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Guideline 2-21 Version 2

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Ontario Health (Cancer Care Ontario)

Systemic therapy for unresectable advanced or metastatic pancreatic and midgut neuroendocrine tumours

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An assessment conducted in December 2025 deferred the review of Guideline 2-21 Version 2. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document
(PEBC Assessment & Review Protocol)

Guideline 2-21 Version 2 is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/31861

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Systemic therapy for unresectable advanced or metastatic pancreatic and midgut neuroendocrine tumours

Section 1: Recommendations

GUIDELINE OBJECTIVES

To make recommendations with respect to systemic therapy for the treatment of patients with pancreatic neuroendocrine tumours (pNETs) and midgut neuroendocrine tumours (midgut NETs).

TARGET POPULATION

Adults with a diagnosis of advanced and metastatic pNETs and midgut NETs that have been deemed unresectable after assessment by a neuroendocrine specialist in a multidisciplinary setting.

Patients with neuroendocrine carcinomas (NECs) (i.e., poorly differentiated), malignant neuroblastoma, pituitary tumours, thymic tumours, goblet cell carcinoma, bronchial NETs, paragangliomas, mixed NETs, pheochromocytoma, small cell lung cancer, and thyroid cancer are excluded.

INTENDED USERS

All clinicians involved in the treatment of patients with pNETs and midgut NETs.

PREAMBLE

All patients with gastroenteropancreatic (GEP) NETs should be assessed in a multidisciplinary setting where surgery, whether curative or for optimal debulking, as well as other local therapies are evaluated as treatment options by clinicians with experience in NET care. Individuals should be re-evaluated for resection or local ablative treatment at regular intervals during treatment with systemic therapies.

Of particular relevance to this guideline are the differences in biology, prognosis, and response to therapy between well-differentiated midgut NETs and pNETs. pNETs are more aggressive clinically, with shorter median survival times. Additionally, response rates to systemic therapy are generally higher in pNETs compared to midgut NETs. These differences are reflected in inclusion criteria for many studies in GEP NETs, and subsequently led the Working Group to develop separate recommendations for pNETs and midgut NETs reflected in this document. Recommendations 2 and 3 discuss systemic therapy options in patients with unresectable advanced or metastatic pNETs and midgut NETs, respectively. The sequencing of the various classes of treatments have not been compared head-to-head. As a result, there is insufficient evidence for recommendations on sequencing of therapy; however, the Working Group has provided some guidance, where possible, based on the inclusion criteria used in specific trials and expert opinion in the qualifying statements.

RECOMMENDATIONS

Recommendation 1
Unresectability and inoperability should be established after assessment in a multidisciplinary setting where treatment options, such as surgery or other local therapies, are considered by experienced care providers.

Recommendation 2
For patients with unresectable advanced or metastatic pNETs:

2.1 Somatostatin analogues
Patients with Ki-67 <10% and somatostatin receptor 2 (SSTR2)-positivity should be offered lanreotide. Based on expert opinion, the use of sustained-release octreotide is also acceptable. Pasireotide is not indicated for use in these patients.

2.2 Chemotherapy
Patients with grade 1 or 2 tumours can be offered chemotherapy with capecitabine plus temozolomide upon progression from somatostatin analogues (SSAs) or as first-line therapy in clinical scenarios with more aggressive disease where clinical response is required.

2.3 Targeted therapy
Patients with grade 1 or 2 tumours can be offered sunitinib or everolimus.

2.4 Peptide Receptor Radionuclide Therapy
Patients with SSTR-positive tumours may be offered peptide receptor radionuclide therapy (PRRT).

2.5 Immunotherapy
The use of immunotherapy is not recommended outside of a clinical trial.

Recommendation 3
For patients with unresectable advanced or metastatic midgut NETs:

3.1 SSAs
Patients with Ki-67 <10% should be offered lanreotide or sustained-release octreotide.

3.2 PRRT
The use of PRRT with ^{177}Lu-DOTATATE in combination with SSA treatment is recommended in patients with SSTR2-positive, grade 1 to 2 NETs after progression on an SSA.

3.3 Targeted therapy
Patients with non-functional grade 1 or 2 tumours may be offered everolimus.

3.4 Chemotherapy
There is insufficient evidence for or against the use of chemotherapy.

3.5 Immunotherapy
The use of immunotherapy is not recommended outside of a clinical trial.

Systemic therapy for unresectable advanced or metastatic pancreatic and midgut neuroendocrine tumours

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

To make recommendations with respect to systemic therapy for the treatment of patients with pancreatic neuroendocrine tumours (pNETs) and midgut neuroendocrine tumours (midgut NETs).

TARGET POPULATION

Adults with a diagnosis of advanced and metastatic pNETs and midgut NETs that have been deemed unresectable after assessment by a neuroendocrine specialist in a multidisciplinary setting.

Patients with NECs (i.e., poorly differentiated), malignant neuroblastoma, pituitary tumours, thymic tumours, goblet cell carcinoma, bronchial NETs, paragangliomas, mixed NETs, pheochromocytoma, small cell lung cancer, and thyroid cancer are excluded.

INTENDED USERS

All clinicians involved in the treatment of patients with pNETs and midgut NETs.

PREAMBLE

All patients with gastroenteropancreatic (GEP) NETs should be assessed in a multidisciplinary setting where surgery, whether curative or for optimal debulking, as well as other local therapies are evaluated as treatment options by clinicians with experience in NET care. Individuals should be re-evaluated for resection or local ablative treatment at regular intervals during treatment with systemic therapies.

Of particular relevance to this guideline are the differences in biology, prognosis, and response to therapy between well-differentiated midgut NETs and pNETs. pNETs are more aggressive clinically, with shorter median survival times. Additionally, response rates to systemic therapy are generally higher in pNETs compared to midgut NETs. These differences are reflected in inclusion criteria for many studies in GEP NETs, and subsequently lead the Working Group to develop separate recommendations for pNETs and midgut NETs reflected in this document. Recommendations 2 and 3 discuss systemic therapy options in patients with unresectable advanced or metastatic pNETs and midgut NETs, respectively. The sequencing of the various classes of treatments have not been compared head-to-head. As a result, there is insufficient evidence for recommendations on sequencing of therapy; however, the Working Group has provided some guidance, where possible, based on the inclusion criteria used in specific trials and expert opinion in the qualifying statements.

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

Recommendation 1
Unresectability and inoperability should be established after assessment in a multidisciplinary setting where treatment options, such as surgery or other local therapies, are considered by experienced care providers.

Qualifying Statement for Recommendation 1

- Defining unresectability and inoperability is a complex scenario for NETS that requires the input of multiple team members in a multidisciplinary setting.

Recommendation 2
For patients with unresectable advanced or metastatic pNETs:

2.1 Somatostatin analogues
Patients with Ki-67 <10% and somatostatin receptor 2 (SSTR2)-positivity should be offered lanreotide. Based on expert opinion, the use of sustained-release octreotide is also acceptable. Pasireotide is not indicated for use in these patients.

Qualifying Statements for Recommendation 2.1

- Somatostatin analogues (SSAs) should be offered as first-line therapy in most patients with Ki-67 <10% and SSTR2-positive metastatic pNETs.
- It is recognized that generic forms of SSAs are increasingly utilized, and clinicians may administer the most appropriate SSA based on the patient's clinical assessment and preferences.
- In patients with rapidly progressing disease and/or a heavy burden of symptomatic disease, in whom optimal clinical response is desirable, clinicians may consider upfront treatment with chemotherapy (see Recommendation for chemotherapy)

2.2 Chemotherapy
Patients with grade 1 or 2 tumours can be offered chemotherapy with capecitabine plus temozolomide upon progression from SSAs or as first-line therapy in clinical scenarios with more aggressive disease where clinical response is required.

Qualifying Statements for Recommendation 2.2

- Chemotherapy may also be indicated in patients with symptomatic bulky or rapidly progressive disease as first-line therapy. It may be a preferred option for tumours with Ki-67 >10%, as these patients were not included in the CLARINET study. It may also be utilized pre-surgery in patients who would benefit from preoperative downsizing. Finally, chemotherapy may be utilized after progression of additional agents such as tyrosine kinase inhibitors (TKIs).
- In patients where chemotherapy is indicated, capecitabine plus temozolomide is preferred.

2.3 Targeted therapy

Patients with grade 1 or 2 tumours can be offered sunitinib or everolimus.

Qualifying Statements for Recommendation 2.3

- The various TKIs and everolimus have not been directly compared with one another, resulting in insufficient evidence to recommend one over the other. Currently, everolimus and sunitinib have the best available level of evidence with cabozantinib also showing promising results in a pre-planned interim analysis currently available in abstract form. The evidence is not mature enough to definitively demonstrate the efficacy of other oral agents, including lenvatinib and pazopanib.
- Cabozantinib may also be considered in patients who have had progression on at least one line of systemic therapy, excluding SSAs. While everolimus and sunitinib are often utilized after disease progression on an SSA, there is insufficient evidence for recommendations on sequencing of therapy.
- Lenvatinib may be offered after progression on sunitinib or everolimus. The TALENT trial evaluating the efficacy of lenvatinib included patients who were previously treated with either sunitinib or everolimus.

2.4 Peptide Receptor Radionuclide Therapy

Patients with SSTR-positive tumours may be offered peptide receptor radionuclide therapy (PRRT).

Qualifying Statements for Recommendation 2.4

- ^{177}Lu-DOTATATE or ^{90}Y-DOTATATE may be utilized, acknowledging the more widespread use of ^{177}Lu-DOTATATE.
- ^{177}Lu-DOTATATE plus octreotide may be considered for first-line treatment in patients with SSTR-positive grade 2 or 3 advanced pNETs (with Ki-67 of at least 3-20% or >20%, respectively). This regimen demonstrates significantly increased progression-free survival (PFS) compared with high-dose long-acting octreotide alone in the NETTER-2 study, which is currently only available in abstract form. Once this study is published a full recommendation can be made.

2.5 Immunotherapy

The use of immunotherapy is not recommended outside of a clinical trial.

Key Evidence for Recommendation 2

SSAs

For the use of SSAs in patients with metastatic pNETs, the evidence comes from two randomized controlled trials (RCTs) [1,2] with an overall low level of certainty.

Lanreotide

The overall CLARINET study [1] compared lanreotide with placebo in patients with well- or moderately differentiated, non-functioning grade 1 or 2 NETs and showed a significant median PFS benefit with lanreotide (hazard ratio [HR], 0.47; 95% confidence interval [CI], 0.30 to 0.73; p<0.001). Approximately 45% of the population was comprised of patients with pNETs. A predefined subgroup analysis of patients with pNETs showed no statistically significant benefit for lanreotide with respect to median PFS (HR, 0.58; 95% CI, 0.32 to 1.04). The p-value was not reported. This subgroup analysis was undertaken to investigate the consistency of treatment effects as the study was not otherwise powered for such analysis.

Three percent of patients in the treatment arm and 1% of patients in the placebo arm experienced a serious treatment-related adverse event with 1% of patients from the treatment arm withdrawing from the study. Adverse event data specific to the subgroup of patients with pNETs was not reported. Quality of life was assessed using European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 and Quality of Life Questionnaire - Neuroendocrine Carcinoid Module (QLQ-GI.NET21) questionnaires and showed no significant between-group differences. No quality-of-life data were reported for the subgroup of patients with pNETs.

Pasireotide

The COOPERATE-2 trial [2] compared everolimus plus pasireotide with everolimus in patients with well-differentiated grade 1 or 2, advanced pNETs. The authors reported no difference in median PFS for the addition of pasireotide to everolimus (HR, 0.99; 95% CI, 0.64 to 1.54; p=0.49).

Grade 3 or 4 adverse events were reported in 77% of patients receiving everolimus plus pasireotide, while 69% of patients receiving everolimus only reported grade 3 or 4 adverse events. Three deaths were suspected to be treatment related, two in the treatment arm and one in the control arm. Quality of life was not assessed.

Chemotherapy

For the use of chemotherapy in patients with metastatic pNETs, the best available evidence comes from one RCT [3] with an overall low level of certainty.

The ECOG-ACRIN E2211 RCT [3] compared capecitabine with temozolomide with temozolomide in patients with advanced low-grade or intermediate-grade pNETs. The final analysis reported no significant difference in median PFS between those who received capecitabine plus temozolomide compared with temozolomide alone after adjusting for tumour grade (23.2 months vs. 15.1 months; HR, 0.63; 95% CI, 0.39 to 1.01); however, it is important to note the clinical significance of these results. Statistical significance was not reached in the final analysis for median overall survival (OS) (58.7 months vs. 53.8 months; HR, 0.82; 95% CI, 0.51 to 1.33; p=0.42).

Targeted therapy

For the use of targeted therapy in patients with metastatic pNETs, the evidence comes from two RCTs [4-6], an indirect comparison study [7], and two prospective, single-arm studies [8,9], with an overall moderate level of certainty.

Everolimus

The RADIANT-3 trial [4,6] compared the use of everolimus with placebo in patients with low- or intermediate-grade, advanced pNETs. The study reported a statistically significant benefit for PFS in favour of everolimus (HR, 0.34; 95% CI, 0.26 to 0.44; p<0.001). There were no between-arm differences in OS; however, patients receiving placebo were allowed to cross over to the treatment arm after disease progression, confounding the results. A rank-preserving structural failure analysis was later performed to correct for crossover bias for OS (HR, 3.27; 95% CI, 0.10 to 13.93). The p-value was not reported.

In the double-blind phase, serious adverse events were reported more often in the everolimus arm. The most common grade 3 or 4 adverse events in the everolimus arm were stomatitis (7.4%), hyperglycemia (5.9%), and anemia (4.9%) while the most common in the control arm were hyperglycemia (2.5%), asthenia (1%) and decreased appetite (1%). There were 12 on-treatment deaths in the everolimus arm and four in the control arm. Quality of life was not assessed in the RADIANT-3 trial.

Sunitinib

The phase III randomized trial by Faivre et al [5] compared the used of sunitinib with placebo in patients with advanced, metastatic, well-differentiated pNETs. A statistically significant benefit for PFS when compared with placebo (HR, 0.315; 95% CI, 0.181 to 0.546; p<0.01) was reported. This trial was closed early due to the significant benefit in PFS in the treatment arm, and the risk of serious adverse events, disease progression, and death among patients receiving placebo; all patients were offered entry into an open label sunitinib extension protocol. After a five-year follow-up, a statistically significant OS benefit was shown (HR, 0.40; 95% CI, 0.23 to 0.71; p=0.001) when patients who crossed over to the treatment arm after disease progression were censored.

Grade 3 or 4 adverse events were more common in patients receiving sunitinib with the most common being neutropenia (12%), hypertension (10%), and palmar-plantar erythrodysesthesia (6%), while the most common in the control arm were abdominal pain (10%), fatigue (8%), and back pain (5%). Five patients who received sunitinib and nine patients who received placebo died during the trial period; one death from each group was considered to be related to the study drug. There were no significant between-group differences in global health-related quality of life, cognitive, emotional, physical, role and social functioning domains, or symptom scales, except for diarrhea with sunitinib (p<0.001) when assessed using the EORTC QLQ-C30.

Everolimus vs. Sunitinib

In a matching-adjusted indirect comparison of patients from the RADIANT-3 trial and the phase III sunitinib trial [7], no statistically significant difference in PFS (p=0.578) and OS (p=0.383) were found for everolimus compared with sunitinib.

Cabozantinib

The CABINET trial [10], a phase III randomized trial by Chan et al compared the use of cabozantinib with placebo in patients with well- to moderately differentiated, grade 1 to 3 NETs who had disease progression after at least one prior systemic therapy, excluding SSAs. A pre-planned interim analysis is currently available in abstract form. Based on these results, the Independent Data and Safety Monitoring Board has voted to stop accrual, to unblind patients,

and to allow patients receiving placebo to crossover to the treatment arm. It reported a median PFS of 11.4 months versus 3.0 months for the cabozantinib and placebo arms, respectively (HR, 0.27; 95% CI, 0.14 to 0.49; p<0.0001), after a median follow-up period of 16.7 months in the cohort of patients with pNETs. No difference in median OS between patients who received cabozantinib (43.5 months) and those who received placebo (31.0 months; HR, 0.77; 95% CI, 0.34 to 1.73; p=0.26) was reported.
In the cohort of patients with pNETs who received cabozantinib, 56.7% and 8.3% experienced grade 3 and 4 treatment-related adverse events, respectively, while 43.3% of patients in the placebo arm experienced grade 3 adverse events. The most common grade 3 or higher adverse events between patients who received cabozantinib or placebo were hypertension (26.7% vs. 20.0%, respectively), fatigue (13.3% vs. 3.3%), and hyperglycemia (8.3% vs. 10.0%).

Lenvatinib
The TALENT trial [8] is a single-arm study that evaluated the efficacy of lenvatinib in patients with NETs previously treated with either sunitinib or everolimus. The cohort of patients with pNETs had a median PFS of 15.6 months (95% CI, 11.4 to not reported) and a median OS of 32 months (95% CI, 26.47 to not reported).
The most common grade 3 to 4 adverse events in patients with pNETs were hypertension (21.8%), vomiting (9.1%), abdominal pain (7.3%), and diarrhea (7.3%) with 10.9% of patients requiring a definitive treatment discontinuation due to severe-treatment related toxicity.

Pazopanib
The single-arm phase II study by Phan et al [9] reported the efficacy of pazopanib with octreotide long-acting repeatable (LAR) in patients with pNETs or carcinoid tumours. The cohort of patients with pNETs had a median PFS of 14.4 months (95% CI, 5.9 to 22.9) and a median OS of 25 months (95% CI, 15.5 to 34.4).
Among the patients in both cohorts, two experienced grade 4 adverse events, hypertriglyceridemia, and a thromboembolic event. The most common grade 3 events were hypertension (12%), fatigue (8%), diarrhea (6%), increases in alanine and aspartate aminotransferase (6%, for each group) and decreased neutrophil count (6%). There were no treatment-related deaths. Adverse event data were not provided specific to patients with pNETs.

PRRT
For the use of PRRT in patients with advanced or metastatic pNETs, the best available evidence comes from one phase III RCT [11] and one prospective single-arm study [12] with an overall very low level of certainty.

^{177}Lu-DOTATATE
The phase III RCT by Singh et al [11], currently available in abstract form, evaluated the efficacy of ^{177}Lu-DOTATATE as first-line therapy in patients with advanced grade 2 or 3 GEP NETs. Patients were randomized to receive ^{177}Lu-DOTATATE plus octreotide LAR or octreotide LAR. Median PFS for all patients was significantly better in the ^{177}Lu-DOTATATE arm than in the octreotide-alone arm (22.8 months vs. 8.5 months; stratified HR, 0.276; 95% CI, 0.182 to 0.418; p<0.0001). Approximately 54.4% of the population was comprised of patients with pNETs. A predefined subgroup analysis of patients with pNETs showed similar PFS results (HR, 0.34; 95% CI, 0.20 to 0.56). No adverse event or quality-of-life data were presented for the subgroup of patients with pNETs. In the overall population, three or fewer patients in the ^{177}Lu-DOTATATE arm experienced grade 3 to 4 leukopenia, anemia and thrombocytopenia, and there was one case of myelodysplastic syndrome in the ^{177}Lu-DOTATATE arm.

^{90}Y-DOTATATE

The phase II, single-arm study by Rogowski et al [12] evaluated the efficacy of ^{90}Y-DOTATATE in patients with unresectable grade 1 or 2 neuroendocrine neoplasms. Patients had received prior treatment. In the cohort of patients with pNETs (n=30), median PFS was 25 months (95% CI, 20.8 to 33.4) and median OS was 42 months (95% CI, 34.0 to 48.2). Adverse event data were not provided.

Immunotherapy

For the use of immunotherapy in patients with metastatic pNETs and midgut NETs, the evidence comes from three prospective, single-arm studies [13-15] for patients with pNETs with an overall very low level of certainty. There were no studies that reported data for solely patients with midgut NETs.

Spartalizumab

The single-arm, phase II study by Yao et al [13] evaluated the use of spartalizumab in patients with NETs and GEP NECs. The NETs cohort consisted of a subgroup of 33 patients with pNETs. All patients were required to have ≥2 prior systemic regimens including everolimus and/or sunitinib. A median PFS of 3.9 months was observed while the median OS was not reached in patients with pNETs.

The most common grade ≥3 treatment-related adverse events included asthenia (3.2%) and arthralgia (2.1%) in all patients who received spartalizumab. Adverse event data specific to patients with pNETs were not provided.

Pembrolizumab

The KEYNOTE-028 phase I study [14] consisted of 16 patients with programmed death-ligand 1 (PD-L1)-positive pNETs treated with pembrolizumab. Ninety-four percent of patients had discontinued the study at data cut-off mainly due to disease progression. A median PFS of 4.5 months (95% CI, 3.6 to 8.3) and a median OS of 21.0 months (95% CI, 20.2 to not reported) were reported. Treatment-related adverse events, most commonly diarrhea and fatigue, occurred in 69% of patients with ≥1 serious treatment-related adverse event occurring in 31% of patients. No grade 4 or 5 treatment-related adverse events were reported.

Atezolizumab

Halperin et al [15] conducted a phase II study with patients treated with atezolizumab plus bevacizumab. In the subgroup of 20 patients with pNETs 25% were PD-L1-positive. A median PFS of 14.9 months (95% CI, 4.4 to 32.0) and a median OS of 30.1 months (95% CI, 17.7 to not reported) were reported. The most common grade 3-4 treatment-emergent adverse events were hypertension (25%), proteinuria (7.5%), and increased alanine aminotransferase (5%) for all patients (n=40) included in the study. Adverse event data were not presented for those with pNETs only.

Justification for Recommendation 2

SSAs

Patients with pNETs made up approximately 45% of the CLARINET trial [1], with the overall study demonstrating a benefit in PFS, but no statistically significant benefit for the pNETs subgroup of patients. Due to the small number of events, results should be interpreted with care. Indirect evidence of the significant PFS for all patients from this trial was used to infer a potential clinically significant benefit of lanreotide for patients with pNETs despite the lack of statistically significant benefit in the pNET subgroup analysis reported in the CLARINET trial. Further, no significant differences between groups were shown for treatment-related adverse events and quality of life, resulting in the benefit of increased PFS outweighing the adverse events. Similarly, the Working Group acknowledges the accepted generalizability of the use of sustained-release octreotide as an SSA. The Working Group could not recommend use of the second-generation SSA pasireotide due to the lack of efficacy data confirming its effectiveness compared to placebo.

Chemotherapy

Reflecting real-life practice, the Working Group believes the evidence from ECOG-ACRIN E2211 [3] was clinically significant and supports the use of capecitabine plus temozolomide in patients with pNETs despite the lack of a statistically significant benefit. The Working Group acknowledges the STEM trial [16]; however, they cannot recommend S-1 plus temozolamide based on concerns of generalizability of the study to non-Asian populations. While the best available evidence for the use of chemotherapy in patients with pNETs comes from one RCT, there are also six non-comparative studies [17-22], each evaluating a different chemotherapy regimen, reporting a median PFS ranging from 14.3 months (95% CI, 8.5 to NE) to 26.3 months (95% CI, 17.4 to not reached) in patients with pNETs.

Targeted therapy

The increased PFS benefit from everolimus and sunitinib is considerable and the adverse events are acceptable for targeted therapy. It is important to note that not all trials routinely collected and reported on quality-of-life data. In the trials that did report these data, no significant differences were found between the treatment and control arms or between pre- and post-treatment. The Working Group recognizes that everolimus and sunitinib are often utilized after disease progression on an SSA; however, a sizeable proportion of patients in both RCTs were SSA naïve, a subset had received chemotherapy and/or PRRT, resulting insufficient evidence for any recommendations on sequencing of therapy. The pre-planned interim analysis results of the CABINET trial are currently available in abstract form, with a large benefit in median PFS for patients with pNETs. The results of the interim analysis have resulted in the Independent Data and Safety Monitoring Board to vote to stop accrual, to unblind patients, and to allow patients receiving placebo to cross over to the treatment arm. While the Working Group acknowledges that results of abstracts or interim analyses are not used in recommendation development, the results of this trial in a rare population warrants consideration as a treatment option until the final results are published. The role of TKIs such as lenvatinib and pazopanib in treatment of pNETs continues to evolve. The Working Group members acknowledge the positive results for surufatinib in the interim analysis by Xu et al [23]; however, interim analyses provide insufficient evidence to make recommendations. Further, surufatinib did not receive Food and Drug Administration (FDA) approval due to lack of inclusion of patients from North America.

PRRT

The Working Group members acknowledge results from two phase II RCTs, OCLURANDOM [24] and AGITG CONTROL NET [25], currently available in abstract form. The OCLURANDOM compared ^{177}Lu-DOTATATE with sunitinib suggesting increased median PFS in patients who received ^{177}Lu-DOTATATE (20.7 months vs. 11 months). The AGITG CONTROL NET study evaluated the addition of ^{177}Lu-DOTATATE to capecitabine plus temozolomide and reported an increased PFS at 27 months in those who received ^{177}Lu-DOTATATE in addition to capecitabine plus temozolomide (61.1% vs. 33.3%; p=0.08). Abstracts of studies are insufficient to make recommendations.

Further, the NETTER-R study [26] retrospectively evaluated the use of ^{177}Lu-DOTATATE in patients with pNETs. Due to its retrospective nature and the presence of prospective studies, this study did not meet the inclusion criteria for this review. However, a median PFS of 24.8 months was reported in patients with available RECIST v1.1 tumour response.

Further, indirect evidence of the significant PFS for all patients with midgut NETs from the NETTER-1 trial [27,28] was used to infer benefit in patients with pNETs. Finally, results of the NETTER-2 trial [11] demonstrate significantly better PFS in patients with grade 2 and 3 GEP NETS who were treated with ^{177}Lu-DOTATATE plus octreotide LAR versus high-dose octreotide LAR alone. The results are similar in the prespecified pNET subgroup. These results are currently only available in abstract form and are therefore insufficient to make a recommendation. Once this trial is published, a recommendation will be forthcoming.

Immunotherapy

The use of immunotherapy has not shown clinically meaningful increases in median PFS or OS compared to other systemic therapies available and are associated with increased adverse events. While new immunotherapy drugs are investigated, the Working Group recommends they not be used outside the context of a clinical trial. The Working Group also notes the NET-002 phase II single-arm study [29] that evaluated the use of avelumab in patients with grade 2 or 3 NETs where approximately 41% of included patients had pNETs. This trial was closed due to futility in response rate.

Recommendation 3

For patients with unresectable advanced or metastatic midgut NETs:

3.1 SSAs

Patients with Ki-67 <10% should be offered lanreotide or sustained-release octreotide.

Qualifying Statements for Recommendation 3.1

- While the CLARINET trial [1] included patients with Ki-67 <10% and SSTR2-positivity in the first-line setting to receive lanreotide, the PROMID trial [30] evaluating the use of octreotide did not include these stipulations.
- It is recognized that generic forms of SSAs are increasingly utilized, and clinicians may administer the most appropriate SSA based on the patient's clinical assessment and preferences.

3.2 PRRT

The use of PRRT with ^{177}Lu-DOTATATE in combination with SSA treatment is recommended in patients with SSTR2-positive, grade 1 to 2 NETs after progression on an SSA.

3.3 Targeted therapy
Patients with non-functional grade 1 or 2 tumours may be offered everolimus.

Qualifying Statements for Recommendation 3.3
- There are no published randomized studies evaluating the sequencing of treatments in patients with metastatic midgut NETs. The RADIANT-4 trial allowed prior treatment with SSAs, PRRT, and up to one line of chemotherapy.

3.4 Chemotherapy
There is insufficient evidence for or against the use of chemotherapy.

Qualifying Statements for Recommendation 3.4
- Clinicians may choose to offer chemotherapy later in a patient's treatment course based on disease trajectory.
- Optimal treatment regimens have not been identified for patients with midgut NETs. Regimens utilizing streptozocin are no longer routinely utilized due to an unfavourable toxicity profile and drug supply limitations. More contemporary regimens such as capecitabine and oxaliplatin (CAPOX), folinic acid, 5-fluorouracil (5-FU), and oxaliplatin (FOLFOX), and capecitabine plus temozolomide are increasingly utilized; however, insufficient evidence exists for their specific recommendation.

3.5 Immunotherapy
The use of immunotherapy is not recommended outside of a clinical trial.

Key Evidence for Recommendation 3

SSAs
For the use of SSAs in patients with metastatic midgut NETs, the evidence comes from two RCTs with an overall moderate level of certainty.

Octreotide
The PROMID trial [30,31] compared octreotide LAR with placebo in patients with locally inoperable or metastatic midgut NETs and showed a significant benefit in median time to tumour progression or tumour-related death, considered as a surrogate for PFS, for the treatment arm over the control arm (HR, 0.34; 95% CI, 0.20 to 0.59; p=0.000072). However, no difference in OS was found (HR, 0.83; 95% CI, 0.47 to 1.46; p=0.51) in patients with midgut NETs. Crossover of majority of the patients receiving placebo to octreotide LAR may have confounded OS data.
Treatment-related adverse events were not reported. There were no statistically significant between-group differences in change from baseline for the functioning scales at any time point when assessed using the EORTC QLQ-C30. Significantly longer time to definitive deterioration was reported for octreotide LAR versus placebo for fatigue (p=0.0006), pain (p=0.0435), and insomnia (p=0.0046).

Lanreotide
The CLARINET trial [1] compared lanreotide with placebo in patients with well- or moderately differentiated, non-functioning grade 1 or 2 NETs and showed a significant median PFS benefit with lanreotide (HR, 0.47; 95% CI, 0.30 to 0.73; p<0.001). Approximately 36% of the population was comprised of patients with midgut NETs. A predefined subgroup analysis of patients with midgut NETs also showed a statistically significant benefit in median PFS for lanreotide (HR,

0.35; 95% CI, 0.16 to 0.80). The p-value was not reported. This subgroup analysis was undertaken to investigate the consistency of treatment effects as the study was not otherwise powered for such analysis.
Three percent of patients in the treatments arm and 1% of patients in the placebo arm experienced a serious treatment-related adverse event with 1% of patients from the treatment arm withdrawing from the study. Adverse event data specific to the subgroup of patients with midgut NETs were not reported. Quality of life was assessed using EORTC QLQ-C30 and QLQ-GI.NET21 questionnaires and showed no significant between-group differences. Quality of life specific to the subgroup of patients with midgut NETs was not reported.

PRRT
For the use of PRRT in patients with metastatic midgut NETs, the evidence comes from two RCTs, one of which is currently available in abstract form only, with an overall low to moderate level of certainty.

^{177}Lu-DOTATATE
The NETTER-1 trial [27,28] compared ^{177}Lu-DOTATATE and best supportive care including octreotide LAR with octreotide LAR alone in patients with locally advanced or metastatic, well differentiated, SSTR-positive midgut NETs and showed that patients who received ^{177}Lu-DOTATATE plus octreotide LAR had a significantly longer median PFS than those who received high-dose octreotide LAR (HR, 0.21; 95% CI, 0.13 to 0.33; p<0.001), although median PFS was not reached in the treatment arm. No difference in OS was reported between patients who received ^{177}Lu-DOTATATE plus octreotide LAR and those who received high-dose octreotide LAR in the intention-to-treat population (HR, 0.84; 95% CI, 0.60 to 1.17; p=0·30).
There was a significant difference in serious treatment-related adverse events between those who received ^{177}Lu-DOTATATE and the control group (9% vs. 1%; p=0.01). Approximately 5% of patients receiving ^{177}Lu-DOTATATE withdrew from the trial due to adverse events related to treatment. Time to quality-of-life deterioration was significantly longer in those that received ^{177}Lu-DOTATATE versus the control arm in many domains of the EORTC QLQ-C30 and QLQ-GINET21 including global health status, physical functioning, role functioning, fatigue, pain, diarrhea, disease-related worries, and body image domains.
The NETTER-2 trial [11], currently available in abstract form, evaluated the efficacy of ^{177}Lu-DOTATATE plus octreotide LAR as first-line therapy in patients with advanced grade 2 or 3 GEP NETs. Median PFS for all patients was significantly better in the ^{177}Lu-DOTATATE arm than in the high-dose long-acting octreotide alone arm (22.8 months vs. 8.5 months; stratified HR, 0.276; 95% CI, 0.182 to 0.418; p<0.0001). Approximately 29.1% of the population was comprised of patients with NETs of the small intestine. A predefined subgroup analysis of patients with NETs of the small intestine showed similar PFS results (HR, 0.30; 95% CI, 0.13 to 0.74). No adverse event or quality of life data were presented for the subgroup of patients with NETs of the small intestine. In the overall population, three or fewer patients in the ^{177}Lu-DOTATATE arm experienced grade 3 to4 leukopenia, anemia and thrombocytopenia, and there was one case of myelodysplastic syndrome in the ^{177}Lu-DOTATATE arm.

^{90}Y-DOTATATE
The phase II, single-arm study by Rogowski et al [12] evaluated the efficacy of ^{90}Y-DOTATATE in patients with nonresectable grade 1 or 2 neuroendocrine neoplasms (NENs) who had received prior treatment. In the cohort of patients with small bowel NETs (n=37), median PFS was 28 months (95% CI, 27.5 to 42.1) and median OS was 40 months (95% CI, 34.7 to 50.1). Adverse event data were not provided; quality of life data were not assessed.

Targeted therapy
For the use of targeted therapy in patients with metastatic midgut NETs, the evidence comes from one RCT with an overall moderate level of certainty.

Everolimus
The overall RADIANT-4 trial [32,33] compared the use of everolimus with placebo in patients with advanced, progressive, well-differentiated, non-functional NETs and showed a significant median PFS benefit with everolimus (HR, 0.48; 95% CI, 0.35 to 0.67; p<0.0001). Approximately 38% of the population was comprised of patients with midgut NETs. An ad-hoc subgroup analysis of patients with non-functional midgut NETs showed no statistically significant benefit for everolimus with respect to median PFS (HR, 0.71; 95% CI, 0.40 to 1.26). The p-value was not reported. This subgroup analysis was undertaken to investigate the consistency of treatment effects as the study was not otherwise designed or powered for such analysis.
Grade 3 or 4 adverse events were more common in patients with gastrointestinal NETs receiving everolimus than those receiving placebo with the most common being diarrhea (9.4% vs. 3.4%), stomatitis (7.7% vs. 0%), and infections (7.7% vs. 0%). Treatment discontinuation as a result of the study drug was higher in those receiving everolimus compared with placebo (12% vs. 3%). Treatment discontinuation due to grade 3 or 4 adverse events related to the study drug were 13% in those receiving everolimus and 2% in those receiving placebo. The rates of on-treatment deaths were similar between those receiving everolimus (3%) and placebo (2%). Adverse event data are presented for all patients with gastrointestinal NETs enrolled in the RADIANT-4 study and are not specific to the subgroup of patients with midgut NETs. There were no significant between-group differences in median time to definitive deterioration in Functional Assessment of Cancer Therapy - General (FACT-G) total score (HR, 0.81; 95% CI, 0.55 to 1.21; p=0.31) [33]. Quality of life data are presented for all patients enrolled in the RADIANT-4 study and are not specific to the subgroup of patients with midgut NETs.

Chemotherapy
No key evidence is available.

Immunotherapy
There were no studies meeting the inclusion criteria that reported data for solely patients with midgut NETs.

Justification for Recommendation 3
SSAs
Patients with midgut NETs made up approximately 36% of the CLARINET trial [1], with the overall study demonstrating a benefit in PFS along with the subgroup of patients with midgut NETs. Due to the small number of events, results should be interpreted with care. Indirect evidence of the significant PFS for all patients from this trial was used to infer a potential clinically significant benefit of lanreotide for patients with midgut NETs. The midgut subgroup analysis was undertaken to investigate the consistency of treatment effects as the study was not otherwise powered for such analysis. Further, the occurrence of treatment-related adverse events and quality of life showed in the both the PROMID and CLARINET trials demonstrated no significant differences between the study groups resulting in the potential benefit of increased PFS outweighing the adverse events.

PRRT

The increased PFS benefit from the addition of ^{177}Lu-DOTATATE to octreotide LAR is large in both the NETTER-1 and NETTER-2 trials and the adverse events are acceptable for PRRT. Further, time to quality-of-life deterioration was significantly longer in those who received ^{177}Lu-DOTATATE in many domains of the EORTC QLQ-C30 and QLQ-GINET21 in the NETTER-1 trial. Due to the availability of robust phase III data supporting benefit, the Working Group recommends the use of ^{177}Lu-DOTATATE as the preferred radionuclide in the treatment of patients with midgut NETs. This recommendation is based on the published results of NETTER-1 trial, and we await the full publication of NETTER-2 to assess the role of PRRT in grade 3 midgut NETs.

The Working Group members acknowledge the negative results from the AGTIG CONTROL NET study [25] regarding the addition of capecitabine plus temozolomide to ^{177}Lu-DOTATATE; however, abstracts of studies are insufficient to make recommendations.

Targeted therapy

Patients with midgut NETs made up approximately 38% of the RADIANT-4 trial [32], with the overall study demonstrating a benefit in PFS and with adverse events being acceptable for targeted therapy. The evidence for everolimus is specific to patients with non-functional tumours. The authors acknowledge that subgroup analysis was undertaken to investigate the consistency of treatment effects, as the study was not otherwise designed or powered for such analysis.

Chemotherapy

The use of chemotherapy in patients with metastatic midgut NETs is less clear and no recent prospective studies have been conducted to validate this.

Immunotherapy

In the absence of midgut-specific data, the Working Group believes immunotherapy should not be used outside of a clinical trial. Further, the data from pNET studies have shown that the use of immunotherapy has not shown clinically meaningful increases in median PFS or OS compared to other systemic therapies available.

IMPLEMENTATION CONSIDERATIONS

The Working Group considered these recommendations to be the best possible recommendations given the currently available data and their feasibility of implementation. Ga^{68}-DOTATATE positron emission tomography scans and PRRT are currently only available at a small number of specialized healthcare centres in Ontario. Research has shown that patients in rural settings have poorer outcomes and standardizing care would reduce this inequity. These recommendations would validate and align with what providers are currently implementing. Funding of drugs for NETs must take into account the difficulty in conducting trials with homogeneous populations in this disease and the need to often have heterogeneous populations in order to feasibly assess new systemic therapies. Accordingly, treatment options that have a biological rationale, such as the use of targeted therapy in the second-line treatment of pNETs, should be considered. Due to the highly specialized nature of NET treatment, community-based clinicians are encouraged to participate in province-wide NET case conferences and/or refer patients to specialized multidisciplinary NET clinics.

Systemic therapy for unresectable advanced or metastatic pancreatic and midgut neuroendocrine tumours

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Ontario Health (Cancer Care Ontario). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of OH (CCO) supported by the Ontario Ministry of Health (OMH). All work produced by the PEBC is editorially independent from the OMH.

BACKGROUND FOR GUIDELINE

The treatment landscape is changing for GEP NETs and requires the inclusion of new substantial evidence on PRRT that is not currently covered in the original guideline.

GUIDELINE DEVELOPERS

This guideline was developed by the GEP NETs GDG (Appendix 1), which was convened at the request of the Gastrointestinal Disease Site Group.

The project was led by a small Working Group of the GEP NETs GDG, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in medical oncology, radiation oncology, surgical oncology, nuclear medicine, and health research methodology. Other members of the GEP NETs GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [34,35]. This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [36] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development and to improve the completeness and transparency of reporting in practice guidelines.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original

evidence-base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on evidence of the magnitude of the desirable and undesirable effects of an intervention or accuracy of a test, and take into account the certainty of the evidence, the values of key stakeholders (e.g., patients, clinicians, policy makers, etc.), and the potential impact on equity, acceptability and feasibility of implementation. A list of any implementation considerations (e.g., costs, human resources, and unique requirements for special or disadvantaged populations, dissemination issues, etc.) is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine whether any guideline could be endorsed.

Evidence-based guidelines with systematic reviews that addressed at least one research question (see Section 4) were included. Guidelines older than three years (published before November 2019) were excluded. Guidelines based on consensus or expert opinion were excluded.

The following sources were searched for guidelines on September 13, 2022 with the search term "neuroendocrine": National Institute for Health and Care Excellence Evidence Search, Canadian Medical Association Journal Infobase, Scottish Intercollegiate Guidelines Network, American Society of Clinical Oncology, National Health and Medical Research Council – Australia Clinical Practice Guidelines Portal, and Cancer Council Australia – Cancer Guidelines Wiki.

The MEDLINE and EMBASE databases were searched for guidelines on September 12, 2022. The search strategy is available in Appendix 2. Three guidelines underwent full-text review, of which none met the inclusion criteria. An update search of guideline sources and databases was conducted on October 30, 2023; one relevant guideline was found [37]. While this guideline addresses the same target population, it does not cover all of the interventions intended in this guideline. Further, it was published in September 2023 near the completion of this current guideline. Any similarities and differences in recommendations are addressed in the discussion section of the systematic review.

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

Patient and Caregiver-Specific Consultation Group

Three patients/survivors/caregivers participated as Consultation Group members for the GEP NETs GDG. They reviewed copies of the project plan/draft recommendations and provided feedback on its/their comprehensibility, appropriateness, and feasibility to the Working Group's Health Research Methodologist. The Health Research Methodologist relayed the feedback to the Working Group for consideration.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey.

DISSEMINATION AND IMPLEMENTATION

The guideline will be published on the OH (CCO) website and may be submitted for publication to a peer-reviewed journal. The Professional Consultation of the External Review is intended to facilitate the dissemination of the guideline to Ontario practitioners. Section 1 of this guideline is a summary document to support the implementation of the guideline in practice. OH (CCO)-PEBC guidelines are routinely included in several international guideline databases including the CPAC Cancer Guidelines Database, the CMA/Joule CPG Infobase database, NICE Evidence Search (UK), and the Guidelines International Network (GIN) Library.

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Systemic therapy for unresectable advanced or metastatic pancreatic and midgut neuroendocrine tumours

Section 4: Systematic Review

INTRODUCTION

NETs are uncommon malignancies that are located throughout the body. Despite their relative rarity, NETs are the second most prevalent gastrointestinal cancer after colon cancer, due to longer survival periods, even in patients with incurable and metastatic disease.

NETs arise from enterochromaffin cells, with the gastrointestinal tract being the most common primary site, accounting for greater than 60% of NETs [38]. Gastrointestinal NETs can be divided into the clinically relevant entities of pNETs and gastroenterohepatic NETS. NETs are classified as functional when associated with an excessive secretion of hormones or non-functional, when symptoms derive from the physical manifestations of the tumour. NETs often over express SSTR2, which is measured in clinical practice with nuclear medicine imaging tests such as octreotide scans (historically), and more commonly ^{68}GA-DOTATATE scan.

Two TNM staging systems are currently available, the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) and the European Neuoroendocrine Tumour Society [39,40]. Staging systems are specific to each primary tumor site. The College of American Pathologists has based their protocol on the AJCC classification. Neither staging system includes patient-level variables or information on associated endocrinopathy. These staging systems are not routinely used by many NETs oncologists.

There is considerable heterogeneity in tumoral and endocrine behaviour among neuroendocrine neoplasms. The 2022 World Health Organization classification divides NENs into NETs and neuroendocrine carcinomas [41]. NETs are diagnosed on immunohistochemistry as being well-differentiated and are characterized by slower growth patterns. They are subdivided based on their proliferation index assessed by the Ki-67: Ki-67 below 3% for grade 1, Ki-67 between 3 and 20% for grade 2, and Ki-67 over 20% for grade 3. NECs are characterized as being poorly differentiated on immunohistochemistry and are aggressive malignancies, with survival often less than 12 months.

The incidence of NETs is increasing, likely as a result of improved classification, the more widespread use of upper and lower bowel endoscopy in screening programs, improved resolution of gastrointestinal imaging techniques, and a heightened awareness of the disease entity. Despite this, the majority of NETs in Ontario present with metastatic disease, with limited likelihood of cure, and with significant impact on quality of life. Data from Ontario reported a NET incidence rate of 5.86 cases per 100,000 individuals; a more than a two-fold increase observed over the 15 years studied [38]. The prevalence of the disease is also rising due to recent progress in therapeutics, as well as earlier identification and, therefore, a longer duration of documented disease. A patient experience study demonstrated the considerable burden of disease from NETs, particularly with respect to symptoms, work and daily life, and health care resource use [42].

Of particular relevance to this guideline are the differences in biology, prognosis, and response to therapy between well-differentiated midgut NETs and pNETs. pNETs are more aggressive clinically, with shorter median survival times. Additionally, response rates to systemic therapy are generally higher in pNETs compared to midgut NETs. These differences are reflected in inclusion criteria for many studies in GEP NETs, and subsequently lead the Working Group to develop separate recommendations for pNETs and midgut NETs reflected in this document.

The long natural history of low- to intermediate-grade NETs in particular, makes the identification of appropriate trial endpoints challenging. However, over the past 15 years, several sufficiently powered therapeutic trials have been successfully conducted in these uncommon tumours, such that that evidence-based guidelines for the management of NETs are feasible and deserve regular updates.

Guidelines produced by the rigorous evaluation of trials, particularly in a rare tumour type such as NETs, are likely to translate into improved patient care, particularly in geographically large and diverse areas such as Ontario. Assimilating new evidence is especially important for NETs to ensure equity of access to therapies that have been proven to have a significant impact on patient outcomes.

In 2016, the PEBC published their first clinical practice guideline on *Systemic Therapy of Incurable Gasteroenteropancreatic Neuroendocrine Tumours* [43]. That guideline reviewed the role of the major systemic therapeutic interventions for pancreatic and non-pancreatic NETs: SSAs, chemotherapy, targeted therapy, and various treatment combinations. Since 2016, the evidence for the treatment of patients with NETs has continued to evolve. The publication of the NETTER-1 trial for the use of PRRT along with the publication of additional trials investigating the use of other therapies such as checkpoint inhibitors has necessitated the update of the original guideline. Given the substantial development of new evidence in this field, which has improved treatment options for patients, this current updated version of the guideline was developed focusing on patients with pNETs and midgut NETs. This review exclusively focuses on the anti-proliferative therapy of pNETs and midgut NETs and does not address the treatment of functional NET symptoms. The objective of the current review is to inform recommendations with respect to systemic therapy for the treatment of patients with pNETs and midgut NETs, and where possible, recommendations include patient subgroups based on grade of tumour. The systematic review focuses on survival outcomes including PFS, OS, and quality of life data, which is now recognized as essential in evaluating treatments for incurable cancer, and adverse event data.

The Working Group of the GEP NETs Guideline Development Group developed this evidentiary base to inform recommendations as part of a clinical practice guideline. Based on the objectives of this guideline, the Working Group derived the research questions outlined below.

RESEARCH QUESTIONS

1. Which of the anti-neoplastic systemic therapies (Table 4-1) is the most effective in improving clinical outcomes (i.e., PFS, OS) and quality of life while minimizing adverse events in patients with unresectable advanced or metastatic pNETs?

2. Which of the anti-neoplastic systemic therapies (Table 4-1) is the most effective in improving clinical outcomes (i.e., PFS, OS) and quality of life while minimizing adverse events in patients with unresectable advanced or metastatic midgut NETs?

Table 4-1. Anti-neoplastic Systemic Therapies

Interventions	pNETs	Midgut NETs
Somatostatin analogues	Lanreotide Octreotide Pasireotide	Lanreotide Octreotide Pasireotide
Targeted therapy	Cabozantinib Everolimus ± bevacizumab Lenvatinib Pazopanib Sorafenib Sunitinib Surufatinib	Axitinib + octreotide Cabozantinib Everolimus Lenvatinib Nintedanib + octreotide Pazopanib Sorafenib Sunitinib Surufatinib
Chemotherapy	Capecitabine ± temozolomide CAPOX CAPOX + bevacizumab Dacarbazine FOLFOX FOLFOX + bevacizumab Temozolomide Temozolomide + bevacizumab Temozolomide + everolimus Temozolomide + thalidomide Streptozocin with 5-FU ± bevacizumab 5-FU + doxorubicin 5-FU + dacarbazine	Capecitabine + bevacizumab Capecitabine ± temozolomide CAPOX + bevacizumab Dacarbazine Docetaxel Etoposide FOLFIRONOX FOLFOX + bevacizumab Gemcitabine ± oxaliplatin Paclitaxel Streptozocin + 5-FU ± (cyclophosphamide OR doxorubicin OR cisplatin) Temozolomide + bevacizumab Temozolomide + thalidomide Topotecan 5-FU + dacarbazine
PRRT	^{90}Y-DOTATATE/^{90}Y-DOTATOC ^{177}Lu-DOTATATE ^{225}Ac-DOTATATE/^{225}Ac-DOTATOC ^{213}Bi-DOTATATE/^{213}Bi-DOTATOC ^{121}Pb-DOTATATE/^{121}Pb-DOTATOC	^{90}Y-DOTATATE/^{90}Y-DOTATOC ^{177}Lu-DOTATATE ^{225}Ac-DOTATATE/^{225}Ac-DOTATOC ^{213}Bi-DOTATATE/^{213}Bi-DOTATOC ^{121}Pb-DOTATATE/^{121}Pb-DOTATOC
Immunotherapy	Avelumab Ipilimumab + nivolumab Pembrolizumab Spartalizumab	Atezolizumab + bevacizumab Avelumab Durvalumab + tremelimumab Ipilimumab + nivolumab Pembrolizumab Spartalizumab Toripalimab

Abbreviations: 5-FU, 5-fluorouracil; CAPOX, capecitabine plus oxaliplatin; FOLFOX, folinic acid, 5-fluorouracil and oxaliplatin; NETs, neuroendocrine tumours; pNETs, pancreatic NETs

METHODS

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

Search for Systematic Reviews

A search was conducted for existing systematic reviews. This included original systematic reviews and systematic reviews published as a component of practice guidelines. The MEDLINE (2019 to October 30, 2023) and EMBASE (2019 to October 30, 2023) databases, as well as the Cochrane Database of Systematic Reviews (2019 to October 30, 2023) were searched. The full search strategy is available in Appendix 2. Systematic reviews were included if they met the following criteria:

- The review addressed at least one research question with similar inclusion/exclusion criteria; and
- The review had a low risk of bias as assessed with the ROBIS tool or a moderate/high overall rating as assessed with the AMSTAR 2 tool; and
- The review had a literature search cut-off after 2020.

If more than one systematic review met the inclusion criteria, then one systematic review for each outcome per comparison was selected by DS based on its age, quality, and the best match with our study selection criteria stated below.

Search for Primary Literature

For each outcome per comparison, if no systematic review was included, then a search for primary literature was conducted. For any included systematic review, an updated search for primary literature was performed. If any included systematic review was limited in scope, then a search for primary literature to address the limitation in scope was conducted.

Literature Search Strategy

The MEDLINE (January 2016 to October 30, 2023) and EMBASE (January 2016 to October 30, 2023) databases were searched for studies related to the use of SSAs, targeted therapy, chemotherapy, and immunotherapy. For PRRT, the same databases were searched but starting from January 2008. The full search strategy is available in Appendix 2. Reference lists of included primary literature were scanned for additional citations. Any trials included in the original guideline were included in the current guideline if they met the inclusion criteria. The following conference proceedings were also searched from 2016 to 2023: ASCO, ASCO Gastrointestinal Cancers Symposium, European Society for Medical Oncology, European Neuroendocrine Tumour Society, North American Neuroendocrine Tumour Society, and NET Research Foundation.

Study Selection Criteria and Process

Inclusion Criteria

1. Studies assessing patients with unresectable advanced or metastatic pNETs or midgut NETs; and
2. Studies that reported on or compared the effects of any of the systemic therapies listed in Table 4-1 for any of the following clinical outcomes: PFS, OS, adverse events, quality of life; and
3. RCTs will be searched within each intervention for each specified drug. If no RCTs are found, then comparative studies controlling for confounders will be included. If no comparative studies are available, then non-randomized, prospective studies will be searched and if none are available then retrospective studies will be included; and
4. Studies with ≥10 patients of interest.

Exclusion Criteria

1. Studies assessing the following conditions: grade 3 GEP NECs (i.e., poorly differentiated), malignant neuroblastoma, pituitary tumours, all neuroendocrine carcinoma, thymic tumours, goblet cell carcinoma, bronchial NETs, paragangliomas, mixed NETs, pheochromocytoma, small cell lung cancer, and thyroid cancer; or
2. Abstracts of non-randomized studies (single-arm clinical trials, case series, etc.); or
3. Abstracts of interim analyses; or
4. Papers or abstracts not available in English; or
5. Letters and editorials that reported clinical trial outcomes; or
6. Papers and abstracts published before 2016 with the exception of trials relating to PRRT.

A review of the titles and abstracts was conducted by one reviewer (DS), independently. For studies that warranted full-text review, one reviewer (DS) reviewed each study independently.

Data Extraction and Assessment of Risk of Bias

All included primary studies underwent data extraction by DS independently, with all extracted data and information audited subsequently by an independent auditor. Ratios, including hazard ratios, were expressed with a ratio of <1.0 indicating improved efficacy for the experimental arm.

Risk of bias per outcome for each included study was assessed using Cochrane's Risk of Bias tool for Randomized Studies tool (RoB 2; Part 2, Chapter 8; http://handbook.cochrane.org/) or Cochrane's Risk of Bias in Non-Randomized Studies – of Interventions (ROBINS-I; Part 4, Chapter 25; http://handbook.cochrane.org/). Risk of bias was deemed to be high for single-arm studies and not assessed using a tool.

Synthesizing the Evidence

Meta-analysis was not planned or conducted due to the heterogeneity across trials. Further, there were not enough studies in any given question or part of a question to warrant the use of meta-analysis.

Assessment of the Certainty of the Evidence

The certainty of the evidence per outcome for each comparison taking into account risk of bias, inconsistency, indirectness, imprecision, and publication bias was assessed.

RESULTS

Search for Systematic Reviews

A search for systematic reviews yielded 1406 deduplicated reference with seven reviews undergoing full-text review. None of the reviews met the pre-specified inclusion criteria. As this is an update of an existing PEBC systematic review, studies included in the original systematic review were included if they met the current inclusion criteria.

Search for Primary Literature

Literature Search Results

A search for primary literature yielded 18863 references of which 15 RCTs, of which four are currently available in abstract form, and 16 non-RCTs were included.

A PRISMA flow diagram of the complete search is available in Appendix 3. Table 4-2 provides a breakdown of the number of studies included from the current search as well as from the original guideline search. Where multiple reports and abstracts were published for a single trial, only the most recent full publication was included, unless other reports contained relevant data that were not available in the most recent publication.

Table 4-2. Studies selected for inclusion.

	Pancreatic NETs	Midgut NETs
Somatostatin analogues	[1,2,44]	[1,30,31,44]
Targeted therapy	[4-10,23,45]	[32]
Chemotherapy	[3,16-22,46]	[46,47]
PRRT	[11,12,24,25]	[11,12,25,27,28]
Immunotherapy	[13-15]	None

Abbreviations: NETs, neuroendocrine tumours; PRRT, peptide receptor radionuclide therapy

While this guideline focuses on pNETs and midgut NETs, a number of RCTs were found that contain NETs of various origins without providing specific subgroup data [48-53]. The results of these RCT studies have been summarized in Appendix 5, Tables A5-1 to A5-3 and are not discussed in detail in the review below.

Certainty of the Evidence

The overall certainty of the evidence was assessed for each comparison for both pNETs and midgut NETs. Abstracts were not assessed. Eleven fully published RCTs were included in this systematic review and assessed using the Cochrane's Risk of Bias Tool (Appendix 4, Table A4-1). Four trials [1,4-6,32,33] had a low risk of bias across all outcomes, while the PROMID trial [30,31] had a low risk of bias across all survival outcomes and a medium risk of bias for quality of life due to incomplete outcome reporting. Six RCTs [2,3,16,23,27,28,45] were open label and consequently were rated as high risk of bias.

One non-randomized comparative study [46] was included and assessed for risk of bias using the ROBINS-I (Appendix 4, Table A4-2). It was determined to have a moderate risk of bias as a result of not controlling for confounding.

The risk of bias of single-arm studies were not assessed and deemed to be high risk of bias.

The overall certainty of the evidence for each comparison is moderate or low as a result of being marked down for risk of bias and indirectness/imprecision (i.e., only one study per comparison, low patient numbers).

Outcomes: pNETs

Research Question 1. Which of the anti-neoplastic systemic therapies (Table 4-1) is the most effective in improving clinical outcomes (i.e., PFS, OS) and quality of life while minimizing adverse events in patients with inoperable or metastatic pNETs?

SSAs

Two RCTs [1,2] assessing the use of SSAs in patients with pNETs and one single-arm phase II study [44] assessing a reduced dosing interval for lanreotide were found (Table 4-3).

Lanreotide vs. Placebo

PFS

The overall CLARINET study [1] compared lanreotide with placebo in patients with well- or moderately differentiated, non-functioning grade 1 or 2 NETs. The pre-defined subgroup analysis of the CLARINET trial reported no difference in median PFS for patients with pNETs receiving lanreotide compared with placebo (HR, 0.58; 95% CI, 0.32 to 1.04). This subgroup analysis was undertaken to investigate the consistency of treatment effects as the study was not powered for such analysis. The results of this subgroup analysis were not consistent with the results of the overall study where there was a significant difference in median PFS for patients who received lanreotide (HR, 0.47; 95% CI, 0.30 to 0.73; p<0.001).

Adverse events

Approximately 50% of patients in the treatment arm experienced an adverse event related to study treatment compared with 28% in the placebo arm. Three percent of patients in the treatment arm and 1% of patients in the placebo arm experienced a serious adverse event related to study treatments with 1% of patients from the treatment arm withdrawing from the study. Adverse event data are presented for all patients enrolled in the CLARINET study and are not specific to the subgroup of patients with pNETs.

Quality of life

Quality of life was assessed using EORTC QLQ-C30 and QLQ-GI.NET21 questionnaires and showed no significant between-group differences. Quality of life data are presented for all patients enrolled in the CLARINET study and are not specific to the subgroup of patients with pNETs.

Lanreotide (reduced dosing interval)

PFS

The CLARINET FORTE [44], a pilot study, assessed the efficacy of a reduced lanreotide dosing interval (120 mg every 14 days) following first-line standard dose lanreotide treatment (120 mg every 28 days) in patients with pNETs or midgut NETs. Recruitment was stopped early for the cohort of patients with pNETs due to recruiting difficulties. The median PFS for patients with pNETs was 5.6 months (95% CI, 5.5 to 8.3).

Adverse events

There were no grade 3 to 5 treatment-related adverse events in patients with pNETs, while two patients withdrew from the study due to treatment-related adverse events.

Quality of life

Quality of life was assessed using EORTC QLQ-C30, EORTC QLQ-GI.NET21, and 5-level EuroQol Group-5D (EQ-5D-5L) questionnaires with no deterioration in quality of life being reported in patients with pNETs.

Everolimus + Pasireotide vs. Everolimus

PFS

The COOPERATE-2 trial [2] compared everolimus plus pasireotide with everolimus in patients with well-differentiated grade 1 or 2, advanced pNETs. The COOPERATE-2 trial reported no difference in median PFS for the addition of pasireotide to everolimus for patients with pNETs (HR, 0.99; 95% CI, 0.64 to 1.54). The p-value was not reported.

Adverse events

Grade 3 or 4 adverse events were reported in 77% of patients receiving pasireotide plus everolimus with the most common being hyperglycemia (37.2%), diabetes mellitus (11.5%), and stomatitis (9.0%), while 69% of patients receiving everolimus only reported grade 3 or 4 adverse events with the most common being hyperglycemia (11.1%), stomatitis (8.6%), and abdominal pain (6.2%). Three deaths were suspected to be treatment-related, two in the treatment arm and one in the control arm.

Quality of life

Quality of life was not assessed.

Table 4-3. Trials Reporting on the Use of Somatostatin Analogues in Patients with Pancreatic Neuroendocrine Tumours

Author, year	Study inclusion criteria	Treatment	Number of patients with pNETs evaluated	Median follow-up (range)	Median PFS	Median OS	Adverse events and quality of life
LANREOTIDE VS. PLACEBO							
Randomized controlled trial							
CLARINET Caplin et al (2014) [1] SUBGROUP	Adults with well- or moderately differentiated, non-functioning grade 1 or 2 NETs, metastatic disease or a locally advanced tumour that was inoperable, Ki-67 <10%, PS ≤2	120 mg lanreotide (Autogel/Depot) subcutaneously every 28 days vs. Placebo every 28 days	42 49	NR	Not reached 12.1 mths (95% CI, 9.4-18.3) HR, 0.58; 95% CI, 0.32-1.04	NA	Serious AEs[a], 3% vs. 1% No significant between-group differences using EORTC QLQ-C30 and QLQ-GI.NET21[a]
LANREOTIDE (reduced dosing interval)							
Prospective, single arm study (phase II)							
CLARINET FORTE Pavel et al (2021) [44] SUBGROUP	Adults with well-differentiated, SSTR2-positive, metastatic, or locally advanced, unresectable, grade 1/2 (Ki-67 ≤20%) pancreatic or midgut NETs, ECOG PS ≤2, with disease progression in the previous 2 years on the standard LAN regimen (120 mg every 28 days) for ≥24 weeks	Lanreotide 120 mg (Autogel/Depot) subcutaneously every 14 days	48	NR	Ki-67 ≤2%, 5.6 mths (95% CI, 5.5-8.3) Ki-67 ≤10%, 8.0 mths (95% CI, 5.6-8.3) Ki-67 >10%, 2.8 mths (95% CI, 2.8-2.9)	NR	Two withdrawals due to treatment-related AEs. No grade 3-5 treatment-related AEs No deterioration in QoL was reported based on EORTC QLQ-C30, EORTC QLQ-GI.NET21, or EQ-5D-5L.

Author, year	Study inclusion criteria	Treatment	Number of patients with pNETs evaluated	Median follow-up (range)	Median PFS	Median OS	Adverse events and quality of life
EVEROLIMUS ± PASIREOTIDE							
Randomized controlled trial							
COOPERATE-2 Kulke et al (2017) [2]	Adults with well differentiated grade 1 or 2, advanced pNET with Disease progression within 12 months before randomization and PS ≤2.	Everolimus 10 mg daily + pasireotide LAR 60 mg every 28 days vs. Everolimus 10 mg daily	79 81	NR	16.8 mths (95% CI, 12.1-19.6) 16.6 mths (95% CI, 11.1-19.5) HR. 0.99; 95% CI, 0.64-1.54; p=0.49	HR, 0.93; 95% CI, 0.49-1.76; p=0.41	Grade 3-4 AEs, 77% vs. 69% Treatment-related deaths, 2 vs. 1 Quality of life, NA
OCTREOTIDE							
No studies met inclusion criteria							

[a] Results reported for all included patients in the trial (n=101 for lanreotide; n=103 for placebo) and are not specific to the cohort of patients with pNETs.

Abbreviations: AE, adverse events; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L, 5-level EuroQol Group-5D; HR, hazard ratio; mths, months; LAN, lanreotide autogel; LAR, long-acting repeatable; mths, months; NA, not assessed; NET, neuroendocrine tumours; NR, not reported; OS, overall survival; PFS, progression-free survival; pNET, pancreatic neuroendocrine tumour; PS, performance scale; QLQ-GI.NET21, Quality of Life Questionnaire - Neuroendocrine Carcinoid Module; QoL, quality of life; SSTR2, somatostatin receptor 2; vs., versus

Targeted Therapy

Five RCTs [4-6,10,45], one indirect-matching comparison study of the RCTs [7] and two prospective, single-arm studies [8,9] were found assessing the use of targeted therapy in patients with pNETs (Table 4-4).

Everolimus vs. Placebo

PFS

The RADIANT-3 trial [4,6] compared the use of everolimus with placebo in patients with low- or intermediate-grade, advanced pNETs. It reported a median PFS of 11.4 months (95% CI, 10.8 to 14.8) versus 5.4 months (95% CI, 4.3 to 5.6) for the everolimus and placebo arms, respectively (HR, 0.34; 95% CI, 0.26 to 0.44; p<0.001), after a median follow-up period of 17 months. In a pre-specified subgroup analysis of the RADIANT-3 trial, everolimus significantly prolonged median PFS regardless of prior chemotherapy use, World Health Organization performance status, age, sex, race, geographic region, use of prior SSA therapy, and tumour grade. Interaction terms were not reported.

OS

The RADIANT-3 trial showed no difference in median OS between patients who received everolimus and those who received placebo (HR, 0.94; 95% CI, 0.73 to 1.20; p=0.30). This trial allowed for patients randomized to placebo to cross over to the treatment arm at disease progression. As a result, 73% of patients crossed over, confounding survival results. Rank-preserving structural failure time analysis was performed to correct for crossover bias (HR, 3.27; 95% CI, 0.10 to 13.93) and a stronger OS advantage was shown at both 12 and 24 months for patients who received everolimus.

Adverse events

In the double-blind phase, serious adverse events were reported more often in the everolimus arm. The most common grade 3 or 4 adverse events in the everolimus arm were stomatitis (7.4%), hyperglycemia (5.9%), and anemia (4.9%) while the most common in the control arm were hyperglycemia (2.5%), asthenia (1%), and decreased appetite (1%). There were 12 on-treatment deaths in the everolimus arm and four in the control arm.

Sunitinib vs. Placebo

PFS

The phase III randomized trial by Faivre et al [5] compared the use of sunitinib with placebo in patients with advanced, metastatic, well-differentiated pNETs. A median PFS by blinded independent central review of 12.6 months versus 5.8 months for the treatment and placebo arms, respectively (HR, 0.32; 95% CI, 0.18 to 0.55; p=0.00001) was reported. This trial was closed early due to the significant benefit in PFS in the treatment arm, and the risk of serious adverse events, disease progression, and death among patients receiving placebo; all patients were offered entry into an open-label sunitinib extension protocol.

OS

A significant benefit in survival was reported for patients receiving sunitinib (HR, 0.40; 95% CI, 0.23 to 0.71; p=0.001). Again, patients receiving placebo were allowed to cross over to the treatment arm at disease progression; however, the results presented here have been adjusted for this by censoring patients at crossover.

Adverse events

Grade 3 or 4 adverse events were more common in patients receiving sunitinib with the most common being neutropenia (12%), hypertension (10%), and palmar-plantar erythrodysesthesia (6%), while the most common in the control arm were abdominal pain (10%), fatigue (8%), and back pain (5%). Five patients who received sunitinib and nine patients who received placebo died during the trial period, of which one death from each group were considered to be related to the study drug.

Quality of life

Patients completed the EORTC QLQ-C30 at baseline, the first day of every four-week cycle and at the end of treatment or withdrawal. There were no significant between-group differences in global health-related quality of life, cognitive, emotional, physical, role and social functioning domains, or symptom scales, with the exception of diarrhea with sunitinib ($p<0.001$).

Everolimus vs. Sunitinib

Survival

In a matching-adjusted indirect comparison of patients from the RADIANT-3 trial and the phase III sunitinib trial [7], everolimus was associated with similar PFS ($p=0.578$) and OS ($p=0.383$) when compared with sunitinib.

Adverse events

There were no significant differences in grade 3 or 4 treatment-related adverse events between the two groups.

Cabozantinib vs. Placebo

PFS

The CABINET trial [10], a phase III randomized trial by Chan et al, currently available in abstract form, compared the use of cabozantinib with placebo in patients with well- to moderately differentiated, grade 1 to 3 NETs who had disease progression after at least one prior FDA-approved systemic therapy, excluding SSAs. Based on preplanned interim analysis, the Independent Data and Safety Monitoring Board has voted to stop accrual, to unblind patients, and to allow patients receiving placebo to cross over to the treatment arm. It reported a median PFS of 11.4 months versus 3.0 months for the cabozantinib and placebo arms, respectively (HR, 0.27; 95% CI, 0.14 to 0.49; $p<0.0001$), after a median follow-up period of 16.7 months in the cohort of patients with pNETs.

OS

The CABINET trial showed no difference in median OS between patients who received cabozantinib (43.5 months) and those who received placebo (31.0 months; HR, 0.77; 95% CI, 0.34 to 1.73; $p=0.26$).

Adverse events

In the cohort of patients with pNETs who received cabozantinib, 56.7% and 8.3% experienced grade 3 and 4 treatment-related adverse events, respectively, while 43.3% of patients in the placebo arm experienced grade 3 adverse events. The most common grade 3 or higher adverse events between patients who received cabozantinib or placebo were hypertension (26.7% vs. 20.0%, respectively), fatigue (13.3% vs. 3.3%), and hyperglycemia (8.3% vs. 10.0%).

Surufatinib vs. Placebo

PFS

In the trial by Xu et al [23], a pre-planned interim analysis determined patients who received surufatinib had a significantly longer median PFS compared with those who received placebo (13.9 months vs. 4.6 months; HR, 0.34; 95% CI, 0.21 to 0.55; p<0.0001). This study was terminated early because of the superior efficacy data for surufatinib.

OS

OS data were not mature at the time of interim analysis. Patients in the placebo arm were allowed to cross over to receive surufatinib after disease progression confounding OS results in the placebo group.

Adverse events

Grade 3 or 4 adverse events were more common in patients receiving surufatinib with the most common being hypertension (38% vs. 7%), proteinuria (10% vs. 2%), and hyperglyceridemia (7% vs. 0%). Three on-treatment deaths, of which two were possibly treatment-related, occurred in the surufatinib group while there was one on-treatment death in the placebo group resulting from disease progression.

Quality of life

Patients completed the EORTC QLQ-C30 and QLQ-GINET21 at baseline, day 15 of the first cycle with day 1 of every cycle thereafter, and at the end of treatment. There were no significant between-group differences in global health-related quality of life, cognitive, emotional, physical, role and social functioning domains, or symptom scales, with the exception of diarrhea with surufatinib (p<0.0001). Quality of life data are presented for all patients enrolled in the trial and are not specific to the subgroup of patients with pNETs.

Everolimus + Bevacizumab vs. Everolimus

PFS

The CALGB 80701 phase II RCT [45] reported no significant difference in median PFS in patients with pNETs who received everolimus plus bevacizumab compared with those who received everolimus only (16.7 months vs. 14.0 months; HR, 0.80; 95% CI, 0.56 to 1.13; p=0.1028).

OS

Similar to median PFS, there was no significant difference in median OS between both arms (42.1 months vs. 42.5 months; HR, 0.90; 95% CI, 0.57 to 1.42; p=0.322).

Adverse events

Grade 3 or 4 non-hematologic adverse events occurred at a higher rate in patients receiving everolimus plus bevacizumab (85%) than in patients receiving everolimus alone (51%); hematologic adverse events occurred at a similar rate between the two groups (18% vs. 15%). The most common grade 3 or 4 adverse events in patients 32 receiving everolimus plus bevacizumab were hypertension (38% vs. 8%), hyperglycemia (19% vs. 15%), and proteinuria (21% vs. 3%).

Lenvatinib

Survival

The TALENT trial [8] evaluated the efficacy of lenvatinib in previously treated patients with NETs. The cohort of patients with pNETs had a median PFS of 15.6 months (95% CI, 11.4 to not reported) and a median OS of 32 months (95% CI, 26.47 to not reported).

Adverse events

The most common grade 3 to 4 adverse events in patients with pNETs were hypertension (21.8%), vomiting (9.1%), abdominal pain (7.3%), and diarrhea (7.3%) with 10.9% of patients requiring a definitive treatment discontinuation due to severe-treatment related toxicity.

Pazopanib

Survival

The phase II study by Phan et al [9] reported the efficacy of pazopanib with octreotide LAR in patients with pNETs or carcinoid tumours. The cohort of patients with pNETs had a median PFS of 14.4 months (95% CI, 5.9 to 22.9) and a median OS of 25 months (95% CI, 15.5 to 34.4).

Adverse events

Among the patients in both cohorts, two experienced grade 4 adverse events (hypertriglyceridemia, and a thromboembolic event). The most common grade 3 events were hypertension (12%), fatigue (8%), diarrhea (6%), increases in alanine and aspartate aminotransferase (6%, each), and decreased neutrophil count (6%). There were no treatment-related deaths. Adverse event data were not provided specific to patients with pNETs.

Table 4-4. Trials Reporting on the Use of Targeted Therapy in Patients with Pancreatic Neuroendocrine Tumours

Author, year	Study inclusion criteria	Treatment	Number of patients with pNETs evaluated	Median follow-up (range)	Median PFS	Median OS	Adverse events and quality of life
EVEROLIMUS VS. PLACEBO							
Randomized controlled trial							
RADIANT-3 Yao et al (2011) (2016) [4,6]	Adults with low- or intermediate-grade, advanced pNETs, who had radiologic disease progression documented within 12 months, PS≤2	Everolimus 10 mg once daily vs. Placebo once daily	207 203	17 mths	11.4 mths (95% CI, 10.8-14.8) 5.4 mths (95% CI, 4.3-5.6) HR, 0.34; 95% CI, 0.26-0.44; p<0.001	44.0 mths (95% CI, 35.6-51.8) 37.7 mths (95% CI, 29.1-45.8)[a] HR, 0.94; 95% CI, 0.73-1.20; p=0.30	Serious AEs were reported more often in the everolimus arm. On-treatment deaths, 12 vs. 4 Quality of life, NA
EVEROLIMUS ± BEVACIZUMAB							
Randomized controlled trial							
CALGB 80701 Kulke et al (2022) [45]	Adults with locally unresectable or metastatic, well or moderately differentiated pNETs with clinical disease progression within 12 months	Everolimus 10 mg daily + bevacizumab 10 mg/kg every 2 weeks vs. Everolimus 10 mg once daily	75 75	37.5 mths (IQR 36.2-60.7)	16.7 mths (95% CI, 13.7-21.9) 14.0 mths (95% CI, 8.9-17.5) HR, 0.80; 95% CI, 0.56-1.13; p=0.10	42.1 mths (95% CI, 35.3-NE) 42.5 mths (95% CI, 32.5-NE) HR, 0.90; 95% CI, 0.57-1.42; p=0.32	Grade 3 or 4 non-hematologic AEs, 85% vs. 51% Grade 3 or 4 hematologic AEs, 18% vs. 15% Quality of life, NA

Author, year	Study inclusion criteria	Treatment	Number of patients with pNETs evaluated	Median follow-up (range)	Median PFS	Median OS	Adverse events and quality of life
SUNITINIB VS. PLACEBO							
Randomized controlled trial							
A6181111 Faivre et al (2017) [5]	Adults with well-differentiated pNETs that were advanced, metastatic, or both and were not candidates for surgery.	Sunitinib 37.5 mg once daily vs. Placebo once daily	86 85	67.4 mths	12.6 mths (95% CI, 11.1-20.6) 5.8 mths (95% CI, 3.8-7.2) HR, 0.32; 95% CI, 0.18-0.55; p=0.000015	38.6 mths (95% CI, 25.6-56.4) 29.1 mths (95% CI, 16.4-36.8)[b] HR, 0.73; 95% CI, 0.50-1.06; p=0.094	Grade 3 or 4 AEs were more common in patients receiving sunitinib Treatment-related deaths, 1 vs. 1 No significant between-group differences using EORTC QLQ-C30 except for diarrhea with sunitinib (p<0.001)
CABOZANTINIB VS. PLACEBO							
Randomized controlled trial							
CABINET Chan et al (2023) [10] *Abstract* COHORT	Adults with well- to moderately differentiated, grade 1 to 3 NETs; disease progression within 12 months and have disease progression after or intolerance of at least 1 prior FDA-approved systemic therapy, excluding SSAs	60 mg cabozantinib once daily vs. Placebo once daily	62 31	16.7 mths	11.4 mths 3.0 mths HR, 0.27; 95% CI, 0.14-0.49; p<0.0001	43.5 mths 31.0 mths HR, 0.77; 95% CI, 0.34-1.73; p=0.26	Grade 3 or 4 AEs were more common in those receiving cabozantinib.

Author, year	Study inclusion criteria	Treatment	Number of patients with pNETs evaluated	Median follow-up (range)	Median PFS	Median OS	Adverse events and quality of life
SURUFATINIB VS. PLACEBO							
Randomized controlled trial							
Xu et al (2020) [23] Interim analysis	Adults with unresectable or metastatic, well differentiated pNETs, grade 1 or 2, ECOG PS 0-1, and life expectancy of more than 12 weeks.	300 mg surufatinib once daily vs. Placebo once daily	113 59	19.3 mths (95% CI, 9.3-19.4) 11.1 mths (95% CI, 5.7-35.9)	13.9 mths (95% CI, 11.0-24.9) 4.6 mths (95% CI, 3.6-7.4) HR, 0.34; 95% CI, 0.21-0.55; p<0.0001	Not mature at interim analysis	Grade 3 or 4 AEs were more common in patients receiving surufatinib On-treatment deaths, 3 vs. 1 No significant between-group differences using EORTC QLQ-C30 and QLQ-GINET21 except for diarrhea with surufatinib (p<0.001)
EVEROLIMUS VS. SUNITINIB							
Indirect-matching comparison study of two randomized controlled trials							
Signorovitch et al (2013) [7]	Adults from the phase III RCTs of everolimus (RADIANT-3) and sunitinib (A6181111) were included in this study	Everolimus 10 mg once daily (RADIANT-3) vs. Sunitinib 37.5 mg once daily (A6181111)	207 86	NR	HR, 0.84; 95% CI, 0.46-1.53; p=0.578	HR, 0.81; 95% CI, 0.49-1.31; p=0.383	No significant differences in grade 3 or 4 AEs between the two groups.

Author, year	Study inclusion criteria	Treatment	Number of patients with pNETs evaluated	Median follow-up (range)	Median PFS	Median OS	Adverse events and quality of life
LENVATINIB							
Prospective, single arm study (phase II trial)							
TALENT Capdevila et al (2021) [8] SUBGROUP	Adults with advanced pNETs or GI NETs with progressive disease after treatment with a targeted agent grade 1 or 2; radiological disease progression during the last 12 months; ECOG PS 0-1.	Lenvatinib 24 mg once daily	55	23 mths	15.6 mths (95% CI, 11.4-NR)	32 mths (95% CI, 26.47-NR)	Most common grade 3 to 4 AEs were hypertension (21.8%), vomiting (9.1%), abdominal pain (7.3%) and diarrhea (7.3%). 10.9% of patients required a definitive treatment discontinuation due to severe treatment-related toxicity. Quality of life, NA
PAZOPANIB							
Prospective, single arm study (phase II trial)							
Phan et al (2015) [9] SUBGROUP	Adults with metastatic or locally advanced grade 1–2 pNETs or carcinoid tumours, and ECOG PS 0-1.	Pazopanib 800 mg orally once per day for 12 treatment cycles, 28 days each + octreotide LAR 30 mg every 28 days	32	64.3 mths (IQR, 60.7-68.1)	14.4 mths (95% CI, 5.9-22.9)	25 mths (95% CI, 15.5-34.4)	The most common grade 3 AEs were hypertension (12%), fatigue (8%), diarrhea (6%), increases in alanine and aspartate aminotransferase (6%, each) and decreased neutrophil count (6%). Two grade 4 AEs occurred hypertriglyceridemia (2%), and a thromboembolic event (2%)[c]. No treatment-related deaths[c]. Quality of life, NA

Author, year	Study inclusion criteria	Treatment	Number of patients with pNETs evaluated	Median follow-up (range)	Median PFS		Median OS		Adverse events and quality of life
SORAFENIB									
No studies met inclusion criteria									

[a] Calculated using RPSFT analysis to account for patients who crossed over from placebo to treatment arm

[b] Patients who crossed over from placebo to treatment arm were censored

[c] Results reported for all included patients in the trial (n=52) and are not specific to the cohort of patients with pNETs.

Abbreviations: AEs, adverse events; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC QLQ, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; FDA, Food and Drug Administration; GI, gastrointestinal; HR, hazard ratio; IQR, interquartile range; LAR, long-acting repeatable; mths, months; NA, not assessed; NR, not reached; OS, overall survival; PFS, progression-free survival; pNET, pancreatic neuroendocrine tumour; PS, performance scale; QLQ-GI NET21, Quality of Life Questionnaire - Neuroendocrine Carcinoid Module; SSA, somatostatin analogue; vs., versus

Chemotherapy

Two RCTs [3,16], four prospective single-arm studies [17-20], one retrospective comparative study [46], and two retrospective single-arm studies [21,22] were found assessing the use of chemotherapy in patients with pNETs with each study evaluating a different chemotherapy regimen (Table 4-5).

S-1/Temozolomide + Thalidomide + S-1/Temozolomide

PFS

The STEM randomized, phase II trial [16] evaluated the addition of thalidomide to S-1/temozolomide in patients with pancreatic and non-pancreatic NETs. Prior treatment was allowed. In the pre-specified group of patients with pNETs, there was no significant difference between those who received S-1/temozolomide plus thalidomide when compared with those who received S-1/temozolomide only (HR, 1.04; 95% CI, 0.37 to 1.90). Approximately 20% of patients had grade 3 pNETs in each arm.

OS

In the STEM trial, median OS was not reached in both arms.

Adverse events

In the subgroup of patients with pNETs, 13% of patients in the S-1/temozolomide plus thalidomide arm and 3% of patients in the S-1/temozolomide arm experienced grade 3 or 4 adverse events. Further adverse event data specific to the treatment arms for patients with pNETs were not provided.

Temozolomide + Capecitabine vs. Temozolomide

PFS

The ECOG-ACRIN E2211 randomized, phase II trial [3] evaluated the addition of capecitabine to temozolomide in patients with pNETs. Prior treatment with temozolomide, dacarbazine (DTIC), capecitabine or 5-FU was not permitted. There was no statistically significant difference in median PFS between those who had received temozolomide only and those who received temozolomide in combination with capecitabine (15.1 months vs. 23.2 months; HR, 0.71; 95% CI, 0.46 to 1.07). The p-value was not reported. After adjusting for tumour grade, there was no statistically significant difference between the two arms (HR, 0.63; 95% CI, 0.39 to 1.01).

OS

In the final analysis of the ECOG-ACRIN E2211 trial, there was no significant difference in median OS between those who had received temozolomide only and those who received temozolomide in combination with capecitabine (53.8 months vs. 58.7 months HR, 0.82; 95% CI, 0.51 to 1.33; p=0.42).

Adverse events

The temozolomide plus capecitabine arm had higher rates of grade 3 and 4 adverse events compared with the temozolomide arm (45% vs. 22%; p=0.005). No treatment-related deaths were reported.

Temozolomide + Everolimus (Dose Escalation)

PFS

In the dose escalation study by Chan et al [17], patients with pNETs were administered temozolomide with everolimus 5 mg and if the treatment was tolerated, the second cohort of patients received temozolomide with everolimus 10 mg. There were seven patients in cohort 1 and 36 patients enrolled in cohort to with a median PFS of 15.4 months (95% CI, 9.4 to 20.4).

Adverse events

Nine patients discontinued treatment due to non-hematologic treatment-related toxicity. The most common grade 3 and 4 adverse events were lymphopenia (44%), thrombocytopenia (16%), and hyperglycemia (19%).

Temozolomide + Bevacizumab

Survival

The prospective study by Chan et al [18] studied the efficacy of patients who received temozolomide with bevacizumab. Prior treatment was allowed. For the small cohort of patients with pNETs (n=15), a median PFS of 14.3 months (95% CI, 8.5 to not estimable) and a median OS of 41.7 months (95% CI, 23.6 to not estimable) were reported.

Adverse events

Adverse events were reported for all patients included in this study (n=34) and were not specific to the cohort of patients with pNETs. The most common grade 3 or 4 hematological adverse event was lymphopenia (52.9%), and the most common grade 3 or 4 non-hematological adverse events were vomiting (8.8%), nausea (5.9%), and fatigue (5.9%).

CAPOX + Bevacizumab

Survival

The prospective study by Kunz et al [19] studied the efficacy of patients who received CAPOX with bevacizumab. Prior treatment was allowed. For the small cohort of patients with pNETs (n=16), a median PFS of 15.7 months (95% CI, 8.2 to 29.3) and a median OS of 38.0 months (95% CI, not reported) were reported.

Adverse events

Adverse events were reported for all patients who received CAPOX with bevacizumab (n=40) and were not specific to the cohort of patients with pNETs. The most common grade 3 or 4 adverse events were diarrhea (20%), hypertension (13%), and rashes (10%).

5-FU + Streptozocin + Bevacizumab

Survival

The single-arm BETTER trial [20] evaluated 34 patients with pNETs. Approximately 74% of patients had prior treatment but none had received systemic anticancer therapy. A median PFS of 26.3 months (95% CI, 17.4 to not reached) was reported. The median OS was not reached.

Adverse events

The BETTER trial reported the most common grade 3 and 4 adverse events were hypertension (21%), abdominal pain (21%) and thromboembolic events (9%). Seven patients permanently discontinued bevacizumab and nine patients permanently discontinued 5-FU and bevacizumab due to adverse events.

Quality of Life

There were no significant changes in global health status using the EORTC QLQ-C30 between baseline, three-month, six-month, and 12-month assessments.

Capecitabine + Temozolomide vs. 5-FU + DTIC

PFS

The retrospective, comparative study by de Mestier et al [46] evaluated the efficacy of 5-FU-DTIC and temozolomide plus capecitabine. In the cohort of patients with pNETs (n=204), median PFS was analyzed using propensity score analysis to reduce confounding bias due to the non-randomized design of the study. There was a significant difference in median PFS between patients with pNETs who received 5-FU-DTIC (23.1 months; 95% CI, 12.2 to 33.7) when compared with those who received capecitabine plus temozolomide (12.8 months; 95% CI, 6.5 to 20.6; p=0.04). Approximately 11% of patients in each arm for the entire study had grade 3 NETs; specific data for patients with pNETs were not provided.

OS

de Mestier et al noted [46] that there were no significant differences between the two treatment groups for patients with pNETs.

Adverse events

Adverse event data were presented for all patients included in this study and subgroup-specific data were not available. The most common grade 3-4 adverse events in the 5-FU-DTIC arm (n=94) were neutropenia (3.2%), thrombocytopenia (3.2%), and anemia (2.1%), while the most common grade 3-4 adverse events in the capecitabine plus temozolomide arm were thrombocytopenia (13.0%), neutropenia (5.5%), and infections (2.7%).

FOLFOX

Survival

The retrospective study by Al-Toubah et al [21] studied patients with pNETs who received FOLFOX, either alone (n=25) or with bevacizumab (n=6). All included patients must have also received capecitabine and temozolomide as a previous line of therapy. Of the included patients, 61.3% had grade 1 or 2 NETs. For the cohort of patients who received FOLFOX only, a median PFS of six months (95% CI, 4.9 to 7.1) and a median OS of 17 months (95% CI, 12.1 to 21.9) were reported.

Adverse events

Al-Toubah et al reported that 26% of all included patients discontinued treatment due to toxicity. Grade 3 treatment-related adverse events included sensory neuropathy (6.5%), neutropenia (6.5%), hepatic encephalopathy (6.5%), fatigue (3.2%), and hypoglycemia (3.2%). Adverse events were reported for all patients included in the study and are not specific to those who received FOLFOX only.

FOLFOX + Bevacizumab

Survival

The prospective study by Kunz et al [19] studied the efficacy of patients who received mFOLFOX-6 with bevacizumab. Prior treatment was allowed. For the small cohort of patients with pNETs (n=12), a median PFS of 21.0 months (95% CI, 7.4 to 31.4) and a median OS of 31.0 months (95% CI, not reported) were reported.

Adverse events

Adverse events were reported for all patients who received FOLFOX with bevacizumab (n=36) and were not specific to the cohort of patients with pNETs. The most common grade 3 or 4 adverse events were neutropenia (25%), neuropathy (17%), and fatigue (17%).

5-FU + Doxorubicin + Streptozocin

Survival

In the single institution retrospective analysis of patients with metastatic pNETs by Rogers et al [22], 86% of patients received 5-FU, doxorubicin and streptozocin as first-line therapy, while the remaining had received therapy prior to 5-FU, doxorubicin and streptozocin. A median PFS of 20 months (95% CI, 15 to 23) and a median OS of 63 months (95% CI, 60 to 71) were reported after a median follow-up of 61 months.

Adverse events

The most common grade 3 and 4 adverse events were neutropenia (10%), nausea/vomiting (5.5%) and oral mucositis (3.6%). Five percent of patients required chemotherapy to be discontinued due to toxicity.

Table 4-5. Trials Reporting on the Use of Chemotherapy in Patients with Pancreatic Neuroendocrine Tumours

Author, year	Study inclusion criteria	Treatment	Number of patients with pNETs evaluated	Median follow-up (range)	Median PFS	Median OS	Adverse events and quality of life
S-1 + TEMOZOLOMIDE ± THALIDOMIDE							
Randomized controlled trial (phase II)							
STEM Chi et al (2022) [16] SUBGROUP	Adults with low or middle grade (G1-G3 G2, typical and atypical carcinoid) well-differentiated pNETs or non-pancreatic NETs with unresectable locally advanced disease or distant metastasis; ECOG PS 0-1, expected survival of >12 weeks and either systemic treatment naïve or had received ≤2 prior systemic anti-tumour therapies	S-1 and temozolomide + thalidomide (100 mg on days 1-7, 200 mg on days 8-14 and 300 mg from day 15) vs. S-1 40-60 mg twice daily on days 1-14 + temozolomide 200 mg daily on days 10-14 in a 21-day cycle	30 30	12.1 mths (IQR, 8.4-16.6)	16.2 mths (95% CI, 7.2-not reached) NR HR, 1.04; 95% CI, 0.37-1.90; p=NR	NR	Incidence of grade 3 or 4 AEs, 13% vs. 3% Quality of life, NA
TEMOZOLOMIDE ± CAPECITABINE							
Randomized controlled trial							
ECOG-ACRIN E2211 Kunz et al (2023) [3]	Adults with metastatic or unresectable, low or intermediate grade pNETs, progression within preceding 12 months, and no	Temozolomide 200 mg/m^2 daily days 1-5 vs. Capecitabine 750 mg/m^2 twice	72 72	59.9 mths	15.1 mths (95% CI, 10.5-21.0) 23.2 mths (95% CI, 16.6-32.2)	53.8 mths (95% CI, 35.7-NA) 58.7 mths (95% CI, 44.7-NA)	Grade 3 or 4 AEs, 45% vs. 22% (p=0.005) No treatment-related deaths Quality of life, NA

Author, year	Study inclusion criteria	Treatment	Number of patients with pNETs evaluated	Median follow-up (range)	Median PFS	Median OS	Adverse events and quality of life
	prior temozolomide, DTIC, capecitabine or 5-FU	daily days 1-14 + temozolomide 200 mg/m^2 daily days 10-14			HR, 0.71; 95% CI, 0.46-1.07	HR, 0.82; 95% CI, 0.51-1.33; p=0.42	
TEMOZOLOMIDE + EVEROLIMUS							
Prospective, single arm study (phase 1/2)							
Chan et al (2013) [17]	Adults with low- or intermediate grade (G1 or G2) metastatic or locally unresectable pNETs.	Cohort 1: Temozolomide 150 mg/m^2 on days 1-7 and days 15-21 of a 28-day cycle + everolimus 5 mg daily Cohort 2: Temozolomide 150 mg/m^2 on days 1-7 and days 15-21 of a 28-day cycle + everolimus 10 mg daily	7 36		15.4 mths (95% CI, 9.4-20.4)	NR	Nine patients discontinued treatment due to non-hematologic treatment-related toxicity. Most common grade 3 and 4 AEs were lymphopenia (44%), thrombocytopenia (16%) and hyperglycemia (19%). Quality of life, NA
TEMOZOLOMIDE + BEVACIZUMAB							
Prospective, single arm study							
Chan et al (2012) [18] SUBGROUP	Adults with metastatic or locally unresectable NETs, excluding small-cell carcinoma, ECOG PS ≥2 and life expectancy of at least 12 weeks	Temozolomide 150 mg/m^2 orally per day on days 1 through 7 and days 15 through 21 + bevacizumab 5 mg/kg per day intravenously on days 1 and 15 of each 28-day cycle	15	28.7 mths (1-65)[a]	14.3 mths (95% CI, 8.5-NE)	41.7 mths (95% CI, 23.6-NE)	Most common grade 3-4 AEs were lymphopenia (53%) and thrombocytopenia (18%)[a] Quality of life, NA

Author, year	Study inclusion criteria	Treatment	Number of patients with pNETs evaluated	Median follow-up (range)	Median PFS	Median OS	Adverse events and quality of life
CAPOX + BEVACIZUMAB							
Prospective, single arm study (phase II trial)							
Kunz et al (2016) [19] SUBGROUP	Adults with advanced, metastatic or locally unresectable pNET, carcinoid, and poorly differentiated NECs; ECOG PS 0-2 and prior chemotherapy was allowed and prior and/or concurrent SSA therapy was allowed, but not required.	CAPOX (oxaliplatin 130 mg/m^2 IV over 2 hours on day 1 plus capecitabine 850 mg/m^2 twice daily by mouth on days 1–14 of a 21-day cycle) plus bevacizumab 7.5 mg/kg IV on day 1.	16	29.1 mths[b]	15.7 mths (95% CI, 8.2-29.3)	38.0 mths	Most common grade 3 or 4 AEs were diarrhea (20%), hypertension (13%), and rashes (10%)[b] Quality of life, NA
STREPTOZOCIN WITH 5-FU ± BEVACIZUMAB							
Prospective, single arm study (phase II trial)							
BETTER Ducreux et al (2014) [20]	Adults with progressive, locally advanced well differentiated pNETs, ECOG ≤2, and no previous systemic anticancer therapy	Bevacizumab 7.5 mg/kg on day 1 over 30 min every 3 wks before chemotherapy + 5-FU 400 mg/m^2 & streptozocin 500 mg/m^2 each day from day 1-5 over 2 hrs and repeated every 6 wks	34	Maximum follow-up, 24 mths	26.3 mths (95% CI, 17.4-not reached)	Not reached (95% CI, 27.0-not reached)	Most common grade 3-4 AEs were hypertension (21%), abdominal pain (21%) and thromboembolic events (9%) Treatment discontinuation due to AEs, 7 vs. 9 There were no significant changes in global health

Author, year	Study inclusion criteria	Treatment	Number of patients with pNETs evaluated	Median follow-up (range)	Median PFS	Median OS	Adverse events and quality of life
							status using the EORTC QLQ-C30 between baseline, 3-month, 6-month, and 12-month assessments
FOLFOX							
Retrospective study							
Al-Toubah et al (2021) [21]	Adults with progressive, well-differentiated pNETs of any grade treated between January 2008 and June 2019, where at least one prior line of therapy consisted of capecitabine plus temozolomide	FOLFOX	25	NR	6 mths (95% CI, 4.9-7.1)	17 mths (95 % CI, 12.1-21.9)	26% of patients discontinued treatment due to toxicity[c]. Quality of life, NA
FOLFOX + BEVACIZUMAB							
Prospective, single arm study (phase II trial)							
Kunz et al (2016) [19] SUBGROUP	Adults with advanced, metastatic or locally unresectable pNET, carcinoid, and poorly differentiated NECs; ECOG PS 0-1 and prior chemotherapy was allowed and prior and/or	Modified FOLFOX-6 (oxaliplatin 85 mg/m^2 and leucovorin 200 mg/m, followed by 2400 mg/m^2 5-FU + bevacizumab 5 mg/kg every 14 days)[d]	12	27.6 mths[e]	21.0 mths (95% CI, 7.4-31.4)	31.0 mths	The most common grade 3 or 4 AEs were neutropenia (25%), neuropathy (17%), and fatigue (17%)[e]. Quality of life, NA

Author, year	Study inclusion criteria	Treatment	Number of patients with pNETs evaluated	Median follow-up (range)	Median PFS	Median OS	Adverse events and quality of life
	concurrent SSA therapy was allowed, but not required.						
5-FU + DOXORUBICIN + STREPTOZOCIN							
Retrospective, single-arm study							
Rogers et al (2022) [22]	Adults with locally advanced unresectable or metastatic well-differentiated pNETs who received 5-FU, doxorubicin, and streptozocin between 1992 and 2013	Bolus 5-FU 400 mg/m^2 + streptozocin 400 mg/m^2 + (both IV, days 1–5), and doxorubicin 40 mg/m^2 (IV, day 1) every 28 days	243 (220 for PFS and adverse events)	61 mths	20 mths (95% CI, 15-23)	63 mths (95% CI, 60-71)	5% of patients required chemotherapy to be discontinued due to toxicity. Quality of life, NA
CAPECITABINE + TEMOZOLOMIDE VS. 5-FU + DACARBAZINE							
Retrospective, comparative study							
de Mestier et al (2019) [46] SUBGROUP	Adults with well-differentiated pNETs or NETs of the small intestine who received 5FU-DTIC or CAPTEM, regardless of line of treatment between July 2004 and December 2017	Dacarbazine 400 mg/m^2 + leucovorin 200 mg/ m^2 + 5-FU 400 mg/m^2 once a day on days 1 and 2, with continuous administration of 5-FU 1200 mg/m^2 on days 1–2, every 21 days[f] VS Capecitabine 750 mg/m^2 twice a day	66	NR	23.1 mths (95% CI, 12.2-33.7)	No significant difference between the treatment groups	Most common grade 3-4 AEs in the 5-FU-DTIC arm were neutropenia (3.2%), thrombocytopenia (3.2%) and anemia (2.1%), while the common in the capecitabine plus temozolomide arm were thrombocytopenia (13.0%), neutropenia (5.5%), and infections (2.7%)[h]

Author, year	Study inclusion criteria	Treatment	Number of patients with pNETs evaluated	Median follow-up (range)	Median PFS	Median OS	Adverse events and quality of life
		on days 1–14 + temozolomide 150 mg/m^2 at cycle 1, then if well tolerated, 200 mg/m^2 at cycle 2 once a day on days 10–14, every 28 days Grade 3 included, approx. 11%	138		12.8 mths (95% CI, 6.5-20.6) p=0.04[g]		Quality of life, NA
TEMOZOLOMIDE							
No studies met inclusion criteria							
CAPOX							
No studies met inclusion criteria							
DACARBAZINE							
No studies met inclusion criteria							
5-FU + DOXORUBICIN							
No studies met inclusion criteria							

[a] Results reported for all patients who received temozolomide with bevacizumab (n=34) and were not specific to the cohort of patients with pNETs.
[b] Results reported for all patients who received CAPOX with bevacizumab (n=40) and were not specific to the cohort of patients with pNETs.
[c] Results reported for all patients included in the study (n=31) not just those who received FOLFOX
[d] The 5-FU IV bolus (400 mg/m^2) was permanently dropped from the protocol regimen after nearly all the first 13 patients required a dose reduction for toxicity
[e] Results reported for all patients who received FOLFOX with bevacizumab (n=36) and were not specific to the cohort of patients with pNETs.
[f] The alternative protocol included dacarbazine 250 mg/m^2 and 5-FU (450 mg/m^2 once a day for 5 consecutive days every 21 days
[g] Patients were matched for propensity-score

[h] Results reported for all patients who received 5-FU-DTIC (n=94) and CAPTEM (n=146) and were not specific to the cohort of patients with pNETs.
Abbreviations: 5-FU, 5-fluorouracil; AEs, adverse events; CAPOX, capecitabine plus oxaliplatin; CAPTEM, capecitabine and temozolomide; CI, confidence interval; DTIC, dacarbazine; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC QLQ, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; FOLFOX, folinic acid, 5-fluorouracil and oxaliplatin; HR, hazard ratio; hrs, hours; IQR, interquartile range; IV, intravenous; mths, months; NA, not assessed; NE, not estimable; NEC, neuroendocrine carcinomas; NET, neuroendocrine tumours; NR, not reported; OS, overall survival; PFS, progression-free survival; pNET, pancreatic neuroendocrine tumours; pt, patient; SSA, somatostatin analogues; vs., versus; wks, weeks

PRRT

Three RCTs [11,24,25], all of which are currently available in abstract form, and one prospective single-arm study [12] were found assessing the use of PRRT in patients with pNETs (Table 4-6).

^{90}Y-DOTATATE

Survival

The phase II, single-arm study by Rogowski et al [12] evaluated the efficacy of ^{90}Y-DOTATATE in patients with nonresectable grade 1 or 2 neuroendocrine neoplasms. Patients had received prior treatment. In the cohort of patients with pNETs (n=30), median PFS was 25 months (95% CI, 20.8 to 33.4) and median OS was 42 months (95% CI, 34.0 to 48.2).

Adverse events

Adverse event data were not provided.

^{177}Lu-DOTATATE + Octreotide LAR

Survival

The NETTER-2 trial [11], currently available in abstract form, evaluated the efficacy of ^{177}Lu-DOTATATE as first-line therapy in patients with grade 2 or 3 advanced GEP NETs. Patients were randomized to receive four cycles of ^{177}Lu-DOTATATE (4 × 7.4 GBq) plus 30 mg octreotide long-acting release (LAR) every eight weeks or 60 mg of octreotide LAR every four weeks. Median PFS for all patients was significantly better in the ^{177}Lu-DOTATATE arm (22.8 months) than in the octreotide alone arm (8.5 months) (stratified HR, 0.276; 95% CI, 0.182 to 0.418; p<0.0001). Approximately 54.4% of the population was comprised of patients with pNETs. A predefined subgroup analysis of patients with pNETs had similar PFS results (HR, 0.34; 95% CI, 0.20 to 0.56).

Adverse events

Adverse event data specific to the subgroup of patients with pNETs were not presented. In the overall population, three or fewer patients in the ^{177}Lu-DOTATATE arm experienced grade 3 or 4 leukopenia, anemia, and thrombocytopenia. There was one case of myelodysplastic syndrome in the ^{177}Lu-DOTATATE arm.

^{177}Lu-DOTATATE vs. Sunitinib

PFS

The OCLURANDOM randomized, phase II trial [24] is currently available in abstract form. The median PFS between those who had received ^{177}Lu-DOTATATE only and those who received sunitinib only was 20.7 months (90% CI, 17.2 to 23.7) and 11 months (90% CI, 8.8 to 12.4), respectively.

Adverse events

Approximately 44% of patients in the ^{177}Lu-DOTATATE arm experienced grade 3-4 adverse events compared with 60% of patients receiving sunitinib.

^{177}Lu-DOTATATE + Capecitabine plus Temozolomide vs. Capecitabine plus Temozolomide

Survival

The AGIGTG CONTROL NET phase II randomized, parallel group trial [25] evaluated the addition of ^{177}Lu-DOTATATE to capecitabine plus temozolomide. The final results are currently available in abstract form. In the predefined cohort of patients with pNETs, at 27 months there was no significant difference in PFS between the treatment and control arm (HR, 0.41; 95% CI, 0.15 to 1.12; p=0.08). Similarly, the was no significant difference in OS between the two arms either (HR, 1.28; 95% CI, 0.33 to 4.95; p=0.72).

Adverse events

No late grade 3-4 adverse events were reported in the cohort of patients with pNETs.

Table 4-6. Trials Reporting on the Use of PRRT in Patients with Pancreatic Neuroendocrine Tumours

Author, year	Study inclusion criteria	Treatment	Number of patients with pNETs evaluated	Median follow-up (range)	Median PFS	Median OS	Adverse events and quality of life
^{177}Lu-DOTATATE vs. SUNITINIB							
Randomized, controlled trial (phase II)							
OCLURANDOM Baudin et al (2022) [24] *Abstract*	Adults with SSTR-positive progressive advanced pNETs	^{177}Lu-DOTATATE 7.4 GBq × 4/8w vs. Sunitinib 37.5 mg/day	41 43	40 mths (95% CI, 35-43)	20.7 mths (90% CI, 17.2-23.7) 11 mths (90% CI, 8.8-12.4)	NA	Grade 3 or 4 adverse events, 44% vs. 60% Quality of life, NA
^{177}Lu-DOTATATE + CAPTEM vs. CAPTEM							
Randomized controlled trial (phase II)							
AGITG CONTROL NET Pavlakis et al (2022) [25] *Abstract* SUBGROUP	Adults with low to intermediate grade, unresectable, metastatic ^{68}Ga-octreotate PET-avid pancreatic and midgut NETs.	^{177}Lu-DOTATATE + CAPTEM CAPTEM	19 9	57.5 mths	27 mths, 61.1% (95% CI, 35.3-79.2) 33.3% (7.8-62.3) HR, 0.41; 95% CI, 0.15-1.12; p=0.08	27 mths, HR, 1.28; 95% CI, 0.33-4.95; p=0.72	No late grade 3-4 adverse events were reported in patients with pNETs. Quality of life, NA

Author, year	Study inclusion criteria	Treatment	Number of patients with pNETs evaluated	Median follow-up (range)	Median PFS	Median OS	Adverse events and quality of life
^{177}Lu-DOTATATE + Octreotide LAR							
Randomized controlled trial (phase III)							
Singh et al (2024) [11] *Abstract*	Adults with advanced grade 2-3 GEP NETS	^{177}Lu-DOTATATE 7.4 GBq + 30 mg Octreotide LAR, 4 cycles at intervals of 8 weeks OR Octreotide LAR 60 mg at intervals of 4 weeks	123	NR	HR, 0.34; 95% CI, 0.20-0.56	NR	Adverse events, NR Quality of life, NR
^{90}Y-DOTATATE							
Prospective, single arm study							
Rogowski et al (2016) [12] SUBGROUP	Adults with metastatic grade 1-2 pNETs or small bowel NETs with 6 months' evidence of progression	Ondansetron 8 mg orally + amino acids 1500 mL + ^{90}Y-DOTATATE for a cumulative activity of 15.2 GBq	30	45.2 mths (95% CI, 36.2-52.1)	25 mths (95% CI, 20.8-33.4)	42 mths (95% CI, 34.0-48.2)	Adverse events, NR Quality of life, NA
^{225}Ac-DOTATATE/^{225}Ac-DOTATOC							
No studies met inclusion criteria							

Author, year	Study inclusion criteria	Treatment	Number of patients with pNETs evaluated	Median follow-up (range)	Median PFS	Median OS	Adverse events and quality of life
^{213}Bi-DOTATATE/^{213}Bi-DOTATOC							
No studies met inclusion criteria							
^{121}Pb-DOTATATE/^{121}Pb-DOTATOC							
No studies met inclusion criteria							

Abbreviations: CAPTEM, capecitabine and temozolomide; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GEP, gastroenteropancreatic; HR, hazard ratio; mths, months; NA, not assessed; NETs, neuroendocrine tumour; NR, not reported; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; pNET, pancreatic neuroendocrine tumours; PRRT, peptide receptor radionuclide therapy; SSTR, somatostatin receptors; vs., versus

Immunotherapy

Three prospective studies [13-15] were found assessing the use of immunotherapy in patients with pNETs (Table 4-7).

Spartalizumab

Survival

The single arm, phase II study by Yao et al [13], evaluated the use of spartalizumab in patients with NETs and GEP NECs. The NETs cohort consisted of a subgroup of 33 patients with pNETs. All patients were required to have ≥2 prior systemic regimens including everolimus and/or sunitinib. A median PFS of 3.9 months was observed while the median OS was not reach in patients with pNETs.

Adverse events

The most common grade ≥3 treatment-related adverse events include asthenia (3.2%) and arthralgia (2.1%) in all patients who received spartalizumab. Adverse event data were not provided specific to patients with pNETs.

Pembrolizumab

Survival

The KEYNOTE-028 phase I study [14] consisted of 16 patients with PD-L1-positive pNETs who received pembrolizumab; 94% of patients had discontinued the study at data cut-off. A median PFS of 4.5 months (95% CI, 3.6 to 8.3) and a median OS of 21.0 months (95% CI, 20.2 to not reached) were reported.

Adverse events

Treatment-related adverse events occurred in 69% of patients with ≥1 serious treatment-related adverse event occurring in 31% of patients. The most common adverse events were diarrhea and fatigue. There were no grade 4 or 5 treatment-related adverse events.

Atezolizumab + Bevacizumab

Survival

Halperin et al [15] conducted a phase II study evaluating the use of atezolizumab with bevacizumab in patients with pNETs and extra-pancreatic NETs. In the subgroup with 20 patients with pNETs, of which 25% were PD-L1-positive, a median PFS of 14.9 months (95% CI, 4.4 to 32.0) and a median OS of 30.1 months (95% CI, 17.7 to not reached) were reported.

Adverse events

The most common grade 3-4 treatment-emergent adverse events are hypertension (25%), proteinuria (7.5%), and increased alanine aminotransferase (5%) for all patients (n=40) included in the study. Adverse event data were not provided specific to patients with pNETs.

Table 4-7. Trials Reporting on the Use of Immunotherapy in Patients with Pancreatic Neuroendocrine Tumours

Author, year	Study inclusion criteria	Treatment	Number of patients with pNETs evaluated	Median follow-up (range)	Median PFS	Median OS	Adverse event and quality of life
SPARTALIZUMAB							
Prospective, single arm study (phase II)							
Yao et al (2021) [13] SUBGROUP	Adults with advanced or metastatic, well-differentiated, grade 1 or 2 non-functional NETs, ECOG PS 0-2 and have received prior treatment for advanced disease.	Spartalizumab 400 mg once every 4 weeks	33	13.4 mths (11-17)[a]	3.9 mths[b]	NR[b]	Most common grade ≥3 treatment-related AEs include asthenia (3.2%) and arthralgia (2.1%)[c]. Quality of life, NA
PEMBROLIZUMAB							
Prospective, single arm study (phase I)							
KEYNOTE-028 Mehnert et al (2020) [14]	Adults with pNETs if they had PD-L1–positive, histologically or cytologically confirmed unresectable and/or metastatic disease and had prior failure of ≥1 standard therapy or declined or had no remaining standard therapy options, ECOG PS 0-1	Pembrolizumab 10 mg/kg every 2 weeks up to 2 years	16	20.7 mths (4.5-31.7)	4.5 mths (95% CI, 3.6-8.3)	21.0 mths (95% CI, 20.2-not reached)	≥1 serious treatment-related AE occurred in 31% of patients. No grade 4 or 5 treatment-related AEs. Quality of life, NA
ATEZOLIZUMAB+BEVACIZUMAB							
Prospective, single arm study (phase II)							
Halperin et al (2022) [15] SUBGROUP	Adults with metastatic or locally advanced, grade 1 to 2 NETs (pancreatic and extra-pancreatic). Somatostatin analogue therapy could be continued if dosed stably for 8 weeks before enrollment.	Bevacizumab 15 mg/kg + atezolizumab 1200 mg every 3 weeks	20	43.8 mths (95% CI, 39.0-46.1)	14.9 mths (95% CI, 4.4-32.0)	30.1 mths (95% CI, 17.7-not reached)	Most common grade 3-4 treatment-emergent AEs include hypertension (25%), proteinuria (7.5%), and increased alanine aminotransferase (5%)[d]. Quality of life, NA

Author, year	Study inclusion criteria	Treatment	Number of patients with pNETs evaluated	Median follow-up (range)	Median PFS	Median OS	Adverse event and quality of life
IPILIMUMAB + NIVOLUMAB							
No studies met inclusion criteria							
AVELUMAB							
No studies met inclusion criteria							

[a] Reported for all patients who received spartalizumab (n=116) and were not specific to the subgroup of patients with pNETs.

[b] Extrapolated from Kaplan Meier curve by HRM

[c] Reported for all patients with well-differentiated NETs who received sparatalizumab (n=95) and were not specific to the subgroup of patients with pNETs.

[d] Reported for all patients included in study who received atezolizumab plus bevacizumab (n=40) and were not specific to the subgroup of patients with pNETs.

Abbreviations: AE, adverse events; ECOG PS, Eastern Cooperative Oncology Group Performance Status; mths, months; NA, not assessed; NR, not reported; OS, overall survival; PFS, progression-free survival; PD-L1, programmed death-ligand 1; pNET, pancreatic neuroendocrine tumours

Outcomes: Midgut NETs

Research Question 2. Which of the anti-neoplastic systemic therapies (Table 4-8) is the most effective in improving clinical outcomes (i.e., PFS, OS) and quality of life while minimizing adverse events in patients with inoperable or metastatic midgut NETs?

SSAs

Two RCTs [1,30,31] were found assessing the use of SSAs in patients with midgut NETs and one single-arm phase II study [44] assessing a reduced dosing interval for lanreotide was found (Table 4-8).

Octreotide vs. Placebo

OS

The PROMID trial [30,31] compared octreotide LAR with placebo in patients with locally inoperable or metastatic midgut NETs. No significant difference between those who received octreotide LAR and those who received placebo (84.7 months vs. 83.7 months; HR, 0.83; 95% CI, 0.47 to 1.46; p=0.51) was reported in patients with midgut NETs. Crossover of majority of the patients receiving placebo to octreotide LAR may have confounded OS data.

Adverse events

Treatment-related adverse events were not reported.

Quality of life

Health-related quality of life was measured with EORTC QLQ-C30 and assessments were completed at baseline and every 12 weeks until tumour progression. There were no statistically significant between-group differences in change from baseline for the functioning scales at any time point. Significantly longer time to definitive deterioration was reported for octreotide LAR versus placebo for fatigue (p=0.0006), pain (p=0.0435), and insomnia (p=0.0046).

Lanreotide vs. Placebo

PFS

The CLARINET trial [1] compared lanreotide with placebo in patients with well- or moderately differentiated, non-functioning grade 1 or 2 NETs. A subgroup analysis of patients with midgut NETs reported a significant difference in median PFS for those receiving lanreotide compared with placebo (HR, 0.35; 95% CI, 0.16 to 0.80). This subgroup analysis was undertaken to investigate the consistency of treatment effects as the study was not otherwise powered for such analysis. The results of this subgroup analysis were consistent with the results of the overall study where there was a significant improvement in median PFS for patients who received lanreotide (HR, 0.47; 95% CI, 0.30 to 0.73; p<0.001).

Adverse events

Approximately 50% of patients in the treatment arm experienced an adverse event related to study treatment compared with 28% in the placebo arm. Three percent of patients in the treatment arm and 1% of patients in the placebo arm experienced a serious adverse event related to study treatments with 1% of patients from the treatment arm withdrawing from the study. Adverse event data are presented for all patients enrolled in the CLARINET study and are not specific to the subgroup of patients with midgut NETs.

Quality of life

Quality of life was assessed using EORTC QLQ-C30 and QLQ-GINET21 questionnaires and showed no significant between-group differences. Quality of life data are presented for all patients enrolled in the CLARINET study and are not specific to the subgroup of patients with midgut NETs.

Lanreotide (Reduced Dosing Interval)

PFS

The CLARINET FORTE, a pilot study, assessed the efficacy of a reduced lanreotide dosing interval (120 mg every 14 days) following first-line standard dose lanreotide treatment (120 mg every 28 days) in patients with pNETs or midgut NETs. In the cohort of patients with midgut NETs, the median PFS was 8.3 months (95% CI, 5.6 to 11.1).

Adverse events

There were no grade 3 to 5 treatment-related adverse events or treatment-related withdrawals in patients with midgut NETs.

Quality of life

Quality of life was assessed using EORTC QLQ-C30, QLQ-GINET21, and EQ-5D-5L questionnaires with no deterioration in quality of life being reported in patients with midgut NETs.

Table 4-8. Trials Reporting on the Use of Somatostatin Analogues in Patients with Midgut Neuroendocrine Tumours

Author, year	Study inclusion criteria	Treatment	Number of patients with midgut NETs evaluated	Median follow-up (range)	Median PFS	Median OS	Adverse events and quality of life
OCTREOTIDE							
Randomized controlled trial							
PROMID Rinke et al (2017) [30,31]	Adults with locally inoperable or metastatic NETs; midgut primary tumour or tumour of unknown origin believed to be of midgut origin with no curative therapeutic options.	Octreotide LAR 30 mg monthly vs. Placebo monthly	42 43	NR	NA	84.7 mths 83.7 mths HR, 0.83; 95% CI, 0.47-1.46; p=0.51	Treatment-related AEs, NR. No significant between-group differences using EORTC QLQ-C30 except longer TTD was reported for octreotide LAR versus placebo for fatigue (p=0.0006), pain (p=0.0435) and insomnia (p=0.0046).
LANREOTIDE							
Randomized controlled trial							
CLARINET Caplin et al (2014) [1] SUBGROUP	Adults with well- or moderately differentiated, non-functioning grade 1 or 2 NETs, metastatic disease or a locally advanced tumour that was inoperable, Ki-67 <10%, PS ≤2	120 mg lanreotide (Autogel/Depot) subcutaneously every 28 days vs. Placebo every 28 days	33 40	NR	Not reached 21 mths (95% CI, 17.0-NC) HR, 0.35; 95% CI, 0.16-0.80	NA	Serious AEs, 3% vs. 1% No significant between-group differences using EORTC QLQ-C30 and QLQ-GINET21

Author, year	Study inclusion criteria	Treatment	Number of patients with midgut NETs evaluated	Median follow-up (range)	Median PFS	Median OS	Adverse events and quality of life
LANREOTIDE (reduced dosing interval)							
Prospective, single arm study							
CLARINET FORTE Pavel et al (2021) [44] SUBGROUP	Adults with well-differentiated, SSTR2+, metastatic or locally advanced, unresectable, grade 1/2 (Ki-67 ≤20%) pancreatic or midgut NETs, ECOG PS ≤2, with disease progression in the previous 2 years on the standard lanreotide regimen (120 mg every 28 days) for ≥24 weeks	Lanreotide 120mg (Autogel/Depot) subcutaneously every 14 days	51	NR	8.3 mths (95% CI, 5.6-11.1)	NR	No grade 3-5 treatment-related AEs No deterioration in QoL was reported based on EORTC QLQ-C30, EORTC QLQ-GINET21, or EQ-5D-5L.
PASIREOTIDE							
No studies met inclusion criteria							

Abbreviations: AEs, adverse events; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC QLQ, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L, 5-level EuroQol Group-5D; HR, hazard ratio; LAR, long-acting repeatable; mths, months; NA, not applicable; NR, not reported; OS, overall survival; PS, performance scale; QoL, quality of life; SSTR2+, somatostatin receptor 2; TTD, time to QoL deterioration; vs., versus

Targeted Therapy

One RCT [32,33] was found assessing the use of targeted therapy in patients with midgut NETs (Table 4-9).

Everolimus vs. Placebo

PFS

The overall RADIANT-4 trial [32,33] compared the use of everolimus with placebo in patients with advanced, progressive, well-differentiated, non-functional NETs. An ad-hoc subgroup analysis of patients with midgut NETs reported no significant difference in median PFS for those receiving everolimus compared with placebo (HR, 0.71; 95% CI, 0.40 to 1.26). The results of this subgroup analysis were not consistent with the results of the overall study where there was a significant improvement in median PFS for patients who received everolimus (HR, 0.48; 95% CI, 0.35 to 0.67; $p<0.0001$).

Adverse events

Grade 3 or 4 adverse events were more common in patients with gastrointestinal NETs receiving everolimus than those receiving placebo with the most common being diarrhea (9.4% vs. 3.4%), stomatitis (7.7% vs. 0%), and infections (7.7% vs. 0%). Treatment discontinuation as a result of the study drug was higher in those receiving everolimus compared with placebo (12% vs. 3%). Treatment discontinuation due to grade 3 or 4 adverse events related to the study drug were 13% in those receiving everolimus and 2% in those receiving placebo. The rates of on-treatment deaths were similar between those receiving everolimus (3%) and placebo (2%). Adverse event data are presented for all patients with gastrointestinal NETs enrolled in the RADIANT-4 study and are not specific to the subgroup of patients with midgut NETs.

Quality of life

Quality of life was assessed using the FACT-G questionnaire at baseline, every eight weeks during the first 12 months after randomization, and every 12 weeks thereafter until study drug discontinuation. There were no significant between-group differences in median time to definitive deterioration in FACT-G total score (HR, 0.81; 95% CI, 0.55 to 1.21; $p=0.31$). Quality of life data are presented for all patients enrolled in the RADIANT-4 study and are not specific to the subgroup of patients with midgut NETs.

Table 4-9. Trials Reporting on the Use of Targeted Therapy in Patients with Midgut Neuroendocrine Tumours

Author, year	Study inclusion criteria	Treatment	Number of patients with midgut NETs evaluated	Median follow-up (range)	Median PFS	Median OS	Adverse events and quality of life
EVEROLIMUS							
Randomized controlled trial							
RADIANT-4 Singh et al (2018) Pavel et al (2017) [32,33] SUBGROUP	Adults with advanced, progressive, well-differentiated, non-functional NETs of lung or GI origin	Everolimus 10 mg once daily vs. Placebo once daily	80 35	NR	17.28 mths (95% CI, 11.17-21.9) 10.87 mths (95% CI, 5.06-19.42) HR, 0.71; 95% CI, 0.40-1.26; p=NR	NR	Grade 3 or 4 AEs were more common in patients receiving everolimus than those receiving placebo with the most common being diarrhea (9.4% vs. 3.4%), stomatitis (7.7% vs. 0%), and infections (7.7% vs. 0%)[a]. Treatment-related discontinuation, 13% vs. 2%[a] On-treatment deaths, 3% vs. 2%[a] No significant between-group differences using FACT-G[b]

[a] Reported for all patients with GI NETs who received everolimus (n=118) and placebo (n=57) and were not specific to the subgroup of patients with pNETs.

[b] Reported for all patients in the RADIANT-4 trial who received everolimus (n=205) and placebo (n=97) and were not specific to the subgroup of patients with pNETs.

Abbreviations: AEs, adverse events; CI, confidence interval; FACT-G, Functional Assessment of Cancer Therapy - General; GI, gastrointestinal; HR, hazard ratio; mths, months; NETs, neuroendocrine tumours; NR, not reported; OS, overall survival; PFS, progression-free survival; vs., versus

Chemotherapy

Two retrospective studies, one comparative [46] and one single-arm [47], were found assessing the use of chemotherapy in patients with midgut NETs (Table 4-10).

Capecitabine + Temozolomide vs. 5-FU + DTIC

PFS

The retrospective, comparative study by de Mestier et al [46] evaluated the efficacy of 5-FU-DTIC and temozolomide plus capecitabine in patients with pNETs or NETs of the small intestine. Median PFS was analyzed using propensity score analysis to reduce confounding bias due to the non-randomized design of the study. In the subgroup of patients with midgut NETs, there was a significant difference in median PFS between those who received 5-FU-DTIC (10.7 months; 95% CI, 5.4 to 40.5) when compared with those who received capecitabine plus temozolomide (6.9 months; 95% CI, 4.4 to 13.8; p=0.04). Approximately 11% of patients in each arm for the entire study population had grade 3 NETs; specific data for patients with midgut NETs were not provided.

OS

de Mestier et al [46] noted that there were no significant differences between the two treatment groups for patients with midgut NETs (p=0.23); a propensity-score analysis was not done for OS.

Adverse events

Adverse event data were presented for all patients included in this study and data specific to the subgroup of patients with midgut NETs were not available. The most common grade 3-4 adverse events in the 5-FU-DTIC arm (n=94) were neutropenia (3.2%), thrombocytopenia (3.2%), and anemia (2.1%), while the most common grade 3-4 adverse events in the capecitabine plus temozolomide arm were thrombocytopenia (13.0%), neutropenia (5.5%), and infections (2.7%).

Capecitabine + Temozolomide

Survival

The retrospective study by Al-Toubah et al [47] evaluated the efficacy of capecitabine plus temozolomide in patients with small bowel NETs. Of the 31 included patients, 23 had low- or intermediate-grade tumours and nine had high-grade tumours. The median PFS in the overall cohort was 31 months (95% CI, 0 to 66.8) and the median OS was 82 months (95% CI, 32.8 to 131.2).

Adverse events

Among patients with low- or intermediate-grade midgut NETs, 44% discontinued treatment due to poor tolerability.

Table 4-10. Trials Reporting on the Use of Chemotherapy in Patients with Midgut Neuroendocrine Tumours

Author, year	Study inclusion criteria	Treatment	Number of patients with midgut NETs evaluated	Median follow-up (range)	Median PFS	Median OS	Adverse events and quality of life
CAPECITABINE + **TEMOZOLOMIDE VS. 5-FU + DACARBAZINE**							
Retrospective comparative study							
de Mestier et al (2019) [46] SUBGROUP	Adults with well-differentiated pNETs or NETs of the small intestine and received at least one cycle of 5FU-DTIC or TEM-CAP whatever the line of treatment between July 2004 and December 2017 Grade 3 included, approx. 11%	Dacarbazine 400 mg/m^2 + leucovorin 200 mg/m^2 + 5-FU 400 mg/m^2 once a day on days 1 and 2, with continuous administration of 5-FU 1200 mg/m^2 on days 1–2, every 21 days[a] VS Capecitabine 750 mg/m^2 twice a day on days 1–14 + temozolomide 150 mg/m^2 at cycle 1, then if well tolerated, 200 mg/m^2 at cycle 2 once a day on days 10–14, every 28 days	28 15	NR	10.7 mths (95% CI, 5.4-40.5) 6.9 mths (95% CI, 4.4-13.8) p=0.04[b]	No significant differences between the two treatment groups for patients with midgut NETs (p=0.23)	Most common grade 3-4 AEs in the 5-FU-DTIC arm (n=94) were neutropenia (3.2%), thrombocytopenia (3.2%) and anemia (2.1%), while the most common grade 3-4 AEs in the capecitabine plus temozolomide arm were thrombocytopenia (13.0%), neutropenia (5.5%), and infections (2.7%)[c]. Quality of life, NA

Author, year	Study inclusion criteria	Treatment	Number of patients with midgut NETs evaluated	Median follow-up (range)	Median PFS	Median OS	Adverse events and quality of life
CAPECITABINE **TEMOZOLOMIDE**							
Retrospective study							
Al-Toubah et al (2022) [47]	Adults with small bowel midgut NETs treated with CAPTEM between 2008-2019	Capecitabine + temozolomide	32	NR	31 mths (95% CI, 0-66.8)	82 mths (95% CI, 32.8-131.2)	44% of patients with low-intermediate midgut NETs discontinued treatment due to poor tolerability. Quality of life, NA

[a] The alternative protocol included dacarbazine 250 mg/m^2 and 5-FU (450 mg/m^2 once a day for 5 consecutive days every 21 days)
[b] Patients were matched for propensity-score
[c] Results reported for all patients who received 5FU-DTIC (n=94) and CAPTEM (n=146) and were not specific to the cohort of patients with midgut NETs.
Abbreviations: CI, confidence interval; 5-FU, 5-fluorouracil; 5FU-DTIC, 5-fluorouracil, dacarbazine; mths, months; NA, not assessed; NETs, neuroendocrine tumours; NR, not reported; OS, overall survival; PFS, progression-free survival; TEM-CAP, capecitabine and temozolomide; QoL, quality of life

PRRT

Two RCTs [11,25,27,28], with two currently only available in abstract form [11,25], and one prospective single-arm study [12] was found assessing the use of PRRT in patients with midgut NETs (Table 4-11).

^{90}Y-DOTATATE

Survival

The phase II, single-arm study by Rogowski et al [12] evaluated the efficacy of ^{90}Y-DOTATATE in patients with nonresectable grade 1 or 2 neuroendocrine neoplasms. Patients had received prior treatment. In the cohort of patients with small bowel NETs (n=37), median PFS was 28 months (95% CI, 27.5 to 42.1) and median OS was 40 months (95% CI, 34.7 to 50.1).

Adverse events

Adverse event data were not provided.

^{177}Lu-DOTATATE + Octreotide LAR vs. Octreotide LAR

PFS

The NETTER-1 randomized, controlled trial compared the efficacy of ^{177}Lu-DOTATATE plus octreotide LAR with high-dose octreotide LAR in patients with metastatic midgut NETs [27,28]. Patients who received ^{177}Lu-DOTATATE plus octreotide LAR had a significantly longer median PFS than those who received high-dose octreotide LAR (HR, 0.21; 95% CI, 0.13 to 0.33; p<0.001), although median PFS was not reached in the treatment arm.

The NETTER-2 trial [11], currently available in abstract form, evaluated the efficacy of ^{177}Lu-DOTATATE as first-line therapy in patients with grade 2 or 3 advanced GEP NETs. Patients were randomized to receive four cycles of ^{177}Lu-DOTATATE (4 × 7.4 GBq) plus 30 mg octreotide LAR every eight weeks or 60 mg of octreotide LAR every four weeks. Median PFS for all patients was significantly better in the ^{177}Lu-DOTATATE arm (22.8 months) than in the octreotide-alone arm (8.5 months) (stratified HR, 0.276; 95% CI, 0.182 to 0.418; p<0.0001). Approximately 29.2% of the population was comprised of patients with NETs of the small intestine. A predefined subgroup analysis of patients with NETs of the small intestine had similar PFS results (HR, 0.30; 95% CI, 0.13 to 0.74).

OS

The NETTER-1 trial showed no difference in OS between patients who received ^{177}Lu-DOTATATE plus octreotide LAR and those who received high-dose octreotide LAR in the intention-to-treat population (48.0 months vs. 36.3 months; HR, 0.84; 95% CI, 0.60 to 1.17; p=0.30). In the long-term follow-up, 12% of patients in the treatment group received further treatment with ^{177}Lu-DOTATATE and 36% of patients from the control group crossed over to the treatment group. Rank-preserving structural failure time analysis was performed to correct for crossover bias (HR, 0.73; 95% CI, 0.40 to 1.34).

Adverse events

In the NETTER-1 trial approximately 9% of patients who received ^{177}Lu-DOTATATE and 1% of patients in the control group had serious treatment-related adverse events (p=0.01). The most common grade 3 or 4 adverse events in the treatment arm included lymphopenia (9%), vomiting (7%), and nausea (4%) while the most common grade 3 or 4 adverse events in the control arm included abdominal pain (5%), decreased appetite (3%), fatigue (2%), diarrhea (2%), and nausea (2%). Approximately 5% of patients receiving ^{177}Lu-DOTATATE withdrew from the trial due to adverse events related to treatment.

The NETTER-2 trial did not present adverse event data specific to the subgroup of patients with NETs of the small intestine. In the overall population, three or fewer patients in the ^{177}Lu-DOTATATE arm experienced grade 3 or 4 leukopenia, anemia, and thrombocytopenia. There was one case of myelodysplastic syndrome in the ^{177}Lu-DOTATATE arm.

Quality of Life

Patients enrolled in the NETTER-1 trial completed the EORTC QLQ-C30 and QLQ-GINET21 questionnaires at baseline and every 12 weeks until tumour progression. More than 80% of patients completed the questionnaires at each visit. Time to quality of life deterioration was significantly longer in those that received ^{177}Lu-DOTATATE versus the control arm in the global health status (HR, 0.41; 95% CI, 0.24 to 0.69; p<0.001), physical functioning (HR, 0.52; 95% CI, 0.30 to 0.89; p=0.015), role functioning (HR, 0.58; 95% CI, 0.35 to 0.96; p=0.030), fatigue (HR, 0.0.62; 95% CI, 0.40 to 0.96; p=0.030), pain (HR, 0.57; 95% CI, 0.34 to 0.94; p=0.025), diarrhea (HR, 0.47; 95% CI, 0.26 to 0.85; p=0.011), disease-related worries (HR, 0.57; 95% CI, 0.36 to 0.91; p=0.018), and body image domains (HR, 0.43; 95% CI, 0.23 to 0.680; p=0.006).

Further, patients were asked to record the occurrence of predefined symptoms in a daily diary. Patients who received ^{177}Lu-DOTATATE experienced a significantly greater decline from baseline in symptom scores for abdominal pain (p<0.001), diarrhea (p=0.0017), and flushing (p=0.0413).

^{177}Lu-DOTATATE + Capecitabine + Temozolomide vs. ^{177}Lu-DOTATATE

Survival

The randomized controlled, parallel group phase II trial [25] evaluated the addition of capecitabine plus temozolomide to ^{177}Lu-DOTATATE in patients with NETs. The final results are currently available in abstract form. In the predefined cohort of patients with midgut NETs, at 36 months, there was no significant difference between the treatment and control arm (HR, 1.17; 95% CI, 0.51 to 2.68; p=0.71). Similarly, there was no significant difference in OS between the two arms (HR, 0.61; 95% CI, 0.19 to 1.94; p=0.40).

Adverse events

Grade 3 and 4 adverse events were reported in 6% of patients in the ^{177}Lu-DOTATATE plus capecitabine plus temozolomide arm while 31% of patients reported grade 3 or 4 adverse events in the control arm in patients with midgut NETs.

Table 4-11. Trials Reporting on the Use of PRRT in Patients with Midgut Neuroendocrine Tumours

Author, year	Study inclusion criteria	Treatment	Number of patients with midgut NETs evaluated	Median follow-up (range)	Median PFS	Median OS	Adverse events and quality of life
OCTREOTIDE ± ^{177}Lu-DOTATATE							
Randomized controlled trial							
NETTER-1 Strosberg et al (2017, 2021) [27,28]	Adults with locally advanced or metastatic, well differentiated, SSTR-positive midgut NETs	^{177}Lu-Dotatate at a dose of 7.4 GBq every 8 weeks + best supportive care including octreotide LAR 30 mg every 4 weeks + best supportive care VS Octreotide LAR 60 mg alone every 4 weeks	116 113	76.3 mths (0.4-95.0) 76.5 mths (0.1-92.3)	Not yet reached 8.4 mths (95% CI, 5.8-9.1) HR, 0.21; 95% CI, 0.13-0.33; p<0.001	48.0 mths (95% CI, 37.4-55.2) 36.3 mths (95% CI, 25.9-51.7) HR, 0·84; 95% CI, 0.60-1.17; p=0·30)	Serious treatment-related AEs, 9% vs. 1% (p=0.01). Approximately 5% of patients receiving ^{177}Lu-DOTATATE withdrew from the trial due to AEs related to treatment. Time to quality-of-life deterioration was significantly longer in those that received ^{177}Lu-DOTATATE versus the control arm in the global health status, physical and role functioning, fatigue, pain, diarrhea, disease-related worries, and body image domains.

Author, year	Study inclusion criteria	Treatment	Number of patients with midgut NETs evaluated	Median follow-up (range)	Median PFS	Median OS	Adverse events and quality of life
NETTER-2 Singh et al (2024) [11] *Abstract*	Adults with advanced grade 2 to 3 GEP NETS	^{177}Lu-DOTATATE 7.4 GBq + 30 mg Octreotide LAR, 4 cycles at intervals of 8 weeks OR Octreotide LAR 60 mg at intervals of 4 weeks	66	NR	HR, 0.30; 95% CI, 0.13-0.74)	NR 63.8 mths (95% CI, 25.9-not reached) p=0.0007	Adverse events, NR Quality of life, NR
^{177}Lu-DOTATATE ± CAPECITABINE + TEMOZOLOMIDE							
Randomized controlled trial							
AGTIG CONTROL NET Pavlakis et al (2022) [25] *Abstract* SUBGROUP	Adults with low to intermediate grade, unresectable, metastatic ^{68}Ga-octreotate PET-avid pNET and midgut NETs.	^{177}Lu-DOTATATE + CAPTEM VS ^{177}Lu-DOTATATE	33 14	60.3 mths	36 mths, 60.4% (95% CI, 40.8-75.3) 61.5% (95% CI, 30.8-81.8) HR, 1.17; 95% CI, 0.51-2.68; p=0.71	36 mths HR, 0.61; 95% CI, 0.19-1.94; p=0.40	Grade 3-4 AEs, 6% vs. 31% Quality of life, NA

Author, year	Study inclusion criteria	Treatment	Number of patients with midgut NETs evaluated	Median follow-up (range)	Median PFS	Median OS	Adverse events and quality of life
^{90}Y-DOTATATE							
Prospective, single arm study							
Rogowski et al (2016) [12] SUBGROUP	Adults with grade 1 or 2 metastatic pNETs or small bowel NETs with a least 6 months' evidence of disease progression	Ondansetron 8 mg orally + amino acids 1500 mL + ^{90}Y-DOTATATE for a cumulative activity of 15.2 GBq	37	45.2 mths (95% CI, 36.2-52.1)	28 mths (95% CI, 27.5-42.1)	40 mths (95% CI, 34.7-50.1)	AEs, NR Quality of life, NA
^{225}Ac-DOTATATE/^{225}Ac-DOTATOC							
No studies met inclusion criteria							
^{213}Bi-DOTATATE/^{213}Bi-DOTATOC							
No studies met inclusion criteria							
^{121}Pb-DOTATATE/^{121}Pb-DOTATOC							
No studies met inclusion criteria							

Abbreviations: AE, adverse events; CAPTEM, capecitabine plus temozolomide; CI, confidence interval; HR, hazard ratio; mths, months; NA, not assessed; NETs, neuroendocrine tumours; NR, not reported; pNETs, pancreatic neuroendocrine tumours; OS, overall survival; PFS, progression-free survival; PRRT, peptide receptor radionuclide therapy; SSTR, somatostatin receptors

Immunotherapy

There are no studies that have evaluated or have presented subgroup data solely for patients with midgut NETs.

Ongoing, Unpublished, or Incomplete Studies

A search for ongoing, unpublished, or incomplete randomized phase II, III, or IV trials was conducted on October 30, 2023 at clinicaltrials.gov using the terms "neuroendocrine tumours" OR "NETs". Nine trials were found; the trial details are provided in Table 4-12 below. The PReCedeNT and STARTER-NET trials were found when searching conference abstracts and have also been added to the list of ongoing trials.

Table 4-12. Ongoing, Unpublished, or Incomplete Studies

COMPOSE: Lutetium ^{177}Lu-Edotreotide Versus Best Standard of Care in Well-Differentiated Aggressive Grade 2 and Grade 3 Gastroenteropancreatic Neuroendocrine Tumors	
Protocol ID:	NCT04919226
Type of trial:	Interventional, phase III
Primary endpoint:	PFS
Accrual:	202
Sponsorship:	ITM Solucin GmbH
Status:	Recruiting
Date last updated:	September 13, 2023
Estimated study completion date:	September 2026

START-NET: An Open-label, Multicenter, Randomized Phase III Trial Comparing Safety and Efficacy of Personalized Versus Non-personalized Radionuclide Therapy With ^{177}Lu-DOTATOC	
Protocol ID:	NCT05387603
Type of trial:	Interventional, phase III
Primary endpoint:	Median PFS
Accrual:	300
Sponsorship:	Lund University Hospital
Status:	Not yet recruiting
Date last updated:	May 24, 2022
Estimated study completion date:	October 2025

A Study Comparing Treatment with ^{177}Lu Oxodotreotide Injection to Octreotide LAR in Patients with Inoperable, Progressive, Well Differentiated, Somatostatin Receptor-Positive Gastroenteropancreatic Neuroendocrine Tumours	
Protocol ID:	NCT05459844
Type of trial:	Interventional, phase III
Primary endpoint:	PFS
Accrual:	196
Sponsorship:	Sinotau Pharmaceutical Group
Status:	Recruiting
Date last updated:	February 13, 2023
Estimated study completion date:	December 2028

COMPETE: A Prospective, Randomised, Controlled, Open-label, Multicentre Phase III Study to Evaluate Efficacy and Safety of Peptide Receptor Radionuclide Therapy with ^{177}Lu-Edotreotide Compared to Targeted Molecular Therapy with Everolimus in Patients with Inoperable, Progressive, Somatostatin Receptor-positive, Neuroendocrine Tumours of Gastroenteric or Pancreatic Origin

Protocol ID:	NCT03049189
Type of trial:	Interventional, phase III
Primary endpoint:	PFS
Accrual:	309
Sponsorship:	ITM Solucin GmbH
Status:	Active, not yet recruiting
Date last updated:	August 22, 2023
Estimated study completion date:	June 2029

PReCedeNT: Phase III Randomised Controlled Trial of PRRT with ^{177}Lu DOTATATE Plus Chemotherapy vs. PRRT Alone in FDG-avid, Well-Differentiated Gastroenteropancreatic Neuroendocrine Tumors

Protocol ID:	Not reported
Type of trial:	Interventional, phase III
Primary endpoint:	PFS and ORR
Accrual:	162
Sponsorship:	Not reported
Status:	Recruiting
Date last updated:	Not reported
Estimated study completion date:	Not reported

SORENTO: A Randomized, Multi-center, Open-label, Active-controlled Phase 3 Trial to Assess the Efficacy and Safety of Octreotide Subcutaneous Depot (CAM2029) Versus Octreotide LAR or Lanreotide ATG in Patients With GEP-NET

Protocol ID:	NCT05050942
Type of trial:	Interventional, phase III
Primary endpoint:	PFS
Accrual:	300
Sponsorship:	Camurus AB
Status:	Recruiting
Date last updated:	October 6, 2023
Estimated study completion date:	December 2026

STARTER-NET: An intergroup phase III study of combination therapy with everolimus and lanreotide versus everolimus monotherapy for unresectable or recurrent gastroenteropancreatic neuroendocrine tumor

Protocol ID:	jRCT1031200023
Type of trial:	Interventional, phase III
Primary endpoint:	PFS
Accrual:	250
Sponsorship:	National Cancer Center Japan
Status:	Recruiting
Date last updated:	December 27, 2021
Estimated study completion date:	December 31, 2031

NET RETREAT: A Phase II Study of 177 Lutetium-DOTATATE Retreatment vs. Everolimus in Metastatic/Unresectable Midgut NET

Protocol ID:	NCT05773274
Type of trial:	Interventional, phase II
Primary endpoint:	PFS
Accrual:	100
Sponsorship:	National Cancer Institute
Status:	Recruiting
Date last updated:	October 19, 2023
Estimated study completion date:	April 2026

[redacted]

Phase II Randomized, Prospective Trial of Lutetium Lu 177 Dotatate PRRT Versus Capecitabine and Temozolomide in Well-Differentiated Pancreatic Neuroendocrine Tumors

Protocol ID:	NCT05247905
Type of trial:	Interventional, phase II
Primary endpoint:	Median PFS
Accrual:	198
Sponsorship:	Alliance for Clinical Trials in Oncology
Status:	Recruiting
Date last updated:	August 31, 2023
Estimated study completion date:	October 2033

DISCUSSION

Neuroendocrine malignancies are among the most diverse group of cancers treated with systemic therapy. Therefore, evaluation of the evidence for the management of NETs involves an appreciation of the heterogeneous behaviours of this diverse group of cancers, where multiple factors such as histology, pathology, anatomical site of origin, functionality, and other clinical factors affect patient outcomes. Due to the complexity of these malignancies, all patients with advanced GEP NETs should be assessed in a multidisciplinary setting where surgery, whether curative or for optimal debulking, as well as other local therapies are evaluated as treatment options. Consequently, these recommendations apply to individuals in whom surgical resection of disease, whether local or metastatic, is not feasible. Individuals should be re-evaluated for resection or local ablative treatment at regular intervals during treatment with systemic therapies.

The Working Group has agreed with other groups, that PFS is an acceptable endpoint in NETs, recognizing that OS benefit is difficult to ascertain given the varied natural history of NETs, which results in a lengthy study period, further amplified by crossover designs. Additionally, the question of lines of therapy, and optimal sequencing of therapy in NETs, is particularly challenging. Considering the availability of multiple treatments, the utmost importance must be placed on patient preference and individual needs. Given the longer survival times compared with many other cancers, quality of life data are essential if clinicians are to properly discuss individualized treatment plans with patients.

The recommendations place emphasis on data from randomized, prospective trials, but do also consider information from large retrospective series, subgroup analyses, and non-randomized phase II studies, recognizing the reality of the limited data available for this disease.

pNETs

There is general recognition that the clinical behaviour of pNETs is distinct from NETs of foregut, midgut, and hindgut origin [38]. This is the rationale for studying these patients in dedicated trials or stratifying according to tumour site within mixed-population studies.

Reflecting real-life practice, the Working Group believes the evidence supported the use of lanreotide in patients with grade 1 to 2 (Ki-67 <10%)1/2 SSTR 2-positive pNETs, despite the lack of statistically significant benefit in the pNET subgroup of the CLARINET study. Due to the small number of events, results should be interpreted with care. Further, the occurrence of treatment-related adverse events and quality of life showed no significant differences between the study groups, resulting in the potential benefit of increased median PFS for pNETs, extrapolated from PFS benefit from the entire trial (approximately 45% of participants had pNETs), outweighing the adverse events. Similarly, the Working Group acknowledges the accepted generalizability of the use of sustained-release octreotide as an SSA. This recommendation is concordant with those of published NET collaboratives including the National Comprehensive Cancer Network (NCCN) and North American Neuroendocrine Tumor Society (NANETS).

No data exist as to the optimal biological agent for treatment, with different cellular pathways having been targeted: mTOR in the case of everolimus; and vascular endothelial growth factor and other kinases in the case of sunitinib. The RADIANT-3 trial was restricted to patients with grade 1 to 2 advanced pNETs who were randomized to everolimus 10 mg daily or placebo, both with best supportive care. The primary endpoint of PFS was significantly prolonged with everolimus (HR, 0.34; 95% CI, 0.27 to 0.45; p<0.001) and present across multiple subgroups. This trial provides randomized, comparative evidence for the use of everolimus in patients with pNETs. The COOPERATE-2 trial of everolimus with the newer SSA agent pasireotide was negative; therefore, the combination therapy of everolimus and an SSA cannot be routinely

recommended at this time for non-functional pNETs. With regards to sunitinib, a large, well-conducted phase III randomized trial demonstrated significantly improved PFS compared with placebo (HR, 0.315; 95% CI, 0.181 to 0.546; p<0.01), with a benefit also for OS (although not statistically significant). No direct comparison of efficacy between everolimus and sunitinib has been undertaken; however, in a matching-adjusted indirect comparison of patients from the RADIANT-3 trial and the phase III sunitinib trial, everolimus was associated with similar PFS (p=0.578) and OS (p=0.383) compared with sunitinib [7]. The different side effect profiles of each of these drugs may direct the physician's choice of agent.

The Working Group recommends the use of capecitabine and temozolomide, as the preferred cytotoxic regimen, in patients with grade 1 to 2 pNETs based on results of ECOG-ACRIN E2211 RCT. The interim results where PFS, the primary endpoint, was met had reported a significant benefit for those who received capecitabine plus temozolomide (22.7 months vs. 14.4 months; HR, 0.58; 95% CI, 0.36 to 0.93); however, the final analysis reported no significant difference in median PFS between those who received capecitabine plus temozolomide compared with temozolomide alone after adjusting for tumour grade (23.2 months vs. 15.1 months; HR, 0.63; 95% CI, 0.39 to 1.01). Despite the non-statistically significant results in the final analysis, it is important to note the clinical significance of these results. The Working Group additionally recommends the consideration of upfront use of capecitabine plus temozolomide in patients with bulky or rapidly progressing tumours, or patients requiring downstaging prior to surgical resection. Finally, upfront treatment might be considered in pNETs with Ki-67 >10% as these patients were not included in the CLARINET study.

The evidence surrounding the use of PRRT in patients with SSTR2-positive receptor pNETs is largely based on results from one phase III RCT and two single arm phase II studies. While acknowledging the very low level of certainty based on the single-arm studies, the Working Group felt that the PFS demonstrated in these trials, and a general acceptance of the efficacy of PRRT in patients with pNETs, including guidelines from the NCCN and NANETs, support the use of PRRT in this patient population. The sequencing of PRRT in pNET patients compared with other therapies is not clear although the NETTER-2 trial shows significant efficacy when used as first-line therapy for those with grade 2 and 3 GEP NETs. These results for the pNET subgroup are similar. Full publication of this important trial is eagerly awaited. Further, the NETTER-R study retrospectively evaluated the use of ^{177}Lu-DOTATATE in patients with pNETs. Due to its retrospective nature and the presence of prospective studies, this study was not included in the review. However, a median PFS of 24.8 months was reported in patients with available RECIST v1.1 tumour response. In exploratory subgroup analyses, both PFS (p=0.0009) and OS (p<0.0001) were longer in patients who had not received prior chemotherapy. The Working Group acknowledges the OCCULORANDOM study in which treatment with PRRT resulted in a doubling of PFS when compared with sunitinib. However, this study has been presented in abstract form only, and therefore could not be incorporated into the guideline recommendations at this time. Although long-term toxicity is rare, it is important to highlight the potential for irreversible myelosuppression, myeloid neoplasia, and chronic renal toxicity associated with treatment.

Midgut NETs

SSAs remain a mainstay of treatment in gastrointestinal NETs, based on results of the PROMID and CLARINET studies. Although limited in sample size, the PROMID trial demonstrated a significant benefit for the long-active SSA, octreotide LAR, in delaying time to progression in midgut NETs. The CLARINET trial demonstrated a significant median PFS benefit of lanreotide in a larger, more heterogeneous population inclusive of all gastrointestinal NETs (approximately 36% of participants had midgut NETs), although it should be noted that the vast majority of patients had stable disease upon enrollment. A pre-defined subgroup analysis of patients with

midgut NETs remained consistent with the findings of the overall population with a statistically significant benefit (HR, 0.35; 95% CI, 0.16 to 0.80); results should be interpreted with care due to the small number of events. The decision to dose escalate in non-functioning NETs after an initial response remains based on clinical experience, with no high-level evidence.

The RADIANT-4 trial established the benefit of everolimus in patients with advanced NETs originating in the gastrointestinal tract, with significant prolongation of PFS compared with placebo. The trial consisted of patients who were SSA treatment naïve as well as patients previously treated with SSAs, with the benefit of everolimus independent of this variable. However, the optimal sequencing and combination of SSA with everolimus in progressive non-functional NETs has yet to be identified.

The Working Group recognizes that given the limited toxicity of SSAs, these agents are an appropriate first-line treatment for the majority of patients with advanced, midgut NETs. There was insufficient evidence to recommend the combination therapy of a SSA plus everolimus over everolimus alone although the toxicity of the combination was acceptable. There are no high-level data to recommend chemotherapy in well- and moderately differentiated non-pancreatic gastroenterohepatic NETs; however, based on expert opinion chemotherapy may be considered in patients with progressive midgut NETs. The limited certainty supporting this recommendation is acknowledged, and the lack of an optimal chemotherapy regimen. However, given the limited number of effective treatments in this disease, and the relatively long survival of gastrointestinal NET patients, chemotherapy will often be considered at some point for many patients. This opinion is concordant with those of the NCCN.

The Working Group recommends PRRT with ^{177}Lu-DOTATATE and standard-dose SSA, after disease progression on standard dose SSA, in SSTR-positive midgut NETs (Ki-67 <20%) based on the results of the NETTER-1 trial. In this pivotal trial, treatment with PRRT and standard-dose SSA resulted in a highly significant improvement in PFS (HR, 0.21; 95% CI, 0.13 to 0.33; p<0.001) compared with dose-escalated SSA. Importantly, time to degradation of quality of life was also longer in patients treated with PRRT compared with dose-escalated SSA, despite the higher rate of serious adverse events (9% vs. 1%) in the PRRT arm. Although long-term toxicity is rare, it is important to highlight the potential for irreversible myelosuppression, myeloid neoplasia, and chronic renal toxicity associated with treatment.

Finally, the evidence does not currently support the use of immunotherapy in the treatment of pancreatic or midgut NETs outside of a clinical trial.

CONCLUSIONS

All patients with GEP NETs should be assessed in a multidisciplinary setting where surgery, whether curative or for optimal debulking, as well as other local therapies are evaluated as treatment options by clinicians with experience in NET care. Patients with metastatic pNETs with Ki-67 <10% and SSTR2 positivity should be offered SSAs (i.e., lanreotide or octreotide). Targeted therapy (i.e., everolimus or sunitinib) can also be offered, as well as chemotherapy with capecitabine plus temozolomide upon progression from SSAs or as first-line therapy in clinical scenarios with more aggressive disease where clinical response is required. Patients with metastatic, SSTR-positive, pNETs may be offered PRRT. Although this evidence has limitations, the rarity of this disease coupled with the difficulty of conducting methodologically sound trials in this population, results in the need to use the best available evidence to make treatment decisions.

Patients with metastatic midgut NETs with Ki-67 <10% should be offered lanreotide or sustained-release octreotide. The use of PRRT with ^{177}Lu-DOTATATE in combination with SSA treatment is recommended in patients with grade 1 to 2, SSRT2-positive metastatic midgut NETs after progression on an SSA. Targeted therapy with everolimus may also be offered to

patients with non-functional grade 1 or 2 midgut NETs. There is insufficient evidence for or against the use of chemotherapy in patients with midgut NETs. The use of immunotherapy is not recommended outside of a clinical trial in patients with metastatic pNETs or midgut NETs. A number of studies have evaluated various therapies and combinations thereof; however, many are not randomized or comparative and are comprised of small patient numbers. As such, an ongoing need remains for randomized studies comparing systemic therapy treatments with one another. Due to the highly specialized nature of NET treatment, community-based clinicians are encouraged to participate in province-wide NET case conferences and/or refer patients to specialized multidisciplinary NET clinics.

Systemic therapy for unresectable advanced or metastatic pancreatic and midgut neuroendocrine tumours

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel and the PEBC Report Approval Panel (RAP) (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the ten members of the GDG Expert Panel, nine members voted and none abstained, for a total of 90% response in September 2023. Of those who voted, all nine approved the document (100%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
1. The order of the recommendations is a bit confusing, in terms of which apply to small bowel tumours, and which to pancreatic, and which to both.	We have now re-organized the recommendations for clarity.
2. Recommendation 1: Regular re-evaluation for resection or local ablative treatment – this does not, in my opinion, apply to all patients. There are many patients where there will never be a role for local treatment. Additionally, this is expert opinion, and that should be stated in the justification	We have moved this statement to the Preamble. The Working Group believes it is better to have patients re-evaluated and deemed as inoperable or not eligible for local therapies than not being considered at all.
3. For Recommendation 2.1, the third Qualifying Statement should be the second Qualifying Statement.	We have modified this.
4. Regarding the Qualifying Statement for Recommendation 2.2: *It (Chemotherapy) may also be utilized, pre-surgery in patients who would benefit from preoperative downsizing*. No supporting data are cited. Would recommend either citing some published evidence, or acknowledging that there is no evidence, but that it could be considered nonetheless.	The Working Group acknowledges the lack of supporting data. However, chemotherapy is one of the very limited therapies for pNETs with an established response rate greater than 10% and thus can be considered and used for downsizing.
5. Regarding the Qualifying Statement for Recommendation 2.3: *While everolimus and sunitinib are often utilized after disease progression on an SSA, there is insufficient evidence for recommendations on sequencing of therapy*. Some of the justification in this document is expert opinion. I think it would be reasonable to comment in recommendation 1.3 that TKIs can reasonably be considered after progression on an SSA. A bit more guidance may be helpful for those with less experience or support for treating pNETs. The qualifying statement can still stand as is, but I think there is room for a recommendation.	The Working Group has added the following statement to the Preamble, "The sequencing of the various classes of treatments have not been compared head-to-head. As a result, there is insufficient evidence for recommendations on sequencing of therapy; however, the Working Group has provided some guidance, where possible, based on the inclusion criteria used in specific trials and expert opinion in the qualifying statements." Further, recently published data

	on the use of capecitabine plus temozolomide, and evolving data supporting the use of PRRT in pNETs makes sequencing more complex and would not always support the sequence suggested by the reviewer.
6. Regarding the Qualifying Statement for Recommendation 2.3: Seems to suggest that everolimus is a TKI. Suggest re-wording slightly to avoid confusion	We have slightly reworded this Qualifying Statement for clarification.
7. It would be helpful to indicate for each therapy what line of treatment it was used in for a particular study in the Key Evidence. The case is made that this is a heterogeneous group of malignancies, and it would be helpful to see where it was used when the evidence is listed. This information is provided in different parts of the document, but it might fit here as well.	The brief inclusion criteria are included in the Key Evidence section without making it lengthier with details. We have provided information on lines of therapy and sequencing where it exists.
8. A few comments were received regarding the recommendations not explicitly addressing sequencing and with suggestions to develop an algorithm.	The Working Group has added the following statement to the Preamble, "The sequencing of the various classes of treatments have not been compared head-to-head. As a result, there is insufficient evidence for recommendations on sequencing of therapy; however, the Working Group has provided some guidance, where possible, based on the inclusion criteria used in specific trials and expert opinion in the qualifying statements." Due to the lack of clear evidence, development of an evidence-based algorithm is currently not possible.
9. A comment may be included in the Conclusions to say that multidisciplinary settings should include counterparts at Centres of Excellence or high-volume centres to encourage collaboration between smaller community centres and their local academic counterparts - to remind individuals to discuss complex cases at provincial rounds, for example	We have added the following sentence to the Conclusions, "Due to the highly specialized nature of NET treatment, community-based clinicians are encouraged to participate in province-wide NET case conferences and/or refer patients to specialized multidisciplinary NET clinics.

RAP Review and Approval

Three RAP members reviewed this document in September 2023. Two RAP members approved the document, and one RAP member did not. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

Table 5-2. Summary of the Working Group's responses to comments from RAP.

Comments	Responses
1. A few comments were received about the recommendations being difficult to follow, with a few suggestions, including splitting the document into two (i.e., pancreatic and midgut) or creating an algorithm or flow chart or a complete reorganization of the recommendations.	We have completely reorganized Section 2 to reflect the comments received about the recommendations being difficult to follow. We now have three recommendations. Recommendations 2.0 and 3.0 address pancreatic and midgut NETS, respectively, and we have provided the recommendations for each class of interventions within these two recommendations in an easy-to-follow manner.
2. The overall objective listed in Section 2 is very general but as one reads the document, one finds that the topic cannot be generalized. In contrast, the guideline questions on page 17 in Section 4 are clear and sufficiently detailed. The Guideline title is not clear as to whether the guideline addresses non-operative cases ONLY. This should be clarified. The title, as it stands, communicates that the guideline directs care in nonoperative cases. However, Recommendation 1 includes surgery. This is confusing.	We have modified the title of the guideline along with the Guideline Objectives and Target Population to those with pancreatic and midgut NETs rather than GEP NETs. We have also modified Recommendation 1 to reflect the eligibility criteria for the patients of this guideline. It clarifies how unresectability should be established rather than recommending surgery.
3. The Intended Users section is far too vague. Please provide more information as to who the intended users will be.	The Intended Users have been slightly modified to include those who treat patients with pNETs and midgut NETs.
4. Re Justification of Evidence for Recommendation 2.4: *In exploratory subgroup analyses of the NETTER-R study, both PFS (p=0.0009) and OS (p<0.0001) were longer in patients who had not received prior chemotherapy, suggesting improved efficacy if treatment is given earlier*. Careful here, this is somewhat speculative. It could mean patients who got it were less ill or less far along their disease trajectory.	Thank you for noting this, we have removed this sentence.
5. Implementation considerations – anything specific needed regarding access to PRRT? This likely requires a specialized centre.	We have added the following to the Implementation Considerations, "Ga^{68}-DOTATATE positron emission tomography scans and PRRT are currently only available at a small number of specialized healthcare centres in Ontario."
6. Should there be a surgeon among the members of the GEP NETS GDP so there is agreement about inoperable and unresectable? Should there be definitions of these?	Dr. Julie Hallett, a surgical oncologist, is a member of the Working Group. We have added the following Qualifying Statement to

	Recommendation 1.0, "Defining unresectability and inoperability is a complex scenario for NETs, which requires the input of multiple team members in a multidisciplinary setting." Including definitions of resectability is beyond the scope of this guideline.
7. Should there be a definition or reference to the staging of these tumours? Is there a definition of maintenance and progression that was agreed upon?	This is now discussed in the Introduction.
8. The health questions are clear, although, the rationale to separate pancreatic and midgut NETs is not provided. There is also no explanation of what are 'functional NET symptoms'.	We have now inserted a few sentences in the Introduction about the rationale for separating pNETs and midgut NETs and have added some of this language to the Preamble as well. Functional NET symptoms have been defined in the Introduction.
9. Section 3 does not include any information on how the evidence was used to formulate recommendations – other than 'interpretation of the evidence by the Working Group'. Some of this information, however, is available in the 'Justification for Recommendation' sections in Section 2.	Section 3 consists mostly of boilerplate language describing the methods of guideline development.

The RAP member who did not approve the guideline reviewed the changes made based on the feedback provided and approved it November 2023.

Patient and Caregiver-Specific Consultation Group

Three patients/survivors/caregivers participated as Consultation Group members for the Working Group. They reviewed the draft recommendations and provided feedback on its comprehensibility, appropriateness, and feasibility to the Working Group's Health Research Methodologist. The main comments from the Consultation Group are summarized in Table 5-3.

Table 5-3. Summary of the Working Group's responses to comments from the Consultation Group.

Comments	Responses
1. The patients found the recommendations clear and unambiguous although the language was out of a patient's depth for understanding (i.e., too medical and technical).	No response required.
2. The patients agreed that the recommendations consider and address outcomes that are important to patients. Adverse events are discussed throughout the document.	No response required.
3. One patient found the recommendations allowed for flexibility based on patient preferences and individual needs while the other couldn't answer due to the technical language used.	No response required.

EXTERNAL REVIEW
External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Two targeted peer reviewers from Australia and the USA, who are considered to be clinical and/or methodological experts on the topic, were identified by the Working Group. Both agreed to be the reviewers (Appendix 1). Two responses were received. Results of the feedback survey are summarized in Table 5-4. The main comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-5.

Table 5-4. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=2)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.				1	1
2. Rate the guideline presentation.					2
3. Rate the guideline recommendations.				2	
4. Rate the completeness of reporting.				1	1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?				1	1
6. Rate the overall quality of the guideline report.				1	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.				2	
8. I would recommend this guideline for use in practice.				1	1
9. What are the barriers or enablers to the implementation of this guideline report?	• Barriers/enablers well discussed in the current document. • No barriers to implementation of this guideline as it is in line with other societal guidelines.				

Table 5-5. Summary of the Working Group's responses to comments from targeted peer reviewers.

Comments	**Responses**
1. SSTR2 positivity in this guideline is analogous to uptake on 68GA-DOTATATE PET. A short point on what this means in the longform test will help clinicians less conversant with PRRT.	We have added a sentence to the Introduction to address this point.
2. CONTROL NETS was described by the working group as "negative" presumably due to the p value of 0.08. However, this was a non-comparative study, not powered to show a significant difference.	We have deleted the qualifier "although not statistically significant".

3. Was omission of discussion re: MGMT planned? eg, comparing MGMT to SSTR, DOTATATE PET avidity.	The Working Group did discuss the utility of MGMT-promoter methylation status as a biomarker to predict the efficacy of capecitabine + temozolomide. However, given the exploratory nature of the analysis and the fact that the test is not widely used nor widely available, the working group did not include this data in the guideline.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All those in the PEBC database whose had a subject of interest of 'gastrointestinal OR neuroendocrine OR nuclear medicine' were contacted by email to inform them of the survey. Of the 138 professionals who were contacted, all practice in Ontario. Twenty (14.5%) responses were received in total. Eight stated that they did not have interest in this area or were unavailable to review this guideline at the time. The results of the feedback survey from 12 people are summarized in Table 5-6. The main comments from the consultation and the Working Group's responses are summarized in Table 5-7.

Table 5-6. Responses to four items on the professional consultation survey.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.			1(8)	6(50)	5(42)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.				6(50)	6(50)
3. I would recommend this guideline for use in practice.				6(50)	6(50)
4. What are the barriers or enablers to the implementation of this guideline report?	Barriers: • Access to multidisciplinary teams and specialized centres. • Access to necessary scans. • Access to therapies which are limited to certain specialized centres. • Access to targeted and chemotherapy drugs in the absence of private coverage. • Access to a robust histological/lab reporting system to flag NETs patients. Enablers: • The guideline itself will assist clinicians in advocating for equitable access for all patients. • A webinar presentation as part of a dissemination strategy would be helpful.				

Table 5-7. Summary of the Working Group's responses to comments from professional consultants.

Comments	Responses
1. It may help clarify for non-experts whether and/or when combinations of lanreotide with targeted agents is appropriate in Section 2.1.	There are no robust data to confirm the efficacy of combining a SSA with targeted agents or chemotherapy. Therefore, it was not incorporated into the guideline.
2. Recommendation 2.4 could be improved by stating which lines of therapy are appropriate in the opening sentence.	Based on currently available evidence, which is not mature enough, the Working Group felt that they could not make a comment on the appropriate line of therapy for which PRRT should be offered for pNETs.
3. The guideline needs greater emphasis on the desirability of referring these patients for expert assessment and recommendations if not care.	This issue is discussed in the guideline conclusions.
4. Greater comment on the biology of these tumours and on the opportunities for additional treatments after tumour progression would be helpful.	These issues are addressed in the Introduction and Discussion sections.

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

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Appendix 1: Affiliations and Conflict of Interest Declarations

Table A1-1. Members of the GEP NETs GDG

Name	Affiliation	Declarations of interest
MEMBERS OF THE WORKING GROUP		
Kevin Zbuk Medical oncologist	Juravinski Cancer Centre Hamilton, ON	Has received $500 or more in a single year in a consulting capacity for Ipsen.
Tim Asmis Medical oncologist	Ottawa Hospital Ottawa, ON	Has received $500 or more in a single year in a consulting capacity for Novartis, Ipsen. Has received a grant from Ipsen to support a Research Fellowship.
Charles Cho Radiation oncologist	Southlake Regional Health Centre Newmarket, ON	None declared
Julie Hallett Medical oncologist	Odette Cancer Centre Toronto, ON	None declared
David Laidley Nuclear medicine	London Health Sciences Centre London, ON	Has received $500 or more in a single year in a consulting capacity for Novartis. Has been an investigator for the NETTER-2 trial as well as trials with Novartis/Point Biopharma/Progenics.
Simron Singh Medical oncologist	Odette Cancer Centre Toronto, ON	Has received $500 or more in a single year in a consulting capacity for Ipsen and Novartis. Is the PI of NETTER-2 trial.
Rebecca Wong Radiation oncologist	Princess Margaret Hospital Toronto, ON	None declared
Duvaraga Sivajohanathan Health Research Methodologist	Program in Evidence-Based Care McMaster University Hamilton, Ontario	None declared
MEMBERS OF THE EXPERT PANEL		
Sean Bennett Surgical oncologist	Kingston Health Sciences Centre Kingston, ON	None declared
Lev Bubis Surgical oncologist	University of Toronto Toronto, ON	None declared
Shivani Dadwal Medical oncologist	Kingston Health Sciences Centre Kingston, ON	None declared
Kristopher Dennis Radiation oncologist	Ottawa Hospital Ottawa, ON	None declared
John Lenehan Medical oncologist	London Health Sciences Centre London, ON	None declared
Lucy Ma Medical oncologist	Princess Margaret Hospital Toronto, ON	None declared

Aruz Mezci Radiation oncologist	Princess Margaret Hospital Toronto, ON	None declared
Michael Sanatani Medical oncologist	London Health Sciences Centre London, ON	None declared
Erica Tsang Medical oncologist	Princess Margaret Hospital Toronto, ON	Has received $500 or more in a single year from Guardant Health as an advisory board member; has received $500 or more for travel from Amgen

Table A1-2. Members of the Patient Consultation Group

Name	**Declaration of Interest**
Randy Conrad	Received a $500 stipend from OICR to act in a consulting capacity
Abeer Salim	None declared
Lisa Salim	None declared

Table A1-3. Members of the GEP NETs Targeted Peer Reviewers

Name	Affiliation	Declarations of interest
MEMBERS OF THE WORKING GROUP		
Alexandra Gangi Surgeon	Cedars-Sinai Medical Center Los Angeles, CA USA	Has received $500 or more in a single year from NANETS to cover travel.
David Chan Medical Oncologist	Royal North Shore Hospital North Shore Private Hospital St. Leonards, NSW Australia	Has received $500 or more in a single year in a consulting capacity for Ipsen and Camerus. Received a research grant from Novartis in 2018. Is the chair of the NET group of COSA (Clinical Oncology Society of Australia), which is the peak cancer body for cancer clinicians.

Appendix 2: Literature Search Strategy

A. Search strategy for for guidelines, systematic reviews and RCTs and non-RCTs for all patients with NETs

MEDLINE(R) 1946 to Present
1 (systematic adj (review: or overview:)).mp. (291801)
2 (meta-analy: or metaanaly:).mp. (280427)
3 (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp. (16388)
4 (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw. (180710)
5 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab. (328306)
6 (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab. (52753)
7 or/1-6 (587557)
8 (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab. (103079)
9 (stud: adj1 select:).ab. (33783)
10 (8 or 9) and review.pt. (55306)
11 7 or 10 (593619)
12 (guideline or practice guideline).pt. (37248)
13 exp consensus development conference/ (12618)
14 consensus/ (19189)
15 (guideline: or recommend: or consensus or standards).ti. (190832)
16 12 or 13 or 14 or 15 (216179)
17 11 or 16 (793856)
18 (neuroendocrine adj2 (cancer$ or tumo?r$)).mp. (22513)
19 (gastroenteropancreatic adj2 (tumo?r$ or neuroendocrine or NET$1)).mp. (1574)
20 or/18-19 (22685)
21 exp phase 3 clinical trial/ or exp "phase 3 clinical trial (topic)"/ or exp clinical trial, phase iii/ or exp clinical trials, phase iii as topic/ or exp phase 4 clinical trial/ or exp "phase 4 clinical trial (topic)"/ or exp clinical trial, phase iv/ or exp clinical trials, phase iv as topic/ or exp randomized controlled trial/ or exp "randomized controlled trial (topic)"/ or exp randomized controlled trials as topic/ or exp controlled clinical trial/ or "controlled clinical trial (topic)"/ or controlled clinical trials as topic/ or exp randomization/ or exp random allocation/ or exp double-blind method/ or exp single-blind method/ or exp double blind procedure/ or exp single blind procedure/ or exp triple blind procedure/ or exp placebos/ or exp placebo/ or ((exp phase 2 clinical trial/ or exp "phase 2 clinical trial (topic)"/ or exp clinical trial, phase ii/ or exp clinical trials, phase ii as topic/ or exp clinical trial/ or exp prospective study/) and random$.tw.) or (((phase II or phase 2 or clinic$) adj3 trial$) and random$).tw. or ((singl$ or double$ or treble$ or tripl$) adj3 (blind$ or mask$ or dummy)).tw. or placebo?.tw. or (allocat: adj2 random:).tw. or (rct or phase III or phase IV or phase 3 or phase 4 or randomi$: or randomly).tw. or (random$ adj3 trial$).mp. (1537155)
22 20 and 21 (902)
23 22 not 17 (777)
24 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt. (2658037)

25 23 not 24 (740)
26 exp animal/ not human/ (5048541)
27 25 not 26 (734)
28 limit 27 to english language (700)
29 limit 28 to yr="2016 -Current" (387)
30 20 not 17 (21766)
31 30 not 21 (20989)
32 31 not 24 (20005)
33 32 not 26 (19615)
34 limit 33 to english language (18014)
35 limit 34 to yr="2016 -Current" (9633)

Embase <1974 to Present>
1 (systematic adj (review: or overview:)).mp. (477825)
2 (meta-analy: or metaanaly:).mp. (401990)
3 (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp. (25007)
4 (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw. (314207)
5 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab. (400100)
6 (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.
(64456)
7 or/1-6 (818913)
8 (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic:quality).ab. (129440)
9 (stud: adj1 select:).ab. (40883)
10 (8 or 9) and review.pt. (59525)
11 7 or 10 (824793)
12 consensus development conference/ (26451)
13 practice guideline/ (513009)
14 *consensus development/ or *consensus/ (14681)
15 *standard/ (4903)
16 (guideline: or recommend: or consensus or standards).kw. (33110)
17 (guideline: or recommend: or consensus or standards).ti. (241388)
18 or/12-17 (678114)
19 11 or 18 (1444022)
20 (neuroendocrine adj2 (cancer$ or tumo?r$)).mp. (45645)
21 (gastroenteropancreatic adj2 (tumo?r$ or neuroendocrine or NET$1)).mp. (3597)
22 or/20-21 (45850)
23 exp phase 3 clinical trial/ or exp "phase 3 clinical trial (topic)"/ or exp clinical trial, phase iii/ or exp clinical trials, phase iii as topic/ or exp phase 4 clinical trial/ or exp "phase 4 clinical trial (topic)"/ or exp clinical trial, phase iv/ or exp clinical trials, phase iv as topic/ or exp randomized controlled trial/ or exp "randomized controlled trial (topic)"/ or exp randomized controlled trials as topic/ or exp controlled clinical trial/ or "controlled clinical trial (topic)"/ or controlled clinical trials as topic/ or exp randomization/ or exp random allocation/ or exp double-blind method/ or exp single-blind method/ or exp double blind procedure/ or exp single blind procedure/ or exp triple blind procedure/ or exp placebos/ or

exp placebo/ or ((exp phase 2 clinical trial/ or exp "phase 2 clinical trial (topic)"/ or exp clinical trial, phase ii/ or exp clinical trials, phase ii as topic/ or exp clinical trial/ or exp prospective study/) and random$.tw.) or (((phase II or phase 2 or clinic$) adj3 trial$) and random$).tw. or ((singl$ or double$ or treble$ or tripl$) adj3 (blind$ or mask$ or dummy)).tw. or placebo?.tw. or (allocat: adj2 random:).tw. or (rct or phase III or phase IV or phase 3 or phase 4 or randomi$: or randomly).tw. or (random$ adj3 trial$).mp. (2258914)
24 22 and 23 (3086)
25 exp animal/ not human/ (5144152)
26 24 not 25 (3056)
27 (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/ (3689614)
28 26 not 27 (2868)
29 28 not 19 (2403)
30 limit 29 to english language (2347)
31 limit 30 to yr="2016 -Current" (1220)
32 22 not 19 (43242)
33 32 not 23 (40650)
34 33 not 25 (39695)
35 34 not 27 (37168)
36 conference abstract.pt. (4536224)
37 35 not 36 (24557)
38 limit 37 to english language (21936)
39 limit 38 to yr="2016 -Current" (10762)

B. Search strategy for non-RCTs, includes search used for guidelines, systematic reviews and RCTs for all patients with NETs who received PRRT

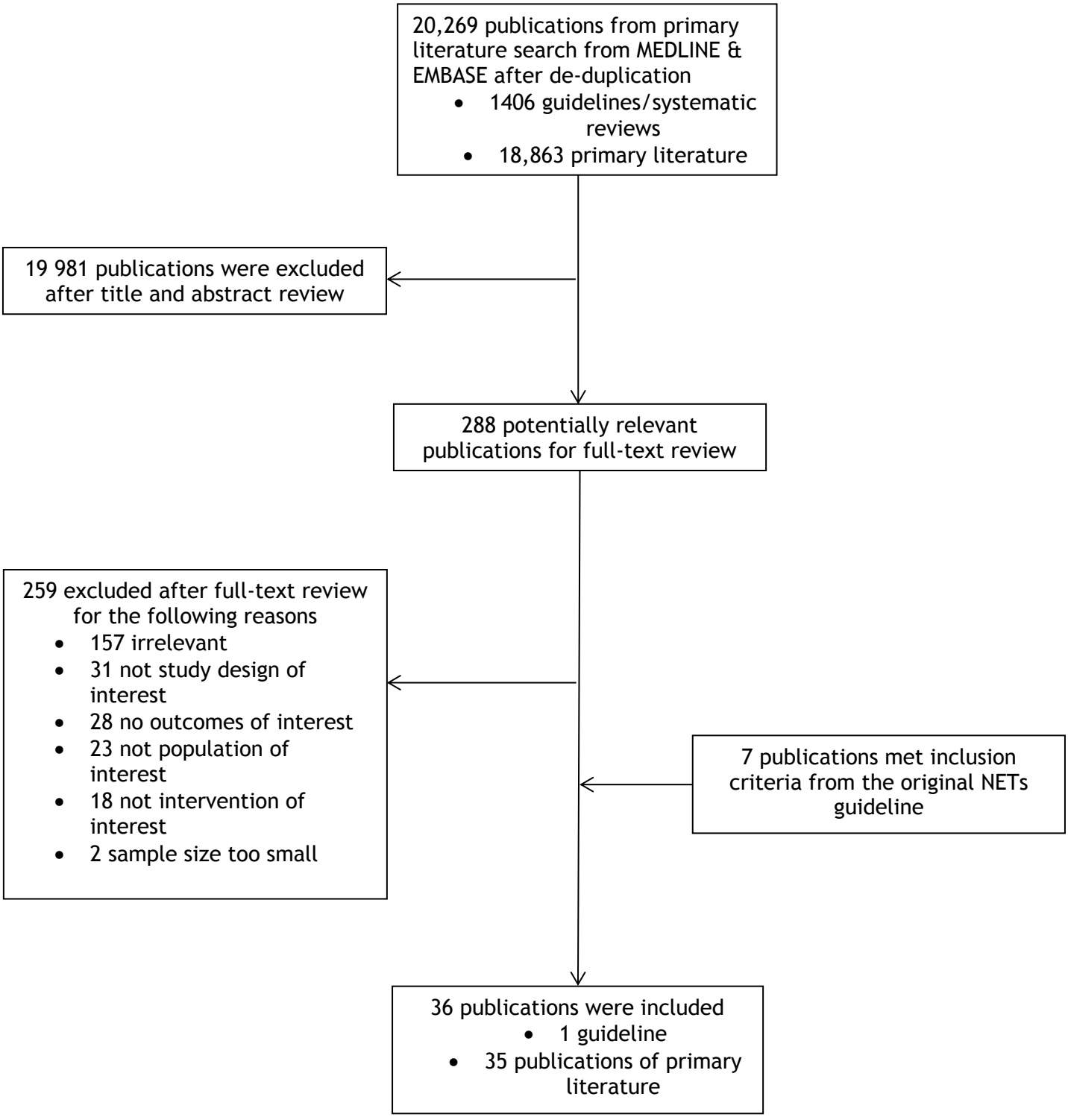
MEDLINE(R) 1946 to Present
1 (systematic adj (review: or overview:)).mp. (310067)
2 (meta-analy: or metaanaly:).mp. (294393)
3 (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp. (17122)
4 (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw. (191745)
5 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab. (346417)
6 (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab. (54159)
7 or/1-6 (616389)
8 (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab. (107480)
9 (stud: adj1 select:).ab. (35101)
10 (8 or 9) and review.pt. (57580)
11 7 or 10 (622671)
12 (guideline or practice guideline).pt. (37485)
13 exp consensus development conference/ (12633)
14 consensus/ (19948)
15 (guideline: or recommend: or consensus or standards).ti. (195554)
16 12 or 13 or 14 or 15 (221149)

17 11 or 16 (827281)
18 (neuroendocrine adj2 (cancer$ or tumo?r$)).mp. (23271)
19 (gastroenteropancreatic adj2 (tumo?r$ or neuroendocrine or NET$1)).mp. (1627)
20 or/18-19 (23449)
21 (("177" adj2 lu$ adj2 octreot$) or 177lu-octreot$ or 177lutetium-octreot$ or lutetium177-octreot$ or lu177-octreot$ or ("177" adj2 lu$ adj2 DOTA$) or 177lu-DOTA$ or 177lutetium-DOTA$ or lu177-DOTA$ or lutetium177-DOTA$ or DOTA, TYR3$).mp. (1266)
22 (("90" adj2 y$ adj2 DOTA$) or ("90" adj2 y$ adj2 octreot$) or (90Y$-octreot$ or 90Y$-DOTA$) or (y$90-octreot$ or y$90-DOTA$) or 90yttrium-DOTA$ or yttrium90-DOTA$).mp. (539)
23 (("212" adj2 pb$ adj2 DOTA$) or ("212" adj2 pb$) or 212pb-DOTA$ or pb212-DOTA$ or 212lead-DOTA$ or lead212-DOTA$).mp. (128)
24 (("225" adj2 ac$ adj2 DOTA$) or ("225" adj2 ac$) or 225ac-DOTA$ or ac225-DOTA$ or 225actinium-DOTA$ or actinium225-DOTA$).mp. (1368)
25 (("213" adj2 bi$ adj2 DOTA$) or ("213" adj2 bi$) or 213bi-DOTA$ or bi213-DOTA$ or 213bismuth-DOTA$ or bismuth213-DOTA$).mp. (576)
26 or/21-25 (3580)
27 20 and 26 (953)
28 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt. (2695184)
29 27 not 28 (918)
30 exp animal/ not human/ (5088377)
31 29 not 30 (894)
32 limit 31 to yr="2008 -Current" (809)
33 (("177" adj2 lu$ adj2 DOTATATE) or 177lu-DOTATATE or lu177-DOTATATE).mp. (748)
34 (("90" adj2 y$ adj2 DOTA$) or 90Y-DOTA$ or y90-DOTA$).mp. (405)
35 (("225" adj2 ac$ adj2 DOTA$) or 225ac-DOTA$ or ac225-DOTA$).mp. (44)
36 (("213" adj2 bi$ adj2 DOTA$) or 213bi-DOTA$ or bi213-DOTA$).mp. (24)
37 33 or 34 or 35 or 36 (1137)
38 20 and 37 (720)
39 38 not 28 (693)
40 39 not 30 (681)
41 limit 40 to english language (660)
42 limit 41 to yr="2008 -Current" (596)
43 32 not 42 (213)

Embase <1974 to Present>
1 (systematic adj (review: or overview:)).mp. (516145)
2 (meta-analy: or metaanaly:).mp. (425899)
3 (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp. (26377)
4 (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw. (341078)
5 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab. (427363)
6 (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.(66776)
7 or/1-6 (868361)
8 (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab. (136301)

9 (stud: adj1 select:).ab. (43203)
10 (8 or 9) and review.pt. (62194)
11 7 or 10 (874365)
12 consensus development conference/ (26599)
13 practice guideline/ (533846)
14 *consensus development/ or *consensus/ (16177)
15 *standard/ (5064)
16 (guideline: or recommend: or consensus or standards).kw. (34699)
17 (guideline: or recommend: or consensus or standards).ti. (249993)
18 or/12-17 (704466)
19 11 or 18 (1515811)
20 (neuroendocrine adj2 (cancer$ or tumo?r$)).mp. (47266)
21 (gastroenteropancreatic adj2 (tumo?r$ or neuroendocrine or NET$1)).mp. (3708)
22 or/20-21 (47480)
23 (("177" adj2 lu$ adj2 octreot$) or 177lu-octreot$ or 177lutetium-octreot$ or lutetium177-octreot$ or lu177-octreot$ or ("177" adj2 lu$ adj2 DOTA$) or 177lu-DOTA$ or 177lutetium-DOTA$ or lu177-DOTA$ or lutetium177-DOTA$ or DOTA, TYR3$).mp. (3018)
24 (("90" adj2 y$ adj2 DOTA$) or ("90" adj2 y$ adj2 octreot$) or (90Y$-octreot$ or 90Y$-DOTA$) or (y$90-octreot$ or y$90-DOTA$) or 90yttrium-DOTA$ or yttrium90-DOTA$).mp. (1136)
25 (("212" adj2 pb$ adj2 DOTA$) or ("212" adj2 pb$) or 212pb-DOTA$ or pb212-DOTA$ or 212lead-DOTA$ or lead212-DOTA$).mp. (513)
26 (("225" adj2 ac$ adj2 DOTA$) or ("225" adj2 ac$) or 225ac-DOTA$ or ac225-DOTA$ or 225actinium-DOTA$ or actinium225-DOTA$).mp. (2728)
27 (("213" adj2 bi$ adj2 DOTA$) or ("213" adj2 bi$) or 213bi-DOTA$ or bi213-DOTA$ or 213bismuth-DOTA$ or bismuth213-DOTA$).mp. (1341)
28 or/23-27 (7708)
29 22 and 28 (2301)
30 exp animal/ not human/ (5236161)
31 29 not 30 (2201)
32 (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/ (3766037)
33 31 not 32 (2104)
34 limit 33 to english language (2058)
35 limit 34 to yr="2008 -Current" (1952)

Appendix 3: PRISMA Flow Diagram



Appendix 4: Risk of Bias Assessments

Table A4-1. Risk of bias for included randomized controlled trials assessed using Cochrane's Risk of Bias tool

	Study	Type of tumour	Comparison	Outcome	SELECTION BIAS		PERFORMANCE BIAS	ATTRITION BIAS	DETECTION BIAS	REPORTING BIAS	OTHER BIAS
					Random sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data	Blinding of outcome assessment	Selective reporting	
Somatostatin analogues	CLARINET Caplin et al (2014)	Pancreatic, midgut	Lanreotide vs. placebo	PFS	Low	Low	Low	Low	Low	Low	Low
				OS	Low	Low	Low	Low	Low	Low	Low
				AE	Low	Low	Low	Low	Low	Low	Low
				QoL	Low	Low	Low	Low	Low	Low	Low
	COOPERATE-2 Kulke et al (2019)	Pancreatic NETs	Everolimus + pasireotide vs. everolimus	PFS	Low	Low	High	Low	High	Low	Low
				OS	Low	Low	High	Low	Low	Low	Low
				AE	Low	Low	High	Low	High	Low	Low
	PROMID Rinke et al (2017)	Midgut NETs	Octreotide vs. placebo	OS	Low	Low	Low	Low	Low	Low	Low
				AE	Low	Low	Low	Low	Low	Low	Low
				QoL	Low	Low	Low	Medium	Low	Low	Low
Targeted therapy	RADIANT-3 Yao JC et al (2016)	Pancreatic NETs	Everolimus vs. placebo	PFS	Low	Low	Low	Low	Low	Low	Low
				OS	Low	Low	Low	Low	Low	Low	Low
				AE	Low	Low	Low	Low	Low	Low	Low
				QoL	Low	Low	Low	Low	Low	Low	Low
	RADIANT-4 Singh et al (2018)	NETs	Everolimus vs. placebo	PFS	Low	Low	Low	Low	Low	Low	Low
				OS	Low	Low	Low	Low	Low	Low	Low
				AE	Low	Low	Low	Low	Low	Low	Low
				QoL	Low	Low	Low	Low	Low	Low	Low
	CALGB 80701 Kulke et al (2022)	Pancreatic NETs	Everolimus + bevacizumab vs. everolimus	PFS	Low	Low	High	Low	High	Low	Low
				OS	Low	Low	High	Low	Low	Low	Low
				AE	Low	Low	High	Low	High	Low	Low
				QoL	Low	Low	High	Low	High	Low	Low
	Faivre et al (2017)	Pancreatic NETs	Sunitinib vs. placebo	PFS	Low	Low	Low	Low	Low	Low	Low
				OS	Low	Low	Low	Low	Low	Low	Low
				AE	Low	Low	Low	Low	Low	Low	Low
				QoL	Low	Low	Low	Low	Low	Low	Low
	Xu et al (2020)	Pancreatic NETs	Surufatinib vs. placebo	PFS	Low	Low	Low	Low	Low	Low	Low
				OS	Low	Low	High	Low	Low	Low	Low
				AE	Low	Low	Low	Low-Medium	Low	Low	Low
				QoL	Low	Low	Low	Low-Medium	Low	Low	Low
Chemotherapy	ECOG ACRIN Kunz et al (2023)	Pancreatic NETs	Temozolomide vs. capecitabine + temozolomide	PFS	Low	Low	High	Low	High	Low	Low
				OS	Low	Low	High	Low	Low	Low	Low
				AE	Low	Low	High	Low	High	Low	Low
	STEM Chi et al (2022)	NETs	S-1 + temozolomide + thalidomide vs. S-1 + temozolomide	PFS	Low	Low	High	Low	High	Low	Low
				OS	Low	Low	High	Low	Low	Low	Low
				AE	Low	Low	High	Low	High	Low	Low

PRRT	NETTER-1 Strosberg et al (2017)	Midgut NETs	^{177}Lu-DOTATATE + octreotide LAR vs. octreotide LAR	PFS	Low	Low	High	Low	High	Low	Low
				OS	Low	Low	High	Low	Low	Low	Low
				AE	Low	Low	High	Low-Medium	High	Low	Low
				QoL	Low	Low	High	Low-Medium	High	Low	Low

Abbreviations: AE, adverse events; LAR, long acting release; NET, neuroendocrine tumours; OS, overall survival; PFS, progression-free survival; PRRT, peptide receptor radionuclide therapy; QoL, quality of life

Table A4-2. Risk of bias for included non-randomized studies assessed using Cochrane's ROBIN-I

	Study	Type of tumour	Comparison	Outcome	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall
Chemotherapy	De Mestier et al (2019)	NETs	Capecitabine + temozolomide vs. 5-FU + dacarbazine	PFS	Moderate	Low	Low	Low	Low	Low	Low	Moderate
				OS	Moderate	Low	Low	Low	Low	Low	Low	Moderate
				AE	Moderate	Low	Low	Low	Low	Low	Low	Moderate

Abbreviations: AE, adverse events; FU, fluorouracil; NET, neuroendocrine tumours; OS, overall survival; PFS, progression-free survival; ROBIN-I, Risk Of Bias In Non-randomized Studies - of Interventions

Appendix 5: Studies consisting of patients with neuroendocrine tumours of various origins

The RCTs summarized below do not provide subgroup specific data for patients with pancreatic or midgut NETs.

Table A5-1. Trials Reporting on the Use of Somatostatin Analogues in Patients with Neuroendocrine Tumours of Various Origins

Author, year	Study inclusion criteria	Treatment	Number of patients evaluated	Median follow-up	Median PFS	Median OS	Primary tumour site
LANREOTIDE							
Randomized controlled trial							
PRODIGE 31 REMINET Lepage et al (2022) [48]	Patients with advanced, non-resectable duodeno-pancreatic NETs who have been treated with at least 3 mths of chemotherapy or 6 mths of targeted therapy according to guidelines	Lanreotide autogel 120mg vs. Placebo	27 25	27 mths (95% CI, 19.5-31.2)	19.4 mths (95% CI, 7.6-32.6) 7.6 mths (95% CI, 3.0-9.0)	NR 41.9 mths	NR
PASIREOTIDE VS. OCTREOTIDE							
Randomized controlled trial							
Wolin et al (2015) [54]	Adults with carcinoid tumours of the digestive tract with confirmed metastatic tumour and one evaluable lesion, inadequately controlled diarrhea and/or flushing while receiving maximum approved doses of the currently available SSA for 3 mths prior to study entry, Karnofsky PS ≥60	Pasireotide LAR 60mg every 28 days vs. Octreotide LAR 10 mg every 28 days	53 57	NR	11.8mths (95% CI, 11.0-not reached) 6.8mths (95% CI, 5.6-not reached) HR, 0.46; 95% CI, 0.20-0.98; p=0.045	NA	Small intestine, 76.4% Colon, 3.6% Liver, 2.7% Pancreas, 1.8% Lung, 0.9% Stomach, 0.9% Other, 13.6%

Abbreviations: CI, confidence interval; HR, hazard ratio; LAR, long acting release; mth, month; NETs, neuroendocrine tumours; NA; not assessed; NR, not reported; OS, overall survival; PFS, progression-free survival; PS, performance status; RCT, randomized controlled trial; SSA, somatostatin analogue; vs., versus

Table A5-2. Trials Reporting on the Use of Targeted Therapy in Patients with Neuroendocrine Tumours of Various Origins

Author, year	Inclusion Criteria	Treatment	Number of patients evaluated	Median follow-up (range)	Median PFS	Median OS	Primary tumour site
OCTREOTIDE ± EVEROLIMUS							
Randomized controlled trial							
RADIANT-2 Pavel ME (2011) [50]	Adults with advanced, well or moderately differentiated NETs and a history of symptoms attributed to carcinoid syndrome and progression within 12 mths	Octreotide LAR 30mg every 28 days + everolimus 10mg once daily vs. Octreotide LAR 30 mg every 28 days + Placebo once daily	216 213	28 mths	16.4 mths (95% CI, 13.7-21.2) 11.3mths (95% CI, 8.4-14.6) HR, 0.77; 95% CI, 0.59-1.00, p=0.026	29.2 mths (95% CI, 23.8-35.9) 35.2 mths (95% CI, 30.0-44.7) HR, 1.16; 95% CI, 0.91-1.49	Small intestine, 52.2% Lung, 10.3% Colon, 6.5% Pancreas, 6.1% Liver, 4.2% Other, 20.5% Missing, 0.2%
OCTREOTIDE ± AXITINIB							
Randomized controlled trial							
AXINET Garcia-Carbonero et al (2021) [51] *Abstract*	Patients with advanced G1-2 extra-pancreatic NETs. Prior therapy with SSA, IFN and up to 2 lines of systemic treatment was allowed, but not prior VEGF- or VEGFR-targeted drugs	Octreotide LAR 30 mg every 4 weeks + axitinib 5mg twice daily vs. Octreotide LAR 30 mg every 4 weeks + placebo twice daily	126 130	NR	16.6 mths 9.9 mths HR, 0.687; 95% CI, NR; p=0.01	NR	Small intestine, 47% Lung, 28% Rectum, 6% Unknown, 8% Gastric, 3% Colon, 2%
PAZOPANIB							
Randomized controlled trial (phase II)							
ALLIANCE A021202	Adults with progressive low-intermediate grade carcinoid tumours	Pazopanib (800 mg/day) VS	97	31 mths	11.6 mths	41 mths	NR

Author, year	Inclusion Criteria	Treatment	Number of patients evaluated	Median follow-up (range)	Median PFS	Median OS	Primary tumour site
Bergsland et al (2019) [55] *Abstract*		Placebo	74		8.5 mths HR, 0.53; p=0.0005	42 mths HR, 1.13; p=0.70	

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal; HR, hazard ratio; IFN, interferon; LAR, long acting release; mth, month; NETs, neuroendocrine tumours; NR, not reported; OS, overall survival; PFS, progression-free survival; PS, performance status; SSA, somatostatin analogues; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; vs., versus; wk, week

Table A5-3: Trials Reporting on the Use of Chemotherapy in Patients with Neuroendocrine Tumours of Various Origins

Author, year	Inclusion Criteria	Treatment	Number of patients evaluated	Median follow-up (range)	Median PFS	Median OS	Primary tumour site
CAPECITABINE AND STREPTOZOCIN ± CISPLATIN							
Randomized Controlled Trial							
NET01 Meyer et al (2014) [53]	Adults with advanced, unresectable NETs of pancreatic, GI foregut or unknown primary site	Three-weekly capecitabine 625 mg/m^2 twice daily orally + streptozocin 1.0 g/m^2 intravenously on day 1, with cisplatin 70 mg/m^2 intravenously on day 1. vs. Three-weekly capecitabine 625 mg/m^2 twice daily orally + streptozocin 1.0 g/m^2 intravenously on day 1	42 44	NR	9.7 mths 10.2 mths	27.5 mths 26.7 mths	Pancreatic, 47.7% Gastroduodenal, 19.8%

Abbreviations: CI, confidence interval; GI, gastrointestinal; mths, months; NETs, neuroendocrine tumours; NR, not reported; OS, overall survival; PFS, progression-free survival; vs., versus

Appendix 6: Guideline Document History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original 2016	2008-2016	Full Report	Peer review publication. Web publication.	Not applicable
Version 2 2024	2016-2024	New data added to original Full Report	Updated web publication.	Includes peptide receptor radionuclide therapy