Highlights of the 2019 annual meeting of the European Neuroendocrine Tumour Society (ENETS)

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NEW WHO CLASSIFICATION OF NEUROENDOCRINE TUMOURS (NETS) AND NEUROENDOCRINE CARCINOMAS (NECS) ANNO 2019

In the first joint session between ENETS and the European Society of Pathology, the pathology of neuroendocrine neoplasms (NENs) was discussed with a focus on high-grade NENs. *Aurel Perren* discussed the grading of NENs according to the World Health Organization (WHO) classification system, which is based on proliferation markers such as Ki-67 and mitotic count. Since 2017, the differentiation grade was reintroduced as an additional parameter for the classification of pancreatic NEN (PNEN). Well-differentiated PNENs are termed pancreatic neuroendocrine tumours (PNETs) and can be Grade (G) 1, G2 or G3 based on their proliferation rate, while neuroendocrine carcinomas (NECs) are poorly differentiated neoplasms with a high proliferation rate (G3). If other NENs are highly proliferative, e.g. G3, they are still NECs by definition, while G1 and 2 GEP-NENs are termed NETs.[1] However, the adaptations implemented for PNENs are expected to be extended to the other NENs, including lung NENs.[2]

In the talk of *Jean-Yves Scoazec*, the difficulties in classifying neoplasms as NET or NEC were discussed. The main hurdles in this identification include limited availability of tissue material, poor microscopic slide quality, tumour heterogeneity, difficulties in assessing differentiation grade of NENs or overlap in morphological features.[3] In addition, there are also inter-observer inaccuracies when performing Ki-67% or mitotic index estimations. Nevertheless, given the big differences in tumour behaviour, prognosis and patient management between different tumour classes, it is very important that a correct diagnosis is made. Molecular analysis of NETs and NECs has indicated differences on the genetic level between the two entities and these differences might provide an interesting additional tool to distinguish and classify them. The latter was recently reviewed by Gitta Boons *et al.*[4]

For oesophageal and appendiceal NENs, genetic data are lacking. Although data are available for G1 and G2 siNEN, data on G3 NECs of the small intestine are lacking, mainly due

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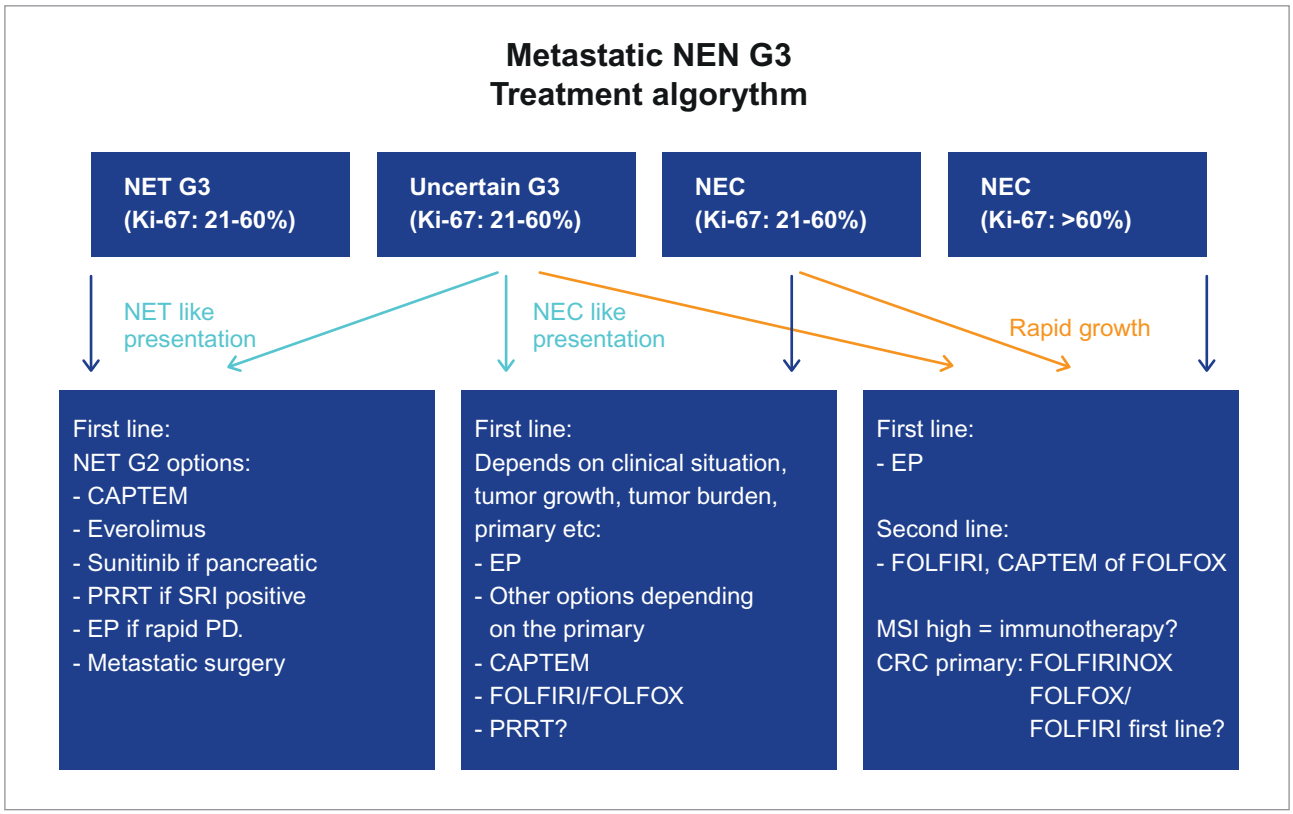

FIGURE 1. Treatment algorithm for metastatic NEN G3 tumours.

to the rarity of these neoplasms. For gastric NENs the available genetic data are limited, but multiple studies have highlighted mutations or loss of TP53 in NECs. In contrast, TP53 is unaffected in NETs. In addition, mutations were found in *KRAS*, RB1, SMAD4 and *BRAF* in gastric NECs. However, the small number of cases in these studies imply that validation of these mutations is still needed.[5-9] The largest part of the colorectal NENs are NECs, and colorectal NECs were found to harbour mutations in APC, *KRAS*, *BRAF* and TP53 and these tumour types often display microsatellite instability.[6,9] In contrast, mutations in these genes were not observed in colorectal NETs.[10]

PNECs and PNETs can also be distinguished based on their genetic profiles. In fact, also G3 PNETs, who show overlap with PNECs regarding Ki-67 values, show a distinct genetic profile. The most frequently affected genes in PNECs are TP53, *KRAS*, RB1 and CDKN2A/p16 while in PNETs, MEN1, DAXX, ATRX and mTOR pathway genes are most frequently affected.[11-13] Mutations in these genes also translate into an altered protein expression profile in these tumour types, which can be detected via immunohistochemistry (IHC).[14] Some genes, however, have been found to be mutated in both, including LRP1B, ARID1A, CDKN2A, APC and TP53.[11] In 2016, Tang *et al.* studied 33 G3 NENs and showed that in two thirds of the cases, pathologists did not reach consensus on the differentiation state of the NENs based on morphologic analysis alone.[3] The use of a Ki-67 cut-off of 55%, where lower levels would indicate a WD-NET and higher levels a PD-NEC, did not enable discrimination of WD-NETs and PD-NECs. This led to a misclassification of approximately 30% of WD-NETs and 30% of PD-NECs.[3,15] To address this, the additional value of IHC staining for p53, SMAD4, Rb, ATRX and DAXX was evaluated, next to an extended pathological review. DAXX or ATRX loss allowed correct classification in 50% of the morphologically ambiguous WD-NET cases, while abnormal expression of p53 or Rb allowed correct classification of 90% of the morphologically ambiguous PD-NEC cases. SMAD4 evaluation didn't provide additional value when p53 and Rb were evaluated. Tang *et al.* demonstrated that, next to additional clinical information and presence of G1/2 regions, which points towards a G3 WD-NET, also IHC analysis can aid in making the correct diagnosis. In more than 60% of the cases IHC analysis could differentiate between a WD-NET and a PD-NEC.[3]

As discussed, genetic differences have been found between NETs and NECs, which could be interesting as markers in cases were histology is inconclusive. However, additional studies with larger sample sizes will be required to further assess the potential of molecular analyses in the differentiation between NETs and NECs and thereby guide patient

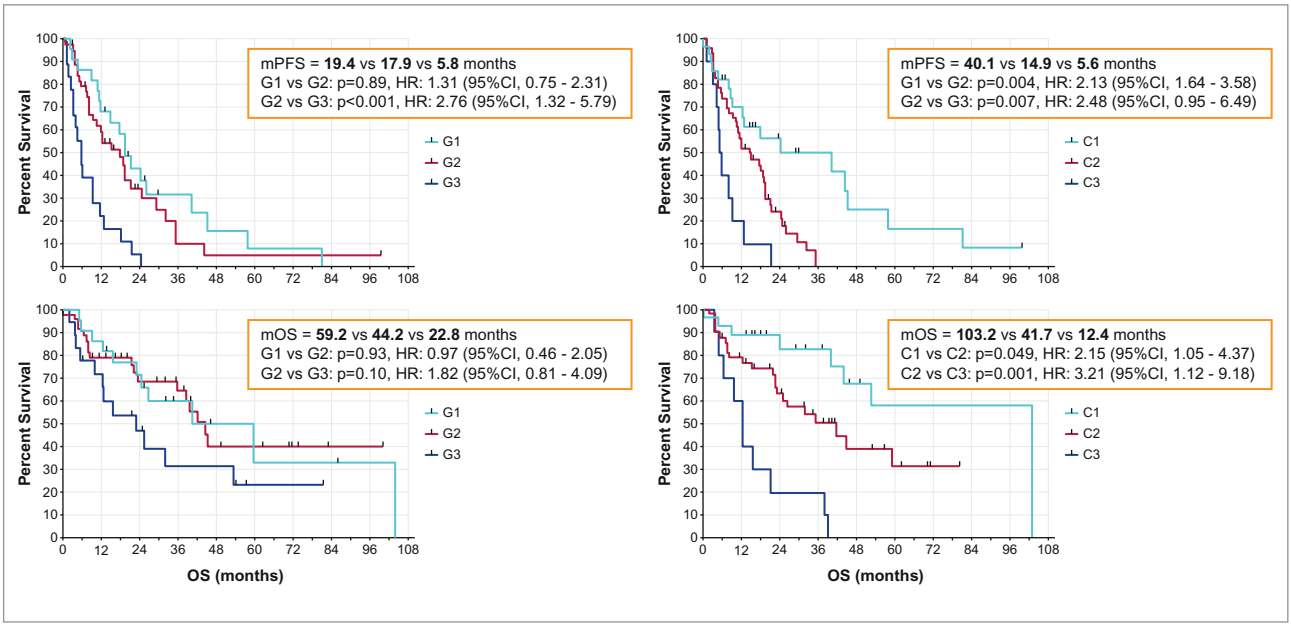

FIGURE 2. Combined Ga-DOTATATE and FDG PET imaging improves the prognostic stratification of metastatic gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs).[18]

management. In addition, overlap between genetic profiles of exocrine tumours and NECs has been described, especially in pancreas and colon, suggesting that NECs might have an exocrine genetic signature. The latter might be relevant for treatment and should be explored further.[9,10]

Halfdan Sorbye discussed the potential difference in response to treatment in G3 NETs in comparison to NECs, using a recently published treatment algorithm (*Figure 1*). Interestingly, novel data indicate that response could be dependent on Rb expression and *KRAS* mutation status in G3 PNEN. G3 PNET patients had a low response rate to platinum-based chemotherapy, while PNEC patients showed a good response. In this analysis, 55% of PNEC patients did not show Rb expression and 49% harboured mutations in *KRAS*. In contrast, no abnormal Rb expression or *KRAS* mutations were observed in G3 PNETs. Rb expression and *KRAS* mutations were both predictive for response to platinum-based chemotherapy in G3 PNENs, while Rb expression was also predictive for response within the PNEC population.[16] Additionally, more data were presented at ENETS indicating that there might be a role for peptide receptor radiotherapy (PRRT) in G3 NETs.

COMBINING ^{68}GA-DOTATATE AND ^{18}F-FDG PET/CT BETTER PREDICTS SURVIVAL IN PATIENTS WITH GASTROENTEROPANCREATIC NETS

A retrospective study was presented to define the role of combination of ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT in prognosis and management of patients with advanced gastroenteropancreatic NETs. An adagio in NET-diagnostics is doing gallium-PET for well differentiated tumours (i.e. grade 1 and 2 NETs) and FDG-PET for poorly differentiated tumours (i.e. grade 3 NECs). The presented study included 52 patients with midgut (58%) and pancreatic (27%) primary tumours who had undergone both ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT within 90 days of each other. Most (87%) patients had hepatic metastases and the median follow-up was 42 months. Patients were divided according to 3 groups based on PET-positivity:

1. ^{68}Ga-positive plus FDG-negative (N= 17; well differentiated, low grade tumours)
2. ^{68}Ga-positive plus FDG-positive (N= 29; less well differentiated tumours)
3. ^{68}Ga-negative plus FDG-positive (N= 6; poorly differentiated tumours).

Results showed that the combined ^{68}Ga/FDG-assessment (p= 0.0005) and age (p< 0.0001) were independently associated with overall survival (OS). In 31 (60%) patients, clinical management was changed by the results of dual scanning and provided additional information to guide the biopsy in three cases.[17]

In conclusion, instead of just reserving FDG-PET for the poorly differentiated tumours, by adding ^{68}Ga-DOTATATE for a larger subset of patients, prognosis can be estimated more accurately. Prospective studies are needed to confirm these data.

These data were nicely replicated in a poster presented by Karfis *et al.*[18] This study included 88 patients who underwent

both a ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT scan within 90 days of each other. Patients were classified into three categories according to histological grade (G1, G2 and G3) and into three categories according to combined PET-imaging: C1 (all lesions FDG-/Ga-DOTATATE positive), C2 (all or part of FDG positive lesions are Ga-DOTATATE positive as well) and C3 (all or part of FDG positive lesions are Ga-DOTATATE negative). Stratification according to histological grade did not show significant statistical difference in median progression-free survival (PFS) between G1 and G2 patients and in median OS between G1, G2 and G3 patients. The survival curves were completely separated between C1, C2 and C3 patients not only regarding mPFS, but also mOS (*Figure 2*).[18]

IMMUNOTHERAPY IN NETS: WHERE DO WE STAND?

ENETS 2019 again featured the presentation of several negative trials evaluating single agent immunotherapy (previously presented at ESMO 2018 [spartalizumab] and ASCO GI 2019 [pembrolizumab]). Earlier findings from the phase I KEYNOTE-028 trial, which studied pembrolizumab in a number of solid tumours, showed activity of immunotherapy in some patients with heavily pre-treated NETs.

A phase II basket trial, KEYNOTE-158, studied the efficacy and safety of pembrolizumab in 10 different tumour types, including NETs. Earlier this year (ASCO GI) *Jonathan Strosberg* presented an analysis of 107 patients from the NET cohort of KEYNOTE-158. This cohort included grade 1/2 NETs of the lung, appendix, small intestine, colon, rectum or pancreas, with disease progression on or intolerance to at least 1 line of standard therapy.[19] Patients in this study received 200 mg of pembrolizumab every 3 weeks for 2 years or until progression, intolerable toxicity, or physician or patient decision. Tumour imaging was performed every 9 weeks for the first year and then every 12 weeks. The median age of patients enrolled was 59 years, 67.3% had received 2 or more prior therapies and 16% of participants had a PD-L1-positive NET. The primary endpoint was ORR, with duration of response, PFS, OS and safety as secondary study objectives. After a median follow-up of 18.6 months, the ORR was 3.7%, with no complete responses and 4 partial responses (3 in patients with a NET of the pancreas and 1 in a patient with a gastrointestinal NET). All 4 patients with a response to pembrolizumab had PD-L1-negative disease. In addition to the partial responses, 61 patients had stable disease as their best response. Three of the four responses were ongoing after 9 months of follow-up. The median PFS was 4.1 months with a 6-month PFS of 38.2%. At 6 months, 84.6% of patients was still alive. Treatment-related adverse events occurred in approximately three-quarters of patients, and 20.6% of patients had grade 3/4 adverse events. The most commonly reported adverse event was fatigue.[19]

In conclusion, pembrolizumab monotherapy showed only limited anti-tumour activity in grade 1/2 NETs and probably will not find its way in routine clinical practice. Maybe other approaches under study like combination therapy, e.g. immunotherapy plus angiogenesis inhibition, or peptide receptor radionuclide therapy (PRRT), are more promising.

A positive premature light at the horizon came from the AACR Meeting 2019 in Atlanta. IN fact, results of a phase II 'basket trial' showed that combined anti-CTLA-4/PD-1 checkpoint blockade had promising activity in heavily pre-treated patients with high-grade neuroendocrine tumours (NETs).[20] Among the 32 patients in the NET cohort, including patients with both low- and high-grade disease, 24% achieved an objective response with ipilimumab plus nivolumab, with 1 complete response. Regardless of primary site, it appeared that the majority of patients who conferred benefit in terms of tumour shrinkage in this study had high-grade neuroendocrine carcinoma. A post-hoc analysis by tumour grade found that none of the 14 patients with lower intermediate-grade NETs responded to ipilimumab plus nivolumab, while 44% of those with high-grade disease did (8 of 18 patients), The latter group included patients with lung, gastrointestinal tract and gynaecologic primary tumours. Prior studies using anti-PD-1 checkpoint inhibitor alone in high-grade disease yielded response rates of around 5%. Interestingly, some of the responses in this study have lasted over a year. After 6 months of therapy, 31% of patients was free of progression and the median OS was reported at 11 months. In summary, this combination might represent a promising strategy for patients who have almost no hope of responding to any form of therapy. Of note, in this study ipilimumab was administered every 6 weeks at 1 mg/kg, which is lower than the approved dose in cancers such as melanoma and kidney cancer. This strategy aimed at reducing potential toxicities. Nivolumab was administered at 240 mg every 2 weeks and the combination was given until progressive disease or unacceptable toxicity. The most common high-grade immune toxicities were liver function abnormalities in 9% of patients and colitis in 6%. No cases of pneumonitis were reported and there were no deaths due to adverse events.[20]

ANY PROMISING TARGETED THERAPIES FOR GRADE 1/2 NETS ON THE HORIZON?

Jaume Capdevila updated the results of the phase II TALENT trial, which studies the efficacy of lenvatinib 24 mg/day in metastatic patients with grade 1/2 advanced pancreatic (pan) NETs and gastrointestinal (gi)NETs. The ORR with current

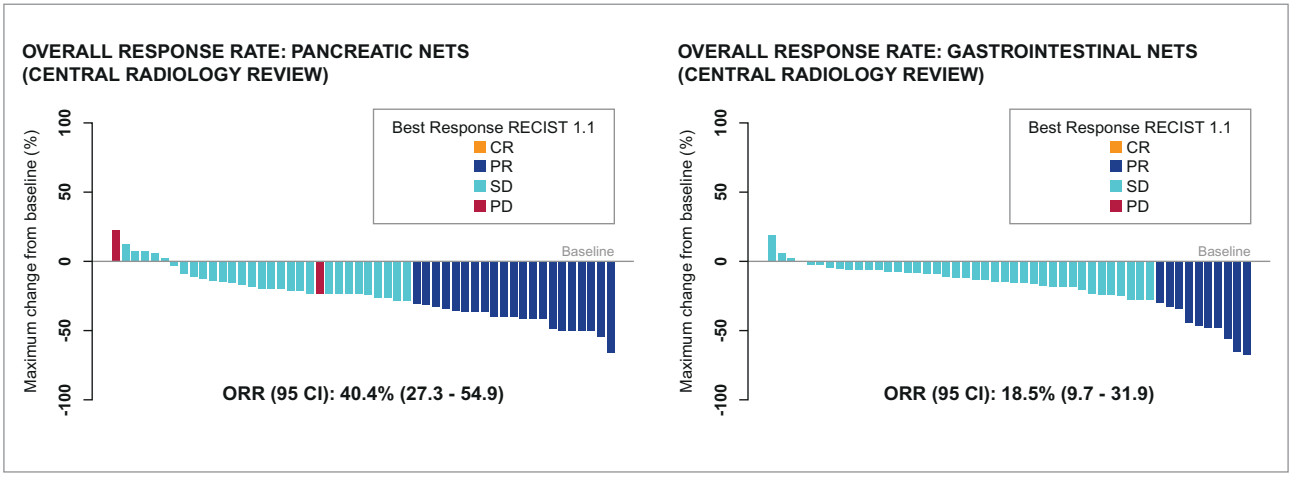

FIGURE 3. ORR in the phase II TALENT trial evaluating lenvatinib 24 mg/day in metastatic patients with grade 1/2 advanced pancreatic (pan)NETs (top) and gastrointestinal (gi)NETs (bottom).[21]

targeted agents like sunitinib and everolimus in NETs ranges between 2-9%. In contrast, the ORR with lenvatinib in panNETs was 40.4% and 18.5% in giNETs (*Figure 3*). The median PFS in pan- and giNETs was 15.8 and 15.4 months, respectively. Dose reductions/interruptions were needed in 91.8% with a median dose of lenvatinib of 20 mg/day. No new toxicities were reported.[21]

In conclusion, lenvatinib showed the highest reported ORR with a targeted agent in panNETs and giNETs with promising PFS in a pre-treated population. The benefit was observed across subgroups analyses, including patients treated with prior targeted agents.

PROMISING ONGOING CLINICAL TRIALS IN NETS AND NECS

Enrique Grande summarised the most promising running trials in the domain of NETs and NECs (*Figure 4*). These trials mostly focus on new angiogenesis inhibitors, combination immunotherapy approaches and optimal sequencing of existing therapeutics. As you can appreciate, lots of exciting data to be expected in the coming years.[22]

WHAT MATTERS IN NURSING CARE IN NETS?

With respect to nursing, ENETS provided the following take home messages

1. **NPF (NET Patient Foundation) project 2019-2020: MIND THE GAP.** For many patients with NETs, the 'what comes next' question is the hardest part of their disease. Living with uncertainty is a consistent and persistent challenge for these patients. The reality of 'chronic cancer' can be an anxiety ridden place, and we have to help the patient carry, not only the physical, but also the psychological burden of disease.
2. **Sexual aspects of QoL.** Living with and having treatment for a NET can have a big effect on how patients feel about sex (NPF). The reported NPF survey is based on a response given by patients (26 females, 22 males) undergoing PRRT and their responses were analysed from January 2018 to January 2019. The authors concluded that it was difficult to assess whether PRRT affects the sexual function during the actual therapy. The ratio from patients who felt unaffected by the therapy to patients who did experience an impact on their sexuality was 3:2. It will be worth repeating the survey/analysis for a longer time frame to get more significant results.
3. **Physical activity during cancer treatment: why and how?** It has already been established that exercise at moderate intensity can reduce cancer-related fatigue, increase health-related QoL, prevent deterioration or improve strength and fitness. In addition to this, there is limited evidence that exercise can reduce the risk of relapse and improve survival in breast, prostate and colon cancer. It also reduces nausea and pain and improves sleep and the ability to complete the chemotherapy treatment. Several exercise recommendations have been formulated, including aerobics and muscle strengthening physical activity. It is also recommended to adapt the exercise during chemotherapy treatment and to start on a lower intensity and slowly increase the exercise intensity and duration. The main message is that any physical activity is better than none. From a caregiver perspective, both written and oral information can be given on the importance of exercise. Patients can next be referred to a physiotherapist or another exercise specialist, perform a pre-exercise fitness assessment and provide supervised exercise in groups.

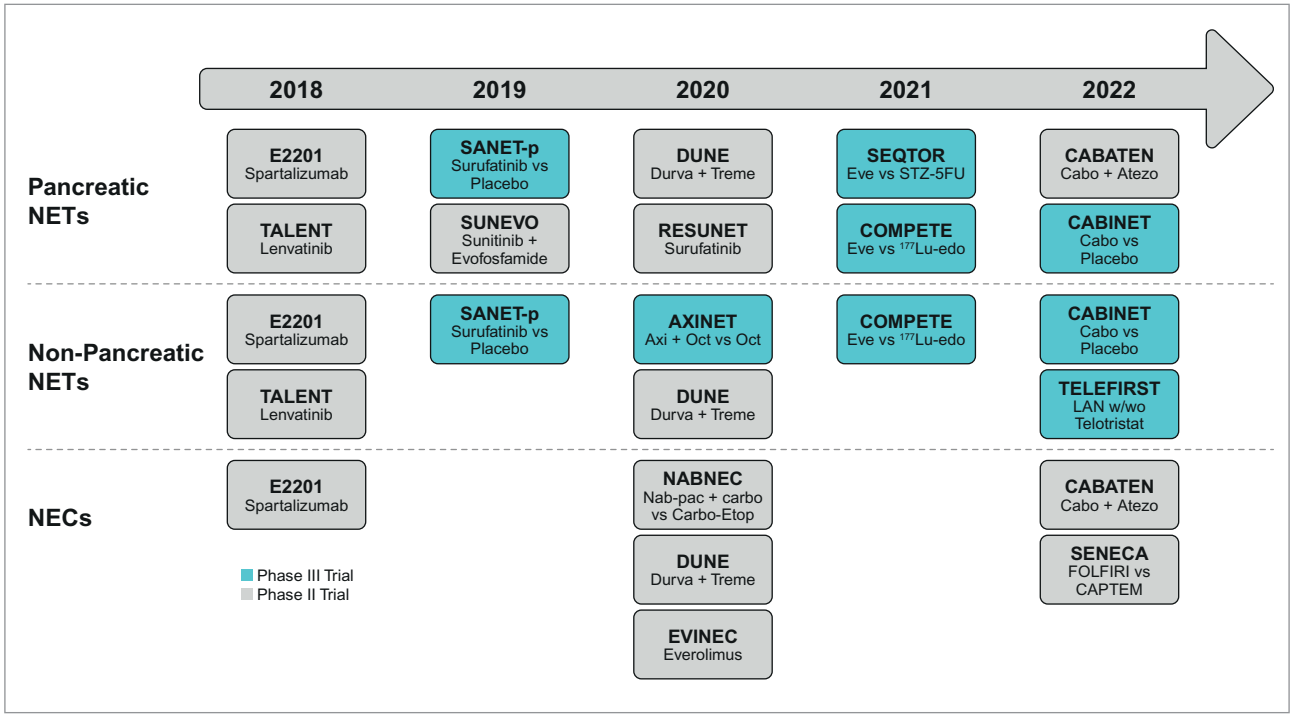

FIGURE 4. Ongoing clinical trials in NETs/NECs.

4. **Carcinoid syndrome:** Carcinoid syndrome has a major impact on QoL. In this respect, the hypothesis was raised that SIRT might improve the QoL in patients with carcinoid syndrome caused by neuroendocrine liver metastases. A large international retrospective study including 244 patients of whom 60% had symptoms (flushing 43%, diarrhoea 40%) concluded that:
   a. QoL is an important consideration in treating patients with NET.
   b. Oncology trials mainly focus on OS and PFS and as a result QoL is poorly reported in NET oncological studies.
   c. Using a NET specific QoL questionnaire will provide more robust data for NET patients.
   d. QoL data is becoming an important factor in demonstrating cost-effectiveness in the current health economy.
5. **Disease-related consequences for patients:** First of all, disease-related symptoms such as diarrhoea, flushes and fatigue can have important social consequences for patients. In addition to this, patients also experience prominent psychological and existential issues. These include the feeling that they wish to play their part in a society but feel left out, financial consequences, insecurities in performing their activities of daily living, fear of disease progression and worries about their loved ones. However, patients do seem to be able to diminish the burden of these consequences. In this respect, a good balance between activity and rest is important. In addition, patients should focus on living with NET instead of having NET. It is self-evident that an adequate social support, a stable financial situation, meaningful activities and enjoying life in general are also factors that influence the disease-related consequences for patients. The main conclusion should be that it is important to talk about the social consequences of their disease.
6. **Genetic counselling.** A genetic study entails important emotional implications for the patient as well as for the relatives in risk. Therefore, a genetic counselling professional should have an in-depth knowledge on the disease, have thorough knowledge on the genetics involved in the disease and have insights into prevention management. However, it is perhaps as important to have the necessary communication skills to share this knowledge with the patient and his/her relatives. Genetic professionals should see the patient and family members as a whole, holistically, evaluating the psycho-emotional consequences of the entire process for everybody who is likely to be affected by the outcome of the genetic analysis. Nurse professionals are key to guide patients through this genetic counselling process.
7. **How to differentiate between side effects of treatment and symptoms of NET?** Interdisciplinary systemic algorithms on diagnosis and treatment of symptoms are in place, but collaboration between different specialties is of pivotal importance. Patient reported outcome (PRO) represent an interesting tool to identify unmet needs. Importantly, nurses can also help patients in case of symptoms

KEY MESSAGES FOR CLINICAL PRACTICE

1. The NET G3 category might soon be extended from pancreatic NENs to all NENs, including tumours of lung origin. Genetic characterisation might help differentiate between NET and NEC.
2. The optimal treatment of NET G3 should be studied further, however CAPTEM-chemotherapy and PRRT seem to be effective in this population and genetics can guide treatment.
3. The use of ^{68}Ga-DOTATATE in combination with FDG-PET in a larger subset of patients allows for a more accurate estimation of the prognosis.
4. Pembrolizumab monotherapy showed only limited anti-tumour activity in NETs grade 1/2 and probably will not find its way in routine clinical practice.
5. Combining anti-CTLA-4/PD-1 checkpoint blockade showed promising activity in heavily pre-treated patients with high-grade neuroendocrine tumours.
6. Lenvatinib showed the highest reported ORR with a targeted agent in panNETs and giNETs with promising PFS in a pre-treated population.
7. Ongoing trials in NETs and NECs are mostly focusing on new angiogenesis inhibitors, combination immunotherapy approaches and optimal sequencing of existing therapeutics.
8. QoL is poorly reported in NET oncological studies. Using a NET specific QoL questionnaire will provide more robust data for NET patients. A dedicated NET nurse can play a pivotal role to guide patients with NET.

for which no quick-fix is possible: just being present, available and willing to listen can be of great help to patients

8. **Person-centred care.** A systematic way to create a culture that recognises the patient as an expert in his own life and make a room for that is the meeting with health care services. Patient concern inventory (PCI) is one example of identifying unmet needs.

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