bohas C, Wolin EM, Van Cutsem E, et al, Rad001 in Advanced Neuroendocrine Tumors, Third Trial Study Group. Everolimus for advanced pancreatic neuroendocrine tumors. *New England Journal of Medicine* 2011;**364**(6):514-23.

Maire 2012 *{published data only}*

* Maire F, Lombard-Bohas C, O'Toole D, Vullierme MP, Rebours V, Couvelard A, et al. Hepatic arterial embolization versus chemoembolization in the treatment of liver metastases from well-differentiated midgut endocrine tumors: a prospective randomized study. *Neuroendocrinology* 2012;**96**(4):294-300.

Meyer 2014 *{published data only}*

* Meyer T, Qian W, Caplin ME, Armstrong G, Lao-Sirieix S, Hardy R, et al. Capecitabine and streptozocin ± cisplatin in advanced gastroenteropancreatic neuroendocrine tumours. *European Journal of Cancer* 2014;**50**(5):902-11.

Meyer T, Qian W, Valle JW, Talbot D, Cunningham D, Reed N, et al. Capecitabine and streptozocin ± cisplatin for gastroenteropancreatic neuroendocrine tumours: predictors of long-term survival in the NET01 trial. *Annals of Oncology* 2016;**27**(6):136-48. [EMBASE: 613912194]

Moertel 1980 *{published data only}*

* Moertel CG, Hanley JA, Johnson LA. Streptozocin alone compared with streptozocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. *New England Journal of Medicine* 1980;**303**(21):1189-94.

Moertel 1992 *{published data only}*

* Moertel CG, Lefkopoulo M, Lipsitz S, Hahn RG, Klaassen D. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. *New England Journal of Medicine* 1992;**326**(8):519-23.

O'Toole 2000 *{published data only}*

* O'Toole D, Ducreux M, Bommelaer G, Wemeau JL, Bouche O, Catus F, et al. Treatment of carcinoid syndrome: a prospective crossover evaluation of lanreotide versus octreotide in terms of efficacy, patient acceptability, and tolerance. *Cancer* 2000;**88**(4):770-6.

Öberg 1989 *{published data only}*

* Oberg K, Norheim I, Alm G. Treatment of malignant carcinoid tumors: a randomized controlled study of streptozocin plus 5-FU and human leukocyte interferon. *European Journal of Cancer and Clinical Oncology* 1989;**25**(10):1475-9.

Pavel 2011 *{published data only}*

Pavel ME, Baudin E, Öberg KE, Hainsworth JD, Voi M, Rouyrre N, et al. Efficacy of everolimus plus octreotide LAR in patients with advanced neuroendocrine tumor and carcinoid syndrome: final overall survival from the randomized, placebo-controlled phase 3 RADIANT-2 study. *Annals of Oncology* 2017;**28**(7):1569-75.

* Pavel ME, Hainsworth JD, Baudin E, Peeters M, Hörsch D, Winkler RE, et al, Radiant-Study Group. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet* 2011;**378**(9808):2005-12.

Wolin E, Castellano D, Kaltsas G, Gross D, Panneerselvam A, Klimovsky J, et al. Correlation of progression-free survival (PFS) with early response of biomarkers chromogranin a (CGA) and 5-hhydroxyindoleacetic acid (5-HIAA) levels in patients with advanced neuroendocrine tumors: phase III radiant-2 study results. *Pancreas* 2012;**41**:350-51. [EMBASE: 70703127]

Yao JC, Hainsworth JD, Baudin E, Peeters M, Hörsch D, Anthony L, et al. Radiant-2: A phase III trial of everolimus + octreotide lar in patients with advanced neuroendocrine tumors (NET). *Pancreas* 2011;**40**:335. [DOI: 10.1097/MPA.0b013e31820e7892]

Pavel 2018 (1) *{published data only}*

* Pavel M, Gross DJ, Benavent M, Perros P, Srirajaskanthan R, Warner RRP, et al. Telotristat ethyl in carcinoid syndrome: safety and efficacy in the TELECAST phase 3 trial. *Endocrine-related Cancer* 2018;**25**(3):309-22.

Pavlakis 2020 *{published data only}*

* Pavlakis N, Ransom DT, Wyld D, Sjoquist KM, Asher R, Gebski V, et al. Australasian Gastrointestinal Trials Group (AGITG) CONTROL NET Study: Phase II study evaluating the activity of Lu-Octreotate peptide receptor radionuclide therapy (LuTate PRRT) and capecitabine, temozolomide CAPTEM)-First results for pancreas and updated midgut neuroendocrine tumors (pNETS, mNETS). *Journal of Clinical Oncology* 2020;**38**(15_suppl):4608. [DOI: 10.1200/JCO.2020.38.15_suppl.4608]

Phan 2015 (1) *{published data only}*

Caplin ME, Pavel M, Cwikla JB, Phan AT, Raderer M, Sedlackova E, et al, Clarinet Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *New England Journal of Medicine* 2014;**371**(3):224-33.

Dasari A, Phan AT, Caplin ME, Pavel ME, Cwikla JB, Raderer M, et al. Lanreotide depot/autogel (LAN) in patients with neuroendocrine tumors (NETs) aged <65 vs. >65 years: subgroup analyses from the CLARINET study. *Journal of Clinical Oncology* 2015;**33**(15_suppl):e15177. [EMBASE: 72012341]

* Phan AT, Caplin ME, Pavel ME, Cwikla JB, Raderer M, Sedláčková E, et al. Effects of lanreotide autogel/depot (LAN) in patients with neuroendocrine tumors (NETs) age 65 or younger versus older than age 65: subgroup analyses from the CLARINET study. *Journal of Clinical Oncology* 2015;**33**:36.

Phan 2015 (2) *{published data only}*

Caplin ME, Pavel M, Cwikla JB, Phan AT, Raderer M, Sedlackova E, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *New England Journal of Medicine* 2014;**371**(3):224-33.

* Phan AT, Caplin ME, Pavel ME, Cwikla JB, Raderer M, Sedláčková E, et al. Effects of lanreotide autogel/depot (LAN) in pancreatic neuroendocrine tumors (pNETs): a subgroup analysis from the CLARINET study. *Journal of Clinical Oncology* 2015;**33**:233.

Pusceddu 2018 *{published data only}*

Caplin ME, Pavel M, Cwikla JB, Phan AT, Raderer M, Sedlackova E, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *New England Journal of Medicine* 2014;**371**(3):224-33.

* Pusceddu S, Vernieri C, Di Maio M, Prinzi N, Torchio M, Buzzoni R, et al. Post-hoc analysis of CLARINET phase III study to investigate the influence of diabetic status on progression-free survival (PFS) of patients with neuroendocrine tumours (NETs) treated with lanreotide(LAN) or placebo (PBO). *Annals of Oncology* 2018;**29**:viii472. [DOI: https://doi.org/10.1093/annonc/mdy293.012]

Raymond 2011 (1) *{published data only}*

Faivre S, Niccoli P, Castellano D, Valle JW, Hammel P, Raoul JL, et al. Sunitinib in pancreatic neuroendocrine tumors: updated progression-free survival and final overall survival from a phase III randomized study. *Annals of Oncology* 2017;**28**(2):339-43.

Raoul JL, Niccoli P, Bang YJ, Borbath I, Lombard-Bohas C, Metrakos P, et al. Sunitinib (SU) vs placebo for treatment of progressive, well-differentiated pancreatic islet cell tumours: results of a phase III, randomised, double-blind trial. *European Journal of Cancer, supplement* 2009;**7**:361. [EMBASE: 70210640]

* Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *New England Journal of Medicine* 2011;**364**(6):501-13.

Raymond E, Niccoli P, Castellano D, Valle J, Hammel P, Raoul JL, et al. Sunitinib (SU) in patients with advanced, progressive pancreatic neuroendocrine tumors (PNET): final overall survival (OS) results from a phase III randomized study including adjustment for crossover. *Neuroendocrinology* 2016;**103**:84. [EMBASE: 613188549]

Raymond E, Niccoli P, Raoul J, Bang Y, Borbath I, Lombard-Bohas C, et al. Updated overall survival (OS) and progression-free survival (PFS) by blinded independent central review (BICR) of sunitinib (SU) versus placebo (PBO) for patients (Pts) with advance unresectable pancreatic neuroendocrine tumors (NET). *Journal of Clinical Oncology* 2011;**29**(15 SUPPL. 1):4008. [EMBASE: 70709834]

Valle J, Niccoli P, Raoul JL, Bang YJ, Borbath I, Van Cutsem E, et al. Updated overall survival data from a phase III study of sunitinib vs. placebo in patients with advanced, unresectable pancreatic neuroendocrine tumour (NET). *European Journal of Cancer* 2011;**47**:S462. [EMBASE: 70549479]

Vinik A, Bottomley A, Korytowsky B, Bang YJ, Raoul J, Valle JW, et al. Patient-reported outcomes and quality of life with sunitinib versus placebo for pancreatic neuroendocrine tumors: results from an international phase III trial. *Targeted Oncology* 2016;**11**(6):815-24.

Vinik A, Cutsem EV, Niccoli P, Raoul JL, Bang YJ, Borbath I, et al. Progression-free survival (PFS) by blinded independent central review (BICR) and updated overall survival (OS) of sunitinib versus placebo for patients with progressive, unresectable, well differentiated pancreatic neuroendocrine tumor (NET). *Pancreas* 2012;**41**:350. [EMBASE: 70703125]

Raymond 2011 (2) *{published data only}*

Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *New England Journal of Medicine* 2011;**364**(6):501-13.

* Raymond E, Harmon C, Niccoli P, Metrakos P, Borbath I, Bang YJ, et al. Impact of baseline Ki-67 index and other baseline characteristics on outcome in a study of sunitinib (SU) for the treatment of advanced, progressive pancreatic neuroendocrine tumor (NET). *Neuroendocrinology* 2011;**94**:41. [EMBASE: 70610285]

Rinke 2009 *{published data only}*

* Rinke A, Muller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *Journal of Clinical Oncology* 2009;**27**(28):4656-63.

Rinke A, Neary MP, Eriksson J, Hunger M, Doan T, Karli D, et al. Health-related quality of life for long-acting octreotide versus placebo in patients with metastatic midgut neuroendocrine tumors in the phase 3 PROMID Trial. *Neuroendocrinology* 2019;**109**(2):141-51.

Rinke A, Wittenberg M, Schade-Brittinger C, Aminossadati B, Ronicke E, Gress TM, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic

neuroendocrine midgut tumors (PROMID): Results of long-term survival. *Neuroendocrinology* 2017;**104**(1):26-32.

Sakata 2006 *{published data only}*

* Sakata H, Iwakiri R, Ootani A, Tsunada S, Ogata S, Ootani H, et al. A pilot randomized control study to evaluate endoscopic resection using a ligation device for rectal carcinoid tumors. *World Journal of Gastroenterology* 2006;**12**(25):4026-8.

Salazar 2018 *{published data only}*

* Salazar R, Garcia-Carbonero R, Libutti SK, Hendifar AE, Custodio A, Guimbaud R, et al. Phase II study of BEZ235 versus everolimus in patients with mammalian target of rapamycin inhibitor-naïve advanced pancreatic neuroendocrine tumors. *Oncologist* 2018;**23**(7):766-71.

Saslow 1998 *{published data only}*

* Saslow SB, Scolapio JS, Camilleri M, Forstrom LA, Thomforde GM, Burton DD, et al. Medium-term effects of a new 5HT3 antagonist, alosetron, in patients with carcinoid diarrhoea. *Gut* 1998;**42**(5):628-34.

Singh 2018 (1) *{published data only}*

* Singh S, Carnaghi C, Buzzoni R, Pommier RF, Raderer M, Tomasek J, et al. Everolimus in neuroendocrine tumors of the gastrointestinal tract and unknown primary. *Neuroendocrinology* 2018;**106**(3):211-20.

Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, et al, Rad001 in Advanced Neuroendocrine Tumours, Fourth Trial Study Group. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet* 2016;**387**(10022):968-77.

Soulen 2020 *{published data only}*

* Soulen M, Avritscher R, El-Haddad G, Fidelman N, Garcia-Monaco R, White S, et al. Randomized embolization trial for neuroendocrine tumors (RETNET): first safety report. *Pancreas* 2020;**49**:488. [EMBASE: 631301779]

Strosberg 2011 *{published data only}*

* Strosberg J, Anthony L, Sideris L, Lebrec J, Tsuchihashi Z, Winkler R, et al. Prognostic value of chromogranin a and neuron-specific enolase in patients with advanced pancreatic neuroendocrine tumors (pNET): phase III RADIANT-3 study results 2011 ACG presidential poster. *American Journal of Gastroenterology* 2011;**106**:S58.

Yao JC, Shah MH, Ito T, Lombard-Bohas C, Wolin EM, Van Cutsem E, et al, Rad001 in Advanced Neuroendocrine Tumors, Third Trial Study Group. Everolimus for advanced pancreatic neuroendocrine tumors. *New England Journal of Medicine* 2011;**364**(6):514-23.

Strosberg 2017 *{published data only}*

* Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 trial of (177)Lu-Dotatate for midgut neuroendocrine tumors. *New England Journal of Medicine* 2017;**376**(2):125-35.

Strosberg J, Wolin E, Chasen B, Kulke M, Bushnell D, Caplin M, et al. QOL improvements in netter-1 phase III trial in patients with progressive midgut neuroendocrine tumors. *Pancreas* 2018;**47**:355. [DOI: 10.1097/MPA.0000000000000997]

Strosberg J, Wolin E, Chasen B, Kulke MH, Bushnell D, Caplin M, et al. NETTER-1 phase III trial: Recent findings on quality of life in patients with midgut neuroendocrine tumors. *Neuroendocrinology* 2017;**105**:257. [DOI: 10.1159/000484263]

Strosberg 2020 *{published data only}*

Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 trial of (177)Lu-Dotatate for midgut neuroendocrine tumors. *New England Journal of Medicine* 2017;**376**(2):125-35.

* Strosberg J, Kunz P, Hendifar A, Yao J, Bushnell D, Kulke M, et al. Impact of baseline liver tumor burden, alkaline phosphatase (ALP) elevation, and target size lesion on therapeutic effect of 177LU-DOTATATE treatment: Analysis of progression free survival, and safety in NETTER-1 study. *Pancreas* 2020;**49**:489. [DOI: 10.1097/MPA.0000000000001516]

Van Der Zwan 2018 *{published data only}*

* Van Der Zwan W, Wyld D, Brabander T, Teunissen J, Kam B, MacFarlane D, et al. A randomized controlled study comparing treatment of gastro-entero-pancreatic neuroendocrine tumors (GEPNET) with 177Lu-Dotatate alone and in combination with capecitabine. *Neuroendocrinology* 2018;**106**:261. [DOI: 10.1159/000487699]

Vinik 2016 *{published data only}*

Duchateau L, Lescrauwaet B, Blot K, Liyanage N, Ray D, Lowenthal SP, et al. An exploratory patientcentricanalysis of the elect trial: A phase 3 study of efficacy and safety of lanreotide autogel/depot (LAN) treatment for patients with carcinoid syndrome (CS). *Pancreas* 2018;**Conference: 10th Annual Meeting of the North American Neuroendocrine Tumor Society. United States. 47**:338. [EMBASE: 621394428]

* Vinik AI, Wolin EM, Liyanage N, Gomez-Panzani E, Fisher GA, Elect Study Group. Evaluation of lanreotide depot/autogel efficacy and safety as a carcinoid syndrome treatment (elect): A randomized, double-blind, placebo-controlled trial. *Endocrine Practice* 2016;**22**(9):1068-80.

Wolin EM, Lowenthal SP, Fisher GA, Liyanage N, Mirakhur B, Pommier RF, et al. Change in patient-reported symptom control in patients with neuroendocrine tumors treated with lanreotide depot. *Pancreas* 2018;**47**:358. [DOI: 10.1097/MPA.0000000000000997]

Wolin 2015 *{published data only}*

* Wolin EM, Jarzab B, Eriksson B, Walter T, Toumpanakis C, Morse MA, et al. Phase III study of pasireotide long-acting release in patients with metastatic neuroendocrine tumors and carcinoid symptoms refractory to available somatostatin analogues. *Drug Design, Development and Therapy* 2015;**9**:5075-86.

Wolin 2016 *{published data only}*

Caplin ME, Pavel M, Cwikla JB, Phan AT, Raderer M, Sedlackova E, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *New England Journal of Medicine* 2014;**371**(3):224-33.

Wolin EM, Caplin ME, Pavel ME, Cwikla JB, Phan AT, Raderer M, et al. Lanreotide depot/autogel (LAN) in intestinal and pancreatic neuroendocrine tumors (NETs) according to body mass index (BMI): Subgroup analyses from the CLARINET study. *Journal of Clinical Oncology* 2015;**33**(15_suppl):e15182. [EMBASE: 72012396]

* Wolin EM, Caplin ME, Pavel ME, Cwikla JB, Phan AT, Raderer M, et al. Lanreotide depot/autogel (LAN) in intestinal and pancreatic neuroendocrine tumors (NETs) according to body mass index (BMI): Subgroup analyses from the CLARINET study. *Pancreas* 2016;**33**(15_suppl):e15182.

Xu 2020 (ep) *{published data only}*

* Xu J, Shen L, Bai C, Wang W, Li J, Yu X, et al. Surufatinib in advanced extrapancreatic neuroendocrine tumours (SANET-ep): a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncology* 2020;**21**(11):1500-12.

Xu J, Shen L, Zhou Z, Li J, Bai C, Chi Y, et al. Efficacy and safety of surufatinib in patients with well-differentiated advanced extrapancreatic neuroendocrine tumors (NETs): results from the randomized phase III study (SANET-ep). *Annals of Oncology* 2019;**30**:v911. [EMBASE: 630606088]

Xu 2020 (p) *{published data only}*

Xu J, Shen L, Bai C, Li J, Zhou Z, Yu X, et al. Surufatinib (S) for patients (Pts) with advanced pancreatic neuroendocrine tumours (SANET-p): a randomized, double-blind, placebo (P)-controlled phase III trial (NCT02589821). *Annals of Oncology* 2020;**31**:S770. [EMBASE: 2007890722]

* Xu J, Shen L, Bai C, Wang W, Li J, Yu X, et al. Surufatinib in advanced pancreatic neuroendocrine tumours (SANET-p): a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncology* 2020;**21**(11):1489-99.

Yao 2008 (1) *{published data only}*

* Yao JC, Phan A, Hoff PM, Chen HX, Charnsangavej C, Yeung SC, et al. Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b. *Journal of Clinical Oncology* 2008;**26**(8):1316-23.

Yao 2011 *{published data only}*

De Vries E, Anthony LB, Sideris L, Chen L, Lebrec J, Tsuchihashi Z, et al. Effect of everolimus treatment on chromogranin A, neuron-specific enolase, gastrin, and glucagon levels in patients with advanced pancreatic neuroendocrine tumors (pNET): phase III RADIANT-3 study results. *Journal of Clinical Oncology* 2011;**29**(15_suppl):10624. [EMBASE: 70712574]

Yao JC, Pavel M, Lombard-Bohas C, Van Cutsem E, Voi M, Brandt U, et al. Everolimus for the treatment of advanced pancreatic neuroendocrine tumors: Overall survival and circulating biomarkers from the randomized, phase III RADIANT-3 study. *Journal of Clinical Oncology* 2016;**34**(32):3906-13.

* Yao JC, Shah MH, Ito T, Lombard-Bohas C, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *New England Journal of Medicine* 2011;**364**(6):514-23.

Yao 2016 *{published data only}*

Pavel ME, Singh S, Strosberg JR, Bubuteishvili-Pacaud L, Degtyarev E, Neary MP, et al. Health-related quality of life for everolimus versus placebo in patients with advanced, non-functional, well-differentiated gastrointestinal or lung neuroendocrine tumours (RADIANT-4): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncology* 2017;**18**(10):1411-22.

* Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet* 2016;**387**(10022):968-77.

Yao 2017 *{published data only}*

* Yao JC, Guthrie KA, Moran C, Strosberg JR, Kulke MH, Chan JA, et al. Phase III prospective randomized comparison trial of depot octreotide plus interferon alfa-2b versus depot octreotide plus bevacizumab in patients with advanced carcinoid tumors: SWOG S0518. *Journal of Clinical Oncology* 2017;**35**(15):1695-703.

Yao 2019 *{published data only}*

Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet* 2016;**387**(10022):968-77.

* Yao JC, Oh DY, Qian J, Park YS, Herbst F, Ridolfi A, et al. Everolimus for the treatment of advanced gastrointestinal or lung nonfunctional neuroendocrine tumors in east asian patients: A subgroup analysis of the RADIANT-4 study. *OncoTargets and Therapy* 2019;**12**:1717-28.

Zhang 2020 *{published data only}*

* Zhang P, Li J, Li J, Zhang X, Zhou J, Wang X, et al. Etoposide and cisplatin versus irinotecan and cisplatin as the first-line therapy for patients with advanced, poorly differentiated gastroenteropancreatic neuroendocrine carcinoma: A randomized phase 2 study. *Cancer* 2020;**126 Suppl 9**(Suppl 9):2086-92.

References to studies excluded from this review

Caplin 2014 *{published data only}*

* Caplin ME, Ruszniewski PB, Pavel ME, Cwikla JB, Phan AT, Raderer M, et al. Progression-free survival (PFS) with lanreotide autogel/depot (LAN) in enteropancreatic NETs patients: The CLARINET extension study. *Journal of Clinical Oncology* 2014;**32**:4107.

Chan 2018 *{published data only}*

* Chan DL, Yao JC, Carnaghi C, Buzzoni R, Herbst F, Ridolfi A, et al. Systemic markers of inflammation in neuroendocrine tumors (NETs) and outcomes with everolimus: A pooled analysis from the randomized, phase 3 RADIANT-3 and RADIANT-4 trials. *Neuroendocrinology* 2018;**Conference: 15th Annual ENETS Conference for the Diagnosis and Treatment of Neuroendocrine Tumor Disease. Spain. 106**:151.

Cwikla 2017 *{published data only}*

* Cwikla JB, Wolin EM, Pavel M, Phan AT, Raderer M, Sedláčková E, et al. Final analysis of time to subsequent disease progression/death in patients with metastatic enteropancreatic neuroendocrine tumours progressing under placebo and switched to lanreotide autogel/depot 120mg in the CLARINET open-label extension. *Annals of Oncology* 2017;**28**:v150.

Fazio 2018 *{published data only}*

* Fazio N, Carnaghi C, Buzzoni R, Valle J, Herbst F, Ridolfi A, et al. Relationship between metabolic toxicity and efficacy of everolimus in patients with neuroendocrine tumors (NETs): A pooled analysis from the randomized, phase 3 RADIANT-3 and RADIANT-4 trials. *Neuroendocrinology* 2018;**Conference: 15th Annual ENETS Conference for the Diagnosis and Treatment of Neuroendocrine Tumor Disease. Spain. 106**:211.

Herrera Cabezón 2019 *{published data only}*

* Herrera Cabezón J, Sánchez Acedo P, Tarifa Castilla A, Zazpe Ripa C. Delayed gastric emptying following pancreatoduodenectomy: a Roux-en-Y gastrojejunostomy vs Billroth II gastrojejunostomy randomized study. *Revista espanola de enfermedades digestivas* 2019;**111**(1):34-9.

Hörsch 2018 *{published data only}*

* Hörsch D, Kulke MH, Caplin ME, Anthony LB, Bergsland E, Oberg K, et al. Efficacy and safety of telotristat ethyl in patients with carcinoid syndrome inadequately controlled by somatostatin analogs: Analysis of the completed telestar extension period. *Pancreas* 2018;**47**:341-2.

Ito 2011 *{published data only}*

* Ito T, Okusaka T, Ikeda M, Tajima T, Kasuga A, Fujita Y, et al. Everolimus versus placebo in Japanese patients with advanced pancreatic neuroendocrine tumors (pNET): japanese subgroup analysis of RADIANT-3. *Journal of Clinical Oncology* 2011;**29**:289.

Kulke 2019 *{published data only}*

* Kulke MH, Ruszniewski P, Van Cutsem E, Lombard-Bohas C, Valle JW, De Herder WW, et al. Erratum: a randomized, open-label, phase 2 study of everolimus in combination with pasireotide LAR or everolimus alone in advanced, well-differentiated, progressive pancreatic neuroendocrine tumors: COOPERATE-2 trial. *Annals of Oncology* 2019;**30**(11):1846.

Lapuerta 2018 *{published data only}*

* Lapuerta P, Kulke MH, Pavel M, Biran T, Fleming R, Zacks JS, et al. Integrated safety analysis of telotristat ethyl in patients with carcinoid heart disease. *Pancreas* 2018;**47**:345.

Meyer 2016 *{published data only}*

* Meyer T, Qian W, Valle JW, Talbot D, Cunningham D, Reed N, et al. Capecitabine and streptozocin ± cisplatin for gastroenteropancreatic neuroendocrine tumours: predictors of long-term survival in the NET01 trial. *Annals of Oncology* 2016;**27**:vi136–48.

Miller 2020 *{published data only}*

* Miller C, Virgolini I, Kjaer A, Gronbaek H, Terve P, Shamsi K, et al. A novel read methodology to evaluate the optimal dose of 68Ga-satoreotide trizoxetan as a PET imaging agent in patients with GEP-NETs in a phase II clinical trial. *Journal of Nuclear Medicine* 2020;**61**(supplement 1):60.

Okusaka 2012 *{published data only}*

* Okusaka T, Ito T, Ikeda M, Igarashi H, Morizane C, Nakachi K, et al. Phase III trial of everolimus in advanced pancreatic neuroendocrine tumors (RADIANT-3): overall population and Japanese subgroup analysis. *Annals of Oncology* 2012;**23**:xi15.

Pavel 2015 *{published data only}*

* Pavel ME, Lombard-Bohas C, Van Cutsem E, Lam DH, Kunz T, Brandt U, et al. Everolimus in patients with advanced, progressive pancreatic neuroendocrine tumors: overall survival results from the phase III RADIANT-3 study after adjusting for crossover bias. *Journal of Clinical Oncology* 2015;**33**(15 SUPPL. 1):4091.

Pavel 2018 (2) *{published data only}*

* Pavel M, Denecke T, Lahner H, Hörsch D, Rinke A, Koch A, et al. Disease control in progressive pancreatic and intestinal neuroendocrine tumours with combined treatment with lanreotide Autogel and temozolomide: The SONNET study. *Oncology Research and Treatment* 2018;**41**:263.

Pavel 2018 (3) *{published data only}*

* Pavel M, Denecke T, Lahner H, Hörsch D, Rinke A, Koch A, et al. Disease control in progressive pancreatic and intestinal neuroendocrine tumors by combined treatment with lanreotide autogel and temozolomide: The sonnet study. *Neuroendocrinology* 2018;**106**:202.

Phan 2017 *{published data only}*

* Phan AT, Pavel M, Caplin M, Wolin EM, Mirakhur B, Massien C, et al. Long-term efficacy and safety with lanreotide autogel/depot (LAN) from CLARINET and Open-Label Extension (OLE) studies. *Neuroendocrinology* 2017;**105**:207.

Raderer 2015 *{published data only}*

* Raderer M, Caplin M, Pavel M, C'wikla JB, Phan A, Sedlackova E, et al. Update on antitumor acitivity of lanreotide autogel (LAN) treatment for enteropancreatic neuroendocrine tumours (NET): the CLARINET open-label extension (OLE) study. *Austrian journal of clinical endocrinology and metabolism* 2015;**8**(SONDERHEFT 1):9.

Salazar 2015 *{published data only}*

* Salazar R, Verslype C, Baudin E, Libutti SK, Yao JC, Buzzoni R, et al. Phase II studies of BEZ235 in patients with advanced pancreatic neuroendocrine tumors (pNET). *Journal of Clinical Oncology* 2015;**33**(15 SUPPL. 1):4102.

Singh 2018 (2) *{published data only}*

* Singh AN, Pal S, Mangla V, Kilambi R, George J, Dash NR, et al. Pancreaticojejunostomy: Does the technique matter? A randomized trial. *Journal of Surgical Oncology* 2018;**117**(3):389-96.

Wolin 2013 *{published data only}*

* Wolin EM, Hainsworth JD, Hörsch D, Luppi G, Jehl V, Peeters M. Effect of open-label everolimus in patients with advanced neuroendocrine tumors after disease progression on somatostatin analog: A RADIANT-2 analysis. *Pancreas* 2013;**42**(2):385.

Wolin 2018 *{published data only}*

* Wolin EM, Pavel ME, Cwikla JB, Phan AT, Raderer M, Sedlackova E, et al. Final progression-free survival analyses for lanreotide autogel/depot 120 mg in metastatic enteropancreatic neuroendocrine tumors: the CLARINET extension study. *Pancreas* 2018;**47**(3):358-9.

Yao 2015 *{published data only}*

* Yao JC, Oh DY, Qian J, Park YS, Herbst F, Ridolfi A, et al. Everolimus for the treatment of advanced gastrointestinal or lung nonfunctional neuroendocrine tumors in east asian patients: A subgroup analysis of the RADIANT-4 study. *OncoTargets and Therapy* 2015;**12**:1717-28.

References to ongoing studies

NCT01744249 *{published data only}*

* NCT01744249. Sandostatin LAR and axitinib versus placebo in patients with advanced well-differentiated non-pancreatic neuroendocrine carcinomas [A phase II/III randomized double-blind study of sandostatin LAR in combination with axitinib versus sandostatin LAR with placebo in patients with advanced G1-G2 neuroendocrine tumours (WHO 2010) of non-pancreatic origin]. clinicaltrials.gov/show/NCT01744249 (first posted 6 December 2012).

NCT02246127 *{published data only}*

* NCT02246127. Efficacy and safety of everolimus and (streptozotocin- fluorouracil) given one upfront the other upon progression in advanced pancreatic neuroendocrine tumour [Randomized open label study to compare the efficacy and safety of everolimus followed by chemotherapy with streptozotocin- fluorouracil upon progression or the reverse sequence, in advanced progressive pancreatic neuroendocrine tumours]. clinicaltrials.gov/show/NCT02246127 (first posted 22 September 2014).

NCT03049189 *{published data only}*

* NCT03049189. Efficacy and safety of 177Lu-edotreotide PRRT in GEP-NET patients [A prospective, randomised, controlled, open-label, multicentre phase III study to evaluate efficacy and safety of peptide receptor radionuclide therapy (PRRT) with 177Lu-edotreotide compared to targeted molecular therapy with everolimus in patients with inoperable, progressive, somatostatin receptor-positive (SSTR+), neuroendocrine tumours of gastroenteric or pancreatic origin (GEP-NET)]. clinicaltrials.gov/show/NCT03049189 (first posted 9 February 2017).

Additional references

Aaronson 1993

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute* 1993;**85**(5):365-76.

Béliveau 2019

Béliveau A, Boyne DJ, Slater J, Brenner D, Arora P. BUGSnet: an R package to facilitate the conduct and reporting of Bayesian network meta-analyses. *BMC Medical Research Methodology* 2019;**19**(1):196.

Brignardello-Petersen 2018

Brignardello-Petersen R, Bonner A, Alexander PE, Siemieniuk RA, Furukawa TA, Rochwerg B, et al, GRADE Working Group. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. *Journal of Clinical Epidemiology* 2018;**93**:36-44.

Cives 2014

Cives M, Strosberg J. An update on gastroenteropancreatic neuroendocrine tumors. *Oncology (Williston Park)* 2014;**28**(9):749-56, 758.

Clift 2020

Clift AK, Kidd M, Bodei L, Toumpanakis C, Baum RP, Oberg K, et al. Neuroendocrine neoplasms of the small bowel and pancreas. *Neuroendocrinology* 2020;**110**(6):444-76.

Dasari 2017

Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncology* 2017;**3**(10):1335-42.

DePalo 2019

DePalo DK, Lee RM, Lopez-Aguiar AG, Gamboa AC, Rocha F, Poultsides G, et al, United States Neuroendocrine Tumor Study Group. Interaction of race and pathology for neuroendocrine tumors: epidemiology, natural history, or racial disparity? *Journal of Surgical Oncology* 2019;**120**(6):919-25.

Fraenkel 2012

Fraenkel M, Kim MK, Faggiano A, Valk GD. Epidemiology of gastroenteropancreatic neuroendocrine tumours. *Best Practice & Research Clinical Gastroenterology* 2012;**26**(6):691-703.

Fraenkel 2014

Fraenkel M, Kim M, Faggiano A, De Herder WW, Valk GD, Knowledge NETwork. Incidence of gastroenteropancreatic neuroendocrine tumours: a systematic review of the literature. *Endocrine-related Cancer* 2014;**21**(3):R153-63.

Hallet 2015

Hallet J, Law CH, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer* 2015;**121**(4):589-97.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. 5.1.0 [updated March 2011] edition. Chichester (UK): John Wiley & Sons, 2011.

Imaoka 2017

Imaoka H, Sasaki M, Takahashi H, Hashimoto Y, Ohno I, Mitsunaga S, et al. Progression-free survival as a surrogate endpoint in advanced neuroendocrine neoplasms. *Endocrine-related Cancer* 2017;**24**(9):475-83.

Klimstra 2019

Klimstra DS, Kloppell G, La Rosa S, Rindi G. Classification of neuroendocrine neoplasms of the digestive system. In: WHO Classification of Tumours Editorial Board, editors(s). WHO Classification of Tumours: Digestive System Tumours. 5th edition. Lyon: International Agency for Research on Cancer, 2019:16.

Kunz 2013

Kunz PL, Reidy-Lagunes D, Anthony LB, Bertino EM, Brendtro K, Chan JA, el al, North American Neuroendocrine Tumor Society. Consensus guidelines for the management and treatment of neuroendocrine tumors. *Pancreas* 2013;**42**(4):557-77.

Lawrence 2011

Lawrence B, Gustafsson BI, Chan A, Svejda B, Kidd M, Modlin IM. The epidemiology of gastroenteropancreatic neuroendocrine tumors. *Endocrinology and Metabolism Clinics of North America* 2011;**40**(1):1-18.

Modlin 2008

Modlin IM, Oberg K, Chung DC, Jensen RT, De Herder WW, Thakker RV, et al. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncology* 2008;**9**(1):61-72.

NCI 2010

National Cancer Institute. Common terminology criteria for adverse events (CTCAE), version 4.03. evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (accessed prior to 10 November 2021).

Pavel 2016

Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, et al, Vienna Consensus Conference participants. ENETS Consensus Guidelines Update for the management of distant metastatic disease of intestinal, pancreatic, bronchial Neuroendocrine Neoplasms (NEN) and NEN of unknown primary site. *Neuroendocrinology* 2016;**103**(2):172-85.

Pildal 2008

Pildal J, Hróbjartsson A, Jørgensen KJ, Hilden J, Altman DG, Gøtzsche PC. Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials. *International Journal of Epidemiology* 2008;**36**(4):847-57.

Puhan 2014

Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al, GRADE Working Group. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 2014;**349**:g5630.

Ramage 2012

Ramage JK, Ahmed A, Ardill J, Bax N, Breen DJ, Caplin ME, et al, UK and Ireland Neuroendocrine Tumour Society. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). *Gut* 2012;**61**(1):6-32.

Raymond 2011

Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *New England Journal of Medicine* 2011;**364**(11):1082.

R Core 2019 [Computer program]

R Foundation for Statistical Computing R: A Language and Environment for Statistical Computing. R Core Team, Version accessed prior to 10 November 2021. Vienna, Austria: R Foundation for Statistical Computing, 2019. www.R-project.org/.

RevMan 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration Review Manager (RevMan). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rücker 2012

Rücker G. Network meta-analysis, electrical networks and graph theory. *Research Synthesis Methods* 2012;**3**(4):312-24.

Rücker 2014

Rücker G, Schwarzer G. Reduce dimension or reduce weights? Comparing two approaches to multi-arm studies in network meta-analysis. *Statistics in Medicine* 2014;**33**(25):4353-69.

Rücker 2015

Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Medical Research Methodology* 2015;**15**:58.

Rücker 2021

Rücker G, Krahn U, König J, Efthimiou O, Davies A, Papakonstantinou T, Schwarzer G. Netmeta: network meta-analysis using frequentist methods. cran.r-project.org/web/packages/netmeta/netmeta.pdf (accessed 17 November 2021).

Saad 2016

Saad ED, Buyse M. Statistical controversies in clinical research: end points other than overall survival are vital for regulatory approval of anticancer agents. *Annals of Oncology* 2016;**27**(3):373-8.

Salanti 2014

Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP. Evaluating the quality of evidence from a network meta-analysis. *PLOS One* 2014;**9**(7):e99682.

Yao 2008 (2)

Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *Journal of Clinical Oncology* 2008;**26**(18):3063-72.

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Anthony 2012

Study characteristics	
Methods	Multicentre (16 countries), double-blind, phase 3 study 1:1 randomisation by interactive voice response system Study group assignments were masked. Enrolment: January 2007-April 2010 Subgroup analysis: effect of previous treatment with a long-acting SSA on PFS in RADIANT-2
Participants	Inclusion criteria • Age ≥ 18 years • Low-grade or intermediate-grade, unresectable locally advanced or distant metastatic neuroendocrine tumour • Disease progression by radiological assessment within the past 12 months • History of diarrhoea or flushing attributable to carcinoid syndrome • Measurable disease according to RECIST version 1.0 • WHO performance status ≤ 2 • Adequate bone marrow, renal, and hepatic function and adequately controlled lipid concentrations Exclusion criteria • Poorly differentiated or high-grade neuroendocrine carcinomas RADIANT-2 overall population Total patients: 429 Median age (study group 1 vs. study group 2): 60 vs. 60 Women, % (1 vs. 2): 55 vs. 42 WHO performance status 0/1/2, % (1 vs. 2): 55/39/6 vs. 66/29/5 Primary tumour site, %: • Small intestine, (1 vs. 2): 51 vs. 53 • Lung, (1 vs. 2): 15 vs. 5 • Colon, (1 vs. 2): 6 vs. 7 • Pancreas, (1 vs. 2): 5 vs. 7 • Liver, (1 vs. 2): 3 vs. 5

References to other published versions of this review

Kaderli 2019

Kaderli RM, Spanjol M, Kollár A, Bütikofer L, Gloy V, Dumont RA, et al. Therapeutic options for neuroendocrine tumors: a systematic review and network meta-analysis. *JAMA Oncology* 2019;**5**(4):480-9.

* Indicates the major publication for the study

Anthony 2012 *(Continued)*

- Other, (1 vs. 2): 19 vs. 23
- Missing, (1 vs. 2): 0 vs. 1

Grade (well differentiated/moderately differentiated/poorly differentiated), % (1 vs. 2): 77/18/1 vs. 82/14/1

Liver involvement, % (1 vs. 2): 92 vs. 92

Previous SSA treatment, % (1 vs. 2): 80 vs. 78

Previous systemic anti-tumour drugs, % (1 vs. 2): 46 vs. 38

Chemotherapy, % (1 vs. 2): 35 vs. 26

Immunotherapy, % (1 vs. 2): 13 vs. 9

Targeted therapy, % (1 vs. 2): 7 vs. 8

Other, % (1 vs. 2): 10 vs. 13

Prior SSA treatment subgroup

Total patients: 429

Previous SSA treatment, % (1 vs. 2): 80 vs. 78

- Primary tumour site (overall in previous SSA treatment group):
  - Foregut: 10%
  - Midgut: 72%
  - Hindgut: 11%
  - Not classified/missing: 7%

SSA naive, % (1 vs. 2): 20 vs. 22

- Primary tumour site (overall in SSA naive group):
  - Foregut: 32%
  - Midgut: 51%
  - Hindgut: 4%
  - Not classified/missing: 13%

Interventions	Study group 1 (RADIANT-2 overall: 216/429, prior SSA treatment subgroup: 173/339, SSA-naive group: 43/90): 10 mg oral everolimus once daily plus intramuscular 30 mg octreotide LAR every 28 days Study group 2 (RADIANT-2 overall: 213/429, prior SSA treatment subgroup: 166/339, SSA-naive group: 47/90): matching placebo plus intramuscular 30 mg octreotide LAR every 28 days Treatment duration: until disease progression, withdrawal from treatment because of adverse events, or withdrawal of consent After disease progression in the placebo plus octreotide LAR group, cross over to open-label everolimus plus octreotide LAR was permitted.
Outcomes	Primary endpoint: • Progression-free survival according to RECIST Secondary endpoints: • Objective response rate according to RECIST • Overall survival • Changes from baseline in 5-hydroxyindoleacetic acid and CgA concentrations • Safety

Anthony 2012 *(Continued)*

	Supportive endpoint: • Investigator-assessed progression-free survival Assessments: • CT or MRI were done at baseline and repeated every 12 weeks. • Serum CgA and 24-h urine samples for 5-hydroxyindoleacetic acid at baseline and on day 1 of each subsequent cycle (if raised at baseline) • Monitoring of adverse events, vital signs and physical examinations every 4 weeks • Chest radiographs every 12 weeks
Notes	Novartis funded the study and was involved in the study design, data collection and statistical analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information about sequence generation
Allocation concealment (selection bias)	Low risk	Allocation was performed centrally.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Central review for primary analysis of progression-free survival by an independent, masked committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients accounted for efficacy analysis according to the intention-to-treat principle.
Selective reporting (reporting bias)	Low risk	Except for one secondary endpoint, every endpoint stated in the study protocol was reported in the publication.
Other bias	Low risk	No other potential sources of bias found

Arnold 2005

Study characteristics

Methods	Randomisation was performed by phone at the study centre and done by computer by using the method of random permuted blocks stratified by carcinoid syndrome versus other tumour entities, age ≤ 65 years versus > 65 years, luminal tumours (midgut tumours and duodenal tumours) versus non-luminal (pancreatic) tumours, prior chemotherapy and prior octreotide treatment. Enrolment: January 1995-March 1998 Follow-up investigations were performed until April 2004.
Participants	Inclusion criteria

Arnold 2005 *(Continued)*

- Age ≥ 18 years
- Metastatic or locally advanced gastroenteropancreatic tumours without curative therapeutic option
- Primary within the pancreas, duodenum, and midgut; tumours of unknown origin believed to belong to the midgut as a result of the presence of a carcinoid syndrome or in nonfunctioning tumours as a result of histologic criteria
- Well differentiated histology by pathologic review
- Tumour progression documented on computed tomography (CT) or magnetic resonance imaging (MRI) according to World Health Organization (WHO) criteria
- Patients receiving ≤ 150 µg octreotide per day subcutaneously against flushing and/or diarrhoea caused by carcinoid syndrome

Exclusion criteria

- Pretreatment with interferon-alpha
- Pregnancy
- Karnofsky Index < 70
- Previous hepatic artery embolisation
- Leukocytes < 2.0 g/L
- Thrombocytes < 75 g/L
- Autoimmune disorders
- History of major depression
- Decompensated organ insufficiency
- Drug or alcohol addiction

Total randomised patients: 109

Total evaluable patients: 105

Age (study arm 1 vs. study arm 2): 58 vs. 57

Women, % (1 vs. 2): 47 vs. 44

Prior treatment, %:

- ≤ 150 µg octreotide per day (1 vs. 2): 14 vs. 11
- Chemotherapy (1 vs. 2): 8 vs. 15

Primary tumour site, %:

- Pancreas (1 vs. 2): 31 vs. 41
- Duodenum (1 vs. 2): 2 vs. 2
- Midgut (1 vs. 2): 49 vs. 37
- Unknown (1 vs. 2): 18 vs. 20

Nonfunctioning tumours, % (1 vs. 2): 53 vs. 56

Interventions	Study arm 1 (51/105): 200 µg octreotide, thrice daily, subcutaneous injection Study arm 2 (54/105): 200 µg octreotide, thrice daily, subcutaneous injection plus 4.5×10^6 IU interferon-alpha thrice weekly Treatment duration: until CT or MRI documented tumour progression Additional antiproliferative therapy was not allowed.
Outcomes	Primary endpoint: • Time to treatment failure Secondary endpoints:

Arnold 2005 *(Continued)*

	• Survival • Adverse events • Quality of life • Symptomatic response (only in patients with carcinoid syndrome) • Biochemical response (CgA in 40 patients, urine 5-hydroxyindoleacetic acid levels in 26 patients) Assessments: • Pretreatment evaluation: biochemical screening, chest radiography, octreoscan, and CT or MRI of pertinent index lesions • Follow-up investigations were performed at 3-month intervals until tumour progression • CT or MRI scans of pertinent indicator lesions were evaluated by one of the authors in a blinded fashion • Biochemical response was evaluated only in patients treated in the hospital of the principal author
Notes	Novartis Pharma and Roche Pharma participated in the development of the study design and provided funding.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified randomisation was done by computer by using the method of random permuted blocks.
Allocation concealment (selection bias)	Low risk	Allocation was performed centrally.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study treatment was not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	CT or MRI scans were evaluated by one of the authors in a blinded fashion, but not by independent personnel.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Biochemical response was evaluated only in one centre. 109 patients were randomised but only 105 were evaluable.
Selective reporting (reporting bias)	Low risk	No study protocol available, but all endpoints were reported.
Other bias	Low risk	No other potential sources of bias found

Bergsland 2020

Study characteristics	
Methods	Multicentre, randomised, double-blind, phase II study
Participants	Inclusion criteria • Progressive low-intermediate grade carcinoid tumours • Radiologic progressive disease < 12 months • Prior SSA mandated for midgut tumours

Bergsland 2020 *(Continued)*

	• Trial had 85% power to detect a difference in median PFS 14 v 9 mo (hazard ratio [HR] 0.64) at 1-sided alpha = 0.1. Stratified log-rank test based on intention-to-treat (ITT) principle used. Unblinding and cross-over allowed if PD confirmed by central review Total patients: 171 Median age (overall): 63 Women (overall): 56% Small bowel primary (overall): 66% Concurrent SSA treatment (overall): 87%
Interventions	Intervention group (97/171): pazopanib, 800 mg/day, oral intake Control group (74/171): placebo Concurrent SSA allowed if previous progressive disease on SSA was documented. Cross-over was allowed if progressive disease was confirmed by central review.
Outcomes	Primary endpoint: • Progression-free survival Secondary endpoints: • Overall survival • Objective response rate • Safety
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Low risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Central review was mentioned, but it remained unclear, when and how it was performed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information given
Selective reporting (reporting bias)	Unclear risk	One secondary endpoint (objective response rate) was not reported.
Other bias	Low risk	No other potential sources of bias found

Caplin 2014

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3 study • 48 secondary or tertiary care centres in 14 countries Duration: 96 weeks Computer-generated randomisation, stratified by presence or absence of tumour progression at baseline and receipt or nonreceipt of previous therapies Conducted between June 2006 and April 2013
Participants	Inclusion criteria • Adults (≥ 18 years of age) • Sporadic well differentiated or moderately differentiated neuroendocrine tumours, located in the pancreas, midgut, hindgut or of unknown origin • Unresectable locally advanced tumour, metastatic disease or declined surgery • Measurable tumour according to RECIST (vers. 1.0) • Ki-67 index of less than 10% or a mitotic index of ≤ 2 mitoses per 10 high-power fields • Nonfunctioning tumours (except for gastrinomas that had been adequately controlled by means of proton-pump inhibitors for 4 months or longer) • Target lesion or lesions that were classified as grade 2 or higher on somatostatin-receptor scintigraphy (0 (no uptake by tumour) to 4 (very intense uptake by tumour)) within the previous 6 months • WHO performance score ≤ 2 • A biopsy of the neuroendocrine tumour within 6 months before study entry was required for patients who had previous cancer and those with evidence of clinical progression. Exclusion criteria • Previous treatment with interferon, chemoembolisation, or chemotherapy within 6 months before study entry, a radionuclide at any time, or a somatostatin analogue at any time (unless they had received it > 6 months previously and for < 15 days) • Major surgery related to the neuroendocrine tumour within 3 months before study entry • Multiple endocrine neoplasia • Previous cancer (except: 1] treated or untreated in situ cervical or uterine carcinoma, or 2] basal-cell skin carcinoma, or 3] other cancers that had been treated with curative intent and had been disease-free for > 5 years) • Baseline abnormalities or medical conditions that could jeopardise the patient's safety or interfere with the study Withdrawal • Tumour progression (RECIST) • Investigator's judgement • Patient's request • Adverse event that could jeopardise the patient's safety Total patients: 204 Age (lanreotide vs. placebo): 63 vs. 62 Women, % (lanreotide vs. placebo): 48 vs. 48 Prior treatment for neuroendocrine tumour, % (lanreotide vs. placebo): 16 vs. 16 Primary tumour resected, % (lanreotide vs. placebo): 40 vs. 38

Caplin 2014 *(Continued)*

	Origin of tumour: • Pancreas, % (lanreotide vs. placebo): 42 vs. 48 • Midgut, % (lanreotide vs. placebo): 33 vs. 39 • Hindgut, % (lanreotide vs. placebo): 11 vs. 3 • Unknown, % (lanreotide vs. placebo): 15 vs. 11 Ki-67 index, 0-2%/3-10%, % (lanreotide vs. placebo): 68/32 vs. 70/28 Hepatic tumour volume: • 0%, % (lanreotide vs. placebo): 16 vs. 17 • > 0-10%, % (lanreotide vs. placebo): 33 vs. 39 • > 10-25%, % (lanreotide vs. placebo): 13 vs. 17 • > 25-50%, % (lanreotide vs. placebo): 23 vs. 12 • > 50%,% (lanreotide vs. placebo): 16 vs. 16
Interventions	Intervention group (101/204): extended-release aqueous-gel formulation of lanreotide, 120 mg, without dose adjustment, deep subcutaneous injection, every 28 days to a maximum of 24 injections Control group (103/204): placebo (sodium chloride), deep subcutaneous injection, every 28 days to a maximum of 24 injections In case of disease progression while receiving placebo, patients crossed over to lanreotide.
Outcomes	Primary endpoint: • Progression-free survival or death within 96 weeks after the first injection of the study drug Secondary endpoints: • Proportion of patients who were alive without disease progression at 48 and 96 weeks • Time to tumour progression • Overall survival • Quality of life • CgA levels • Pharmacokinetic data • Safety Exploratory endpoints: • Data on other tumour biomarkers Assessments: • Study visits: at weeks 1 (baseline), 12, 24, 36, 48, 72, and 96 • CT or MRI of the chest, abdomen, and pelvis was performed twice during screening to determine the baseline disease-progression status. Results of the second imaging test were considered to be the baseline findings and were used to determine target-lesion sizes. • Single scans were obtained at all post-baseline visits. • Disease progression was assessed centrally according to RECIST, version 1.0. • Two quality of life questionnaires (QLQ-C30 and QLQ-GI.NET21) were completed at post-screening visits. • Serum chromogranin A levels: all visits and also at weeks 60 and 84 • Serum lanreotide levels: prior to drug administration at all study visits and after the first and sixth administration • Safety assessments: monitoring for adverse events, physical examination and monitoring of vital signs (at all visits), electrocardiography and ultrasonography of the gallbladder (at baseline and at weeks 48 and 96), and clinical laboratory tests (at screening, baseline, and at weeks 48 and 96)

Caplin 2014 *(Continued)*

Notes	The study was designed, funded, and conducted by Ipsen in collaboration with the European Neuroendocrine Tumor Society and the UK and Ireland Neuroendocrine Tumour Society.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation lists were created by a statistician employed by the sponsor who was independent of the study.
Allocation concealment (selection bias)	Low risk	The blinded database was held at a third-party contract clinical research organisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded study design. Independent health professionals prepared and administered injections.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Disease progression was assessed centrally, but it remained unclear whether it was performed by independent personnel.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients accounted for in ITT analysis
Selective reporting (reporting bias)	Low risk	Study protocol available. One secondary endpoint mentioned in the protocol was not reported as a endpoint in the publication, but was reported in the supplementary appendix.
Other bias	Low risk	No other potential sources of bias found

Castellano 2013

Study characteristics

Methods	Multicentre (16 countries), double-blind, phase 3 study 1:1 randomisation by interactive voice response system Study group assignments were masked. Enrolment: January 2007-April 2010 Subgroup analysis: to assess the efficacy and safety of everolimus plus octreotide LAR in patients with colorectal primary NETs
Participants	Inclusion criteria • Age ≥ 18 years • Low-grade or intermediate-grade, unresectable locally advanced or distant metastatic neuroendocrine tumour • Disease progression by radiological assessment within the past 12 months • History of diarrhoea or flushing attributable to carcinoid syndrome • Measurable disease according to RECIST version 1.0 • WHO performance status ≤ 2

Castellano 2013 *(Continued)*

- Adequate bone marrow, renal, and hepatic function and adequately controlled lipid concentrations

Exclusion criteria

- Poorly differentiated or high-grade neuroendocrine carcinomas

RADIANT-2 overall population

Total patients: 429

Median age (study group 1 vs. study group 2): 60 vs. 60

Women, % (1 vs. 2): 55 vs. 42

WHO performance status 0/1/2, % (1 vs. 2): 55/39/6 vs. 66/29/5

Primary tumour site, %:

- Small intestine, (1 vs. 2): 51 vs. 53
- Lung, (1 vs. 2): 15 vs. 5
- Colon, (1 vs. 2): 6 vs. 7
- Pancreas, (1 vs. 2): 5 vs. 7
- Liver, (1 vs. 2): 3 vs. 5
- Other, (1 vs. 2): 19 vs. 23
- Missing, (1 vs. 2): 0 vs. 1

Grade (well differentiated/moderately differentiated/poorly differentiated), % (1 vs. 2): 77/18/1 vs. 82/14/1

Liver involvement, % (1 vs. 2): 92 vs. 92

Previous SSA treatment, % (1 vs. 2): 80 vs. 78

Previous systemic anti-tumour drugs, % (1 vs. 2): 46 vs. 38

Chemotherapy, % (1 vs. 2): 35 vs. 26

Immunotherapy, % (1 vs. 2): 13 vs. 9

Targeted therapy, % (1 vs. 2): 7 vs. 8

Other, % (1 vs. 2): 10 vs. 13

Colorectal NET subgroup

Total patients: 39

Age < 65 years, % (study group 1 vs. study group 2): 79 vs. 70

Women, % (1 vs. 2): 58 vs. 40

WHO performance status 0/1/2, % (1 vs. 2): 58/32/11 vs. 60/30/10

Grade (well differentiated/moderately differentiated/poorly differentiated), % (1 vs. 2): 74/11/0 vs. 60/40/0

Previous SSA treatment, % (1 vs. 2): 68 vs. 90

Previous chemotherapy, % (1 vs. 2): 37 vs. 45

Interventions	Study group 1 (RADIANT-2 overall: 216/429, colorectal NET subgroup: 19/39): 10 mg oral everolimus once daily plus intramuscular 30 mg octreotide LAR every 28 days Study group 2 (RADIANT-2 overall: 213/429, colorectal NET subgroup: 20/39): matching placebo plus intramuscular 30 mg octreotide LAR every 28 days

Castellano 2013 *(Continued)*

	Treatment duration: until disease progression, withdrawal from treatment because of adverse events, or withdrawal of consent After disease progression in the placebo plus octreotide LAR group, cross-over to open-label everolimus plus octreotide LAR was permitted.
Outcomes	Primary endpoint: • Progression-free survival according to RECIST Secondary endpoints: • Objective response rate according to RECIST • Overall survival • Changes from baseline in 5-hydroxyindoleacetic acid and CgA concentrations • Safety Supportive endpoint: • Investigator-assessed progression-free survival Assessments: • CT or MRI were done at baseline and repeated every 12 weeks. • Serum CgA and 24-h urine samples for 5-hydroxyindoleacetic acid at baseline and on day 1 of each subsequent cycle (if raised at baseline) • Monitoring of adverse events, vital signs and physical examinations every 4 weeks • Chest radiographs every 12 weeks
Notes	Novartis funded the study and was involved in the study design, data collection and statistical analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information about sequence generation
Allocation concealment (selection bias)	Low risk	Allocation was performed centrally.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Central review for primary analysis of progression-free survival by an independent, masked committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients accounted for efficacy analysis according to the intention to treat principle.
Selective reporting (reporting bias)	Low risk	Except for one secondary endpoint, every endpoint stated in the study protocol was reported in the publication.
Other bias	Low risk	No other potential sources of bias found

Dasari 2015

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3 study • 48 secondary or tertiary care centres in 14 countries Duration: 96 weeks Computer-generated randomisation, stratified by presence or absence of tumour progression at baseline and receipt or nonreceipt of previous therapies Conducted between June 2006 and April 2013
Participants	Inclusion criteria • Adults (≥ 18 years of age) • Sporadic well differentiated or moderately differentiated neuroendocrine tumours, located in the pancreas, midgut, hindgut or of unknown origin. • Unresectable locally advanced tumour, metastatic disease or declined surgery • Measurable tumour according to RECIST (vers. 1.0) • Ki-67 index of less than 10% or a mitotic index of ≤ 2 mitoses per 10 high-power fields • Nonfunctioning tumours (except for gastrinomas that had been adequately controlled by means of proton-pump inhibitors for 4 months or longer) • Target lesion or lesions that were classified as grade 2 or higher on somatostatin-receptor scintigraphy (0 (no uptake by tumour) to 4 (very intense uptake by tumour)) within the previous 6 months • WHO performance score ≤ 2 • A biopsy of the neuroendocrine tumour within 6 months before study entry was required for patients who had previous cancer and those with evidence of clinical progression. Exclusion criteria • Previous treatment with interferon, chemoembolisation, or chemotherapy within 6 months before study entry, a radionuclide at any time, or a somatostatin analogue at any time (unless they had received it > 6 months previously and for < 15 days) • Major surgery related to the neuroendocrine tumour within 3 months before study entry • Multiple endocrine neoplasia • Previous cancer (except: 1] treated or untreated in situ cervical or uterine carcinoma, or 2] basal-cell skin carcinoma, or 3] other cancers that had been treated with curative intent and had been disease-free for > 5 years) • Baseline abnormalities or medical conditions that could jeopardise the patient's safety or interfere with the study Withdrawal • Tumour progression (RECIST) • Investigator's judgement • Patient's request • Adverse event that could jeopardise the patient's safety CLARINET overall study population Total patients: 204 Age (lanreotide vs. placebo): 63 vs. 62 Women, % (lanreotide vs. placebo): 48 vs. 48 Prior treatment for neuroendocrine tumour, % (lanreotide vs. placebo): 16 vs. 16

Dasari 2015 *(Continued)*

	Primary tumour resected, % (lanreotide vs. placebo): 40 vs. 38 Origin of tumour: • Pancreas, % (lanreotide vs. placebo): 42 vs. 48 • Midgut, % (lanreotide vs. placebo): 33 vs. 39 • Hindgut, % (lanreotide vs. placebo): 11 vs. 3 • Unknown, % (lanreotide vs. placebo): 15 vs. 11 Ki-67 index, 0-2%/3-10%, % (lanreotide vs. placebo): 68/32 vs. 70/28 Hepatic tumour volume: • 0%, % (lanreotide vs. placebo): 16 vs. 17 • > 0-10%, % (lanreotide vs. placebo): 33 vs. 39 • > 10-25%, % (lanreotide vs. placebo): 13 vs. 17 • > 25-50%, % (lanreotide vs. placebo): 23 vs. 12 • > 50%,% (lanreotide vs. placebo): 16 vs. 16 Midgut subgroup analysis Total patients: 73 Mean age: 64 Previous NET surgery: 48% Hepatic tumour volume: • 0-10%: 66% • > 10%: 34%
Interventions	Intervention group (CLARINET overall: 101/204; midgut subgroup: 33/73): extended-release aqueous-gel formulation of lanreotide, 120 mg, without dose adjustment, deep subcutaneous injection, every 28 days to a maximum of 24 injections Control group (CLARINET overall: 103/204; midgut subgroup: 40/73): placebo (sodium chloride), deep subcutaneous injection, every 28 days to a maximum of 24 injections In case of disease progression while receiving placebo, patients crossed over to lanreotide.
Outcomes	Primary endpoint: • Progression-free survival or death within 96 weeks after the first injection of the study drug Secondary endpoints: • Proportion of patients who were alive without disease progression at 48 and 96 weeks • Time to tumour progression • Overall survival • Quality of life • CgA levels • Pharmacokinetic data • Safety Exploratory endpoints: • Data on other tumour biomarkers Assessments: • Study visits: at weeks 1 (baseline), 12, 24, 36, 48, 72, and 96

Dasari 2015 *(Continued)*

- CT or MRI of the chest, abdomen, and pelvis was performed twice during screening to determine the baseline disease-progression status. Results of the second imaging test were considered to be the baseline findings and were used to determine target-lesion sizes.
- Single scans were obtained at all post-baseline visits.
- Disease progression was assessed centrally according to RECIST, version 1.0.
- Two quality of life questionnaires (QLQ-C30 and QLQ-GI.NET21) were completed at post-screening visits.
- Serum chromogranin A levels: all visits and also at weeks 60 and 84
- Serum lanreotide levels: prior to drug administration at all study visits and after the first and sixth administration
- Safety assessments: monitoring for adverse events, physical examination and monitoring of vital signs (at all visits), electrocardiography and ultrasonography of the gallbladder (at baseline and at weeks 48 and 96), and clinical laboratory tests (at screening, baseline, and at weeks 48 and 96)

Notes	The study was designed, funded, and conducted by Ipsen in collaboration with the European Neuroendocrine Tumor Society and the UK and Ireland Neuroendocrine Tumour Society.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation lists were created by a statistician employed by the sponsor who was independent of the study.
Allocation concealment (selection bias)	Low risk	The blinded database was held at a third-party contract clinical research organisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded study design. Independent health professionals prepared and administered injections.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Disease progression was assessed centrally, but it remained unclear whether it was performed by independent personnel.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients accounted for in ITT analysis
Selective reporting (reporting bias)	Low risk	Study protocol available. One secondary endpoint mentioned in the protocol was not reported as an endpoint in the publication, but was reported in the supplementary appendix.
Other bias	Low risk	No other potential sources of bias found

Di Gialleonardo 2020

Study characteristics

Methods	International (11 countries), multicentre, randomised, double-blind, placebo-controlled phase 3 companion study (TELECAST) 1:1:1 randomisation stratified by baseline u5-HIAA levels Enrolment: April 2014 to April 2015

Di Gialleonardo 2020 *(Continued)*

	Subgroup analysis: assessment of efficacy and safety of telotristat in the TELECAST study population with 2 or fewer bowel movements per day

Participants	Inclusion criteria
	• Age ≥ 18 years
	• Histopathologically confirmed, well differentiated metastatic NETs
	• Documented history of carcinoid syndrome
	• No SSA treatment or stable-dose SSA treatment (long-acting release, depot or infusion pump) for at least 3 months prior to enrolment
	• Average of < 4 bowel movements/day
	• At least 1 of the following signs or symptoms:
	  ○ Daily stool consistency ≥ 5 on the Bristol Stool Form scale for ≥ 50% of the days during the screening period
	  ○ Average daily cutaneous flushing frequency of ≥ 2
	  ○ Average daily rating of ≥ 3 for abdominal pain
	  ○ Nausea present ≥ 20% of days
	  ○ u5-HIAA above the upper limit of normal
	• For patients not receiving SSA therapy: at least 1 of the above symptoms or an average of ≥ 4 bowel movements/day
	
	Exclusion criteria
	• Diarrhoea attributable to any condition other than carcinoid syndrome
	• ≥ 4 BMs/day while on concomitant SSA therapy
	• Enteric infection
	• Karnofsky performance status ≤ 60%
	• History of short bowel syndrome
	• Chronic or idiopathic constipation
	• Clinically important baseline elevation in liver function tests
	• Tumour-directed therapy within 4 weeks prior to screening
	• Hepatic embolisation, radiotherapy, radiolabeled SSA therapy and/or tumour debulking within 12 weeks prior to screening
	
	TELECAST overall population
	
	Total patients: 76
	
	Mean age (A vs. B vs. C): 62 vs. 64 vs. 63
	
	Women, % (A vs. B vs. C): 50 vs. 44 vs. 40
	
	SSA therapy at study entry, %:
	• Octreotide (A vs. B vs. C): 46 vs. 68 vs. 64
	• Lanreotide (A vs. B vs. C): 54 vs. 20 vs. 12
	• Unknown (A vs. B vs. C): 0 vs. 0 vs. 4
	• Not on SSA (A vs. B vs. C): 0 vs. 12 vs. 20
	
	Subgroup: ≤ 2 bowel movements per day population
	
	Total patients: 28

Interventions	Study group A (TELECAST overall: 26/76, subgroup: 9/28): placebo, oral doses, three times per day for 12 weeks Study group B (TELECAST overall: 25/76, subgroup: 10/28): telotristat ethyl 250 mg, oral doses, three times per day for 12 weeks

Di Gialleonardo 2020 *(Continued)*

	Study group C (TELECAST overall: 25/76, subgroup: 9/28): telotristat ethyl 500 mg, oral doses, three times per day for 12 weeks Patients continued to receive their baseline stable-dose SSA therapy. Rescue short-acting SSA use was allowed. After the study, all patients were offered treatment with telotristat ethyl 500 mg, three times per day in a 36-week open-label extension.
Outcomes	Primary endpoints: • Incidence of treatment-emergent adverse events • Percent change from baseline in 24-h u5-HIAA levels at week 12 Secondary endpoints: • Change from baseline averaged over the 12-weeks period for daily bowel movement frequency • Stool consistency • Cutaneous flushing episodes • Abdominal pain • Frequency of rescue short-acting SSA treatment Additional endpoint: • Durability of response to treatment Assessments: • Screening period of at least 3 weeks • Electronic patient diary (identical to the one used in the TELESTAR study) for patient-reported measures
Notes	Trial supported by Lexicon Pharmaceuticals, Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	Nearly equal amount of participants per study group
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study design
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The majority of endpoints were self-reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	In the main study, all randomised patients accounted for safety analysis but 10 of 76 (13%) randomised patients were excluded from the u5-HIAA which was the second primary endpoint. It is not clear, if these patients would have been in this subgroup.

Di Gialleonardo 2020 *(Continued)*

Selective reporting (reporting bias)	Low risk	No study protocol available, but every stated endpoint was reported.
Other bias	Low risk	No other potential sources of bias found

Elf 2018

Study characteristics	
Methods	Randomised phase II study Start: January 2014 Closed: September 2016
Participants	Inclusion criteria • Multiple SI-NET liver metastases • Grade 1 or 2 • Not accessible to curative resection or ablation • Elevated serum chromogranin A (CgA) and/or 24-h urinary 5-HIAA excretion (du5-HIAA). Exclusion criteria • Remaining extrahepatic metastases • Previous locoregional or systemic anti-tumoural treatment (except SSA) • Impaired liver function • Tumour volume exceeding 50% of total liver volume Total patients: 11 Median age (RE vs. HAE): 66.5 vs. 67 Women, % (RE vs. HAE): 67 vs. 80 Primary tumour grade 1, % (RE vs. HAE): 83 vs. 40 Primary tumour grade 2, % (RE vs. HAE): 17 vs. 60 Functional tumours: not reported
Interventions	RE group (6/11): radioembolisation with bilobar infusion in a standard manner. Protective coil embolisation was used when necessary to prevent non-target embolisation. The administered activity of ^{90}Y resin microspheres (SIR-spheres™) was calculated using the partition model. HAE group (5/11): hepatic arterial embolisation was performed by infusion of PVA particles (45–150 µm) until stasis was achieved. The right liver lobe was treated first, embolising the remaining left lobe about 6 weeks later.
Outcomes	Primary endpoint: • Treatment response of hepatic metastases at 3 months after therapy Secondary endpoints: • Radiological response at 6 months • Biochemical response • Toxicity

Elf 2018 *(Continued)*

- Evaluation of usefulness of early changes in diffusion-weighted imaging parameters in predicting later treatment response

Assessments:

- MRI or CT before treatment, 1 month after treatment followed by response evaluation with MRI or CT according to RECIST 1.1 at 3 and 6 months
- CgA in serum and du5-HIAA were measured at 3 and 6 months after treatment.
- Toxicity was assessed weekly during the first month after treatment and 3 and 6 months after treatment by laboratory analysis.

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	No evidence for blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No evidence for independent assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for final analysis
Selective reporting (reporting bias)	Low risk	No study protocol available. But all endpoints mentioned were reported.
Other bias	Low risk	No other potential sources of bias found

Faiss 2003

Study characteristics

Methods	Prospective, randomised, multicentre trial Stratified block-wise randomisation, carried out centrally, stratified by primary tumour localisation (foregut, midgut, hindgut, unknown) and functional or non-functional tumours Enrolment: July 1995-October 1998
Participants	Inclusion criteria • Documented tumour progression of neuroendocrine tumour disease Exclusion criteria

Faiss 2003 *(Continued)*

- ECOG performance score of 3 or 4
- Previous therapy for more than 4 weeks with any of the study agents, any chemotherapy or chemoembolisation of liver metastases
- Leukocyte count less than 2.5 x 10^9/L
- Platelet count less than 100 x 10^9/L
- Any other concurrent or recent malignant disease

Total patients: 80

Median age (lanreotide vs. interferon alfa vs. combination): 60 vs. 56 vs. 58

Women, % (lanreotide vs. interferon alfa vs. combination): 52 vs. 37 vs. 36

Functional tumour, % (lanreotide vs. interferon alfa vs. combination): 48 vs. 33 vs. 29

Liver metastases, % (lanreotide vs. interferon alfa vs. combination): 92 vs. 93 vs. 89

Localisation of the primary, %:

- Foregut (lanreotide vs. interferon alfa vs. combination): 56 vs. 37 vs. 43
- Midgut (lanreotide vs. interferon alfa vs. combination): 32 vs. 41 vs. 39
- Hindgut (lanreotide vs. interferon alfa vs. combination): 0 vs. 4 vs. 7
- Unknown (lanreotide vs. interferon alfa vs. combination): 12 vs. 19 vs. 11

Previous surgical resection, % (lanreotide vs. interferon alfa vs. combination): 56 vs. 44 vs. 54

Interventions	Study arm 1 (27/80): lanreotide, 1 mg, three times a day, subcutaneous injection Study arm 2 (28/80): interferon alfa, 5 x 10^6 U, three times a week, subcutaneous injection Study arm 3 (29/80): lanreotide, 1 mg three times a day, subcutaneous injection and interferon alfa, 5 x 10^6 U, three times a week, subcutaneous injection Patients showing progressive disease while receiving the initially assigned treatment with lanreotide or interferon alfa received the combination of lanreotide and interferon alfa.
Outcomes	Primary endpoint: • 1-year tumour progression rate Secondary endpoints: • Symptom control • Biochemical response assessed by serum chromogranin A levels, serum serotonin levels, and urinary 5-hydroxyindoleacetic acid (5-HIAA) levels Assessments: • Transabdominal ultrasound and CT scans every 3 months
Notes	Ipsen Pharma and Essex Pharma participated in the development of the study design, provided funding and participated also in the collection of the data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A stratified block-wise randomisation with block size 6 was carried out centrally by telephone using randomisation tables.

Faiss 2003 *(Continued)*

Allocation concealment (selection bias)	Low risk	Done centrally
Blinding of participants and personnel (performance bias) All outcomes	High risk	No masking
Blinding of outcome assessment (detection bias) All outcomes	High risk	Only critical cases were re-reviewed by an independent radiologist.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4 patients had to be excluded after randomisation.
Selective reporting (reporting bias)	Low risk	No study protocol available but all endpoints in 'methods' were reported in 'results'.
Other bias	Low risk	No other potential sources of bias found

Fisher 2016

Study characteristics	
Methods	3-phase, multicentre study in 12 countries • 16-week randomised, double-blind phase (reported here) • 32-week initial open-label phase (not reported here) • Long-term open-label extension (not reported here) 1:1 randomisation using 2 computer-generated lists (one for the US and one for all other countries) stratified by previous treatment with any long- or short-acting somatostatin analog or SSA-naive patients Start: May 2009 End: May 2013 Subgroup analysis: Efficacy and safety of lanreotide in the ELECT study subgroup of patients with prior octreotide therapy
Participants	Inclusion criteria • Age ≥ 18 years • Histopathologically confirmed diagnosis of neuroendocrine tumour or a carcinoid tumour of unknown location with liver metastases (documented biopsy) • History of carcinoid syndrome (flushing and/or diarrhoea) • Positive somatostatin-receptor scintigraphy • SSA-naive or responsive to conventional octreotide LAR doses (≤ 30 mg/4 weeks) or short-acting octreotide (≤ 600 µg daily) • Absence of tumour progression on 2 sequential computed tomography/magnetic resonance imaging scans ≥ 3 months apart • Last scan ≤ 6 months from study entry Exclusion criteria

Fisher 2016 *(Continued)*

- History of treatment-refractory carcinoid syndrome with conventional SSA doses
- Treatment with interferon, chemotherapy, and/or peptide receptor radionuclide therapy
- Tumour debulking < 3 months before study entry
- Hepatic artery embolisation/chemoembolisation and/or selective internal radiation therapy < 6 months before study entry
- Short-bowel syndrome
- Uncontrolled diabetes
- Hypertension
- Severe renal and/or hepatic impairment
- Cardiac disease New York Heart Association classification > class 1
- Any malignancy except NET, basocellular skin carcinoma, or in situ cervical carcinoma
- Life expectancy < 1 year

ELECT overall population

Total patients: 115

Mean age (lanreotide vs. placebo): 58 vs. 59

Women, % (lanreotide vs. placebo): 54 vs. 62

Prior SSA therapy, % (lanreotide vs. placebo): 56 vs. 55

Short-acting octreotide during screening, % (lanreotide vs. placebo): 51 vs. 52

Subgroup: prior octreotide therapy

Total patients: 64

Mean age (overall): 59

Women (overall): 55%

Interventions	Intervention group (ELECT overall population: 59/115, prior octreotide therapy subgroup: 33/64): lanreotide depot/autogel 120 mg, every 4 weeks by deep subcutaneous injection Control group (ELECT overall population: 56/115, prior octreotide therapy subgroup: 31/64): placebo (0.9% saline solution), every 4 weeks by deep subcutaneous injection Self-injected subcutaneous short-acting octreotide for symptom rescue at patients' discretion After ≥ 4 weeks in the double-blind phase, patients could roll over into the open-label phase if they used octreotide for ≥ 21 days of the 28-day cycle and used a dose ≥ 300 µg/day for ≥ 14 of the 21 days.

Outcomes	Primary endpoint:
	
	• Adjusted mean percentage of days short-acting octreotide was used for symptom control
	
	Secondary endpoints:
	
	• Average daily frequency of diarrhoea and flushing
	• Percentage of days non-octreotide rescue medications were used
	• Proportion of patients who rolled over early into the initial open-label phase
	• Change from baseline to week 12 in:
	  ◦ Health-related quality of life
	  ◦ Plasma chromogranin
	  ◦ Urinary 24-hour 5-hydroxyindoleacetic acid levels
	• Safety
	
	Assessments:

Fisher 2016 *(Continued)*

	• Prior to randomisation, patients completed a 31-day (± 3 days) screening period. • Daily diary by Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS) (number and severity of diarrhoea and flushing events; and use and dose of short-acting octreotide and any other rescue medications)
Notes	Trial funded by Ipsen

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, stratified randomisation
Allocation concealment (selection bias)	Unclear risk	Insufficient information given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded trial design with same injection schedules
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Patient-reported results
Incomplete outcome data (attrition bias) All outcomes	Low risk	Efficacy analyses were performed with all randomised patients on an ITT principle.
Selective reporting (reporting bias)	Low risk	No study protocol available, but every stated endpoint was reported.
Other bias	Low risk	No other potential sources of bias found

Ito 2012

Study characteristics

Methods	International, multicentre, double-blind, phase 3 study • 82 centres in 18 countries worldwide Randomisation: • Ratio 1:1 • Stratified by whether or not patients have received prior cytotoxic chemotherapy and by WHO performance status (0 vs. 1-2) at baseline Start: July 2007 Closed: May 2009
Participants	Inclusion criteria: • 18 years of age or older

Ito 2012 *(Continued)*

- Low-grade or intermediate-grade advanced (unresectable or metastatic) pancreatic neuroendocrine tumours
- Radiologic documentation of disease progression in the previous 12 months
- Measurable disease (RECIST, vers. 1.0)
- World Health Organization (WHO) performance status of 2 or less
- Adequate bone marrow, renal, and hepatic function
- Adequately controlled lipid and glucose concentrations

Exclusion criteria:

- Hepatic-artery embolisation within 6 months before enrolment or within 1 month if there were other sites of measurable disease or cryoablation or radiofrequency ablation of hepatic metastasis within 2 months before enrolment
- Severe or uncontrolled medical conditions
- Prior therapy with an mTOR inhibitor
- Long-term treatment with glucocorticoids or other immunosuppressive agents

RADIANT-3 overall population:

- Total patients: 410
- Median age (everolimus vs. placebo): 58 vs. 57
- Women % (everolimus vs. placebo): 47 vs 42
- WHO performance status 0 (everolimus vs. placebo): 67% vs. 66%
- Well differentiated % (everolimus vs. placebo): 82 vs. 84
- Moderately differentiated % (everolimus vs. placebo): 17 vs. 15
- Liver involvement, % (everolimus vs. placebo): 92% vs. 92%
- Functional tumours (overall): 24%
- Prior therapy for NET, %:
  - Radiotherapy (everolimus vs. placebo): 23 vs. 20
  - Chemotherapy (everolimus vs. placebo): 50 vs. 50
  - Somatostatin analogue therapy (everolimus vs. placebo): 49 vs. 50

RADIANT-3 Japanese subgroup:

- Total patients: 40
- Median age (everolimus vs. placebo): 45 vs. 53
- Women % (everolimus vs. placebo): 44 vs. 53
- WHO performance status 0 (everolimus vs. placebo): 87% vs. 88%
- Well differentiated % (everolimus vs. placebo): 100 vs. 94
- Moderately differentiated % (everolimus vs. placebo): 0 vs. 6
- Prior therapy for NET, %:
  - Radiotherapy (everolimus vs. placebo): 13 vs. 12
  - Chemotherapy (everolimus vs. placebo): 61 vs. 53
  - Somatostatin analogue therapy (everolimus vs. placebo): 22 vs. 35

Interventions	Intervention group (overall: 207/410; Japanese subgroup: 23): oral everolimus, at a dose of 10 mg once daily, in conjunction with best supportive care (e.g. somatostatin analogue therapy) Control group (overall: 203/410; Japanese subgroup: 17): oral matching placebo in conjunction with best supportive care (e.g. somatostatin analogue therapy) Length of treatment: until progression of the disease, development of an unacceptable toxic effect, drug interruption for 3 weeks or longer, or withdrawal of consent Patients who had been assigned to placebo initially could switch to open-label everolimus after documented progression of disease (RECIST).

Ito 2012 *(Continued)*

	Doses were delayed/reduced if patients had clinically significant adverse events that were considered to be related to the study treatment.
Outcomes	Primary endpoint: • Progression-free survival (RECIST) Secondary endpoints: • Confirmed objective response rate (RECIST) • Duration of response • Overall survival • Safety Assessments: • Tumour measurements (computed tomography or magnetic resonance imaging): at baseline and every 12 weeks • Safety assessments: monitoring and recording of all adverse events, haematologic and clinical biochemical levels and vital signs, and physical examinations every 4 weeks Data collection: sponsor's data management Data analysis: sponsor's statistical team
Notes	Funding/Sponsor: Novartis Oncology and Novartis Pharma K.K.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised randomisation through interactive voice response system. Stratified by performance status and prior treatment (+/- chemotherapy)
Allocation concealment (selection bias)	Low risk	Centralised randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded trial design with same schemes for each study group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Endpoints were documented by the local investigator according to RECIST, with independent adjudicated central assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for in final analysis
Selective reporting (reporting bias)	Unclear risk	Not all secondary endpoints mentioned in the study protocol were published.
Other bias	Low risk	No other potential sources of bias found

Jacobsen 1995

Study characteristics	
Methods	Randomised, double-blind, cross-over trial
Participants	Inclusion criteria • Histologically proven neuroendocrine tumour with liver metastases • One symptom related to the tumour: ○ Symptoms had to interfere with daily activity. Exclusion criteria • Previous therapy with octreotide Total patients: 11 Mean age (overall): 56.5 Women (overall): 55% Primary tumour site (overall): • Pancreas: 18% • Small intestine: 82%
Interventions	Intervention group: 100 µg octreotide, subcutaneous injection, twice daily for 4 weeks Control group: placebo, subcutaneous injection, twice daily for 4 weeks After the first 4 weeks, patients were shifted from placebo to octreotide and vice versa.
Outcomes	Endpoints: • Quality of life • Side effects • Changes in urine 5-HIAA concentration • Change in diarrhoea and flushing episodes Assessments: • Flushes and diarrhoea: daily 1 week prior to start of the study and during the duration of the entire study • Biochemical marker: at the start and after 4 and 8 weeks • Quality of life: at the start and after 4 and 8 weeks
Notes	The study drug was supplied by Sandoz AG.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation was performed by the study drug supplier.
Allocation concealment (selection bias)	Unclear risk	At half time, the groups shifted from active treatment to placebo and vice versa. The inclusion criterion "the symptoms had to interfere with daily activity" was not precisely defined.

Jacobsen 1995 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind trial, but patients knew they would get both placebo and active treatments. Yet they did not know the order of administration.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Several patients left the study but it remained unclear whether they were accounted for in final analysis.
Selective reporting (reporting bias)	Unclear risk	No study protocol available and no clear endpoints stated
Other bias	Low risk	No other potential sources of bias found

Kölby 2003

Study characteristics	
Methods	Prospective randomised multicentre study • 10 centres in Sweden Randomisation stratified by the presence or absence of carcinoid heart disease on ultrasonography and urinary 5-HIAA level Start: April 1991 Enrolment closed: July 1998 Follow up: until April 2001
Participants	Inclusion criteria • Verified midgut carcinoid tumour • Primary tumour excised at surgery • Presence of liver metastases on ultrasonography or CT • Carcinoid symptoms (flush and/or diarrhoea) • Urinary 5-HIAA ≥ twice upper reference value • Age ≤ 75 years • Performance status WHO classification < IV Exclusion criteria • Other concomitant malignancy • Severe coronary heart disease Total patients: 68 Mean age (study arm 1 vs. 2): 62 vs. 63 Women (overall): 56% Ki-67 index: not reported

Kölby 2003 *(Continued)*

	All patients underwent hepatic arterial embolisation before randomisation.
Interventions	Study arm 1 (35/68): Octreotide 100 µg twice daily. If there were persistent carcinoid symptoms, the dose was increased up to 200 µg three times daily. Study arm 2 (33/68): Octreotide 100 µg twice daily. If there were persistent carcinoid symptoms, the dose was increased up to 200 µg three times daily. With interferon-α. Interferon treatment started with 3×10^6 units on each of 3 days per week and was increased to a maximal dose of 5×10^6 units on each of 5 days per week.
Outcomes	Endpoints: • Death • Progressive tumour growth • Life-threatening side effects Assessments: • Clinical examination and laboratory investigations every 3 months • Ultrasonography or CT of the liver and non-invasive heart examination every 6 months
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was stratified according to the presence or absence of carcinoid heart disease on ultrasonography (stenosis and/or regurgitation in the pulmonary and tricuspid valves) and urinary 5-HIAA level more or less than 500 µmol per 24-h; but it remained unclear how the randomisation process was performed.
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Personnel and participants were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No evidence for independent assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for in ITT analysis
Selective reporting (reporting bias)	Low risk	No protocol available. Every stated endpoint was reported in the results section.
Other bias	Low risk	No other potential sources of bias found

Kulke 2016

Study characteristics	
Methods	Randomised phase II trial Randomisation: 1:1
Participants	Inclusion criteria: • Advanced pNET Total patients: 150 Median age: 59 Women: 44% ECOG 0: 57%; ECOG 1: 43% Grade: not reported Functionality: not reported
Interventions	Study arm E: everolimus, 10 mg, p.o. qd. Study arm E + B: everolimus, 10 mg, p.o., qd; with bevacizumab, 10 mg/kg, i.v. q2 weeks. All patients received octreotide.
Outcomes	Primary endpoint: • Progression-free survival Secondary endpoints: • Overall survival • Response rate • Safety
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Two different application schemes for the study drugs
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias)	Unclear risk	Insufficient information given

Kulke 2016 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Insufficient information given
Other bias	Low risk	No other potential sources of bias found

Kulke 2017 (1)

Study characteristics	
Methods	Randomised, global, multicentre, open-label, phase 2 trial 1:1 randomisation, stratified by prior SSA treatment (yes or no) and the presence of elevated biomarkers at baseline Start: July 2011 Closed: December 2021
Participants	Inclusion criteria: • Age ≥ 18 years • Histologically confirmed, well differentiated, advanced pNET [WHO grade 1 or 2] • Radiological documentation of disease progression within 12 months before randomisation • Measurable disease (RECIST v1.0) • WHO performance status ≤ 2 • Adequate bone marrow, renal and hepatic function Exclusion criteria: • Prior treatment with mTOR inhibitors • Clinical requirement of SSA treatment Total patients: 160 Median age (everolimus + pasireotide LAR vs. everolimus): 57 vs. 59 Women % (everolimus + pasireotide LAR vs. everolimus): 51 vs. 42 WHO performance status 0-1 (everolimus + pasireotide LAR vs. everolimus): 100% vs. 96% Grade 1 or 2, % (everolimus + pasireotide LAR vs. everolimus): 97.5 vs. 97.5 Functionality: not reported Prior antineoplastic treatment, % (everolimus + pasireotide LAR vs. everolimus): 65 vs. 62 Prior SSA treatment, % (everolimus + pasireotide LAR vs. everolimus): 33 vs. 33
Interventions	Study arm 1 (79/160): everolimus, 10 mg/day, per oral; with pasireotide LAR, 60 mg/28 days, intramuscular injection Study arm 2 (81/160): everolimus, 10 mg/day, per oral Length of treatment: until radiologically documented disease progression, start of a new anticancer therapy, intolerable toxicity or withdrawal of consent Dose modifications were permitted for any adverse event suspected to be drug related.

Kulke 2017 (1) *(Continued)*

	Cross-over: not allowed
Outcomes	Primary endpoint: • Treatment effect on progression-free survival (RECIST v 1.0) Secondary endpoints: • Objective response rate • Disease control rate • Overall survival • Pharmacokinetics • Safety Biomarker response was evaluated as an exploratory analysis. Assessments: • Tumour assessments: at screening and every 12 weeks from date of randomisation until radiologically documented disease progression • Clinical suspicion of disease progression at any time required a physical examination and radiological confirmation. • Patients who discontinued the study treatment prior to progression of disease continued to have tumour assessments performed every 12 weeks from randomisation until radiologically documented disease progression or start of a new antineoplastic therapy. • Patients who discontinued the study treatment and were no longer followed for tumour evaluation were contacted every 12 weeks for survival. • Blood samples: before and during treatment at prespecified time points for assessing pharmacodynamic markers
Notes	Funding: Novartis Pharmaceuticals Corporation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation with stratification, but unclear how it was performed
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Trial was open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No evidence of independent assessment of radiological outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for; one patient in the combination arm did not receive study treatment.
Selective reporting (reporting bias)	Low risk	No protocol available. Not all endpoints mentioned were shown in the official publication, but can be found in the supplementary data.

Kulke 2017 (1) *(Continued)*

Other bias	Low risk	No other potential sources of bias found

Kulke 2017 (2)

Study characteristics	
Methods	International (12 countries), multicentre, randomised, double-blind, placebo-controlled phase III trial (TELESTAR) 1:1:1 randomisation
Participants	Inclusion criteria • Age ≥ 18 years • Histopathologically confirmed, well differentiated metastatic NETs • Documented history of carcinoid syndrome • Average of four or more bowel movements per day • Stable-dose SSA treatment (long-acting release, depot or infusion pump) for ≥ 3 months before enrolment Exclusion criteria • More than 12 watery bowel movements per day associated with volume contraction, dehydration or hypotension • Enteric infection • Karnofsky performance status ≤ 60% • History of short bowel syndrome • Clinically important baseline elevation in liver function tests • Recently tumour-directed therapy Total patients: 135 Mean age (A vs. B vs. C): 63 vs. 62 vs. 65 Women, % (A vs. B vs. C): 47 vs. 53 vs. 44 SSA therapy at study entry, %: • Octreotide LAR (A vs. B vs. C): 67 vs. 89 vs. 73 • Lanreotide depot (A vs. B vs. C): 33 vs. 11 vs. 27
Interventions	Study group A (45/135): placebo, oral doses, three times per day for 12 weeks Study group B (45/135): telotristat ethyl 250 mg, oral doses, three times per day for 12 weeks Study group C (45/135): telotristat ethyl 500 mg, oral doses, three times per day for 12 weeks Continued baseline SSA therapy for all 12 weeks Allowed rescue use of short-acting octreotide and antidiarrhoeal agents After the study, all patients were offered treatment with telotristat ethyl 500 mg, three times per day in a 36-week open-label extension.
Outcomes	Primary endpoint: • Mean reduction from baseline in daily bowel movements averaged over 12 weeks (self-reported) Secondary endpoints:

Kulke 2017 (2) *(Continued)*

- Change from baseline in u5-HIAA at week 12
- Number of daily flushing episodes (self-reported)
- Abdominal pain severity (on a scale of 0 to 10) averaged over 12 weeks (self-reported)

Additional efficacy endpoints:

- Quality of life (self-reported)
- Rescue short-acting SSA use (self-reported)
- Stool consistency (self-reported)
- Proportion of days with urgency to defecate (self-reported)
- Safety

Assessments:

- Screening period of 3 or 4 weeks for baseline symptoms
- Self-reporting by daily electronic diaries

Notes	Study was supported by Lexicon Pharmaceuticals.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	No information regarding allocation concealment; all study groups with the same number of patients
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial design
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessment was done by self-reporting in the majority of endpoints.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients accounted for in the efficacy analyses in ITT fashion
Selective reporting (reporting bias)	Low risk	No study protocol available, but all stated endpoints were reported.
Other bias	Low risk	No other potential sources of bias found

Lange 1992

Study characteristics

Methods	Randomised, double-blinded, placebo-controlled trial Randomisation was stratified for diagnosis (gastrinoma vs. insulinoma) and for type of excision (enucleation vs. resection) Start: 1989

Lange 1992 *(Continued)*

	Closed: 1991
Participants	Inclusion criteria: • Resection of pancreatic endocrine tumour at the National Institutes of Health Exclusion criteria: • Diabetes • No pancreatic incision Total patients: 21 Median age (octreotide vs. placebo): 47 vs. 46 Women, % (octreotide vs. placebo): 70 vs. 27 Functionality, % (octreotide vs. placebo): 100 vs. 100 Tumour grade: not reported Prior treatment for NET: not reported
Interventions	Experimental arm (10/21): octreotide, subcutaneous injection, beginning the day of surgery. Dosage: day 1, 50 µg every 8 hours; day 2, 100 µg every 8 hours; day 3 and for the duration of treatment, 150 µg every 8 hours Control arm (11/21): saline solution, subcutaneous injection, same schedule and in a volume to match that of the experimental arm Octreotide and saline solution injections were continued until 3 days after drain removal. Drain removal was regulated by a standardised algorithm.
Outcomes	Endpoints: • Adverse reactions • Development of gallstones • Daily drain output • Days to drain removal • Total drainage • Complications related to pancreatic drainage Assessments: • Daily blood glucose tests • Ultrasonography for assessment of gallstones before operation, each month during treatment and after drain removal • Amylase content in drain fluid was measured on postoperative days 1, 3 and 7. • It was not stated how the other endpoints were measured.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation with stratification, but unclear how it was performed

Lange 1992 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Same protocols for each study arm
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for in final analysis
Selective reporting (reporting bias)	Low risk	No protocol available, but all endpoints stated in the paper as measured were reported.
Other bias	Low risk	No other potential sources of bias found

Lepage 2020

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled study 1:1 randomisation
Participants	Inclusion criteria • Aggressive G1-G2 well differentiated duodeno-pancreatic NET • Patients who received a first-line treatment Total patients: 53 G2 tumour (overall): 81% Metastatic disease (overall): 91% Previous SSA treatment, % (lanreotide vs. placebo): 15 vs. 19 First-line treatment (overall): • Temozolomide-based: 53% • Dacarbazine-based: 19% • Streptozotocin-based: 13% • Oxaliplatin-based: 11% • Sunitinib: 4%
Interventions	Intervention group: lanreotide autogel (LAN) every 28 days Control group: placebo every 28 days Treatment duration: until progression or toxicity
Outcomes	Main endpoint:

Lepage 2020 *(Continued)*

	• Progression-free survival at 6 months Secondary endpoints: • Median progression-free survival • Median overall survival • Toxicity
Notes	Trial was funded by Ipsen.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information given
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	No other potential sources of bias found

Liu 2020

Study characteristics

Methods	1:1:1:2 randomisation Enrolment: August 2017 to February 2019
Participants	Inclusion criteria • High tracer uptake in tumour on ^{68}Ga-DOTATATE PET/CT, evaluated within 1 week before inclusion • Histological confirmed or inoperable/metastatic NET • White blood cells ≥ 3 × 10^9/L • Platelets ≥ 60 × 10^9/L • Hemoglobin ≥ 10 g/dL • Serum creatinine clearance > 40 mL/min • No pregnancy or lactation • Age > 18

Liu 2020 *(Continued)*

	Total patients: 33 Age (A vs. B vs. C vs. D): 43 vs. 55 vs. 55 vs. 50 Women, % (A vs. B vs. C vs. D): 67 vs. 29 vs. 33 vs. 50 Primary tumour site, %: • Pancreas (A vs. B vs. C vs. D): 50 vs. 43 vs. 50 vs. 50 • Duodenum (A vs. B vs. C vs. D): 0 vs. 29 vs. 17 vs. 21 • Rectum (A vs. B vs. C vs. D): 0 vs. 14 vs. 0 vs. 14 • Lung (A vs. B vs. C vs. D): 17 vs. 0 vs. 17 vs. 0 • Ovary (A vs. B vs. C vs. D): 17 vs. 0 vs. 0 vs. 0 • CUP (A vs. B vs. C vs. D): 17 vs. 0 vs. 0 vs. 7 • MEN 1 (A vs. B vs. C vs. D): 0 vs. 0 vs. 17 vs. 0 • Paraganglioma (A vs. B vs. C vs. D): 0 vs. 0 vs. 0 vs. 7 • Pheochromocytoma (A vs. B vs. C vs. D): 0 vs. 14 vs. 0 vs. 0 Tumour grade, %: • G1 (A vs. B vs. C vs. D): 50 vs. 29 vs. 17 vs. 21 • G2 (A vs. B vs. C vs. D): 33 vs. 57 vs. 67 vs. 71 • G3 (A vs. B vs. C vs. D): 17 vs. 14 vs. 17 vs. 7 Liver involvement, % (A vs. B vs. C vs. D): 100 vs. 100 vs. 83 vs. 100 Prior treatment, %: • Surgery (A vs. B vs. C vs. D): 17 vs. 71 vs. 33 vs. 50 • SSA (A vs. B vs. C vs. D): 83 vs. 29 vs. 83 vs. 36 • Everolimus (A vs. B vs. C vs. D): 17 vs. 0 vs. 50 vs. 7 • Tyrosine kinase inhibitor (A vs. B vs. C vs. D): 17 vs. 43 vs. 83 vs. 64 • Chemotherapy (A vs. B vs. C vs. D): 50 vs. 43 vs. 50 vs. 43 • Radiotherapy (A vs. B vs. C vs. D): 0 vs. 0 vs. 17 vs. 7 • TACE (A vs. B vs. C vs. D): 17 vs. 14 vs. 17 vs. 21
Interventions	Group A (6/33): 3.7 GBq (100 mCi) ^{177}Lu-DOTATATE, one dose Group B (7/33): 1.11 GBq (30 mCi) ^{177}Lu-DOTA-EB-TATE, one dose Group C (6/33): 1.85 GBq (50 mCi) ^{177}Lu-DOTA-EB-TATE, one dose Group D (14/33): 3.7 GBq (100 mCi) ^{177}Lu-DOTA-EB-TATE, one dose
Outcomes	Endpoints: • Tumour response referring to EORTC criteria • Safety Assessments: • ^{68}Ga-DOTATATE PET/CT at baseline and 2–3 months post-therapy • Treatment-related adverse events (AEs) recorded over a period of 2 months after the administration of PRRT • Haematological parameters, liver and renal function at baseline, and 1-week and 4-week post-therapy
Notes	
Risk of bias	

Liu 2020 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised sequence was generated by computer.
Allocation concealment (selection bias)	Unclear risk	Was performed by different people
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information given
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All images were measured by the same physician who was masked to the clinical data.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for in analysis
Selective reporting (reporting bias)	Low risk	All stated endpoints were reported.
Other bias	Low risk	No other potential sources of bias found

Lombard-Bohas 2015

Study characteristics	
Methods	International, multicentre, double-blind, phase 3 study • 82 centres in 18 countries worldwide Randomisation: • Ratio 1:1 • Stratified by whether or not patients have received prior cytotoxic chemotherapy and by WHO performance status (0 vs. 1-2) at baseline Start: July 2007 Closed: May 2009
Participants	Inclusion criteria: • 18 years of age or older • Low-grade or intermediate-grade advanced (unresectable or metastatic) pancreatic neuroendocrine tumours • Radiologic documentation of disease progression in the previous 12 months • Measurable disease (RECIST) • World Health Organization (WHO) performance status of 2 or less • Adequate bone marrow, renal, and hepatic function • Adequately controlled lipid and glucose concentrations Exclusion criteria:

Lombard-Bohas 2015 *(Continued)*

- Hepatic-artery embolisation within 6 months before enrolment or within 1 month if there were other sites of measurable disease or cryoablation or radiofrequency ablation of hepatic metastasis within 2 months before enrolment
- Severe or uncontrolled medical conditions
- Prior therapy with an mTOR inhibitor
- Long-term treatment with glucocorticoids or other immunosuppressive agents

RADIANT-3 overall population:

- Total patients: 410
- Median age (everolimus vs. placebo): 58 vs. 57
- Women % (everolimus vs. placebo): 47 vs 42
- WHO performance status 0 (everolimus vs. placebo): 67% vs. 66%
- Well differentiated % (everolimus vs. placebo): 82 vs. 84
- Moderately differentiated % (everolimus vs. placebo): 17 vs. 15
- Liver involvement, % (everolimus vs. placebo): 92% vs. 92%
- Functional tumours (overall): 24%
- Prior therapy for NET, %:
  - Radiotherapy (everolimus vs. placebo): 23 vs. 20
  - Chemotherapy (everolimus vs. placebo): 50 vs. 50
  - Somatostatin analogue therapy (everolimus vs. placebo): 49 vs. 50

Subgroup analysis:

- Previous chemotherapy: 206 of 410 (104 everolimus arm vs. 102 placebo arm)

Median age (previous chemotherapy vs. chemo-naive): 58 vs. 58

Women % (previous chemotherapy vs. chemo-naive): 43 vs 47

WHO performance status 0 (previous chemotherapy vs. chemo-naive): 61% vs. 72%

Race (%, white): 79 vs. 78

- Well differentiated % (previous chemotherapy vs. chemo-naive): 85 vs. 82
- Moderately differentiated % (previous chemotherapy vs. chemo-naive): 15 vs. 17
- Functional tumours (previous chemotherapy vs. chemo-naive): 22% vs. 26%
- Prior therapy for NET, %:
  - Radiotherapy (previous chemotherapy vs. chemo-naive): 22 vs. 21
  - Somatostatin analogue therapy (previous chemotherapy vs. chemo-naive): 54 vs. 45

Interventions	Intervention group (207/410): oral everolimus, at a dose of 10 mg once daily, in conjunction with best supportive care (e.g. somatostatin analogue therapy) Control group (203/410): oral matching placebo in conjunction with best supportive care (e.g. somatostatin analogue therapy) Length of treatment: until progression of the disease, development of an unacceptable toxic effect, drug interruption for 3 weeks or longer, or withdrawal of consent Patients who had been assigned to placebo initially could switch to open-label everolimus after documented progression of disease (RECIST). Doses were delayed/reduced if patients had clinically significant adverse events that were considered to be related to the study treatment.
Outcomes	Primary endpoint: • Progression-free survival (RECIST)

Lombard-Bohas 2015 *(Continued)*

	Secondary endpoints: • Confirmed objective response rate (RECIST) • Duration of response • Overall survival • Safety Assessments: • Tumour measurements (computed tomography or magnetic resonance imaging): at baseline and every 12 weeks • Safety assessments: monitoring and recording of all adverse events, haematologic and clinical biochemical levels and vital signs, and physical examinations every 4 weeks Data collection: sponsor's data management Data analysis: sponsor's statistical team
Notes	Funding/Sponsor: Novartis Oncology

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised randomisation through interactive voice response system. Stratified by performance status and prior treatment (+/- chemotherapy)
Allocation concealment (selection bias)	Low risk	Centralised randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded trial design with same schemes for each study group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Endpoints were documented by the local investigator according to RECIST, with independent adjudicated central assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for in final analysis
Selective reporting (reporting bias)	Unclear risk	Not all secondary endpoints mentioned in the study protocol were published.
Other bias	Low risk	No other potential sources of bias found

Maire 2012

Study characteristics

Methods	Prospective randomised trial • 2 centres in France Central randomisation with an adaptive randomisation procedure stratified per centre and progression group

Maire 2012 *(Continued)*

	Start: 2002 Closed: 2008 Follow-up: 24 months after inclusion
Participants	Inclusion criteria • Age ≥ 18 years • Histologically confirmed endocrine liver metastases from midgut tumours • Either progressive liver metastases within 12 months before the inclusion, i.e. progression of > 25% between two consecutive imaging procedures, or liver tumoural involvement of > 50% on CT scan Exclusion criteria • Extrahepatic metastases, with the exception of lymph node involvement • Liver dysfunction • Renal dysfunction • History of HAE or HACE • Hepatic or portal vein thrombosis • Cardiac insufficiency • Unstable coronary disease • Heart stroke within the previous 3 months • Uncontrolled hyperthyroidism • Karnofsky index < 70% • Contrast allergy • Pregnant, breastfeeding or fertile women without contraceptive Total patients: 26 Median age (HAE vs. HACE): 56 vs. 65 Women, % (HAE vs. HACE): 36 vs. 42 Median Karnofsky index (overall): 90 Carcinoid syndrome, % (HAE vs. HACE): 79 vs. 67 Liver involvement, < 25%/25-50%/> 50%, % (HAE vs. HACE): 43/36/21 vs. 58/25/17 Ki-67 index, ≤ 2%/3-5%/6-10%/unknown, % (overall): 62/19/4/15 Resection of primary tumour, % (HAE vs. HACE): 86 vs. 83 Previous resection of liver metastases, % (HAE vs. HACE): 14 vs. 17 Concomitant treatment with SSA, % (HAE vs. HACE): 79 vs. 67 Primary tumour location unknown (overall): 15%
Interventions	Study arm 1 (14/26): hepatic arterial embolisation (HAE): transfemoral, embolisation with gelatin sponge particles Study arm 2 (12/26): hepatic arterial chemoembolisation (HACE): transfemoral, doxorubicin (50 mg/m^2) dissolved in normal saline and combined with 10–15 mL of iodised oil, injected into the branches of the hepatic artery distal to the gastroduodenal artery, followed by embolisation with gelatin sponge particles Treatment was administered after randomisation and was repeated 3 months thereafter. Carcinoid syndrome had to be controlled by somatostatin analogues.

Maire 2012 *(Continued)*

	Patients with carcinoid syndrome were administered octreotide 200 µg subcutaneously before the procedure and every 8 h afterward during 48 h to prevent a carcinoid crisis.
Outcomes	Primary endpoint • Progression-free survival rate Secondary endpoints • Side effects • Morphological and biological response rates • Overall survival rate Assessments • Tumour assessment by the same imaging method throughout the follow-up period after 3, 6, 12, 18 and 24 months or earlier if clinically indicated • Physical examination, pain assessment using a visual analogue scale, and analgesic intake and toxicity were recorded after 3, 6, 12, 18 and 24 months.
Notes	Funding: Novartis Pharma

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was performed centrally with the use of an adaptive randomisation procedure stratified per centre and progression group, but it remained unclear how this adaptive randomisation procedure worked.
Allocation concealment (selection bias)	Low risk	Randomisation was performed centrally.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No evidence of independent assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All patients accounted for in primary endpoint. For morphological response and for biological response only 23 and 20 patients were evaluable.
Selective reporting (reporting bias)	Low risk	No study protocol available, but every endpoint mentioned in 'methods' was reported in 'results'.
Other bias	Low risk	No other potential sources of bias found

Meyer 2014

Study characteristics

Methods	Multicentre, randomised trial

Meyer 2014 *(Continued)*

	• 13 United Kingdom centres 1:1 randomisation by stratified random block method Stratification factors: functional or non-functional tumour, previous somatostatin analogues/interferon treatment versus none and known primary tumour site versus unknown Enrolment start: November 2006 Enrolment closed: October 2010
Participants	Inclusion criteria • Chemo-naive patients • Histologically confirmed, unresectable, advanced and/or metastatic NETs of the pancreas, other gastrointestinal foregut, or unknown primary site suggestive of abdominal foregut origin • Measurable disease by RECIST (version 1.0) • ECOG performance status ≤ 2 • Adequate bone marrow, hepatic and renal function with creatinine clearance > 60 mL/min Total patients: 86. Median age (CapStrep vs. CapStrepCis): 57 vs. 59 Women, % (CapStrep vs. CapStrepCis): 39 vs. 45 Site of origin, %: • Pancreas (CapStrep vs. CapStrepCis): 45.5 vs. 50 • Foregut (CapStrep vs. CapStrepCis): 20.5 vs. 19 • Unknown (CapStrep vs. CapStrepCis): 33 vs. 31 Functional tumour, % (CapStrep vs. CapStrepCis): 30 vs. 43 Liver metastases, % (CapStrep vs. CapStrepCis): 93 vs. 81 Ki-67 index (%) ≤ 9/10-24/≥ 25, % (CapStrep vs. CapStrepCis): 46/33/21 vs. 50/27/24 Prior treatment received, %: • SSA and interferon (CapStrep vs. CapStrepCis): 2 vs. 0 • SSA (CapStrep vs. CapStrepCis): 27 vs. 29 • Interferon (CapStrep vs. CapStrepCis): 2 vs. 0 • None (CapStrep vs. CapStrepCis): 68 vs. 71
Interventions	CapStrep regimen group (44/86): capecitabine 625 mg/m^2 administered orally, twice daily on days 1–21, and streptozocin 1.0 g/m^2 (2-h infusion intravenously in normal saline) on day 1 CapStepCis regimen group (42/86): capecitabine 625 mg/m^2 administered orally, twice daily on days 1–21, and streptozocin 1.0 g/m^2 (2-h infusion intravenously in normal saline) on day 1 plus cisplatin 70 mg/m^2 (2-h infusion intravenously in normal saline with hydration) on day 1, directly after the streptozocin infusion Treatment duration: six cycles (and beyond six cycles if there was evidence of benefit)
Outcomes	Primary endpoint: • Objective response rate Secondary endpoints: • Biochemical response

Meyer 2014 *(Continued)*

- Safety
- Progression-free survival
- Overall survival
- Quality of life

Assessments

- Adverse events: every cycle
- Disease progression: every 12 weeks
- Survival: every 12 weeks
- Tumour assessments with CT scans: baseline, every three cycles while on treatment and every 12 weeks until progression
- Retrospective central radiology review was undertaken for objective tumour response assessments in 10% of randomly selected patients who completed at least three treatment cycles.
- 24-h urinary 5-hyroxyindoleacetic acid (5-HIAA) and serum chromogranin A (CgA): prior to treatment and if above the normal range were repeated every three cycles while on treatment and at 12 weeks from the end of treatment
- Patient quality of life: before randomisation, after three and six cycles of treatment or at the time of stopping treatment and at 12 weeks post-treatment

Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by stratified random block method
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	No evidence for blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Retrospective central radiology review in 10% of randomly selected patients who completed at least three treatment cycles
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No study protocol available, but every mentioned endpoint in 'methods' is reported in 'results'.
Selective reporting (reporting bias)	High risk	Four patients were not included in the primary analysis. There was a big loss of patient numbers in the 'quality of life' endpoint.
Other bias	Low risk	No other potential sources of bias found

Moertel 1980

Study characteristics

Methods	Multicentric, randomised trial

Moertel 1980 *(Continued)*

	• 28 centres Randomisation was stratified according to: performance status, either functioning or nonfunctioning tumour, and use of either laboratory assay or measurable feature to assess objective response. Start: December 1972 Closed: December 1978
Participants	Inclusion criteria: • Not resectable islet-cell carcinoma • Histologic proof of residual, recurrent or metastatic carcinoma • Measurable malignant disease (laboratory assay (e.g. serum gastrin) or measurable area of known tumour). In case of liver involvement (bioptically confirmed), with liver edge extension at least 5 cm below the xiphoid or costal margin, malignant hepatomegaly was accepted as a measurable feature. Radioactive liver scans were also accepted, if a clearly demarcated perfusion defect of at least 5 cm was detectable. • Recommendation to only include patients with symptoms or disability resulting from the malignant disease Exclusion criteria: • Diagnosis without biopsy confirmation • Prior therapy with either fluorouracil or streptozocin • Active infectious process • Severe malnutrition • Frequent vomiting • Leukocyte count below 4500 per cubic millimetre • Platelet count below 150,000 per cubic millimetre • Renal disease (creatinine above 1.5 mg/mL [133 µmol/L] or urea nitrogen above 30 mg per 100 mL [10.7 mmol/L] Exploratory surgery with biopsy within two weeks of treatment start and a resection or anastomosis within three weeks of treatment start Previous radiation therapy or treatment with cytotoxic drugs within one month after registration Present haematologic or renal toxic effect from therapy 103 patients were randomised; 19 were excluded. Mean age (study arm 1 vs. 2): 52 vs. 54 Women % (1 vs. 2): 57 vs. 45 ECOG performance status 0-1 (1 vs. 2): 71% vs. 71% Functional tumour % (1 vs. 2): 52 vs. 44% Tumour grade: not reported. Prior chemotherapy (overall): 2%
Interventions	Study arm 1 (42/84): streptozocin, by rapid intravenous injection, 500 mg per square metre of body-surface area, for five consecutive days, repeated every 6 weeks if disease improved or remained objectively stable Study arm 2 (42/84): streptozocin, by rapid intravenous injection, 500 mg per square metre of body-surface area, for five consecutive days; and fluorouracil, by rapid intravenous injection, 400 mg per square metre of body-surface area, for five consecutive days, concurrently with streptozocin, repeated every 6 weeks if disease improved or remained objectively stable

Moertel 1980 *(Continued)*

	Streptozocin dosage was reduced by 50%, if the patient had severe nausea and vomiting or any evidence of renal toxicity was present. Streptozocin was discontinued if these problems persisted after dose reduction. Flourouracil dosage was reduced by 25% if severe leukopenia or thrombocytopenia was present. Phenothiazine antiemetics were recommended for prophylaxis and therapy of nausea and vomiting.
Outcomes	No clear endpoints were set. Assessments: • Therapeutic results: every six weeks before initiation of the next course of therapy • White cell and platelet counts at weekly intervals after therapy • Renal and liver function before of initiation of each course of therapy
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation with stratification, but unclear how it was performed
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	In two patients, the investigators failed to record serial tumour measurements.
Selective reporting (reporting bias)	High risk	19 patients were excluded after randomisation.
Other bias	High risk	Investigator-dependent measurement methods were used.

Moertel 1992

Study characteristics

Methods	Multinational, randomised trial • 25 centres in 3 countries Randomisation: stratified according to ECOG performance score and indicator of response (measurable tumour or laboratory assays) Start: November 1978

Moertel 1992 *(Continued)*

	Closed: June 1985
Participants	Inclusion criteria: • Histologic proof of unresectable or metastatic islet-cell carcinoma • Measurable indicator of response to therapy: 1) tumour on physical examination, or 2) chest films or well-defined metastatic lesions in the liver on radioisotope or CT scanning > 5 cm, or 3) malignant hepatomegaly if the liver edge is at least 5 cm below the xiphoid process or the costal margins during quiet respiration, or 4) for patients without measurable tumour, laboratory assays demonstrating excessive hormone production Exclusion criteria: • ECOG performance score of 4 • Severe nutritional impairment • Major surgery within three weeks • Previous therapy with any of the study agents • Chemotherapy or radiation therapy within the previous month • Active infection • Leukocyte count < 4×10^9 per litre or a platelet count < 150×10^9 per litre • Active heart disease • Serum creatinine level > 132.6 mmol per litre (1.5 mg per decilitre) or a blood urea nitrogen level > 10.7 mmol per litre (30 mg per decilitre) • Any elevation of serum bilirubin • Any other concurrent or recent malignant disease except cutaneous epitheliomas or cervical carcinoma in situ Total patients: 125; 18 patients were subsequently found to be ineligible and two withdrew from the study. Median age (1 vs. 2 vs. 3): 57 vs. 51 vs. 53 Women % (1 vs. 2 vs. 3): 61 vs. 41 vs. 53 ECOG performance status 0-1 (1 vs. 2 vs. 3): 70% vs. 71% vs. 71% Nonfunctional tumours (overall): 52.4% Tumour grade: not reported Prior therapy for NET: not reported
Interventions	Study arm 1 (33/105): chlorozotocin, intravenous injection, 150 mg per square metre of body-surface area, every seven weeks Study arm 2 (34/105): streptozocin, intravenous injection, 500 mg per square metre, for five consecutive days, every six weeks. And, fluorouracil intravenous injection, 400 mg per square metre, for five days, concurrently with streptozocin Study arm 3 (38/105): doxorubicin along with streptozocin, intravenous injection, 50 mg per square metre, days 1 and 22 of each six-week treatment cycle, with a maximal total dose of 500 mg per square metre Dosages of streptozocin or chlorozotocin were reduced if 1) severe nausea or vomiting, stomatitis, diarrhoea, leukopenia, or thrombocytopenia occurred, or 2) creatinine level became elevated or persistent proteinuria developed. If these abnormalities persisted, treatment with these agents was discontinued. Length of therapy: until disease progression was noted
Outcomes	Endpoints:

Moertel 1992 *(Continued)*

- Disease progression
- Survival
- Rates of regression

Assessments:

- Re-evaluation every seven weeks for study arm 1
- Re-evaluation every six weeks for study arms 2 and 3
- Leukocyte and platelet counts weekly, serum creatinine and urinalyses before each cycle of therapy

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation with stratification, but unclear how it was performed
Allocation concealment (selection bias)	Unclear risk	Insufficient information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Different application schemes and control intervals for each study arm
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias) All outcomes	High risk	20 patients were excluded after randomisation.
Selective reporting (reporting bias)	Low risk	No study protocol available, but the endpoints mentioned in 'methods' were reported in 'results'.
Other bias	High risk	Investigator-dependent measurement methods were used.

O'Toole 2000

Study characteristics

Methods

Prospective, open, comparative, cross-over study

- 15 centres in France

Participants

Inclusion criteria

- Histologically confirmed carcinoid tumours
- At least one of the following symptoms: diarrhoea (at least 3 stools every 24 hours) or flushes (at least 1 flush every 24 hours)

Exclusion criteria

O'Toole 2000 *(Continued)*

- Previous treatment with SSA or discontinuation for a sufficient time to allow reappearance of clinical symptoms
- Symptoms of bowel obstruction
- Surgery for the tumour or its metastases scheduled in the 3 months after inclusion

Withdrawal

- Development of bowel obstruction
- Requirement of another therapy (e.g. radiotherapy, chemotherapy, immunotherapy or chemoembolisation)

Total patients: 33

Age (A vs. B): 63 vs. 64

Women, % (A vs. B): 50 vs. 53

Previous treatment with octreotide/lanreotide, % (A vs. B): 63/13 vs. 59/0

Primary tumour site, %:

- Intestine (A vs. B): 63 vs. 76
- Pancreas (A vs. B): 0 vs. 6
- Lung (A vs. B): 19 vs. 0
- Unknown (A vs. B): 19 vs. 0
- Stomach (A vs. B): 0 vs. 12
- Ovary (A vs. B): 0 vs. 6

Metastases, % (A vs. B): 100 vs. 100

Interventions	Group A (16/33): octreotide, 200 mg, subcutaneously twice or thrice daily for 30 days followed by lanreotide, 30 mg, intramuscularly every 10 days on days 1, 10, and 20 for 30 days Group B (17/33): lanreotide, 30 mg, intramuscularly every 10 days on days 1, 10, and 20 for 30 days followed by octreotide, 200 mg, subcutaneously twice or thrice daily for 30 days A wash-out period of at least 3 days was applied between the two treatments. Antidiarrhoea agents were prohibited during the study period.
Outcomes	Endpoints: • Quality of life • Clinical symptoms • Tumour markers • Adverse events Assessments: • Day 1 and day 30 of each treatment period
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given

O'Toole 2000 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Personnel and participants were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Analysis was performed by an independent expert who was blinded to the treatment group.
Incomplete outcome data (attrition bias) All outcomes	High risk	5 of 33 (15%) randomised patients were excluded; therefore 28 patients accounted for in efficacy analysis (14 patients per group)
Selective reporting (reporting bias)	Low risk	No study protocol available, but all stated endpoints were reported.
Other bias	Low risk	No other potential sources of bias found

Öberg 1989

Study characteristics	
Methods	1:1 randomised trial, stratified by urinary 5-hydroxyindoleacetic acid level, sex and age
Participants	Inclusion criteria • Malignant carcinoid tumour Total patients: 20 Mean age (overall): 61.5 Women, % (overall): 45% Liver metastases (overall): 100% Carcinoid symptoms (overall): 100% Primary tumour location (overall): 95% ileum, 5% bronchial Previous therapy for NET: not reported
Interventions	Study arm 1 (10/20): streptozotocin, 1 g, intravenous, for three consecutive days in combination with 5-fluorouracil, 400 mg/m^2. Treatment was repeated every 6 weeks. Study arm 2 (10/20): interferon, 6 MU daily, subcutaneous injection; for the first three days, only half the dose was given. No other treatment for carcinoid syndrome was used. Cross-over of 8 patients in the study arm 1 to study arm 2 after 6 months; and of 1 patient from study arm 2 to study arm 1
Outcomes	No clear primary or secondary endpoints stated Endpoints reported:

Öberg 1989 *(Continued)*

- Objective tumour response
- Adverse reactions

Assessments:

- CT and ultrasound of the abdomen prior to treatment start and then every 3rd month
- Laboratory analysis prior to every new course of chemotherapy and every 3rd month in patients on interferon treatment
- Daily number of flush attacks and episodes of diarrhoea were monitored and evaluated in the subjective response.

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No sufficient information given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients and personal not blinded. Different application and assessment schemes
Blinding of outcome assessment (detection bias) All outcomes	High risk	No evidence for independent evaluation
Incomplete outcome data (attrition bias) All outcomes	High risk	All patients accounted for in analysis, but group cross-over was done. Not mentioned if ITT or per-protocol analysis was performed
Selective reporting (reporting bias)	Unclear risk	No clear endpoints stated. No study protocol available
Other bias	Low risk	No other potential sources of bias found

Pavel 2011

Study characteristics

Methods	Multicentre (16 countries), double-blind, phase 3 study 1:1 randomisation by interactive voice response system Study group assignments were masked. Enrolment: January 2007-April 2010
Participants	Inclusion criteria • Age ≥ 18 years

Pavel 2011 *(Continued)*

- Low-grade or intermediate-grade, unresectable locally advanced or distant metastatic neuroendocrine tumour
- Disease progression by radiological assessment within the past 12 months
- History of diarrhoea or flushing attributable to carcinoid syndrome
- Measurable disease according to RECIST version 1.0
- WHO performance status ≤ 2
- Adequate bone marrow, renal, and hepatic function and adequately controlled lipid concentrations

Exclusion criteria

- Poorly differentiated or high-grade neuroendocrine carcinomas

Total patients: 429

Median age (study group 1 vs. study group 2): 60 vs. 60

Women, % (1 vs. 2): 55 vs. 42

WHO performance status 0/1/2, % (1 vs. 2): 55/39/6 vs. 66/29/5

Primary tumour site, %:

- Small intestine, (1 vs. 2): 51 vs. 53
- Lung, (1 vs. 2): 15 vs. 5
- Colon, (1 vs. 2): 6 vs. 7
- Pancreas, (1 vs. 2): 5 vs. 7
- Liver, (1 vs. 2): 3 vs. 5
- Other, (1 vs. 2): 19 vs. 23
- Missing, (1 vs. 2): 0 vs. 1

Grade (well differentiated/moderately differentiated/poorly differentiated), % (1 vs. 2): 77/18/1 vs. 82/14/1

Liver involvement, % (1 vs. 2): 92 vs. 92

Previous SSA treatment, % (1 vs. 2): 80 vs. 78

Previous systemic anti-tumour drugs, % (1 vs. 2): 46 vs. 38

Chemotherapy, % (1 vs. 2): 35 vs. 26

Immunotherapy, % (1 vs. 2): 13 vs. 9

Targeted therapy, % (1 vs. 2): 7 vs. 8

Other, % (1 vs. 2): 10 vs. 13

Interventions	Study group 1 (216/429): 10 mg oral everolimus once daily plus intramuscular 30 mg octreotide LAR every 28 days Study group 2 (213/429): matching placebo plus intramuscular 30 mg octreotide LAR every 28 days Treatment duration: until disease progression, withdrawal from treatment because of adverse events, or withdrawal of consent After disease progression in the placebo plus octreotide LAR group, cross-over to open-label everolimus plus octreotide LAR was permitted.
Outcomes	Primary endpoint: • Progression-free survival according to RECIST Secondary endpoints:

Pavel 2011 *(Continued)*

- Objective response rate according to RECIST
- Overall survival
- Changes from baseline in 5-hydroxyindoleacetic acid and CgA concentrations
- Safety

Supportive endpoint:

- Investigator-assessed progression-free survival

Assessments:

- CT or MRI were done at baseline and repeated every 12 weeks.
- Serum CgA and 24-h urine samples for 5-hydroxyindoleacetic acid at baseline and on day 1 of each subsequent cycle (if raised at baseline)
- Monitoring of adverse events, vital signs and physical examinations every 4 weeks
- Chest radiographs every 12 weeks

Notes	Novartis funded the study and was involved in the study design, data collection and statistical analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information about sequence generation
Allocation concealment (selection bias)	Low risk	Allocation was performed centrally
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Central review for primary analysis of progression-free survival by an independent, masked committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients accounted for in efficacy analysis according to the intention-to-treat principle.
Selective reporting (reporting bias)	Low risk	Except for one secondary endpoint, every endpoint stated in the study protocol was reported in the publication.
Other bias	Low risk	No other potential sources of bias found

Pavel 2018 (1)

Study characteristics

Methods	International (11 countries), multicentre, randomised, double-blind, placebo-controlled phase 3 companion study (TELECAST) 1:1:1 randomisation stratified by baseline u5-HIAA levels

Pavel 2018 (1) *(Continued)*

	Enrolment: April 2014 to April 2015

Participants	Inclusion criteria
	• Age ≥18 years
	• Histopathologically confirmed, well differentiated metastatic NETs
	• Documented history of carcinoid syndrome
	• No SSA treatment or stable-dose SSA treatment (long-acting release, depot or infusion pump) for at least 3 months prior to enrolment
	• Average of < 4 bowel movements/day
	• At least 1 of the following signs or symptoms:
	  ○ Daily stool consistency ≥ 5 on the Bristol Stool Form scale for ≥ 50% of the days during the screening period
	  ○ Average daily cutaneous flushing frequency of ≥ 2
	  ○ Average daily rating of ≥ 3 for abdominal pain
	  ○ Nausea present ≥ 20% of days
	  ○ u5-HIAA above the upper limit of normal
	• For patients not receiving SSA therapy: at least 1 of the above symptoms or an average of ≥ 4 bowel movements/day
	
	Exclusion criteria
	• Diarrhoea attributable to any condition other than carcinoid syndrome
	• ≥ 4 BMs/day while on concomitant SSA therapy
	• Enteric infection
	• Karnofsky performance status ≤ 60%
	• History of short bowel syndrome
	• Chronic or idiopathic constipation
	• Clinically important baseline elevation in liver function tests
	• Tumour-directed therapy within 4 weeks prior to screening
	• Hepatic embolisation, radiotherapy, radiolabeled SSA therapy and/or tumour debulking within 12 weeks prior to screening
	
	Total patients: 76
	
	Mean age (A vs. B vs. C): 62 vs. 64 vs. 63
	
	Women, % (A vs. B vs. C): 50 vs. 44 vs. 40
	
	SSA therapy at study entry, %:
	• Octreotide (A vs. B vs. C): 46 vs. 68 vs. 64
	• Lanreotide (A vs. B vs. C): 54 vs. 20 vs. 12
	• Unknown (A vs. B vs. C): 0 vs. 0 vs. 4
	• Not on SSA (A vs. B vs. C): 0 vs. 12 vs. 20

Interventions	Study group A (26/76): placebo, oral doses, three times per day for 12 weeks Study group B (25/76): telotristat ethyl 250 mg, oral doses, three times per day for 12 weeks Study group C (25/76): telotristat ethyl 500 mg, oral doses, three times per day for 12 weeks Patients continued to receive their baseline stable-dose SSA therapy. Rescue short-acting SSA use was allowed. After the study, all patients were offered treatment with telotristat ethyl 500 mg, three times per day in a 36-week open-label extension.

Pavel 2018 (1) *(Continued)*

Outcomes	Primary endpoints: • Incidence of treatment-emergent adverse events • Percent change from baseline in 24-h u5-HIAA levels at week 12 Secondary endpoints: • Change from baseline averaged over the 12-weeks period for daily bowel movement frequency • Stool consistency • Cutaneous flushing episodes • Abdominal pain • Frequency of rescue short-acting SSA treatment Additional endpoint: • Durability of response to treatment Assessments: • Screening period of at least 3 weeks • Electronic patient diary (identical to the one used in the TELESTAR study) for patient-reported measures
Notes	Trial supported by Lexicon Pharmaceuticals, Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	Nearly equal numbers of participants per study group
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study design
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The majority of endpoints were self-reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All randomised patients accounted for in safety analysis but 10 of 76 (13%) randomised patients were excluded from the u5-HIAA which was the second primary endpoint. These excluded patients were from all three study groups.
Selective reporting (reporting bias)	Low risk	No study protocol available, but every stated endpoint was reported.
Other bias	Low risk	No other potential sources of bias found

Pavlakis 2020

Study characteristics

Pavlakis 2020 *(Continued)*

Methods	Non-comparative randomised open-label parallel-group phase II trial 2:1 randomisation to PRRT/CAPTEM (experimental arm) vs. PRRT (mNETs control) and CAPTEM (pNETS control) Enrolment: December 2015–November 2018
Participants	Inclusion criteria • Pancreatic and midgut neuroendocrine tumours Total patients: 75
Interventions	Experimental arm (33 mNETs and 19 pNETS/75): 7.8 GBq LuTate day 10, 8 weekly x 4, with twice a day oral CAP 750 mg/m^2 on days 1-14 & TEM 75 mg/m^2 on days 10-14, 8 wkly x 4 mNETs control (14/75): PRRT, 8 weekly x 4 pNETS control (9/75): CAPTEM, 8 weekly x 4
Outcomes	Primary endpoint: • Progression-free survival Secondary endpoints: • Objective tumour response rate • Clinical benefit rate • Toxicity • Quality of life
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information given
Selective reporting (reporting bias)	Low risk	All stated endpoints were reported.

Pavlakis 2020 *(Continued)*

Other bias	Low risk	No other potential sources of bias found

Phan 2015 (1)

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3 study • 48 secondary or tertiary care centres in 14 countries Duration: 96 weeks Computer-generated randomisation, stratified by presence or absence of tumour progression at baseline and receipt or nonreceipt of previous therapies Conducted between June 2006 and April 2013 Subgroup analysis: Comparison of progression-free survival and safety data for patients aged < 65 vs. > 65 years
Participants	Inclusion criteria • Adults (≥ 18 years of age) • Sporadic well differentiated or moderately differentiated neuroendocrine tumours, located in the pancreas, midgut, hindgut or of unknown origin • Unresectable locally advanced tumour, metastatic disease or declined surgery • Measurable tumour according to RECIST (vers. 1.0) • Ki-67 index of less than 10% or a mitotic index of ≤ 2 mitoses per 10 high-power fields • Nonfunctioning tumours (except for gastrinomas that had been adequately controlled by means of proton-pump inhibitors for 4 months or longer) • Target lesion or lesions that were classified as grade 2 or higher on somatostatin-receptor scintigraphy (0 (no uptake by tumour) to 4 (very intense uptake by tumour)) within the previous 6 months • WHO performance score ≤ 2 • A biopsy of the neuroendocrine tumour within 6 months before study entry was required for patients who had previous cancer and those with evidence of clinical progression Exclusion criteria • Previous treatment with interferon, chemoembolisation, or chemotherapy within 6 months before study entry, a radionuclide at any time, or a somatostatin analogue at any time (unless they had received it > 6 months previously and for < 15 days) • Major surgery related to the neuroendocrine tumour within 3 months before study entry • Multiple endocrine neoplasia • Previous cancer (except: 1] treated or untreated in situ cervical or uterine carcinoma, or 2] basal-cell skin carcinoma, or 3] other cancers who had been treated with curative intent and had been disease-free for >5 years) • Baseline abnormalities or medical conditions that could jeopardise the patient's safety or interfere with the study Withdrawal • Tumour progression (RECIST) • Investigator's judgement • Patient's request • Adverse event that could jeopardise the patient's safety CLARINET overall population:

Phan 2015 (1) *(Continued)*

Total patients: 204

Age (lanreotide vs. placebo): 63 vs. 62

Women, % (lanreotide vs. placebo): 48 vs. 48

Prior treatment for neuroendocrine tumour, % (lanreotide vs. placebo): 16 vs. 16

Primary tumour resected, % (lanreotide vs. placebo): 40 vs. 38

Origin of tumour:

- Pancreas, % (lanreotide vs. placebo): 42 vs. 48
- Midgut, % (lanreotide vs. placebo): 33 vs. 39
- Hindgut, % (lanreotide vs. placebo): 11 vs. 3
- Unknown, % (lanreotide vs. placebo): 15 vs. 11

Ki-67 index, 0-2%/3-10%, % (lanreotide vs. placebo): 68/32 vs. 70/28

Hepatic tumour volume:

- 0%, % (lanreotide vs. placebo): 16 vs. 17
- > 0-10%, % (lanreotide vs. placebo): 33 vs. 39
- > 10-25%, % (lanreotide vs. placebo): 13 vs. 17
- > 25-50%, % (lanreotide vs. placebo): 23 vs. 12
- > 50%,% (lanreotide vs. placebo): 16 vs. 16

Subgroup analysis:

- Patients < 65 years old: 115
- Patients > 65 years old: 89
- Age (< 65 vs. > 65): 57 vs. 71
- Tumour origin, %:
  - Pancreas (< 65 vs. > 65): 43 vs. 46
  - Midgut (< 65 vs. > 65): 34 vs. 38
- Hepatic tumour load > 25%, % (< 65 vs. > 65): 30 vs. 37

Interventions	Intervention group (101/204): extended-release aqueous-gel formulation of lanreotide, 120 mg, without dose adjustment, deep subcutaneous injection, every 28 days to a maximum of 24 injections Control group (103/204): placebo (sodium chloride), deep subcutaneous injection, every 28 days to a maximum of 24 injections In case of disease progression while receiving placebo, patients crossed over to lanreotide.
Outcomes	Primary endpoint: • Progression-free survival or death within 96 weeks after the first injection of the study drug Secondary endpoints: • Proportion of patients who were alive without disease progression at 48 and 96 weeks • Time to tumour progression • Overall survival • Quality of life • CgA levels • Pharmacokinetic data • Safety Exploratory endpoints:

Phan 2015 (1) *(Continued)*

- Data on other tumour biomarkers

Assessments:

- Study visits: at weeks 1 (baseline), 12, 24, 36, 48, 72, and 96
- CT or MRI of the chest, abdomen, and pelvis was performed twice during screening to determine the baseline disease-progression status. Results of the second imaging test were considered to be the baseline findings and were used to determine target-lesion sizes.
- Single scans were obtained at all post-baseline visits.
- Disease progression was assessed centrally according to RECIST, version 1.0.
- Two quality of life questionnaires (QLQ-C30 and QLQ-GI.NET21) were completed at post-screening visits.
- Serum chromogranin A levels: all visits and also at weeks 60 and 84
- Serum lanreotide levels: prior to drug administration at all study visits and after the first and sixth administration
- Safety assessments: monitoring for adverse events, physical examination and monitoring of vital signs (at all visits), electrocardiography and ultrasonography of the gallbladder (at baseline and at weeks 48 and 96), and clinical laboratory tests (at screening, baseline, and at weeks 48 and 96)

Notes	The study was designed, funded, and conducted by Ipsen in collaboration with the European Neuroendocrine Tumor Society and the UK and Ireland Neuroendocrine Tumour Society.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation lists were created by a statistician employed by the sponsor who was independent of the study.
Allocation concealment (selection bias)	Low risk	The blinded database was held at a third-party contract clinical research organisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded study design. Independent health professionals prepared and administered injections.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Disease progression was assessed centrally, but it remained unclear whether it was performed by independent personnel.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients accounted for in ITT analysis
Selective reporting (reporting bias)	Low risk	Study protocol available. One secondary endpoint mentioned in the protocol was not reported as an endpoint in the publication, but was reported in the supplementary appendix.
Other bias	Low risk	No other potential sources of bias found

Phan 2015 (2)

Study characteristics

Methods	Randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3 study

Phan 2015 (2) *(Continued)*

- 48 secondary or tertiary care centres in 14 countries

Duration: 96 weeks

Computer-generated randomisation, stratified by presence or absence of tumour progression at baseline and receipt or nonreceipt of previous therapies

Conducted between June 2006 and April 2013

Subgroup analysis: investigation on consistency of treatment effects of lanreotide compared with placebo for patients with pNET

Participants	Inclusion criteria

- Adults (≥ 18 years of age)
- Sporadic well differentiated or moderately differentiated neuroendocrine tumours, located in the pancreas, midgut, hindgut or of unknown origin
- Unresectable locally advanced tumour, metastatic disease or declined surgery
- Measurable tumour according to RECIST (vers. 1.0)
- Ki-67 index of less than 10% or a mitotic index of ≤ 2 mitoses per 10 high-power fields
- Nonfunctioning tumours (except for gastrinomas that had been adequately controlled by means of proton-pump inhibitors for 4 months or longer)
- Target lesion or lesions that were classified as grade 2 or higher on somatostatin-receptor scintigraphy (0 (no uptake by tumour) to 4 (very intense uptake by tumour)) within the previous 6 months
- WHO performance score ≤ 2
- A biopsy of the neuroendocrine tumour within 6 months before study entry was required for patients who had previous cancer and those with evidence of clinical progression.

Exclusion criteria

- Previous treatment with interferon, chemoembolisation, or chemotherapy within 6 months before study entry, a radionuclide at any time, or a somatostatin analogue at any time (unless they had received it > 6 months previously and for < 15 days)
- Major surgery related to the neuroendocrine tumour within 3 months before study entry
- Multiple endocrine neoplasia
- Previous cancer (except: 1] treated or untreated in situ cervical or uterine carcinoma, or 2] basal-cell skin carcinoma, or 3] other cancers that had been treated with curative intent and had been disease-free for > 5 years)
- Baseline abnormalities or medical conditions that could jeopardise the patient's safety or interfere with the study

Withdrawal

- Tumour progression (RECIST)
- Investigator's judgement
- Patient's request
- Adverse event that could jeopardise the patient's safety

CLARINET overall population:

Total patients: 204.

Age (lanreotide vs. placebo): 63 vs. 62

Women, % (lanreotide vs. placebo): 48 vs. 48

Prior treatment for neuroendocrine tumour, % (lanreotide vs. placebo): 16 vs. 16

Primary tumour resected, % (lanreotide vs. placebo): 40 vs. 38

Origin of tumour:

Phan 2015 (2) *(Continued)*

- Pancreas, % (lanreotide vs. placebo): 42 vs. 48
- Midgut, % (lanreotide vs. placebo): 33 vs. 39
- Hindgut, % (lanreotide vs. placebo): 11 vs. 3
- Unknown, % (lanreotide vs. placebo): 15 vs. 11

Ki-67 index, 0-2%/3-10%, % (lanreotide vs. placebo): 68/32 vs. 70/28

Hepatic tumour volume:

- 0%, % (lanreotide vs. placebo): 16 vs. 17
- > 0-10%, % (lanreotide vs. placebo): 33 vs. 39
- > 10-25%, % (lanreotide vs. placebo): 13 vs. 17
- > 25-50%, % (lanreotide vs. placebo): 23 vs. 12
- > 50%,% (lanreotide vs. placebo): 16 vs. 16

Subgroup analysis:

Total patients: 91

Mean age, (lanreotide vs. placebo): 64 vs. 64

Hepatic tumour load > 25% (overall): 37%

Previous surgery on the tumour (overall): 38%

No previous treatment (overall): 77%

Interventions	Intervention group (CLARINET overall: 101/204; pNET subgroup: 42/91): extended-release aqueous-gel formulation of lanreotide, 120 mg, without dose adjustment, deep subcutaneous injection, every 28 days to a maximum of 24 injections Control group (CLARINET overall: 103/204; pNET subgroup: 49/91): placebo (sodium chloride), deep subcutaneous injection, every 28 days to a maximum of 24 injections In case of disease progression while receiving placebo, patients crossed over to lanreotide.
Outcomes	Primary endpoint: • Progression-free survival or death within 96 weeks after the first injection of the study drug Secondary endpoints: • Proportion of patients who were alive without disease progression at 48 and 96 weeks • Time to tumour progression • Overall survival • Quality of life • CgA levels • Pharmacokinetic data • Safety Exploratory endpoints: • Data on other tumour biomarkers Assessments: • Study visits: at weeks 1 (baseline), 12, 24, 36, 48, 72, and 96 • CT or MRI of the chest, abdomen, and pelvis was performed twice during screening to determine the baseline disease-progression status. Results of the second imaging test were considered to be the baseline findings and were used to determine target-lesion sizes. • Single scans were obtained at all post-baseline visits.

Phan 2015 (2) *(Continued)*

- Disease progression was assessed centrally according to RECIST, version 1.0.
- Two quality of life questionnaires (QLQ-C30 and QLQ-GI.NET21) were completed at post-screening visits.
- Serum chromogranin A levels: all visits and also at weeks 60 and 84
- Serum lanreotide levels: prior to drug administration at all study visits and after the first and sixth administration
- Safety assessments: monitoring for adverse events, physical examination and monitoring of vital signs (at all visits), electrocardiography and ultrasonography of the gallbladder (at baseline and at weeks 48 and 96), and clinical laboratory tests (at screening, baseline, and at weeks 48 and 96)

Notes	The study was designed, funded, and conducted by Ipsen in collaboration with the European Neuroendocrine Tumor Society and the UK and Ireland Neuroendocrine Tumour Society.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation lists were created by a statistician employed by the sponsor who was independent of the study.
Allocation concealment (selection bias)	Low risk	The blinded database was held at a third-party contract clinical research organisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded study design. Independent health professionals prepared and administered injections.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Disease progression was assessed centrally, but it remained unclear whether it was performed by independent personnel.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients accounted for in ITT analysis
Selective reporting (reporting bias)	Low risk	Study protocol available. One secondary endpoint mentioned in the protocol was not reported as an endpoint in the publication, but was reported in the supplementary appendix.
Other bias	Low risk	No other potential sources of bias found

Pusceddu 2018

Study characteristics

Methods	Randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3 study • 48 secondary or tertiary care centres in 14 countries Duration: 96 weeks Computer-generated randomisation, stratified by presence or absence of tumour progression at baseline and receipt or nonreceipt of previous therapies Conducted between June 2006 and April 2013

Pusceddu 2018 *(Continued)*

	Evaluation on impact of diabetes on progression-free survival in patients with advanced, nonfunctioning GEP-NETs
Participants	Inclusion criteria • Adults (≥ 18 years of age) • Sporadic well differentiated or moderately differentiated neuroendocrine tumours, located in the pancreas, midgut, hindgut or of unknown origin • Unresectable locally advanced tumour, metastatic disease or declined surgery • Measurable tumour according to RECIST (vers. 1.0) • Ki-67 index of less than 10% or a mitotic index of ≤ 2 mitoses per 10 high-power fields • Nonfunctioning tumours (except for gastrinomas that had been adequately controlled by means of proton-pump inhibitors for 4 months or longer) • Target lesion or lesions that were classified as grade 2 or higher on somatostatin-receptor scintigraphy (0 (no uptake by tumour) to 4 (very intense uptake by tumour)) within the previous 6 months • WHO performance score ≤ 2 • A biopsy of the neuroendocrine tumour within 6 months before study entry was required for patients who had previous cancer and those with evidence of clinical progression Exclusion criteria • Previous treatment with interferon, chemoembolisation, or chemotherapy within 6 months before study entry, a radionuclide at any time, or a somatostatin analogue at any time (unless they had received it > 6 months previously and for < 15 days) • Major surgery related to the neuroendocrine tumour within 3 months before study entry • Multiple endocrine neoplasia • Previous cancer (except: 1] treated or untreated in situ cervical or uterine carcinoma, or 2] basal-cell skin carcinoma, or 3] other cancers who had been treated with curative intent and had been disease-free for >5 years) • Baseline abnormalities or medical conditions that could jeopardise the patient's safety or interfere with the study Withdrawal • Tumour progression (RECIST) • Investigator's judgement • Patient's request • Adverse event that could jeopardise the patient's safety CLARINET overall population: Total patients: 204 Age (lanreotide vs. placebo): 63 vs. 62 Women, % (lanreotide vs. placebo): 48 vs. 48 Prior treatment for neuroendocrine tumour, % (lanreotide vs. placebo): 16 vs. 16 Primary tumour resected, % (lanreotide vs. placebo): 40 vs. 38 Origin of tumour: • Pancreas, % (lanreotide vs. placebo): 42 vs. 48 • Midgut, % (lanreotide vs. placebo): 33 vs. 39 • Hindgut, % (lanreotide vs. placebo): 11 vs. 3 • Unknown, % (lanreotide vs. placebo): 15 vs. 11 Ki-67 index, 0-2%/3-10%, % (lanreotide vs. placebo): 68/32 vs. 70/28

Pusceddu 2018 *(Continued)*

	Hepatic tumour volume: • 0%, % (lanreotide vs. placebo): 16 vs. 17 • > 0-10%, % (lanreotide vs. placebo): 33 vs. 39 • > 10-25%, % (lanreotide vs. placebo): 13 vs. 17 • > 25-50%, % (lanreotide vs. placebo): 23 vs. 12 • > 50%,% (lanreotide vs. placebo): 16 vs. 16 Subgroup analysis: Patients with diabetes mellitus (DM): 79 Patients without diabetes mellitus (N-DM): 125
Interventions	Intervention group (101/204): extended-release aqueous-gel formulation of lanreotide, 120 mg, without dose adjustment, deep subcutaneous injection, every 28 days to a maximum of 24 injections Control group (103/204): placebo (sodium chloride), deep subcutaneous injection, every 28 days to a maximum of 24 injections In case of disease progression while receiving placebo, patients crossed over to lanreotide.
Outcomes	Primary endpoint: • Progression-free survival or death within 96 weeks after the first injection of the study drug Secondary endpoints: • Proportion of patients who were alive without disease progression at 48 and 96 weeks • Time to tumour progression • Overall survival • Quality of life • CgA levels • Pharmacokinetic data • Safety Exploratory endpoints: • Data on other tumour biomarkers Assessments: • Study visits: at weeks 1 (baseline), 12, 24, 36, 48, 72, and 96 • CT or MRI of the chest, abdomen, and pelvis was performed twice during screening to determine the baseline disease-progression status. Results of the second imaging test were considered to be the baseline findings and were used to determine target-lesion sizes. • Single scans were obtained at all post-baseline visits. • Disease progression was assessed centrally according to RECIST, version 1.0. • Two quality of life questionnaires (QLQ-C30 and QLQ-GI.NET21) were completed at post-screening visits. • Serum chromogranin A levels: all visits and also at weeks 60 and 84 • Serum lanreotide levels: prior to drug administration at all study visits and after the first and sixth administration • Safety assessments: monitoring for adverse events, physical examination and monitoring of vital signs (at all visits), electrocardiography and ultrasonography of the gallbladder (at baseline and at weeks 48 and 96), and clinical laboratory tests (at screening, baseline, and at weeks 48 and 96)
Notes	The study was designed, funded, and conducted by Ipsen in collaboration with the European Neuroendocrine Tumor Society and the UK and Ireland Neuroendocrine Tumour Society.

Pusceddu 2018 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation lists were created by a statistician employed by the sponsor who was independent of the study.
Allocation concealment (selection bias)	Low risk	The blinded database was held at a third-party contract clinical research organisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded study design. Independent health professionals prepared and administered injections.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Disease progression was assessed centrally, but it remained unclear whether it was performed by independent personnel.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients accounted for in ITT analysis
Selective reporting (reporting bias)	Low risk	Study protocol available. One secondary endpoint mentioned in the protocol was not reported as an endpoint in the publication, but was reported in the supplementary appendix.
Other bias	Low risk	No other potential sources of bias found

Raymond 2011 (1)

Study characteristics	
Methods	Multinational, randomised, double-blind, placebo-controlled phase 3 trial • 42 centres in 11 countries 1:1 randomisation ratio by centralised internet/telephone registration system (IMPALA), balanced by country/region Start: June 2007 Closed: April 2009 (discontinuation because of the greater number of deaths and serious adverse events in the placebo group and the difference in progression-free survival favouring sunitinib)
Participants	Inclusion criteria: • Pathologically confirmed, well differentiated pancreatic endocrine tumours (advanced, metastatic, or both) that were not candidates for surgery • Documented disease progression within the previous 12 months according to RECIST • One or more measurable target lesions • Eastern Cooperative Oncology Group performance status of 0 or 1 • Adequate haematologic, hepatic, and renal function Exclusion criteria: • Poorly differentiated pancreatic neuroendocrine tumours

Raymond 2011 (1) *(Continued)*

- Previous tyrosine kinase or VEGF inhibitor treatment
- Cardiac events or pulmonary embolism in the previous 12 months
- Ongoing cardiac dysrhythmias or a prolonged QT interval corrected for heart rate (QTc)
- Symptomatic brain metastases
- Left ventricular ejection fraction of 50% or less

Total patients: 171

Median age (sunitinib vs. placebo): 56 vs. 57

Women % (sunitinib vs. placebo): 51 vs. 53

Ethnicity (sunitinib vs. placebo): 56% white vs. 62% white

Geographic region (sunitinib vs. placebo): 69% Europe vs. 66% Europe

ECOG performance status 0 (sunitinib vs. placebo): 62% vs. 48%

Nonfunctional tumours % (sunitinib vs. placebo): 49 vs. 52

Liver metastases, % (sunitinib vs. placebo): 95 vs. 94

Ki-67 index ≤ 2%/> 2%-5%/> 5%-10%/> 10%/not reported, % (sunitinib vs. placebo): 8/19/6/9/58 vs. 7/16/12/7/58

Previous treatment for NET:

- Surgery, % (sunitinib vs. placebo): 88 vs. 91
- Radiation therapy, % (sunitinib vs. placebo): 10 vs. 14
- Chemoembolisation, % (sunitinib vs. placebo): 8 vs. 16
- Radiofrequency ablation, % (sunitinib vs. placebo): 3 vs. 7
- Percutaneous ethanol injection, % (sunitinib vs. placebo): 1 vs. 2
- SSA, % (sunitinib vs. placebo): 35 vs. 38
- Any chemotherapy, % (sunitinib vs. placebo): 66 vs. 72
  - Streptozocin, % (sunitinib vs. placebo): 28 vs. 33
  - Anthracyclines, % (sunitinib vs. placebo): 31 vs. 41
  - Fluoropyrimidines, % (sunitinib vs. placebo): 23 vs. 29

Interventions	Intervention group (86/171): once-daily oral sunitinib at a dose of 37.5 mg per day Control group (85/171): once-daily oral matching placebo per day Treatment interruptions and a dose reduction to 25 mg per day were permitted to manage adverse events, with a subsequent increase in dose if toxicity of grade 2 or higher did not recur. The dose could be increased up to 50 mg per day, if 1) there was no objective tumour response, and 2) patients had grade 1 or lower non-haematologic or grade 2 or lower haematologic treatment-related adverse events during the first 8 weeks. Treatment continued until RECIST-defined progression was documented, unacceptable adverse events occurred, or the patient died. Patients with disease progression while receiving placebo could enter an open-label sunitinib extension protocol. Patients could receive somatostatin analogues at the investigator's discretion.
Outcomes	Primary endpoint: progression-free survival Secondary endpoints: overall survival, objective response rate (RECIST), time to tumour response, duration of response, safety, patient-reported outcomes (QLQ-C30, version 3.0)

Raymond 2011 (1) *(Continued)*

	Assessments: • Full tumour imaging: at screening • Subsequent imaging: during week 5 and week 9 and every 8 weeks thereafter • Data and patient-reported outcomes: every 4 weeks
Notes	Funding: Pfizer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Done by centralised internet/telephone registration system. Balanced by country/region
Allocation concealment (selection bias)	Low risk	Centralised allocation system used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded trial design with same schemes for each study group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No sufficient information given
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for in final analysis. Equal numbers (n = 3) in each arm did not receive allocated treatment.
Selective reporting (reporting bias)	Low risk	Data collection and statistical analysis were performed by the sponsor. Every study protocol mentioned endpoint was published.
Other bias	Low risk	No other potential sources of bias found

Raymond 2011 (2)

Study characteristics

Methods	Multinational, randomised, double-blind, placebo-controlled phase 3 trial • 42 centres in 11 countries 1:1 randomisation ratio by centralised internet/telephone registration system (IMPALA), balanced by country/region Start: June 2007 Closed: April 2009 (discontinuation because of the greater number of deaths and serious adverse events in the placebo group and the difference in progression-free survival favouring sunitinib)
Participants	Inclusion criteria: • Pathologically confirmed, well differentiated pancreatic endocrine tumours (advanced, metastatic, or both) who were not candidates for surgery • Documented disease progression within the previous 12 months according to RECIST

Raymond 2011 (2) *(Continued)*

- One or more measurable target lesions
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Adequate haematologic, hepatic, and renal function

Exclusion criteria:

- Poorly differentiated pancreatic neuroendocrine tumours
- Previous tyrosine kinase or VEGF inhibitor treatment
- Cardiac events or pulmonary embolism in the previous 12 months
- Ongoing cardiac dysrhythmias or a prolonged QT interval corrected for heart rate (QTc)
- Symptomatic brain metastases
- Left ventricular ejection fraction of 50% or less

Total patients: 171

Median age (sunitinib vs. placebo): 56 vs. 57

Women % (sunitinib vs. placebo): 51 vs. 53

Ethnicity (sunitinib vs. placebo): 56% white vs. 62% white

Geographic region (sunitinib vs. placebo): 69% Europe vs. 66% Europe

ECOG performance status 0 (sunitinib vs. placebo): 62% vs. 48%

Nonfunctional tumours % (sunitinib vs. placebo): 49 vs. 52

Liver metastases, % (sunitinib vs. placebo): 95 vs. 94

Ki-67 index ≤ 2%/> 2%-5%/> 5%-10%/> 10%/not reported, % (sunitinib vs. placebo): 8/19/6/9/58 vs. 7/16/12/7/58

Previous treatment for NET:

- Surgery, % (sunitinib vs. placebo): 88 vs. 91
- Radiation therapy, % (sunitinib vs. placebo): 10 vs. 14
- Chemoembolisation, % (sunitinib vs. placebo): 8 vs. 16
- Radiofrequency ablation, % (sunitinib vs. placebo): 3 vs. 7
- Percutaneous ethanol injection, % (sunitinib vs. placebo): 1 vs. 2
- SSA, % (sunitinib vs. placebo): 35 vs. 38
- Any chemotherapy, % (sunitinib vs. placebo): 66 vs. 72

Subgroup analysis:

- In 72 of 171 patients, Ki-67 values were available.

Interventions	Intervention group (86/171): once-daily oral sunitinib at a dose of 37.5 mg per day Control group (85/171): once-daily oral matching placebo per day Treatment interruptions and a dose reduction to 25 mg per day were permitted to manage adverse events, with a subsequent increase in dose if toxicity of grade 2 or higher did not recur. The dose could be increased up to 50 mg per day, if 1) there was no objective tumour response, and 2) patients had grade 1 or lower non-haematologic or grade 2 or lower haematologic treatment-related adverse events during the first 8 weeks. Treatment continued until RECIST-defined progression was documented, unacceptable adverse events occurred, or the patient died. Patients with disease progression while receiving placebo could enter an open-label sunitinib extension protocol.

Raymond 2011 (2) *(Continued)*

	Patients could receive somatostatin analogues at the investigator's discretion.
Outcomes	Primary endpoint: progression-free survival Secondary endpoints: overall survival, objective response rate (RECIST), time to tumour response, duration of response, safety, patient-reported outcomes (QLQ-C30, version 3.0) Aims of subgroup analysis: • Impact of baseline Ki-67 index and other baseline characteristics on outcome Assessments: • Full tumour imaging: at screening • Subsequent imaging: during week 5 and week 9 and every 8 weeks thereafter • Data and patient-reported outcomes: every 4 weeks
Notes	Funding: Pfizer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Done by centralised internet/telephone registration system. Balanced by country/region
Allocation concealment (selection bias)	Low risk	Centralised allocation system used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded trial design with same schemes for each study group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No sufficient information given
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for in final analysis. Equal numbers (n = 3) in each arm did not receive allocated treatment.
Selective reporting (reporting bias)	Low risk	Data collection and statistical analysis were performed by the sponsor. Every study protocol mentioned endpoint was published.
Other bias	Low risk	No other potential sources of bias found

Rinke 2009

Study characteristics

Methods	Randomised, double-blind, placebo-controlled trial • conducted at 18 German academic centres Central, computer-generated 1:1 randomisation, stratified by study centre, tumour functionality, presence of distant metastases (liver or elsewhere), Ki-67 index and age

Rinke 2009 *(Continued)*

	Start of enrolment: March 2001 Enrolment closed: January 2008
Participants	Inclusion criteria • Midgut primary tumour or tumour of unknown origin believed to be of midgut origin if a primary within the pancreas, chest, or elsewhere was excluded by CT or MRI • Locally inoperable or metastatic disease • Proof of a well differentiated histology by pathology • Measurable disease by CT or MRI • Karnofsky performance status more than 60% • No curative therapeutic options • Tolerating flushing without intervention or responding to treatment with loperamide or cholestyramine in case of diarrhoea • Declined surgery for regional or distant tumour in the institutional tumour boards of the study hospitals Exclusion criteria • Pretreatment with somatostatin analogs for ≥ 4 weeks • Previous treatment with interferon alfa, chemotherapy or chemoembolisation Total patients: 85 Median age (octreotide LAR vs. placebo): 63.5 vs. 61 Women % (octreotide LAR vs. placebo): 52% vs. 47% Karnofsky performance status > 80 % (octreotide LAR vs. placebo): 83% vs. 88% Ki-67 up to 2%, % (octreotide LAR vs. placebo): 97.6 vs. 93 Liver involvement, % (octreotide LAR vs. placebo): 83.3 vs. 88.4 Carcinoid syndrome, % (octreotide LAR vs. placebo): 40.5 vs. 37.2 Resection of primary tumour, % (octreotide LAR vs. placebo): 69 vs. 63 Unknown site of primary tumour, % (overall): 25%
Interventions	Intervention arm (42/85): octreotide LAR, 30 mg, intramuscularly, every 28 days Control arm (43/85): placebo (sodium chloride), intramuscularly, every 28 days Length of therapy: until CT- or MRI-documented tumour progression Additional antiproliferative therapy was not allowed. Poststudy treatment in patients with tumour progression was at the discretion of the investigator.
Outcomes	Primary endpoint: • Time to tumour progression Secondary endpoints: • Survival time • Quality of life • Clinical and biochemical response • Adverse events

Rinke 2009 *(Continued)*

Notes	Research funding through Novartis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, stratified randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded trial. Same application schemes for each study arm
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All clinical assessments were performed without knowledge of the assigned treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients accounted for in ITT analysis 2/42 of patients in the study arm and 1/43 in the placebo arm were censored for conservative ITT analysis. 12/42 of patients in the study arm and 3/43 in the placebo arm were censored for per-protocol analysis.
Selective reporting (reporting bias)	Low risk	No study protocol available, but every endpoint mentioned in the 'methods' section was mentioned in the 'results' section. The timing of the assessment for most endpoints was unclear. Progression-free survival and overall survival were both reported.
Other bias	Low risk	No other potential sources of bias found

Sakata 2006

Study characteristics

Methods	Randomisation according to a table of random permutations Start: 1993 Closed: 2002 Follow-up: > 3 years
Participants	Inclusion criteria • Rectal carcinoid tumour < 10 mm Total patients: 15 Mean age (group 1 vs. 2): 60.2 vs. 62.6 Women, % (1 vs. 2): 43 vs. 38

Sakata 2006 *(Continued)*

	Carcinoid symptoms (overall): 0% Tumour grade: not reported Metastatic disease: not reported Previous treatment for NET: not reported
Interventions	Group 1 (7/15): endoscopic mucosal resection, snare with a conventional single-channel colonoscopy Group 2 (8/15): endoscopic resection, ligation device
Outcomes	Endpoints: • Complete resection rate • Recurrence rate Assessments: not reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	According to a table of random permutations
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Personnel not blinded; unclear, if participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	No evidence for independent assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for in final analysis
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	No other potential sources of bias found

Salazar 2018

Study characteristics

Methods	Randomised, phase II trial Randomisation: 1:1
Participants	Inclusion criteria:

Salazar 2018 *(Continued)*

	• Advanced pNET • Naïve to mTOR inhibition therapy Total patients: 62 Median age (BEZ235 vs. everolimus): 56 vs. 57 Women % (BEZ235 vs. everolimus): 45 vs. 52 ECOG performance status 0-1 (BEZ235 vs. everolimus): 97% vs. 100% Functional tumours: not reported Tumour grade: not reported Every patient had 2 prior therapy regimens.
Interventions	Study arm 1 (31/62): oral BEZ235 400 mg, twice daily Study arm 2 (31/62): oral everolimus 10 mg, once daily
Outcomes	Primary endpoint: • Progression-free survival Secondary endpoints: • Safety • Overall response rate • Overall survival • Time to treatment failure
Notes	• Funding: Novartis Pharmaceuticals Corporation • Study terminated before completion due to toxicity

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Different schemes for study drug intake
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for in final analysis
Selective reporting (reporting bias)	Low risk	No protocol available, but all outcomes stated in the paper as measured were reported.

Salazar 2018 *(Continued)*

Other bias	Low risk	No other potential sources of bias found

Saslow 1998

Study characteristics	
Methods	Single-centre, randomised, double-blind trial 1:1:1 randomisation Duration: 4 weeks
Participants	Inclusion criteria • Diarrhoea due to metastatic small bowel carcinoid syndrome Exclusion criteria • Small bowel or right colon resection exceeding 100 cm • Intake of antidiarrhoeal medication or agents that alter gut transit within 48 hours of entry to the study (e.g. codeine, diphenoxylate, loperamide, calcium channel blockers, anticholinergic agents) Total patients: 26 Mean age (0.1 vs. 0.5 vs. 2.0): 65 vs. 65 vs. 71 Women, % (0.1 vs. 0.5 vs. 2.0): 38 vs. 66 vs. 22 Metastases in abdominal nodes or liver, % (0.1 vs. 0.5 vs. 2.0): 100 vs. 100 vs. 100 Urinary 5-hydroxyindoleacetic acid concentration, mg/24-h (0.1 vs. 0.5 vs. 2.0): 37 vs. 12 vs. 32
Interventions	Group 0.1 (8/26): placebo for 1 week, followed by alosetron 0.1 mg twice daily as two tablets with breakfast and dinner Group 0.5 (9/26): placebo for 1 week, followed by alosetron 0.5 mg twice daily as two tablets with breakfast and dinner Group 2.0 (9/26): placebo for 1 week, followed by alosetron 2.0 mg twice daily as two tablets with breakfast and dinner During the 24-h test period, caffeine-free drinks were allowed; cigarette smoking was not permitted.
Outcomes	Primary endpoints: • Weekly self-rating for diarrhoea (visual analog scale); median of the seven daily scores • Rescue loperamide capsules used Secondary endpoints: • Small bowel transit time • Geometric centre of colonic radioisotopic count at four hours • Proximal colon emptying rate Assessments: • Haematology screening, chemistry screening and electrocardiography at baseline and at the end (after 4 weeks) • Urinary 5-hydroxyindoleacetic acid concentration prior to entry into the study • Study instructions and review of symptoms at day 4

Saslow 1998 *(Continued)*

- Gastric, small bowel and colonic transit test over a period of 24 h: one day in week 1 and one day in week 4. Stool was collected to measure volume and fat content. All meals were standardised (during this 24-hours period).
- Daily diary for all four weeks for stool frequency, consistency, urgency, abdominal pain, loperamide capsules used and diarrhoea score

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial design
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	24 of 26 patients had evaluable data.
Selective reporting (reporting bias)	Low risk	No study protocol available, but all stated endpoints were reported.
Other bias	Low risk	No other potential sources of bias found

Singh 2018 (1)

Study characteristics

Methods	International, multicentre, randomised, double-blind, placebo-controlled, phase 3 study • 97 centres in 25 countries worldwide 2:1 randomisation by interactive voice response systems, stratified by 1) previous somatostatin analogue treatment for at least 12 weeks, 2) tumour origin (stratum A: appendix, caecum, jejunum, ileum, duodenum, or neuroendocrine tumour of unknown primary origin vs. stratum B: lung, stomach, colon or rectum, and 3) WHO performance status (0 vs. 1). Start enrolment: April 2012 Closed enrolment: August 2013 Subgroup analysis: effect of everolimus in patients with advanced, progressive, nonfunctional GI or unknown primary NET
Participants	Inclusion criteria

Singh 2018 (1) *(Continued)*

- Aged ≥ 18 years
- Pathologically confirmed, advanced (unresectable or metastatic), nonfunctional, well differentiated (grade 1 or 2 according to the 2010 WHO classification) neuroendocrine tumours of lung or gastrointestinal origin
- Within 6 months from documented radiological disease progression
- Measurable disease according to modified Response Evaluation Criteria In Solid Tumours (RECIST vers. 1.0)
- WHO performance status score of 0 or 1
- Adequate bone marrow, liver, and kidney function
- Despite a previous treatment with somatostatin analogue, interferon, one line of chemotherapy, peptide receptor radionuclide therapies, or a combination of these: if disease progression was documented during or after their last treatment. Antineoplastic therapy must have been discontinued for at least 4 weeks (or 6 months in the case of peptide receptor radionuclide therapies) before randomisation.

Exclusion criteria

- History of or present carcinoid syndrome
- Poorly differentiated histology
- Pancreatic neuroendocrine tumours
- Previous treatment with more than one line of chemotherapy
- Treatment with mTOR inhibitors (sirolimus, temsirolimus, or everolimus)
- Hepatic intra-arterial embolisation within 6 months of randomisation
- Cryoablation or radiofrequency ablation of hepatic metastases within 2 months of randomisation
- Chronic treatment with corticosteroids or other immunosuppressive agents

RADIANT-4 overall population

Total patients: 302

Age (everolimus vs. placebo): 65 vs. 60

Women, % (everolimus vs. placebo): 57 vs. 45

WHO performance status 0, % (everolimus vs. placebo): 73 vs. 75

Tumour grade 1, % (everolimus vs. placebo): 63 vs. 67

Primary tumour site, %:

- Lung (everolimus vs. placebo): 31 vs. 28
- Ileum (everolimus vs. placebo): 23 vs. 25
- Rectum (everolimus vs. placebo): 12 vs. 16
- Unknown origin (everolimus vs. placebo): 11 vs. 13
- Jejunum (everolimus vs. placebo): 8 vs. 6
- Stomach (everolimus vs. placebo): 3 vs. 4
- Duodenum (everolimus vs. placebo): 4 vs. 2
- Colon (everolimus vs. placebo): 2 vs. 3
- Other (everolimus vs. placebo): 3 vs. 2
- Caecum (everolimus vs. placebo): 2 vs. 1
- Appendix (everolimus vs. placebo): 1 vs. 0

Liver involvement, % (everolimus vs. placebo): 80 vs. 78

Previous treatment, %:

- Surgery (everolimus vs. placebo): 59 vs. 72
- Chemotherapy (everolimus vs. placebo): 26 vs. 24
- Radiotherapy including PRRT (everolimus vs. placebo): 22 vs. 20
- Locoregional and ablative therapies (everolimus vs. placebo): 11 vs. 10

Singh 2018 (1) *(Continued)*

- SSA (everolimus vs. placebo): 53 vs. 56

Subgroup analysis: gastrointestinal tract

Total patients: 175

Age (everolimus vs. placebo): 63 vs. 60

Women, % (everolimus vs. placebo): 59 vs. 46

WHO performance status 0, % (everolimus vs. placebo): 75 vs. 84

Tumour grade 1, % (everolimus vs. placebo): 74 vs. 77

Primary tumour site, %:

- Ileum (everolimus vs. placebo): 40 vs. 42
- Rectum (everolimus vs. placebo): 21 vs. 26
- Jejunum (everolimus vs. placebo): 14 vs. 11
- Stomach (everolimus vs. placebo): 6 vs. 7
- Duodenum (everolimus vs. placebo): 7 vs. 4
- Colon (everolimus vs. placebo): 4 vs. 5
- Other (everolimus vs. placebo): 4 vs. 4
- Caecum (everolimus vs. placebo): 3 vs. 2
- Appendix (everolimus vs. placebo): 1 vs. 0

Without liver involvement, % (everolimus vs. placebo): 14 vs. 11

Previous treatment, %:

- Surgery (everolimus vs. placebo): 70 vs. 84
- Chemotherapy (everolimus vs. placebo): 19 vs. 12
- Radiotherapy including PRRT (everolimus vs. placebo): 14 vs. 7
- SSA (everolimus vs. placebo): 59 vs. 63

Subgroup analysis: unknown primary

Total patients: 36

Age (everolimus vs. placebo): 61 vs. 54

Women, % (everolimus vs. placebo): 65 vs. 46

WHO performance status 0, % (everolimus vs. placebo): 61 vs. 54

Tumour grade 1, % (everolimus vs. placebo): 65 vs. 62

Primary tumour site, %:

- Unknown origin (everolimus vs. placebo): 100 vs. 100

Without liver involvement, % (everolimus vs. placebo): 9 vs. 23

Previous treatment, %:

- Surgery (everolimus vs. placebo): 26 vs. 31
- Chemotherapy (everolimus vs. placebo): 30 vs. 23
- Radiotherapy including PRRT (everolimus vs. placebo): 9 vs. 15
- SSA (everolimus vs. placebo): 52 vs. 54

Interventions	Study group (203/302): oral everolimus, 10 mg per day Control group (97/302): identical placebo

Singh 2018 (1) *(Continued)*

	Duration of treatment: until 1) documented radiological disease progression, 2) start of new cancer therapy, 3) development of an intolerable adverse event, or 4) withdrawal of consent Allowed: • Best supportive care (including analgesics and anti-diarrhoeals) • Dose reduction and treatment interruption to manage adverse events that were judged to be related to study treatment Not allowed: • Anti-tumour agents like somatostatin analogues, interferons, tumour ablative procedures, radiation and concurrent chemotherapy • Cross-over from placebo to open-label everolimus after progression Exceptions: • Radiation and surgery were allowed only for palliative intent. • Concomitant somatostatin analogues only for control of emergent carcinoid symptoms that were not manageable by standard treatment (e.g. loperamide)
Outcomes	Primary endpoint: • Central radiology-assessed progression-free survival Secondary endpoints: • Overall survival • Objective response rate • Disease control rate • Health-related quality of life • WHO performance status • Pharmacokinetics • Changes in CgA and neuron-specific enolase levels • Safety Assessments: • Multiphasic CT or MRI every 8 weeks during the first 12 months and every 12 weeks thereafter
Notes	Trial sponsored by Novartis Pharmaceuticals Corporation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified randomisation by interactive voice response systems
Allocation concealment (selection bias)	Low risk	Randomisation centrally managed by Novartis Pharmaceutical
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel were blinded. Study drugs looked identical. Assessments were the same in both groups.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Central radiology review, masked to treatment

Singh 2018 (1) *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were included in the full analysis set.
Selective reporting (reporting bias)	High risk	Not all endpoints reported in the study protocol were published.
Other bias	Low risk	No other potential sources of bias found

Soulen 2020

Study characteristics	
Methods	Prospective randomised controlled trial
Participants	Inclusion criteria • Progressive or symptomatic neuroendocrine tumour (NET) liver metastases Total patients: not reported (first safety report)
Interventions	Study arm 1: bland embolisation. Study arm 2: cTACE (conventional transarterial chemoembolisation) Study arm 3: DEB-TACE (drug-eluting bead transarterial chemoembolisation)
Outcomes	Endpoint: • Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information given
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded review was performed by independent oncologists.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information given

Soulen 2020 *(Continued)*

Selective reporting (reporting bias)	Low risk	The stated endpoint was reported.
Other bias	Low risk	No other potential sources of bias found

Strosberg 2011

Study characteristics	
Methods	International, multicentre, double-blind, phase 3 study • 82 centres in 18 countries worldwide Randomisation: • Ratio 1:1 • Stratified by whether or not patients had received prior cytotoxic chemotherapy and by WHO performance status (0 vs. 1-2) at baseline Start: July 2007 Closed: May 2009

Participants	Inclusion criteria:
	• 18 years of age or older
	• Low-grade or intermediate-grade advanced (unresectable or metastatic) pancreatic neuroendocrine tumours
	• Radiologic documentation of disease progression in the previous 12 months
	• Measurable disease (RECIST)
	• World Health Organization (WHO) performance status of 2 or less
	• Adequate bone marrow, renal, and hepatic function
	• Adequately controlled lipid and glucose concentrations
	Exclusion criteria:
	• Hepatic-artery embolisation within 6 months before enrolment or within 1 month if there were other sites of measurable disease or cryoablation or radiofrequency ablation of hepatic metastasis within 2 months before enrolment
	• Severe or uncontrolled medical conditions
	• Prior therapy with an mTOR inhibitor
	• Long-term treatment with glucocorticoids or other immunosuppressive agents
	RADIANT-3 overall population:
	• Total patients: 410
	• Median age (everolimus vs. placebo): 58 vs. 57
	• Women % (everolimus vs. placebo): 47 vs 42
	• WHO performance status 0 (everolimus vs. placebo): 67% vs. 66%
	• Well differentiated % (everolimus vs. placebo): 82 vs. 84
	• Moderately differentiated % (everolimus vs. placebo): 17 vs. 15
	• Liver involvement, % (everolimus vs. placebo): 92% vs. 92%
	• Functional tumours (overall): 24%
	• Prior therapy for NET, %:
	  ○ Radiotherapy (everolimus vs. placebo): 23 vs. 20
	  ○ Chemotherapy (everolimus vs. placebo): 50 vs. 50

Strosberg 2011 *(Continued)*

- Somatostatin analogue therapy (everolimus vs. placebo): 49 vs. 50

Interventions	Intervention group (207/410): oral everolimus, at a dose of 10 mg once daily, in conjunction with best supportive care (e.g. somatostatin analogue therapy) Control group (203/410): oral matching placebo in conjunction with best supportive care (e.g. somatostatin analogue therapy) Length of treatment: until progression of the disease, development of an unacceptable toxic effect, drug interruption for 3 weeks or longer, or withdrawal of consent Patients who had been assigned to placebo initially could switch to open-label everolimus after documented progression of disease (RECIST). Doses were delayed/reduced if patients had clinically significant adverse events that were considered to be related to the study treatment.
Outcomes	Primary endpoint: • Progression-free survival (RECIST) Secondary endpoints: • Confirmed objective response rate (RECIST) • Duration of response • Overall survival • Safety Subgoup analysis: • Changes in serum CgA and NSE levels over time and the prognostic value of these biomarkers for risk of disease progression Assessments: • Tumour measurements (computed tomography or magnetic resonance imaging): at baseline and every 12 weeks • Safety assessments: monitoring and recording of all adverse events, haematologic and clinical biochemical levels and vital signs, and physical examinations every 4 weeks Data collection: sponsor's data management Data analysis: sponsor's statistical team
Notes	Funding/Sponsor: Novartis Oncology

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised randomisation through interactive voice response system. Stratified by performance status and prior treatment (+/- chemotherapy)
Allocation concealment (selection bias)	Low risk	Centralised randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded trial design with same schemes for each study group

Strosberg 2011 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Endpoints were documented by the local investigator according to RECIST, with independent adjudicated central assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for in final analysis
Selective reporting (reporting bias)	Unclear risk	Not all secondary endpoints mentioned in the study protocol were published in the main study (Yao 2011), but one secondary endpoint was analysed as an exploratory endpoint in this study.
Other bias	Low risk	No other potential sources of bias found

Strosberg 2017

Study characteristics	
Methods	International multicentre, open-label, randomised phase 3 trial • 41 centres in 8 countries 1:1 randomisation performed with a centralised permuted block randomisation scheme, stratified by highest tumour uptake score on somatostatin receptor scintigraphy and the length of time that a patient had been receiving a constant dose of octreotide Start: September 2012 Closed: January 2016
Participants	Inclusion criteria • Adults • Metastasised or locally advanced midgut neuroendocrine tumours • Inoperable tumours • Histologically confirmed and centrally verified • Disease progression (RECIST, vers. 1.1) on CT or MRI over the course of a maximum period of 3 years during treatment with octreotide LAR • Karnofsky performance status score > 60 • Tumour with well differentiated histologic features, and somatostatin receptors present on all target lesions Exclusion criteria • Serum creatinine level of more than 150 µmol per litre (1.7 mg per decilitre) or a creatinine clearance of less than 50 mL per minute • Haemoglobin level of less than 8.0 g per decilitre • White cell count of less than 2000 per cubic millimetre • Platelet count of less than 75,000 per cubic millimetre • Total bilirubin level of more than 3 times the upper limit of the normal range • Serum albumin level of more than 3.0 g per decilitre (unless the prothrombin time value was within the normal range) • Treatment with more than 30 mg of octreotide LAR within 12 weeks before randomisation.Peptide receptor radionuclide therapy at any time before randomisation • Any surgery, liver-directed transarterial therapy, or chemotherapy within 12 weeks before randomisation

Strosberg 2017 *(Continued)*

	Total patients: 229 Age (^{177}Lu-Dotatate group vs. control group): 63 vs. 64 Women, % (^{177}Lu-Dotatate group vs. control group): 46 vs. 53 Primary tumour site: • Ileum, % (^{177}Lu-Dotatate group vs. control group): 74 vs. 73 • Small intestine (not otherwise specified), % (^{177}Lu-Dotatate group vs. control group): 9 vs. 11 • Midgut (not otherwise specified), % (^{177}Lu-Dotatate group vs. control group): 8 vs. 6 • Jejunum, % (^{177}Lu-Dotatate group vs. control group): 5 vs. 8 • Right colon, % (^{177}Lu-Dotatate group vs. control group): 3 vs. 1 • Appendix, % (^{177}Lu-Dotatate group vs. control group): 1 vs. 2 Previous surgical resection, % (^{177}Lu-Dotatate group vs. control group): 78 vs. 82 Previous systemic therapy other than SSA, % (^{177}Lu-Dotatate group vs. control group): 41 vs. 45 Liver metastases (^{177}Lu-Dotatate group vs. control group): 84 vs. 83 Low-grade tumours (Ki-67 of 0 to 2%) (^{177}Lu-Dotatate group vs. control group): 66% vs. 72%. Functional tumours: not reported
Interventions	^{177}Lu-Dotatate group (116/229): ^{177}Lu-Dotatate, 7.4 GBq (200 mCi), intravenously over a period of 30 minutes, four infusions every 8 weeks, unless 1) unacceptable toxic effects occurred, 2) centrally confirmed disease progression was present on imaging, 3) the patient was unable or unwilling to adhere to trial procedures, 4) the patient withdrew consent, or 5) the patient died. For renal protection, an intravenous amino acid solution was administered concomitantly. And octreotide LAR at a dose of 30 mg every 4 weeks, intramuscularly at a dose of 30 mg, approximately 24 hours after each infusion of ^{177}Lu-Dotatate Control group (113/229): high-dose octreotide LAR, at a dose of 60 mg, intramuscularly every 4 weeks Subcutaneous rescue injections of octreotide in the event of hormonal symptoms associated with their carcinoid syndrome were allowed in both groups.
Outcomes	Primary endpoint: • Progression-free survival Secondary endpoints: • Objective response rate • Overall survival • Safety • Side effect profile Assessments: • CT or MRI every 12 weeks • Safety was assessed every 2 to 12 weeks (depending on treatment phase or follow-up phase).
Notes	Trial sponsored and designed by Advanced Accelerator Applications

Risk of bias

Bias	Authors' judgement	Support for judgement

Strosberg 2017 *(Continued)*

Random sequence generation (selection bias)	Low risk	Stratified 1:1 randomisation performed with a centralised permuted block randomisation scheme
Allocation concealment (selection bias)	Low risk	Centralised randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	CT and MRI images were reviewed by independent central reviewers.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients were included in the analyses of efficacy, demographics, and baseline characteristics. Safety analyses, were performed with all randomised patients who received at least one dose of trial treatment.
Selective reporting (reporting bias)	High risk	Study protocol available. Not all secondary outcomes were reported.
Other bias	Low risk	No other potential sources of bias found

Strosberg 2020

Study characteristics	
Methods	International multicentre, open-label, randomised phase 3 trial • 41 centres in 8 countries 1:1 randomisation performed with a centralised permuted block randomisation scheme, stratified by highest tumour uptake score on somatostatin receptor scintigraphy and the length of time that a patient had been receiving a constant dose of octreotide Start: September 2012 Closed: January 2016
Participants	Inclusion criteria • Adults. • Midgut neuroendocrine tumours that had 1) metastasised, or 2) were locally advanced, or 3) were inoperable • Histologically confirmed and centrally verified • Disease progression (RECIST, vers. 1.119) on CT or MRI over the course of a maximum period of 3 years during treatment with octreotide LAR • Karnofsky performance-status score > 60 • Tumour with well differentiated histologic features, and somatostatin receptors present on all target lesions Exclusion criteria

Strosberg 2020 *(Continued)*

- Serum creatinine level of more than 150 µmol per litre (1.7 mg per decilitre) or a creatinine clearance of less than 50 mL per minute
- Haemoglobin level of less than 8.0 g per decilitre
- White-cell count of less than 2000 per cubic millimetre
- Platelet count of less than 75,000 per cubic millimetre
- Total bilirubin level of more than 3 times the upper limit of the normal range
- Serum albumin level of more than 3.0 g per decilitre (unless the prothrombin time value was within the normal range)
- Treatment with more than 30 mg of octreotide LAR within 12 weeks before randomisation. Peptide receptor radionuclide therapy at any time before randomisation
- Any surgery, liver-directed transarterial therapy, or chemotherapy within 12 weeks before randomisation

Total patients: 229

Age (^{177}Lu-Dotatate group vs. control group): 63 vs. 64

Women, % (^{177}Lu-Dotatate group vs. control group): 46 vs. 53

Primary tumour site:

- Ileum, % (^{177}Lu-Dotatate group vs. control group): 74 vs. 73
- Small intestine (not otherwise specified), % (^{177}Lu-Dotatate group vs. control group): 9 vs. 11
- Midgut (not otherwise specified), % (^{177}Lu-Dotatate group vs. control group): 8 vs. 6
- Jejunum, % (^{177}Lu-Dotatate group vs. control group): 5 vs. 8
- Right colon, % (^{177}Lu-Dotatate group vs. control group): 3 vs. 1
- Appendix, % (^{177}Lu-Dotatate group vs. control group): 1 vs. 2

Previous surgical resection, % (^{177}Lu-Dotatate group vs. control group): 78 vs. 82

Previous systemic therapy other than SSA, % (^{177}Lu-Dotatate group vs. control group): 41 vs. 45

Liver metastases (^{177}Lu-Dotatate group vs. control group): 84 vs. 83

Low-grade tumours (Ki-67 of 0 to 2%) (^{177}Lu-Dotatate group vs. control group): 66% vs. 72%

Functional tumours: not reported

Interventions	^{177}Lu-Dotatate group (116/229): ^{177}Lu-Dotatate, 7.4 GBq (200 mCi), intravenously over a period of 30 minutes, four infusions every 8 weeks, unless 1) unacceptable toxic effects occurred, 2) centrally confirmed disease progression was present on imaging, 3) the patient was unable or unwilling to adhere to trial procedures, 4) the patient withdrew consent, or 5) the patient died. For renal protection, an intravenous amino acid solution was administered concomitantly. And octreotide LAR at a dose of 30 mg every 4 weeks, intramuscularly at a dose of 30 mg, approximately 24 hours after each infusion of ^{177}Lu-Dotatate Control group (113/229): high-dose octreotide LAR, at a dose of 60 mg, intramuscularly every 4 weeks Subcutaneous rescue injections of octreotide in the event of hormonal symptoms associated with their carcinoid syndrome were allowed in both groups.
Outcomes	Primary endpoint: • Progression-free survival or death Secondary endpoints: • Objective response rate • Overall survival • Safety

Strosberg 2020 *(Continued)*

	• Side-effect profile Assessments: • CT or MRI every 12 weeks • Safety was assessed every 2 to 12 weeks (depending on treatment phase or follow-up phase). In this subgroup analysis, progression-free survival was stratified by liver tumour burden, alkaline phosphatase elevation and presence or absence of a large target lesion (> 30 mm) at any site of the body on CT or MRI.
Notes	Trial sponsored and designed by Advanced Accelerator Applications

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified 1:1 randomisation performed with a centralised permuted block randomisation scheme
Allocation concealment (selection bias)	Low risk	Centralised randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	CT and MRI images were reviewed by independent central reviewers.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients were included in the analyses of efficacy, demographics, and baseline characteristics. Safety analyses were performed with all randomised patients who received at least one dose of trial treatment.
Selective reporting (reporting bias)	High risk	Study protocol available. Not all secondary outcomes were reported.
Other bias	Low risk	No other potential sources of bias found

Van Der Zwan 2018

Study characteristics

Methods	Two-arm, randomised controlled, prospective, non-blinded study Enrolment: 2006-2013
Participants	Inclusion criteria • Metastatic or inoperable GEP-NETs receiving treatment with 177Lu-DOTATATE Total patients: 111

Van Der Zwan 2018 *(Continued)*

Interventions	Investigational arm (50/111): 29.6 GBq (800 mCi) 177Lu-DOTATATE and capecitabine, 1650 mg/m^2/day, two divided doses, for the first two weeks of each cycle starting on the morning of the day of administration of LuTate Control arm (61/111): 29.6 GBq (800 mCi) 177Lu-DOTATATE
Outcomes	Endpoints: • Overall survival • Progression-free survival • Haematological toxicity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study was non-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information given
Selective reporting (reporting bias)	Low risk	All stated endpoints were reported.
Other bias	Low risk	No other potential sources of bias found

Vinik 2016

Study characteristics

Methods	3-phase, multicentre study in 12 countries • 16-week randomised, double-blind phase (reported here) • 32-week initial open-label phase (not reported here) • Long-term open-label extension (not reported here) 1:1 randomisation using 2 computer-generated lists (one for the U.S. and one for all other countries) stratified by previous treatment with any long- or short-acting somatostatin analog or SSA-naive patients

Vinik 2016 *(Continued)*

	Start: May 2009 End: May 2013
Participants	Inclusion criteria • Age ≥ 18 years • Histopathologically confirmed diagnosis of neuroendocrine tumour or a carcinoid tumour of unknown location with liver metastases (documented biopsy) • History of carcinoid syndrome (flushing and/or diarrhoea) • Positive somatostatin-receptor scintigraphy • SSA-naive or responsive to conventional octreotide LAR doses (≤ 30 mg/4 weeks) or short-acting octreotide (≤ 600 µg daily) • Absence of tumour progression on 2 sequential computed tomography/magnetic resonance imaging scans ≥ 3 months apart • Last scan ≤ 6 months of study entry Exclusion criteria • History of treatment-refractory carcinoid syndrome with conventional SSA doses • Treatment with interferon, chemotherapy, and/or peptide receptor radionuclide therapy • Tumour debulking < 3 months before study entry • Hepatic artery embolisation/chemoembolisation and/or selective internal radiation therapy < 6 months before study entry • Short-bowel syndrome • Uncontrolled diabetes • Hypertension • Severe renal and/or hepatic impairment • Cardiac disease New York Heart Association classification > class 1 • Any malignancy except NET, basocellular skin carcinoma, or in situ cervical carcinoma • Life expectancy < 1 year Total patients: 115 Mean age (lanreotide vs. placebo): 58 vs. 59 Women, % (lanreotide vs. placebo): 54 vs. 62 Prior SSA therapy, % (lanreotide vs. placebo): 56 vs. 55 Short-acting octreotide during screening, % (lanreotide vs. placebo): 51 vs. 52
Interventions	Intervention group (59/115): lanreotide depot/autogel 120 mg, every 4 weeks by deep subcutaneous injection Control group (56/115): placebo (0.9% saline solution), every 4 weeks by deep subcutaneous injection Self-injected subcutaneous short-acting octreotide for symptom rescue at patients' discretion After ≥ 4 weeks in the double-blind phase, patients could roll over into the open-label phase if they used octreotide for ≥ 21 days of the 28-day cycle and used a dose ≥ 300 µg/day for ≥ 14 of the 21 days.
Outcomes	Primary endpoint: • Adjusted mean percentage of days short-acting octreotide was used for symptom control Secondary endpoints: • Average daily frequency of diarrhoea and flushing • Percentage of days non-octreotide rescue medications were used

Vinik 2016 *(Continued)*

- Proportion of patients who rolled over early into the initial open-label phase
- Change from baseline to week 12 in:
  - Health-related quality of life
  - Plasma chromogranin
  - Urinary 24-hour 5-hydroxyindoleacetic acid levels
- Safety

Assessments:

- Prior to randomisation, patients completed a 31-day (± 3 days) screening period.
- Daily diary by Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS) (number and severity of diarrhoea and flushing events; and use and dose of short-acting octreotide and any other rescue medications)

Notes	Trial funded by Ipsen

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, stratified randomisation
Allocation concealment (selection bias)	Unclear risk	Insufficient information given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded trial design with same injection schedules
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Patient-reported results
Incomplete outcome data (attrition bias) All outcomes	Low risk	Efficacy analyses were performed with all randomised patients by an ITT principle.
Selective reporting (reporting bias)	Low risk	No study protocol available, but every stated endpoint was reported.
Other bias	Low risk	No other potential sources of bias found

Wolin 2015

Study characteristics

Methods	Multicentre, randomised, blinded, efficacy and safety, phase III study • 47 centres in 15 countries 1:1 randomisation by interactive voice response system Treatment and evaluation period: 6 months for core study and up to 2 years (except in the UK) Enrolment: April 2008-April 2012

Wolin 2015 *(Continued)*

Participants	Inclusion criteria • Age ≥ 18 years • Histopathologically confirmed metastatic NET of the digestive system • Inadequately controlled carcinoid symptoms (diarrhoea and/or flushing) while receiving maximum approved doses of the currently available SSA for 3 months prior to study entry (octreotide LAR 30 mg every 28 days, octreotide SC 600 µg (total daily dose), lanreotide autogel 120 mg every 28 days, lanreotide SR 30 mg every 14 days) • Measurable or evaluable disease according to RECIST • Karnofsky performance status ≥ 60 • Adequate bone marrow, renal, and hepatic function Exclusion criteria • SSA at a higher than approved dose (except a short-acting formulation) within 3 months before screening • Radiolabeled SSA therapy within 3 months before recording baseline symptoms • Any cytotoxic chemotherapy or interferon therapy within 4 weeks • Major surgery within 1 month before recording baseline symptoms • Surgical therapy of locoregional metastases within 3 months • Hepatic artery embolisation, chemoembolisation, or radioembolisation within 6 months or 1 month if there were other disease sites • Cryoablation or radiofrequency ablation of hepatic metastases within 2 months before recording baseline symptoms • Prior therapy with pasireotide • Diabetes and poorly controlled blood glucose levels Total patients: 110 Median age (pasireotide LAR vs. octreotide LAR): 61 vs. 63 Women, % (pasireotide LAR vs. octreotide LAR): 45 vs. 40 Karnofsky performance status 80-100/< 80/missing, % (pasireotide LAR vs. octreotide LAR): 93/6/2 vs. 88/11/2 Primary tumour site, %: • Small intestine (pasireotide LAR vs. octreotide LAR): 72 vs. 81 • Colon (pasireotide LAR vs. octreotide LAR): 6 vs. 2 • Liver (pasireotide LAR vs. octreotide LAR): 6 vs. 0 • Pancreas (pasireotide LAR vs. octreotide LAR): 2 vs. 2 • Lung (pasireotide LAR vs. octreotide LAR): 0 vs. 2 • Stomach (pasireotide LAR vs. octreotide LAR): 0 vs. 2 • Other (pasireotide LAR vs. octreotide LAR): 15 vs. 12 Grade, %: • Well differentiated (pasireotide LAR vs. octreotide LAR): 77 vs. 84 • Moderately differentiated (pasireotide LAR vs. octreotide LAR): 4 vs. 2 • Unknown (pasireotide LAR vs. octreotide LAR): 19 vs. 14 Previous therapies, %: • Chemotherapy (pasireotide LAR vs. octreotide LAR): 19 vs. 21 • Immunotherapy (pasireotide LAR vs. octreotide LAR): 23 vs. 25 • Targeted therapy (pasireotide LAR vs. octreotide LAR): 13 vs. 14 • Other (pasireotide LAR vs. octreotide LAR): 26 vs. 18

Wolin 2015 *(Continued)*

	• Missing (pasireotide LAR vs. octreotide LAR): 49 vs. 42 Previous SSA treatment, %: • Octreotide LAR (pasireotide LAR vs. octreotide LAR): 85 vs. 88 • Octreotide SC (pasireotide LAR vs. octreotide LAR): 21 vs. 16 • Lanreotide autogel (pasireotide LAR vs. octreotide LAR): 11 vs. 23 • Lanreotide SR (pasireotide LAR vs. octreotide LAR): 6 vs. 2
Interventions	Group A (53/110): pasireotide LAR 60 mg, via intragluteal depot, every 28 days Group B (57/110): octreotide LAR 40 mg, via intragluteal depot, every 28 days Rescue medication was permitted after the first injection: pasireotide 600 µg bid SC for patients randomised to pasireotide LAR and octreotide 100 µg tid SC for patients randomised to octreotide LAR. Dose reductions to pasireotide LAR 40 mg and octreotide LAR 30 mg for safety and tolerability were allowed. Cross-over to pasireotide after 6 months without benefit from octreotide was allowed for entry into the extension phase.
Outcomes	Primary endpoint: • Symptom control (diarrhoea and/or flushing) based on patient reports Secondary endpoints: • Frequency of bowel movements alone and the number of flushing episodes alone during month 6 relative to the baseline assessment • Objective tumour response rate • Tumour control rate at month 6 according to RECIST Assessments: • Tumour measurements by computed tomography or magnetic resonance imaging at baseline and every 3 months thereafter
Notes	Study funded by Novartis Pharmaceuticals Corporation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by interactive voice response system
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	True double blinding was not feasible due to the different appearances of the LAR formulations.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias)	Low risk	All randomised patients accounted for in ITT analysis

Wolin 2015 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	No study protocol available, but every stated endpoint was reported.
Other bias	Low risk	No other potential sources of bias found

Wolin 2016

Study characteristics

Methods	Randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3 study • 48 secondary or tertiary care centres in 14 countries Duration: 96 weeks Computer-generated randomisation, stratified by presence or absence of tumour progression at baseline and receipt or nonreceipt of previous therapies Conducted between June 2006 and April 2013 Subgroup analysis: treatment effects within subgroups defined post hoc by baseline BMI
Participants	Inclusion criteria • Adults (≥ 18 years of age) • Sporadic well differentiated or moderately differentiated neuroendocrine tumours, located in the pancreas, midgut, hindgut or of unknown origin • Unresectable locally advanced tumour, metastatic disease or declined surgery • Measurable tumour according to RECIST (vers. 1.0) • Ki-67 index of less than 10% or a mitotic index of ≤ 2 mitoses per 10 high-power fields • Nonfunctioning tumours (except for gastrinomas that had been adequately controlled by means of proton-pump inhibitors for 4 months or longer) • Target lesion or lesions that were classified as grade 2 or higher on somatostatin-receptor scintigraphy (0 (no uptake by tumour) to 4 (very intense uptake by tumour)) within the previous 6 months • WHO performance score ≤ 2 • A biopsy of the neuroendocrine tumour within 6 months before study entry was required for patients who had previous cancer and those with evidence of clinical progression. Exclusion criteria • Previous treatment with interferon, chemoembolisation, or chemotherapy within 6 months before study entry, a radionuclide at any time, or a somatostatin analogue at any time (unless they had received it > 6 months previously and for < 15 days) • Major surgery related to the neuroendocrine tumour within 3 months before study entry • Multiple endocrine neoplasia • Previous cancer (except: 1] treated or untreated in situ cervical or uterine carcinoma, or 2] basal-cell skin carcinoma, or 3] other cancers that had been treated with curative intent and had been disease-free for > 5 years) • Baseline abnormalities or medical conditions that could jeopardise the patient's safety or interfere with the study Withdrawal • Tumour progression (RECIST) • Investigator's judgement

Wolin 2016 *(Continued)*

- Patient's request
- Adverse event that could jeopardise the patient's safety

CLARINET overall study population:

Total patients: 204

Age (lanreotide vs. placebo): 63 vs. 62

Women, % (lanreotide vs. placebo): 48 vs. 48

Prior treatment for neuroendocrine tumour, % (lanreotide vs. placebo): 16 vs. 16

Primary tumour resected, % (lanreotide vs. placebo): 40 vs. 38

Origin of tumour:

- Pancreas, % (lanreotide vs. placebo): 42 vs. 48
- Midgut, % (lanreotide vs. placebo): 33 vs. 39
- Hindgut, % (lanreotide vs. placebo): 11 vs. 3
- Unknown, % (lanreotide vs. placebo): 15 vs. 11

Ki-67 index, 0-2%/3-10%, % (lanreotide vs. placebo): 68/32 vs. 70/28

Hepatic tumour volume:

- 0%, % (lanreotide vs. placebo): 16 vs. 17
- > 0-10%, % (lanreotide vs. placebo): 33 vs. 39
- > 10-25%, % (lanreotide vs. placebo): 13 vs. 17
- > 25-50%, % (lanreotide vs. placebo): 23 vs. 12
- > 50%,% (lanreotide vs. placebo): 16 vs. 16

Interventions	Intervention group (101/204): extended-release aqueous-gel formulation of lanreotide, 120 mg, without dose adjustment, deep subcutaneous injection, every 28 days to a maximum of 24 injections Control group (103/204): placebo (sodium chloride), deep subcutaneous injection, every 28 days to a maximum of 24 injections In case of disease progression while receiving placebo, patients crossed over to lanreotide.
Outcomes	Primary endpoint: • Progression-free survival or death within 96 weeks after the first injection of the study drug Secondary endpoints: • Proportion of patients who were alive without disease progression at 48 and 96 weeks • Time to tumour progression • Overall survival • Quality of life • CgA levels • Pharmacokinetic data • Safety Exploratory endpoints: • Data on other tumour biomarkers Assessments: • Study visits: at weeks 1 (baseline), 12, 24, 36, 48, 72, and 96

Wolin 2016 *(Continued)*

- CT or MRI of the chest, abdomen, and pelvis was performed twice during screening to determine the baseline disease-progression status. Results of the second imaging test were considered to be the baseline findings and were used to determine target-lesion sizes.
- Single scans were obtained at all post-baseline visits.
- Disease progression was assessed centrally according to RECIST, version 1.0.
- Two quality of life questionnaires (QLQ-C30 and QLQ-GI.NET21) were completed at post-screening visits.
- Serum chromogranin A levels: all visits and also at weeks 60 and 84
- Serum lanreotide levels: prior to drug administration at all study visits and after the first and sixth administration
- Safety assessments: monitoring for adverse events, physical examination and monitoring of vital signs (at all visits), electrocardiography and ultrasonography of the gallbladder (at baseline and at weeks 48 and 96), and clinical laboratory tests (at screening, baseline, and at weeks 48 and 96)

Notes	The study was designed, funded, and conducted by Ipsen in collaboration with the European Neuroendocrine Tumor Society and the UK and Ireland Neuroendocrine Tumour Society.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation lists were created by a statistician employed by the sponsor who was independent of the study.
Allocation concealment (selection bias)	Low risk	The blinded database was held at a third-party contract clinical research organisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded study design. Independent health professionals prepared and administered injections.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Disease progression was assessed centrally, but it remained unclear whether it was performed by independent personnel.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients accounted for in ITT analysis
Selective reporting (reporting bias)	Low risk	Study protocol available. One secondary endpoint mentioned in the protocol was not reported as a endpoint in the publication, but was reported in the supplementary appendix.
Other bias	Low risk	No other potential sources of bias found

Xu 2020 (ep)

Study characteristics

Methods	Randomised, double-blind, placebo-controlled, phase 3 study • 24 hospitals across China

Xu 2020 (ep) *(Continued)*

	2:1 randomisation performed centrally using block randomisation; stratified by previous systemic anti-tumour treatment for advanced disease, pathological grade and primary tumour site; implemented via an interactive web response system Enrolment: December 2015 to March 2019
Participants	Inclusion criteria • Age ≥ 18 years • Unresectable or metastatic, well differentiated (grad 1 or 2 according to the WHO classification 2010) NETs originating from any extrapancreatic location • Expected survival of more than 12 weeks • ECOG performance status of 0 or 1 • Measurable disease according to RECIST version 1.1 • Radiological progression within 1 year before enrolment • Progression on no more than two types of previous systemic regimens for advanced disease (e.g. SSAs, chemotherapy, IFNα, serine/threonine protein kinase mTOR inhibitor, or peptide receptor radionuclide therapies) Exclusion criteria • Patients with functioning NETs requiring long-acting SSA therapy • Progression on previous VEGF or VEGFR inhibitors • Unstable or untreated brain metastases Total patients: 198 Age (surufatinib vs. placebo): 52 vs. 54 Women, % (surufatinib vs. placebo): 43 vs. 49 ECOG performance status 0, % (surufatinib vs. placebo): 56 vs. 67 Primary tumour site, %: • Rectum (surufatinib vs. placebo): 29 vs. 22 • Stomach (surufatinib vs. placebo): 8 vs. 13 • Small intestine (surufatinib vs. placebo): 8 vs. 9 • Colon (surufatinib vs. placebo): 2 vs. 3 • Appendix (surufatinib vs. placebo): 1 vs. 0 • Lung (surufatinib vs. placebo): 9 vs. 16 • Thymus or mediastinum (surufatinib vs. placebo): 14 vs. 10 • Liver (surufatinib vs. placebo): 7 vs. 3 • Other (surufatinib vs. placebo): 9 vs. 12 • Unknown (surufatinib vs. placebo): 14 vs. 13 Ki-67, %: • < 3% (surufatinib vs. placebo): 16 vs. 16 • 3-10% (surufatinib vs. placebo): 60 vs. 64 • > 10% (surufatinib vs. placebo): 23 vs. 20 Functioning tumours, % (surufatinib vs. placebo): 4 vs. 3 Liver involvement, % (surufatinib vs. placebo): 75 vs. 77 Previous systematic anti-tumour drug for advanced disease, % (surufatinib vs. placebo): 69 vs. 64 • Everolimus, % (surufatinib vs. placebo): 8 vs. 12 • SSA, % (surufatinib vs. placebo): 34 vs. 28

Xu 2020 (ep) *(Continued)*

- Chemotherapy, % (surufatinib vs. placebo): 40 vs. 39

Interventions	Intervention group (129/198): oral surufatinib 300 mg, once daily in 4-week treatment cycles Control group (69/198): matching placebo, once daily in 4-week treatment cycles Treatment duration: until disease progression or intolerable toxicity, withdrawal of patient consent, poor compliance, use of other anti-tumour medication, pregnancy, loss to follow-up, or if the investigator deemed discontinuation was in the patient's best interest At disease progression confirmed by the independent image reviewers, treatment assignments were unblinded, and patients who had been receiving placebo were permitted to switch to open-label surufatinib.
Outcomes	Primary endpoint: • Investigator-assessed progression-free survival Secondary endpoints: • Objective response rate • Disease control rate • Best overall response • Time to response • Duration of response • Overall survival • Safety Supportive outcome: • Independent image reviewer-assessed progression-free survival Exploratory outcome: • Change in quality of life Assessments: • Contrasted CT or MRI scans at baseline, every 8 weeks during the first year, and every 12 weeks thereafter • Adverse events and laboratory abnormalities were collected throughout treatment and up to 30 days after the last dose. • Patient-reported outcome questionnaires and the Quality of Life Questionnaire-Gastrointestinal Neuroendocrine Tumour 21 (QLQ-GINET21) at baseline, day 15 of the first cycle, day 1 of every cycle thereafter, and at treatment discontinuation • Vital signs, laboratory tests, ECOG performance status, and ECGs at day 15 of the first cycle, day 1 of every cycle thereafter, and at the end of treatment • Echocardiograms at screening and every fourth cycle thereafter, and at the end of treatment • During follow-up, survival was assessed every 3 months.
Notes	Trial funded by Hutchison MediPharma. The funder and authors were involved in the data collection, data analysis, interpretation of the results, and writing of the report. In the interim analysis, the results met the predefined criteria for early discontinuation of the study, therefore the trial was terminated on recommendation of the independent data monitoring committee.

Risk of bias

Bias	Authors' judgement	Support for judgement

Xu 2020 (ep) *(Continued)*

Random sequence generation (selection bias)	Low risk	Stratified block randomisation implemented via an interactive web response system
Allocation concealment (selection bias)	Low risk	Randomisation was performed centrally and the allocation sequence was concealed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Tumour assessment was done by investigators (primary endpoint), but scans were reviewed in parallel by a blinded independent image review committee (supportive outcome).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Eight patients were excluded from the interim intention-to-treat set (three in the surufatinib group, five in the placebo group).
Selective reporting (reporting bias)	Low risk	Primary and secondary endpoints stated in the protocol were published, except overall survival (not mature at the time of interim analysis). A few exploratory endpoints stated in the protocol were not published.
Other bias	Low risk	No other potential sources of bias found

Xu 2020 (p)

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled, multicenter, phase 3 study • 21 hospitals across China 2:1 randomisation via an interactive web response system. Done centrally using stratified block randomisation, stratified by pathological grade, previous systemic anti-tumour treatment, and ECOG performance status score Start: February 2016 Closed: November 2019
Participants	Inclusion criteria: • 18 years of age or older • Unresectable or metastatic, well differentiated pancreatic NET (grade 1 or 2 [2010 WHO classification]) • ECOG performance status score of 0 or 1 • Life expectancy of more than 12 weeks • Measurable disease (RECIST, vers. 1.1) • Documented radiological progression within 1 year before randomisation • Progression on no more than two previous systemic regimens for advanced disease • Adequate organ function on laboratory tests Exclusion criteria: • High grade (grade 3) neuroendocrine cancer • Functioning neuroendocrine tumours requiring treatment with long-acting SSAs

Xu 2020 (p) *(Continued)*

- Progression on previously received VEGF or VEGFR inhibitors
- Unstable or uncontrolled brain metastases
- Other malignancies
- Clinically significant comorbidities including cardiovascular, haemorrhagic, hepatic, or gastrointestinal disease

Total patients: 172

Median age (surufatinib vs. placebo): 51 vs. 48

Women % (surufatinib vs. placebo): 47 vs. 53

ECOG performance status score 0 (surufatinib vs. placebo): 65% vs. 73%

Functional tumours, % (surufatinib vs. placebo): 10 vs. 5

Ki-67 index < 5%/5-10%/> 10%, % (surufatinib vs. placebo): 35.5/50.5/14 vs. 35.5/52.5/12

Any previous systemic anti-tumour treatment, % (surufatinib vs. placebo): 65 vs. 66

Previous SSA treatment, % (surufatinib vs. placebo): 42 vs. 47

Previous systemic chemotherapy, % (surufatinib vs. placebo): 29 vs. 20

Previous everolimus treatment, % (surufatinib vs. placebo): 11 vs. 7

Previous antiangiogenic treatment, % (surufatinib vs. placebo): 4 vs. 10

- Sunitinib, % (surufatinib vs. placebo): 4 vs. 10
- Endostatin, % (surufatinib vs. placebo): 2 vs. 2
- Famitinib, % (surufatinib vs. placebo): 1 vs. 0
- Apatinib, % (surufatinib vs. placebo): 0 vs. 2

Interventions	Intervention group (113/172): surufatinib, 300 mg, p.o., once per day, p.o., in consecutive 4-week treatment cycles Control group (59/172): placebo, p.o., once per day, p.o., in consecutive 4-week treatment cycles Length of treatment: until disease progression, intolerable toxicity, withdrawal of consent, poor compliance, use of other anti-tumour medication, pregnancy, loss to follow-up, or if the investigator deemed discontinuation in the patient's best interest Cross-over to surufatinib was permitted for patients in the placebo group with disease progression.
Outcomes	Primary endpoint: • Investigator-assessed progression-free survival Secondary endpoints: • Objective response rate • Disease control rate • Tumour shrinkage • Best overall response • Time to response • Duration of response • Overall survival • Safety Exploratory endpoint: • Mean change in quality of life (EORTC QLQ-C30 and QLQ-GI.NET21 questionnaires)

Xu 2020 (p) *(Continued)*

	Assessment: • Tumour assessments: every 8 weeks during the first year, and every 12 weeks thereafter; by contrasted CT or MRI scans
Notes	• Trial met the early stopping criteria at the interim analysis and was terminated on recommendation from the independent data monitoring committee. • Funding: Hutchison MediPharma

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified randomisation via an interactive web response system
Allocation concealment (selection bias)	Low risk	Done centrally
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients, investigators, research staff, and the sponsor study team were masked to treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Measurement of endpoints by investigator assessment, but also by a blinded independent image review committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for in final analysis
Selective reporting (reporting bias)	Unclear risk	The primary and secondary endpoints that were published corresponded to those in the study protocol. However, not all exploratory endpoints were published.
Other bias	Low risk	No other potential sources of bias found

Yao 2008 (1)

Study characteristics

Methods	Two-stage random assignment phase II trial Enrolment: May 2002-May 2003
Participants	Inclusion criteria • Pathologically confirmed metastatic carcinoid tumour • ≤ 1 prior cytotoxic chemotherapy • Zubrod performance status ≤ 2 • Granulocyte count greater than 1500/mm^3 • Haemoglobin greater than 8 g/dL • Platelet count greater than 100,000/mm^3 • Bilirubin less than 1.5 times the upper limit of normal • Creatinine ≤ 1.5 mg/dL

Yao 2008 (1) *(Continued)*

- AST and ALT ≤ 2.5 × the upper limit of the normal
- Stable dose of depot octreotide not exceeding 30 mg every 3 weeks

Exclusion criteria

- Poorly differentiated, small-cell, and high-grade neuroendocrine tumours
- Prior liver-directed therapy, if no measurable disease remained
- Prior interferon therapy

Total patients: 44

Mean age (study arm 1 vs. study arm 2): 55 vs. 55

Women, % (study arm 1 vs. study arm 2): 41 vs. 50

Primary tumour site, %:

- Stomach (study arm 1 vs. study arm 2): 0 vs. 5
- Lung (study arm 1 vs. study arm 2): 9 vs. 9
- Thymus (study arm 1 vs. study arm 2): 5 vs. 0
- Ileum (study arm 1 vs. study arm 2): 18 vs. 32
- Small intestine (study arm 1 vs. study arm 2): 27 vs. 27
- Caecum (study arm 1 vs. study arm 2): 5 vs. 0
- Rectum (study arm 1 vs. study arm 2): 18 vs. 0
- Unknown (study arm 1 vs. study arm 2): 18 vs. 27

Liver metastases, %:

- None (study arm 1 vs. study arm 2): 18 vs. 5
- 0-25% (study arm 1 vs. study arm 2): 46 vs. 46
- 26-50% (study arm 1 vs. study arm 2): 18 vs. 27
- 51-75% (study arm 1 vs. study arm 2): 9 vs. 14
- > 75% (study arm 1 vs. study arm 2): 9 vs. 9

Interventions	Study arm 1 (22/44): PEG interferon alfa-2b 0.5 mcg/kg subcutaneously once per week for 18 weeks Study arm 2 (22/44): bevacizumab 15 mg/kg intravenously once every 3 weeks for 18 weeks All patients continued depot octreotide at the prestudy dosage. After the completion of the 18-week therapy, or at first evidence of disease progression, patients received both PEG interferon and bevacizumab.
Outcomes	Endpoints: • Progression-free survival • Overall survival • Biochemical response • Safety • Tumour blood flow changes Assessments: • History, physical examination, laboratory tests, and tumour markers (chromogranin A and urinary 5-hydroxyindoleacetic acid (5-HIAA)) • Tumour measurements by computer tomography (CT) scans or magnetic resonance imaging (MRI) at baseline and every 9 weeks
Notes	Disclosures:

Yao 2008 (1) *(Continued)*

- Compensations by Genentech and GE Medical Systems

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information given
Allocation concealment (selection bias)	Unclear risk	No information regarding allocation concealment and identical numbers of patients in all treatment groups
Blinding of participants and personnel (performance bias) All outcomes	High risk	Different application intervals for each study arm, so at least study personnel were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No evidence for independent assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for response rate and progression-free survival data.
Selective reporting (reporting bias)	Low risk	No study protocol available, but every endpoint was reported in 'results'.
Other bias	Low risk	No other potential sources of bias found

Yao 2011

Study characteristics

Methods	International, multicentre, double-blind, phase 3 study • 82 centres in 18 countries worldwide Randomisation: • Ratio 1:1 • Stratified by whether or not patients had received prior cytotoxic chemotherapy and by WHO performance status (0 vs. 1-2) at baseline Start: July 2007 Closed: May 2009
Participants	Inclusion criteria: • 18 years of age or older • Low-grade or intermediate-grade advanced (unresectable or metastatic) pancreatic neuroendocrine tumours • Radiologic documentation of disease progression in the previous 12 months • Measurable disease (RECIST) • World Health Organization (WHO) performance status of 2 or less • Adequate bone marrow, renal, and hepatic function

Yao 2011 *(Continued)*

	• Adequately controlled lipid and glucose concentrations
	
	Exclusion criteria:
	
	• Hepatic-artery embolisation within 6 months before enrolment or within 1 month if there were other sites of measurable disease or cryoablation or radiofrequency ablation of hepatic metastasis within 2 months before enrolment
	• Severe or uncontrolled medical conditions
	• Prior therapy with an mTOR inhibitor
	• Long-term treatment with glucocorticoids or other immunosuppressive agents
	
	RADIANT-3 overall population:
	
	• Total patients: 410
	• Median age (everolimus vs. placebo): 58 vs. 57
	• Women % (everolimus vs. placebo): 47 vs 42
	• WHO performance status 0 (everolimus vs. placebo): 67% vs. 66%
	• Well differentiated % (everolimus vs. placebo): 82 vs. 84
	• Moderately differentiated % (everolimus vs. placebo): 17 vs. 15
	• Liver involvement, % (everolimus vs. placebo): 92% vs. 92%
	• Functional tumours (overall): 24%
	• Prior therapy for NET, %:
	  ◦ Radiotherapy (everolimus vs. placebo): 23 vs. 20
	  ◦ Chemotherapy (everolimus vs. placebo): 50 vs. 50
	  ◦ Somatostatin analogue therapy (everolimus vs. placebo): 49 vs. 50

Interventions	Intervention group (207/410): oral everolimus, at a dose of 10 mg once daily, in conjunction with best supportive care (e.g. somatostatin analogue therapy) Control group (203/410): oral matching placebo in conjunction with best supportive care (e.g. somatostatin analogue therapy) Length of treatment: until progression of the disease, development of an unacceptable toxic effect, drug interruption for 3 weeks or longer, or withdrawal of consent Patients who had been assigned to placebo initially could switch to open-label everolimus after documented progression of disease (RECIST). Doses were delayed/reduced if patients had clinically significant adverse events that were considered to be related to the study treatment.
Outcomes	Primary endpoint: • Progression-free survival (RECIST) Secondary endpoints: • Confirmed objective response rate (RECIST) • Duration of response • Overall survival • Safety Assessments: • Tumour measurements (computed tomography or magnetic resonance imaging): at baseline and every 12 weeks • Safety assessments: monitoring and recording of all adverse events, haematologic and clinical biochemical levels and vital signs, and physical examinations every 4 weeks Data collection: sponsor's data management

Yao 2011 *(Continued)*

	Data analysis: sponsor's statistical team
Notes	Funding/Sponsor: Novartis Oncology

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised randomisation through interactive voice response system. Stratified by performance status and prior treatment (+/- chemotherapy)
Allocation concealment (selection bias)	Low risk	Centralised randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded trial design with same schemes for each study group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Endpoints were documented by the local investigator according to RECIST, with independent adjudicated central assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for in final analysis
Selective reporting (reporting bias)	Unclear risk	Not all secondary endpoints mentioned in the study protocol were published.
Other bias	Low risk	No other potential sources of bias found

Yao 2016

Study characteristics

Methods	International, multicentre, randomised, double-blind, placebo-controlled, phase 3 study • 97 centres in 25 countries worldwide 2:1 randomisation by interactive voice response systems, stratified by 1) previous somatostatin analogue treatment for at least 12 weeks, 2) tumour origin (stratum A: appendix, caecum, jejunum, ileum, duodenum, or neuroendocrine tumour of unknown primary origin vs. stratum B: lung, stomach, colon or rectum, and 3) WHO performance status (0 vs. 1) Start enrolment: April 2012 Closed enrolment: August 2013
Participants	Inclusion criteria • Aged ≥ 18 years • Pathologically confirmed, advanced (unresectable or metastatic), nonfunctional, well differentiated (grade 1 or 2 according to the 2010 WHO classification) neuroendocrine tumours of lung or gastrointestinal origin • Within 6 months from documented radiological disease progression

Yao 2016 *(Continued)*

- Measurable disease according to modified Response Evaluation Criteria In Solid Tumours (RECIST vers. 1.0)
- WHO performance status score of 0 or 1
- Adequate bone marrow, liver, and kidney function
- Despite previous treatment with somatostatin analogue, interferon, one line of chemotherapy, peptide receptor radionuclide therapies, or a combination of these; if disease progression was documented during or after their last treatment. Antineoplastic therapy must have been discontinued for at least 4 weeks (or 6 months in the case of peptide receptor radionuclide therapies) before randomisation.

Exclusion criteria

- History of or present carcinoid syndrome
- Poorly differentiated histology
- Pancreatic neuroendocrine tumours
- Previous treatment with more than one line of chemotherapy
- Treatment with mTOR inhibitors (sirolimus, temsirolimus, or everolimus)
- Hepatic intra-arterial embolisation within 6 months of randomisation
- Cryoablation or radiofrequency ablation of hepatic metastases within 2 months of randomisation
- Chronic treatment with corticosteroids or other immunosuppressive agents

Total patients: 302

Age (everolimus vs. placebo): 65 vs. 60

Women, % (everolimus vs. placebo): 57 vs. 45

WHO performance status 0, % (everolimus vs. placebo): 73 vs. 75

Tumour grade 1, % (everolimus vs. placebo): 63 vs. 67

Primary tumour site, %:

- Lung (everolimus vs. placebo): 31 vs. 28
- Ileum (everolimus vs. placebo): 23 vs. 25
- Rectum (everolimus vs. placebo): 12 vs. 16
- Unknown origin (everolimus vs. placebo): 11 vs. 13
- Jejunum (everolimus vs. placebo): 8 vs. 6
- Stomach (everolimus vs. placebo): 3 vs. 4
- Duodenum (everolimus vs. placebo): 4 vs. 2
- Colon (everolimus vs. placebo): 2 vs. 3
- Other (everolimus vs. placebo): 3 vs. 2
- Caecum (everolimus vs. placebo): 2 vs. 1
- Appendix (everolimus vs. placebo): 1 vs. 0

Liver involvement, % (everolimus vs. placebo): 80 vs. 78

Previous treatment, %:

- Surgery (everolimus vs. placebo): 59 vs. 72
- Chemotherapy (everolimus vs. placebo): 26 vs. 24
- Radiotherapy including PRRT (everolimus vs. placebo): 22 vs. 20
- Locoregional and ablative therapies (everolimus vs. placebo): 11 vs. 10
- SSA (everolimus vs. placebo): 53 vs. 56

Interventions	Study group (203/302): oral everolimus, 10 mg per day Control group (97/302): identical placebo

Yao 2016 *(Continued)*

	Duration of treatment: until 1) documented radiological disease progression, 2) start of new cancer therapy, 3) development of an intolerable adverse event, or 4) withdrawal of consent Allowed: • Best supportive care (including analgesics and anti-diarrhoeals) • Dose reduction and treatment interruption to manage adverse events that were judged to be related to study treatment Not allowed: • Anti-tumour agents like somatostatin analogues, interferons, tumour ablative procedures, radiation and concurrent chemotherapy • Cross-over from placebo to open-label everolimus after progression Exceptions: • Radiation and surgery were allowed only for palliative intent. • Concomitant somatostatin analogues only for control of emergent carcinoid symptoms that were not manageable by standard treatment (e.g. loperamide)
Outcomes	Primary endpoint: • Central radiology-assessed progression-free survival Secondary endpoints: • Overall survival • Objective response rate • Disease control rate • Health-related quality of life • WHO performance status • Pharmacokinetics • Changes in CgA and neuron-specific enolase levels • Safety Assessments: • Multiphasic CT or MRI every 8 weeks during the first 12 months and every 12 weeks thereafter
Notes	Trial sponsored by Novartis Pharmaceuticals Corporation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified randomisation by interactive voice response systems
Allocation concealment (selection bias)	Low risk	Randomisation centrally managed by Novartis Pharmaceutical
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel were blinded. Study drugs looked identical. Assessments were the same in both groups.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Central radiology review, masked to treatment

Yao 2016 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were included in the full analysis set.
Selective reporting (reporting bias)	High risk	Not all endpoints reported in the study protocol were published.
Other bias	Low risk	No other potential sources of bias found

Yao 2017

Study characteristics	
Methods	Open-label, phase III study 1:1 randomisation using a dynamic balancing algorithm by Pocock and Simon, stratified by primary site, progressive disease, grade, and prior octreotide (treatment within 2 months before registration vs- none within 2 months) Enrolment: December 2007-September 2012
Participants	Inclusion criteria • Age ≥ 18 years • Pathologically confirmed, unresectable or metastatic, grade 1 or grade 2 NET • One of the following features: progressive disease, refractory carcinoid syndrome, grade 2 histology and more than six sites of metastasis, metastatic hindgut NET, or metastatic gastric NET • Measurable disease according to RECIST, version 1.0 • Zubrod performance status ≤ 2 • Adequate bone marrow, liver, and kidney function • Urine protein creatinine ratio ≤ 0.5, or 24-hour urine protein < 1000 mg • Controlled blood pressure (< 150/90 mmHg) • ≤ 1 prior regimen of cytotoxic chemotherapy or targeted therapy, excluding VEGF inhibitors • No surgery, liver-directed therapy, and radiotherapy 28 days before the start of study • No depot octreotide 21 days within the start of study therapy Total patients: 402 Median age (study arm 1 vs. study arm 2): 61 vs. 61 Women, % (1 vs. 2): 49 vs. 55 Zubrod performance status 0/1/2, % (1 vs. 2): 54/44/3 vs. 49/49/2 Primary tumour site: • Small bowel, cecum or appendix, % (1 vs. 2): 35 vs. 36 • Other, % (1 vs. 2): 64 vs. 64 Grade 1/2, % (1 vs. 2): 84/15 vs. 85/15 Liver involvement, % (1 vs. 2): 86 vs. 86 Prior therapy: • Octreotide within 2 months, % (1 vs. 2): 57 vs. 57 • Radiation therapy, % (1 vs. 2): 34 vs. 31 • Chemotherapy, % (1 vs. 2): 28 vs. 25

Yao 2017 *(Continued)*

	Radiologic disease progression, % (1 vs. 2): 91 vs. 93
Interventions	Study arm 1 (200/402): depot octreotide 20 mg intramuscularly on day 1 of each 21-day cycle and bevacizumab 15 mg/kg intravenously on day 1 Study arm 2 (202/402): depot octreotide 20 mg intramuscularly on day 1 of each 21-day cycle and 5 million units of interferon alfa-2b three times per week as a subcutaneous injection
Outcomes	Primary endpoint: • Progression-free survival by central radiology review Secondary endpoints: • Site-reported progression-free survival • Overall survival • Time to treatment failure • Objective response • Toxicity Assessment: • Multiphasic CT scans or MRI at baseline and every 9 weeks
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed by dynamic balancing algorithm
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded, central and independent radiology review was performed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All eligible patients were included in the ITT analysis.
Selective reporting (reporting bias)	Low risk	No study protocol available, but all endpoints stated in 'methods' were reported in 'results'.
Other bias	Low risk	No other potential sources of bias found

Yao 2019

Study characteristics

Yao 2019 *(Continued)*

Methods	International, multicentre, randomised, double-blind, placebo-controlled, phase 3 study • 97 centres in 25 countries worldwide (RADIANT-4 overall (core study)) • 20 centres in 5 countries (China, Japan, South Korea, Taiwan, and Thailand) (RADIANT-4 subgroup analysis) 2:1 randomisation by interactive voice response systems, stratified by 1) previous somatostatin analogue treatment for at least 12 weeks, 2) tumour origin (stratum A: appendix, caecum, jejunum, ileum, duodenum, or neuroendocrine tumour of unknown primary origin vs. stratum B: lung, stomach, colon or rectum, and 3) WHO performance status (0 vs. 1) Start enrolment: April 2012 Closed enrolment: August 2013
Participants	Inclusion criteria • Aged ≥ 18 years • Pathologically confirmed, advanced (unresectable or metastatic), nonfunctional, well differentiated (grade 1 or 2 according to the 2010 WHO classification) neuroendocrine tumours of lung or gastrointestinal origin • Within 6 months from documented radiological disease progression • Measurable disease according to modified Response Evaluation Criteria In Solid Tumours (RECIST vers. 1.0) • WHO performance status score of 0 or 1 • Adequate bone marrow, liver, and kidney function • Despite previous treatment with somatostatin analogue, interferon, one line of chemotherapy, peptide receptor radionuclide therapies, or a combination of these; if disease progression was documented during or after their last treatment. Antineoplastic therapy must have been discontinued for at least 4 weeks (or 6 months in the case of peptide receptor radionuclide therapies) before randomisation Exclusion criteria • History of or present carcinoid syndrome • Poorly differentiated histology • Pancreatic neuroendocrine tumours • Previous treatment with more than one line of chemotherapy • Treatment with mTOR inhibitors (sirolimus, temsirolimus, or everolimus) • Hepatic intra-arterial embolisation within 6 months of randomisation • Cryoablation or radiofrequency ablation of hepatic metastases within 2 months of randomisation • Chronic treatment with corticosteroids or other immunosuppressive agents <u>Core study:</u> • Total patients: 302 • Age (everolimus vs. placebo): 65 vs. 60 • Women, % (everolimus vs. placebo): 57 vs. 45 • WHO performance status 0, % (everolimus vs. placebo): 73 vs. 75 • Tumour grade 1, % (everolimus vs. placebo): 63 vs. 67 Primary tumour site, %: • Lung (everolimus vs. placebo): 31 vs. 28 • Ileum (everolimus vs. placebo): 23 vs. 25 • Rectum (everolimus vs. placebo): 12 vs. 16 • Unknown origin (everolimus vs. placebo): 11 vs. 13 • Jejunum (everolimus vs. placebo): 8 vs. 6 • Stomach (everolimus vs. placebo): 3 vs. 4

Yao 2019 *(Continued)*

- Duodenum (everolimus vs. placebo): 4 vs. 2
- Colon (everolimus vs. placebo): 2 vs. 3
- Other (everolimus vs. placebo): 3 vs. 2
- Caecum (everolimus vs. placebo): 2 vs. 1
- Appendix (everolimus vs. placebo): 1 vs. 0
- Liver involvement, % (everolimus vs. placebo): 80 vs. 78

Previous treatment, %:

- Surgery (everolimus vs. placebo): 59 vs. 72
- Chemotherapy (everolimus vs. placebo): 26 vs. 24
- Radiotherapy including PRRT (everolimus vs. placebo): 22 vs. 20
- Locoregional and ablative therapies (everolimus vs. placebo): 11 vs. 10
- SSA (everolimus vs. placebo): 53 vs. 56

Subgroup analysis:

- Total patients: 46
- Age (everolimus vs. placebo): 57 vs. 53
- Women, % (everolimus vs. placebo): 64 vs. 33
- WHO performance status 0, % (everolimus vs. placebo): 68 vs. 67
- Tumour grade 1, % (everolimus vs. placebo): 21 vs. 28

Primary tumour site, %:

- Rectum (everolimus vs. placebo): 39 vs. 44
- Lung (everolimus vs. placebo): 18 vs. 11
- Jejunum (everolimus vs. placebo):11 vs. 0
- Duodenum (everolimus vs. placebo):11 vs. 6
- Stomach (everolimus vs. placebo): 4 vs. 11
- Ileum (everolimus vs. placebo): 0 vs. 6
- Unknown origin (everolimus vs. placebo): 11 vs. 22
- Other (everolimus vs. placebo): 7 vs. 0
- Liver involvement, % (everolimus vs. placebo): 86 vs. 89

Previous treatment, %:

- Surgery (everolimus vs. placebo): 54 vs. 50
- SSA (everolimus vs. placebo): 36 vs. 28
- Chemotherapy (everolimus vs. placebo): 29 vs. 22
- Locoregional and ablative therapies (everolimus vs. placebo): 21 vs. 17
- Radiotherapy including PRRT (everolimus vs. placebo): 11 vs. 0

Interventions	Study group (core study: 203/302; subgroup analysis: 28/46): oral everolimus, 10 mg per day Control group (core study: 97/302; subgroup analysis: 18/46): identical placebo Duration of treatment: until 1) documented radiological disease progression, 2) start of new cancer therapy, 3) development of an intolerable adverse event, or 4) withdrawal of consent Allowed: • Best supportive care (including analgesics and anti-diarrhoeals) • Dose reduction and treatment interruption to manage adverse events that were judged to be related to study treatment Not allowed:

Yao 2019 *(Continued)*

	• Anti-tumour agents like somatostatin analogues, interferons, tumour ablative procedures, radiation and concurrent chemotherapy • Cross-over from placebo to open-label everolimus after progression Exceptions: • Radiation and surgery were allowed only for palliative intent. • Concomitant somatostatin analogues only for control of emergent carcinoid symptoms that were not manageable by standard treatment (e.g. loperamide)
Outcomes	Primary endpoint: • Central radiology-assessed progression-free survival Secondary endpoints: • Overall survival • Objective response rate • Disease control rate • Health-related quality of life • WHO performance status • Pharmacokinetics • Changes in CgA and neuron-specific enolase levels • Safety Assessments: • Multiphasic CT or MRI every 8 weeks during the first 12 months and every 12 weeks thereafter
Notes	Core study was sponsored by Novartis Pharmaceuticals Corporation. Novartis shared their data with researchers.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified randomisation by interactive voice response systems
Allocation concealment (selection bias)	Unclear risk	Randomisation centrally managed by Novartis Pharmaceutical
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel were blinded. Study drugs looked identical. Assessments were the same in both groups.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Central radiology review, masked to treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were included in the full analysis set.
Selective reporting (reporting bias)	High risk	Not all endpoints reported in the study protocol were published. Data was shared by core study sponsor.
Other bias	Low risk	No other potential sources of bias found

Zhang 2020

Study characteristics	
Methods	Investigator-initiated, randomised, open-label, phase 2 study 1:1 randomisation Enrolment: June 2017 to February 2019
Participants	Inclusion criteria • Advanced or recurrent and/or metastatic poorly differentiated GEP-NECs • Chemotherapy-naive or adjuvant chemotherapy > 6 months before recurrence • Measurable disease according to RECIST version 1.1 • Age 18-75 years • ECOG performance status of 0 to 1 • Life expectancy ≥ 3 months • Adequate renal, hepatic and bone marrow function • Female patients of childbearing potential: negative serum or urine pregnancy test result within 7 days before study enrolment • Fertile patients: Contraception during the study until 30 days after the end of the study Exclusion criteria • History of palliative chemotherapy or disease recurrence < 6 months from the time of last adjuvant chemotherapy and/or radiotherapy • Known hypersensitivity to irinotecan, etoposide, or cisplatin • Surgery within the past 4 weeks before study enrolment • Severe, uncontrolled, concurrent diarrhoea • Concurrent severe infection • Severe, uncontrolled medical condition that would affect compliance or obscure the interpretation of toxicity determination or adverse events (including severe liver disease, heart disease, uncontrolled diabetes, hypertension, or pulmonary disease) • Another previous malignancy diagnosed within the past 5 years except for non-melanoma skin cancer • Presence of neurological or psychiatric abnormalities that affect cognition Total patients: 66 Age < 65/≥ 65, % (EP vs. IP): 55/46 vs. 52/49 Women, % (EP vs. IP): 33 vs. 27 ECOG performance score 0/1, % (EP vs. IP): 70/30 vs. 67/33 Primary tumour site, %: • Pancreas (EP vs. IP): 6 vs. 15 • Esophagus (EP vs. IP): 30 vs. 9 • Stomach (EP vs. IP): 27 vs. 33 • Duodenum (EP vs. IP): 3 vs. 9 • Small intestine (EP vs. IP): 3 vs. 6 • Colorectum (EP vs. IP): 15 vs. 18 • CUP (EP vs. IP): 15 vs. 9 Ki-67 index < 55%/≥ 55%, % (EP vs. IP): 6/94 vs. 9/91 Morphology, %:

Zhang 2020 *(Continued)*

	• Small cell (EP vs. IP): 58 vs. 39 • Large cell (EP vs. IP): 27 vs. 49 • MiNEC (EP vs. IP): 9 vs. 6 • Uncertain (EP vs. IP): 6 vs. 6 Surgery of primary tumour, % (EP vs. IP): 18 vs. 21 Liver metastases, % (EP vs. IP): 39 vs. 30
Interventions	EP arm 1 (33/66): 100 mg/m^2 of etoposide on days 1, 2, and 3 and cisplatin at a dose of 75 mg/m^2 on day 1 of a 21-day cycle IP arm 2 (33/66): 60 mg/m^2 of irinotecan on days 1 and 8 and cisplatin at a dose of 60 mg/m^2 on day 1 of a 21-day cycle Treatment duration: 6 cycles or until disease progression, patient refusal, or the occurrence of unacceptable toxicity Maintenance irinotecan for patients on IP regimen who achieved objective response or stable disease after 6 cycles
Outcomes	Primary endpoint: • Objective response rate Secondary endpoints: • Overall survival • Progression-free survival • Toxicity Assessments: • Pretreatment evaluations: medical history, physical examination, performance status score, complete blood count, serum chemistry, tumour staging and a bone scan (if bone metastases were suspected) • CT scans or magnetic resonance imaging of the chest, abdomen, pelvis, and/or brain at baseline and every 2 cycles • Post-treatment follow-up: at 6-week to 8-week intervals
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	No information given Identical number of patients in both study arms
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given

Zhang 2020 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	5 patients (2 in the EP arm and 3 in the IP arm) were excluded from the efficacy assessment. The planned size of the study population was 144 patients, but enrolment was terminated early (at 66 patients) because the premature analysis found similar responses in the two treatment arms.
Selective reporting (reporting bias)	Low risk	No study protocol available, but all endpoints stated were reported.
Other bias	Low risk	No other potential sources of bias found

AE: adverse event
ALT: alanine aminotransferase
AST: aspartate aminotransferase
BEZ235: dactolisib
bid: two times a day
BM: bowel movement
BMI: body mass index
CAP: capecitabine
CapStrep: capecitabine and streptozocin
CapStrepCis: capecitabine, streptozocin and cisplatin
CAPTEM: capecitabine and temozolomide
CgA: chromogranin A
CT: computed tomography
(c)TACE: (conventional) transarterial chemoembolization
CUP: cancer of unknown primary
DEB-TACE: drug-eluting bead transarterial chemoembolization
DM: diabetes mellitus
(d)u5-HIAA: 24-h urinary 5-hydroxyindoleacetic acid excretion
ECG: electrocardiogram
ECOG: Eastern Cooperative Oncology Group
ELECT: evaluation of lanreotide depot/autogel efficacy and safety as a carcinoid syndrome treatment
EORTC: European Organization for Research and Treatment of Cancer
EP: etoposide cisplatin
G(1/2/3): grade (1/2/3)
GBq: gigabecquerel
GEP-NEC: gastroenteropancreatic neuroendocrine carcinoma
GEP-NET: gastroenteropanreatic neuroendocrine tumour
h: hour
HACE: hepatic artery chemoembolization
HAE: hepatic artery embolization
HR: hazard ratio
IFNα: interferon alpha
IMPALA: centralised internet/telephone registration system
IP: irinotecan cisplatin
ITT: intention-to-treat
IU: international unit
i.v.: intravenous
IVRS: interactive voice response system
IWRS: interactive web response system
Ki-67: nuclear protein encoded by the MKI67 gene
LAN: lanreotide
LAR: long-acting release
mCi: millicurie

MEN1: multiple endocrine neoplasia type 1
MiNEC: mixed neuroendocrine non-neuroendocrine carcinoma
(m)(p)NET: (midgut)/(pancreatic) neuroendocrine tumour
MRI: magnetic resonance imaging
mTOR: mammalian target of rapamycin
MU: million units
N-DM: without diabetes mellitus
NSE: neuron-specific enolase
PD: progressive disease
PEG: pegylated
PET: positron emission tomography
PFS: progression-free survival
p.o.: peroral
PRRT: peptide receptor radionuclide therapy
PVA: polyvinyl alcohol
q2: every second
qd: once a day
QLQ-C30: quality of life questionnaire C30
QLQ-GI.NET21: quality of life questionnaire - neuroendocrine carcinoid module
QT(c): corrected QT interval (time from the start of the Q wave to the end of the T wave)
RADIANT: radiotherapy assessments during intervention and treatment
RE: radio embolization
RECIST: response evaluation criteria in solid tumours
SC: subcutaneous
SI: small intestinal
SIR: sirtex
SR: slow release
SSA: somatostatin analogue
TELECAST: telotristat ethyl in carcinoid syndrome
TELESTAR: telotristat etiprate for somatostatin analogue not adequately controlled carcinoid syndrome
TEM: temozolomide
tid: three times a day
(u)5-HIAA: (urine) 5-hydroxyindoleacetic acid
VEGF(R): vascular endothelial growth factor (receptor)
vs.: versus
WHO: World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Caplin 2014	Not randomised controlled trial study design
Chan 2018	Not randomised controlled trial study design
Cwikla 2017	Not randomised controlled trial study design
Fazio 2018	Not randomised controlled trial study design
Herrera Cabezón 2019	Not investigating therapeutic procedures in NET
Hörsch 2018	Not randomised controlled trial study design
Ito 2011	Duplicate report
Kulke 2019	Erratum (funding information added)

Study	Reason for exclusion
Lapuerta 2018	Not randomised controlled trial study design
Meyer 2016	Duplicate report
Miller 2020	Not investigating therapeutic procedures in NET
Okusaka 2012	Duplicate report
Pavel 2015	Not randomised controlled trial study design
Pavel 2018 (2)	Not randomised controlled trial study design
Pavel 2018 (3)	Duplicate report
Phan 2017	Not randomised controlled trial study design
Raderer 2015	Not randomised controlled trial study design
Salazar 2015	Not randomised controlled trial study design
Singh 2018 (2)	Not investigating therapeutic procedures in NET
Wolin 2013	Not randomised controlled trial study design
Wolin 2018	Not randomised controlled trial study design
Yao 2015	Not randomised controlled trial study design

NET: Neuroendocrine tumour

Characteristics of ongoing studies *[ordered by study ID]*

NCT01744249

Study name	NCT01744249
Methods	Phase II/III, prospective, multicenter, randomized (1:1), double-blind study.
Participants	Patients diagnosed with advanced G1-G2 neuroendocrine tumors (WHO 2010) of nonpancreatic origin that have presented documented disease progression in the 12 months prior to entering the study.
Interventions	Experimental: axitinib + sandostatin LAR Placebo comparator: placebo + sandostatin LAR
Outcomes	Primary outcome: effectiveness of axitinib in terms of progression-free survival. Secondary outcomes: • Objective response rate and the duration of the response • Functional response rate using F-DOPA-PET • Biochemical response (5-OH-indoleacetic acid and chromogranin A) • Safety and tolerability of axitinib

NCT01744249 *(Continued)*

	• Explore potential biomarkers • Evaluate overall survival
Starting date	November 2011
Contact information	
Notes	

NCT02246127

Study name	NCT02246127
Methods	Randomized Open Label Study
Participants	Patients with advanced progressive pancreatic neuroendocrine tumours
Interventions	Active comparator: everolimus first (everolimus (10mg/daily, oral) followed by STZ-5FU (injection/infusion; Moertel or Uppsala regime). Experimental: STZ-5FU first (STZ-5FU (injection/infusion; Moertel or Uppsala regime) followed by everolimus (10 mg/ daily, oral).
Outcomes	Primary outcome: first progression-free survival (time frame: up to 84 weeks). Secondary outcomes: • Second progression-free survival (time frame: up to 140 +/- 8 weeks) • Hazard ratio • Time to first progression • Time to second progression • Adverse events • Ratio of incremental cost-efficacy • Response rate • Early biochemical response
Starting date	27 October 2014
Contact information	
Notes	

NCT03049189

Study name	NCT03049189
Methods	Prospective, randomised, controlled, open-label, multicentre phase III study
Participants	Patients with inoperable, progressive, somatostatin receptor-positive (SSTR+), neuroendocrine tumours of gastroenteric or pancreatic origin (GEP-NET)

NCT03049189 *(Continued)*

Interventions	Experimental: 177Lu-edotreotide PRRT (maximum of four cycles of 7.5 ± 0.7 GBq) Active comparator: everolimus (10mg/d)
Outcomes	Primary outcome: progression-free survival. Secondary outcome: overall survival.
Starting date	2 February 2017
Contact information	info@itm-solucin.de
Notes	

G(1/2): grade (1/2)
GBq: gigabecquerel
GEP-NET: gastroenteropanreatic neuroendocrine tumour
LAR: long-acting release
PRRT: peptide receptor radionuclide therapy
STZ-5FU: streptozotocin-fluorouracil
SSTR+: somatostatin receptor-positive
WHO: World Health Organization

ADDITIONAL TABLES

Table 1. Comparison of all treatment options from the network meta-analysis of disease control in pancreatic neuroendocrine tumours (pNET)

Dactolisib	0.17 (0.04 to 0.68)	0.19 (0.04 to 0.87)	0.22 (0.03 to 1.41)	0.19 (0.04 to 1.04)	0.56 (0.13 to 2.37)	0.24 (0.05 to 1.07)	0.32 (0.07 to 1.58)	0.28 (0.06 to 1.38)
5.89 (1.46 to 23.7)	**Everolimus**	1.14 (0.63 to 2.04)	1.27 (0.36 to 4.49)	1.14 (0.44 to 2.95)	3.29 (2.21 to 4.90)	1.40 (0.79 to 2.46)	1.91 (0.90 to 4.06)	1.65 (0.76 to 3.61)
5.18 (1.14 to 23.5)	0.88 (0.49 to 1.58)	**Everolimus + SSA**	1.12 (0.33 to 3.79)	1.00 (0.41 to 2.46)	2.89 (1.61 to 5.19)	1.23 (0.77 to 1.97)	1.68 (0.71 to 4.00)	1.46 (0.60 to 3.54)
4.62 (0.71 to 30.2)	0.78 (0.22 to 2.76)	0.89 (0.26 to 3.02)	**Interferon**	0.90 (0.29 to 2.79)	2.58 (0.75 to 8.81)	1.09 (0.36 to 3.37)	1.50 (0.37 to 5.98)	1.30 (0.32 to 5.26)
5.16 (0.96 to 27.8)	0.88 (0.34 to 2.26)	1.00 (0.41 to 2.43)	1.12 (0.36 to 3.47)	**Interferon + SSA**	2.88 (1.16 to 7.13)	1.22 (0.57 to 2.61)	1.67 (0.55 to 5.07)	1.45 (0.47 to 4.47)
1.79 (0.42 to 7.64)	0.30 (0.20 to 0.45)	0.35 (0.19 to 0.62)	0.39 (0.11 to 1.33)	0.35 (0.14 to 0.86)	**Placebo**	0.42 (0.26 to 0.70)	0.58 (0.31 to 1.10)	0.50 (0.26 to 0.98)
4.22 (0.94 to 19.0)	0.72 (0.41 to 1.26)	0.81 (0.51 to 1.31)	0.91 (0.30 to 2.81)	0.82 (0.38 to 1.75)	2.36 (1.43 to 3.88)	**SSA**	1.37 (0.61 to 3.08)	1.19 (0.51 to 2.73)
3.09 (0.63 to 15.1)	0.52 (0.25 to 1.11)	0.60 (0.25 to 1.42)	0.67 (0.17 to 2.67)	0.60 (0.20 to 1.82)	1.72 (0.91 to 3.27)	0.73 (0.32 to 1.65)	**Sunitinib**	0.87 (0.34 to 2.19)
3.56 (0.72 to 17.6)	0.60 (0.28 to 1.32)	0.69 (0.28 to 1.67)	0.77 (0.19 to 3.12)	0.69 (0.22 to 2.13)	1.99 (1.02 to 3.88)	0.84 (0.37 to 1.94)	1.15 (0.46 to 2.91)	**Surufatinib**

Effects are odds ratios with 95% confidence intervals.
SSA: somatostatin analogues

Table 2. Comparison of all treatment options from the network meta-analysis of progression-free survival in pancreatic neuroendocrine tumours (pNET)

Bevacizumab + SSA	0.66 (0.21 to 2.13)	1.02 (0.42 to 2.47)	0.76 (0.31 to 1.90)	0.95 (0.41 to 2.19)	0.90 (0.41 to 1.96)	1.08 (0.85 to 1.37)	0.36 (0.15 to 0.89)	0.71 (0.32 to 1.58)	0.87 (0.32 to 2.38)	0.74 (0.28 to 2.01)
1.51 (0.47 to 4.83)	**Dactolisib**	1.53 (0.72 to 3.25)	1.15 (0.46 to 2.89)	1.43 (0.62 to 3.33)	1.35 (0.44 to 4.16)	1.62 (0.52 to 5.07)	0.55 (0.25 to 1.21)	1.08 (0.46 to 2.53)	1.31 (0.52 to 3.27)	1.12 (0.45 to 2.76)

Table 2. Comparison of all treatment options from the network meta-analysis of progression-free survival in pancreatic neuroendocrine tumours (pNET) *(Continued)*

0.98 (0.40 to 2.40)	0.65 (0.31 to 1.39)	**Everolimus**	0.75 (0.44 to 1.28)	0.94 (0.65 to 1.36)	0.89 (0.38 to 2.04)	1.06 (0.45 to 2.49)	0.36 (0.28 to 0.46)	0.70 (0.47 to 1.05)	0.85 (0.50 to 1.44)	0.73 (0.45 to 1.20)
1.31 (0.53 to 3.27)	0.87 (0.35 to 2.19)	1.33 (0.78 to 2.27)	**Everolimus + bevacizumab + SSA**	1.25 (0.86 to 1.82)	1.18 (0.50 to 2.78)	1.41 (0.58 to 3.41)	0.48 (0.28 to 0.83)	0.94 (0.60 to 1.47)	1.14 (0.55 to 2.34)	0.98 (0.48 to 1.96)
1.05 (0.46 to 2.41)	0.70 (0.30 to 1.62)	1.07 (0.73 to 1.55)	0.80 (0.55 to 1.17)	**Everolimus + SSA**	0.94 (0.44 to 2.04)	1.13 (0.51 to 2.50)	0.38 (0.26 to 0.57)	0.75 (0.58 to 0.96)	0.91 (0.49 to 1.68)	0.78 (0.43 to 1.41)
1.11 (0.51 to 2.43)	0.74 (0.24 to 2.27)	1.13 (0.49 to 2.60)	0.85 (0.36 to 2.00)	1.06 (0.49 to 2.29)	**Interferon**	1.20 (0.57 to 2.52)	0.41 (0.18 to 0.94)	0.80 (0.38 to 1.65)	0.96 (0.37 to 2.51)	0.83 (0.32 to 2.12)
0.93 (0.73 to 1.18)	0.62 (0.20 to 1.93)	0.94 (0.40 to 2.22)	0.71 (0.29 to 1.71)	0.89 (0.40 to 1.96)	0.84 (0.40 to 1.76)	**Interferon + SSA**	0.34 (0.14 to 0.80)	0.66 (0.31 to 1.42)	0.81 (0.30 to 2.15)	0.69 (0.26 to 1.81)
2.75 (1.12 to 6.71)	1.82 (0.83 to 4.02)	2.79 (2.19 to 3.55)	2.09 (1.21 to 3.63)	2.62 (1.75 to 3.91)	2.47 (1.07 to 5.70)	2.95 (1.25 to 6.98)	**Placebo**	1.96 (1.30 to 2.96)	2.38 (1.49 to 3.79)	2.04 (1.32 to 3.15)
1.40 (0.63 to 3.09)	0.93 (0.40 to 2.18)	1.42 (0.95 to 2.12)	1.07 (0.68 to 1.68)	1.33 (1.04 to 1.71)	1.26 (0.61 to 2.61)	1.50 (0.71 to 3.20)	0.51 (0.34 to 0.77)	**SSA**	1.21 (0.65 to 2.26)	1.04 (0.57 to 1.89)
1.15 (0.42 to 3.16)	0.77 (0.31 to 1.92)	1.17 (0.69 to 1.98)	0.88 (0.43 to 1.81)	1.10 (0.59 to 2.03)	1.04 (0.40 to 2.70)	1.24 (0.47 to 3.30)	0.42 (0.26 to 0.67)	0.82 (0.44 to 1.53)	**Sunitinib**	0.86 (0.45 to 1.62)
1.35 (0.50 to 3.63)	0.89 (0.36 to 2.20)	1.37 (0.83 to 2.24)	1.03 (0.51 to 2.06)	1.28 (0.71 to 2.31)	1.21 (0.47 to 3.10)	1.45 (0.55 to 3.79)	0.49 (0.32 to 0.76)	0.96 (0.53 to 1.75)	1.17 (0.62 to 2.20)	**Surufatinib**

Effects are hazard ratios with 95% confidence intervals.
SSA: somatostatin analogues

Table 3. Estimates of effects and quality ratings for disease control in pancreatic neuroendocrine tumours (pNET)

	Direct evidence		Indirect evidence		Network meta-analysis	
Comparison	Odds ratio (95% CI)	Quality of evidence	Odds ratio (95% CI)	Quality of evidence	Odds ratio (95% CI)	Quality of evidence
Dactolisib vs everolimus	0.17 (0.04 to 0.68)	Low*,§			0.17 (0.04 to 0.68)	Low§
Dactolisib vs everolimus + SSA			0.19 (0.04 to 0.87)	Very low||,§	0.19 (0.04 to 0.87)	Very low§
Dactolisib vs interferon			0.22 (0.03 to 1.41)	Very low|||,§§	0.22 (0.03 to 1.41)	Very low§§
Dactolisib vs interferon + SSA			0.19 (0.04 to 1.04)	Very low||,¶,§§	0.19 (0.04 to 1.04)	Very low§§
Dactolisib vs placebo			0.56 (0.13 to 2.37)	Very low|,§§	0.56 (0.13 to 2.37)	Very low§§
Dactolisib vs SSA			0.24 (0.05 to 1.07)	Very low|,§§	0.24 (0.05 to 1.07)	Very low§§
Dactolisib vs sunitinib			0.32 (0.07 to 1.58)	Very low|,§§	0.32 (0.07 to 1.58)	Very low§§
Dactolisib vs surufatinib			0.28 (0.06 to 1.38)	Very low|,§§	0.28 (0.06 to 1.38)	Very low§§
Everolimus vs everolimus + SSA	1.41 (0.65 to 3.08)	Very low**,§	0.86 (0.35 to 2.08)	Very low|,¶,§	1.14 (0.63 to 2.04)	Very low§
Everolimus vs interferon			1.27 (0.36 to 4.49)	Very low|||,§§	1.27 (0.36 to 4.49)	Very low§§
Everolimus vs interferon + SSA			1.14 (0.44 to 2.95)	Very low||,¶,§	1.14 (0.44 to 2.95)	Very low§
Everolimus vs placebo	3.08 (2.01 to 4.72)	High	5.06 (1.68 to 15.2)	Very low||,¶¶	3.29 (2.21 to 4.90)	High
Everolimus vs SSA			1.40 (0.79 to 2.46)	Low|,§	1.40 (0.79 to 2.46)	Low§
Everolimus vs sunitinib			1.91 (0.90 to 4.06)	Moderate§	1.91 (0.90 to 4.06)	Moderate§
Everolimus vs surufatinib			1.65 (0.76 to 3.61)	Moderate§	1.65 (0.76 to 3.61)	Moderate§
Everolimus + SSA vs interferon			1.12 (0.33 to 3.79)	Very low|||,¶,§§	1.12 (0.33 to 3.79)	Very low§§
Everolimus + SSA vs interferon + SSA			1.00 (0.41 to 2.46)	Very low||,¶,§	1.00 (0.41 to 2.46)	Very low§
Everolimus + SSA vs placebo			2.89 (1.61 to 5.19)	Moderate|	2.89 (1.61 to 5.19)	Moderate

Table 3. Estimates of effects and quality ratings for disease control in pancreatic neuroendocrine tumours (pNET) *(Continued)*

Everolimus + SSA vs SSA	1.36 (0.80 to 2.30)	Low‡,§	0.83 (0.29 to 2.37)	Very low‖,§§	1.23 (0.77 to 1.97)	Moderate
Everolimus + SSA vs sunitinib			1.68 (0.71 to 4.00)	Very low|,§	1.68 (0.71 to 4.00)	Very low§
Everolimus + SSA vs surufatinib			1.46 (0.60 to 3.54)	Very low|,§	1.46 (0.60 to 3.54)	Very low§
Interferon vs interferon + SSA	1.07 (0.31 to 3.72)	Very low**,‡,§§	0.39 (0.03 to 5.94)	Very low|||,¶,§§	0.90 (0.29 to 2.79)	Very low#,§§
Interferon vs placebo			2.58 (0.75 to 8.81)	Very low|||,§§	2.58 (0.75 to 8.81)	Very low§§
Interferon vs SSA	0.93 (0.28 to 3.16)	Very low**,‡,§§	2.64 (0.15 to 46.3)	Very low|||,¶,§§	1.09 (0.36 to 3.37)	Very low#,§§
Interferon vs sunitinib			1.50 (0.37 to 5.98)	Very low|||,§§	1.50 (0.37 to 5.98)	Very low§§
Interferon vs surufatinib			1.30 (0.32 to 5.26)	Very low|||,§§	1.30 (0.32 to 5.26)	Very low§§
Interferon + SSA vs placebo			2.88 (1.16 to 7.13)	Very low||,¶	2.88 (1.16 to 7.13)	Very low
Interferon + SSA vs SSA	1.22 (0.57 to 2.61)	Very low*,‡,§			1.22 (0.57 to 2.61)	Very low§
Interferon + SSA vs sunitinib			1.67 (0.55 to 5.07)	Very low||,¶,§§	1.67 (0.55 to 5.07)	Very low§§
Interferon + SSA vs surufatinib			1.45 (0.47 to 4.47)	Very low||,¶,§§	1.45 (0.47 to 4.47)	Very low§§
Placebo vs SSA	0.38 (0.21 to 0.67)	Moderate‡	0.62 (0.22 to 1.75)	Very low||,¶,§§	0.42 (0.26 to 0.70)	Moderate
Placebo vs sunitinib	0.58 (0.31 to 1.10)	Moderate§			0.58 (0.31 to 1.10)	Moderate§
Placebo vs surufatinib	0.50 (0.26 to 0.98)	High			0.50 (0.26 to 0.98)	High
SSA vs sunitinib			1.37 (0.61 to 3.08)	Low|,§	1.37 (0.61 to 3.08)	Low§
SSA vs surufatinib			1.19 (0.51 to 2.73)	Low|,§	1.19 (0.51 to 2.73)	Low§
Sunitinib vs surufatinib			0.87 (0.34 to 2.19)	Moderate§	0.87 (0.34 to 2.19)	Moderate§

The confidence assessment addressed *risk of bias, †inconsistency, ‡indirectness, §imprecision, and #incoherence. Indirect estimates were potentially rated down for intransitivity.

Severe limitations are indicated by two symbols. Contributing direct evidence was of |moderate, ||low or |||very low quality.

Abbreviations: SSA: somatostatin analogues; CI: confidence interval

Table 4. Estimates of effects and quality ratings for progression-free survival in pancreatic neuroendocrine tumors (pNET)

	Direct evidence		Indirect evidence		Network meta-analysis	
Comparison	Hazard ratio (95% CI)	Quality of evidence	Hazard ratio (95% CI)	Quality of evidence	Hazard ratio (95% CI)	Quality of evidence
Bevacizumab + SSA vs dactolisib			0.66 (0.21 to 2.13)	Very low|||,¶,§§	0.66 (0.21 to 2.13)	Very low§§
Bevacizumab + SSA vs everolimus			1.02 (0.42 to 2.47)	Very low|||,¶,§	1.02 (0.42 to 2.47)	Very low§
Bevacizumab + SSA vs everolimus + bevacizumab + SSA			0.76 (0.31 to 1.90)	Very low|||,¶¶,§	0.76 (0.31 to 1.90)	Very low§
Bevacizumab + SSA vs everolimus + SSA			0.95 (0.41 to 2.19)	Very low|||,¶¶,§	0.95 (0.41 to 2.19)	Very low§
Bevacizumab + SSA vs interferon			0.90 (0.41 to 1.96)	Very low|||,¶,§	0.90 (0.41 to 1.96)	Very low§
Bevacizumab + SSA vs interferon + SSA	1.08 (0.85 to 1.37)	Low*,‡			1.08 (0.85 to 1.37)	Low
Bevacizumab + SSA vs placebo			0.36 (0.15 to 0.89)	Very low|||,¶	0.36 (0.15 to 0.89)	Very low
Bevacizumab + SSA vs SSA			0.71 (0.32 to 1.58)	Very low|||,¶,§	0.71 (0.32 to 1.58)	Very low§
Bevacizumab + SSA vs sunitinib			0.87 (0.32 to 2.38)	Very low|||,¶,§§	0.87 (0.32 to 2.38)	Very low§§
Bevacizumab + SSA vs surufatinib			0.74 (0.28 to 2.01)	Very low|||,¶,§	0.74 (0.28 to 2.01)	Very low§
Dactolisib vs everolimus	1.53 (0.72 to 3.25)	Low*,§			1.53 (0.72 to 3.25)	Low§
Dactolisib vs everolimus + bevacizumab + SSA			1.15 (0.46 to 2.89)	Very low||,¶,§	1.15 (0.46 to 2.89)	Very low§
Dactolisib vs everolimus + SSA			1.43 (0.62 to 3.33)	Very low||,§	1.43 (0.62 to 3.33)	Very low§
Dactolisib vs interferon			1.35 (0.44 to 4.16)	Very low||,§§	1.35 (0.44 to 4.16)	Very low§§
Dactolisib vs interferon + SSA			1.62 (0.52 to 5.07)	Very low||,§§	1.62 (0.52 to 5.07)	Very low§§
Dactolisib vs placebo			0.55 (0.25 to 1.21)	Low|,§	0.55 (0.25 to 1.21)	Low§

Table 4. Estimates of effects and quality ratings for progression-free survival in pancreatic neuroendocrine tumors (pNET) *(Continued)*

Dactolisib vs SSA			1.08 (0.46 to 2.53)	Low|,§	1.08 (0.46 to 2.53)	Low§
Dactolisib vs sunitinib			1.31 (0.52 to 3.27)	Low|,§	1.31 (0.52 to 3.27)	Low§
Dactolisib vs surufatinib			1.12 (0.45 to 2.76)	Low|,§	1.12 (0.45 to 2.76)	Low§
Everolimus vs everolimus + bevacizumab + SSA			0.75 (0.44 to 1.28)	Very low||,¶,§	0.75 (0.44 to 1.28)	Very low§
Everolimus vs everolimus + SSA	1.01 (0.65 to 1.57)	Low**	0.78 (0.39 to 1.57)	Very low|,¶,§	0.94 (0.65 to 1.36)	Low
Everolimus vs interferon			0.89 (0.38 to 2.04)	Very low||,§	0.89 (0.38 to 2.04)	Very low§
Everolimus vs interferon + SSA			1.06 (0.45 to 2.49)	Very low||,§	1.06 (0.45 to 2.49)	Very low§
Everolimus vs placebo	0.35 (0.27 to 0.45)	High	0.45 (0.21 to 0.99)	Very low||,¶¶	0.36 (0.28 to 0.46)	High
Everolimus vs SSA			0.70 (0.47 to 1.05)	High	0.70 (0.47 to 1.05)	High
Everolimus vs sunitinib			0.85 (0.50 to 1.44)	Moderate§	0.85 (0.50 to 1.44)	Moderate§
Everolimus vs surufatinib			0.73 (0.45 to 1.20)	High	0.73 (0.45 to 1.20)	High
Everolimus + bevacizumab + SSA vs everolimus + SSA	1.25 (0.86 to 1.82)	Moderate*			1.25 (0.86 to 1.82)	Moderate
Everolimus + bevacizumab + SSA vs interferon			1.18 (0.50 to 2.78)	Very low||,¶,§	1.18 (0.50 to 2.78)	Very low§
Everolimus + bevacizumab + SSA vs interferon + SSA			1.41 (0.58 to 3.41)	Very low||,¶¶,§	1.41 (0.58 to 3.41)	Very low§
Everolimus + bevacizumab + SSA vs placebo			0.48 (0.28 to 0.83)	Low|,¶	0.48 (0.28 to 0.83)	Low
Everolimus + bevacizumab + SSA vs SSA			0.94 (0.60 to 1.47)	Moderate|	0.94 (0.60 to 1.47)	Moderate
Everolimus + bevacizumab + SSA vs sunitinib			1.14 (0.55 to 2.34)	Very low|,¶,§	1.14 (0.55 to 2.34)	Very low§
Everolimus + bevacizumab + SSA vs surufatinib			0.98 (0.48 to 1.96)	Very low|,¶,§	0.98 (0.48 to 1.96)	Very low§
Everolimus + SSA vs interferon			0.94 (0.44 to 2.04)	Very low||,¶,§	0.94 (0.44 to 2.04)	Very low§

Table 4. Estimates of effects and quality ratings for progression-free survival in pancreatic neuroendocrine tumors (pNET) *(Continued)*

Everolimus + SSA vs interferon + SSA			1.13 (0.51 to 2.50)	Very low‖,¶,§	1.13 (0.51 to 2.50)	Very low§
Everolimus + SSA vs placebo			0.38 (0.26 to 0.57)	Low|	0.38 (0.26 to 0.57)	Low
Everolimus + SSA vs SSA	0.77 (0.59 to 1.00)	Moderate‡	0.60 (0.27 to 1.30)	Very low‖,§	0.75 (0.58 to 0.96)	Moderate
Everolimus + SSA vs sunitinib			0.91 (0.49 to 1.68)	Very low|,§	0.91 (0.49 to 1.68)	Very low§
Everolimus + SSA vs surufatinib			0.78 (0.43 to 1.41)	Very low|,§	0.78 (0.43 to 1.41)	Very low§
Interferon vs interferon + SSA	1.20 (0.57 to 2.52)	Very low**,‡,§			1.20 (0.57 to 2.52)	Very low§
Interferon vs placebo			0.41 (0.18 to 0.94)	Very low|||	0.41 (0.18 to 0.94)	Very low
Interferon vs SSA	0.80 (0.38 to 1.65)	Very low**,‡,§			0.80 (0.38 to 1.65)	Very low§
Interferon vs sunitinib			0.96 (0.37 to 2.51)	Very low|||,§	0.96 (0.37 to 2.51)	Very low§
Interferon vs surufatinib			0.83 (0.32 to 2.12)	Very low|||,§	0.83 (0.32 to 2.12)	Very low§
Interferon + SSA vs placebo			0.34 (0.14 to 0.80)	Very low|||	0.34 (0.14 to 0.80)	Very low
Interferon + SSA vs SSA	0.66 (0.31 to 1.42)	Very low**,‡,§			0.66 (0.31 to 1.42)	Very low§
Interferon + SSA vs sunitinib			0.81 (0.30 to 2.15)	Very low|||,§	0.81 (0.30 to 2.15)	Very low§
Interferon + SSA vs surufatinib			0.69 (0.26 to 1.81)	Very low|||,§	0.69 (0.26 to 1.81)	Very low§
Placebo vs SSA	1.72 (0.96 to 3.11)	Moderate§	2.22 (1.25 to 3.95)	Very low‖,¶	1.96 (1.30 to 2.96)	High
Placebo vs sunitinib	2.38 (1.49 to 3.79)	High			2.38 (1.49 to 3.79)	High
Placebo vs surufatinib	2.04 (1.32 to 3.15)	High			2.04 (1.32 to 3.15)	High
SSA vs sunitinib			1.21 (0.65 to 2.26)	Moderate§	1.21 (0.65 to 2.26)	Moderate§
SSA vs surufatinib			1.04 (0.57 to 1.89)	Moderate§	1.04 (0.57 to 1.89)	Moderate§

Table 4. Estimates of effects and quality ratings for progression-free survival in pancreatic neuroendocrine tumors (pNET) *(Continued)*

Sunitinib vs surufatinib	0.86 (0.45 to 1.62)	Moderate§	0.86 (0.45 to 1.62)	Moderate§

The confidence assessment addressed *risk of bias, †inconsistency, ‡indirectness, §imprecision, and #incoherence. Indirect estimates were potentially rated down for intransitivity.
Severe limitations are indicated by two symbols. Contributing direct evidence was of |moderate, ||low or |||very low quality.
Abbreviations: SSA: somatostatin analogues; CI: confidence interval

Table 5. Comparison of all treatment options from the network meta-analysis of disease control in gastrointestinal neuroendocrine tumours (GI-NET)

177-Lu-DOTATATE + SSA	0.68 (0.05 to 10.1)	12.0 (2.33 to 62.1)	2.02 (0.30 to 13.8)	7.55 (1.37 to 41.6)	5.33 (1.42 to 20.0)	30.4 (8.19 to 113)	10.4 (3.59 to 30.1)	229 (6.16 to 8512)	8.69 (1.60 to 47.1)
1.48 (0.10 to 22.1)	**Bevacizumab + SSA**	17.8 (1.10 to 288)	2.99 (0.15 to 57.6)	11.2 (0.74 to 168)	7.87 (0.74 to 83.5)	45.0 (3.32 to 609)	15.4 (1.28 to 185)	338 (5.14 to 22282)	12.8 (0.77 to 214)
0.08 (0.02 to 0.43)	0.06 (0.00 to 0.91)	**Everolimus**	0.17 (0.02 to 1.28)	0.63 (0.10 to 3.91)	0.44 (0.10 to 1.94)	2.53 (0.95 to 6.79)	0.87 (0.25 to 3.02)	19.1 (0.48 to 752)	0.72 (0.17 to 3.08)
0.49 (0.07 to 3.38)	0.33 (0.02 to 6.45)	5.95 (0.78 to 45.3)	**Everolimus + SSA**	3.74 (0.47 to 30.0)	2.64 (0.44 to 15.7)	15.1 (2.55 to 88.9)	5.14 (1.04 to 25.5)	113 (2.51 to 5106)	4.30 (0.54 to 34.1)
0.13 (0.02 to 0.73)	0.09 (0.01 to 1.35)	1.59 (0.26 to 9.90)	0.27 (0.03 to 2.15)	**Interferon**	0.71 (0.18 to 2.70)	4.03 (0.86 to 18.8)	1.38 (0.36 to 5.22)	30.3 (1.25 to 735)	1.15 (0.18 to 7.47)
0.19 (0.05 to 0.71)	0.13 (0.01 to 1.35)	2.26 (0.51 to 9.89)	0.38 (0.06 to 2.26)	1.42 (0.37 to 5.41)	**Interferon + SSA**	5.71 (1.90 to 17.2)	1.95 (0.89 to 4.29)	43.0 (1.35 to 1365)	1.63 (0.35 to 7.54)
0.03 (0.01 to 0.12)	0.02 (0.00 to 0.30)	0.39 (0.15 to 1.06)	0.07 (0.01 to 0.39)	0.25 (0.05 to 1.16)	0.18 (0.06 to 0.53)	**Placebo**	0.34 (0.16 to 0.74)	7.52 (0.22 to 259)	0.29 (0.10 to 0.83)
0.10 (0.03 to 0.28)	0.07 (0.01 to 0.78)	1.16 (0.33 to 4.04)	0.19 (0.04 to 0.96)	0.73 (0.19 to 2.76)	0.51 (0.23 to 1.13)	2.93 (1.36 to 6.32)	**SSA**	22.0 (0.70 to 698)	0.84 (0.23 to 3.10)
0.00 (0.00 to 0.16)	0.00 (0.00 to 0.19)	0.05 (0.00 to 2.07)	0.01 (0.00 to 0.40)	0.03 (0.00 to 0.80)	0.02 (0.00 to 0.74)	0.13 (0.00 to 4.58)	0.05 (0.00 to 1.44)	**Streptozocin + 5FU**	0.04 (0.00 to 1.53)
0.12 (0.02 to 0.62)	0.08 (0.00 to 1.30)	1.38 (0.32 to 5.89)	0.23 (0.03 to 1.84)	0.87 (0.13 to 5.64)	0.61 (0.13 to 2.83)	3.50 (1.21 to 10.1)	1.20 (0.32 to 4.44)	26.4 (0.65 - 1062)	**Surufatinib**

Effects are odds ratios with 95% confidence intervals.
SSA: somatostatin analogues

Table 6. Comparison of all treatment options from the network meta-analysis of progression-free survival in gastrointestinal neuroendocrine tumours (GI-NET)

177-Lu-DOTATATE + SSA	0.40 (0.07 to 2.32)	0.13 (0.03 to 0.64)	0.62 (0.12 to 3.22)	0.26 (0.06 to 1.22)	0.32 (0.07 to 1.47)	0.07 (0.02 to 0.26)	0.21 (0.08 to 0.57)	0.22 (0.04 to 1.09)

Table 6. Comparison of all treatment options from the network meta-analysis of progression-free survival in gastrointestinal neuroendocrine tumours (GI-NET) *(Continued)*

2.51 (0.43 to 14.6)	**Bevacizumab + SSA**	0.32 (0.05 to 2.20)	1.55 (0.22 to 10.9)	0.66 (0.16 to 2.80)	0.79 (0.34 to 1.86)	0.18 (0.04 to 0.94)	0.53 (0.12 to 2.24)	0.55 (0.08 to 3.73)
7.75 (1.55 to 38.7)	3.09 (0.45 to 20.9)	**Everolimus**	4.78 (0.78 to 29.4)	2.05 (0.37 to 11.2)	2.45 (0.44 to 13.6)	0.56 (0.21 to 1.49)	1.63 (0.46 to 5.71)	1.70 (0.42 to 6.78)
1.62 (0.31 to 8.43)	0.64 (0.09 to 4.54)	0.21 (0.03 to 1.28)	**Everolimus + SSA**	0.43 (0.07 to 2.44)	0.51 (0.09 to 2.96)	0.12 (0.03 to 0.54)	0.34 (0.09 to 1.26)	0.35 (0.06 to 2.18)
3.79 (0.82 to 17.4)	1.51 (0.36 to 6.36)	0.49 (0.09 to 2.68)	2.34 (0.41 to 13.4)	**Interferon**	1.20 (0.38 to 3.81)	0.27 (0.07 to 1.10)	0.80 (0.25 to 2.51)	0.83 (0.15 to 4.55)
3.16 (0.68 to 14.8)	1.26 (0.54 to 2.96)	0.41 (0.07 to 2.27)	1.95 (0.34 to 11.3)	0.84 (0.26 to 2.66)	**Interferon + SSA**	0.23 (0.06 to 0.93)	0.66 (0.21 to 2.14)	0.69 (0.12 to 3.85)
13.8 (3.87 to 49.5)	5.51 (1.06 to 28.6)	1.79 (0.67 to 4.75)	8.54 (1.85 to 39.4)	3.65 (0.91 to 14.7)	4.37 (1.07 to 17.9)	**Placebo**	2.90 (1.32 to 6.38)	3.03 (1.14 to 8.07)
4.76 (1.75 to 13.0)	1.90 (0.45 to 8.05)	0.61 (0.18 to 2.16)	2.94 (0.79 to 10.9)	1.26 (0.40 to 3.97)	1.50 (0.47 to 4.83)	0.34 (0.16 to 0.76)	**SSA**	1.04 (0.30 to 3.66)
4.56 (0.91 to 22.8)	1.82 (0.27 to 12.3)	0.59 (0.15 to 2.35)	2.82 (0.46 to 17.3)	1.21 (0.22 to 6.62)	1.44 (0.26 to 8.01)	0.33 (0.12 - 0.88)	0.96 (0.27 to 3.37)	**Surufatinib**

Effects are hazard ratios with 95% confidence intervals.
SSA: somatostatin analogues

Table 7. Estimates of effects and quality ratings for disease control in gastrointestinal neuroendocrine tumors (GI-NET)

	Direct evidence		Indirect evidence		Network meta-analysis	
Comparison	Odds ratio (95% CI)	Quality of evidence	Odds ratio (95% CI)	Quality of evidence	Odds ratio (95% CI)	Quality of evidence
177-Lu-DOTATATE + SSA vs bevacizumab + SSA			0.68 (0.05 to 10.1)	Very low‖,¶¶,§§	0.68 (0.05 to 10.1)	Very low§§
177-Lu-DOTATATE + SSA vs everolimus			12.0 (2.33 to 62.1)	Very low‖,¶,§	12.0 (2.33 to 62.1)	Very low§
177-Lu-DOTATATE + SSA vs everolimus + SSA			2.02 (0.30 to 13.8)	Very low‖,§§	2.02 (0.30 to 13.8)	Very low§§
177-Lu-DOTATATE + SSA vs interferon			7.55 (1.37 to 41.6)	Very low‖,¶,§	7.55 (1.37 to 41.6)	Very low§
177-Lu-DOTATATE + SSA vs interferon + SSA			5.33 (1.42 to 20.0)	Very low‖,¶,§	5.33 (1.42 to 20.0)	Very low§
177-Lu-DOTATATE + SSA vs placebo			30.4 (8.19 to 113)	Very low‖,¶,§	30.4 (8.19 to 113)	Very low§
177-Lu-DOTATATE + SSA vs SSA	10.4 (3.59 to 30.1)	Low**			10.4 (3.59 to 30.1)	Low
177-Lu-DOTATATE + SSA vs streptozocin + 5FU			229 (6.16 to 8512)	Very low‖,¶,§	229 (6.16 to 8512)	Very low§
177-Lu-DOTATATE + SSA vs surufatinib			8.69 (1.60 to 47.1)	Very low‖,¶,§	8.69 (1.60 to 47.1)	Very low§
Bevacizumab + SSA vs everolimus			17.8 (1.10 to 288)	Very low‖,¶¶,§	17.8 (1.10 to 288)	Very low§
Bevacizumab + SSA vs everolimus + SSA			2.99 (0.15 to 57.6)	Very low‖,¶¶,§§	2.99 (0.15 to 57.6)	Very low§§
Bevacizumab + SSA vs interferon			11.2 (0.74 to 168)	Very low‖,¶¶,§§	11.2 (0.74 to 168)	Very low§§
Bevacizumab + SSA vs interferon + SSA	7.88 (0.74 to 83.5)	Very low**,‡,§§			7.87 (0.74 to 83.5)	Very low§§
Bevacizumab + SSA vs placebo			45.0 (3.32 to 609)	Very low‖,¶¶,§	45.0 (3.32 to 609)	Very low§
Bevacizumab + SSA vs SSA			15.4 (1.28 to 185)	Very low‖,¶¶,§	15.4 (1.28 to 185)	Very low§
Bevacizumab + SSA vs streptozocin + 5-FU			338 (5.14 to 22282)	Very low‖,¶¶,§	338 (5.14 to 22282)	Very low§

Table 7. Estimates of effects and quality ratings for disease control in gastrointestinal neuroendocrine tumors (GI-NET) *(Continued)*

Bevacizumab + SSA vs surufatinib			12.8 (0.77 to 214)	Very low|||,¶¶,§§	12.8 (0.77 to 214)	Very low§§
Everolimus vs everolimus + SSA			0.17 (0.02 to 1.28)	Very low||,¶,§§	0.17 (0.02 to 1.28)	Very low§§
Everolimus vs interferon			0.63 (0.10 to 3.91)	Very low|||,¶,§§	0.63 (0.10 to 3.91)	Very low§§
Everolimus vs interferon + SSA			0.44 (0.10 to 1.94)	Very low|||,¶,§§	0.44 (0.10 to 1.94)	Very low§§
Everolimus vs placebo	2.53 (0.95 to 6.79)	Very low*,‡,§			2.53 (0.95 to 6.79)	Very low§
Everolimus vs SSA			0.87 (0.25 to 3.02)	Very low||,§§	0.87 (0.25 to 3.02)	Very low§§
Everolimus vs streptozocin + 5-FU			19.1 (0.48 to 752)	Very low|||,¶,§§	19.1 (0.48 to 752)	Very low§§
Everolimus vs surufatinib			0.72 (0.17 to 3.08)	Very low||,§§	0.72 (0.17 to 3.08)	Very low§§
Everolimus + SSA vs interferon			3.74 (0.47 to 30.0)	Very low|||,¶,§§	3.74 (0.47 to 30.0)	Very low§§
Everolimus + SSA vs interferon + SSA			2.64 (0.44 to 15.7)	Very low|||,¶,§§	2.64 (0.44 to 15.7)	Very low§§
Everolimus + SSA vs placebo			15.1 (2.55 to 88.9)	Very low|,¶,§	15.1 (2.55 to 88.9)	Very low§
Everolimus + SSA vs SSA	5.14 (1.04 to 25.5)	Moderate§			5.14 (1.04 to 25.5)	Moderate§
Everolimus + SSA vs streptozocin + 5-FU			113 (2.51 to 5106)	Very low|||,¶,§	113 (2.51 to 5106)	Very low§
Everolimus + SSA vs surufatinib			4.30 (0.54 to 34.1)	Very low|,¶,§§	4.30 (0.54 to 34.1)	Very low§§
Interferon vs interferon + SSA	1.07 (0.24 to 4.74)	Very low**,‡,§§	0.13 (0.01 to 2.66)	Very low|||,¶,§§	0.71 (0.18 to 2.70)	Very low§§
Interferon vs placebo			4.03 (0.86 to 18.8)	Very low|||,¶,§§	4.03 (0.86 to 18.8)	Very low§§
Interferon vs SSA	0.93 (0.21 to 4.06)	Very low**,‡,§§	8.41 (0.35 to 201)	Very low|||,¶,§§	1.38 (0.36 to 5.22)	Very low§§
Interferon vs streptozocin + 5-FU	30.3 (1.25 to 735)	Very low**,‡,§			30.3 (1.25 to 735)	Very low§
Interferon vs surufatinib			1.15 (0.18 to 7.47)	Very low|||,¶,§§	1.15 (0.18 to 7.47)	Very low§§

Table 7. Estimates of effects and quality ratings for disease control in gastrointestinal neuroendocrine tumors (GI-NET) *(Continued)*

Interferon + SSA vs placebo			5.71 (1.90 to 17.2)	Very low|||,¶	5.71 (1.90 to 17.2)	Very low
Interferon + SSA vs SSA	1.95 (0.89 to 4.29)	Very low*,††,‡,§			1.95 (0.89 to 4.29)	Very low§
Interferon + SSA vs streptozocin + 5-FU			43.0 (1.35 to 1365)	Very low|||,§	43.0 (1.35 to 1365)	Very low§
Interferon + SSA vs surufatinib			1.63 (0.35 to 7.54)	Very low|||,¶,§§	1.63 (0.35 to 7.54)	Very low§§
Placebo vs SSA	0.34 (0.16 to 0.74)	Moderate‡			0.34 (0.16 to 0.74)	Moderate
Placebo vs streptozocin + 5-FU			7.52 (0.22 to 259)	Very low|||,¶,§§	7.52 (0.22 to 259)	Very low§§
Placebo vs surufatinib	0.29 (0.10 to 0.83)	Moderate‡			0.29 (0.10 to 0.83)	Moderate
SSA vs streptozocin + 5-FU			22.0 (0.70 to 698)	Very low|||,§§	22.0 (0.70 to 698)	Very low§§
SSA vs surufatinib			0.84 (0.23 to 3.10)	Very low|,§§	0.84 (0.23 to 3.10)	Very low§§
Streptozocin + 5-FU vs surufatinib			0.04 (0.00 to 1.53)	Very low|||,¶,§§	0.04 (0.00 to 1.53)	Very low§§

The confidence assessment addressed *risk of bias, †inconsistency, ‡indirectness, §imprecision, and #incoherence. Indirect estimates were potentially rated down for intransitivity.
Severe limitations are indicated by two symbols. Contributing direct evidence was of \|moderate, \|\|low or \|\|\|very low quality.
Abbreviations: SSA: somatostatin analogues; 5-FU: 5-Fluorouracil; Lu: Lutetium; CI: confidence interval

Table 8. Estimates of effects and quality ratings for progression-free survival in gastrointestinal neuroendocrine tumors (GI-NET)

	Direct evidence		Indirect evidence		Network meta-analysis	
Comparison	Hazard ratio (95% CI)	Quality of evidence	Hazard ratio (95% CI)	Quality of evidence	Hazard ratio (95% CI)	Quality of evidence
177-Lu-DOTATATE + SSA vs bevacizumab + SSA			0.40 (0.07 to 2.32)	Very low|||,¶¶,§§	0.40 (0.07 to 2.32)	Very low§§
177-Lu-DOTATATE + SSA vs everolimus			0.13 (0.03 to 0.64)	Very low||,¶,§	0.13 (0.03 to 0.64)	Very low§
177-Lu-DOTATATE + SSA vs everolimus + SSA			0.62 (0.12 to 3.22)	Very low||,§§	0.62 (0.12 to 3.22)	Very low§§
177-Lu-DOTATATE + SSA vs interferon			0.26 (0.06 to 1.22)	Very low|||,¶,§§	0.26 (0.06 to 1.22)	Very low§§

Table 8. Estimates of effects and quality ratings for progression-free survival in gastrointestinal neuroendocrine tumors (GI-NET) *(Continued)*

177-Lu-DOTATATE + SSA vs interferon + SSA			0.32 (0.07 to 1.47)	Very low|||,¶,§§	0.32 (0.07 to 1.47)	Very low§§
177-Lu-DOTATATE + SSA vs placebo			0.07 (0.02 to 0.26)	Very low||,¶,§	0.07 (0.02 to 0.26)	Very low§
177-Lu-DOTATATE + SSA vs SSA	0.21 (0.08 to 0.57)	Low**			0.21 (0.08 to 0.57)	Low
177-Lu-DOTATATE + SSA vs surufatinib			0.22 (0.04 to 1.09)	Very low||,¶,§§	0.22 (0.04 to 1.09)	Very low§§
Bevacizumab + SSA vs everolimus			0.32 (0.05 to 2.20)	Very low|||,¶¶,§§	0.32 (0.05 to 2.20)	Very low§§
Bevacizumab + SSA vs everolimus + SSA			1.55 (0.22 to 10.9)	Very low|||,¶¶,§§	1.55 (0.22 to 10.9)	Very low§§
Bevacizumab + SSA vs interferon			0.66 (0.16 to 2.80)	Very low|||,¶¶,§§	0.66 (0.16 to 2.80)	Very low§§
Bevacizumab + SSA vs interferon + SSA	0.79 (0.34 to 1.86)	Very low*,††,‡,§			0.79 (0.34 to 1.86)	Very low§
Bevacizumab + SSA vs placebo			0.18 (0.04 to 0.94)	Very low|||,¶¶,§	0.18 (0.04 to 0.94)	Very low§
Bevacizumab + SSA vs SSA			0.53 (0.12 to 2.24)	Very low|||,¶¶,§§	0.53 (0.12 to 2.24)	Very low§§
Bevacizumab + SSA vs surufatinib			0.55 (0.08 to 3.73)	Very low|||,¶¶,§§	0.55 (0.08 to 3.73)	Very low§§
Everolimus vs everolimus + SSA			4.78 (0.78 to 29.4)	Very low|,¶,§§	4.78 (0.78 to 29.4)	Very low§§
Everolimus vs interferon			2.05 (0.37 to 11.2)	Very low|||,¶,§§	2.05 (0.37 to 11.2)	Very low§§
Everolimus vs interferon + SSA			2.45 (0.44 to 13.6)	Very low|||,¶,§§	2.45 (0.44 to 13.6)	Very low§§
Everolimus vs placebo	0.56 (0.21 to 1.49)	Low*,§			0.56 (0.21 to 1.49)	Low§
Everolimus vs SSA			1.63 (0.46 to 5.71)	Very low|,¶,§§	1.63 (0.46 to 5.71)	Very low§§
Everolimus vs surufatinib			1.70 (0.42 to 6.78)	Very low|,§§	1.70 (0.42 to 6.78)	Very low§§
Everolimus + SSA vs interferon			0.43 (0.07 to 2.44)	Very low|||,¶,§§	0.43 (0.07 to 2.44)	Very low§§
Everolimus + SSA vs interferon + SSA			0.51 (0.09 to 2.96)	Very low|||,¶,§§	0.51 (0.09 to 2.96)	Very low§§

Table 8. Estimates of effects and quality ratings for progression-free survival in gastrointestinal neuroendocrine tumors (GI-NET) *(Continued)*

Everolimus + SSA vs placebo			0.12 (0.03 to 0.54)	Very low|,¶,§	0.12 (0.03 to 0.54)	Very low§
Everolimus + SSA vs SSA	0.34 (0.09 to 1.26)	Very low‡,§§			0.34 (0.09 to 1.26)	Very low§§
Everolimus + SSA vs surufatinib			0.35 (0.06 to 2.18)	Very low|,¶,§§	0.35 (0.06 to 2.18)	Very low§§
Interferon vs interferon + SSA	1.20 (0.38 to 3.81)	Very low**,‡,§§			1.20 (0.38 to 3.81)	Very low§§
Interferon vs placebo			0.27 (0.07 to 1.10)	Very low|||,¶,§§	0.27 (0.07 to 1.10)	Very low§§
Interferon vs SSA	0.80 (0.25 to 2.51)	Very low**,‡,§§			0.80 (0.25 to 2.51)	Very low§§
Interferon vs surufatinib			0.83 (0.15 to 4.55)	Very low|||,¶,§§	0.83 (0.15 to 4.55)	Very low§§
Interferon + SSA vs placebo			0.23 (0.06 to 0.93)	Very low|||,¶,§	0.23 (0.06 to 0.93)	Very low§
Interferon + SSA vs SSA	0.66 (0.21 to 2.14)	Very low**,‡,§§			0.66 (0.21 to 2.14)	Very low§§
Interferon + SSA vs surufatinib			0.69 (0.12 to 3.85)	Very low|||,¶,§§	0.69 (0.12 to 3.85)	Very low§§
Placebo vs SSA	2.90 (1.32 to 6.38)	High			2.90 (1.32 to 6.38)	High
Placebo vs surufatinib	3.03 (1.14 to 8.07)	Moderate‡			3.03 (1.14 to 8.07)	Moderate
SSA vs surufatinib			1.04 (0.30 to 3.66)	Very low|,§§	1.04 (0.30 to 3.66)	Very low§§

The confidence assessment addressed *risk of bias, †inconsistency, ‡indirectness, §imprecision, and #incoherence. Indirect estimates were potentially rated down for intransitivity.
Severe limitations are indicated by two symbols. Contributing direct evidence was of |moderate, ||low or |||very low quality.
Abbreviations: SSA: somatostatin analogues; Lu: Lutetium; CI: confidence interval

Table 9. Overall survival in months according to the treatment

	Placebo	Sunitinib	Everolimus	Everolimus + SSA	Everolimus + bevacizumab + SSA	Interferon + SSA	SSA	Streptozocin	Streptozocin + 5-FU	Streptozocin + doxorubicin	Chlorozotocin	Capecitabine + streptozocin + cisplatin	Capecitabine + streptozocin	Pabenezopanib	Bevacizumab + SSA	177-Lu-DOTATATE	177-Lu-DOTATATE + capecitabine	Interferon + SSA	Etoposide + cisplatin	Irinotecan + cisplatin
Arnold 2005						51	35													
Bergsland 2020	42													41						
Kulke 2016				35	36.7															
Lepage 2020	41.9						not reached													
Meyer 2014												27.5	26.7							
Moertel 1980								16.5	26											
Moertel 1992									16.8	26.4	18									
Pavel 2011				29.2 (23.8 to 35.9)			35.2 (30.0 to 44.7)													
Raymond 2011 (1)	29.1 (16.4 to 36.8)	38.6 (25.6 to 56.4)																		
Rinke 2009	83.7						84.7													
Van Der Zwan 2018																64.6 (39.7 to 89.4)	75.8 (54.3 to 97.2)			
Yao 2011	37.7		44.0																	

Table 9. Overall survival in months according to the treatment *(Continued)*

	(29.1 to 45.8)	(35.6 to 51.8)								
Yao 2017						35.2 (33.1 to 42.8)		47.3 (35.8 to 52.6)		
Zhang 2020									11.3	10.2

Values represent the median survival (95% confidence interval).

Table 10. Changes in quality of life during treatment based on EORTC QLQ-30

	Placebo	SSA	Interferon + SSA	Telotristat	Capecitabine + Strepto-zocin	Capecitabine + Strepto-zocin + Cis-platin	Sunitinib	Surufatinib
Arnold 2005		11.4 ± 18.6	-6.4 ± 18.6					
Caplin 2014	-4.87 ± 3.7	-5.18 ± 3.73						
Kulke 2017 (2)	8.5			21.6				
Meyer 2014					2.2	-3.8		
Raymond 2011 (1)	-2.7						-4.6	
Rinke 2009	-2.1 ± 15.8	0.0 ± 18.5						
Vinik 2016	1.2 ± 2.6	5.3 ± 2.1						
Xu 2020 (ep)	-6.43 ± 2.61							-9.97 ± 1.87
Xu 2020 (p)	-11.2 ± 2.6							-8.8 ± 1.9

Table 11. Number of adverse events according to the treatment

Treatment	Patients, no.	Grade 3 or 4 (total no.)[1]	All grades (total no.)	Sources
177-Lu-DOTATATE + octreotide	111	10	95	Strosberg 2017
Capecitabine + streptozocin	43	33	195	Meyer 2014
Capecitabine + streptozocin + cisplatin	40	67	302	Meyer 2014
Chlorozotocin	51	29	198	Moertel 1992
Dactolisib	31	39	220	Salazar 2018
Doxorubicin + streptozocin	44	29	202	Moertel 1992
Etoposide + cisplatin	33	29	69	Zhang 2020
Everolimus	518	219	2095	Kulke 2017 (1), Salazar 2018, Yao 2011, Yao 2016
Everolimus + SSA	293	149	975	Kulke 2017 (1), Pavel 2011
Hepatic arterial chemoembolisation	12	3	15	Maire 2012
Hepatic arterial embolisation	14	2	12	Maire 2012
Interferon + SSA	33	1	7	Kölby 2003
Irinotecan + cisplatin	33	15	62	Zhang 2020
Placebo	670	107	1300	Caplin 2014, Raymond 2011 (1), Vinik 2016, Xu 2020 (ep), Xu 2020 (p), Yao 2011, Yao 2016
SSA	610	38	389	Caplin 2014, Kölby 2003, Pavel 2011, Strosberg 2017, Vinik 2016, Wolin 2015
Streptozocin + 5-FU	42	86	271	Moertel 1992
Tyrosine kinase inhibitors	331	317	2590	Raymond 2011 (1), Xu 2020 (ep), Xu 2020 (p)

[1]Adverse events were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events: grade 1, mild; grade 2, moderate; grade 3, severe or medically significant; and grade 4, life-threatening.

APPENDICES

Appendix 1. Search strategy for the Cochrane Central Register of Controlled Trials

	([mh "Neuroendocrine Tumors"] or [mh "Adenoma, Acidophil"] or [mh "Adenoma, Basophil"] or [mh "Adenoma, Chromophobe"] or [mh Apudoma] or [mh "Carcinoid Tumor"] or [mh "Malignant Carcinoid Syndrome"] or [mh "Carcinoma, Neuroendocrine"] or [mh "Carcinoma, Medullary"] or [mh "Carcinoma, Merkel Cell"] or [mh Somatostatinoma] or [mh Vipoma] or [mh Neurilemmoma] or [mh Paraganglioma]) and [mh "Gastrointestinal Neoplasms"]) OR (((Gastroenteropancreatic or Gastro-enteric pancreatic or Gastro-entero-pancreatic or pancreas or pancreatic) and (neuroendocrine and (tumor* or tumour* or neoplasm* or carcinoma*))) or GEPNET* or GEP-NET* or GEPNEC* or GEP-NEC*
Therapy search filter	therapy or "diet therapy" or "drug therapy" or radiotherapy or surgery or segmentectomy or resection or debulk* or cryoablat* or cryosurger* or radioablat* or radiofrequency ablat* or radio-frequency ablat* or RFablat* or thermoablat* or Cryosurgery or Hepatectomy or "Liver transplant*" or "local ablat*" or "transarterial embolization" or "transarterial embolisation" or "transarterial chemoembolization" or "transarterial chemoembolisation" or radioembolization or radioembolisation or somatostatin or chemotherapy or chemotherapies or "peptide receptor radiotherapy" or "targeted molecular therapy" or radiopeptide or DOTATOC or DOTATATE or PRRT

Appendix 2. Search strategy for MEDLINE (Ovid)

	("Neuroendocrine Tumors"[Mesh:NoExp] OR "Adenoma, Acidophil"[Mesh] OR "Adenoma, Basophil"[Mesh] OR "Adenoma, Chromophobe"[Mesh] OR "Apudoma"[Mesh] OR "Carcinoid Tumor"[Mesh] OR "Malignant Carcinoid Syndrome"[Mesh] OR "Carcinoma, Neuroendocrine"[Mesh] OR "Carcinoma, Medullary"[Mesh] OR "Carcinoma, Merkel Cell"[Mesh] OR "Somatostatinoma"[Mesh] OR "Vipoma"[Mesh] OR "Neurilemmoma"[Mesh] OR "Paraganglioma"[Mesh]) AND "Gastrointestinal Neoplasms"[Mesh]) OR ("Pancreatic Neoplasms"[Mesh:NoExp] AND neuroendocrine[tiab]) OR "Adenoma, Islet Cell"[Mesh] OR "Insulinoma"[Mesh] OR "Carcinoma, Islet Cell"[Mesh] OR "Gastrinoma"[Mesh] OR "Glucagonoma"[Mesh] OR ((gastroenteropancreatic OR gastro-enteric pancreatic OR gastro-entero-pancreatic OR pancreas OR pancreatic) AND (neuroendocrine AND (tumor OR tumors OR tumour OR tumours OR neoplasm OR neoplasms OR carcinoma OR carcinomas)) OR GEPNET* OR GEP-NET* OR GEPNEC* OR GEP-NEC*
Therapy search filter	therapy[sh] OR "diet therapy"[sh] OR "drug therapy"[sh] OR radiotherapy[sh] OR surgery[sh] OR segmentectomy OR resection OR debulk* OR cryoablat* OR cryosurger* OR radioablat* OR radiofrequency ablat* OR radio-frequency ablat* OR RFablat* OR thermoablat* OR "Cryosurgery"[Mesh] OR "Hepatectomy"[MeSH] OR Liver transplant OR local ablat* OR transarterial embolization OR transarterial embolisation OR transarterial chemoembolization OR transarterial chemoembolisation OR radioembolization OR radioembolisation OR somatostatin OR chemotherapy OR chemotherapies OR peptide receptor radiotherapy OR targeted molecular therapy OR radiopeptide OR DOTATOC OR DOTATATE OR PRRT
Study design filter	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR "drug therapy"[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT ("animals"[mh] NOT ("humans"[mh] AND "animals"[mh])

Appendix 3. Search strategy for Embase.com

	(('neuroendocrine tumor'/de OR 'gastroenteropancreatic neuroendocrine tumor'/de OR (adenoma NEAR/3 acidophil*):ti,ab OR (adenoma NEAR/3 basophil):ti,ab OR 'chromophobe adenoma'/de OR 'apudoma'/de OR 'carcinoid'/de OR 'carcinoid syndrome'/de OR (carcinoma NEAR/3 neuroendocrine):ti,ab OR 'medullary carcinoma'/de OR 'merkel cell carcinoma'/de OR 'somatostatinoma'/de OR 'vipoma'/de OR 'neurilemoma'/de OR 'paraganglioma'/de) **AND** ('gastrointestinal tumor'/de OR 'gastrointestinal stromal tumor'/de OR 'intestine tumor'/exp OR 'pancreas tumor'/exp OR 'stomach tumor'/exp)) or ('pancreas islet cell tumor'/de OR 'glucagonoma'/de OR 'insulinoma'/de OR 'pancreas islet cell carcinoma'/de OR 'gastrinoma'/de) OR (((gastroenteropancreatic OR 'gastro-enteric pancreatic' OR 'gastro-entero-pancreatic' OR pancreas OR pancreatic) AND (neuroendocrine AND (tumor* OR tumour* OR neoplasm* OR carcinoma*))) OR GEPNET OR 'GEP-NET*' OR GEPNEC* OR GEP-NEC*)
Therapy search filter	('disease management':lnk OR 'drug therapy':lnk OR 'surgery':lnk OR 'therapy':lnk OR 'radiotherapy':lnk) OR segmentectomy OR resection OR debulk* OR cryoablat* OR cryosurger* OR radioablat* OR 'radiofrequency ablat*' OR 'radio-frequency ablat*' OR RFablat* OR thermoablat* OR 'cryosurgery'/de OR 'liver resection'/exp OR 'liver transplant' OR 'local ablat*' OR 'transarterial embolization' OR 'transarterial embolisation' OR 'transarterial chemoembolization' OR 'transarterial chemoembolisation' OR radioembolization OR radioembolisation OR somatostatin OR chemotherapy OR chemotherapies OR 'peptide receptor radiotherapy' OR 'targeted molecular therapy' OR radiopeptide or DOTATOC or DOTATATE or PRRT
Study design filter	((random* OR factorial* OR crossover* OR cross NEXT/1 over* OR placebo* OR doubl* NEXT/1 blind* OR singl* NEXT/1 blind* OR assign* OR allocat* OR volunteer*):de,ab,ti OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp) NOT ('animal'/exp NOT 'human'/exp)

HISTORY

Protocol first published: Issue 8, 2020

CONTRIBUTIONS OF AUTHORS

- Designing and writing the protocol: MAW, LB, MB and RMK
- Co-ordinating the protocol: RMK
- Designing the search strategies: MAW and RMK
- Title and abstract screening: MAW, AK, CAS, ERC, PR, RMK
- Full-text screening: MAW, AK, CAS, ERC, PR, RMK
- Data extraction: AK, CAS, ERC, PR, RMK
- Analysing data: CN, LB, RMK
- Risk of bias: CN, MS, AK, CAS, ERC, PR, RMK
- GRADE assessment: LB

All authors approved the final version of the protocol and the final manuscript.

DECLARATIONS OF INTEREST

Martin Alexander Walter: None known.
Marko Spanjol: None known.
Cédric Nesti: Meeting honoraria from IPSEN.
Attila Kollár: Advisory board and meeting honoraria from IPSEN.
Lukas Bütikofer: Affiliation with CTU Bern, University of Bern, which has a staff policy of not accepting honoraria or consultancy fees. However, CTU Bern is involved in design, conduct, or analysis of clinical studies funded by not-for-profit and for-profit organizations. In particular, pharmaceutical and medical device companies provide direct funding to some of these studies. For an up-to-date list of CTU Bern's conflicts of interest see http://www.ctu.unibe.ch/research/declaration_of_interest/index_eng.html.
Viktoria L Gloy: None known.
Rebecca Anne Dumont: None known.
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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are no differences between protocol and review.

INDEX TERMS

Medical Subject Headings (MeSH)

Indoles; Network Meta-Analysis; *Pancreatic Neoplasms [drug therapy]; Positron-Emission Tomography; Pyrimidines; Radionuclide Imaging; *Sulfonamides

MeSH check words

Humans