Supplementary Table 1: summary of selected studies for the treatment of carcinoid syndrome (CS). Study quality and risk of bias is scored according to a three-scale evaluation: low (red), medium (orange) or high (red). Seven items were weighed: randomization (low: unknown or not present, medium: present, without a description of the procedure, high: present, with adequate description of the procedure), inclusion criteria (considering data on histological confirmation of NET, the description of CS symptoms and clear inclusion and exclusion criteria), control arm (low: none, medium: other intervention, high: placebo controlled), allocation concealment (low: open label, medium: single blinded, high: double blinded), incomplete data handling (low: not reported, medium: reported without complete description, high: reported, including adequate handling), selective reporting (low: limited description of CS-related outcomes, medium: medium description of more than 1 CS-related outcome, high: dedicated description of more than 1 CS-related outcome, including adequate quantification), and industry funding (low: study was industry funded, medium: study drug provided by industry, high: no potential conflicts of interest). Outcome is rated as partial (PR), complete (CR) or total response (TR), according to the description within the publication. SSA: somatostatin analog, IFN: interferon-alpha, na: not available or unclear. * Percentage of patients pretreated with SSAs relates to the overall study population; information on the CS-specific subgroup was not available. # M: multicenter study.

Category	Reference	Design	Phase	Center number	Randomization	Inclusion criteria	Control arm	Blinded	Incomplete data	Selective reporting	Industry	Patient numbers	Pre-treatment SSA	intervention group	5-HIAA levels				Symptoms				Diarrhea				Flushes			
															PR	CR	TR	other	PR	CR	TR	PR	CR	TR	other	PR	CR	TR	other
Placebo	Pavel *et al.* 2018	prospective	3	M								26	100%	placebo				0.36							0.00	0,05 stools/day more				0.33 less/day
Placebo	Kulke *et al.* 2017	prospective	3	M								45	100%	placebo				0.1							0.20	0,9 stools/day less				0.16 less/day
Placebo	Kulke *et al.* 2014	prospective	1+2	M								5	100%	placebo				0							0.00					
Placebo	Vinik *et al.* 2016	prospective	3	M								56	55%	placebo				120,8 µmol decrease	0.05	0.23	0.29									
SSA	Martin-Richard *et al.* 2013	prospective	2	M								18	20%*	lanreotide 120mg q28 days				30% decrease		0.56	0.56									
SSA	Ducreux *et al.* 2000	prospective	2	M								29	37%	lanreotide 30mg q10-14 days				0.41										0.40	0.40	
SSA	Di Bartolomeo *et al.* 1996	prospective	2	M								15	na	octreotide 500-1000 µg tid	0.46	0.31	0.77		0.33	0.40	0.73	0.10	0.30	0.40		0.29	0.21	0.50	
SSA	Nikou *et al.* 2005	retrospective	2	1								33	na	octreotide or lanreotide					0.24	0.76	1.00									
SSA	Wymenga *et al.* 1999	prospective	2	M								48	29%*	lanreotide 30mg q14 days	0.27		0.27				0.38				36.8% decrease				47.6% decrease
SSA	Anthony and Vinik 2011	retrospective	na	M								284	na	octreotide LAR								0.36	0.26	0.62		0.39	0.25	0.64	
SSA	Vinik *et al.* 2016	prospective	3	M								59	0.56	lanreotide 120mg q28 days					0.07	0.41	0.47									
SSA	Khan *et al.* 2011	retrospective	na	1								69	0.16	lanreotide autogel qm							0.94			0.62				0.94		
SSA	Rubin *et al.* 1999	prospective	3	M								18	na	octreotide LAR 10mg q28 days				5% decrease			0.67									
				M								15	na	octreotide LAR 20mg q28 day				54% decrease			0.73									
				M								22	na	octreotide LAR 30mg q28 days				7% decrease			0.64									
SSA	Ruszniewski *et al.* 2016	prospective	na	M								273	na	lanreotide autogel										0.76				0.73		
SSA	Ruszniewski *et al.* 2004	prospective	2+3	M								71	66%	lanreotide 60-120 mg q28 days				24% decrease						0.18				0.65		
SSA	Garland *et al.* 2003	retrospective	na	1								27	48%	octreotide LAR qm							0.85									
SSA	Arnold *et al.* 1993	prospective	na	1								11	na	octreotide 200 µg tid	0.38	0.00	0.38											1.00		
SSA	Arnold *et al.* 1996	prospective	2	M								48	0	octreotide 50-500 µg tid								0.32	0.32	0.64		0.40	0.35	0.75		
SSA	Tomassetti *et al.* 2000	na	na	1								10	80%	octreotide LAR 20mg q28 days				75% decrease				0.10	0.90	1.00				1.00		
SSA	Scherubl *et al.* 1994	na	na	1								12	na	lanreotide 30mg q7-14 days									0.42	0.42				0.86		
SSA	Ruszniewski *et al.* 1996	prospective	na	M								39	41%	lanreotide 30mg q14 days			0.46						0.30	0.30			0.39	0.39		
SSA	Kvols *et al.* 1986	na	na	1								25	0	octreotide 150 µg tid			0.72					0.60	0.16	0.76		0.50	0.29	0.79		
SSA	Aparicio *et al.* 2001	retrospective	na	1								18	0	octreotide 300 µg tid or lanreotide 30mg q14 days							0.86			0.89						
SSA	O'Toole *et al.* 2000	prospective	na	M								28	61%	octreotide 200 µg bid-tid			0.64							0.83				0.68		
				M								28	61%	lanreotide 30mg q10 days			0.60							0.54				0.54		
SSA	Eriksson *et al.* 1997	prospective	2	1								13	47%*	octreotide 750-12000 µg qid			0.54													
SSA	Bajetta *et al.* 2006	prospective	3	M								9	53%*	lanreotide autogel 120mg q6 weeks					0.33	0.33	0.67									
				M								3	53%*	lanreotide microparticles 60mg q3 weeks					0.33		0.33									
SSA	Oberg *et al.* 1991	na	na	1								22	0	octreotide 50-200 µg bid-tid			0.27				0.50									
SSA	Vinik and Moattari 1989	na	na	1								14	0	octreotide 100-250 µg bid-qid			0.75							0.83				1.00		
SSA	Welin *et al.* 2004	na	na	1								12	92%*	octreotide pamoate 160mg qm			0.17													
SSA	Tomassetti *et al.* 1998	prospective	na	1								10	50%*	lanreotide 30mg q10 days				no change						1.00						
SSA	Arnold *et al.* 2005	prospective	3	M								20	14%	octreotide 200 µg tid	0.50		0.50				0.33			0.57				0.83		
SSA	Janson and Oberg 1993	retrospective	na	1								51	0%	octreotide 100-1200 µg, if no response also α-IFN 2-6 MU tiw	0.28	0.09	0.37							0.69				0.70		
SSA	Pavel *et al.* 2011	prospective	3	M								213	78%	octreotide LAR 30 mg q28 days			0.54													
SSA-2nd line	Al-Efraij *et al.* 2015	retrospective	na	1								37	100%	octreotide LAR beyond 30 mg per month			0.23				0.47			0.62				0.62		
SSA-2nd line	Kvols *et al.* 2012	prospective	2	M								44	100%	pasireotide 150-900 µg bid				5% decrease	0.20	0.07	0.27									
SSA-2nd line	Wolin *et al.* 2015	prospective	3	M								43	100%	pasireotide LAR 60 mg q28 days							0.21									
SSA-2nd line	Ferolla *et al.* 2011	prospective	na	M								10	100%	octreotide LAR 30 mg q21 days			0.57					0.30	0.70	1.00		0.29	0.71	1.00		
SSA-2nd line	Strosberg *et al.* 2014	retrospective	na	3								188	100%	octreotide LAR dose escalation and/or dose-frequency escalation above 30 mg q28 days										0.79				0.81		
SSA-2nd line	O'Toole *et al.* 2000	prospective	na	M								28	61%	octreotide 200 µg bid-tid										0.36				0.54		
				M								28	61%	lanreotide 30mg q10 days										0.33				0.54		
IFN	Frank *et al.* 1999	prospective	2	1								9	76%	α-IFN 5 MU tiw + octreotide 200 µg tid	1.00		1.00													
IFN	Janson *et al.* 1993	prospective	1+2	1								12	na	γ-IFN 0.5-1.0 MU qd + previous α-IFN			0.00							0.50				0.50		
IFN	Veenhof *et al.* 1992	prospective	na	M								15	na	Intron-A 3-12 MU tiw	0.33		0.33							0.54				0.62		
IFN	Nobin *et al.* 1989	prospective	na	1								13	0%	IFN 3-6 MU 5 days a week	0.08		0.08							0.00				0.50		
IFN	Valimaki *et al.* 1991	na	na	1								8	na	human leukocyte IFN or IFN-alpha2b 1.5-6 MU qd	0.25		0.25							0.29				0.40		
IFN	Janson and Oberg 1993	retrospective	na	1								19	0%	octreotide 100-1200 µg + α-IFN 2-6 MU tiw	0.50	0.22	0.72				0.47									
IFN	Janson *et al.* 1992	na	na	1								22	100%	3 MU α-IFN tiw 3-5 MU	0.59	0.18	0.77		0.39	0.17	0.56									
IFN	Arnold *et al.* 2005	prospective	3	M								19	11%	octreotide 200 µg tid + 4.5 MU α-IFN tiw	0.67		0.67				0.43			0.67				0.80		
IFN	Saltz *et al.* 1994	prospective	2	1								8	na	5FU 400-750 mg/m2 5 days + α-IFN-2a 3 MU qd	0.25		0.25													
IFN	Basser *et al.* 1991	retrospective	na	2								10	12%*	α-IFN-2b 3MU tiw			0.40							0.71				0.50		
IFN	Moertel *et al.* 1989	prospective	na	1								23	41%*	rhleukocyte A interferon tiw 12=24 MU/m2			0.39							0.33				0.65		
IFN	Di Bartolomeo *et al.* 1993	prospective	na	M								22	na	α-IFN-2z 3-6 MU qd-tiw	0.24	0.35	0.59					0.50	0.40	0.90		0.30	0.50	0.80		
IFN	Oberg *et al.* 1986	na	na	1								36	na	human leukocyte IFN 3-6 MU qd	0.77		0.77							0.39				0.64		
IFN	Oberg *et al.* 1989	prospective	na	1								10	na	human leukocyte IFN 3-6 MU qd	0.50		0.50				0.70									
IFN	Pavel *et al.* 2006	retrospective	na	1								10	100%	PEG-IFN-α2b 50-100 µg qw			0.70													
IFN	Nikou *et al.* 2005	retrospective	2	1								9	na	adding IFN, octreotide or lanreotide							1.00									
chemo	Moertel and Hanley 1979	na	na	M								33	na	streptozotocin 500 mg/m2 5 days q6 weeks + 5-FU 400 mg/m2 5 days q6 weeks	0.25	0.15	0.40													
				M								34	na	streptozotocin 500 mg/m2 5 days q6 weeks + cyclophosphamide 1000 mg/m2 q3 weeks	0.20	0.04	0.24													
chemo	Moertel *et al.* 1984	na	na	1								16	na	cyclophosphamide 1000 mg/m2 q5 weeks + methotrexate 20 mg/m2 qw			0.00							0.07				0.00		
chemo	Pavel *et al.* 2011	prospective	3	M								216	80%	everolimus 10 mg qd + octreotide LAR 30 mg q28 days			0.61													
chemo	Kunz *et al.* 2016	prospective	2	2								15	31%	oxaliplatin 85 mg/m2 + leucovorin 200 mg/m2 + 5-FU 2400 mg/m2 + bevacizumab 5mg/kg q14 days	0.27		0.27													
chemo	Moertel *et al.* 1986	prospective	2	1								15	na	cisplatin 90mg/m2 q3-4 weeks	0.07		0.07				0.00									
chemo	Kaltsas *et al.* 2002	retrospective	na	1								15	na	lomustine 150 mg/m2 q6 weeks + 5-FU 500 mg/m2 weekly	0.40	0.10	0.50		0.40	0.20	0.60									
chemo	Bainbridge *et al.* 2015	retrospective	na	1								10	100%	everolimus 10mg qd										0.60				0.71		
chemo	Oberg *et al.* 1989	prospective	na	1								10	na	streptozocin 1 g 3 days + 5FU 400 mg/m2 q6 weeks	0.00		0.00													
Liver-directed	Norton *et al.* 2003	retrospective	na	1								8	na	combination of surgical liver resections and bowel resection							1.00									
Liver-directed	Carrasco *et al.* 1986	retrospective	na	1								23	na	bland embolization with Ivalon particles			0.67				0.87									
Liver-directed	Mitty *et al.* 1985	retrospective	na	1								18	na	bland embolization with gelfoam							0.94									
Liver-directed	Bilchik *et al.* 1997	na	na	1								8	47%*	cryosurgery with AccuProbe			0.71			0.75	0.75									
Liver-directed	Hajarizadeh *et al.* 1992	retrospective	na	1								8	na	octreotide 100 ug tid + intraarterial 5-FU 2 gr/day 5 days + chemoembolization cisplatin, mitomycin C, doxorubicin						1.00	1.00									
Liver-directed	Wangberg *et al.* 1993	retrospective	na	1								27	na	bland embolisation + octreotide 100 µg bid			0.48													
Liver-directed	Martensson *et al.* 1984	retrospective	na	1								8	na	bland embolization with gelfoam	0.50	0.13	0.63			0.63	0.63									
Liver-directed	Odurny and Birch 1985	retrospective	na	1								5	na	bland embolization with lyophilised dura mater						1.00										
Liver-directed	Drougas *et al.* 1998	retrospective	na	1								12	1	5-FU 1 g/m2 5days, chemoembolization doxorubicin, cisplatin, mitomycin C				60% decrease						0.67				0.58		
Liver-directed	Gupta *et al.* 2003	retrospective	na	1								42	51%	bland embolization with polyvinyl alcohol or Gelfoam, or chemoembolization with different agents							0.64									
Liver-directed	Schell *et al.* 2002	retrospective	na	1								14	93%	bland embolization with Lipiodol/Gelfoam					0.36	0.64	1.00									
Liver-directed	Sjoblom *et al.* 1987	retrospective	na	1								14	na	surgical interruption of arterial connections to liver or embolization	0.57	0.36	0.93			1.00	1.00									
Liver-directed	Chambers *et al.* 2008	retrospective	na	1								56	1	initial surgical resection of regional and/or hepatic disease followed by appropriate medical therapy							0.75									
Liver-directed	Brown *et al.* 1999	retrospective	na	1								10	na	embolization with polyvinylalcohol particles							0.80									
Liver-directed	Strosberg *et al.* 2012	prospective	2	1								19	79%*	bland embolization with embospheres + sunitinib 37.5 mg q42 days day 1-28			0.84													
Liver-directed	Sward *et al.* 2009	retrospective	na	1								107	na	embolization with polyvinylalcohol particles			0.48				0.71									
Liver-directed	Maton *et al.* 1984	retrospective	na	1								12	na	bland embolization with gelatin or sterispon/dura mater				73% decrease		0.92	0.92			1.00				1.00		
Liver-directed	Jia *et al.* 2017	retrospective	na	1								16	53%*	radioembolization with Yttrium-90 particles	0.86	0.14	1.00				0.94									
Liver-directed	Eriksson *et al.* 2008	retrospective	na	1								17	na	liver resection and/or radiofrequency ablation							0.71									
Liver-directed	Boudreaux *et al.* 2005	retrospective	na	1								59	na	multimodal surgical therapy				53% decrease			0.90									
Liver-directed	Fiore *et al.* 2014	retrospective	na	1								7	97%*	embolizing agents							1.00									
				1								4	97%*	epirubicin + embolizing agents							1.00									
Liver-directed	Osborne *et al.* 2006	retrospective	na	1								36	na	embolization or surgical cytoreduction							0.97									
Liver-directed	Pericleous *et al.* 2016	retrospective	na	1								28	na	transarterial embolization or transarterial chemoembolization	0.43	0.08	0.51													
Liver-directed	McEntee *et al.* 1990	retrospective	na	1								11	na	palliative cytoreductive hepatic surgery					0.45	0.45	0.91									
Liver-directed	Roche *et al.* 2003	retrospective	na	1								10	0%	chemoembolization with doxorubicin emulsified in lipiodol and gelatin sponge particles					0.20	0.70	0.90									
Radionuclide	Pathirana *et al.* 2001	retrospective	na	1								12	45%	single dose of 7.4 GBq I131-MIBG					0.25	0.58	0.83									
Radionuclide	Taal *et al.* 2000	na	na	1								5	20%	single dose of 7.4 GBq I131-MIBG after loading non-labelled MIBG	0.60		0.60					1.00		1.00						
Radionuclide	Ezziddin *et al.* 2013	retrospective	na	1								11	100%	minimum 2 doses of 11.1 GBq I131-MIBG					0.27	0.55	0.82									
Radionuclide	Taal *et al.* 1996	prospective	na	1								20	13%	1-3 doses of 7,4 GBq I131-MIBG							0.70									
Radionuclide	Hamiditabar *et al.* 2017	prospective	2	1								59	na	>1 dose of 7.4 GBq 177Lu-DOTATATE			0.16							0.71				0.64		
Radionuclide	Seregni *et al.* 2014	prospective	2	1								21	100%	four cycles of alternating 177Lu-DOTATATE (5.55 GBq) and 90Y-DOTATATE (2.6 GBq)							0.90									
Radionuclide	Waldherr *et al.* 2002	prospective	2	1								14	100%	four doses of 7.4 GBq/m2 90Y-DOTATOC								0.50	0.50	1.00		0.43	0.21	0.64		
Radionuclide	Khan *et al.* 2011	prospective	2	1								62	62%*	four cycles 177Lu-DOTATATE			0.19													
Serotonin	Pavel *et al.* 2018	prospective	3	M								25	100%	telotristat 250 mg tid			0.88							0.40	0,45 stools/day less				0,06 less/day	
				M								25	100%	telotristat 500 mg tid			1.00							0.40	0,60 stools/day less				0,11 more/day	
Serotonin	Kulke *et al.* 2017	prospective	3	M								45	100%	telotristat 250 mg tid			0.78							0.44	1,7 stools/day less				0.30 less/day	
				M								45	100%	telotristat 500 mg tid			0.87							0.42	2,1 stools/day less				0.53 less/day	
Serotonin	Kulke *et al.* 2014	prospective	1+2	M								18	100%	telotristat 150-500 mg tid			0.56							0.28						
Serotonin	Pavel *et al.* 2015	prospective	1	M								15	67%	telotristat 150-500 mg tid			0.00							0.40	2,6 stools/day less				0,75 less/day	
Serotonin	Wymenga *et al.* 1998	prospective	na	1								11	0%	ondansetron 8mg tid				no change						1.00				0.00		
Serotonin	Moertel *et al.* 1991	prospective	na	1								16	na	cyproheptadine 4-16 mg tid	0.00		0.00					0.50		0.50		0.17		0.17		
Serotonin	Kiesewetter *et al.* 2018	retrospective	na	1								13	100%	ondansetron 8mg bid-qd										0.85						