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Anti-Tumour Treatment

# A systematic review of non-surgical treatments for pancreatic neuroendocrine tumours

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ABSTRACT

*Introduction:* Pancreatic neuroendocrine tumours (pNETs) are rare and the majority of patients present with advanced disease. Such patients have limited treatment options. We conducted a systematic review of published clinical trials of non-surgical interventions in pNET, to understand the efficacy, safety and health related quality of life (HRQoL) outcomes from the current evidence base.
*Methods:* Electronic databases and manual bibliographic searches were conducted to identify relevant studies. Data were extracted by two independent reviewers.
*Results:* Forty seven clinical studies met the predefined inclusion criteria. The following interventions were included: targeted therapies (two RCTs and six single-arm studies), chemotherapy (two RCTs, one prospective nonrandomised, comparative study and 14 single-arm studies);somatostatin analogues (SSA) and radiolabeled SSA therapies (nine single-arm studies), liver-directed therapies (six single-arm studies), mixed treatment regimens (one RCT, four single-arm studies) and other interventions such as interferon and recombinant human endostatin (one single-arm study for each). The paucity of RCT data and lack of consistency in reporting validated study outcomes and differing patient inclusion criteria between studies made it difficult to compare the relative efficacy of therapies.
*Discussion:* The majority of published studies assessing treatment regimens for the management of pNET are single arm, non-randomised studies, often enrolling a small number of patients and not reporting clinically meaningful outcomes. However data from recently conducted studies assessing targeted therapies indicate that it is possible to conduct adequately powered RCTs reporting standardised oncological endpoints in this rare cancer. Further, similarly robust studies should be conducted to define the optimal treatment algorithm.



## Introduction

Pancreatic neuroendocrine tumours (pNETs) are rare. Worldwide, the annual incidence of pNET is estimated to range from 0.2 to 0.4 per 100,000 population, although due to the relatively indolent nature of these tumours the true prevalence may be much higher [1–3]. At presentation, 65% of patients have unresectable or metastatic disease. The 5-year survival rate of patients with metastatic disease is 30–40% and has not changed significantly over the last 30 years [4].

Clinically, pNETs are divided into two groups: functional (10–30%) or non-functional (70–90%). Functional pNETs secrete biologically active peptides, or hormones producing one of nine recognised specific hormonal syndromes. These tumours are associated with a reduced quality of life (QoL) in patients [5]. The hormones secreted by functional tumours include gastrin, insulin, glucagon, somatostatin, vasoactive intestinal polypeptide (VIP), growth hormone-releasing factor and adrenocorticotrophic hormone [5]. The hormonal syndromes are associated with diverse clinical features with regard to both metastatic potential and

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survival. For example 10% of patients who present with an insulinoma will develop metastases, compared with 50% of those with somatostatinoma and up to 70% of patients with VIPoma [6].

Surgery, where possible, is considered the first-line treatment for pNET patients. Due to the presence of distant metastatic disease or local extension of the tumour, surgery is often non-curative, but even in advanced cases surgical debulking of disease can reduce symptoms related to tumour burden and hormone production [7]. For patients who are not candidates for surgery, the choice of treatment depends on the stage of the disease, symptoms and histological features of the tumour [8]. Treatment options include SSA and liver-directed therapies (for example, chemoembolisation, radioembolisation, arterial embolisation and radiofrequency ablation, which are palliative options for liver-dominant disease) [6,7,9–11]. In clinical practice, systemic chemotherapy is commonly used in the treatment of pNET, but with modest efficacy (responses are rarely complete) and the attendant toxicity profiles. Such chemotherapy agents include streptozocin, doxorubicin, 5-fluorouracil, dacarbazine, capecitabine and temozolomide [6,7,9,12].

There have been limited developments in the management of advanced pNET over the last two decades [13,14]. However, an improved understanding of the molecular mechanisms underlying pNET has led to more recent treatment options that include agents directed at inhibiting growth factors or their receptors that are produced by these tumours [15,16]. Several of these agents are still investigational and to date, only the tyrosine kinase inhibitor sunitinib and the mTOR inhibitor everolimus have been licensed by the European Medicines Agency and the FDA for the treatment of unresectable or metastatic, well-differentiated pNETs with disease progression in adults.

A number of reviews of treatments specifically for pNET have been previously published [7,15,17], as well as reviews of treatments for all NETs [12,18–20]. Several evidence-based guidelines on the management of pNET are available which include recommendations for the treatment of pNET (e.g. guidelines from the UK and Ireland Neuroendocrine Tumour Society (UKINETS) [6], the National Comprehensive Cancer Network (NCCN) [21] and the European Neuroendocrine Tumour Society (ENETS) [9].

More recently, key recommendations from the NET Clinical Trials Planning Meeting included the separate examination of carcinoid tumours and pancreatic NETS in clinical trials and the avoidance of SSA washout periods when evaluating novel agents for the control of hormonal syndromes [22]. An update to the UKINETS guidelines covers genetics, diagnosis, imaging, pathology, treatment, ablation and carcinoid heart disease [23]. Updated consensus guidelines from ENETS are also available [24].

As new targeted therapies emerge and become more widely used in the management of pNET, this review was undertaken to understand the current evidence base in terms of efficacy and safety of non-surgical treatments and to assess the trial methodology supporting the use of chemotherapies and new agents in this setting.

## Methods

### *Inclusion criteria*

Randomised controlled trials (RCTs), non-RCTs and prospective single-arm studies were included if they enrolled adult patients with a confirmed diagnosis of pNET (as defined by recognised clinical guidelines). Studies enrolling patients with NETs of any aetiology (including pancreas) were included as long as relevant efficacy/safety outcomes were reported for the pNET subset of patients. Only studies with at least 10 pNET patients were included in

**Table 1**
Inclusion and exclusion criteria.

| Criterion | Included | Excluded |
|---|---|---|
| Population | • Age: ⩾18 years<br>• Race: any<br>• Qualifying disease: pancreatic neuroendocrine tumours (pNET)†<br>• No restriction on previous treatment/surgery (ie treatment naïve & refractory patients) | • Age:⩽18 years• Non-pancreatic neuroendocrine tumours |
| Perspective of study | • Prospective (concurrent)<br>• Comparative<br>• Non-comparative | • Retrospective |
| Study characteristics | RCTs: parallel/Cross-over design (with adequate wash-out period between treatments<br>Non-RCTs: cohort/case series | • Case report• Case studies with single patient |
| Language | • Any | - |
| Trial length | • All study durations | - |
| Sample size | • ⩾10 pNET patients | • <10 pNET patients |
| Interventions/ treatments | • Systemic chemotherapy<br>• Targeted therapies (including everolimus, bevacizumab, sorafenib, sunitinib, gefitinib)<br>• Somatostatin analogue<br>• Interferon/Biotherapy<br>• Radionuclide therapy, including peptide receptor radionuclide therapy<br>• Radiofrequency ablation<br>• Chemo-embolisation<br>• Hepatic artery embolisation (HAE) with/without chemotherapy (HACE)<br>• Combination regimens.<br>• No restriction on dose, formulation, or mode of delivery | • Surgery |
| Control intervention/ treatments | • Any of the interventions listed abovePlacebo/usual careNo treatment | - |
| Included trial outcomes | *Efficacy*, including but not restricted to overall survival, progression free survival, objective overall response rate (PR + SD), Time to progression (TTP)/duration of response<br>*Safety*, including withdrawals due to:<br>• Any reason<br>• Lack of efficacy<br>• Adverse events<br>• *Health-related quality of life* | Studies only reporting symptomatic relief outcomes for functioning tumours |

AE, adverse event; PR, partial response; RCT, randomised controlled trial; SD, stable disease.
† Studies enrolling patients with neuroendocrine tumours of any aetiology (including pancreas) were be included as long as relevant efficacy/safety outcomes were reported for the pNET subset of patients.

this review as the robustness of results from smaller studies was felt to be questionable (Table 1).

*Identification of studies*

A systematic review of electronic databases and conference proceedings was conducted to identify relevant studies. Medline, Embase, The Cochrane Library, BIOSIS and ISI Web of Knowledge were accessed in April 2012. The search combined pNET terms 'neuroendocrine tumor' and 'pancreas' with intervention terms for somatostatin, chemotherapy and pharmacotherapy agents, interferon, radionuclide therapies and liver-directed therapies. Conference proceedings from the American Society of Clinical Oncology (ASCO), European Neuroendocrine Tumor Society (ENETS) and the European Society for Medical Oncology (ESMO) were handsearched (2006–2012 inclusive).

Identified studies were independently assessed by two researchers in order to ascertain whether they met a set of pre-defined inclusion/exclusion criteria for inclusion in the systematic review (Table 1).

*Data extraction*

A pre-determined data extraction table was designed in an Excel® spreadsheet. The primary efficacy outcomes extracted included overall survival (OS), progression free survival (PFS), objective overall response rate (ORR), tumour response and time to progression (TTP)/duration of response. The safety outcomes of interest included incidence of death, incidence of withdrawal, and incidence of serious adverse events (AE). Health related quality of life (HRQoL) data (reported using generic- or disease-specific questionnaires) were also extracted.

*Quality assessment*

Study quality was assessed independently by two reviewers using the methods recommended in the Cochrane Reviewer's handbook [25] for RCTs and the Chambers quality assessment checklist for single-arm studies [26]. Any differences of opinion were resolved by discussion and consensus.

*Data analysis*

As discussed in more detail in the results section, there was considerable variation between the studies meeting eligibility criteria for inclusion in the review in terms of study design (majority of studies enrolled single-arm cohorts), reported outcomes and included populations. Therefore as a robust meta-analysis comparing the efficacy and safety of all available treatments was not feasible, results were summarised qualitatively.

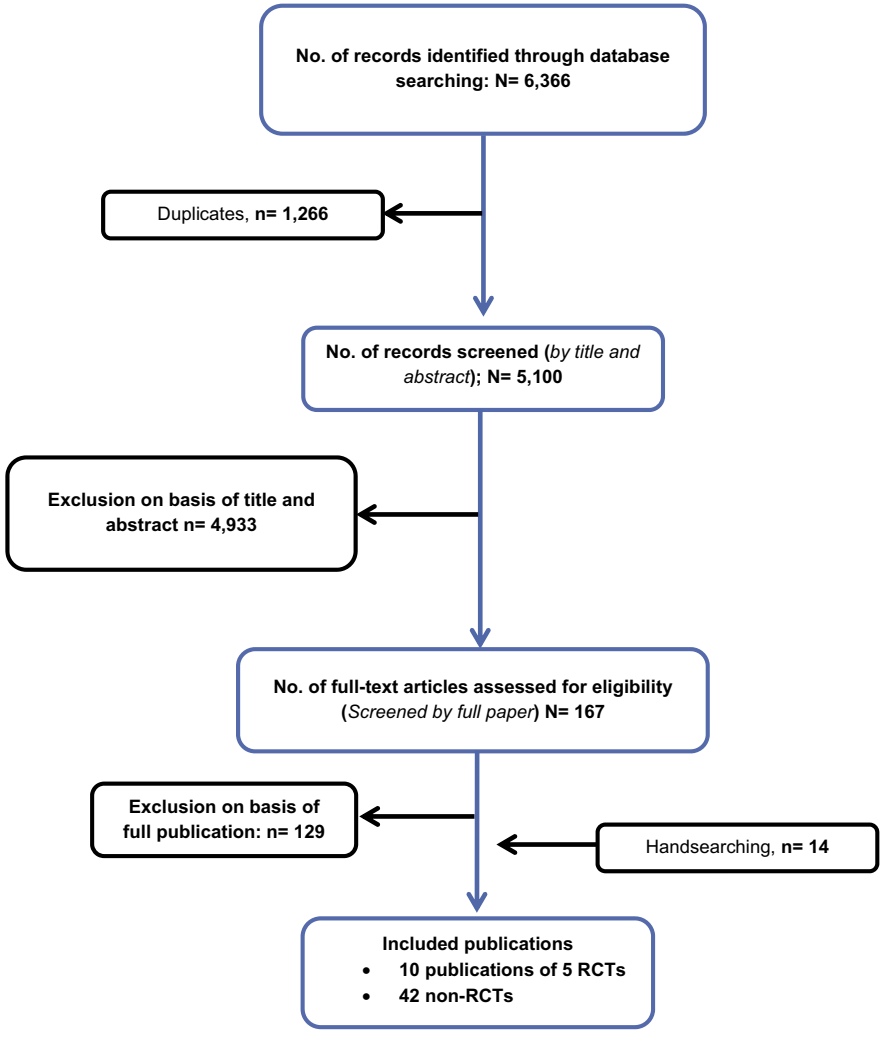


**Fig. 1.** Study Flow Diagram.

**Table 2**
Study characteristics of included studies. Primary outcome shown in bold.

| Study reference | Study location | No. of patients | Treatment, dose and duration | Study population | Outcomes reported |
|---|---|---|---|---|---|
| *Randomised controlled trials (n = 5)* | | | | | |
| *Targeted therapies (n = 2)* | | | | | |
| Raymond 2011 [33] | France, UK, Germany, | 86 | Sunitinib, 37.5 mg/day, continuous daily dosing | Well differentiated, pNET; disease | **PFS**, ORR, OS, safety, QoL |
| Full text | Belgium, Taiwan, | 85 | Placebo, continuous daily dosing | progression < 12 months | |
| | South Korea,Canada | | | | |
| Yao 2011, RADIANT-3 [34] | USA, Japan, France, | 207 | Everolimus, 10 mg/day, continuous daily dosing | Low-grade or intermediate-grade advanced | **PFS**, objective response rate, |
| Full text | Belgium, Spain, | 203 | Placebo, continuous daily dosing | pNET and radiological documentation of | duration of response, OS, safety. , |
| | Netherlands, Italy, | | | disease progression in the 12 months | |
| | Germany, Sweden | | | preceding randomisation | |
| *Chemotherapy (n = 2)* | | | | | |
| Moertel 1992 [28] | USA | 33 | Chlorozotocin IV 150 mg m2 BSA, every 7 weeks | Unresectable or metastatic islet-cell | Regression, progression, survival, |
| Full text | | 33 | Streptozocin IV 500 mg and Fluorouracil 400 mg per m2 BSA; 5 days, repeated every 6 weeks. | carcinoma | safety |
| | | 36 | Streptozocin IV 500 mg per m2 BSA (5 days)Doxorubicin 50 mg m2 BSA, , day 1 and day 22 of each 6 week cycle | | |
| Moertel 1980 [27] | USA | 42 | Streptozocin IV 500 mg per m2 BSA/day; 5 days, repeated every 6 weeks | Unresectable, metastatic islet-cell carcinoma diagnosed histologically. | ORR, CR, median survival, safety |
| Full text | | 40 | Streptozocin IV 500 mg per m2 BSADoxorubicin 50 mg m2 BSA5 days, repeated every 6 weeks | | |
| *Mixed treatment (n = 1)* | | | | | |
| Pavel 2008 [32] | NR | 8 | Streptozotocin 500 mg/m2 + 5-FU 400 mg/m2 IV, day 1-5, repeated on day 43 for 9 cycles. | Histologically proven, therapy-naïve pNET | Response (CR, PR, SD), TTP, safety |
| Abstract | | 8 | Octreotide LAR 30 mg IM, monthly | | |
| *Non-randomised studies (n = 42)* | | | | | |
| *Targeted therapies (n = 6)* | | | | | |
| Hobday 2007 [38] | USA | 41 | Sorafenib 400 mg BID, continuous daily dosing | pNET and carcinoid tumours ($n = 50$); prior interferon/ prior or concurrent octreotide allowed. | Response **(PR**, MR), PFS, safety |
| Abstract | | | | | |
| Hobday 2006 [37] | USA | 39 | Gefitinib 250 mg BID, continuous daily dosing | pNET and carcinoid tumours ($n = 57$); prior interferon/ prior or concurrent octreotide allowed. | **PFS**, response (PR, MR, SD), safety |
| Abstract | | | | | |
| Yao 2010 [49] | International (11 | 115 | Everolimus 10 mg/day, continuous daily dosing | Histologically confirmed, well to moderately | **ORR**, PFS, duration of response, |
| Full text | countries) | 45 | Everolimus 10 mg/day + octreotide LAR ($\leqslant$30 mg) | differentiated, advanced pNET | OS, safety |
| Duran 2006 [51] | USA, Canada | 15 | Temsirolimus 25 mg IV/week for 8 weeks | Histological/cytological confirmed carcinoid/ | **ORR**, SD, duration of SD, TTP, OS, |
| Full text | | | | pancreatic islet cell tumour with documented progressive metastatic disease | safety |
| Kulke 2010 [52] | USA | 24 | Everolimus 5 mg or 10 mg qd with temozolomide 150 mg/ m2 qd given for 7 days, maximum of 6 4-week cycles | Histologic evidence of pNET, not suitable for curative surgery | Response (PR, SD, PD); safety |
| Abstract | | | | | |
| Kulke 2008 [36] | USA | 66 | Sunitinib, 50 mg/daily for 4 weeks | Histologic evidence of PNET; not candidates for curative surgery | **ORR**, TTP, OS, safety |
| Full text | | | | | |
| *Chemotherapy (n = 15)* | | | | | |
| Bukowski [53] | USA | 44 | Good-risk. Chlorozotocin (CTZ) 175 mg/m$^2$ IV day 1 + 5-FU 800 mg/m2/d IV days 1-4; maintenance dose of 100 mg CTZ and 600 mg of 5-FU. Poor-risk pts given lower dosage.Maximum of 18 months | Biopsy-proven islet-cell carcinoma, not amenable to surgery | PR, ORR, OS Safety |
| Full text | | | | | |
| Eriksson [54] | Sweden | 25 | STZ IV 0.5 g/m$^2$ for 5 days, maintenance of 1 gm/m$^2$ every third week + doxorubicin 40 mg/m$^2$ every third week.Median 12 months | Clinically verified endocrine pancreatic tumour (benign/ malignant tumours included) | ORR, OS, safety |
| Full text | | 19 | As above + 5-FU IV 400 mg/m$^2$ every third week.Median 12 months | | |
| Fjallskog [55] | Norway | 30 | Doxorubicin 30 mg/m$^2$ on day 1 with 1 g Streptozotocin as bolus injection days 1-5. Median of 13 courses (course every | Histopathologic confirmation of non-resectable pNET | ORR, PFS, OS, safety |
| Full text | | | | | |

(*continued on next page*)

**Table 2** (*continued*)

| Study reference | Study location | No. of patients | Treatment, dose and duration | Study population | Outcomes reported |
|---|---|---|---|---|---|
| | | | 3 weeks) administered | | |
| Ramanathan [56] Full text | USA | 50 | DTIC 850 mg/m$^2$ IV. At least 2 courses(course every 4 weeks), continued until progression | Histopathologic confirmation of non-resectable, malignant islet cell carcinoma | ORR, OS, safety |
| Bajetta [57] Full text | Italy | 28‡ | 5-FU 500 mg/m$^2$, DTIC 200 mg/m$^2$, epiadriamycin 30 mg/m$^2$) IV on days 1-3. Median: 4 months | NET confirmed by pathology | ORR, TTP, OS, safety |
| Moertel [58] Full text | USA, Canada, France, Switzerland | 20 | Doxorubicin 60 mg/m2 IV, repeated at 3 weeks, 6 weeks and then every 4 weeks.Until evidence of disease progression or until a total of doxorubicin dose of 500 mg/m2 had been administered | Histopathologic confirmation of locally unresectable or metastatic islet cell carcinoma | ORR, OS, safety |
| Bajetta [59] Full text | Italy | 11 | Oxaliplatin 130 mg/mq day 1 IV + capecitabine 2000 mg/mq/die from day 2-15 every 3 weeks.6cycles maximum(each cycle 3 weeks) | High- low-grade malignant NETs | ORR, OS, TTP, safety |
| Fjallskog [60] Full text | Sweden | 14 | Etoposide 100 mg/m$^2$ /day for 3 days + cisplatin 45 mg/m$^2$ per day on days 2 and 3.Cycles repeated every 4 weeks | Histopathologic confirmation of NET | **ORR, OS, safety** |
| Bajetta [61] Full text | Italy | 15 | Fluorouracil 500 mg/m$^2$, DTIC 200 mg/m$^2$ + Epirubicin 30 mg/m$^2$ IV, 3 consecutive days. Cycles repeated every 3 weeks | Histologically proven locally advanced/metastatic NETs, not amenable to surgery | **ORR, PR, CR, safety** |
| Kulke [62] Full text | USA | 29 | Temozolomide 150 mg/m2 on days 1 to 7 and days 15 to 21. Thalidomide 200 mg /day. Cycle repeated every 28 days | Histologically confirmed, locally unresectable or metastatic neuroendocrine tumours | **ORR, PR, SD, PD, safety** |
| Moertel [63] Full text | USA | NR | Etoposide 130 mg/m$^2$/day IV for 3 days, Cisplatin 45 mg/m$^2$ on days 2 and 3. Cycle repeated every 4 weeks | Histologic confirmation of metastatic neuroendocrine tumour | **ORR, SD, OS safety** |
| Rivera [64] Full text | USA | 11 | Doxorubicin 40 mg/m$^2$i.v on day 1, Streptozocin 400 mg/m$^2$i.v and 5-Fluouracil 400 mg/$^2$i.v on days 1 to 5. Cycle repeated every 4 weeks | Confirmed pNET | **PR, SD, MR, OS, safety** |
| Sprenger [65] Abstract | Germany | 14 | 650 mg/m$^2$Dacarbacine once monthly i.v. | Metastatic neuroendocrine tumour | **PR, SD, safety** |
| Strosberg [66] Abstract | USA | 17 | Capecitabine 750 mg/m$^2$ twice daily on days 1-14 and temozolomide 200 mg/m$^2$ daily on days 10-14 | Progressive metastatic pNET | **SD, PR, safety** |
| Brixi-Benmansour [67] Full text | France | 20 | FOLFIRI chemotherapy: (irinotecan 180 mg/m2 infusion combined with simplifiedLV5FU2) every 14 days. Cycles repeated every 14 days using a chemotherapy free-interval scheme | Metastatic or advanced well-differentiated pNET and progressive disease. | **6 month non-PR, PFS, TTF, OS, disease duration control, safety, biological responses at 6, 12, 18, 24 months** |
| *SSA/radionuclide therapy (n = 9)* | | | | | |
| Kwekkeboom [68] Full text | Netherlands | 42 | Radiolabeled $^{177}$Lu-DOTA,Tyr Octreotate injected IV over 4 hours with saline. | Octreoscan-positive pNET | Response (CR, MR, SD, PD), safety |
| Butturini [69] Full text | Italy | 21 | Octreotide 100ug TID s.c. for 2 weeks followed by Octreotide LAR 20 mg every 28 days. | Octreoscan-positive well-differentiated nonfunctioning pNET | PFS, SD, safety |
| Kvols [70] Full text | USA | 22 | SSA given s.c. 50ug BID day 1, 100ug BID day 2 then 150ug TID ($n$ = 12).Dose increased to 250ug, 500ug and 500ug TID ($n$ = 10).Median 5 months(range 1–15) | Histologically confirmed metastatic islet cell carcinoma | Response (PR, MR, SD), safety |
| Forrer [71] Full text | Switzerland | 11 | IV $^{77}$Lu-DOTATOC 7,400 MB with saline. | Histologically confirmed metastatic neuroendocrine tumour | Response (PR, MR, SD), safety |
| Frilling [72] Full text | Switzerland | 15 | Two applications of $^{90}$Lu-DOTATOC (37 to 11 MBq of $^{111}$ In-DOTATOC injected). Each patent underwent at least 2 treatment sessions | Advanced histologically or cytologically proven progressive metastatic NET. | Response (PR, MR, SD, safety), |
| Panzuto [73] Full text | Italy | 18 | Octreotide LAR 30 mg or Lanreotide SR 60 mg IM injection every 28 days. Median 18 months (range 6–60) | Well-differentiated endocrine carcinoma | Response, OS |
| Saltz [74] Full text | USA | 13 | Octreotide IM 50ug bid increasing to 250ug tid | Advanced, incurable NET with confirmed pathologic status | ORR, OS, safety |
| Shojamanesh [75] Full text | USA | 15 | Short acting Octreotide 200 ug every 12 hours, LR formulation then used monthly (30 mg IM) | Gastrinoma with histologically proven liver metastases and disease progression | Response, duration of response, safety |
| Waldherr [76] Full text | Switzerland | 13 | 4 applications of $^{90}$Lu-DOTATOC (total 7.4 GBq/m$^2$) | Histologically confirmed metastatic neuroendocrine tumour | **Response (SD, PR), OS, safety** |

**Table 2** (*continued*)

| Study reference | Study location | No. of patients | Treatment, dose and duration | Study population | Outcomes reported |
|---|---|---|---|---|---|
| *Mixed treatments (n = 4)* | | | | | |
| Eriksson [77]<br>Full text | Sweden | 92 | Chemotherapy: IV Streptozotocin0.5 g/m$^2$ for 5 days followed by 1 gm/m$^2$ every third week + 5-FU IV 400 mg/m$^2$ for 3 days and then every third week.<br>Interferon: 5 MU 3 times a week. Octreotide: 100ug bd | Clinically verified malignant endocrine pancreatic tumour | Response, duration of response |
| Yao [78]<br>Full text | USA | 30 | Octreotide LAR 30 mg every 28 days + everolimus 5-10 mg/d. Maximum of 12 cycles | Histologically confirmed metastatic/unresectablelocoregional LGNETs. Prior treatment permitted | PFS, OS,ORR, response (PR, PD, SD), safety |
| Fjallskog [79]<br>Full text | Sweden | 16 | Median dose 9 MU/week interferon + Octreotide (450ug/day; *n* = 14) or Lanreotide (3000ug bd; *n* = 2). Follow up every 3 months | Histopathologic confirmed pNET | Response, duration of response, safety |
| Hobday [80]<br>Abstract | USA | 35 | Temsirolimus 25 mg IV q week and bevacizumab 10 mg/kg IV q 2 weeks | Patients with well or moderately differentiated pNET and PD by RECIST within seven months of study entry | ORR and 6-month PFS |
| *Liver-directed therapies (n = 6)* | | | | | |
| Moertel 1994 [81]<br>Full text | USA | 17 | Surgical patients: ligation of hepatic artery; other: catheterisation and embolisation. | Histologically confirmed carcinoid or islet cell carcinoma with liver metastases | ORR, duration of response; TTP, median survival; safety |
| | | 29 | Hepatic artery occlusion + chemotherapy<br>Alternating cycles of doxorubcin and dacarbazine: 5 weeks later with streptozocin and 5-FU | | |
| Rhee 2008 [82]<br>Full text | USA | 11 | 90Y radioembolization. 3 month follow up | Metastatic NET liver disease that had failed prior treatment | Response (PR, SD, PD); safety |
| Eriksson 1998 [83]<br>Full text | Sweden | 12 | Hepatic artery embolisation | Metastatic NET liver disease that had failed prior treatment | Response, duration of response, median survival; safety |
| Ajani 1988 [84]<br>Full text | USA | 20 | Hepatic artery embolisation | Histologically confirmed islet cell carcinoma | Complete/any response; safety |
| Kim 1999 [85]<br>Full text | USA | 14 | Hepatic artery chemo-embolisation. Subsequent treatments every 8-12 weeks (+ concurrent octreotide) | Histologically confirmed carcinoid/islet cell carcinoma with liver metastases | Response, median survival, median duration of response, safety |
| Capitanio 2010 [86]<br>Abstract | Italy | 11 | Doxorubicin emulsified in Lipidol, followed by gelatine sponge particles embolisation | Multifocal metastases with diameter less than 5 cm, without extrahepatic disease | Safety , long term survival |
| *Interferon (n = 1)* | | | | | |
| Eriksson 1986 [87]<br>Full text | Sweden | 22 | Human leucocyte interferon, 3-6x106 IU | Malignant PNET with histopathological diagnosis | Response (SD, PD); duration of response; safety |
| *Endostatin (n = 1)* | | | | | |
| Kulke 2006 [88]<br>Full text | USA | 20 | Recombinant human endostatin, 30 mg/m2 bid (28 day cycle). Median: 6.4 months | Metastatic pNET; prior chemo permitted; ECOG 0 or 1 | Response (PR; CR; SD; progression); median PFS, OS; safety |

pNET, pancreatic neuroendocrine tumour; BSA, body surface area; CR, complete response; DTIC, dacarbazine; FU, fluorouracil; IM, intramuscular; IV, intravenous; ORR, objective response rate; OS, overall survival; MR, minor response; PFS, progression free survival; PR, partial response; SC, subcutaneous; SD, stable disease; PD, progressive disease; SSA, somatostatin analogue; STZ, streptozotocin; TTP, time to progression; TTF, time-to-treatment failure; QoL, quality of life; BID, twice daily; TID, three times daily; MU, milliunits.

## Results

### Study flow

In total, 5,100 studies were identified from the literature search (following removal of duplicates). A further fourteen relevant publications were identified from searching reference lists and conference proceedings. After excluding papers not meeting the inclusion criteria, 52 publications of 47 studies were included in the systematic review (Fig. 1).

### Study characteristics

Systemic chemotherapy was the most common intervention (two RCTs, 15 non-randomised studies) with many single-arm studies evaluating a wide range of agents (Table 2). The second most frequently reported treatments were SSAs and radiolabeled SSA therapies (nine non-randomised studies), followed by novel targeted agents (two RCTs and six non-randomised studies), liver-directed therapies (six non-randomised studies), mixed treatment regimens (one RCT, four non-randomised studies) and other interventions such as interferon and recombinant human endostatin (one non-randomised study each).

A summary of the included studies is reported in Table 2. The included studies were highly varied in terms of study design; duration and outcomes; sample size; doses and schedules of the interventions employed (particularly in systemic chemotherapy studies) and features of the enrolled patient populations. A significant proportion (15%) of the included studies were published over 15 years ago including two of the pivotal RCTs [27,28]. These early studies often used criteria (e.g. physical examination) which are no longer considered appropriate to measure response to treatment. More recent studies have reported response rates using validated radiological criteria such as WHO [29] and RECIST [30].

### Study quality

Two of the early conducted RCTs [27,28] had an open-label study design and reported ambiguous allocation methods. Both of these criteria have been reported to be important determinants

**Table 3**
Survival/response data reported in RCT studies. Additional HRs are reported in footnotes.

| Study reference | Treatment | Survival | | | Tumour response | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Median PFS, months (95% CI) | OS, HR (95% CI) | Median OS, years | Complete response, % | Partial response, % | Stable disease, % | Progressive disease, % | Any response, % | Objective response rate, % | Median duration of response, months |
| *Targeted therapy (n = 2)* | | | | | | | | | | | |
| Raymond 2011 [33,35] | Sunitinib | 11.4 (7.4–19.8)[†] | 0.74 (0.47–1.17); $p = 0.19$[‡‡‡] | 30.5 mo (20.6, NR)[†] | 2[§] | 7[§] | 63[§] | 14[§] | | 9.3[‡,§] | |
| | Placebo | 5.5 (3.6–7.4)[†] HR 0.42 (0.26–0.66); $p < 0.0001$ vs. placebo[†††] | | 24.4 mo (16.3, NR)[†] | 0[§] | 0[§] | 60[§] | 27[§] | | 0[§] | |
| Yao 2011 RADIANT-3 [34] | Everolimus | 11.0 (8.4–13.9)[†] | HR 0.89 (0.64-1.23); $p = 0.59$[¶¶] | Not reached[†] | | | 73 | 14 | | | |
| | Placebo | 4.6 (3.1–5.4)[†] HR 0.35 (0.27–0.45); $p < 0.001$[§§§] | | 36.6 mo[†] | | | 51 | 42 | | | |
| *Chemotherapy (n = 2)* | | | | | | | | | | | |
| Moertel 1992 [28] | Chlorozotocin | NR | N | 1.5[¶] | 6[‡‡] | NR | NR | NR | 30[‡‡] | NR | 21 |
| | Streptozocin + Fluorouracil | | | 1.4[††] | 4[‡‡] | | | | 45[‡‡] | | 13 |
| | Streptozocin + Doxorubicin | | | 2.2 | 14[‡‡] | | | | 69[‡‡] | | 22 |
| Moertel 1980 [27] | Streptozocin | NR | NR | 16.5 mo | 12 | NR | NR | NR | 36 | NR | NR[§§] |
| | Streptozocin + Fluorouracil | | | 26 mo | 33 | | | | 63 | | |
| *Mixed treatments (n = 1)* | | | | | | | | | | | |
| Pavel 2008 [32] | Streptozotocin/ Fluorouracil | NR | NR | NR | 13 | 25 | 63 | NR | NR | NR | NR |
| | Octreotide | | | | 0 | 13 | 75 | | | | |

CI, confidence interval; mo, months; NR, not reported; OS, overall survival; PFS, progression-free survival; HR, hazard ratio.
[†] Investigator assessed.
[‡] $p = 0.007$ vs. placebo.
[§] Assessed using RECIST criteria.
[¶] $p < 0.03$ vs. Streptozocin + Doxorubicin.
[††] $p < 0.004$ vs. Streptozocin + Doxorubicin.
[‡‡] Response/regression definition used : Favourable objective response if tumour mass reduced by > 50% or 30% if malignant hepatomegaly was used, lab assay reduced by 50% tumour regression.
[§§] Median duration of response: 'all responses', 17 months; 'complete responses', 24 months.
[¶¶] OS Analysis cut-off Feb 2011 (146 events: 68 everolimus; 78 placebo). The result is confounded by crossover, 85% of patients crossed from placebo to everolimus. Median OS not reached for everolimus treatment arm, so data immature [80]. No crossover adjusted OS estimates have currently been published.
[†††] (i) Investigator assessed PFS: revised HR based on excluding patients who had WHO performance status of 2 from the RADIANT-3 trial (to match inclusion criteria of the Raymond, 2011 study: 0.38 (0.29–0.49) [42]; (ii) Analysis of data for a subgroup of 84 patients for whom MRI/CT scans were available to compare the results with central review assessment: sunitinib, 19.8 months vs. placebo, 5.8 months: investigator assessed HR 0.45 HR 0.45 (0.22–0.92) [39]; (iii) Retrospective blinded independent central review of the tumour imaging scans: sunitinib 12.6 months vs. placebo 5.8 months; HR 0.32 (0.18–0.55) [49].
[‡‡‡] Analysis conducted June 2010. The result is confounded by crossover; 69% of patients crossed from placebo to sunitinib. Additional HRs (95% CI) reported using four models to adjust for crossover (median follow-up 34.1 months): (i) censoring at crossover, 0.43 (0.24–0.77); $p = 0.004$; (ii) time-dependent Cox model, 0.49 (0.29–0.85); $p = 0.01$; (iii) RPSFT model, 0.43 (0.17–1.20); $p = 0.12$; (iv) RPSFT model adjusted for crossover time, 0.57 (0.18–1.09); $p = 0.12$ [48].
[§§§] Central review assessment of final PFS: everolimus 11.4 months (10.8-14.8) vs. placebo 5.4 months (4.3-5.6); HR 0.34 (0.26–0.44) [34].

**Table 4**
Survival/response data reported in non-RCT studies.

| Outcome | Chemotherapy ($n$ = 15) | Mixed treatments ($n$ = 4) | Targeted therapy ($n$ = 6) | SSA/radionuclide therapy ($n$ = 9) | Liver directed therapies ($n$ = 6) | Interferon ($n$ = 1) | Recombinant endostatin ($n$ = 1) |
|---|---|---|---|---|---|---|---|
| *Survival. No. of studies (no. PNET patients receiving the intervention)* | | | | | | | |
| No. studies reporting OS | 2 (30) | NR | NR | NR | NR | NR | 1 (20) |
| Reported range in OS (%) | 65–72[†] | NR | NR | NR | NR | NR | 17.2 |
| No. studies reporting median survival | 7 (169) | NR | NR | 1 (13) | 3 (72) | NR | NR |
| Reported range in median survival (months) | 6–66 | NR | NR | 23 | 9–40 | NR | NR |
| No. studies reporting 1-year survival rate | NR | NR | 2 (226) | NR | NR | NR | NR |
| Reported range in 1-year survival rate (%) | NR | NR | 75–81 | NR | NR | NR | NR |
| No. studies reporting median TTP | NR | NR | NR | NR | 1 (46) | NR | NR |
| Reported range in median TTP (months) | NR | NR | NR | NR | 4–22 | NR | NR |
| No. studies reporting median PFS | 2 (30) | 2 (65) | 1 (160) | 1 (21) | NR | NR | 1 (20) |
| Reported range in median PFS (months) | 9.1-13 | 6-12 | 10–17 | 41 | NR | NR | 5.8 |
| *Response No. of studies (no. PNET patients receiving the intervention)* | | | | | | | |
| No. studies reporting median duration of response | 5 (163) | 1 (107) | 1 (115) | NR | 3 (72) | 1 (22) | NR[‡] |
| Reported range in median duration of response (months) | 9–36 | 16–23 | 10.6 | NR | 3.6–24 | 8.5 | NR[‡] |
| No. studies reporting any response | NR | NR | NR | NR | 4 (57) | 1 (22) | NR[‡] |
| Reported range in no. of patients with any response, % | NR | NR | NR | NR | 17–80 | 77 | NR[‡] |
| No. studies reporting complete response | 13 (278) | 3 (153) | 6 (338) | 5 (102) | NR | 1 (22) | 1 (20) |
| Reported range in no. of patients with complete response % | 0–8 | 0 | 0 | 0–8 | NR | 5 | 0 |
| No. studies reporting partial response | 13 (278) | 3 (153) | 6 (338) | 6 (113) | 1 | 1 (22) | 1 (20) |
| Reported range in no. of patients with partial response % | 0–71 | 19–27 | 4–32 | 0–73 | NR | 5 | 0 |
| No. studies reporting minor response | NR | NR | NR | 2 (63) | NR | NR | NR |
| Reported range in no. of patients with minor response % | NR | NR | NR | 0–21 | NR | NR | NR |
| No. studies reporting stable disease | 11 (184) | 3 (153) | 4 (280) | 7 (133) | 1 | NR | NR[‡] |
| Reported range in no. of patients with stable disease % | 11–75 | 19–69 | 10–80 | 27–60 | NR | NR | NR[‡] |

OS, overall survival; TTP, time to progression; SSA, somatostatin analogue.
[†] 2-year OS.
[‡] Data not reported for subset of pNET patients (20/42).

of trial bias and studies with inadequate reporting tend to overestimate the treatment effect [31]. The mixed treatment RCT [32] was reported as a conference abstract only and therefore limited information on determinants of bias was reported. Two further placebo-controlled RCTs examining the targeted therapies sunitinib [33] and everolimus [34] were powered to show standard oncological end-points (PFS and OS) and employed the standardised RECIST criteria to measure response.

Many of the non-randomised studies enrolled small numbers of patients and are therefore underpowered to detect significant treatment effects. Forty of the 42 non-randomised studies enrolled 50 patients or less (median 19, [range 11–50] patients). The older studies tended to lack standardised inclusion criteria (e.g. including heterogenous tumour subtypes, patients with different exposure to prior therapy, severity of disease or evidence of disease progression at study entry).

The majority of non-randomised studies reported partial information making it difficult to appraise study quality using the Chambers checklist [26].

### *Efficacy*

A summary of the survival and response data reported in RCT and non-randomised studies is reported in Tables 3 and 4 respectively; given the higher level of evidence they provide we will focus on the RCTs.

Chemotherapy was the subject of two early RCTs published in 1980 [27] and 1992 [28]. The first study established that doublet chemotherapy (streptozocin and 5-FU) resulted in a superior response rate (63% vs. 36%) and OS (26 vs. 16.5 months) compared with streptozocin monotherapy in 82 randomised patients [27]. In the follow-on study comparing chlorozotocin vs. streptozocin/doxorubicin vs. streptozocin/5-FU, patients receiving combination chemotherapy once again fared better, with a response rate of 69% and OS of 2.2 years reported for the streptozocin/doxorubicin combination which appeared to be the most active regimen, although associated with significant toxicity [28]. Chemotherapy was adopted as the standard of care based on the results of these two early RCTs [27,28].

The two most recent RCTs (assessing the targeted agents sunitinib and everolimus), are the first and only published studies to documented an improvement in PFS compared with best supportive care (BSC)/placebo. Both studies had a similar design: selection of a homogeneous patient subgroup (pathologically-confirmed well-differentiated pNET with evidence of disease progression), use of a double-blind placebo-controlled design using a robust oncological end-point (PFS, by RECIST) and ability of

**Table 5**
Summary of safety data reported in RCT studies.

| Study reference | Treatment | Treatment-related deaths, % | Withdrawals due to AEs, % | Neutropenia, % | Thrombocytopenia, % | Nausea, % | Vomiting, % | Diarrhoea, % | Stomatitis, % |
|---|---|---|---|---|---|---|---|---|---|
| *Targeted therapy (n = 2)* | | | | | | | | | |
| Raymond 2011 [33] | Sunitinib | 1 | 17 | All grade, 29 Grade 3/4, 12 | All grade, 17 Grade 3/4, 4 | All grade, 45 Grade 3/4, 1 | All grade, 34 Grade 3/4, 0 | All grade, 59 Grade 3/4, 5 | All grade, 22 Grade 3/4, 4 |
| | Placebo | 1 | 8 | All grade, 4 Grade 3/4, 0 | All grade, 5 Grade 3/4, 0 | All grade, 29 Grade 3/4, 1 | All grade, 30 Grade 3/4, 2 | All grade, 39 Grade 3/4, 2 | All grade, 2 Grade 3/4, 0 |
| Yao 2011 [34]¶¶¶ | Everolimus | 2 | 17 | NR | All grade, 13 Grade 3/4, 4 | All grade, 20 Grade 3/4, 2 | All grade, 15 Grade 3/4, 0 | All grade, 34 Grade 3/4, 3 | All grade, 64 Grade 3/4, 7 |
| | Placebo | 1 | 3 | NR | All grade,<1 Grade 3/4, 0 | All grade, 18 Grade 3/4, 0 | All grade, 6 Grade 3/4, 0 | All grade, 10 Grade 3/4, 0 | All grade, 17 Grade 3/4, 0 |
| *Chemotherapy (n = 2)* | | | | | | | | | |
| Moertel 1992 [28] | Chlorozotocin | 0 | NR | Any§, 43 Severe¶, 2 | Any, 22† Severe‡, 6 | NR | Any, 43 Severe, 2 | Any, 6 Severe, 0 | Any, 0 Severe, 0 |
| | Streptozocin + Fluorouracil | 3 | | Any§, 81 Severe¶, 41 | Any†, 8 Severe‡, 6 | | Any, 81 Severe, 41 | Any, 33 Severe, 2 | Any, 19 Severe, |
| | Streptozocin + Doxorubicin | 0 | | Any§, 80 Severe¶, 20 | Any†, 0 Severe‡, 0 | | Any, 80 Severe, 20 | Any, 5 Severe, 0 | Any, 5 Severe, 0 |
| Moertel 1980 [27] | Streptozocin | 5 | 4†† | Mild‡‡, 5%; moderate§§, 0%; severe¶¶, 0% | Mild†††, 5%; moderate‡‡‡, 0%; severe§§§, 0% | Mild, 24%; moderate, 24%; severe, 36% | | NR | 0 |
| | Streptozocin + Fluorouracil | 0 | | Mild‡‡, 52%; moderate§§, 10%; severe¶¶, 10% | Mild†††, 4%; moderate‡‡‡, 12%; severe§§§, 12% | Mild, 32%; moderate, 32%; severe, 22% | | | 5 |
| *Mixed treatments (n = 1)* | | | | | | | | | |
| Pavel 2008 [32] | Streptozotocin/ Fluorouracil | NR | NR | Main AEs nausea, emesis, mucositis, electrolyte disturbance and thromboembolism | | | | | |
| | Octreotide | | | Main AEs: abdominal pain and meteorism | | | | | |

† Thrombocytopenia: any,<100 × $10^9$ cells/litre.
‡ Thrombocytopenia: severe:<50 × $10^9$ cells/litre.
§ Leukopenia: any,<4 × $10^9$ cells/litre.
¶ Leukopenia: severe:<2 × $10^9$ cells/litre.
†† Treatment group not reported.
‡‡ <4000 to ⩾2000/$mm^3$.
§§ <2000 to ⩾1000/$mm^3$.
¶¶ <1000/$mm^3$.
††† <150,000 to ⩾100,000/$mm^3$.
‡‡‡ <100,000 to ⩾50,000/$mm^3$.
§§§ <50,000/$mm^3$.
¶¶¶ Extended follow up (20.1 months) [everolimus vs. placebo]: Diarrhoea, all grade: 34.3 vs. 10.3%; stomatitis, all grade: 52.9 vs. 12.3%; stomatitis, grade 3/4, 4.9% vs. 0%.

patients to cross over from placebo to active drug on disease progression. Sunitinib demonstrated an improved PFS of 11.4 vs. 5.5 months (vs. placebo, HR 0.42 (0.26–0.66); $p < 0.0001$ vs. placebo) [33] and everolimus also had a similar magnitude of effect with an improved PFS of 11.0 vs. 4.6 months (vs. placebo, HR 0.35 (0.27–0.45); $p < 0.001$) [34]. Although neither of the targeted agents reported a significantly improved OS compared with placebo [33,34], this endpoint could not be reliably assessed due to extensive crossover from placebo to active treatment (69% of patients in the sunitinib trial and 74% of patients in the everolimus trial) [34,35]. An exploratory analysis attempting to correct for such patient crossover suggests an improved OS for sunitinib compared with placebo [48].

The final RCT (comparing streptozocin / 5-FU vs. octreotide) will not be discussed further given its small size ($n = 16$ patients) and the limited abstract-only available information.

It was not possible to draw conclusions on the comparable efficacy of different interventions due to the significant heterogeneity between studies. There was significant variation in the duration of follow up between studies, which limits the assessment of survival outcomes. The comparability of efficacy between studies was also hampered by differences in eligibility criteria, baseline characteristics, and response criteria employed in these studies. For example, differences in PFS between studies could be attributed to studies not requiring disease progression or prior chemotherapy prior to enrolment. The importance of response criteria is illustrated by two RCTs which established streptozocin combined with either fluorouracil or doxorubicin as the treatment of choice in pNET based on "response rates" of 45–69%; however, these "responses" included reduction in clinical hepatomegaly, biochemical improvement and/or radiological regression [27,28]. Over the last 30 years, significant advances in imaging techniques have resulted

**Table 6**
Summary of safety data reported in non-RCT studies.

| Study reference | Targeted therapy (*n* = 6) | Chemotherapy (*n* = 15) | Mixed treatments (*n* = 4) | SSA/radionuclide therapy (*n* = 9) | Liver directed therapies (*n* = 6) | Interferon (*n* = 1) | Endostatin (*n* = 1) |
|---|---|---|---|---|---|---|---|
| Incidence of withdrawals: no. of studies (enrolled patients) | NR | 1 (29) | NR | 1 (15) | NR | NR | NR |
| Incidence of withdrawals: range, % | – | 100 | – | 13 | – | – | |
| Incidence of treatment-related deaths: no. of studies (enrolled patients) | 1 (15) | NR | NR | NR | 1[††] | NR | NR |
| Incidence of treatment-related deaths: range, % | 7 | – | – | – | – | – | – |
| Incidence of AEs: no. of studies (enrolled patients) | NR | NR | 1 (35) | NR | NR | NR | NR[†] |
| Incidence of AEs: range, % | – | – | – | – | – | – | – |
| Incidence of SAEs: no. of studies (enrolled patients) | NR | 1 | NR | 1 (27) | NR | NR | NR |
| Incidence of SAEs: range, % | – | 8 | – | 0 | – | – | – |
| Incidence of neutropenia: no. of studies (enrolled patients) | 1 (160) | 4 (148) | NR | NR | NR | 1 (22) | NR |
| Grade 1-2 neutropenia: range, % | 6 | 51-16 | – | – | – | 66[‡] | – |
| Grade 3–4 neutropenia: range, % | 3 | 23–64 | – | – | – | | |
| Incidence of thrombocytopenia: no. of studies (enrolled patients) | 3 (182) | 1 (51) | 1 (30) | NR | NR | 1 (22) | NR |
| Grade 1–2 thrombocytopenia: range, % | 5–50 | 14 | – | – | – | 38[¶] | – |
| Grade 3–4 thrombocytopenia: range, % | 3–17 | 22 | 5% | – | – | – | – |
| Incidence of nausea: no. of studies (enrolled patients) | 2 (175) | 4 (86) | 2 (46) | NR | NR | NR | NR |
| Grade 1–2 nausea: range, % | 30–36 | 8–21 | 13 | – | – | – | – |
| Grade 3–4 nausea: range, % | 0–1 | 3–13 | 2 | – | – | – | – |
| Incidence of diarrhoea: no. of studies (enrolled patients) | 2 (54) | 6 (221) | 2 (46) | NR | NR | NR | NR |
| Grade 1–2 diarrhoea: range, % | 30 | 5–12 | 18 | – | – | – | – |
| Grade 3–4 diarrhoea: range, % | 5–9 | 0–13 | 11 | – | – | – | – |
| Incidence of vomiting: no. of studies (enrolled patients) | 1 (150) | 4 (126) | NR | NR | NR | NR | NR |
| Grade 1–2 vomiting: range, % | 16 | 38–71 | – | – | – | – | – |
| Grade 3–4 vomiting: range, % | 0 | 3–14 | – | – | – | – | – |
| Incidence of fatigue: no. of studies (enrolled patients) | 3 (95) | 1 (29) | 2 (65) | NR | NR | NR | NR |
| Grade 1–2 fatigue: range, % | 78 | 76 | – | – | – | – | – |
| Grade 3–4 fatigue: range, % | 0–9 | 7 | 9––11 | – | – | – | – |
| Incidence of hypertriglyceridaemia: no. of studies (enrolled patients) | 2 (32) | NR | 1 (30) | NR | NR | 1 (22) | NR |
| Grade 1–2 hypertriglyceridaemia: range, % | 42 | – | 44 | – | – | 33[§] | – |
| Grade 3–4 hypertriglyceridaemia: range, % | 3–6 | – | 3 | – | – | – | – |
| Incidence of rash: no. of studies (enrolled patients) | 4 (231) | 1 (29) | 1 (30) | NR | NR | NR | NR |
| Grade 1–2 rash: range, % | 41–61 | 35 | – | – | – | – | – |
| Grade 3–4 rash: range, % | 1–6 | 3 | 5 | – | – | – | – |
| Incidence of pneumonitis: no. of studies (enrolled patients) | 2 (175) | NR | NR | NR | NR | NR | NR |
| Grade 1–2 pneumonitis: range, % | 8–19 | NR | – | – | – | – | – |
| Grade 3–4 pneumonitis: range, % | 0 | NR | – | – | – | – | – |
| Incidence of hypertension: no. of studies (enrolled patients) | NR | NR | 2 (65) | NR | NR | NR | NR |
| Grade 1–2 hypertension: range, % | – | – | – | – | – | – | – |
| Grade 3–4 hypertension: range, % | – | – | 2–12 | – | – | – | – |

[†] AE data not reported for the subset of patients (20/42) with pNET.
[‡] Leukocyte count <4.0 × $10^9$/l: grade not explicitly reported.
[§] Rise in serum triglycerides: grade not explicitly reported.
[¶] Platelet count fall to <150 × $10^9$/l: grade not explicitly reported.
[††] All patients were alive at time of publication of the abstract.

in more accurate determination of tumour bulk and validated criteria to describe tumour response such as the WHO criteria or, more recently, RECIST. Several subsequent studies, using these stricter radiological definitions of response rather than clinical ones, have, however failed to confirm the high response rates seen in the early RCTs [27,28].

*Health related quality of life (HRQoL)*

Despite the increasing importance of patient reported outcomes (PRO) in assessing the effectiveness of treatments, HRQoL has been rarely assessed in this patient population. Indeed, only two studies, both investigating the targeted therapy sunitinib, assessed QoL using validated PRO measures (EORTC Quality of Life Questionnaire

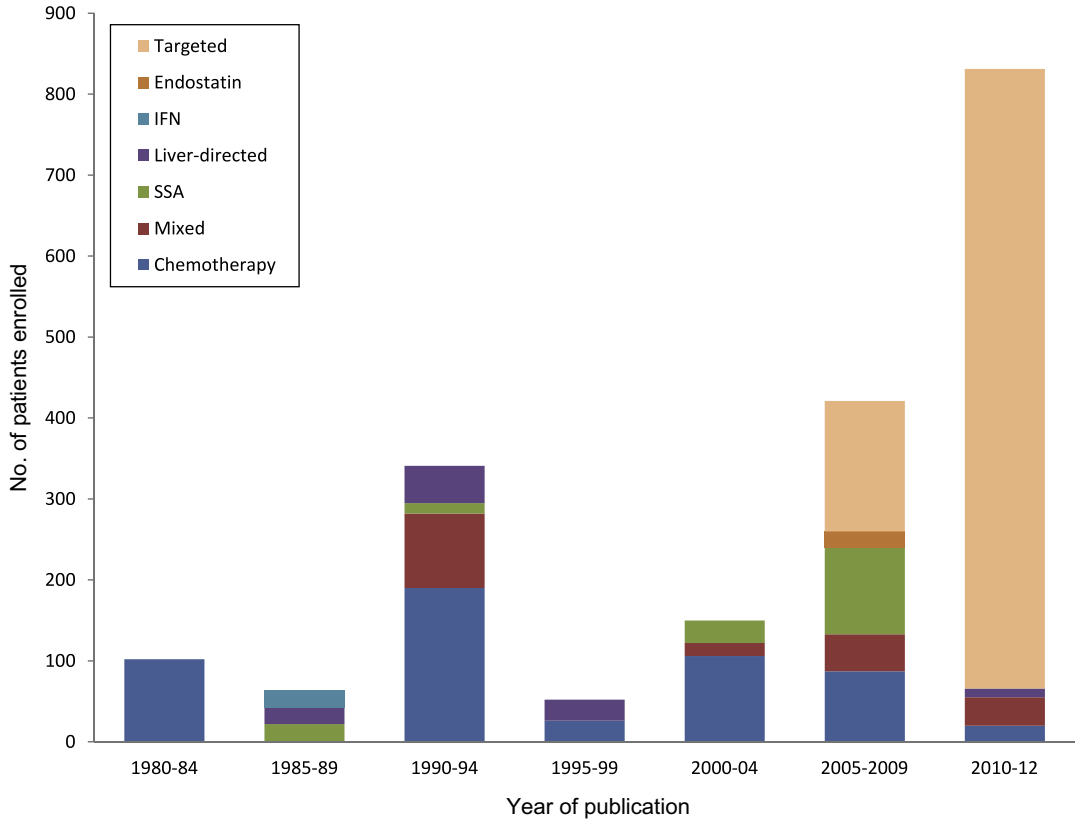


**Fig. 2.** Relationship between date of publication and number of patients enrolled in clinical studies.

[33] and EQ-5D/FACIT Questionnaire [36], in the absence of a NET-specific quality of life tool). In both studies, despite its inherent toxicities, active treatment did not result in significant detriment from baseline in overall QoL measures compared with best supportive care.

*Safety*

A summary of selected AEs are reported in Table 5 (RCTs) and Table 6 (non-randomised studies). In general, the reported incidence of grade 3–4 AEs was similar to the previously characterised profile for the different classes of agents. Chemotherapy agents have high levels of reversible myelosuppression, emesis (especially prior to the use of modern anti-emetics) and agent-specific toxicities (e.g. doxorubicin-induced cardiotoxicity; fluoropyrimidine-induced diarrhea). The targeted therapies (sunitinib and everolimus) have fewer grade 3–4 toxicities compared with chemotherapeutic agents in keeping with experience of these drugs in other tumour types.

## Discussion

This systematic review was undertaken to assess non-surgical treatments for pNET. Robust methods were used to identify all relevant studies and assess the methodological quality of the included studies.

RCTs represent the gold standard study design for assessment of treatment efficacy. However, there are few RCTs performed to date to assess the efficacy and tolerability of treatment options in the management of pNET. This is partly due to the complexity and clinical heterogeneity of pNETs and a perception that these tumours were "too rare" to undertake adequately-powered RCTs. As a result, most of the published evidence base comes from single-arm non-randomised studies. While recently conducted non-randomised studies have employed validated criteria to measure patient response [36–38], many older 'historical' studies lacked standardised inclusion criteria (e.g. including heterogenous tumour subtypes, and patients with varied severity of disease, extent of prior therapy, evidence of disease progression at study entry and other prognostic factors) and standardised outcomes [22] are were not adequately powered to provide robust information on treatment responses and survival [40,41]. Fig. 2 indicates that over the last three decades, while studies examining chemotherapy regimens have continued to enrol a consistently small number of patients (<50 patients), the last five years has seen the publication of adequately powered studies (both observational and RCTs) examining targeted therapies enrolling a larger number of patients. Such studies are both sufficiently powered and report clinically meaningful endpoints such as PFS and OS and have indicated the feasibility of conducting robust RCTs.

There are currently no head-to-head RCTs comparing the efficacy of licensed treatments in this indication in the first-line setting or studies evaluating the optimal sequencing of available therapies.

Results from the present review indicate that over the last three decades, the criteria used to address response in pNET have progressed from clinical / biological responses to the use of validated WHO and RECIST criteria. However, these criteria have been validated for cytotoxic chemotherapy. As the use of targeted agents increases, patients may benefit from novel criteria (e.g. Choi) which assess both tumour density/necrosis in addition to change in tumour size. Targeted therapies can induce extensive regions of necrosis within a tumour. Although the induction of tumour necro-

sis may be associated with clinical benefit, RECIST criteria are restricted to measuring tumour size and so unlike the Choi criteria, they are insensitive to changes in tumour density and may therefore underestimate the anti-tumour effect of targeted agents in pNET, which are generally insidious in nature. While the utility of the Choi criteria have been established in the management of gastrointestinal stromal tumours (GIST) [43], ongoing studies will report on their sensitivity and precision in assessing the response of pNET to targeted therapies [44–46].

Despite the limitations in the robustness of its data, systemic cytotoxic chemotherapy has a role in the management of pNET; indeed it is recommended as a first-line treatment option by the European Neuroendocrine Tumour Society [9]. However, there is scope for improved, robust evidence of its efficacy from future RCTs.

Several new targeted agents have been developed and investigated in recent studies although again the majority of these have been assessed in non-randomised studies (Table 2). This review identified two RCTs assessing targeted therapies: one examining sunitinib [33] and one everolimus [34]. Based on these results, these agents are valid and applicable treatment options for patients with advanced pNET in daily practice. However, there remain as yet a number of unexplored issues such as the optimal positioning of these drugs with respect to each other and, indeed, chemotherapy; the feasibility, safety and efficacy of combining these treatments with other modalities (e.g. liver-directed therapy, or radionuclide therapy); as well as their role in other stages of the disease pathway (e.g. neoadjuvant or as an adjuvant therapy to surgery) [47].

Furthermore, the concept of personalised patient-specific treatment depending on tumour histology, comorbid conditions and objectives of treatment as part of an optimised treatment algorithm is becoming increasingly important [41]. For example, patients with a high tumour burden or mitotically active tumour (as measured by Ki67 index) may benefit from an antiproliferative treatment such as chemotherapy. However, for those patients with low-grade tumours or lower tumour burden, consideration of the patient's quality of life is of utmost importance. In such cases, results from the phase III sunitinib RCT indicate that clinical benefits were gained without adversely affecting quality of life [33].

Whilst the majority of published evidence comes from non-randomised studies, the two recently published studies [33,34] assessing the targeted therapies have indicated the feasibility of conducting robust trials which report clinically meaningful endpoints such as PFS and OS. Following publication of the sunitinib trial, the United States Food and Drug Administration (FDA) has issued a recommendation that interim efficacy analyses should be carefully planned in order to reduce the risk of overestimating treatment effects [35]. Further research will be required to confirm the efficacy of these novel therapies and to define the ideal treatment algorithm for the management of pNET. These trials will require international collaboration and should ideally be designed following multidisciplinary clinical input and include patients classified according to histological guidelines specifically developed for pNETs to ensure homogenous enrolment of patients. In addition, future trials should assess alternative treatment strategies incorporating effective agents, used concurrently or sequentially dependent on tumour characteristics, which may replace the concept of a single therapy per patient.

## Conflict of interest statement

Stephen Mitchell is an employee of Abacus International and was a paid consultant to Pfizer in connection with the development of this manuscript. Juan Valle and Martin Eatock received an honorarium in conjunction with development of the manuscript. Zahava Gabriel, Roxanne Ferdinand and Ben Clueit are paid employees of Pfizer.

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