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Maintenance therapy after first-line platinum-based chemotherapy in gastroenteropancreatic neuroendocrine carcinomas: A literature review

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ABSTRACT

Neuroendocrine carcinomas are rare and aggressive malignancies, often diagnosed at advanced stages, leading to poor prognosis. Platinum-based chemotherapy is the standard first-line treatment for advanced neuroendocrine carcinomas; however after achieving response no consensus exists on maintenance therapies and the results are inconsistent. This review examines the role of maintenance therapy following response to first-line chemotherapy in gastroenteropancreatic neuroendocrine carcinomas. We identified limited supporting evidence, primarily from phase II trials and case reports, that suggested maintenance therapy could be considered for prolonging progression-free survival, balancing toxicity, and maintaining quality of life. Nevertheless, prospective studies are needed to validate its clinical efficacy.

Introduction

Neuroendocrine carcinomas (NECs) are a rare and diverse group of neuroendocrine neoplasms characterized by poor differentiation, aggressive nature, and propensity for early and widespread metastasis [1]. Based on morphology, NECs are classified into small-cell and large-cell types. Additionally, they can be categorized by their primary site, either as pulmonary NECs or extrapulmonary NECs (EP-NECs) [1–3]. EP-NECs account for 8.7% of all NEC cases [4]. Among EP-NECs, gastroenteropancreatic (GEP) NECs are the most prevalent, comprising 37% of cases, with 64% originating in the colon, rectum, or anus, and 23% in the pancreas [5].

At diagnosis, up to 85% of GEP-NEC patients present an advanced-stage disease, for which systemic chemotherapy (ChT) is the current standard of care [6]. Treatment strategies in GEP-NECs are largely based on the management of small-cell lung cancer (SCLC) due to their similar histology and clinical behavior [7]. The first-line treatment for advanced GEP-NEC patients is based on the combination of etoposide and platinum (EP) or irinotecan and platinum (IP) for four to six cycles [8,9]. Retrospective studies have shown response rates to platinum-based ChT between 31–67%, with most initial responders experiencing progression within 4 to 6 months and a median survival of 11–12 months [10–12]. Approximately 30% of patients, primarily those with colorectal NEC, show no response to ChT [10,12]. Despite ongoing efforts to improve outcomes through immunotherapy and targeted therapies, no second-line treatment has emerged, and overall benefits remain limited [13].

For NEC patients who respond to first-line ChT, there is significant uncertainty regarding the optimal treatment strategy. Oncologists must decide whether to continue with maintenance therapy (MT), first line ChT or observation. MT is a treatment strategy that aims to prolong the benefits of initial response to ChT by delaying disease progression in cases where a curative treatment is not possible [14]. MT can be delivered either by continuing with one or all components of first-line regimens (continuous MT) or by introducing a new non-cross-resistant agent in an alternating or sequential fashion to prevent progression (switch MT or sequential therapy), while minimizing toxicity[15,16]. By delaying the need for second-line ChT, MT seeks to maintain quality of life without compromising survival. Fig. 1 illustrates the differences between traditional ChT schemas and a conceptual scheme for MT in metastatic GEP-NEC.

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Given the limited benefits of second-line treatments in GEP-NECs, there is a growing need to explore the evidence supporting continued therapy after an initial positive response to first-line ChT. While MT is a well-established strategy in ovarian, lung, and colorectal cancers, its application in GEP-NECs remains relatively unexplored [15–18]. This literature review aims to evaluate the existing evidence on MT in GEP-NECs, focusing on its potential impact on patient outcomes and current standards of care.

Methods

Search strategy

We conducted a comprehensive literature review by searching PubMed for prospective and retrospective studies, case reports, and review articles published from July 2017 to November 2024, the period following the release of the updated WHO pathology classification of poorly differentiated NECs. The search aimed to identify studies investigating the role of MT following first-line platinum-based ChT in GEP-NECs. We used the following search terms: "neuroendocrine carcinoma", "chemotherapy", and "maintenance therapy".

Selection criteria

We applied the PICO criteria to define the eligibility criteria: (1) Population: patients diagnosed with advanced GEP-NECs; (2) Intervention: MT following first-line platinum-based ChT regimens; (3) Comparison: no MT or other MT; (4) Outcome: Overall survival (OS), progression-free survival (PFS), and quality of life. Studies including patients with neuroendocrine tumors G3 were excluded.

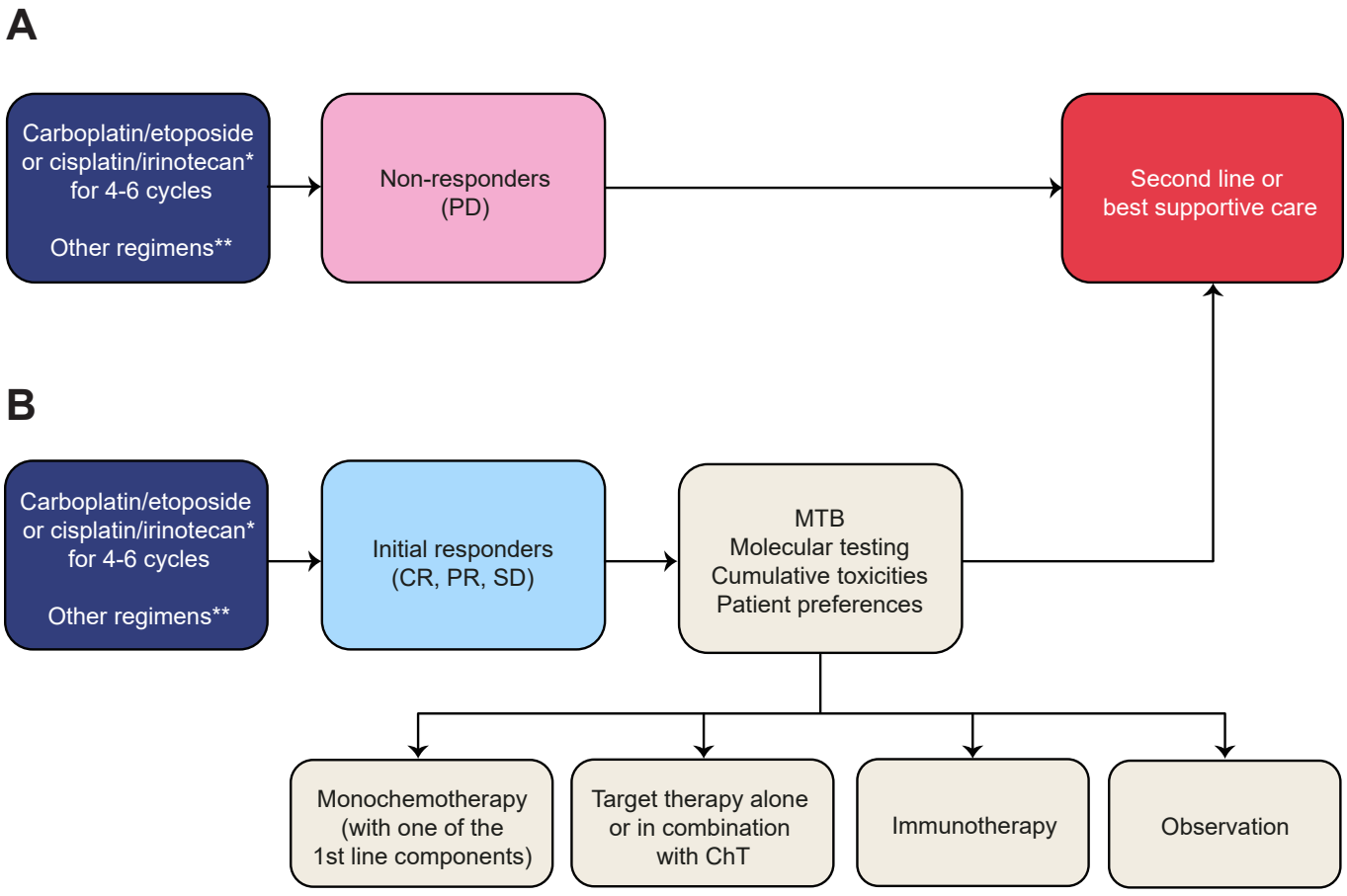
Study selection

The initial search yielded 32 results. Additionally, we identified one case report and three phase II trials through a supplementary manual search. From 36 records, 10 met the inclusion criteria on relevance to our research question. The study selection process is represented in a flowchart adapted from PRISMA (Preferred reporting Items for Systematic Reviews and Meta-analyses) guidelines (Fig. 2). We searched additional references from selected articles and clinical practice guidelines from the European Society for Medical Oncology (ESMO), European Neuroendocrine Tumor Society (ENETS) and The North American Neuroendocrine Tumor Society (NANETS). A detailed description of the search query is provided in the Supplementary Appendix.

Results

Maintenance therapy (MT) in GEP-NECs beyond first-line treatment. A concise overview of key evidence

The studies selected for this review explored various strategies, including simplified ChT regimens, immunotherapy, and targeted therapies. The results, summarized in Table 1, highlight both the potential benefits and the limitations of MT in prolonging PFS and OS.



Abbreviations: GEP-NEC (gastroenteropancreatic neuroendocrine carcinoma); MTB (multidisciplinary tumor board); PD (progression disease); CR (complete response); PR (partial response); SD (stable disease); ChT (chemotherapy); * Alternative option; **According to MTB discussion

Fig. 1. The flowchart illustrates the selection process for the literature review.

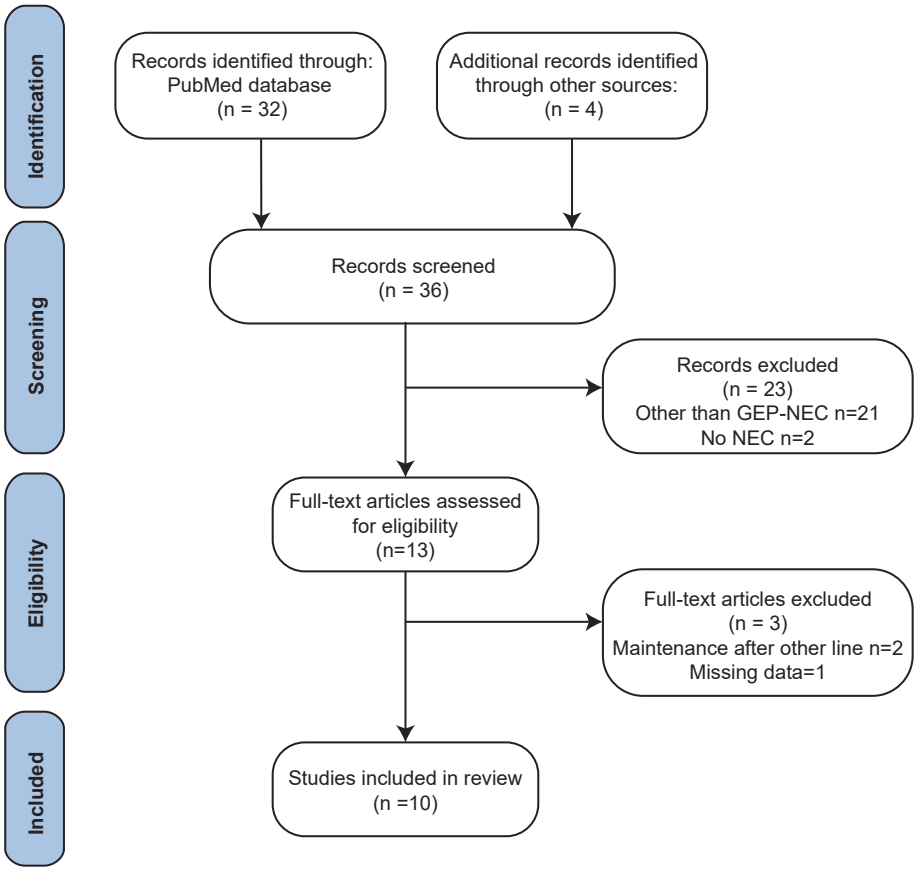


Fig. 2. Current management of advanced gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC) after first-line chemotherapy in non-responders, compared to a conceptual scheme for the maintenance strategy in patients who are initial responders. (A) Current management of advanced GEP-NEC after first-line chemotherapy in non-responders: According to ENETS guidelines, first-line treatment for advanced GEP-NEC consists of 4 to 6 cycles of chemotherapy with carboplatin plus etoposide, with cisplatin plus irinotecan as an alternative option. Other regimens should be discussed in a multidisciplinary tumor board (MTB). Upon disease progression, second-line treatment or best supportive care are recommended. (B) Conceptual scheme for the maintenance strategy in patients who are initial responders: For patients who achieve an initial response (complete response [CR], partial response [PR], or stable disease [SD]) to first-line treatment, a maintenance strategy should be determined on a case-by-case basis by the MTB. Treatment decisions should incorporate molecular testing, cumulative toxicities and patient preferences. Maintenance options may include monochemotherapy, target therapy (alone or in combination with chemotherapy), immunotherapy or observation.

Chemotherapy as MT

The use of ChT as MT in managing GEP-NECs remains a subject of ongoing research, with treatment strategies often extrapolated from extensive-stage SCLC [19]. In SCLC, MT has shown inconsistent results, with some studies suggesting a survival advantage for MT with ChT and interferon-alpha, although further studies are needed to confirm its clinical impact [15]. MT with thoracic radiotherapy and prophylactic cranial irradiation has also been considered for initial responders in SCLC patients [19]. In addition, limited evidence suggests that etoposide capsules as MT significantly prolong the PFS in patients with extensive SCLC who responded to etoposide plus platinum (EP) [20,21]. However, we found no robust evidence supporting the use of MT for SCLC in the context of GEP-NECs.

Most MT strategies aim to simplify the first-line multiagent ChT regimens. In GEP-NECs, combinations such as EP or irinotecan plus platinum (IP) can be reduced to a single-agent therapy like irinotecan or platinum alone. This reduction helps eliminate cumulative toxicity while potentially delaying therapeutic resistance. Such strategies allow for additional treatment options to be preserved for later lines of therapy. However, the evidence supporting this approach is limited, primarily consisting of a phase II trial and a case report.

Irinotecan, which is associated with less hematological toxicity than cisplatin in first-line regimens, was investigated in a phase II trial involving 66 patients with advanced, recurrent or metastatic GEP-NECs [22]. This study compared EP and IP regimens, each administered for six cycles or until disease progression or unacceptable toxicity. Between 33% and 48.5% of patients completed six cycles with the EP and IP treatment, respectively. Among those treated with IP, 68.75% of responders received irinotecan as MT, with a median maintenance duration of 2.8 months (range 0.7-6.3 months). Although no significant differences in response rates (42.4% in both arms), OS (11.3 months vs 10.2 months), or PFS (6.4 months vs 5.8 months) were observed between the EP and IP arms, there was a trend toward improved objective response rate in patients with large cell morphology (30% vs 14.3%). Furthermore, IP was less toxic in terms of grade 3/4 neutropenia compared to EP (12.1% vs 45.4%). This study suggests that irinotecan may offer a potential role in MT for patients with large-cell GEP-NECs, particularly given its reduced hematological toxicity. However, further randomized trials, including assessments of quality of life and biomarkers, are necessary to identify the subgroup of patients who would benefit the most.

Carboplatin monotherapy has been explored in a limited context. Elm'hadi et al. [23] reported a case of a 49-year-old woman diagnosed with an advanced small cell NEC of the gallbladder, which metastasized to the liver and exhibited a Ki-67 level of 90%. After achieving a partial response (PR) to carboplatin and etoposide (two cycles), the patient continued carboplatin monotherapy based on a decision by the multidisciplinary team. She tolerated the therapy well and maintained disease

Table 1
Summary of literature review on the role of maintenance therapy after first line chemotherapy in metastatic gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC).

Authors	Study Design	Number of GEP-NEC Patients	Primary Site (%)	Morphology (%)	First-line Treatment	Maintenance Therapy	Response Type	Main toxicity (%)	Median PFS (months)	Median OS (months)
Elm'hadi et al. [23]	Case report	1	Gallbladder	Small cell	Carboplatin and etoposide (2 cycles)	Carboplatin monotherapy (11 cycles)	PR	Thrombocytopenia G3	16	18
Zhang et al. [22]	Phase II	EP arm: 33, IP arm: 33	Pancreas (6.1% vs 15.2%), oesophagus (30.3% vs 9.1%, stomach (27.3% vs 33.3%), duodenum (3% vs 9.1%), small intestine (3% vs 6.1%), colorectum (15.2% vs 18.2%), unknown primary (15.2% vs 9.1%)	Small cell (57.6% vs 39.4%), large cell (27.3% vs 48.5%) MiNEC (9.1% vs 6.1%) uncertain (6.1% vs 6.1%)	EP (6 cycles) vs IP (6 cycles)	Irinotecan plus cisplatin: Irinotecan maintenance	Both arms ORR: 42.4%; large cell NEC ORR: 30% vs 14.3%	Hematological G3: EP vs with IP arm (45.4% vs 12.1%; P=0.002). Non-hematological G1-2: EP vs IP arm (18.2% vs 54.5%)	EP: 6.4 vs IP: 5.8	EP: 11.3 vs IP: 10.2
Alfieris et al. (2020)	Phase II	19	Small intestine (31.6%), cecum (21.1%), appendix (31.6%), colon (15.7%)	NR	Capecitabine, oxaliplatin, irinotecan and bevacizumab (6 cycles)	Pazopanib plus capecitabine	ORR: 47.4% (3 CR, 6 PR)	Leukopenia G3 (15.8%), neutropenia G3 (15.8%), diarrhea G3 (15.8%), hand foot G3 (15.8%)	Responders (CR+PR): 18 vs non-responders (SD+PD): 5	Responders: 30.5 versus SD/PD: 14
Kang et al. [26]	Case report	1	Pancreas	Small cell	Irinotecan plus nivolumab (8 cycles)	Nivolumab (30 months)	CR	Hepatitis G2	NR	48
Levy et al. [31]	Phase II	25	Colorectum (28.1%), pancreas (15.4%), oesophagus (10.3%), stomach (7.7%), appendix (1%)	NR	Cisplatin plus everolimus (up to 6 cycles)	Everolimus	ORR: 58.9% (CR: 2.6%, PR: 56.4%, SD: 23.1%)	Hematological G3-4 (36%) and renal G3-4 (21%)	6	8.7
Keane et al. [36]	Case report	1	Pancreas	NR	EP (6 cycles) plus atezolizumab (added after 3 cycles)	Olaparib (17 months)	CR	Fatigue and peripheral neuropathy	17	26
Antonuzzo et al. [34]	Phase II	15	Pancreas (35%), other (17%)	NR	Platinum-based (38%), non platinum-based (62%)	Everolimus vs observation	SD: 65% vs 33%, PR: 35% vs 67%	Mucositis/ stomatitis G3 (27.7%), neutropenia (27.7%)	11.8 vs 1.8	38.3 vs 38.2
M.C. Riesco Martinez et al. [25]	Phase II	25	Oesophagus (8%), gastric (20%), pancreas (36%), colon (12%), rectum (8%), unknown primary (16%)	NR	Nivolumab plus carboplatin and etoposide (up to 6 cycles)	Nivolumab (up to 24 months), PD, death or unacceptable toxicity	PR: 60%	Neutropenia G3 (39.5%), febrile neutropenia (10.5%), anemia (7.9%), fatigue (7.9%) and thrombocytopenia (5.2%)	5.7	13.9
Lie et al. (2024)	Case report	1	Gallbladder	NR	Tislelizumab plus EP (8 cycles)	Tislelizumab	CR	None	NR	10

(continued on next page)

Table 1 (*continued*)

Authors	Study Design	Number of GEP-NEC Patients	Primary Site (%)	Morphology (%)	First-line Treatment	Maintenance Therapy	Response Type	Main toxicity (%)	Median PFS (months)	Median OS (months)
McKinley et al. [35]	Case report	1	Pancreas	Large cell	Carboplatin and etoposide (4 cycles)	Selpercatininb (2 months)	PD	Diarrhea G1, hepatitis G1	NR	NR

Abreviatures: GEP (gastroenteropancreatic); NEC (neuroendocrine carcinoma);EPNEC (extrapulmonary neuroendocrine carcinoma); EP (etoposide plus cisplatin); IP (irinotecan plus cisplatin); EPNEC (extrapulmonary neuroendocrine carcinoma); CR (complete response); PR (partial response); SD (stable disease); G3 (grade 3); PFS (progression free survival); OS (overall survival); ORR (objective response rate).

stability through 11 cycles, until the appearance of thrombocytopenia. Five months later, she experienced disease progression, and she received irinotecan as a second-line treatment. She died 18 months after initiation of medical treatment due to hepatocellular insufficiency. Despite the limited evidence, this case emphasizes the importance of individualized decision-making, guided by multidisciplinary tumor boards.

Overall, evidence on ChT MT in GEP-NECs after response to first line treatment is very limited. However, it suggests manageable toxicities and a potential benefit according to the histology. Further prospectives studies, including assessment of efficacy and patient-reported toxicity, are needed.

Chemotherapy and immunotherapy as MT

In GEP-NECs, immunotherapy has emerged as a potential MT option, particularly immune checkpoint inhibitors (ICIs), which are being tested in combination with ChT in the first-line setting. Preclinical studies have revealed a high tumor mutational burden (TMB) and high expression of programmed death receptor-1 ligand (PD-L1) in NECs, suggesting potential immunogenicity and responsiveness to ICIs [24]. Although the evidence supporting ICIs as MT following first-line ChT plus ICIs is limited, it remains promising, based on a phase II and two case reports. Nivolumab (human IgG4 monoclonal antibody against PD-1) and tislelizumab (an anti-human monoclonal antibody against PD-1) have been explored in this context [25–27].

The NICE-NEC phase II trial involved 25 patients with metastatic or locally advanced unresectable GEP-NEC. Patients received nivolumab along with up to six cycles of platinum-based ChT, followed by nivolumab as MT for up to 24 months. The median OS and PFS was 13.9 months and 5.7 months, respectively [25]. Although the response rates and OS seem to be higher than with standard first-line ChT, further comparative studies and toxicity and quality-of-life assessments are needed. An ongoing trial is investigating a combination of ChT and ICIs, followed by camrelizumab as MT in GEP-NECs [28].

Case reports offer additional insights into ICI use as MT. Kang et al. presented a case of a 59-year-old male patient with small cell NEC and a Ki-67 index of 60%. Following pancreatectomy and six cycles of adjuvant ChT with EP, the disease progressed within three months. After next-generation sequencing (NGS) revealed a TMB of 18.9 mutations/Mb and microsatellite stability, the patient was treated with irinotecan and nivolumab, followed by nivolumab as MT. This resulted in a durable disease-free status for two and a half years, with treatment halted due to grade 2 hepatitis. The patient remained disease-free at four years follow-up [26]. Another case reported a 52-year-old woman with advanced gallbladder-NEC and liver metastasis, who achieved a complete response after eight cycles of tislelizumab plus EP ChT, followed by MT with tislelizumab. She remained in CR for over 10 months with no major side effects [27].

Although limited, these cases suggest that combining ChT with ICI-based MT can result in durable responses with low toxicity. Additionally, biomarkers like TMB may help identify GEP-NEC patients who are likely to benefit from ICI treatments.

Chemotherapy +/- targeted therapies as MT

Up to 66 % of metastatic GEP-NEC cases display potentially targetable mutations, such as in the case of colorectal NEC, where 49% of patients have *BRAF V600E* mutation [24]. Although the *BRAF/MEK* inhibitor combination (dabrafenib plus trametinib) is typically used after first-line progression [29], other less common mutations (*KRAS G12C*, *RET*, *HRAS*, and *NTRK* fusions) could potentially be targeted with therapies. However, the use of targeted therapies as MT in GEP-NEC remains under-investigated.

Tyrosine kinase inhibitors (TKIs), which target multiple pathways involved in tumor growth and angiogenesis, have shown promise in MT settings. For instance, a phase II study investigated the combination of pazopanib (a multi-targeted receptor TKI) and capecitabine (oral fluoropiridimidine) as MT in 19 patients with high-grade poorly differentiated GEP-NECs. Patients who had responded or achieved stable disease (SD) after six cycles of capecitabine (CP), oxaliplatin, irinotecan, and bevacizumab (CAPOXIRI-BEV) received MT with pazopanib and CP. The objective response rate (ORR) was 47.4% (3 complete responses and 6 partial responses). The median PFS was 13 months, and the median OS was 29 months. Responders had significantly better OS (30.5 months) compared to those with SD or disease progression (14 months) [30]. This suggests that pazopanib-based MT may provide additional benefits for patients who respond well to initial ChT, but biomarkers are needed to predict treatment response.

Two phase II studies explored the use of everolimus as MT after first-line ChT. The first study investigated the combination of everolimus and cisplatin as MT. This study included 39 patients with advanced EP-NEC, 64% of whom had GEP-NECs. The response rate was 58.9% with three patients (8%) achieving durable responses beyond 12 months. The median PFS was 6 months, the median OS was 8.7 months, and the most common grade 3/4 toxicities were hematological and renal [31]. Given its synergistic antitumor activity with cisplatin, everolimus could be a viable MT option, offering similar efficacy to traditional cytotoxic regimens while potentially improving quality of life due to the absence of alopecia and other side effects [32,33]. The second study assessed the efficacy and safety of everolimus alone as MT in metastatic GEP-NEC. The MAVERIC study, was a randomized phase II trial presented as poster at the ESMO Congress 2023, included 30 patients (20 were randomized to everolimus and 10 to observation). Fifty-two percent of patients had a diagnosis of GEP-NEC, mainly represented by pancreas origin, and 48% had large cellNEC. The median PFS was 11.8 months with everolimus and 1.8 in the control arm. Median OS was 38.3 and 38.2 months for the experimental and control arms, respectively. In the experimental arm, grade 3 adverse events occurred in 55% of patients, most commonly mucositis/stomatitis (27.7%) and neutropenia (27.7%). This study suggests a potential role for everolimus as a MT following first-line ChT in selected patients with metastatic GEP-NEC. However, homogeneous prospective studies are warranted to validate this hypothesis [34].

McKinley et al. (2024) reported a case of a patient diagnosed with advanced large-cell pancreatic NEC. NGS of the tumor and blood showed a *RET* gene fusion. He was initially treated with four cycles of carboplatin and etoposide. Following this induction therapy, selpercatinib was administered as MT. However, after two months, a computed tomography scan revealed disease progression. Mild adverse events, including grade 1 hepatitis and diarrhea, were observed during

treatment [35]. This case highlights the need for further research to better identify patients who could benefit from targeted therapies as part of their treatment strategies.

Lastly, olaparib, a PARP inhibitor, was used as MT in a male patient with advanced pancreatic NEC. Genomic analysis demonstrated a germline pathogenic variant in *BRCA2* with somatic loss-of-heterozygosity of the *BRCA2* wild-type allele. After responding well to platinum-based ChT and atezolizumab, the patient received MT with olaparib, achieving systemic control for 17 months before developing brain metastases. He received post-operative stereotactic radiation twice [36]. Although the patient eventually succumbed 26 months after the initial diagnosis, this case highlights the potential of precision therapies, such as Olaparib, in specific genetic subtypes of GEP-NEC. It also supports the consideration of comprehensive genomic profiling in the management of patients with rare tumor types. Additionally, it underscores the importance of considering treatment paradigms from other malignancies with shared genomic features when randomized data is scarce in rare tumors.

Targeted therapies demonstrate durable responses post-initial treatment, emphasizing the importance of early molecular profiling for informed decision-making. Further investigation of predictive biomarkers is crucial to optimize patient selection and treatment outcomes in this setting.

Conclusions

The current guidelines do not offer a standard approach to maintenance treatment for patients who respond to first-line chemotherapy. Our literature review did not uncover robust evidence supporting the use of MT following response to first-line platinum-based ChT in advanced GEP-NECs. While we identified promising case studies showcasing MT strategies, several limitations were noted. First, we did not search other databases, potentially underestimating the number of relevant articles. Second, most available evidence largely comes from case reports or phase II studies, which do not provide a comprehensive understanding of MT efficacy. Third, due to the rarity of GEP-NECs, many studies involve highly heterogeneous populations, limiting the generalizability of the findings. Given these limitations, the role of MT in advanced GEP-NECs after response to first-line treatment remains to be elucidated. To better address the needs of this underrepresented population, further prospective studies are essential. Until then, we recommend a case-by-case approach to treatment decision-making, ideally involving a multidisciplinary tumor board, to consider cumulative toxicities, quality of life, patient preferences, and molecular testing results.

CRediT authorship contribution statement

Natalia Soledad Tissera: Conceptualization, Data curation, Formal analysis, Methodology, Investigation, Resources, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Francesca Balconi:** Conceptualization, Data curation, Formal analysis, Methodology, Investigation, Resources, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Alejandro García-Álvarez:** Conceptualization, Writing – review & editing. **Jorge Hernando Cubero:** Conceptualization, Writing – review & editing. **Juan Manuel Óconnor:** Conceptualization, Writing – review & editing. **Matías Chacón:** Conceptualization, Writing – review & editing. **Jaume Capdevila:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Natalia Soledad Tissera** reports a grant from Fundació Catalunya La Pedrera—VHIO MD-PhD fellowship. **Alejandro Garcia-Álvarez** declares the following potential conflicts of interest: Speakers' Bureau: EISAI Europe, Lilly; Travel, Accommodations, Expenses: Advanz, EISAI, Ipsen, ADACAP (Novartis), Amgen, Pfizer, Lilly. **Jaume Capdevila** declares scientific consultancy role (speaker and advisory roles) from Novartis, Pfizer, Ipsen, Exelixis, Bayer, Eisai, Advanced Accelerator Applications, Amgen, Sanofi, Lilly, Hudchmed, ITM, Merck Serono, Roche, Esteve, Advanz; research grants from Novartis, Pfizer, Astrazeneca, Advanced Accelerator Applications, Eisai, Amgen, ITM, Roche, Gilead and Bayer. All other authors have declared no conflicts of interest.

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Appendix A. Supplementary data

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References

[1] Garcia-Carbonero R, Capdevila J, Crespo-Herrero G, Díaz-Pérez JA, Martínez Del Prado MP, Alonso Orduña V, et al. Incidence, patterns of care and prognostic factors for outcome of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): results from the National Cancer Registry of Spain (RGETNE). Ann Oncol Off J Eur Soc Med Oncol 2010 Sep;21(9):1794–803.
[2] Niederle MB, Hackl M, Kaserer K, Niederle B. Gastroenteropancreatic neuroendocrine tumours: the current incidence and staging based on the WHO and European Neuroendocrine Tumour Society classification: an analysis based on prospectively collected parameters. Endocr Relat Cancer 2010 Dec;17(4):909–18.
[3] Kaltsas GA, Besser GM, Grossman AB. The diagnosis and medical management of advanced neuroendocrine tumors. Endocr Rev 2004 Jun;25(3):458–511.
[4] Dasari A, Mehta K, Byers LA, Sorbye H, Yao JC. Comparative study of lung and extrapulmonary poorly differentiated neuroendocrine carcinomas: A SEER database analysis of 162,983 cases. Cancer 2018 Feb 15;124(4):807–15.
[5] Dasari A, Shen C, Devabhaktuni A, Nighot R, Sorbye H. Survival According to Primary Tumor Location, Stage, and Treatment Patterns in Locoregional Gastroenteropancreatic High-grade Neuroendocrine Carcinomas. Oncologist 2022 Apr 5;27(4):299–306.
[6] Heetfeld M, Chougnet CN, Olsen IH, Rinke A, Borbath I, Crespo G, et al. Characteristics and treatment of patients with G3 gastroenteropancreatic neuroendocrine neoplasms. Endocr Relat Cancer 2015 Aug;22(4):657–64.
[7] Rossi A, Di Maio M, Chiodini P, Rudd RM, Okamoto H, Skarlos DV, et al. Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. J Clin Oncol Off J Am Soc Clin Oncol 2012 May 10;30(14):1692–8.
[8] Ohmoto A, Fujiwara Y, Horita N, Nakano K, Takahashi S. Platinum-doublet chemotherapy for advanced gastroenteropancreatic neuroendocrine carcinoma: a systematic review and meta-analysis. Discov Oncol 2022 May;30(13):40.
[9] Morizane C, Machida N, Honma Y, Okusaka T, Boku N, Kato K, et al. Effectiveness of Etoposide and Cisplatin vs Irinotecan and Cisplatin Therapy for Patients With Advanced Neuroendocrine Carcinoma of the Digestive System: The TOPIC-NEC Phase 3 Randomized Clinical Trial. JAMA Oncol 2022 Oct 1;8(10):1447–55.
[10] Sorbye H, Welin S, Langer SW, Vestermark LW, Holt N, Osterlund P, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): The NORDIC NEC study. Ann Oncol 2013 Jan 1;24(1):152–60.
[11] Mitry E, Baudin E, Ducreux M, Sabourin JC, Rufié P, Aparicio T, et al. Treatment of poorly differentiated neuroendocrine tumours with etoposide and cisplatin. Br J Cancer 1999 Dec;81(8):1351–5.
[12] Yamaguchi T, Machida N, Morizane C, Kasuga A, Takahashi H, Sudo K, et al. Multicenter retrospective analysis of systemic chemotherapy for advanced neuroendocrine carcinoma of the digestive system. Cancer Sci 2014 Sep;105(9):1176–81.
[13] McGarrah PW, Leventakos K, Hobday TJ, Molina JR, Finnes HD, Westin GF, et al. Efficacy of Second-Line Chemotherapy in Extrapulmonary Neuroendocrine Carcinoma. Pancreas 2020 Apr;49(4):529–33.
[14] Berinstein NL. Principles of maintenance therapy. Leuk Res 2006 Mar;30(Suppl 1):S3–.
[15] Rossi A, Garassino MC, Cinquini M, Sburlati P, Di Maio M, Farina G, et al. Maintenance or consolidation therapy in small-cell lung cancer: a systematic review and meta-analysis. Lung Cancer Amst Neth 2010 Nov;70(2):119–28.
[16] Gerber DE, Schiller JH. Maintenance Chemotherapy for Advanced Non–Small-Cell Lung Cancer: New Life for an Old Idea. J Clin Oncol 2013 Mar 10;31(8):1009–20.

[17] Ray-Coquard I, Pautier P, Pignata S, Pérol D, González-Martín A, Berger R, et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. N Engl J Med 2019 Dec 19;381(25):2416–28.
[18] Sonbol MB, Mountjoy LJ, Firwana B, Liu AJ, Almader-Douglas D, Mody K, et al. The Role of Maintenance Strategies in Metastatic Colorectal Cancer: A Systematic Review and Network Meta-analysis of Randomized Clinical Trials. JAMA Oncol 2020 Mar 12;6(3):e194489.
[19] Dingemans AMC, Früh M, Ardizzoni A, Besse B, Faivre-Finn C, Hendriks LE, et al. Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up☆. Ann Oncol 2021 Jul 1;32(7):839–53.
[20] Zhang C, Duan J, He Z, Yang L, Yang S, Zhang Z, et al. The benefits of etoposide capsules as maintenance therapy for patients with extensive-stage small cell lung cancer: a prospective two-stage, two-center study. Jan [cited 2024 Nov 22];13(1). Available from: J Thorac Dis [Internet] 2021. https://jtd.amegroups.org/article/view/48563.
[21] He Z, Zhang C, Wang Q, Xu C. Benefits of Etoposide Maintenance Therapy for Patients With Extensive SCLC Who Experienced PR/CR/SD After 4-6 Cycles of First-Line Chemotherapy With Etoposide Plus Cisplatin/Carboplatin. J Glob Oncol 2018 Oct;4(Supplement 2):229s–s.
[22] Zhang P, Li J, Li J, Zhang X, Zhou J, Wang X, et al. Etoposide and cisplatin versus irinotecan and cisplatin as the first-line therapy for patients with advanced, poorly differentiated gastroenteropancreatic neuroendocrine carcinoma: A randomized phase 2 study. Cancer 2020 May 1;126(Suppl 9):2086–92.
[23] Elm'hadi C, Zerrik M, Errihani H, Ichou M. A Long Survival Woman with Primary Small-Cell Carcinoma of the Gallbladder. Role of Chemotherapy Maintenance Cureus 2017. Jun 19;9(6):e1368.
[24] Venizelos A, Elvebakken H, Perren A, Nikolaienko O, Deng W, Lothe IMB, et al. The molecular characteristics of high-grade gastroenteropancreatic neuroendocrine neoplasms. Endocr Relat Cancer 2021 Nov 11;29(1):1–14.
[25] Riesco-Martinez MC, Capdevila J, Alonso V, Jimenez-Fonseca P, Teule A, Grande E, et al. Nivolumab plus platinum-doublet chemotherapy in treatment-naive patients with advanced grade 3 Neuroendocrine Neoplasms of gastroenteropancreatic or unknown origin: The multicenter phase 2 NICE-NEC trial (GETNE-T1913). Nat Commun 2024 Aug 8;15(1):6753.
[26] Kang NW, Tan KT, Li CF, Kuo YH. Complete and Durable Response to Nivolumab in Recurrent Poorly Differentiated Pancreatic Neuroendocrine Carcinoma with High Tumor Mutational Burden. Curr Oncol Tor Ont 2021 Nov 10;28(6):4587–96.
[27] Li H, Qiao J, Kou X, Wu C, Liu H, Qiu J. Complete remission of gallbladder neuroendocrine carcinoma with liver metastasis by tislelizumab plus chemotherapy: a case report. Front Oncol 2024;14:1346290.
[28] Li X, Ma Q, Chang C, Li H, Cao D. First-line treatment of camrelizumab combined with chemotherapy in advanced gastroenteropancreatic neuroendocrine carcinoma: Study protocol for a prospective, multicenter, phase II study. Front Oncol 2022 Sep;16(12):958905.
[29] Research C for DE and. FDA grants accelerated approval to dabrafenib in combination with trametinib for unresectable or metastatic solid tumors with BRAF V600E mutation. FDA [Internet]. 2022 Jun 23 [cited 2023 Mar 20]; Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-dabrafenib-combination-trametinib-unresectable-or-metastatic-solid.
[30] Alifieris CE, Griniatsos J, Delis SG, Nikolaou M, Avgoustou C, Panagiotidis MI, et al. Capecitabine, Oxaliplatin, Irinotecan, and Bevacizumab Combination Followed by Pazopanib Plus Capecitabine Maintenance for High-Grade Gastrointestinal Neuroendocrine Carcinomas. Am J Clin Oncol 2020 May;43(5):305–10.
[31] Levy S, Verbeek WHM, Eskens FALM, van den Berg JG, de Groot DJA, van Leerdam ME, et al. First-line everolimus and cisplatin in patients with advanced extrapulmonary neuroendocrine carcinoma: a nationwide phase 2 single-arm clinical trial. Ther Adv Med Oncol 2022;14:17588359221077088.
[32] Mondesire WH, Jian W, Zhang H, Ensor J, Hung MC, Mills GB, et al. Targeting mammalian target of rapamycin synergistically enhances chemotherapy-induced cytotoxicity in breast cancer cells. Clin Cancer Res Off J Am Assoc Cancer Res 2004 Oct 15;10(20):7031–42.
[33] Capdevila J, Salazar R, Halperín I, Abad A, Yao JC. Innovations therapy: mammalian target of rapamycin (mTOR) inhibitors for the treatment of neuroendocrine tumors. Cancer Metastasis Rev 2011 Mar;30(Suppl 1):27–34.
[34] Antonuzzo L, Pillozzi S, Marconcini R, Spada F, Gelsomino F, Amoroso V, et al. 1199P MAVERIC: Phase II randomized study of everolimus as maintenance therapy for metastatic neuroendocrine neoplasms (mNEN) with pulmonary or gastroenteropancreatic (GEP) origin. Results on behalf of the GOIRC. Ann Oncol 2023 Oct;1(34):S707–8.
[35] McKinley BJ, Coston TW, Starr JS. Primary Resistance to RET Inhibition in a RET Fusion-Positive Pancreatic Neuroendocrine Carcinoma. Oncologist 2024. Mar 13;oyae034.
[36] Keane F, Bajwa R, Selenica P, Park W, Roehrl MH, Reis-Filho JS, et al. Dramatic, durable response to therapy in gBRCA2-mutated pancreas neuroendocrine carcinoma: opportunity and challenge. NPJ Precis Oncol 2023 Apr 22;7(1):40.