Neuroendocrine tumors; measures to improve treatment and supportive care

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Clinical benefit of systemic treatment in patients with advanced pancreatic and gastro intestinal neuroendocrine tumors according to ESMO-MCBS and ASCO framework

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Abstract:

Background

Assessment of clinical benefit of systemic treatments of rare diseases including gastro-enteropancreatic neuroendocrine tumors (GEP-NET) is challenging. Recently several tools have been developed to grade clinical benefit of cancer drugs. European Society for Medical Oncology (ESMO) has developed the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS). The American Society of Clinical Oncology (ASCO) developed and revised the ASCO framework consisting of the Net Health Benefit (NHB) score juxtaposed against the costs of the treatment. In this review we graded systemic treatments for GEP-NET patients with both frameworks.

Methods

The electronic databases (PubMed, Embase) were searched for papers reporting comparative trials, conducted in adult GEP-NET patients in the English language. Papers were assessed according to the ESMO-MCBS and the NHB part of the ASCO revised Framework (NHB-ASCO-F) by 4 independent assessors, discrepancies were discussed.

Results

The search yielded 32 trials of which 6 trials were eligible for grading with the ESMO-MCBS resulting in scores of 2 or 3. Eight trials were eligible for grading with the NHB-ASCO-F; resulting in scores between 37.6 and 57.4. Trials that were not primary assessable by the tools were analyzed separately. Consensus between assessors was reached in 68% of trials with the ESMO-MCBS and in 23% of trials with the NHB-ASCO-F.

Conclusion

The currently used systemic treatments for GEP-NET patients had low scores according to the NHB-ASCO-F and none could be graded as meaningful clinical beneficial according to the ESMO-MCBS. Despite the low incidence, the heterogeneous patient population and relatively long natural course of NET, future studies on new treatment modalities should aim for high clinical benefit outcomes.

Keywords: ESMO-MCBS, ASCO, pancreatic and gastro-intestinal, neuroendocrine tumors, clinical benefit, value

Introduction

Neuroendocrine tumors are rare malignancies with an incidence of 3.5/100,000 per year and a prevalence of 21.6/100,000 in the last decade (1). Median survival time is 77 months in patients with regional and 24 months in patients with distant metastatic pancreatic NET (pNET) and 105 months and 56 months in case of respectively regional and distant metastatic intestinal NET disease (2). GEP-NET patients are frequently metastasized at the time of initial diagnosis. Surgery is the only curative treatment. Non-curative systemic treatment options include somatostatin analogues (SSA), chemotherapy, targeted agents, and peptide receptor radionuclide therapy (PRRT) with variable, limited success (3-12).

Ideally, in clinical trials investigating novel drugs, the primary aim should be to study endpoints such as the overall survival (OS), quality of life (QoL) and treatment toxicity. However, for trials investigating new agents in GEP-NET patients, survival analysis can be challenging as the prolonged (natural) course of the disease often results in trials allowing crossover towards the experimental arm, which influences OS. Crossover to the experimental arm or to second line therapies has impact on OS data (13). Therefore, progression-free survival (PFS) was recommended as a feasible and relevant primary end point for both, phase II and III trials in GEP-NET, by the expert consensus report of the National Cancer Institute Neuroendocrine Tumor Clinical Trials Planning Meeting (13).

Recently, among others, ESMO has developed a validated and reproducible tool to assess the magnitude of clinical benefit for drugs for solid tumors, the ESMO-MCBS (14). The ASCO developed the ASCO framework for solid tumors and haematological malignancies consisting of the NHB score juxtaposed against the costs of the treatment (15,16). Both tools have been applied in several solid malignancies (14-18). However, the ASCO framework was assessed only in a few studies. Treatments for GEP-NET are not yet evaluated using the tools. In this review we therefore investigated the value of current systemic antitumor treatments for GEP-NET patients and their eligibility for grading with both ESMO-MCBS and NHB-ASCO-F.

Methods

Search strategy

For detailed description of methods see supplementary data. In brief, trials were searched between Aug 1st 2015 to Jan 31th 2016, in the databases PubMed and EMBASE. The articles that were found, were screened using title and abstract to select trials published in the English language and comparing systemic treatment modalities

for the treatment of GEP-NET in humans. Furthermore the reference lists of national and international guidelines, included trials and conference abstracts were reviewed for additional relevant articles.

Selection criteria for trials

Comparative trials investigating systemic antitumor treatment for well-differentiated GEP-NET patients were analyzed. Studies in patients with grade 3 neuroendocrine neoplasms were not included. Criteria for assessment are summarized in Table S1. Trials were selected if at least 50 % of participants were diagnosed with GEP-NET, and the other participants had a NET of unknown or other origin. Abstracts were not included.

ESMO-MCBS and the NHB-ASCO-F

ESMO-MCBS grades, in the non-curative setting, range from 1-5, with grade 4 and 5 representing meaningful clinical benefit (14). The NHB-ASCO-F ranges from -20 to 180, with a higher score representing a better score, no cut-off value was provided to define clinical benefit (15,16,18). All relevant comparative trials were assessed according to both tools. Relevant trials that did not meet all criteria as mentioned in Table S1 were assessed separately, based on the available data.

Assessment of trials

Four members from all Dutch European Neuroendocrine Tumor Society (ENETS) centres of excellence independently scored the trials according to the ESMO-MCBS and the NHB-ASCO-F. After obtaining scores of these assessors we noticed a wide variation in results. During a consensus meeting additional agreements were defined. Next, trials were assessed again according to the additional agreements. The number of trials to which the same score was awarded between three or four assessors was registered after each of the two scoring sessions. Two phase III trials were published after the consensus meeting and were assessed according our agreements (8,12). Therefore an additional assessment session was not necessary for these trials.

Results

Trial selection and characterization

The primary search strategy yielded 1,942 potentially relevant papers, of which 1,676 remained when duplicates were discarded (Figure S1). After screening of title and abstract, 223 papers were preselected evaluating systemic antitumor treatment for GEP-NET patients.

Thirty nine papers in which 35 comparative trials in GEP-NET patients were described were selected for further analysis. Nine trials fulfilled all criteria as summarized in Table S1 and were assessable according to the ESMO-MCBS and the NHB-ASCO-F (Table 1) (3-12). Only one trial, the RADIANT-4, described in their protocol that crossover was not allowed (10,11). None of the trials investigated adjuvant treatment in GEP-NET or had a curative intent.

The other 26 comparative trials, investigating systemic treatment in GEP-NET patients, did not meet all criteria for assessment with both tools (Table S1), or evaluated participants of which less than 50% had a GEP-NET. Main difficulties for assessment with the tools were summarized in Figure S2. As currently used national and international guidelines are based upon these trials, we analyzed them separately with the available data (Table S2, supplementary data; references).

Assessment according to the ESMO-MCBS

Six trials were assessable with the ESMO-MCBS. The calculated score ranged from 2 to 3 corresponding with a low level of clinical benefit. RADIANT-3 and RADIANT-4 analyzed everolimus versus placebo in pNET and non-functional advanced NET, respectively (9-11). Application of ESMO-MCBS for RADIANT-3 and RADIANT-4 resulted in a preliminary score of 3 reflecting a longer PFS. A hazard ratio with a lower limit of the 95% confidence interval ≤ 0.65 for PFS determined the preliminary score. No significant difference in important adverse events as compared to the placebo control arm was detected. QoL of everolimus in pNET patients was reported in a recent abstract which described a single-arm phase IV study, performed in patients who started with everolimus (19). After 6 months, no improvement in QoL was detected. Because this was a single-arm study and the ESMO-MCBS could only be applied to comparative outcome studies, the preliminary score of the RADIANT-3 will not be downgraded, despite lack of improvement of QoL, when these data are published in full-report. QoL of RADIANT-4 trial was reported in a post-hoc analysis and recently published (11). No improvement of QoL by everolimus versus the control arm was demonstrated. Therefore the preliminary score of the RADIANT-4 was downgraded to a final score 2. The NETTER-1 trial investigated ^{177}Lu-dotatate with octreotide LAR versus octreotide LAR alone in patients with metastatic midgut NET (8). The calculated ESMO-MCBS score was 3, which implies a longer PFS in the intervention group as compared with control arm. Furthermore, there was no significant difference in important adverse events as compared to the control arm and no QoL data were documented. In the CLARINET trial GEP-NET patients or patients with NET of unknown origin were treated with lanreotide in the intervention arm versus placebo in the control arm (3). This trial showed an improvement in PFS. Data of QoL did not show an improvement in QoL for the intervention group, resulting in a score of 2. In the PROMID trial patients with a metastasized midgut NET were

Table 1: Clinical benefit of systemic treatment for GEP-NET according to ESMO-MCBS (ESMO-MCBS) and according ASCO revised framework (NHB)

				ESMO-MCBS			ASCO revised framework			
Intervention vs control	**Setting and reference**	**Primary Outcome**	**HR of primary outcome/ RR**	**Intoxication data**	**Improvement QOL (Yes/No)**	**ESMO-MCBS**	**Clinical benefit score**	**Intoxication data**	**Bonus points**	**Net health benefit**
Lanreotide vs placebo	GEP-NET or NET of unknown origin (3)	PFS	0.47 (0.30-0.73)	NS	No	**2**	42.4	NC	0	**NA**
Capecitabine and streptozocin and cisplatin vs capecitabine and streptozocin	Advanced, irresectable, NET of pancreas, gastroduodenum, or unknown primary (4)	RR	16 % vs 12 %	NS	No	**NA**	0	NC	0	**NA**
Octreotide and everolimus vs octreotide and placebo	Advanced, progressive NET with carcinoid syndrome (5)	PFS	0.77 (0.59-1.00)	NS	NA	**NA**	18.4	NC	0	**NA**
Sunitinib vs placebo	Progressive, advanced pancreatic NET (6)	PFS	0.42 (0.26-0.66)	NS	No	**2**	46.4	-5	16	**57.4**
Octreotide LAR vs placebo	First line metastatized midgut NET (7)	PFS	0.34 (0.20-0.59)	NS	No	**2**	52.8	NC	16	**NA**
177Lu-Dotatate vs octreotide LAR	Metastastatic midgut NET (8)	PFS	0.21 (0.13-0.33)	NS	NA	**3**	63.8	NC	16	**NA**
Everolimus vs placebo	Advanced pancreatic NET (9)	PFS	0.34 (0.26-0.44)	NS	NA	**3**	52.8	-20	16	**48.8**
Everolimus vs placebo	Advanced, progressive non-functional lung or GI-NET (10,11)	PFS	0.48 (0.35-0.67)	NS	No	**2**	41.6	-20	16	**37.6**
Bevacizumab and octreotide LAR vs interferon alfa-2b and octreotide LAR	Advanced, NET with progression or other poor prognostic features (12)	RR	0.90 (0.72-1.12)	NS	NA	**NA**	8.4	NC	0	**8.4**

A: Name of first author. References are reported in reference list.

ASCO= American Society of Clinical Oncology, ESMO-MCBS= European Society of Medical Oncology- Magnitude of Clinical Benefit Scale, GEP-NET=gastrointestinal and/ or pancreatic neuro-endocrine tumor, HR= hazard ratio, NET=neuroendocrine tumor, vs=versus, LAR=long acting reagents, NA= not applicable, NC= no consensus, NS=no significant difference. OS=overall survival. PFS=progression free survival. QoL=quality of life. RR=response rate. SSA=somatostatin analogue vs= versus.

randomized between octreotide LAR and placebo (7). Further enrolment was stopped after inclusion of 85 patients instead of the planned 162 patients, because of observed positive effects of octreotide LAR on tumor growth and a slow recruitment rate. This trial resulted in an ESMO-MCBS score of 2. The trial reported by Raymond et al. analyzed sunitinib versus placebo in patients with progressive, advanced pancreatic NET (6). Application of ESMO-MCBS resulted in a score of 2. An improvement in PFS was shown. Because reported QoL data did not show improvement, the preliminary score of 3 had to be downgraded one point. This trial had an early closure after randomization of 171 patients, as observed and recommended by the safety monitoring board due to more serious adverse events and a higher frequency of death in the placebo group as well as a difference in PFS favoring sunitinib. The trial analyzing SSA and interferon versus SSA and bevacizumab, in advanced NET patients with progression or other poor prognostic features, showed no significant difference in its primary endpoint PFS (12). The RADIANT-2 analyzed everolimus with long acting octreotide in advanced NET tumor patients associated with carcinoid syndrome (5). The PFS with a hazard ratio of 0.77 (0.59-1.00) did not show a statistically significant clinical benefit. The trial analyzing capecitabine and streptozocin with or without cisplatin did also not show a statistically significant clinical benefit (4). Furthermore in these trials no improvement in toxicity, Qol, or OS was seen, and therefore the ESMO-MCBS was not applicable .

Consensus in the ESMO-MCBS score was reached in 2 of 6 trials after the first scoring session (3-7,9-11). The variation in awarded scores was related to differences in interpretation of data, like the significance of the primary endpoint, and adjustment of the preliminary score for lack of improvement in QoL. After the second scoring session consensus was reached in 4 of 6 trials (3-7,9-11).

Assessment according to the NHB-ASCO-F

Nine trials were assessable for the NHB-ASCO-F (3-12). The CBS varied from 0 to 63.8. In the trial reported by Raymond et al. and the RADIANT-3 and RADIANT-4 trials the treatment arm experienced more adverse events, resulting in a toxicity score of -5 and -20, respectively (6,9-11). Bonus points were awarded for long term disease control; if, at a time point that was twice the median PFS for the control regimen, the percentage of patients having PFS was at least 50% higher for the intervention arm compared with the control arm, to the trial reported by Raymond et al, PROMID-trial, RADIANT-4, RADIANT-3 and the NETTER-1 (6-11). No consensus was obtained for the score of the trials assessed by the NHB-ASCO-F after 2 scoring sessions. This was generally related to discrepancies in interpretation of toxicity score. Finally, after an additional discussion in 4 trials consensus was obtained for NHB and in 5 trials consensus was reached for the CBS and bonus points.

Discussion

To define the clinical benefit of systemic antitumor treatment in GEP-NET patients, we systematically applied the ESMO-MCBS and the NHB-ASCO-F to relevant trials. Six out of 35 trials fulfilled all requirements to be assessed with the ESMO-MCBS resulting in an ESMO-MCBS score of 2 or 3, while 9 trials could be assessed with the NHB-ASCO-F and resulted in scores between 37.6 to 57.4. No clear cut-off value to define clinical benefit with the ASCO framework was provided (15,16). None of the trials that were included in our analysis could demonstrate a meaningful clinical benefit according to the employed tools. The ESMO-MCBS scores were generally lower than in other tumor types, like metastasized breast or colorectal cancer (14,17). In more common tumor types, sufficient numbers of patients can be included in trials powered to detect a difference in OS between the intervention and control group. In NET, such large trials are scarce. In addition, OS difference detection is challenging in NET patients. Therefore, PFS is a frequently used, primary endpoint in NET trials. An improvement in PFS has less impact compared to OS in the ESMO-MCBS scores and the NHB-ASCO-F. Furthermore, none of the assessable trials in GEP-NET, showed an improvement in QoL or less toxicity as compared to the control arm. Therefore, these outcomes did not result in an upgrade of the preliminary score in the ESMO-MCBS.

Ideally OS and QoL should be the primary endpoint of all trials with new drugs (20). This is challenging in NET. Reasons for this include the heterogeneous patient population, the long natural course of the disease and the wide variability of subsequent lines of therapy after progression. The heterogeneity of the patients composing the NET population is important to take into account. This illustrates the importance of well-defined inclusion criteria. The eligibility criteria of the RADIANT-2 trial included patients with; serotonin producing NET and progressive, low- or intermediate-grade and advanced disease (5). Despite these clear criteria still large variation in patient and tumor characteristics between patients exists. Despite the randomized design of the trial, this could have influenced PFS.

Current guidelines for GEP-NET anti-tumor treatment are based on clinical trials and on expert opinion. These guidelines influence our daily clinical practice. Therefore, we also assessed trials that could not be fully assessed by the ESMO-MCBS and ASCO framework (table S2). The control arms of trials analyzing chemotherapy included interferon, dacarbazine, and other kinds of chemotherapy, respectively. Given current knowledge about the effects of chemotherapy, the control arm, nowadays, likely would not have contained chemotherapy. With this analysis we demonstrated, that current guidelines are partially based on studies not powered to determine endpoints that show clinical benefit.

Large trials were conducted by enormous efforts of the international NET community (3-12). This has provided us with important data. Improvements could include trials using a pre-selected patient population. This is already implemented in PRRT, where somatostatin-receptor-positive patients are selected for treatment (8). Furthermore, sequential multiple assignment randomized trials can be used for hypothesis generation followed by a confirmatory randomized controlled trial (RCT) (21). In addition, trials should be focused on reporting QoL and be of sufficient follow-up duration. For GEP-NET patients, use of QoL could be of additional importance because OS is generally prolonged in this cohort.

The importance of long follow-up was previously demonstrated in a trial in patients with anaplastic oligodendrogliomas. OS of adjuvant chemoradiotherapy versus radiotherapy was not improved at a median follow-up of 60 months, but was improved in the chemo-radiotherapy arm at a median follow-up of 140 months (22).

International collaboration in clinical trials and investigator-driven trials should be further expanded to increase evidence based data to support treatment decisions and lead to meaningful clinical benefit for GEP-NET patients.

Although not the aim of our analysis, we found some limitations of the tools. The ESMO-MCBS downgrades the preliminary score of a trial if no significant improvement of QoL data was shown (14). If QoL was not reported, the preliminary score did not have to be downgraded (8,9).

Furthermore, we noticed during the scoring process, a difference in consensus achieved by assessing trials according to the ESMO-MCBS, compared to trials assessed according to the NHB-ASCO-F. With the ESMO-MCBS for more trials consensus was achieved. A possible reason for this is the complex toxicity data reporting according to the NHB-ASCO-F. Potentially, a clearer definition of ‘clinical relevant toxicity’ could facilitate the scoring. With the ASCO framework, eight clinicians completed the tool for 11 anticancer drugs. A Cohen’s kappa coefficient of the interrater reliability (ICC) of 0.11 for NHB and 0.06 for toxicity was found, corresponding with ´slightly reliable agreement’ (18).

However in another study where convergent validity and interrater reliability of assessment frameworks were analyzed; the ASCO framework had an ICC of 0.80 (23). In another report, 109 RCTs were included and ESMO scores and scores using the concept and revised version of the ASCO framework were determined. Weak to moderate correlations were demonstrated, suggesting different constructs of clinical benefit measured (24). Other tools, used to define the value and also addressing the costs of drugs, include the National Comprehensive Cancer Network evidence blocks, Institute for Clinical and Economic Review value assessment framework and Memorial Sloan Kettering Drug Abacus (25-27). Every tool has its own aspects. In the future converging

of tools is expected which will allow to combine the best aspects of these tools to guide policy makers and patient-doctor discussions (28).

Conclusion

The ESMO-MCBS and the NHB of ASCO revised framework could be applied, respectively, to only 6 and 9 trials investigating systemic treatments in NET patients. The currently used systemic treatments for GEP-NET patients had low scores according to the NHB-ASCO-F and none could be graded as meaningful clinical beneficial according to the ESMO-MCBS. Despite the low incidence of NET, the heterogeneous patient population and the relatively long natural course, future studies on new treatment modalities should aim for high clinical benefit outcomes.

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Supplementary Table S1: Eligibility criteria for assessment with ESMO-MCBS and NHB of the revised ASCO framework

	ESMO-MCBS	NHB part of revised ASCO framework
Design	Comparative outcome studies: (one of these) • Randomized design • Comparative cohort-design • Systematic review	New treatment compared with a prevailing standard of care[A] in a well-designed, well-conducted prospective randomized trial[B].
Outcome	Relative benefit of treatments; (one of these, if given as primary endpoint) • Survival • QoL • Surrogate outcomes for survival or QoL, • Treatment toxicities	Benefit: (one of these) • If available -> OS • If OS data is not available ->PFS • If OS and PFS data are not available ->RR
Toxicity	Toxicity data (Can up- or down grade the final score)	Toxicity data graded in accordance with WHO criteria in grade 1,2 and grade 3,4. (Can up- or down grade the final score)
Disease	Solid cancers	Advanced disease or potentially curable clinical presentations[B] in medical oncology setting[A].
Same clinical question evaluated in more studies	Results derived from well-powered registration trial should be given priority.	Only the highest quality evidence available[A].
Pre-planned subgroups	These can be scored with a maximum of three subgroups, scoring should be done separately when for more than one subgroup statistically significant results are reported.	NA
Post-hoc subgroup analysis	These are not graded, except for studies that incorporate collection of tissue samples to enable re-stratification based on new genetic or other biomarkers.	NA
In addition (Only if data are available)	QoL (Can up- or down grade the final score)	Bonus: • Tail of the curve • Palliation • QoL • Treatment free interval[B] (Can upgrade the final score)

ASCO= American Society of Clinical Oncology, ESMO-MCBS= European Society of Medical Oncology- Magnitude of Clinical Benefit Scale, NA= not applicable, NHB= net health benefit, OS= overall survival, PFS=progression free survival, QoL=quality of life, RR=response rate

A) In conceptual framework

B) In revised framework

Supplementary Table S2: Clinical benefit of systemic treatment for GEP-NET according to ESMO-MCBS (ESMO-MCBS) and according ASCO revised framework (NHB)

			ESMO-MCBS			ASCO revised framework					
Intervention vs control	**Setting**	**Primary Outcome**	**HR of primary outcome/ RR**	**Intoxication data**	**Improvement QOL (Yes/No)**	**ESMO-MCBS**	**Clinical benefit score**	**Intoxication data**	**Bonus points**	**NHB**	**References**
Everolimus versus placebo	Previous SSA use before participating in RADIANT_2 trial	PFS	NS	NS	NA	**NA**	0	NC	0	**NA**	Anthony (1)
Everolimus versus placebo	SSA-naive before participating in RADIANT_2 trial	PFS	NS	NS	NA	**NA**	0	NC	0	**NA**	Anthony (1)
Octreotide vs no or other treatment	Intestinal neuro-endocrine tumor	PFS	NS	NA	NA	**NA**	0	NA	0	**NA**	Arauyo (2)
Octreotide and interferon vs octreotide	Progressive. metastatic GEP-NET	OS (and TTF)	NS	NS	No	**NA**	0	NC	0	**NA**	Arnold (3)
Lanreotide autogel vs lanreotide microparticels	Sporadic NET. new diagnosis or progression	RR	NS	NS	NA	**NA**	0	NC	0	**NA**	Bajetta (4)
Streptozocin and 5FU vs interferon	Unresectable malignant carcinoid tumor	PFS	NS	NS	No	**NA**	0	NC	0	**NA**	Dahan (5)
Streptozocin and 5FU vs doxorubicin	Unresectable. progressive metastatic carcinoid.	OS and response rate	NS	NS	NA	**NA**	0	NC	0	**NA**	Engstrom (6)
Interferon vs lanreotide	Progressive. metastatic. treatment-naive GEP NET	RR	NS	NS	NA	**NA**	0	NC	0	**NA**	Faiss (7)
Lanreotide vs interferon and lanreotide	Progressive. metastatic. treatment-naive GEP NET	RR	NS	NS	NA	**NA**	0	NC	10	**NA**	Faiss (7)
Octreotide vs placebo	Gastro-intestinal NET	Number of symptom episodes and 5-HIAA	NA	NA	Yes. in 2/5 domains of PAIS	**3**	0	NA	10	**NA**	Jacobsen (8)

Supplementary Table S2: Clinical benefit of systemic treatment for GEP-NET according to ESMO-MCBS (ESMO-MCBS) and according ASCO revised framework (NHB) (*continued*)

Intervention vs control	Setting	Primary Outcome	ESMO-MCBS				ASCO revised framework				
			HR of primary outcome/ RR	Intoxication data	Improvement QOL (Yes/No)	ESMO-MCBS	Clinical benefit score	Intoxication data	Bonus points	NHB	References
Interferon alfa. streptozocin and doxorubicin vs interferon	Carcinoid tumor	RR	NS	NS	NA	**NA**	0	NC	0	**NA**	Janson (9)
Octreotide and interferon vs octreotide	Carcinoid tumor of midgut with liver metastases	Risk of tumor progression	0.28 (0.16-0.45)	NS	NA	**NA**	NC	NA	0	**NA**	Kölby (10)[B]
Telotristat Ethyl and SSA vs placebo and SSA	Metastatic NET with carcinoid syndrome and ≥ 4 BM a day	BM freq reduction	44 vs 20%	NS	NA	**NA**	NA	NA	10	**NA**	Kulke (11)
Telotristat Ethyl and SSA vs placebo and SSA	Metastatic NET with carcinoid syndrome and ≥ 4 BM a day	BM freq reduction	42 vs 20%	NS	NA	**NA**	NA	NA	10	**NA**	Kulke (11)
Chemotherapy before everolimus or placebo	Chemo-naive participants of the RADIANT-3 trial	PFS	0.32 (0.21-0.48)	NA	NA	**3**	44	-20	0	**24**	Lombard-Bohas (12)
Chemotherapy before everolimus or placebo	Participants with prior chemotherapy of the RADIANT-3 trial	PFS	0.45 (0.29-0.70)	NA	NA	**3**	54.4	-20	16	**50.4**	Lombard-Bohas (12)
Streptozocin and Cyclophosphamide vs Streptozocin and 5FU	Unresecatble metastastic carcinoid tumor	RR	26% vs 33 %	No	NA	**NA**	0	0	0	**0**	Moertel '79 (13)
Streptozocin and 5FU vs streptozocin	Advanced islet cell carcinoma	RR	63 vs 36%	No	NA	**2**	44	NC	0	**NA**	Moertel '80 (14)
Chlorozotocin vs streptozocin and FU vs Streptozocin and doxorubicin	Unresectable or metastatic islet cell carcinoma.	RR. but also OS is given	1.4yr vs 2.2 yr Strep/FU vs Strep/dox	NS	NA	**4**	151.9	NC	16	**NA**	Moertel '92 (15)[C]

Supplementary Table S2: Clinical benefit of systemic treatment for GEP-NET according to ESMO-MCBS (ESMO-MCBS) and according ASCO revised framework (NHB) (*continued*)

Intervention vs control	Setting	Primary Outcome	ESMO-MCBS			ASCO revised framework					References
			HR of primary outcome/ RR	Intoxication data	Improvement QOL (Yes/No)	ESMO-MCBS	Clinical benefit score	Intoxication data	Bonus points	NHB	
Interferon vs Streptozocin and 5FU	Carcinoid tumor	RR or stable disease	0 vs 20 %	NS	NA	**2**	14	NC	0	**NA**	Oberg '89 (16)
Streptozocin and 5FU vs streptozocin and 5FU followed by interferon	Carcinoid tumor with liver metastases.	RR. but also OS is given	8 vs72 m p<0.001	NS	NA	**4**	NC	NC	20	**NA**	Oberg '91 (17)[D]
Streptozocin and 5FU vs first-line interferon	Carcinoid tumor with liver metastases.	RR. but also OS is given	8 vs 56 m	NS	NA	**4**	NC	NA	20	**NA**	Oberg '91 (17)[D]
Lanreotide vs octreotide	Carcinoid tumor with carcinoid syndrome.	QoL disappearance of flushes	NS	NS	No	**NA**	0	NA	0	**NA**	O' Toole (18)
Octreotide LAR vs no or other treatment	Metastasized NET patients of ≥ 65 years registered in the SEER database	OS	0.61 (0.47-0.79)	NA	NA	**4**	39	NA	0	**NA**	Shen (19)
Octreotide LAR vs no treatment with octreotide LAR	NET patients ≥ 65 year registered in the SEER database. with loco-regional disease.	OS	NS	NA	NA	**NA**	0	NA	0	**NA**	Shen (19)
Octreotide LAR with previous SSA vs Octreotide LAR without previous SSA	Foregut. midgut or hindgut NET-patients included in the placebo arm of the RADIANT-2 trial.	OS	33.5 m vs 50.6 m	NA	NA	**NA**	NA	NA	NA	**NA**	Strosberg (20)[E]
Streptozocin /5FU vs doxorubicin/5FU followed by DTIC if PD	Unresectable. advanced carcinoid tumors	RR or OS	15.7m vs 24.3m OS p=0.0267	NS	NA	**4**	54.8	NC	0	**NA**	Sun (21)

Supplementary Table S2: Clinical benefit of systemic treatment for GEP-NET according to ESMO-MCBS (ESMO-MCBS) and according ASCO revised framework (NHB) (*continued*)

Intervention vs control	Setting	Primary Outcome	ESMO-MCBS				ASCO revised framework				
			HR of primary outcome/ RR	Intoxication data	Improvement QOL (Yes/No)	ESMO-MCBS	Clinical benefit score	Intoxication data	Bonus points	NHB	References
Y-DOTATOC vs Y-DOTATOC and LU-DOTATOC	Progressive. metastatic neuroendocrine tumor.	OS	0.64 (0.47-0.88)	NS	NA	**4**	36	NC	0	**NA**	Villard (22)
Lanreotide vs placebo	NET patients with carcinoid syndrome	Symptom control (days of octreotide)	NS	NS	NS	**NA**	NA	NA	0	**NA**	Vinik (23)
Pasireotide LAR vs octreotide LAR	Carcinoid tumor of digestive tract with inadequately controlled diarrhea and/or flushing.	Symptom control	NS	NS	NA	**3**	43.2	NC	0	**NA**	Wolin (24)
Octreotide and bevacizumab vs PEG-interferon and Octreotide	Metastatic carcinoid tumor	Response (and PFS)	NS	NS	NA	**NA**	0	NC	0	**NA**	Yao '08 (25)
Everolimus with octreotide LAR vs everolimus without octreotide LAR	Advanced pancreatic NET with progressive disease after chemotherapy	RR	NA	NS	NA	**NA**	0	NC	0	**NA**	Yao '10 (26)[F]

ASCO= American Society of Clinical Oncology. BM= bowel movements. BM freq reduction= reponse. defined as a bm frequency reduction ≥ 30% from baseline for ≥ 50% of the treatment period. ESMO-MCBS= European Society of Medical Oncology- Magnitude of Clinical Benefit Scale. GEP-NET=gastrointestinal and/ or pancreatic neuro-endocrine tumor. GI=gastro-intestinal. HR= hazard ratio. NET=neuroendocrine tumor. vs=versus. LAR=long acting reagents. NA= not applicable NC. no consensus. ND= no improvement or no important difference. NS=no significant difference. OS=overall survival. PFS=progression free survival. QoL=quality of life. RR=response rate. SSA=somatostatin analogue vs= versus.

A First author. References are reported in the supplementary reference list.

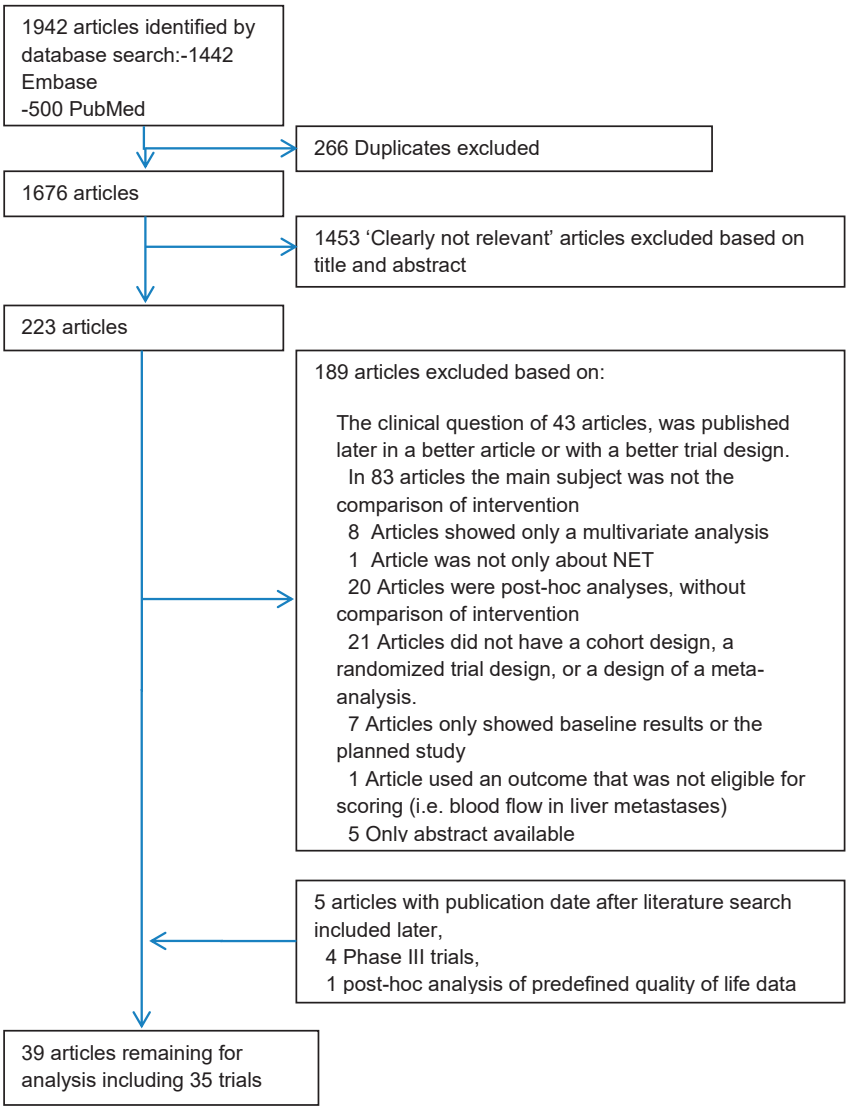
B Although the risk of tumor progression is significant different. this endpoint can not be used in the ESMO-MCBS. nor in the ASCO Framework. Some centers used this endpoint as being a HR of PFS. or used instead of this endpoint the response rate (although no p-value or significance level was given with the response rate).

C Although the time to tumor progression is significant different this endpoint can not be used in the ESMO-MCBS and ASCO Framework. In ASCO framework overall survival is not permitted because cross over.

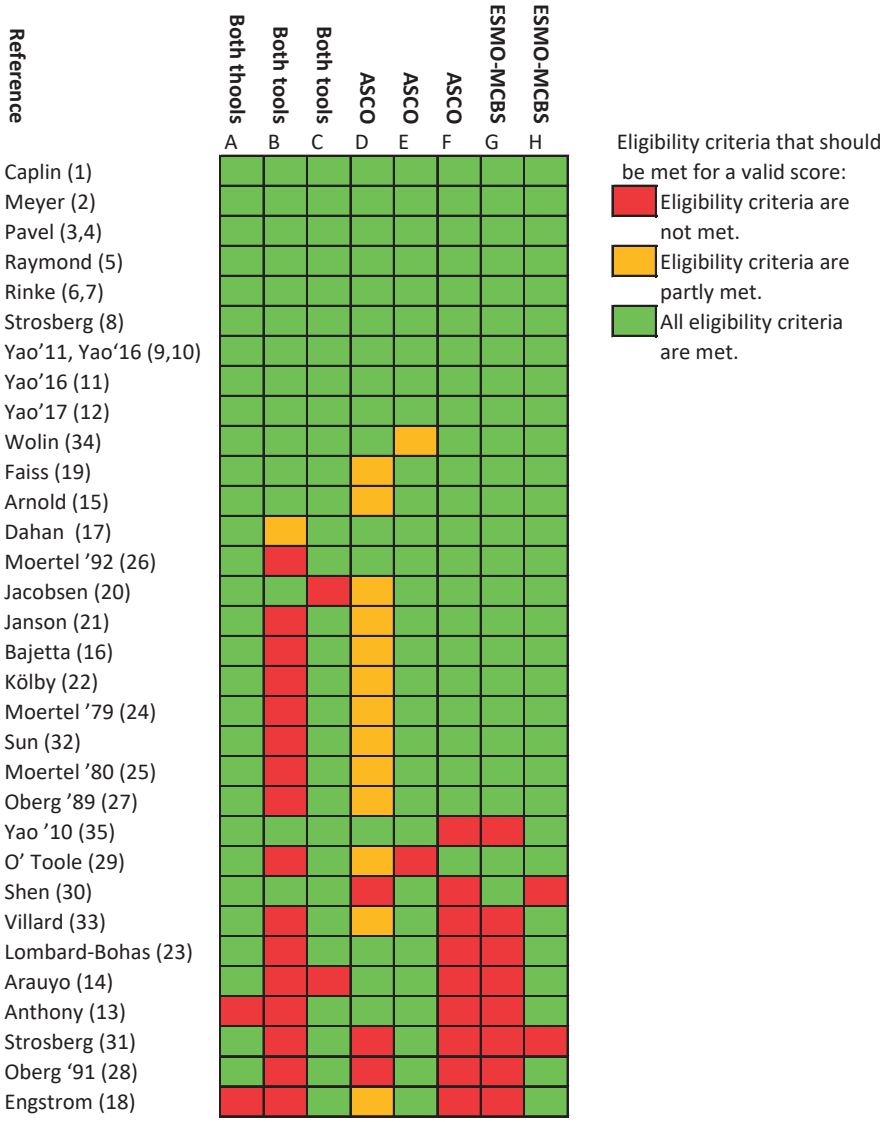
D Patients were not randomized. but assigned to a treatment. This probably have led to bias.

E Patients were divided based on the treatment the participant had before inclusion in the RADIANT-2 trial. No statistical analysis is performed between the two groups.

F Patients were stratified no statistical analysis is performed between the two strata



Supplementary Figure S1. Inclusion process for the literature analysis



A; More than 50% of participants has another NET than a gastro-intestinal or pancreatic NET
B; Sample size of pre-planned power analysis not reached
C; Same clinical question evaluated in more studies
D; Toxicity data are not available and graded
E; Outcome data available
F; No prospective, randomized design
G; No randomized, comparative cohort design, or meta-analysis
H; No toxicity data available

Figure 2. Eligibility criteria for a valid evaluation with the tools

Supplementary data; Extensive methods

Search strategy

Trials were searched in the databases PubMed and EMBASE between Aug 1st 2015 to Jan 31th 2016. The following search terms were used in various combinations 'neuroendocrine', 'tumor', 'pNET', 'neoplasm', 'survival', 'disease-free survival', 'quality of life', 'QOL', 'toxicity', 'adverse events', 'chemotherapy', 'cytostatic', 'interferon', 'somatostatin analogue', 'everolimus', 'sunitinib', 'indium', 'lutetium', 'peptide receptor radionuclide', 'controlled trial' and 'clinical trial'. The articles that were found were screened using title and abstract to select trials published in the English language and comparing systemic treatment modalities for the treatment of GEP-NET in humans. Furthermore the reference lists of the European Neuroendocrine Tumor Society (ENETS), National Comprehensive Cancer Network, (NCCN) and North American Neuroendocrine Tumor Society (NANETS), guidelines were reviewed for comparative trials that support the guidelines (suppl ref 27-29). Also reference lists of included trials and conference abstracts were reviewed for additional relevant articles.

Selection criteria for trials

Comparative trials investigating systemic antitumor treatment for GEP-NET patients were analyzed. Criteria for assessment are summarized in Table S1. Trials were eligible for grading with the ESMO-MCBS if either a randomized or comparative cohort design was used or if a meta-analysis was used reporting a statistically significant benefit in any of the evaluated outcomes. With the NHB of the revised ASCO framework only randomized controlled trials (RCTs) could be graded. Furthermore for both tools only well-powered trials evaluating survival, QoL, surrogate outcomes of survival (disease-free interval, event-free survival, time to response, PFS and time to progression), or treatment toxicity could be graded. When more than one trial, that fulfilled the selection criteria, analyzed the same clinical question, results derived from well powered registration trials, prevailed. Trials were selected if at least 50% of participants were diagnosed with GEP-NET, and the other participants had a NET of unknown or other origin. Abstracts reporting clinical trials in GEP-NET patients were only permitted for analysis if they showed additional data to an already published article.

ESMO-MCBS and the NHB of the revised ASCO framework

ESMO-MCBS grades in the non-curative setting ranges from 1-5, with grade 4 and 5 representing meaningful clinical benefit. To evaluate different endpoints three forms are available; form 2a and 2b for 'trials with primary endpoint OS', and 'PFS', respectively and form 2c for trials with 'with primary endpoint other than OS or PFS or equivalence studies'. The NHB of the revised ASCO framework consists of the clinical benefit score

(CBS), (i.e. the hazard ratio or median of OS or PFS, or response rate (RR)) toxicity and bonus points (for long term disease control, palliation, treatment free interval and QoL). The NHB of the revised ASCO framework ranges from -20 to 180, with a higher score representing a better NHB, no cutoff value was provided to define clinical benefit. All relevant comparative trials were assessed according to both tools. Relevant trials that did not meet all criteria as mentioned in Table 1 were assessed separately, based on the available data.

Assessment of trials

Four members from all Dutch European Neuroendocrine Tumor Society (ENETS) centers of excellence (Academic Medical Center, Erasmus Medical Center, Netherlands Cancer Institute, and University Medical Center Groningen) independently scored the trials according to the ESMO-MCBS and the NHB of the revised ASCO framework. After obtaining scores of these assessors we noticed a wide variation in results. During a consensus meeting additional agreements were defined. Next, trials were assessed again according to the additional agreements. The number of trials to which the same score was awarded between three or four assessors was registered after each of the two scoring sessions. Two phase III trials were published after the consensus meeting and were assessed according our agreements. Therefore an additional assessment session was not necessary for these trials.

Supplementary data; references

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