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Comparative analysis of international guidelines on the management of advanced non-functioning well-differentiated pancreatic neuroendocrine tumors

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ABSTRACT

This review presents a comprehensive comparative analysis of international guidelines for managing advanced, non-functioning, well-differentiated pancreatic neuroendocrine tumors (panNETs). PanNETs, which represent a significant proportion of pancreatic neuroendocrine neoplasms, exhibit diverse clinical behaviors and prognoses based on differentiation, grading, and other molecular markers. The varying therapeutic strategies proposed by different guidelines reflect their distinct emphases and regional considerations, such as the ESMO guideline's focus on advanced disease management and the ENETS guidance paper's multidisciplinary approach. This review examines the most recent guidelines from ESMO, NCCN, ASCO, ENETS, and NANETS, analyzing the recommendations for first-line therapies and subsequent treatment pathways in different clinical scenarios. Significant variations are observed in the recommendations, particularly concerning the choice and sequence of systemic therapies, the role of tumor grading and the Ki-67 index in therapeutic decisions, and the integration of regional regulatory and clinical practices. The analysis highlights the need for a tailored approach to managing advanced NF panNETs, advocating for flexibility in applying guidelines to account for individual patient circumstances and the evolving evidence base. This work underscores the complexities of managing this patient population and the critical role of a multidisciplinary team in optimizing treatment outcomes.

Introduction

Pancreatic neuroendocrine neoplasms (panNENs) are considered rare tumors, although their incidence has been significantly increasing over the last few decades [1]. Despite this increase being mainly related to the incidental finding of small, localized panNENs identified at an abdominal morphological imaging conducted for reasons unrelated to the search for a pancreatic tumor [2], a relevant proportion of patients with a new diagnosis of panNEN present with advanced disease (unresectable locally-advanced or metastatic) at the time of diagnosis. On the other hand, while generally considered low-grade malignancies compared to pancreatic adenocarcinoma, they are neoplasms with extremely variable clinical behavior and prognosis. These depend on numerous factors, including the degree of differentiation (well-differentiated, also called neuroendocrine tumors, NETs, or poorly differentiated, also called neuroendocrine carcinomas, NECs), grading (mitotic index and Ki67 proliferative index), the TNM stage, the immunohistochemical expression of somatostatin receptors (sstr), and further histological and molecular factors including DAXX/ATRX [3,4]. Based on the degree of differentiation and grading, it is possible to distinguish four main categories of panNENs: NET G1 (well-differentiated with Ki67 < 3 %), NET G2 (well-differentiated with Ki67 3–20 %), NET G3 (well-differentiated with Ki67 > 20 %), and NEC (poorly differentiated) [5]. From a clinical standpoint, as is the case for all NENs, they can be distinguished into functioning (F) (if associated with a specific clinical syndrome caused by the tumor-hypersecretion of some hormones/substances) and non-functioning (NF), the latter representing around 80 % of cases [6]. PanNENs can present as completely

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asymptomatic or associated with some symptoms related to tumor growth, such as pain, weight loss, jaundice, or duodenal obstruction. The ideal management of panNEN patients is within a NEN-dedicated multidisciplinary team (MDT). The need for coordinated multidisciplinarity also arises from the complexity of the available treatments for these patients [7]. While for NECs, the therapeutic approach is often based on systemic chemotherapy only [8], the treatment of advanced panNET patients, which represent most of the cases, includes various therapies, such as somatostatin analogs (SSAs), molecular-targeted agents (MTAs) such as everolimus and sunitinib, peptide radionuclide receptor therapy (PRRT) with [177Lu]Lu-DOTA-TATE, and several chemotherapy regimens, mainly based on alkylating agents, like temozolomide and streptozotocin. Guidelines for NF pan-NENs vary. Both oncological international scientific societies, like ESMO [10], NCCN [11], and the very recent ones from ASCO [12], and disease-specific societies, like ENETS [9] and NANETS [13], have published guidelines for the management of these neoplasms. In addition, some national NEN-related scientific societies have released local guidelines on NENs [14–16]. This plethora of guidelines can create confusion for the readers, as clinical messages and recommendations may sometimes be discrepant for the same clinical scenario. The paradigm of this challenging clinical context is represented by metastatic NF panNETs, that is, the NEN clinical context with the highest number of approved therapeutic options, although no therapeutic sequence or priority has been validated to date. Therefore, the purpose of this review is to analyze in detail how advanced NF pan-NETs were addressed in the main reference NET-related guidelines, providing a detailed and critical analysis of the controversial points.

Guidelines analysis strategy

To identify the guidelines available in the literature on the management of NF pan-NETs, a comprehensive PubMed search was conducted using the terms 'guidelines' AND 'pancreatic neuroendocrine tumors'. This search revealed numerous guidelines, including those produced by national scientific societies and prominent international scientific societies such as ENETS, ESMO, NCCN, and ASCO [9–12]. While all identified guidelines were considered during the preparation of this review, it primarily focuses on those with the broadest international application. This approach was chosen to concentrate focus on the most universally relevant guidelines and to avoid excessively detailed analysis of regional recommendations that may have limited applicability outside their specific geographical contexts. The data analysis was conducted on the most recent versions of international guidelines available, namely the ENETS 2023 guidance papers [9], the ESMO 2020 guidelines [10], the NCCN practice guidelines version 1.2023 [11], and the ASCO 2023 guidelines [12]. A brief mention of other national guidelines is, however, included in Section 4 of this review. The NANETS guidelines [13] have also been analyzed; however, a direct comparison of therapeutic pathways is not feasible because they do not provide a therapeutic algorithm but only offer recommendations in specific clinical contexts. For uniformity, the analysis will focus on advanced NF panNETs, which represent a common clinical scenario faced by physicians dealing with NENs, and for which the therapeutic goals are tumor growth control and patient quality of life (QoL). We decided to focus on this context since it is challenging to analyze the recommendations provided by the guidelines when mixing non-functioning and functioning forms, as in the latter, the primary therapeutic objective is represented by symptom control [17].

Key messages from the guidelines in different clinical scenarios

In the subsequent section, we delve into various clinical scenarios in managing advanced NF panNETs. For each scenario, we will apply the recommendations provided by the most influential international guidelines, specifically those from ENETS 2023 [9], ESMO 2020 [10], NCCN version 1.2023 [11], ASCO 2023 [12], and NANETS [13]. This comparative approach aims to underscore the commonalities across these guidelines and illuminate the differences, thereby offering a comprehensive perspective on potential therapeutic paths.

First-line therapy in a patient with NF advanced/unresectable pan-NET

The ENETS guidance paper [9] reserved a specific chapter to NF Pan-NETs. This chapter groups patients with G1 or G2 tumors, regardless of the specific Ki67 value. Initially, it distinguishes scenarios based on positive or negative sstr-imaging (SRI). Then, a clinical evaluation is incorporated based on tumor-related symptoms and the tumor growth rate. Specifically, in SRI positive, the approach differs if the patient is asymptomatic and/or has stable/slowly progressive disease versus symptomatic and/or with rapid tumor growth. In the first case, octreotide or lanreotide is recommended as first-line therapy, with "preferably for Ki-67 < 10 %" reported in the footnote. In SRI negative, it is recommended to use everolimus or sunitinib upfront. In the case of a symptomatic patient and/or with rapid tumor growth, a first-line alkylating-based chemotherapy is recommended. While no specific regimen is indicated for G1-G2, the combination of capecitabine and temozolomide (CAP-TEM) is suggested as a first-line therapy for a G3 NET.

Unlike the ENETS, ESMO guidelines emphasize the role of Ki-67 [10] in decision-making, not distinguishing NF from functioning (F) Pan-NETs. In the reported algorithm, octreotide or lanreotide is suggested as first-line therapy for G1 and "low" G2 (those with Ki-67 $< 10\%$) pan-NET. For G2 pan-NET with 10–20 % Ki-67 ("high" G2), CAP-TEM or 5-fluorouracil and streptozotocin (5FU-STZ) or MTAs, such as everolimus or sunitinib, could be recommended as first-line therapy. For a G3 NET, chemotherapy with CAP-TEM or 5FU-STZ is the recommended first line, provided that Ki67 is < 50 %. Finally, for "high" G2 or G3 sstr-negative, CAP-TEM or 5FU-STZ, everolimus or sunitinib are suggested.

Like the ENETS guidance paper, the NCCN guidelines [11] delineate a different approach between G1/G2 and G3 tumors, primarily using the clinical picture as the primary discriminator in addressing the first-line therapy. In a favorable scenario, including G1/G2, absence of symptoms, low tumor burden, and stable disease (SD), the recommended first-line approach is observation, with periodic checks of tumor markers and imaging, without anti-cancer therapy. However, as an alternative, octreotide or lanreotide can also be considered "for symptom and/or tumor control," as specified in the footnote. In a patient with symptoms or "clinically significant" tumor burden or "clinically significant" PD, NCCN suggests the introduction of octreotide or lanreotide (if the patient was previously on active surveillance) or even a more intensive approach, as in tumors with PD after SSA first-line therapy.

The clinical scenario is also critical in deciding the first approach in NET G3 cases. For NET G3, NCCN did not distinguish NF pan-NETs from other NETs G3. In favorable scenarios (i.e., Ki67 < 55 %, slow tumor growth, and sstr-PET positivity), observation without an anti-cancer therapy through close radiological checks in selected patients is again mentioned. The options of SSA (mainly for F NETs) or radiotherapy in the case of oligometastatic disease are also proposed. In cases with the same biological characteristics but with "clinically significant" tumor burden or evident PD, inclusion in a clinical trial is the preferred recommendation, other than systemic therapeutic options such as chemotherapy (CAP-TEM, FOLFOX, CAP-OX, cisplatin/etoposide, carboplatin/etoposide), MTAs (everolimus or sunitinib), possibly high-dose SSA, pembrolizumab (in selected cases) or PRRT or locoregional treatments. Finally, in the unfavorable biological scenario, i.e., Ki67 > 55 %, rapid tumor growth, FDG PET positive, and SRI negative, chemotherapy with various regimens (cisplatin/etoposide or carboplatin/etoposide, irinotecan-based therapy, oxaliplatin-based therapy, CAP-TEM), or pembrolizumab (in selected cases) or nivolumab plus ipilimumab are recommended.

Like the other guidelines, the ASCO guidelines [12] use tumor grading as the primary discriminant for deciding the first-line therapy,

distinguishing between G1/G2 and G3 tumors. There is not a specific session for NF Pan-NETs. First-line octreotide or lanreotide is recommended for a G1/G2 Pan-NETs SSTR-positive, not associated with symptoms and with a low tumor burden. In the presence of symptoms and/or high tumor burden sstr-positive or negative, chemotherapy is recommended as first-line, specifically CAP-TEM. In the case of a G3 NET, the recommended approach is similar to that of G1/G2 pan-NETs but emphasizes the Ki67 value, symptoms, tumor growth rate, and tumor burden. The lack of scientific evidence supporting a choice in this setting and the availability of ongoing clinical trials have been highlighted. Indeed, no specific therapy is recommended in general for advanced Pan-NETs G3.

As mentioned, the NANETS guidelines [13] did not provide therapeutic algorithms. However, they agree on the use of SSA in advanced, unresectable panNETs with slow progression while recommending chemotherapy (preferably with CAP-TEM) in cases with a high tumor burden or tumor-related symptoms.

Similarities and differences in First-Line therapy recommendations

All the guidelines mentioned above consider tumor grading as a critical element in choosing first-line therapy in NF panNETs, primarily distinguishing between G1/G2 and G3 forms and SRI-positive vs. negative. The ESMO guidelines [10] are the ones that gave the highest relevance to the Ki-67 value, considering "low" versus "high" G2 pan-NETs differently. Furthermore, ESMO guidelines [10] also stand out because they do not consider the clinical element of the presence of tumor-related symptoms, tumor burden, or tumor growth as discriminating criteria for decision-making. These latter elements are mentioned in all the other guidelines, albeit with varying degrees of relevance. Generally, all guidelines agree that for sstr-positive tumors, G1-G2 (<10 % Ki-67), in the absence of tumor-related symptoms, with low tumor burden, and in the absence of rapid growth, the first-line therapy should be represented by octreotide or lanreotide [9–13]. The sstr-positivity is related to functional imaging rather than immunohistochemistry (IHC), although various terminology has been utilized for this aspect in the different guidelines. Notably, the US guidelines (NCCN and NANETS) are the only ones that propose the "watch & wait" approach [11,13]. The molecular targeted agents (MTAs) everolimus and sunitinib were suggested as possible first-line only by the ENETS guidelines [9] in sstr-negative NET, without symptoms and with slow tumor growth, and by the ESMO guidelines [10] either in "high" G2 NET or in sstr-negative NETs. Chemotherapy based on CAP-TEM or 5FU-STZ is suggested as a first-line option by the ESMO guidelines [10] in all cases of panNET, except when Ki67 is < 10 %. The ENETS [9] and ASCO guidelines [12] focused on the use of chemotherapy mainly in symptomatic patients, those with a high tumor burden, or rapid tumor growth (particularly ASCO refers only to CAP-TEM, whereas ENETS also includes 5FU-STZ).

Notably, the NCCN guidelines [11] recommend the "watch & wait" option even in selected cases of NET G3, provided that the Ki67 is < 55 %, there are no tumor-related symptoms, and there is a low tumor burden. Unlike the others, the NCCN guidelines [11] provided a more detailed therapeutic pathway for NET G3, which includes various chemotherapy regimens, possible options for immunotherapy, and, even in a NET G3 setting, provided it has a favorable biological profile, the possibility of high-dose SSA; many of these options are not mentioned by the other guidelines.

Next steps after First-Line therapy failure

In patients with sstr-positive NF pan-NETs, the ENETS guidelines recommend everolimus, sunitinib, or PRRT as a second-line therapy [9]. The first line would have been SSA in cases of asymptomatic, slowly progressive tumors and chemotherapy in symptomatic or rapidly progressive tumors. In patients with sstr-negative NF pan-NETs, the recommended second-line therapy is chemotherapy with alkylating agents or everolimus or sunitinib for patients with asymptomatic, slow-growing, or rapidly progressive NETs, respectively. No specific recommendation for NET G3 is given.

The ESMO guidelines [10], following the initial distinction made for patients with NET G1-G2 and sstr-positive tumors based on the Ki67 value (<10 % vs. 10 %-20 %), recommend as a second-line therapy the possible choice between chemotherapy (CAP-TEM or 5FU-STZ) and everolimus or sunitinib for tumors with Ki67 < 10 %. Meanwhile, for those with Ki67 10 %-20 %, where chemotherapy with alkylating agents is suggested as a first line, the MTAs come into consideration for the second line. In the first clinical setting (Ki67 < 10 %), PRRT appears in the therapeutic algorithm as a third-line option after chemotherapy and MTAs. A possible role for PRRT is also indicated for NET G3, in this case as a third-line option, again following initial chemotherapy and a subsequent line of therapy with MTAs, provided that the tumor is sstr-positive.

The subsequent approach recommended by the NCCN guidelines [11] after first-line failure is differentiated according to the specific clinical picture and the goal. Beyond everolimus or sunitinib, considered as a category 1 choice, further options are recommended explicitly in specific clinical settings: in particular, PRRT in cases of sstr-positive tumors after the failure of octreotide or lanreotide; CAP-TEM if the goal is to reduce symptoms related to the presence of the tumor and/or to reduce the tumor burden. Additional chemotherapy combinations such as FOLFOX or CAP-OX have also been reported as possible options. The use of high-dose SSA in specific circumstances is also mentioned. Interestingly, as a primary option, even before considering the indications above, the NCCN guidelines advise evaluating enrollment in a clinical trial [11].

According to the ASCO guidelines [12], patients with sstr-positive G1-G2 pan-NETs, with low tumor burden, absence of symptoms, and PD at the first-line therapy with an SSA, are directed towards treatment with one of the following options: everolimus or sunitinib, chemotherapy, or PRRT. In patients with more aggressive tumors (presence of symptoms or high tumor burden) who had progressed after chemotherapy (preferably CAP-TEM), MTAs are recommended, with the additional option of PRRT for sstr-positive tumors. Similar to the specifications for the first line, no specific recommendations are provided in the setting of NET G3.

Notably, the NANETS guidelines [13] recommend a therapeutic sequence after the failure of the first line based on the objective to be achieved. For instance, if there is a need for tumor shrinkage, PRRT or chemotherapy should be considered. Otherwise, the possibility of MTAs should be considered; PRRT is also mentioned. However, there needs to be a clear indication of its use after SSA failure in this clinical context.

Regarding the further continuation of therapeutic pathways after the failure of second-line therapy, it is difficult to identify recommendations that are truly based on scientific evidence. Generally, the choice of a third-line therapy in various guidelines depends on what was previously chosen after the first-line failure. Thus, having positioned chemotherapy or MTAs as second-line, the ESMO guidelines suggest following up with PRRT. On the other hand, since the ENETS guidelines position PRRT as a second-line option, they recommend chemotherapy or MTAs as subsequent lines (if not previously used). Beyond the recommendations of the guidelines, unfortunately, there is no scientific evidence to support a therapeutic decision after the failure of the second-line therapy in NF pan-NETs, as data from studies on therapeutic sequences are scarce and usually focused on the choice of the second −line after the failure of SSAs [18,19].

National guidelines

Among the national-level European guidelines, the Scandinavian guidelines from the Nordic group [14], the UKINET guidelines from UK [15], and the Spanish [20], French [21], and Polish [22] guidelines were identified from the literature review. Moving beyond European borders, Japanese [16] and Canadian [23] guidelines were also found.

In the section of the NORDIC group's guidelines [14] dedicated to advanced pan-NETs, the discriminant factor for the choice of first-line therapy is again a Ki67 value of 10 %. The guidelines suggest SSAs if the value is lower or chemotherapy if it is higher. After progression at first-line, subsequent suggested options include MTAs or PRRT.

The UKINET guidelines [15] provide more generic recommendations, primarily focusing on the opportunity to direct patients towards clinical trials; however, it is important to note that these were published in 2012, before the inclusion of new targeted therapies and PRRT in the standard treatments for pan-NETs.

The Spanish guidelines [20] primarily rely on the ESMO recommendations, with a particular focus on tumor shrinkage as a goal to be included in the decision-making algorithm when choosing the first-line therapy for cases with a Ki67 $>$ 10 %, favoring chemotherapy when this is among the primary objectives.

The French guidelines [21], while adhering to the principle of using SSAs as first-line, also add the option of active surveillance, followed by chemotherapy, MTAs, or PRRT in case of tumor progression. They emphasize some additional factors such as liver tumor load covering more than 50 % of the liver surface, bone metastases, or FDG-PET positivity in considering therapeutic approaches in more aggressive diseases.

Finally, the Polish guidelines [22], propose SSAs as first-line, followed by either PRRT or MTAs in tumors that are not rapidly progressive, or by chemotherapy in these latter cases, in analogy to what is reported by other international guidelines.

Also, the Japanese guidelines [16] consider SSAs as first-line, followed by MTAs or streptozocin in case of tumor progression. They do not mention PRRT, as this treatment was not yet approved in Japan at the time the guidelines were published (2021).

The Canadian guidelines [23] do not provide a therapeutic algorithm, and thus it is impossible to extract a proposed therapeutic sequence. They merely suggest a chemotherapeutic approach for rapidly progressive tumors, while recommending SSAs, MTAs, or PRRT for indolent tumors.

Discussion

This critical analysis showed that the main international guidelines addressed the treatment of advanced NF pan-NETs differently. Alongside some commonalities, there are relevant discrepancies in the tools utilized for the initial assessment of the patient and in the type of recommended therapies and their sequence (Fig. 1). In detail, it is noteworthy that the clinical factor, in addition to tumor grading, is emphasized for the initial assessment of the patient. Only ESMO guidelines [10] did not remark on this aspect, whereas the other guidelines considered tumor-related symptoms, tumor burden, and tumor growth rapidity as discriminating elements for decision-making. This calls into question the absolute relevance of Ki67 for therapeutic decision-making, given its variability according to the detection site in the tissue sample and the fact that, while its prognostic value is widely accepted, its predictive value still needs to be validated.

From a comparative analysis of the guidelines, several points are of particular interest:

The U.S guidelines (NCCN and NANETS) [11,13] are the only ones to consider the possibility of a non-interventionist "watch & wait" strategy in cases with a favorable biological profile, even in selected cases of NET G3 [11]. This message is in discrepancy with the recent scientific literature. In fact, according to the phase 3 CLARINET trial [24], even in G1 and G2 stable or slowly progressive diseases, the use of SSA-based therapy significantly prolongs PFS compared to placebo. Previously, it had been noted that, within the scope of metastatic pancreatic NENs, the absence of active treatment was a highly predictive factor of worse clinical outcomes [25]. Finally, current knowledge regarding the natural history and behavior of NENs clearly shows that pancreatic primaries have a worse prognosis compared to small intestine forms, particularly in the G3 subgroup, which naturally possess a highly aggressive biological behavior [26]. The hypothesis of a "watchful waiting" attitude in the absence of active therapy is, therefore, difficult to accept today in a context (such as that of panNETs) where several therapeutic options are available. It is likely that, in an indolent advanced NF-Pan-NET, the "watch-&-wait" policy could mean delaying rather than avoiding the first-line therapy [27]. Another challenging point reported in the NCCN

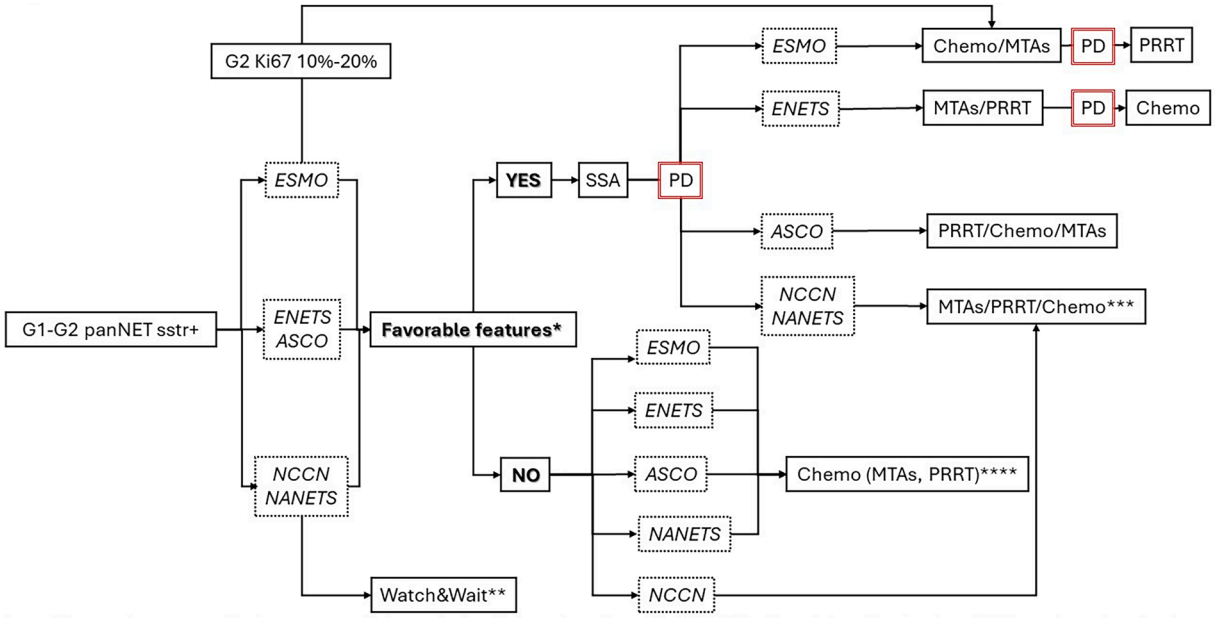

Fig. 1. A proposed synthesis of the therapeutic algorithms suggested by the various guidelines is presented. It is specified that the NANETS guidelines do not provide a therapeutic algorithm; therefore, the indications reported are extracted from the recommendations provided in the text. In the figure, "chemotherapy" refers to the combination of CAPTEM or 5FU-STZ unless specified otherwise.

guidelines is the above standard-dose SSA option (i.e., octreotide LAR 30 mg or lanreotide slow-release 120 mg, each given every 28 days) in case of failure of first-line therapy with SSA, [11]. This message also seems to disagree with the most recent evidence from the scientific literature. Although old retrospective studies, often conducted on limited population samples, had reported a benefit in increasing the SSA dose when progression was observed with the standard dose [28], the recent phase 2 prospective study CLARINET FORTE [29] has effectively rejected this hypothesis, indicating a median PFS of about five months in pancreatic primaries and eight months in those of the small intestine, once progression with a standard dose of SSA has occurred. These data have effectively changed the scientific landscape regarding high-dose SSA, as confirmed by a recent *meta*-analysis [30] that included the aforementioned prospective trial in addition to retrospective studies. While there is no absolute evidence in favor of above-label-dose SSA in advanced NF Pan-NET, two randomized phase III studies reported a significant advantage of PRRT over high-dose Octreotide LAR in SRI-positive advanced GEP NETs [31,32]. Based on the data above, it does not seem adequate to increase the dose of SSA in patients with NF Pan-NET progressing to label-dose SSA, given the availability of potentially effective options such as MTAs, PRRT, and chemotherapy. Beyond the need to control the syndrome, particularly in the case of carcinoid syndrome refractory to standard therapy [33], or as an option serving as a bridge to more intensive treatments in patients with small bowel NET with low Ki-67 and minimal/tumor burden [34], the role of above label dose SSAs today does not seem justified with antiproliferative intents. Regarding PRRT, it is recommended by all the guidelines as a potentially effective therapeutic option in SRI-positive G1-G2 GEP-NET. However, as far as NF Pan-NETs are concerned, some differences exist in the indicated timing. Most guidelines considered PRRT for SSTR-positive G1-G2 Pan-NET progression after SSA, alongside MTAs, whereas ESMO guidelines [10] placed PRRT at the end of a sequence including SSA, MTAs, and chemotherapy with CAP-TEM or STZ-5FU. However, ESMO guidelines suggested PRRT also for tumors with Ki67 $>$ 10 % or G3. The NANETS guidelines [13] do not provide a clear indication for the use of PRRT after SSA failure unless there is a need to achieve tumor shrinkage in patients with a high tumor burden.

This late placement of PRRT in the therapeutic sequence could partly result from the different publication dates of the guidelines (the ESMO and NANETS ones are updated as of 2020, whereas the others are 2023). However, by the time the ESMO and NANETS guidelines were published, the scientific data supporting the regulatory approval of PRRT in GEP-NETs progressing after SSA were already available. Moreover, the NCCN guidelines suggest a series of additional options compared to the other guidelines, including other chemotherapeutic regimens, even some not usually used in NETs, like platinum/etoposide. This is even though data supporting such therapeutic regimes in well-differentiated forms is scarce. Finally, the NCCN guidelines are the only ones that emphasize the option of clinical trials. This last recommendation only confirms the complexity that still exists today in choosing the optimal therapeutic sequence for these patients. Some recent studies have focused on this topic [18,19]. In recent multicentric studies, the greater efficacy of the PRRT sequence followed by targeted therapy or chemotherapy than the reverse sequence was noted, suggesting that earlier use of PRRT can benefit the long-term outcome of patients [18]. Lastly, it is interesting that the various guidelines provide limited guidance regarding managing G3 NETs. This is partly due to the scarcity of scientific evidence for this specific patient setting. In many cases, the data used by the guidelines to formulate recommendations for G3 are derived from scientific evidence available for G1 and G2 tumors. For this reason, the recent ASCO guidelines recommend evaluating a G3 panNET as a G1-G2, provided there are favorable conditions (low tumor burden, slow progression, and not high Ki67 without specifying a cut-off). The ESMO guidelines recommend an upfront approach with chemotherapy (CAP-TEM or 5FU-STZ), provided that the Ki67 is $<$ 50 %, while the ENETS guidelines provide generic recommendations without an accurate therapeutic algorithm. This confirms that in the specific setting of G3 pancreatic NETs, there is a clear need for scientific evidence that still needs to be added to date. Recent data from the novel phase-3 NETTER-2 trial will likely alter therapeutic algorithms for this patient population [32]. The trial reported a significant increase in progression-free survival (PFS) among patients with G2-G3 GEP NETs treated with PRRT (^{177}Lu-Dotatate) compared to high-dose octreotide (22.8 months vs. 8.5 months). PRRT induced an objective response in 43 % of cases. Importantly, similar efficacy was observed regardless of tumor grade (G2 vs. G3) or primary tumor site (pancreas vs. GI tract), suggesting a comprehensive clinical benefit for patients with G2-G3 GEP NETs receiving PRRT as a first-line treatment. Based on these findings, it is reasonable to anticipate updates to international guidelines regarding the first-line approach in this patient setting soon.

A further ongoing international randomized phase III clinical trial, the COMPOSE, compares PRRT with FOLFOX, CAP-TEM, or Everolimus at the investigator's choice [35]. Another distinct feature to note is the propensity of the ENETS guidelines to emphasize the importance of multidisciplinary discussion within a NEN-dedicated MDT. By contrast, the NCCN guidelines particularly stress the utility of including the patient in a clinical trial, if available, already in the early stages of the therapeutic pathway.

Finally, all the mentioned guidelines considered the Ki67 value to some extent as one of the several criteria for decision-making in NF Pan-NETs, although at different levels. Although Ki-67 can be utilized to classify a pan NET and to give an idea about its prognosis, its value could not be so closely related to the clinical behavior of the tumor and even less predict the response to some therapy. Furthermore, the rigid use of specific cut-offs for such a continuous variable could be misleading [36]. Some issues, including sampling technical aspects, intra-tumor heterogeneity, inter-observer discrepancies, and lack of solid evidence about its predictive value, make the absolute role of Ki67 in decision-making relatively weak [37]. According to the Pan-NET WHO classification, Ki-67 should be assessed by manually counting on a printed image, including at least 500 neoplastic cells from the regions of highest labeling (hotspots) [38]. Although digital pathology could help reduce some of these issues, it is far from attributing to some Ki-67 cut-off an absolute value in decision-making.

As a final consideration, one might question whether the community of physicians managing NETs truly needs the extensive availability of guidelines from various scientific societies. However, the most reasonable response to this question is affirmative. Several factors can justify this: Firstly, it is essential to recognize that each guideline has its unique characteristics (for example, the ESMO guidelines primarily focus on managing advanced disease, whereas the ENETS guidelines provide a more multidisciplinary approach covering a variety of clinical scenarios). Secondly, the guidelines consider the geographical context in which they are developed, addressing local regulatory requirements and the scenarios for drug reimbursement or approval, which is particularly apparent in the NCCN guidelines.

Conclusions

This review aimed to critically analyze how the main international NEN guidelines addressed therapeutic decision-making in patients with advanced NF Pan-NETs. Our analysis highlights the heterogeneity between the various guidelines regarding the general approach, sequence of therapies, and type of options (Fig. 2). This is true, especially regarding the choice of second-line treatment. In this setting, where there has been considerable progress in the evidence supporting the use of PRRT in SRI-positive pan-NET over recent years, there still needs to be a clear choice indication. On the other hand, most guidelines have been increasingly remarking on the need to make a therapeutic choice based not only on tumor grading but also on the patient's clinical picture and the course and burden of the disease. Studies focused on the efficacy of different therapeutic sequences, in addition to the already available

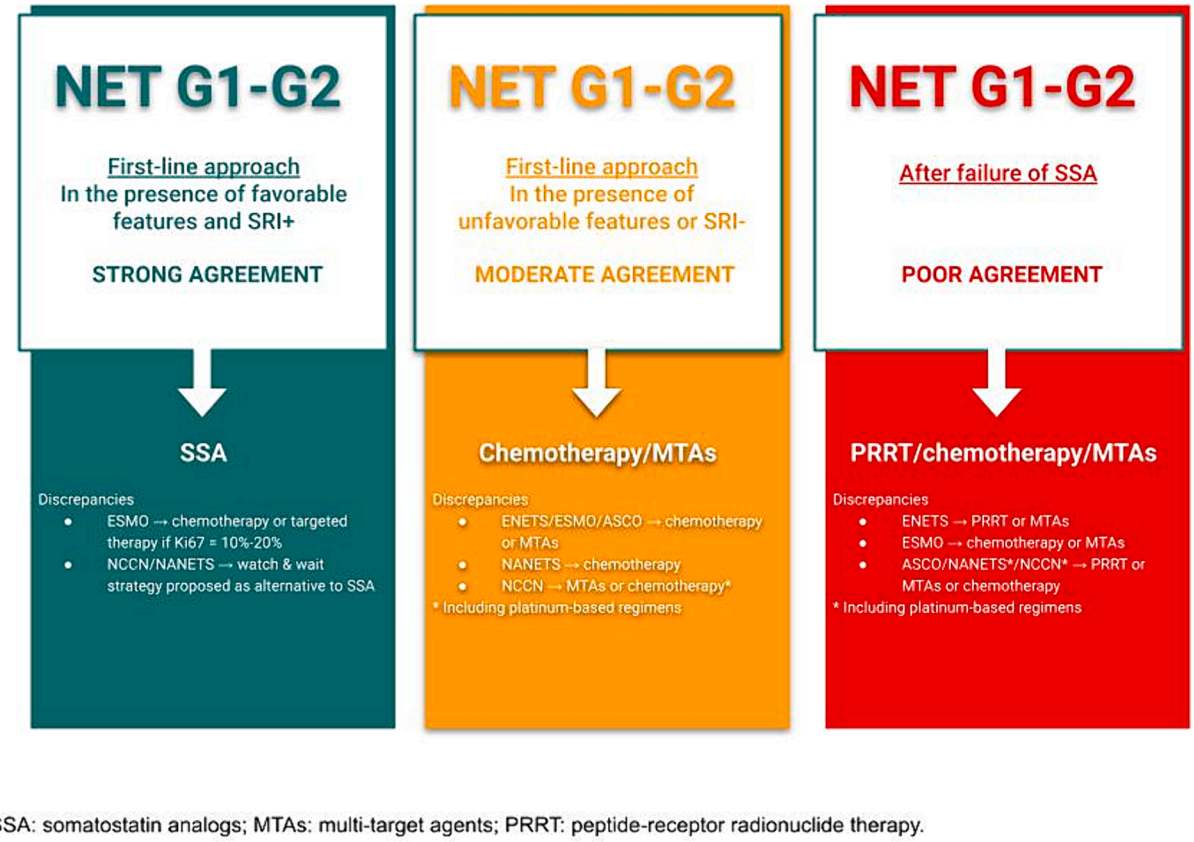

Fig. 2. The figure shows specific clinical contexts in the management of panNETs where aspects of agreement and disagreement among various guidelines are highlighted.

phase 3 clinical trials, are necessary to outline better the therapeutic pathway for advanced NF Pan-NETs, particularly the G3. While the positive results of the NETTER-2 trial [32] strengthen the role of PRRT in terms of earlier line and higher tumor grade, it is hoped that useful information for guidelines will come soon from studies such as COMPOSE [35] and SEQTOR [39]. Both these trials have the primary objective of comparing head-to-head different treatments typically used as second-line after the failure of SSAs. Particularly for SEQTOR, comparing everolimus followed by streptozotocin + 5-fluorouracil versus the inverse sequence is expected to be fully published soon, whereas COMPOSE, comparing PRRT with everolimus or chemotherapy, is ongoing and actively recruiting; therefore, no preliminary data are known at the present time.

This comparative review of available guidelines highlights discrepancies in practice and recommendations by different guidelines. Despite this, universal agreement would be extremely difficult, especially since drug approval processes vary across the globe. Thus, we strongly believe that guidelines should be available not only at an international level but also at a national level so that recommendations can be adjusted to drug availability and variability in access to care, which plays an important role in our daily practice. The guidelines above represent a valuable tool to be utilized as a general basis for therapeutic decision-making in patients with advanced NF Pan-NETs. It is never enough to remind that guidelines are not a tool to be applied *verbatim* but a valuable support to guide the clinical reasoning with the goal to contextualize the evidence into the case of the individual patient, ideally within a multi-disciplinary group dedicated to the topic.

CRediT authorship contribution statement

Francesco Panzuto: Conceptualization, Writing – original draft, Project administration, Supervision. **Angela Lamarca:** Writing – original draft. **Nicola Fazio:** Conceptualization, Writing – original draft.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Angela Lamarca declares travel and educational support from Ipsen, Pfizer, Bayer, AAA, SirtEx, Novartis, Mylan, Delcath Advanz Pharma and Roche. Speaker honoraria from Merck, Pfizer, Ipsen, Incyte, AAA/Novartis, QED, Servier, Astra Zeneca, EISAI, Roche, Advanz Pharma and MSD; advisory and consultancy honoraria from EISAI, Nutricia, Ipsen, QED, Roche, Servier, Boston Scientific, Albireo Pharma, AstraZeneca, Boehringer Ingelheim, GENFIT, TransThera Biosciences, Taiho and MSD; principal Investigator-associated Institutional Funding form QED, Merck, Boehringer Ingelheim, Servier, Astra Zeneca, GenFit, Panbela Therapeutics, Novocure GmbH, Camurus AB, Albireo Pharma, Taiho, TransThera, Jazz Therapeutics and Roche; she was also a member of the Knowledge Network and NETConnect Initiatives funded by Ipsen. Nicola Fazio: IPSEN, Advisory Board, Personal; Merck, Advisory Board, Personal; MSD, Advisory Board, Personal; NOVARTIS, Other, Personal, Steering committee; NOVARTIS, Invited Speaker, Personal; NOVARTIS, Advisory Board, Personal; Astellas, Local PI, Institutional, Financial interest; Beigene, Local PI, Institutional, Financial interest; Boehringer, Local PI, Institutional, Financial interest; FIBROGEN, Local PI, Institutional, Financial interest; IPSEN, Local PI, Institutional, Financial interest; IPSEN, Research Grant, Institutional, Financial interest; ITM, Local PI, Institutional, Financial interest; Merck, Research Grant, Institutional, Financial interest; MSD, Local PI, Institutional, Financial interest; NOVARTIS, Research Grant, Institutional, Financial interest; NUCANA, Local PI, Institutional, Financial interest. Non-Financial

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