How I treat neuroendocrine tumours

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ABSTRACT
Neuroendocrine tumours (NETs) constitute a heterogeneous group of neoplasms characterised by variable endocrine activity and somatostatin receptor expression, with the latter allowing the use of targeted therapeutic concepts. Currently accepted treatment strategies for advanced well-differentiated NET include somatostatin analogues octreotide and lanreotide, peptide receptor radionuclide therapy using radiolabelled somatostatin analogues, mammalian target of Rapamycin inhibitor everolimus, tyrosine kinase inhibitor sunitinib, interferon alpha and classical cytostatic, such as streptozotocin-based and temozolomide-based treatment. Indication, use and approval of these treatments differ based on primary tumour origin, grading and symptomatic burden and require an optimised multidisciplinary cooperation of medical oncologists, endocrinologists and nuclear medicine specialists. Interestingly, hot topics in oncology including immunotherapy and use of next-generation-sequencing techniques currently play a minor role for the treatment of NETs. The recent revision of the WHO classification including the recognition of the novel NET G3 category allows for potentially more tailored treatment strategies in the near future. However, this new entity also poses a therapeutic challenge as only limited data are currently available. The present article aims to provide an overview on our personal treatment concepts for advanced NETs with a focus on tumours of gastroenteropancreatic origin.

INTRODUCTION
Neuroendocrine neoplasms (NEN) constitute a heterogeneous group of malignancies originating from the diffuse neuroendocrine cell system. While NEN can develop in any organ of the body, tumours of gastroenteropancreatic (GEP) origin are the most common accounting for 70%. In analogy to other malignancies, an increase of NEN has been documented over recent years and the latest Surveillance, Epidemiology and End Results (SEER) database numbers reported 6.98 cases per 100 000 including all subtypes and stages. The only curative treatment for NEN is surgery but a significant percentage of patients present with primary metastatic disease. During the last decade, the therapeutic options for advanced NEN have increased, particularly with the wider approval of mammalian target of Rapamycin (mTOR) inhibitors and of peptide receptor radionuclide therapy (PRRT) using radiolabelled somatostatin analogues (SSA) allowing for a more precise treatment algorithm. In addition, the recent revision of the WHO classification with the recognition of the new neuroendocrine tumour G3 (NET G3) category is an important step towards more individualised treatment for patients with highly proliferating but well-differentiated tumours. In the current review, we provide an overview of our personal treatment concept for advanced well-differentiated NETs with a focus on tumours of GEP origin.

UPDATE WHO CLASSIFICATION
The most relevant factor for prognosis and risk stratification is the number of proliferating cells in the tumour defined by the Ki67 index stratifying GEP-NENs into well-differentiated NET grade (G) 1 and 2 (Ki67 ≤20%) and more rapidly growing G3 tumours (>20%). While all G3 tumours historically had been termed neuroendocrine carcinomas (NEC G3) implicating an aggressive biology with clinical course and treatment in analogy to small cell lung cancer, emerging observations in recent years have defined some tumours with preserved neuroendocrine morphology and more indolent clinical behaviour. Thus, the new entity of well-differentiated NET G3 was defined and this concept is supported by distinct genetic aberrations documented specifically in NEC G3 including loss of tumour suppressor genes TP53 and RB, while for example alterations in DAXX/ATRX and MEN1 relate to pancreatic NET G3. In 2017, the NET G3 category was accepted in the WHO-classification for pancreatic NET and can now be applied to all GEP–NET. However, this also highlights the need for a separate treatment algorithm as platin-based therapy being the previous standard for all NEC is not comparably effective for NET G3. Whereas current concepts rely on expert consensus and retrospective data, this is clearly an emerging topic for trials in the near future. Below we discuss our treatment approach to NET G3, the treatment of NEC G3 is not in the focus of this review on well-differentiated NET.
Systemic treatment for neuroendocrine tumours

Somatostatin analogues

Somatostatin receptor (SSR) expression is an important feature of NENs and the five subtypes SSR 1–5 can be detected at varying frequency depending on tumour grading (decrease with aggressive morphology) and primary localisation (GEP>lung) on tumour cells. Assessment by immunohistochemistry or functional imaging is an essential tool for diagnostic purpose and treatment eligibility and SSR imaging, at our centre preferably performed by $^{68}$Ga-DOTA SSA positron emission tomography (PET)—CT is mandatory for staging of well-differentiated NETs. As SSRs are usually homogeneously distributed, they constitute an optimal target for ‘personalised’ treatment. SSA targeting SSRs have been introduced already in the 1980s for symptomatic treatment of endocrine-active NETs and still constitute the treatment standard for these patients. However, despite the assumption of antiproliferative activity based on inhibitory effects on secretion of growth factors and autocrine signalling, it took another 20 years for proof of efficacy for antitumour treatment. In 2009, the PROMID study, a placebo controlled phase III, showed a significant benefit in time-to-progression for SSA octreotide in long-acting release (LAR) formulation versus placebo, with an increase from 6 to 14.3 months (HR: 0.34, 95% CI: 0.20 to 0.59) in 85 midgut NETs. More than 95% of patients had G1 tumours highlighting the indolent character of this collective. The CLARINET trial evaluated the SSA lanreotide autogel in a more extensive patient collective including non-functioning midgut, hindgut and pancreatic NET (n=204) with a Ki67 <10%. The primary endpoint of progression-free survival (PFS) was highly significant in favour of the lanreotide arm, with a PFS of 18 months in the placebo arm and not reached in the experimental cohort (HR: 0.47, 95% CI: 0.30 to 0.73). The separation in median PFS of the placebo arms indicates discrepancies in the trial populations, with the main differences beside primary localisations and grading found in time since diagnosis, which was longer in CLARINET (median 13.2 months in the treatment arm and 16.5 months in the placebo arm) than in PROMID (7.5 and 3.3 months, respectively). This is further underlined by the fact that 96% of patients had documented stable disease at treatment start in the lanreotide study.

Based on these results, both compounds are approved, that is, octreotide (LAR 30 mg intramuscular every 28 days) for midgut NET G1/2 and lanreotide (autogel 120 mg deep subcutaneous every 28 days) for midgut and pancreatic NET with a Ki67 <10% and long-term data have confirmed durable efficacy with excellent tolerability. In general, SSR positivity confirmed by SSR imaging is considered a prerequisite for initiation of SSA treatment, but in the PROMID trial, this was not part of the inclusion criteria, and given the mechanism of action, we believe that particularly in low-grade midgut NET, SSA may also be used if SSR imaging is not (yet) available. The use of SSA for antitumour treatment in patients with a Ki67 above 10% is controversially discussed and while it is assumed that antiproliferative activity is a class effect, we prefer lanreotide in pancreatic NETs based on the pivotal studies. Finally, SSA stabilise but rarely induce an objective response; thus patients with a high symptomatic burden should be considered for alternative treatment options.

To conclude, octreotide and lanreotide are effective first-line treatment options within the approved indications, but clinical risk factors such as proliferation rate, previous progressive disease, functional status and hepatic tumour burden should be taken into consideration and potentially influence interval of follow-up and choice of the compound. For more detailed information on the approval trials, see table 1.

Peptide receptor radionuclide therapy

PRRT, using radiolabelled SSA, is an effective and well-tolerated treatment extending the concept of targeting SSR in NET. The phase III NETTER-1 trial assessed efficacy of PRRT versus high dose SSA (octreotide LAR 60 mg) in 229 patients with midgut NET progressive on previous SSA treatment. The study was the first large randomised trial confirming the high value of this treatment strategy. Primary endpoint PFS was clearly positive with an estimated PFS at 20 months of 65.2% for PRRT versus 10.8% in the control group (HR: 0.21, 95% CI: 0.13 to 0.33), suggesting a new standard for patients in this setting. To date, PRRT is both approved for midgut and also pancreatic NET with SSR expression, and PRRT can be considered for any type of SSR-positive disease in qualified multidisciplinary tumour boards.

mTOR inhibitors

Following early investigations that activation of the mTOR pathway has a driving role in NETs, the RADIANT trials evaluated everolimus for their treatment and additional sequencing studies have supported the concept of mTOR activation as the most relevant target. While the RADIANT-2 study including only symptomatic NETs was formally negative potentially due to concomitant SSA-use affecting PFS in the placebo arm, the RADIANT-3 study resulted in approval of everolimus for pancreatic NET based on a PFS increase from 4.6 months for placebo to 11 months (HR: 0.35, 95% CI: 0.27 to 0.45). More recently, the RADIANT-4 trial reported benefit also for non-functional midgut and lung NETs (PFS 3.9 vs 11 months; HR: 0.48, 95% CI: 0.35 to 0.67), and everolimus 10 mg is approved for progressive NET of the pancreas, midgut and lung. No new safety flags were documented and patient reported outcomes from the RADIANT-4 trial confirmed preserved quality of life particularly connected to prolonged PFS. None of the trials showed a significant survival benefit, but the long-term data from RADIANT-3 list a surplus of 37.7 versus 44 months despite crossover in 85% of patients.25

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Kiesewetter B, Raderer M. ESMO Open 2020;5:e000811. doi:10.1136/esmoopen-2020-000811
Everolimus is currently a widely used drug in NET, but we generally recommend treatment initiation only in progressive or symptomatic patients due to the indolent clinical course in many NETs and the RADIANT-trial inclusion criteria of documented progression. The optimal sequencing of available treatment option remains undefined. For midgut NET, the NETTER1-trial has reported convincing benefit for the use in patients progressive on previous SSA and in view of the convenience of therapy and minimal side effects, PRRT is currently our treatment of choice in these patients.17 Everolimus is a widely used upfront option for pancreatic NET in our practice. Ongoing studies (COMPETE trial) currently address this explicit question by randomising progressive SSR- positive GEP-NET to PRRT versus everolimus (NCT03049189). In addition, it has to be acknowledged that everolimus constitutes a continuous treatment, while PRRT may provide durable remissions with a possibility for retreatment; finally also the spectrum of side effects and comorbidities (ie, diabetes, renal insufficiency) may influence choice of treatment in the decision-making process together with the patient.

Sunitinib

Multityrosine kinase inhibitor (TKI) sunitinib is currently the only approved TKI for NENs with its use limited to pancreatic NET. Approval is based on a randomised phase III trial including a total of 171 progressive patients continuously treated with either sunitinib 37.5 mg daily or placebo.24 Final results showed a median PFS of 11.4 versus 5.5 months (HR: 0.42, 95% CI: 0.26 to 0.66). Long-term data indicate positive survival effects but remain statistically non-significant.25 In line with everolimus, we recommend use in patients with progressive disease, as toxicities and in particular diarrhoea showed impact on quality of life.26

**Chemotherapy**

Classical cytostatic compounds play no relevant role for the treatment of midgut NET G1/2 but the beta-cell specific compound streptozotocin (STZ) has been the only validated treatment for pancreatic NETs for decades. STZ should be combined with 5-flourouracil (5-FU) or doxorubicin, with the latter combination being more active regarding response rates and overall survival in a small randomised trial.27 While it is difficult to put these data into perspective with the modern WHO classification, several more recent series support efficacy of STZ/5FU, which is more feasible in terms of (cardio-) toxicity, especially in patients pretreated with targeted therapies.28–30 This is also supported by the recommendations provided in the most recent European Society for Medical Oncology (ESMO) guideline,6 but in contrast to historical data suggesting responses in up to 70% of patients, more recent data for STZ/5FU (±doxorubicin) are in the range of 40%–55% in series applying strict radiological criteria.28–30 The SEQTOR trial is currently evaluating the optimal sequencing of STZ/5FU and everolimus in pancreatic NET and will provide further prospective data (NCT02246127).

The oral alkylator temozolomide has widely been used for relapsed NEN, but lacked larger prospective data.
until ASCO 2018, where a randomised trial evaluating 144 pancreatic NETs G1/2 treated with temozolomide±capecitabine (CAPTEM) was presented.\textsuperscript{31} Despite imbalances and lack of stratification for tumour grade, the study showed first evidence that the combination (CAPTEM) is generally active and more effective than monotherapy (PFS 22.7 vs 14.4 months; HR: 0.58). Interestingly, the response rate was much lower (roughly 30%) than in the initial report by Strosberg and coworkers of 70%.\textsuperscript{32} In addition to these prospective data, there is evidence for the efficacy of CAPTEM at various sites of NEN, but documented activity seems to be highest in pancreatic and lung NET.\textsuperscript{33–35} There are still unanswered questions including optimal sequencing and impact of the MGMT-methylation status as biomarker.

**NET G3—an emerging entity**

Due to the novelty of this cohort, there are no prospective data on treatment of patients with NET G3. There is, however, consensus that first line platin-based treatment is suboptimal and strategies rather in line with NET G2 should be considered.\textsuperscript{10,36,37} The NORDIC NEC study showed significantly inferior response rates for G3 tumours with a Ki67 <55% versus higher-graded tumours (15% vs 42%) despite a better overall survival in NET G3 if compared with NEC patients.\textsuperscript{5–7} Nevertheless, the higher proliferation rate compared with G1/2 probably requires a more aggressive approach than targeted treatment strategies.

Based on available data, CAPTEM appears to be an effective treatment option and is currently our preferred approach for advanced NET G3 irrespective of tumour site.\textsuperscript{10,33,36} Treatment duration, however, remains individual and should be based on best response and tolerance, usually ranging from 6 to 12 cycles.

Further treatment options for NET G3 include PRRT in SSR-positive disease and STZ-based treatment for pancreatic primaries.\textsuperscript{29,38} mTOR inhibitors and TKIs should currently be restricted to clinical trials. It is conceivable that both the use of chemotherapy will increase with the recognition of this new cohort and also the use of multimodality concepts, as particularly the combination of active systemic treatments such as CAPTEM plus concomitant PRRT appear appealing based on the concept of adding a radiosensitizer and an active systemic treatment to PRRT.\textsuperscript{39,40} An important factor in this context is also the use of multimodality imaging that is, \textsuperscript{68}Ga-DOTA plus F-18-(fluorodeoxyglucose) FDG-PET/CT, as the heterogeneity of SSR expression is much higher in NET G3, and F-18-FDG-PET potentially visualises more aggressive cases.\textsuperscript{41} The increasing application of
next-generation-sequencing panels might allow insights into distinct biological behaviour of this novel entity.

Carcinoid syndrome
In addition to antiproliferative treatments, patients with endocrine active tumours and carcinoid syndrome (CS) pose a particular challenge in preserving quality of life. A recently approved agent in this setting is telotristat ethyl, a serotonin synthesis inhibitor which is active as add-on to SSA in refractory carcinoid diarrhea. Furthermore, shortening of SSA intervals, increase of SSA-dose or application of oral ondansetron may be considered for patients with refractory CS together with optimal supportive care and dietetic counselling, but the real value is still undefined and should be evaluated in the individual case. It is important to be aware of potential acute adverse effects during treatment initiation such as carcinoid crisis and late complications of CS like carcinoid heart syndrome, highlighting the importance of consistent use of SSA also beyond progression in patients with verified functional tumours.

CONCLUSION
NETs constitute a clinically heterogeneous group of tumours and challenge experts in performing an optimised multidisciplinary approach. In this review, we discuss common treatment options for antiproliferative therapy of advanced NET covering SSA, PRRT, everolimus, sunitinib, but also chemotherapy for pancreatic NET and NEN G3. Focusing on the view of a medical oncologist, we did not discuss the value of local therapy, but particularly liver-directed strategies constitute a further relevant option for patients with high hepatic tumour burden. Further systemic treatment strategies not mentioned but currently evaluated are novel TKIs such as lenvatinib, cabozantinib and surufatinib or monotherapy/combination therapy with checkpoint inhibitors.

In figure 1, we suggest a potential treatment algorithm but also warmly recommend use of the recent 2020 ESMO guidelines as well as the European Neuroendocrine Tumor Society (ENETS) guidelines. Finally, we like to emphasise the wide spectrum of clinical behaviour of these tumours ranging from indolent to aggressive, hence demanding an individual treatment approach based on risk-benefit evaluation on a per-patient basis.

Contributors Concept, writing and final approval of the manuscript: BK and MR.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests BK declares honoraria for lectures from Novartis, Ipsen and Celgene, MR declares honoraria for lectures from Novartis, Ipsen, Eisai and Celgene.

Patient consent for publication Not required.

Provenance and peer review Commissioned; externally peer reviewed.

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