Supplementary Online Content

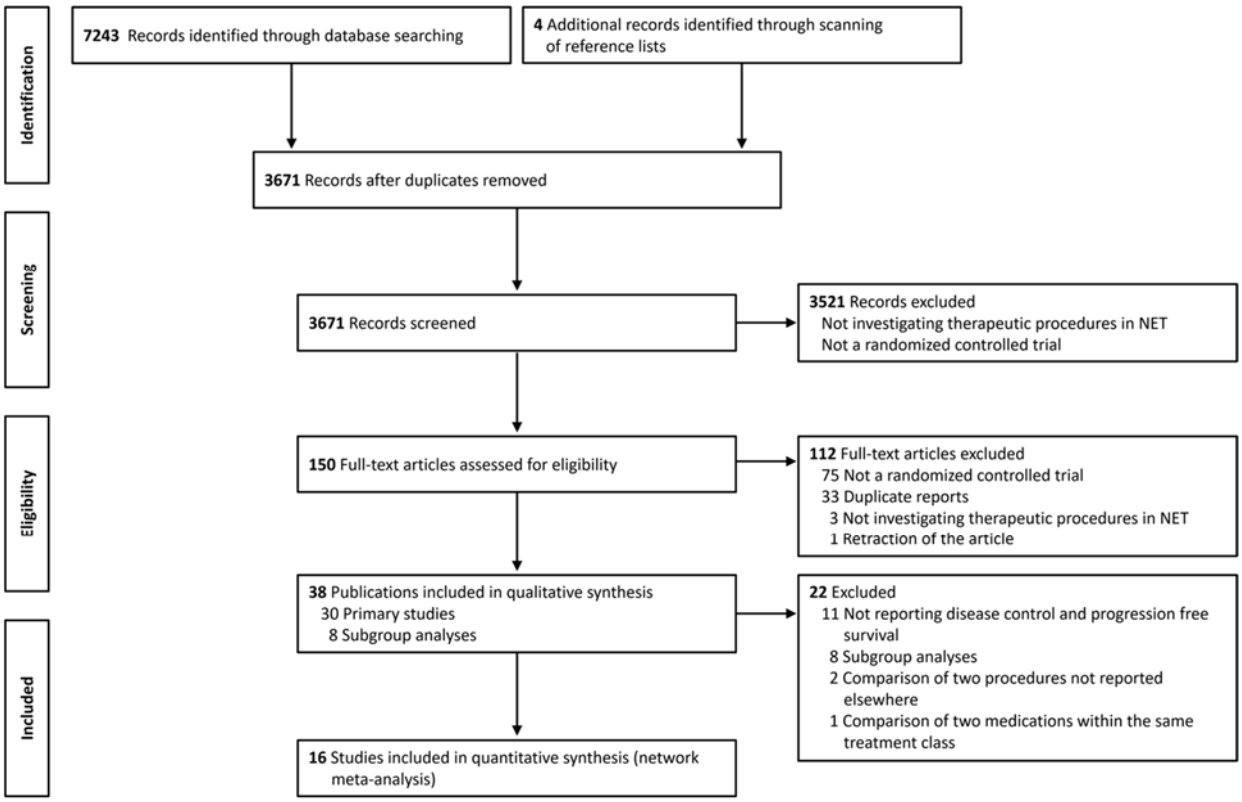
Kaderli RM, Spanjol M, Kollár A, et al. Therapeutic options for neuroendocrine tumors: a systematic review and network meta-analysis. *JAMA Oncol*. Published online February 14, 2019. doi:10.1001/jamaoncol.2018.6720

This supplementary material has been provided by the authors to give readers additional information about their work.

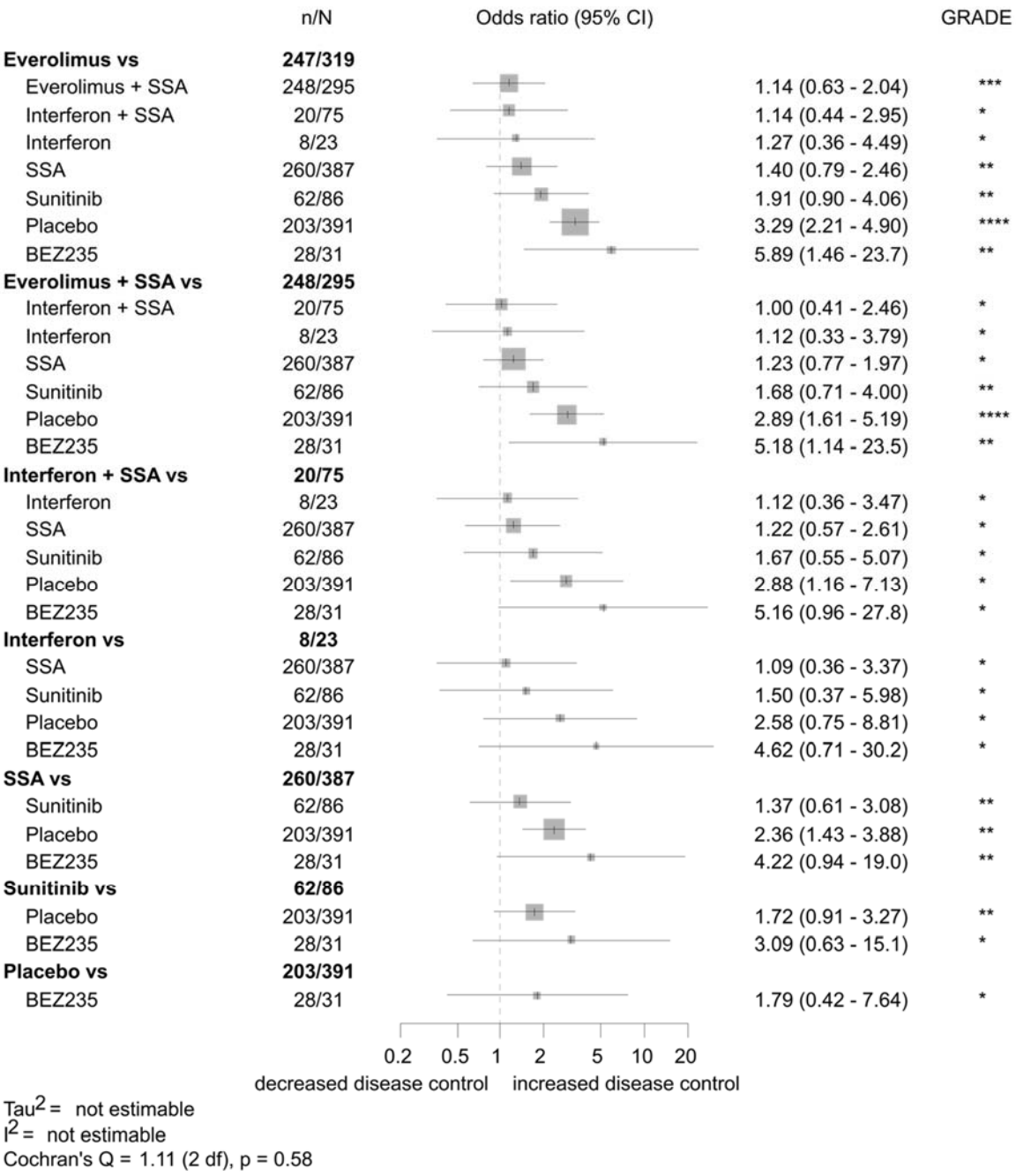
eMethods. Detailed Methods*

We assessed the risk of bias for all included RCTs with the *Cochrane Risk of Bias Tool* [1], which utilizes the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selectivity of reporting, and other bias, including baseline imbalance, protocol deviations, and inappropriate influence of funders. We judged each domain as low, high, or unclear risk of bias [1]. Three investigators (RMK, MS, AK) working in duplicate independently assessed all RCTs. Discordances were discussed with a third reviewer (MAW), and resolved by consensus.

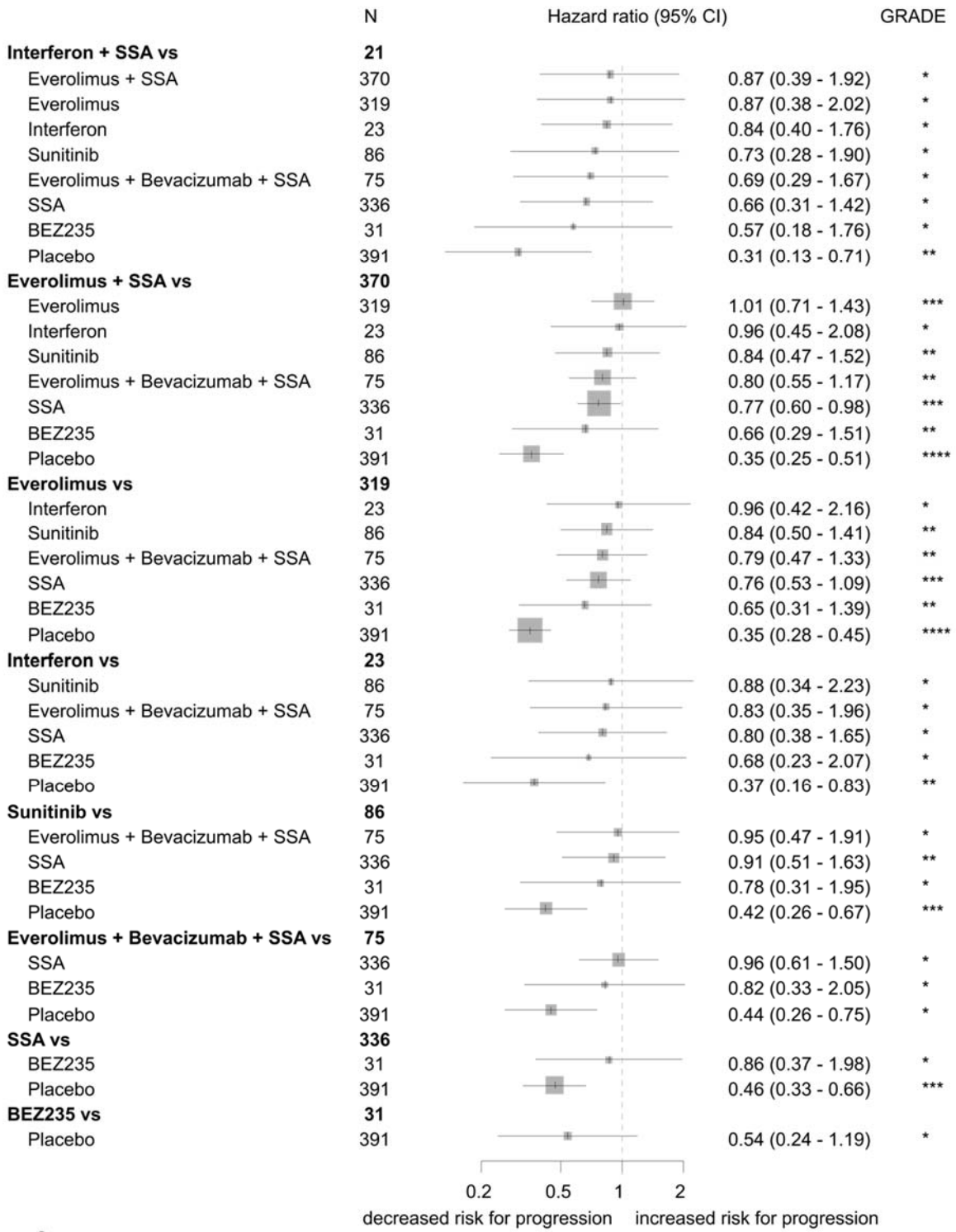
We used the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) approach to assess confidence in estimates of effect (quality of evidence) associated with specific comparisons, including estimates from direct, indirect, and final network meta-analysis [2,3]. Our confidence assessment 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. 95% confidence intervals are wide and include or are close to null effect). Limitations in any of these domains resulted in rating down the certainty of evidence from high to moderate, low, or very low certainty by -1 (serious concern) or -2 (very serious concern). Indirect evidence was based on the most dominant loops (i.e. the shortest path between two treatments) and potentially rated down for intransitivity (differences in study characteristics that may modify treatment effect in the direct comparisons along the path). The final network meta-analysis confidence rating was obtained from the higher of the direct and indirect rating excluding imprecision and was potentially rated down for imprecision and incoherence (difference between direct and indirect estimates).



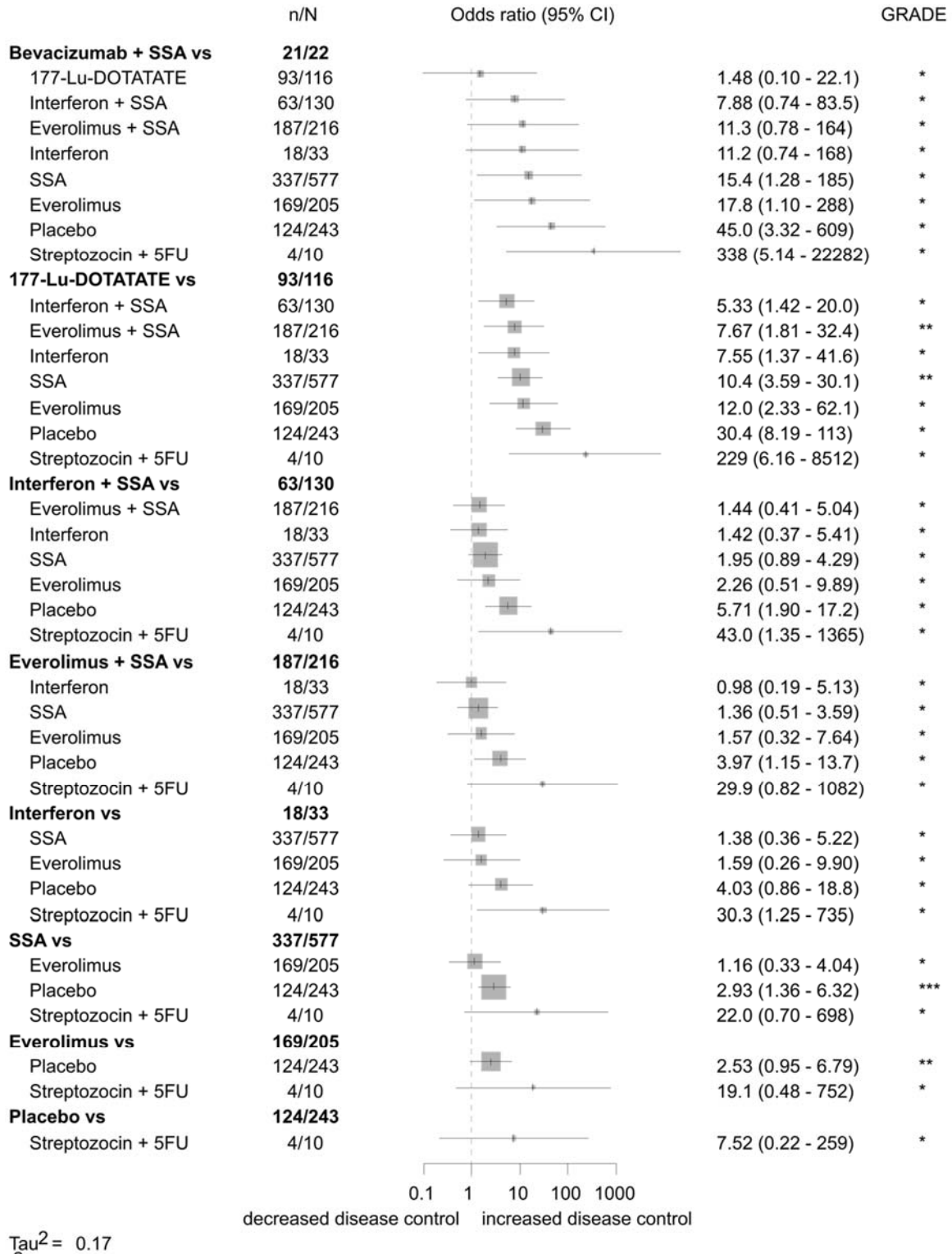
eFigure 1. Flowchart of Search Results



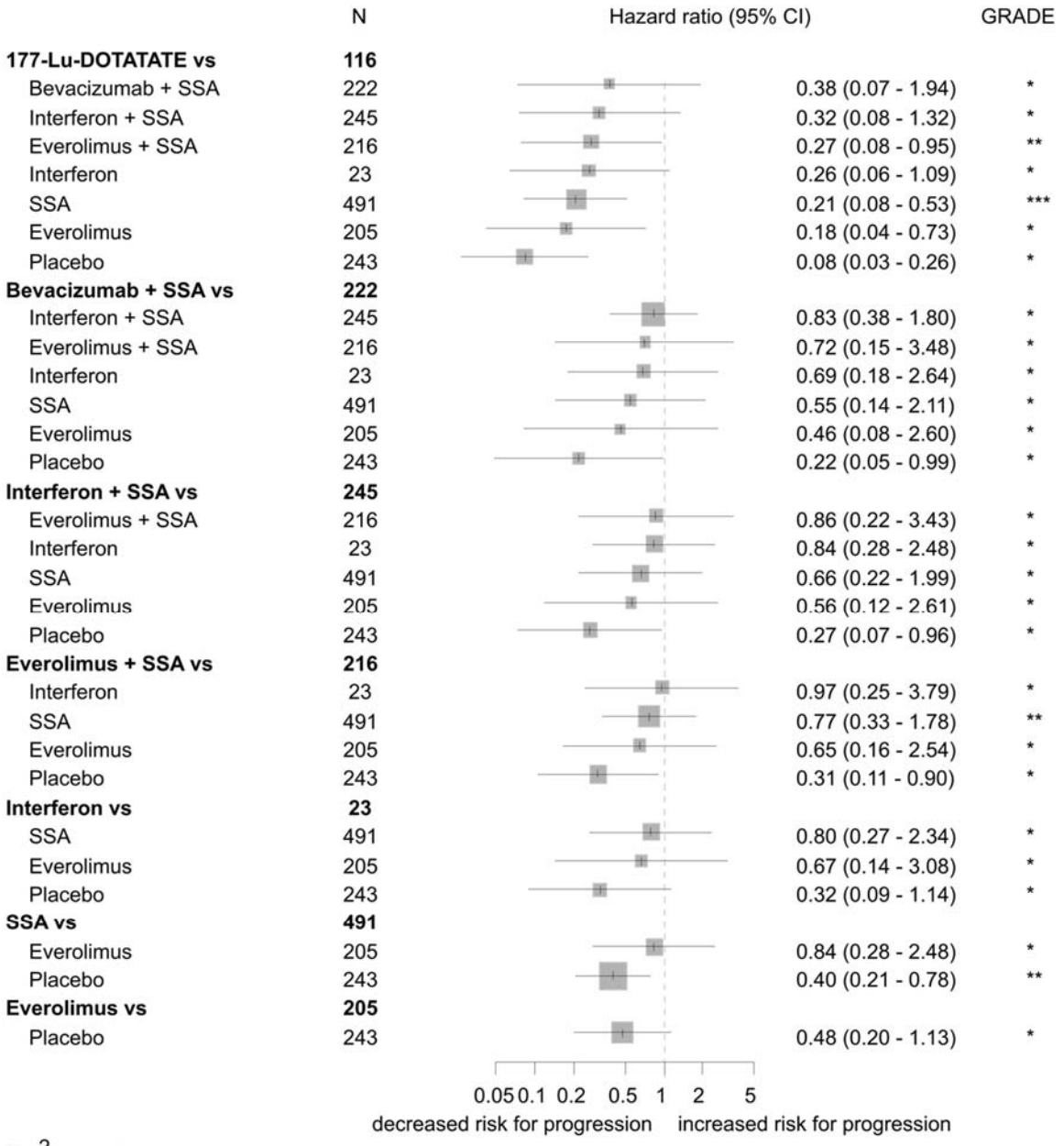
eFigure 2. Disease Control in pNET



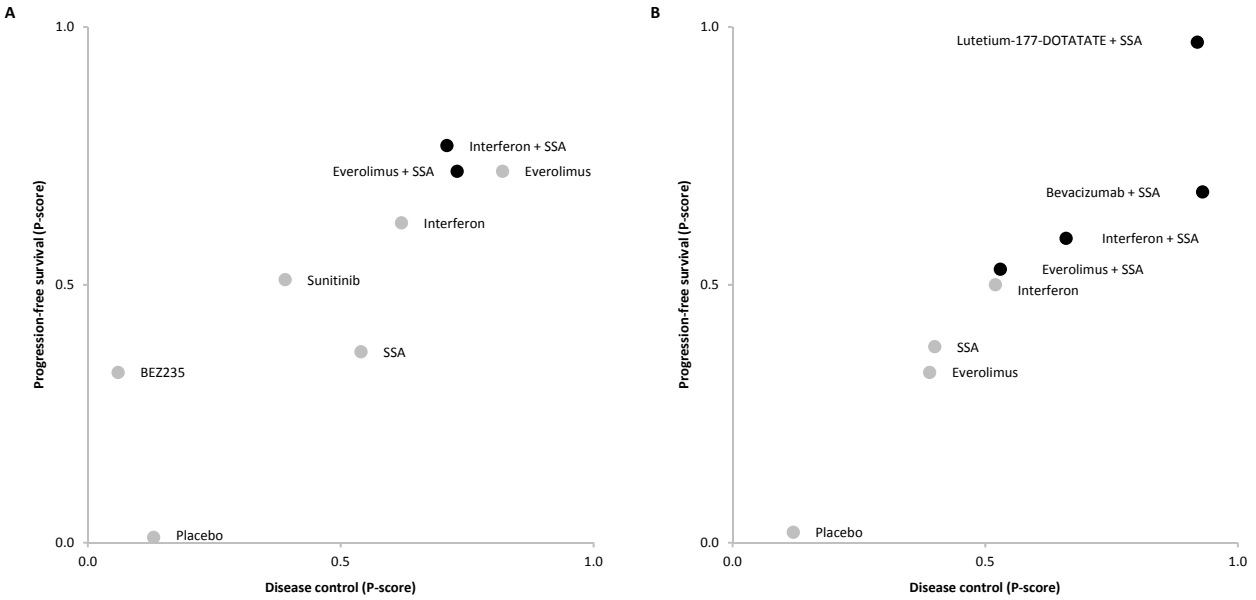
eFigure 3. PFS in pNET



eFigure 4. Disease Control in GI-NET



eFigure 5. PFS in GI-NET



eFigure 6. 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 is 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 5FU in GI-NET are not depicted.

eTABLE 1a. Search Strategy for PubMed	
	("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])

eTABLE 1b. Search strategy for Embase

	((Neuroendocrine tumor/ or (adenoma adj3 acidophil*).ti,ab. or (adenoma adj3 basophil).ti,ab. or Chromophobe adenoma/ or Apudoma/ or Carcinoid/ or Carcinoid syndrome/ or (carcinoma adj3 neuroendocrine).ti,ab. or Medullary carcinoma/ or Merkel cell tumor/ or Somatostatinoma/ or Vipoma/ or Neurilemoma/ or Paraganglioma/) and (Gastrointestinal tumor/ or Gastrointestinal stromal tumor/ or exp Intestine tumor/ or exp Pancreas tumor/ or exp Stomach tumor/)) or (Pancreatic neuroendocrine tumor/ or Pancreas islet cell tumor/ or Glucagonoma/ or Insulinoma/ or Pancreas islet cell carcinoma/ or Gastrinoma/ or Glucagonoma/) 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*).mp.
Therapy Search Filter	(dm or dt or su or th or rt).fs. or segmentectomy.mp. or resection.mp. or debulk*.mp. or cryoablat*.mp. or cryosurger*.mp. or radioablat*.mp. or radiofrequency ablat*.mp. or radio-frequency ablat*.mp. or RFablat*.mp. or thermoablat*.mp. or Cryosurgery/ or Liver resection/ or liver transplant.mp. or local ablat*.mp. or transarterial embolization.mp. or transarterial embolisation.mp. or transarterial chemoembolization.mp. or transarterial chemoembolisation.mp. or radioembolization.mp. or radioembolisation.mp. or somatostatin.mp. or chemotherapy.mp. or chemotherapies.mp. or peptide receptor radiotherapy.mp. or targeted molecular therapy.mp. or radiopeptide.mp. or DOTATOC.mp. or DOTATATE.mp. or PRRT.mp.
Study design Filter	(random* or factorial* or crossover* or (cross adj over*) or placebo* or (doubl* adj blind*) or (singl* adj blind) or assign* or allocat* or volunteer*).mp. or Crossover-procedure/ or Double-blind-procedure/ or Single-blind-procedure/ or Randomized-controlled-trial/

eTABLE 1c. 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

eTable 2. Characteristics of Randomized Controlled Trials Included in the Network Meta-analysis

Trial	Origin	Type of treatment	Median duration of treatment	Median follow-up [months]	Complete follow-up [%]	Sample size calculation	Number of participants randomized	Included in NANETS guidelines	Included in ENETS guidelines	Industry sponsorship
Trials in pNET:										
Raymond (2011) [4], Vinik (2016) [5], Faivre (2017) [6]	11 countries	Sunitinib 37.5 mg/d Placebo	4.6 3.7	n.d. n.d.	99	Yes	86 85	Yes	Yes	Yes
Yao (2011/2016) [7,8]	18 countries	Everolimus 10 mg/d Placebo	8.8 3.7	17 17	62	Yes	207 203	Yes	Yes	Yes
Kulke (2016) [9]	USA	Everolimus 10 mg/d Everolimus 10 mg/d + bevacizumab 10 mg/kg/2w	13 12	n.d. n.d.	100	Yes	75 75	No	No	n.d.
Kulke (2017) [10]	10 countries	Everolimus 10 mg/d + pasireotide LAR 60 mg/28 d Everolimus 10 mg/d	12.0 11.1	n.d. n.d.	100	Yes	79 81	No	Yes	Yes
Salazar (2017) [11]	8 countries	BEZ235 400 mg 2x/d Everolimus 10 mg/d	5.3 9.1	n.d. n.d.	100	No	31 31	No	No	Yes
Trials in GI-NET:										
Kolby (2003) [12]	Sweden	Octreotide 2-3x100-200 µg/d Interferon alfa 3 MU 3-5d/w + octreotide 2-3x100-200 µg/d	n.d. n.d.	33-120 33-120	100	No	35 33	Yes	No	No
Rinke (2009) [13]	Germany	Octreotide LAR 30 mg/28 d Placebo	n.d. n.d.	n.d. n.d.	99	Yes	42 43	Yes	Yes	Yes
Strosberg (2017) [14]	8 countries	^{177}Lu-DOTATATE 7.4 GBq/8 w + octreotide LAR 30 mg/28 d Octreotide LAR 60mg/4 w	n.d. n.d.	14 n.d.	100	Yes	116 113	Yes	Yes	Yes
Trials in mixed populations:										
Oberg (1989) [15]	Sweden	Human leukocyte interferon 6 MU/d Streptozocin 1 g + 5FU 400 mg/m^2	6.6 12	6.6 12	90	Yes	10 10	No	No	n.d.
Faiss (2003) [16]	Germany	Interferon alfa 5 MU 3x/w + lanreotide 3x1 mg/d Interferon alfa 5 MU 3x/w Lanreotide 3x1 mg/d	12 12 12	n.d. n.d. n.d.	79	Yes	29 28 27	Yes	Yes	Yes
Arnold (2005) [17]	Germany	Interferon alfa 4.5 MU 3d/w + octreotide 3x200 µg/d Octreotide 3x200 µg/d	n.d. n.d.	n.d. n.d.	96	Yes	55 54	Yes	Yes	Yes
Yao (2008) [18]	USA	PEG Interferon alfa-2b 0.5 µg/kg/w + octreotide (prestudy dosage) Bevacizumab 15 mg/kg/3w+ octreotide (prestudy dosage)	n.d. n.d.	n.d. n.d.	100	Yes	22 22	Yes	No	Yes
Pavel (2011) [19]	16 countries	Everolimus 10 mg/d + octreotide LAR 30 mg/28 d Placebo + octreotide LAR 30 mg/28 d	9.3 9.2-	n.d. n.d.	100	Yes	216 213	Yes	Yes	Yes
Caplin (2014) [20], Phan (2016) [21]	14 countries	Lanreotide 120 mg/28 d Placebo	24.0 15.0	n.d. n.d.	100	Yes	101 103	Yes	Yes	Yes
Yao (2016) [22], Pavel (2017) [23]	25 countries	Everolimus 10 mg/d Placebo	9.3 4.5	21 21	100	Yes	205 97	Yes	Yes	Yes
Yao (2017) [24]	USA	PEG interferon alfa-2b 5 MU 3x/w + octreotide LAR 20 mg/3 w Bevacizumab 15 mg/kg/3 w + octreotide LAR 20 mg	n.d. n.d.	n.d. n.d.	100	Yes	213 214	Yes	Yes	Yes

Abbreviations: NANETS, North American Neuroendocrine Tumor Society; ENETS, European Neuroendocrine Tumor Society; 5FU, 5-Fluorouracil; n.d., not described; d, day; w, week.

eTable 3. Participants' Characteristics of Randomized Controlled Trials Included in the Network Meta-Analysis								
Trial	**Primary tumor site (% of patients included)**	**Mainly pNET**	**Mainly GI-NET**	**Grading (% of patients included)**	**Metastases [%]**	**Functional tumors [%]**	**Females [%]**	**Median/mean age [years]**
Trials in pNET:								
Raymond (2011) [4], Vinik (2016) [5], Faivre (2017) [6]	Pancreas (100) Pancreas (100)	Yes	No	G1 (8), G2 (34), n.d. (58) G1 (7), G2 (35), n.d. (58)	Any (95), extrahepatic (24) Any (94), extrahepatic (40)	29 25	51 53	Median: 56 Median: 57
Yao (2011/2016) [7,8]	Pancreas (100) pancreas (100)	Yes	No	G1 (82), G2 (17), unknown (1) G1 (84), G2 (15), unknown (1)	Liver (92), LN (33), lung (14), bone (6), other (28) Liver (92), LN (36), lung (15), bone (17), other (28)	n.d. n.d.	47 42	Median: 58 Median: 57
Kulke (2016) [9]	Pancreas (100) Pancreas (100)	Yes	No	n.d. n.d.	n.d. n.d.	n.d. n.d.	n.d. n.d.	n.d. n.d.
Kulke (2017) [10]	Pancreas (100) Pancreas (100)	Yes	No	G1/G2 (100), G3 (0) G1/G2 (97.5), G3 (1.2), unknown (1.2)	n.d. n.d.	n.d. n.d.	52 42	Median: 57 Median: 59
Salazar (2017) [11]	Pancreas (100) Pancreas (100)	Yes	No	n.d. n.d.	n.d n.d.	n.d. n.d.	45 52	Median: 56 Median: 57
Trials in GI-NET:								
Kolby (2003) [12]	GI (100) GI (100)	No	Yes	n.d. n.d.	Liver (100) Liver (100)	100 100	46 67	Mean: 62 Mean: 63
Rinke (2009) [13]	GI (100) GI (100)	No	Yes	G1 (98), G2 (2) G1 (93), G2 (7)	Liver (83), LN (n.d.) Liver (88), LN (n.d.)	41 37	52 47	Median: 64 Median: 61
Strosberg (2017) [14]	GI (100) GI (100)	No	Yes	G1 (66), G2 (35) G1 (72), G2 (28)	Liver (84) , LN (66), lung (9), bone (11), other (34) Liver (83) , LN (58), lung (4), bone (11), other (33)	n.d. n.d.	46 53	Mean: 63 Mean: 64
Trials in mixed populations:								

Oberg (1989) [15]	GI (n.d.), lung (n.d.) GI (n.d.), lung (n.d.)	No	Yes	n.d. n.d.	Liver (100) Liver (100)	100 100	n.d. n.d.	n.d. n.d.
Faiss (2003) [16]	Pancreas (n.d.), GI (n.d.), lung (n.d.), common bile duct (n.d.), unknown (n.d.) Pancreas (n.d.), GI (n.d.), lung (n.d.), common bile duct (n.d.), unknown (n.d.) Pancreas (n.d.), GI (n.d.), lung (n.d.), common bile duct (n.d.), unknown (n.d.)	Yes	Yes	n.d. n.d. n.d.	Liver (89), other (57) Liver (93), other (59) Liver (92), other (44)	29 33 48	36 37 52	Median: 58 Median: 56 Median: 60
Arnold (2005) [17]	Pancreas (41), GI (39), unknown (20) Pancreas (31), GI (51), unknown (18)	Yes	Yes	n.d. n.d.	n.d. (100) n.d. (100)	44 45	44 47	Median: 57 Median: 58
Yao (2008) [18]	GI (68), lung (9), thymus (5), unknown (18) GI (64), lung (9), unknown (27)	No	Yes	n.d. n.d.	Liver (82 Liver (95)	n.d. n.d.	41 50	Mean: 55 Mean: 55
Pavel (2011) [19]	Pancreas (5), GI (61), lung (15), other (19) Pancreas (7), GI (65), lung (5), other (23)	Yes	Yes	G1 (77), G2 (18), G3 (0), unknown (5) G1 (82), G2 (14), G3 (0), unknown (3)	Liver (92), LN (37), lung (30), bone (16), other (48) Liver (92), LN (40), lung (24), bone (11), other (48)	79 81	55 42	Median: 60 Median: 60
Caplin (2014) [20], Phan (2016) [21]	Pancreas (42), GI (44), unknown/other (15) Pancreas (48), GI (42), unknown/other (11)	Yes	Yes	G1 (68), G2 (32) G1 (70), G2 (28), unknown (2)	Liver (84) Liver (83)	2 2	48 48	Mean: 63 Mean: 62
Yao (2016) [22], Pavel (2017) [23]	GI (69), Lung (31), other (0) GI (72), lung (28)	No	Yes	G1 (63), G2 (37), unknown (0) G1 (67), G2 (33)	Liver (80), LN (42), lung (22), bone (21), peritoneum (12) Liver (78), LN (46), lung (21), bone (16), peritoneum (8)	0 0	57 45	Median: 65 Median: 60
Yao (2017) [24]	GI (36), other (64) GI (35), other (64)	No	Yes	G1 (85), G2 (15) G1 (84), G2 (15)	Liver (86), LN (21), bone (17), other (47) Liver (86), LN (24), bone (19), other (47)	59 66	55 49	Median: 61 Median: 61

Abbreviations: GI, gastrointestinal; pNET, pancreatic neuroendocrine tumor; LN, lymph nodes; n.d., not described.

eTable 4. Characteristics of Randomized Controlled Trials Not Included in the Network Meta-analysis

Trial	Origin	Type of treatment	Median duration of treatment [months]	Median follow-up [months]	Complete follow-up [%]	Sample size calculation	Number of participants randomized	Included in NANETS guidelines	Included in ENETS guidelines	Industry sponsor-Ship
Trials in pNET:										
Moertel (1980) [25]	5 countries	Streptozocin 500 mg/m^2 Streptozocin 500 mg/m^2 + 5FU 400 mg/m^2	n.d. n.d.	n.d. n.d.	82	No	42 42	No	Yes	n.d.
Moertel (1992) [26]	4 countries	Streptozocin 500 mg/m^2 + doxorubicin 50 mg/m^2 Streptozocin 500 mg/m^2 + 5FU 400 mg/m^2 Chlorozotocin 150 mg/m^2	n.d. n.d. n.d.	n.d. n.d. n.d.	97	No	38 34 33	Yes	Yes	No
Lange (1992) [27]	USA	Octreotide 3x150 µg/d Placebo	n.d. n.d.	n.d. n.d.	100	No	10 11	No	No	n.d.
* Ito (2012) [28]	Japan	Everolimus 10 mg/d Placebo	15 3	16.1 16.1	100	No	Total: 410	No	No	Yes
* Phan (2015) [29]	14 countries	Lanreotide 120 mg/28 d Placebo	n.d. n.d.	n.d. n.d.	100	No	Total: 204	No	No	Yes
* Lombard-Bohas (2015) [30]	18 countries	Everolimus 10 mg/d+ previous chemotherapy Placebo + previous chemotherapy Everolimus 10 mg/d + no previous chemotherapy Placebo + no previous chemotherapy	9.0 3.4 10.5 6.0	n.d. n.d. n.d. n.d.	100	No	Total: 410	No	No	Yes
Kunz (2018)[31]	USA	Temozolomide 200mg/m^2 Temozolomide 200mg/m^2 + capecitabine 2x750mg/m^2	n.d. n.d.	n.d. n.d.	n.d.	Yes	72 72	No	No	No
Trials in GI-NET:										
Saslow (1998) [32]	USA	Placebo, alosetron 2x0.1 mg/d Placebo, alosetron 2x0.5 mg/d Placebo, alosetron 2x2.0 mg/d	1 1 1	1 1 1	92	No	8 9 9	No	No	Yes
Sakata (2006) [33]	Japan	Ligation device Conventional resection	n.d. n.d.	n.d. n.d.	100	No	8 7	No	No	n.d.
Maire (2012) [34]	France	Chemoembolization: doxorubicin 50 mg/m^2 Hepatic arterial embolization: gelatin sponge particle	n.d. n.d.	17.2 15.4	100	Yes	12 14	Yes	Yes	Yes

* Castellano (2013) [35]	17 countries	Everolimus 10 mg/d + octreotide LAR 30 mg/28 d Placebo +octreotide LAR 30 mg/28 d	8.8 7.0	n.d. n.d.	100	No	Total: 429	No	Yes	Yes
* Dasari (2015) [36]	14 countries	Lanreotide 120 mg/28 d Placebo	n.d. n.d.	n.d. n.d.	100	No	Total: 204	No	No	Yes
Trials in mixed populations:										
Oberg (1989) [37]	Sweden	Octreotide 2x50 µg/d Placebo	12 h 12 h	36 h 36 h	100	No	20 20	No	No	Yes
Jacobsen (1995) [38]	Norway	Octreotide 2x100 µg/d Placebo	1 1	1 1	82	Yes	11 11	No	No	n.d.
O'Toole (2000) [39]	France	Octreotide 2-3x200 µg/d, lanreotide30 mg/10 d Lanreotide 30 mg/10 d, octreotide 2-3x200 µg/d	2 2	2 2	85	No	16 17	Yes	Yes	n.d.
Meyer (2014) [40], Meyer (2016) [41]	UK	Capecitabine 2x625 mg/m^2+ streptozocin 1 g/m^2 + cisplatin 70 mg/m^2 Capecitabine 2x625 mg/m^2+ streptozocin 1 g/m^2	n.d. n.d.	41 41	100	Yes	42 44	No	Yes	No
Wolin (2015) [42]	15 countries	Pasireotide LAR 60 mg/28 d Octreotide LAR 40 mg/28 d	n.d. n.d.	n.d. n.d.	63	Yes	53 57	No	Yes	Yes
Vinik (2016) [43]	12 countries	Lanreotide 120 mg/28 d Placebo	n.d. n.d.	n.d. n.d.	100	Yes	59 56	Yes	No	Yes
Kulke (2017) [44]	12 countries	Telotristat ethyl 3x500 mg/d Telotristat ethyl 3x250 mg/d Placebo	n.d. n.d. n.d.	n.d. n.d. n.d.	99	No	46 45 45	Yes	Yes	Yes
* Phan (2015) [45]	14 countries	Lanreotide 120 mg/28 d (age < 65 y) Lanreotide 120 mg/28 d (age > 65 y) Placebo (age < 65 y) Placebo (age > 65 y)	n.d. n.d. n.d. n.d.	n.d. n.d. n.d. n.d.	100	No	Total: 204	No	No	Yes
* Fisher (2015/2016) [46,47], Anselmo (2016) [48]	12 countries	Lanreotide 120 mg/28 d + previous octreotide use Placebo + previous octreotide use	n.d. n.d.	n.d. n.d.	100	No	Total: 115	No	No	Yes
* Wolin (2016) [48]	14 countries	Lanreotide 120 mg/28 d (BMI 18.5 - <25.0) Placebo (BMI 18.5 - <25.0) Lanreotide 120 mg/28 d (BMI 25.0 - 30.0) Placebo (BMI 25.0 - 30.0) Lanreotide 120 mg/28 d (BMI ≥30) Placebo (BMI ≥30)	n.d. n.d. n.d. n.d. n.d. n.d.	n.d. n.d. n.d. n.d. n.d. n.d.	90	No	Total: 204	No	No	Yes

*Abbreviations: * Subgroup-analysis of randomized controlled trial, ENETS, NANETS, North American Neuroendocrine Tumor Society; European Neuroendocrine Tumor Society; 5FU, 5-Fluorouracil; n.d, not described; d, day; w, week; BMI, body mass index [kg/m^2].*

eTable 5. Participants' Characteristics of Randomized Controlled Trials Not Included in the Network Meta-analysis

Trial	Primary tumor site (% of patients included)	Mainly pNET	Mainly GI-NET	Grading (% of patients included)	Metastases [%] treatment	Functional tumors [%]	Females [%]	Median/mean age [years]
Trials in pNET:								
Moertel (1980) [25]	Pancreas (100) Pancreas (100)	Yes	No	n.d. n.d.	n.d. n.d.	52 45	57 45	Mean: 52 Mean: 54
Moertel (1992) [26]	Pancreas (100) Pancreas (100) Pancreas (100)	Yes	No	n.d. n.d. n.d.	n.d. n.d. n.d.	47 44 52	53 41 61	Median: 53 Median: 51 Median: 57
Lange (1992) [27]	Pancreas (100) Pancreas (100)	Yes	No	n.d. n.d.	n.d. n.d.	100 100	70 27	Median: 47 Median: 46
* Ito (2012) [28]	Pancreas (100) Pancreas (100)	Yes	No	G1 (100) G1 (94), G2 (6)	n.d. n.d.	n.d. n.d.	44 53	Median: 45 Median: 53
* Phan (2015) [29]	Pancreas (100) Pancreas (100)	Yes	No	n.d. n.d.	n.d. n.d.	n.d. n.d.	n.d. n.d.	Mean: 64 Mean: 64
* Lombard-Bohas (2015) [30]	Pancreas (100) Pancreas (100) Pancreas (100) Pancreas (100)	Yes	No	n.d. n.d. n.d. n.d.	n.d. n.d. n.d. n.d.	n.d. n.d. n.d. n.d.	n.d. n.d. n.d. n.d.	n.d. n.d. n.d. n.d.
Kunz (2018) [31]	Pancreas (100) Pancreas (100)	Yes	No	n.d. n.d.	n.d. n.d.	n.d. n.d.	n.d. n.d.	n.d. n.d.
Trials in GI-NET:								
Saslow (1998) [32]	GI (100) GI (100) GI (100)	No	Yes	n.d. n.d. n.d.	n.d. (100) n.d. (100) n.d. (100)	100 100 100	38 56 22	Mean: 65 Mean: 65 Mean: 71
Sakata (2006) [33]	GI (100) GI (100)	No	Yes	n.d. n.d.	n.d. n.d.	0 0	38 43	Mean: 63 Mean: 60
Maire (2012) [34]	GI (100) GI (100)	No	Yes	n.d. n.d.	Liver (100) Liver (100)	67 79	42 36	Median: 65 Median: 56

* Castellano (2013) [35]	GI (100) GI (100)	No	Yes	G1 (74), G2 (11), unknown (16) G1 (60), G2 (40)	n.d. n.d.	84 95	58 40	n.d. n.d.
* Dasari (2015) [36]	GI (100) GI (100)	No	Yes	n.d. n.d.	n.d. n.d.	0 0	n.d. n.d.	n.d. n.d.
Trials in mixed populations:								
Oberg (1989) [37]	GI (100) GI (100)	No	Yes	n.d. n.d.	Liver (100) Liver (100)	100 100	50 50	Median: 66 Median: 66
Jacobsen (1995) [38]	Pancreas (18), GI (82) Pancreas (18), GI (82)	Yes	Yes	n.d. n.d.	Liver (100) Liver (100)	100 100	55 55	Mean: 57 Mean: 57
O'Toole (2000) [39]	GI (63), lung (19), unknown (19) Pancreas (6), GI (76), other (18)	Yes	Yes	n.d. n.d.	n.d. (100) n.d. (100)	100 100	50 53	Mean: 63 Mean: 64
Meyer (2014) [40], Meyer (2016) [41]	Pancreas (50), GI (19), unknown (31) Pancreas (46), GI (21), unknown (34)	Yes	Yes	G1 (17), G2 (50), G3 (17), unknown (17) G1 (11), G2 (50), G3 (16), unknown (23)	Regional (14), distant (86) Regional (5), distant (96)	43 30	45 39	Median: 59 Median: 57
Wolin (2015) [42]	Pancreas (2), GI (83), other (15) Pancreas (2), GI (84), lung (2), other (12)	Yes	Yes	G1 (77), G2 (4), unknown (19) G1 (84), G2 (2), unknown (14)	n.d. (87) n.d. (83)	100 100	45 40	Median: 61 Median: 63
Vinik (2016) [43]	n.d. n.d.	n.d.	n.d.	n.d. n.d.	Liver (100) Liver (100)	100 100	54 63	Mean: 58 Mean: 59
Kulke (2017) [44]	n.d. n.d. n.d.	n.d.	n.d.	n.d. n.d. n.d.	n.d. (100) n.d. (100) n.d. (100)	100 100 100	44 53 47	Mean: 65 Mean: 62 Mean: 63
* Phan (2015) [45]	n.d. n.d. n.d. n.d.	Yes	Yes	n.d. n.d. n.d. n.d.	n.d. n.d. n.d. n.d.	n.d. n.d. n.d. n.d.	n.d. n.d. n.d. n.d.	n.d. n.d. n.d. n.d.
* Fisher (2015/2016) [46,47], Anselmo (2016) [48]	n.d. n.d.	n.d.	n.d.	n.d. n.d.	Liver (100) Liver (100)	100 100	n.d. n.d.	n.d. n.d.
* Wolin (2016) [48]	n.d. n.d. n.d. n.d. n.d. n.d.	Yes	Yes	n.d. n.d. n.d. n.d. n.d. n.d.	n.d. n.d. n.d. n.d. n.d. n.d.	n.d. n.d. n.d. n.d. n.d. n.d.	n.d. n.d. n.d. n.d. n.d. n.d.	n.d. n.d. n.d. n.d. n.d. n.d.

*Abbreviations: * Subgroup-analysis of randomized controlled trial; GI, gastrointestinal; pNET, pancreatic neuroendocrine tumor; LN, lymph nodes; n.d., not described; BMI, body mass index [kg/m^2].*

eTable 6. Risk of Bias Summary: Authors' Judgments About Each Risk of bias item for Each Included Study							
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Raymond (2011), [4] Vinik (2016) [5], Faivre (2017) [6]	?	?	-	-	?	-	?
Yao (2011/2016) [7,8]	-	-	-	-	-	-	?
Kulke (2016) [9]	?	?	?	?	-	-	?
Kulke (2017) [10]	?	?	?	?	-	-	-
Salazar (2017) [11]	?	?	?	?	-	-	?
Kolby (2003) [12]	?	?	?	?	-	-	?
Rinke (2009) [13]	-	-	-	-	-	-	-
Strosberg (2017) [14]	-	-	+	+	-	-	?
Oberg (1989) [15]	+	?	?	?	-	-	?
Faiss (2003) [16]	-	-	+	+	-	-	-
Arnold (2005) [17]	-	-	?	?	-	-	-
Yao (2008) [18]	?	?	+	+	-	-	-
Pavel (2011) [19]	?	-	-	-	-	-	?
Caplin (2014) [20], Phan (2016) [21]	-	-	-	-	-	-	?
Yao (2016) [22], Pavel (2017) [23]	-	-	-	-	-	-	-
Yao (2017) [24]	-	-	+	+	-	-	?
Moertel (1980) [25]	?	?	?	?	?	-	?
Moertel (1992) [26]	?	?	?	?	+	-	?
Lange (1992) [27]	?	?	-	-	-	-	?
Ito (2012) [28]	-	-	-	-	-	-	?
Phan (2015) [29]	-	-	-	-	-	-	?
Lombard-Bohas (2015) [30]	-	-	-	-	-	-	?
Kunz (2018)[31]	?	?	?	?	?	-	?
Saslow (1998) [32]	?	?	-	-	?	+	?
Sakata (2006) [33]	-	?	?	?	-	+	?
Maire (2012) [34]	-	-	+	+	-	+	?
Castellano (2013) [35]	?	-	-	-	-	-	?
Dasari (2015) [36]	-	-	-	-	-	+	?
Oberg (1989) [37]	?	?	-	-	-	-	?
Jacobsen (1995) [38]	?	?	-	-	-	-	?

O'Toole (2000) [39]	?	?	+	+	?	+	?
Meyer (2014) [40], Meyer (2016) [41]	-	?	?	?	-	+	-
Wolin (2015) [42]	-	-	-	-	-	-	?
Vinik (2016) [43]	-	-	-	?	-	-	-
Kulke (2017) [44]	?	?	-	-	-	-	?
Phan (2015) [45]	-	-	-	-	-	-	?
Fisher (2015/2016) [46,47], Anselmo (2016) [48]	-	-	-	?	-	-	-
Wolin (2016) [48]	-	-	-	-	-	-	?

Each domain was judged as 'low risk of bias' (-), 'high risk of bias' (+), or 'unclear risk of bias' (?) in each study according to the Cochrane Handbook for Systematic Reviews of Interventions [1].

eTable 7. Estimates of Effects and Quality Ratings for Disease Control in Pancreatic Neuroendocrine Tumors (pNET)						
	Direct evidence		Indirect evidence		Network meta-analysis	
Comparison	**OR (95% CI)**	**Quality of evidence**	**OR (95% CI)**	**Quality of evidence**	**OR (95% CI)**	**Quality of evidence**
BEZ235 vs everolimus	0.17 (0.04 - 0.68)	Low[*§]			0.17 (0.04 - 0.68)	Low[§]
BEZ235 vs everolimus + SSA			0.19 (0.04 - 0.87)	Low[‖§]	0.19 (0.04 - 0.87)	Low[§]
BEZ235 vs interferon + SSA			0.19 (0.04 - 1.04)	Very low[‖¶§]	0.19 (0.04 - 1.04)	Very low[§]
BEZ235 vs interferon			0.22 (0.03 - 1.41)	Very low[‖§§]	0.22 (0.03 - 1.41)	Very low[§§]
BEZ235 vs SSA			0.24 (0.05 - 1.07)	Low[‖§]	0.24 (0.05 - 1.07)	Low[§]
BEZ235 vs sunitinib			0.32 (0.07 - 1.58)	Very low[‖§§]	0.32 (0.07 - 1.58)	Very low[§§]
BEZ235 vs placebo			0.56 (0.13 - 2.37)	Very low[‖§§]	0.56 (0.13 - 2.37)	Very low[§§]
Everolimus vs everolimus + SSA	1.41 (0.65 - 3.08)	Moderate[§]	0.86 (0.35 - 2.08)	Very low[‖¶§]	1.14 (0.63 - 2.04)	Moderate[§]
Everolimus vs interferon + SSA			1.14 (0.44 - 2.95)	Very low[‖¶§§]	1.14 (0.44 - 2.95)	Very low[§§]
Everolimus vs interferon			1.27 (0.36 - 4.49)	Very low[‖§§]	1.27 (0.36 - 4.49)	Very low[§§]
Everolimus vs SSA			1.40 (0.79 - 2.46)	Low[‖§]	1.40 (0.79 - 2.46)	Low[§]
Everolimus vs sunitinib			1.91 (0.90 - 4.06)	Low[‖§]	1.91 (0.90 - 4.06)	Low[§]
Everolimus vs placebo	3.08 (2.01 - 4.72)	High	5.06 (1.68 - 15.2)	Very low[‖¶¶§]	3.29 (2.21 - 4.90)	High
Everolimus + SSA vs interferon + SSA			1.00 (0.41 - 2.46)	Very low[‖¶§§]	1.00 (0.41 - 2.46)	Very low[§§]
Everolimus + SSA vs interferon			1.12 (0.33 - 3.79)	Very low[‖¶§§]	1.12 (0.33 - 3.79)	Very low[§§]
Everolimus + SSA vs SSA	1.36 (0.80 - 2.30)	Low[‡§]	0.83 (0.29 - 2.37)	Very low[‖§§]	1.23 (0.77 - 1.97)	Very low[#§]
Everolimus + SSA vs sunitinib			1.68 (0.71 - 4.00)	Low[‖§]	1.68 (0.71 - 4.00)	Low[§]
Everolimus + SSA vs placebo			2.89 (1.61 - 5.19)	High	2.89 (1.61 - 5.19)	High
Interferon vs interferon + SSA	1.07 (0.31 - 3.72)	Very low[*‡§§]	0.39 (0.03 - 5.94)	Very low[‖¶§§]	0.90 (0.29 - 2.79)	Very low[#§§]

Interferon vs SSA	0.93 (0.28 - 3.16)	Very low[*‡§§]	2.63 (0.15 - 46.2)	Very low[‖¶§§]	1.09 (0.36 - 3.37)	Very low[#§§]
Interferon vs sunitinib			1.50 (0.37 - 5.98)	Very low[‖§§]	1.50 (0.37 - 5.98)	Very low[§§]
Interferon vs placebo			2.58 (0.75 - 8.81)	Very low[‖§§]	2.58 (0.75 - 8.81)	Very low[§§]
Interferon + SSA vs SSA	1.22 (0.57 - 2.61)	Very low[*‡§]			1.22 (0.57 - 2.61)	Very low[§]
Interferon + SSA vs sunitinib			1.67 (0.55 - 5.07)	Very low[‖¶§§]	1.67 (0.55 - 5.07)	Very low[§§]
Interferon + SSA vs placebo			2.88 (1.16 - 7.13)	Very low[‖¶§]	2.88 (1.16 - 7.13)	Very low[§]
Placebo vs SSA	0.38 (0.21 - 0.67)	Moderate[‡]	0.62 (0.22 - 1.75)	Very low[‖¶§§]	0.42 (0.26 - 0.70)	Low[#]
Placebo vs sunitinib	0.58 (0.31 - 1.10)	Moderate[*]			0.58 (0.31 - 1.10)	Low[§]
SSA vs sunitinib			1.37 (0.61 - 3.08)	Low[‖§]	1.37 (0.61 - 3.08)	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. Abbreviation: SSA, somatostatin analogues.

eTable 8. Estimates of Effects and Quality Ratings for Progression-Free Survival in pNET						
	Direct evidence		Indirect evidence		Network meta-analysis	
Comparison	**HR (95% CI)**	**Quality of evidence**	**HR (95% CI)**	**Quality of evidence**	**HR (95% CI)**	**Quality of evidence**
BEZ235 vs interferon + SSA			1.75 (0.57 - 5.41)	Very low‖§§	1.75 (0.57 - 5.41)	Very low§§
BEZ235 vs everolimus + SSA			1.52 (0.66 - 3.49)	Low‖§	1.52 (0.66 - 3.49)	Low§
BEZ235 vs everolimus	1.53 (0.72 - 3.25)	Low*§			1.53 (0.72 - 3.25)	Low§
BEZ235 vs interferon			1.46 (0.48 - 4.44)	Very low‖§§	1.46 (0.48 - 4.44)	Very low§§
BEZ235 vs sunitinib			1.28 (0.51 - 3.21)	Very low‖§§	1.28 (0.51 - 3.21)	Very low§§
BEZ235 vs everolimus + bevacizumab + SSA			1.22 (0.49 - 3.03)	Very low‖§§	1.22 (0.49 - 3.03)	Very low§§
BEZ235 vs SSA			1.16 (0.50 - 2.69)	Very low‖§§	1.16 (0.50 - 2.69)	Very low§§
BEZ235 vs placebo			0.54 (0.24 - 1.19)	Low‖§	0.54 (0.24 - 1.19)	Very low§§
Everolimus vs interferon + SSA			1.14 (0.49 - 2.65)	Very low‖§§	1.14 (0.49 - 2.65)	Very low§§
Everolimus vs everolimus + SSA	1.01 (0.65 - 1.57)	Moderate§	0.97 (0.54 - 1.72)	Low‖¶	0.99 (0.70 - 1.41)	Moderate§
Everolimus vs interferon			0.96 (0.42 - 2.16)	Very low‖§	0.96 (0.42 - 2.16)	Very low§§
Everolimus vs sunitinib			0.84 (0.50 - 1.41)	Low‖§	0.84 (0.50 - 1.41)	Low§
Everolimus vs everolimus + bevacizumab + SSA			0.79 (0.47 - 1.33)	Low‖§	0.79 (0.47 - 1.33)	Low§
Everolimus vs SSA			0.76 (0.53 - 1.09)	Moderate‖	0.76 (0.53 - 1.09)	Moderate
Everolimus vs placebo	0.35 (0.27 - 0.45)	High	0.37 (0.18 - 0.72)	Very low‖¶¶	0.35 (0.28 - 0.45)	High
Everolimus + bevacizumab + SSA vs interferon + SSA			1.44 (0.60 - 3.47)	Very low‖¶¶§§	1.44 (0.60 - 3.47)	Very low§§
Everolimus + bevacizumab + SSA vs everolimus + SSA	1.25 (0.86 - 1.82)	Low*§			1.25 (0.86 - 1.82)	Low§
Everolimus + bevacizumab + SSA vs interferon			1.20 (0.51 - 2.84)	Very low‖¶¶§§	1.20 (0.51 - 2.84)	Very low§§
Everolimus + bevacizumab + SSA vs sunitinib			1.05 (0.52 - 2.13)	Very low‖¶§§	1.05 (0.52 - 2.13)	Very low§§
Everolimus + bevacizumab + SSA vs SSA			0.96 (0.61 - 1.50)	Very low‖¶§	0.96 (0.61 - 1.50)	Very low§
Everolimus + bevacizumab + SSA vs placebo			0.44 (0.26 - 0.75)	Very low‖¶¶	0.44 (0.26 - 0.75)	Very low
Everolimus + SSA vs interferon + SSA			1.15 (0.52 - 2.55)	Very low‖¶§§	1.15 (0.52 - 2.55)	Very low§§
Everolimus + SSA vs interferon			0.96 (0.45 - 2.08)	Very low‖¶§§	0.96 (0.45 - 2.08)	Very low§§
Everolimus + SSA vs sunitinib			0.84 (0.47 - 1.52)	Low‖§	0.84 (0.47 - 1.52)	Low§
Everolimus + SSA vs SSA	0.77 (0.59 - 1.00)	Moderate‡	0.74 (0.37 - 1.45)	Low‖§	0.77 (0.60 - 0.98)	Moderate
Everolimus + SSA vs placebo			0.35 (0.25 - 0.51)	High	0.35 (0.25 - 0.51)	High
Interferon vs interferon + SSA	1.20 (0.57 - 2.52)	Very low*‡§§			1.20 (0.57 - 2.52)	Very low§§
Interferon vs sunitinib			0.88 (0.34 - 2.23)	Very low‖§§	0.88 (0.34 - 2.23)	Very low§§

Interferon vs SSA	0.80 (0.38 - 1.65)	Very low[*‡§§]			0.80 (0.38 - 1.65)	Very low[§§]
Interferon vs placebo			0.37 (0.16 - 0.83)	Very low[‖§]	0.37 (0.16 - 0.83)	Low
Interferon + SSA vs sunitinib			0.73 (0.28 - 1.90)	Very low[‖§§]	0.73 (0.28 - 1.90)	Very low[§§]
Interferon + SSA vs SSA	0.66 (0.31 - 1.42)	Very low[*‡§§]			0.66 (0.31 - 1.42)	Very low[§§]
Interferon + SSA vs placebo			0.31 (0.13 - 0.71)	Low[‖]	0.31 (0.13 - 0.71)	Low
Placebo vs sunitinib	2.38 (1.49 - 3.79)	Moderate[*]			2.38 (1.49 - 3.79)	Moderate
Placebo vs SSA	2.13 (1.36 - 3.32)	Moderate[‡]	2.22 (1.25 - 3.95)	Low[¶]	2.16 (1.52 - 3.07)	Moderate
SSA vs sunitinib			1.10 (0.61 - 1.97)	Low[§]	1.10 (0.61 - 1.97)	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. Abbreviation: SSA, somatostatin analogues.

eTable 9. Estimates of Effects and Quality Ratings for Disease Control in Gastrointestinal Neuroendocrine Tumors (GI-NET)

	Direct evidence		Indirect evidence		Network meta-analysis	
Comparison	**OR (95% CI)**	**Quality of evidence**	**OR (95% CI)**	**Quality of evidence**	**OR (95% CI)**	**Quality of evidence**
Lutetium-177-DOTATATE + SSA vs bevacizumab + SSA			0.68 (0.05 - 10.1)	Very low[‖¶¶§§]	0.68 (0.05 - 10.1)	Very low[§§]
Lutetium-177-DOTATATE + SSA vs interferon + SSA			5.33 (1.42 - 20.0)	Very low[‖¶§]	5.33 (1.42 - 20.0)	Very low[§]
Lutetium-177-DOTATATE + SSA vs everolimus + SSA			7.67 (1.81 - 32.4)	Low[‖§]	7.67 (1.81 - 32.4)	Low[§]
Lutetium-177-DOTATATE + SSA vs interferon			7.55 (1.37 - 41.6)	Very low[‖¶§]	7.55 (1.37 - 41.6)	Very low[§]
Lutetium-177-DOTATATE + SSA vs SSA	10.4 (3.59 - 30.1)	Moderate[*]			10.4 (3.59 - 30.1)	Low[§]
Lutetium-177-DOTATATE + SSA vs everolimus			12.0 (2.33 - 62.1)	Very low[¶§]	12.0 (2.33 - 62.1)	Very low[§]
Lutetium-177-DOTATATE + SSA vs placebo			30.4 (8.19 - 113)	Very low[¶§]	30.4 (8.19 - 113)	Very low[§§]
Lutetium-177-DOTATATE + SSA vs streptozocin + 5FU			229 (6.16 - 8512)	Very low[‖¶¶§§]	229 (6.16 - 8512)	Very low[§§]
Bevacizumab + SSA vs interferon + SSA	7.88 (0.74 - 83.5)	Very low[**‡§§]			7.88 (0.74 - 83.5)	Very low[§§]
Bevacizumab + SSA vs everolimus + SSA			11.3 (0.78 - 164)	Very low[‖¶¶§§]	11.3 (0.78 - 164)	Very low[§§]
Bevacizumab + SSA vs interferon			11.2 (0.74 - 168)	Very low[‖¶¶§§]	11.2 (0.74 - 168)	Very low[§§]
Bevacizumab + SSA vs SSA			15.4 (1.28 - 185)	Very low[‖¶¶§§]	15.4 (1.28 - 185)	Very low[§§]
Bevacizumab + SSA vs everolimus			17.8 (1.10 - 288)	Very low[‖¶¶§§]	17.8 (1.10 - 288)	Very low[§§]
Bevacizumab + SSA vs placebo			45.0 (3.32 - 609)	Very low[‖¶¶§]	45.0 (3.32 - 609)	Very low[§§]
Bevacizumab + SSA vs streptozocin + 5FU			338 (5.14 - 22282)	Very low[‖¶¶§§]	338 (5.14 - 22282)	Very low[§§]
Everolimus vs interferon + SSA			0.44 (0.10 - 1.94)	Very low[‖¶§§]	0.44 (0.10 - 1.94)	Very low[§§]
Everolimus vs everolimus + SSA			0.64 (0.13 - 3.11)	Very low[¶§§]	0.64 (0.13 - 3.11)	Very low[§§]
Everolimus vs interferon			0.63 (0.10 - 3.91)	Very low[‖¶§§]	0.63 (0.10 - 3.91)	Very low[§§]
Everolimus vs SSA			0.87 (0.25 - 3.02)	Very low[¶§§]	0.87 (0.25 - 3.02)	Very low[§§]
Everolimus vs placebo	2.53 (0.95 - 6.79)	Moderate[‡]			2.53 (0.95 - 6.79)	Low[§]
Everolimus vs streptozocin + 5FU			19.1 (0.48 - 752)	Very low[‖¶¶§§]	19.1 (0.48 - 752)	Very low[§§]
Everolimus + SSA vs interferon + SSA			0.69 (0.20 - 2.43)	Very low[‖¶§§]	0.69 (0.20 - 2.43)	Very low[§§]
Everolimus + SSA vs interferon			0.98 (0.19 - 5.13)	Very low[‖¶§§]	0.98 (0.19 - 5.13)	Very low[§§]
Everolimus + SSA vs SSA	1.36 (0.51 - 3.59)	Very low[‡§§]			1.36 (0.51 - 3.59)	Very low[§§]
Everolimus + SSA vs placebo			3.97 (1.15 - 13.7)	Very low[¶§]	3.97 (1.15 - 13.7)	Very low[§]

Everolimus + SSA vs streptozocin + 5FU			29.9 (0.82 - 1082)	Very low[‖¶¶§§]	29.9 (0.82 - 1082)	Very low[§§]
Interferon vs interferon + SSA	1.07 (0.24 - 4.74)	Very low[*‡§§]	0.13 (0.01 - 2.66)	Very low[‖‖¶§§]	0.71 (0.18 - 2.70)	Very low[#§§]
Interferon vs SSA	0.93 (0.21 - 4.06)	Very low[*‡§§]	8.42 (0.35 - 201)	Very low[‖‖¶§§]	1.38 (0.36 - 5.22)	Very low[#§§]
Interferon vs placebo			4.03 (0.86 - 18.8)	Very low[‖¶§§]	4.03 (0.86 - 18.8)	Very low[§§]
Interferon vs streptozocin + 5FU	30.3 (1.25 - 735)	Very low[‡§§]			30.3 (1.25 - 735)	Very low[§§]
Interferon + SSA vs SSA	1.95 (0.89 - 4.29)	Very low[*†‡§]			1.95 (0.89 - 4.29)	Very low[§§]
Interferon + SSA vs placebo			5.71 (1.90 - 17.2)	Very low[‖‖¶§]	5.71 (1.90 - 17.2)	Very low[§]
Interferon + SSA vs streptozocin + 5FU			43.0 (1.35 - 1365)	Very low[‖¶§§]	43.0 (1.35 - 1365)	Very low[§§]
Placebo vs SSA	0.34 (0.16 - 0.74)	Moderate[‡]			0.34 (0.16 - 0.74)	Moderate
Placebo vs streptozocin + 5FU			7.52 (0.22 - 259)	Very low[‖¶¶§§]	7.52 (0.22 - 259)	Very low[§§]
SSA vs streptozocin + 5FU			22.0 (0.70 - 698)	Very low[‖¶§§]	22.0 (0.70 - 698)	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. Abbreviation: SSA, somatostatin analogues; 5FU, 5-Fluorouracil.

eTable 10. Estimates of Effects and Quality Ratings for Progression-Free Survival in GI-NET						
	Direct evidence		Indirect evidence		Network meta-analysis	
Comparison	**HR (95% CI)**	**Quality of evidence**	**HR (95% CI)**	**Quality of evidence**	**HR (95% CI)**	**Quality of evidence**
Lutetium-177-DOTATATE + SSA vs bevacizumab + SSA			0.38 (0.07 - 1.94)	Very low‖¶¶§§	0.38 (0.07 - 1.94)	Very low§§
Lutetium-177-DOTATATE + SSA vs interferon + SSA			0.32 (0.08 - 1.32)	Very low‖¶§§	0.32 (0.08 - 1.32)	Very low§§
Lutetium-177-DOTATATE + SSA vs everolimus + SSA			0.27 (0.08 - 0.95)	Low‖§	0.27 (0.08 - 0.95)	Low§
Lutetium-177-DOTATATE + SSA vs interferon			0.26 (0.06 - 1.09)	Very low‖¶§	0.26 (0.06 - 1.09)	Very low§
Lutetium-177-DOTATATE + SSA vs SSA	0.21 (0.08 - 0.53)	Moderate*			0.21 (0.08 - 0.53)	Moderate
Lutetium-177-DOTATATE + SSA vs everolimus			0.18 (0.04 - 0.73)	Very low‖¶§	0.18 (0.04 - 0.73)	Very low§
Lutetium-177-DOTATATE + SSA vs placebo			0.08 (0.03 - 0.26)	Very low‖¶	0.08 (0.03 - 0.26)	Very low
Bevacizumab + SSA vs interferon + SSA	0.83 (0.38 - 1.80)	Very low**‡§§			0.83 (0.38 - 1.80)	Very low§§
Bevacizumab + SSA vs everolimus + SSA			0.72 (0.15 - 3.48)	Very low‖¶¶§§	0.72 (0.15 - 3.48)	Very low§§
Bevacizumab + SSA vs interferon			0.69 (0.18 - 2.64)	Very low‖¶§§	0.69 (0.18 - 2.64)	Very low§§
Bevacizumab + SSA vs SSA			0.55 (0.14 - 2.11)	Very low‖¶¶§§	0.55 (0.14 - 2.11)	Very low§§
Bevacizumab + SSA vs everolimus			0.46 (0.08 - 2.60)	Very low‖¶¶	0.46 (0.08 - 2.60)	Very low§§
Bevacizumab + SSA vs placebo			0.22 (0.05 - 0.99)	Very low‖¶¶§	0.22 (0.05 - 0.99)	Very low§
Everolimus vs interferon + SSA			1.79 (0.38 - 8.36)	Very low‖¶§§	1.79 (0.38 - 8.36)	Very low§§
Everolimus vs everolimus + SSA			1.55 (0.39 - 6.07)	Very low‖¶§§	1.55 (0.39 - 6.07)	Very low§§
Everolimus vs interferon			1.50 (0.32 - 6.90)	Very low‖¶§§	1.50 (0.32 - 6.90)	Very low§§
Everolimus vs SSA			1.19 (0.40 - 3.51)	Very low‖¶§§	1.19 (0.40 - 3.51)	Very low§§
Everolimus vs placebo	0.48 (0.20 - 1.13)	Low‡§			0.48 (0.20 - 1.13)	Very low§§
Everolimus + SSA vs interferon + SSA			1.16 (0.29 - 4.60)	Very low‖¶§§	1.16 (0.29 - 4.60)	Very low§§
Everolimus + SSA vs interferon			0.97 (0.25 - 3.79)	Very low‖¶§§	0.97 (0.25 - 3.79)	Very low§§
Everolimus + SSA vs SSA	0.77 (0.33 - 1.78)	Low‡§			0.77 (0.33 - 1.78)	Low§
Everolimus + SSA vs placebo			0.31 (0.11 - 0.90)	Very low‖¶§	0.31 (0.11 - 0.90)	Very low§
Interferon vs interferon + SSA	1.20 (0.40 - 3.55)	Very low*‡§§			1.20 (0.40 - 3.55)	Very low§§
Interferon vs SSA	0.80 (0.27 - 2.34)	Very low*‡§§			0.80 (0.27 - 2.34)	Very low§§
Interferon vs placebo			0.32 (0.09 - 1.14)	Very low‖¶§§	0.32 (0.09 - 1.14)	Very low§§
Interferon + SSA vs SSA	0.66 (0.22 - 1.99)	Very low*‡§§			0.66 (0.22 - 1.99)	Very low§§

Interferon + SSA vs placebo			0.27 (0.07 - 0.96)	Very low[‖¶§]	0.27 (0.07 - 0.96)	Very low[§]
Placebo vs SSA	2.48 (1.28 - 4.80)	Low[†‡]			2.48 (1.28 - 4.80)	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. Abbreviation: SSA, somatostatin analogues.

eTable 11. Overall Survival in Months According to the Treatment

Trial	Placebo	Sunitinib	Everolimus	Everolimus + somatostatin analogues	Everolimus + bevacizumab + somatostatin analogues	Interferon + somatostatin analogues	Somatostatin analogues	Streptozocin	Streptozocin + FU	Streptozocin + doxorubicin	Chlorozotocin	Temozolomide	Capecitabine + streptozocin + cisplatin	Capecitabine + streptozocin
Raymond (2011) [4], Vinik (2016) [5], Faivre (2017) [6]	29.1 (16.4-36.8)	38.6 (25.6-6.4)	-	-	-	-	-	-	-	-	-	-	-	-
Yao (2011/2016) [7,8]	37.7 (29.1-45.8)	-	44.0 (35.6-51.8)	-	-	-	-	-	-	-	-	-	-	-
Kulke (2016) [9]	-	-	-	35	36.7	-	-	-	-	-	-	-	-	-
Arnold (2005) [17]	-	-	-	-	-	51	35	-	-	-	-	-	-	-
Moertel (1980) [25]	-	-	-	-	-	-	-	16.4	26	-	-	-	-	-
Moertel (1992) [26]	-	-	-	-	-	-	-	-	16.8	26.4	18	-	-	-
Kunz (2018)[31]	-	-	-	-	-	-	-	-	-	-	-	38	-	-
Meyer (2014) [40], Meyer (2016) [41]	-	-	-	-	-	-	-	-	-	-	-	-	26	27

Values represent the median survival (95% confidence interval).

eTable 12. Changes in Quality of Life During Treatment Based on EORTC QLQ-30

Trial	Somatostatin analogues	Placebo	Interferon + somatostatin analogues	Sunitinib	Capecitabine + streptozocin + cisplatin	Capecitabine + streptozocin	Telotristat
Rinke (2009) [13]	0.0 ± 18.5	-2.1 ± 15.8	-	-	-	-	-
Raymond (2011) [4], Vinik (2016) [5], Faivre (2017) [6]	-	-2.7	-	-4.6	-	-	-
Arnold (2005) [17]	11.4 ± 18.6	-	-6.4 ± 18.6	-	-	-	-
Caplin (2014) [20], Phan (2016) [21]	-5.2 ± 3.7	-4.9 ± 3.7	-	-	-	-	-
Meyer (2014) [40], Meyer (2016) [41]	-	-	-	-	-3.8	2.2	-
Vinik (2016) [43]	5.3 ± 2.1	1.2 ± 2.6	-	-	-	-	-
Kulke (2017) [44]	-	8.5	-	-	-	-	21.6 19.2

Values are mean ± standard deviation. Abbreviation: EORTC QLQ-30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; GHQ-30. Two values are indicated for telotristat, as the two dosages 3x500mg/d and 2x250mg/d have been evaluated separately in the study of Kulke (2017) [44].

eReferences.

1. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions.* The Cochrane Collaboration; 2011.
2. Puhan MA, Schunemann HJ, Murad MH, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ.* 2014;349:g5630.
3. Brignardello-Petersen R, Bonner A, Alexander PE, et al. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. *J Clin Epidemiol.* 2018;93:36-44.
4. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med.* 2011;364(6):501-513.
5. Vinik A, Bottomley A, Korytowsky B, et al. Patient-Reported Outcomes and Quality of Life with Sunitinib Versus Placebo for Pancreatic Neuroendocrine Tumors: Results From an International Phase III Trial. *Target Oncol.* 2016;11(6):815-824.
6. Faivre S, Niccoli P, Castellano D, et al. Sunitinib in pancreatic neuroendocrine tumors: updated progression-free survival and final overall survival from a phase III randomized study. *Ann Oncol.* 2017;28(2):339-343.
7. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med.* 2011;364(6):514-523.
8. Yao JC, Pavel M, Lombard-Bohas C, et al. Everolimus for the Treatment of Advanced Pancreatic Neuroendocrine Tumors: Overall Survival and Circulating Biomarkers From the Randomized, Phase III RADIANT-3 Study. *J Clin Oncol.* 2016.
9. Kulke MH, Niedzwiecki D, Foster NR, 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.
10. Kulke MH, Ruszniewski P, Van Cutsem E, 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. *Ann Oncol.* 2017;28(6):1309-1315.
11. Salazar R, Garcia-Carbonero R, Libutti SK, et al. Phase II Study of BEZ235 versus Everolimus in Patients with Mammalian Target of Rapamycin Inhibitor-Naive Advanced Pancreatic Neuroendocrine Tumors. *Oncologist.* 2017.
12. Kolby 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. *Br J Surg.* 2003;90(6):687-693.
13. Rinke A, Muller HH, Schade-Brittinger C, 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. *J Clin Oncol.* 2009;27(28):4656-4663.
14. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med.* 2017;376(2):125-135.
15. Oberg K, Norheim I, Alm G. Treatment of malignant carcinoid tumors: a randomized controlled study of streptozocin plus 5-FU and human leukocyte interferon. *Eur J Cancer Clin Oncol.* 1989;25(10):1475-1479.
16. Faiss S, Pape UF, Bohmig M, 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. *J Clin Oncol.* 2003;21(14):2689-2696.
17. Arnold R, Rinke A, Klose KJ, et al. Octreotide versus octreotide plus interferon-alpha in endocrine gastroenteropancreatic tumors: a randomized trial. *Clin Gastroenterol Hepatol.* 2005;3(8):761-771.
18. Yao JC, Phan A, Hoff PM, 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. *J Clin Oncol.* 2008;26(8):1316-1323.
19. Pavel ME, Hainsworth JD, Baudin E, 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):2005-2012.
20. Caplin ME, Pavel M, Cwikla JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med.* 2014;371(3):224-233.
21. 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). *J Clin Oncol.* 2016;Conference 34(4 SUPPL. 1).
22. Yao JC, Fazio N, Singh S, 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):968-977.

23. Pavel ME, Singh S, Strosberg JR, 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 Oncol.* 2017;18(10):1411-1422.
24. Yao JC, Guthrie KA, Moran C, 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. *J Clin Oncol.* 2017;35(15):1695-1703.
25. Moertel CG, Hanley JA, Johnson LA. Streptozocin alone compared with streptozocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. *N Engl J Med.* 1980;303(21):1189-1194.
26. Moertel CG, Lefkopoulo M, Lipsitz S, Hahn RG, Klaassen D. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. *N Engl J Med.* 1992;326(8):519-523.
27. Lange JR, Steinberg SM, Doherty GM, et al. A randomized, prospective trial of postoperative somatostatin analogue in patients with neuroendocrine tumors of the pancreas. *Surgery.* 1992;112(6):1033-1037; discussion 1037-1038.
28. Ito T, Okusaka T, Ikeda M, et al. Everolimus for advanced pancreatic neuroendocrine tumours: a subgroup analysis evaluating Japanese patients in the RADIANT-3 trial. *Jpn J Clin Oncol.* 2012;42(10):903-911.
29. Phan AT, Caplin ME, Pavel ME, et al. Effects of lanreotide autogel/depot (LAN) in pancreatic neuroendocrine tumors (pNETs): A subgroup analysis from the CLARINET study. *J Clin Oncol.* 2015;33(3_suppl):233-233.
30. Lombard-Bohas C, Yao JC, Hobday T, 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):181-189.
31. Kunz PL, Catalano PJ, Nimeiri H, et al. A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: A trial of the ECOG-ACRIN Cancer Research Group (E2211). *J Clin Oncol.* 2018;36(15_suppl):4004-4004.
32. Saslow SB, Scolapio JS, Camilleri M, et al. Medium-term effects of a new 5HT3 antagonist, alosetron, in patients with carcinoid diarrhoea. *Gut.* 1998;42(5):628-634.
33. Sakata H, Iwakiri R, Ootani A, et al. A pilot randomized control study to evaluate endoscopic resection using a ligation device for rectal carcinoid tumors. *World J Gastroenterol.* 2006;12(25):4026-4028.
34. Maire F, Lombard-Bohas C, O'Toole D, 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.
35. Castellano D, Bajetta E, Panneerselvam A, 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.
36. Dasari A, Phan AT, Caplin ME, et al. Lanreotide depot/autogel (LAN) in midgut neuroendocrine tumors (NETs): A subgroup analysis from the CLARINET study. *J Clin Oncol.* 2015;33(15_suppl):4104-4104.
37. Oberg K, Norheim I, Theodorsson E, Ahlman H, Lundqvist G, Wide L. The effects of octreotide on basal and stimulated hormone levels in patients with carcinoid syndrome. *J Clin Endocrinol Metab.* 1989;68(4):796-800.
38. Jacobsen MB, Hanssen LE. Clinical effects of octreotide compared to placebo in patients with gastrointestinal neuroendocrine tumours. Report on a double-blind, randomized trial. *J Intern Med.* 1995;237(3):269-275.
39. O'Toole D, Ducreux M, Bommelaer G, 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):770-776.
40. Meyer T, Qian W, Caplin ME, et al. Capecitabine and streptozocin +/- cisplatin in advanced gastroenteropancreatic neuroendocrine tumours. *Eur J Cancer.* 2014;50(5):902-911.
41. Meyer T, Qian W, Valle JW, et al. Capecitabine and streptozocin ± cisplatin for gastroenteropancreatic neuroendocrine tumours: predictors of long-term survival in the NET01 trial. *Ann Oncol.* 2016;27(Supplement 6):vi136–vi148.
42. Wolin EM, Jarzab B, Eriksson B, 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 Des Devel Ther.* 2015;9:5075-5086.
43. Vinik AI, Wolin EM, Liyanage N, Gomez-Panzani E, Fisher GA. EVALUATION OF LANREOTIDE DEPOT/AUTOGEL EFFICACY AND SAFETY AS A CARCINOID SYNDROME TREATMENT (ELECT): A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL. *Endocr Pract.* 2016;22(9):1068-1080.

44. Kulke MH, Horsch D, Caplin ME, et al. Telotristat Ethyl, a Tryptophan Hydroxylase Inhibitor for the Treatment of Carcinoid Syndrome. *J Clin Oncol.* 2017;35(1):14-23.
45. Phan AT, Caplin ME, Pavel ME, 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. *J Clin Oncol.* 2015;33(3_suppl):367-367.
46. Fisher GA, Wolin EM, Kunz P, et al. Safety and efficacy of lanreotide depot versus placebo in neuroendocrine tumor patients with a history of carcinoid syndrome and prior octreotide therapy. *Am J Gastroenterol.* 2015;1):S1007.
47. Fisher GA, Wolin EM, Kunz P, 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. *Pancreas.* 2016;45(3):475.
48. Anselmo L, Shaheen M, Casellini C, et al. Safety and efficacy of lanreotide depot vs. placebo in neuroendocrine tumor patients with a history of carcinoid syndrome and prior octreotide therapy. *J Oncol Pharm Pract.* 2016;22(2 Supplement 1):19-20.

