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Preface

Dear Colleagues,

Members of the professional neuroendocrine community gathered at the North American Neuroendocrine Tumor Society (NANETS) Symposium that took place in Washington, D.C., from 27th to 29th October 2022 to discuss new therapeutic options and the future of neuroendocrine tumor research. The scientific program, featuring 16 oral- and 91 poster presentations, made the NANETS tagline “educating medical and professional researchers in the diagnosis and treatment of NET disease, and supporting research and innovation in the field”, more than just a slogan.

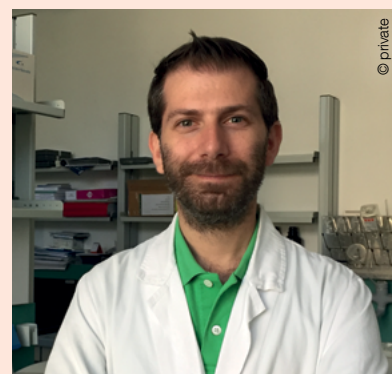
This report features three of the most actively investigated areas in the field: advances in peptide receptor radionuclide therapy (PRRT), potential applications of “passive” and “active” immunotherapy and novel biomarkers.

Not surprisingly, PRRT has been a major topic of discussion at this year’s Symposium. Head-to-head investigations comparing PRRT to other approved agents are starting to answer some of the most burning questions in the field, and the results of the COMPOSE trial, comparing the β -emitter

^{177}Lu -DOTATOC to the best standard of care will certainly shape the treatment algorithm of the next decades. The growing interest in α -emitter therapy was reflected in a number of presentations, with preliminary data on ^{212}Pb -DOTAMTATE supporting the potential of α -emitters to improve the efficacy of PRRT. Combinations of PRRT with epigenetic agents or drugs targeting the DNA repair pathways are under active scrutiny, and some pre-clinical studies are summarized here.

The latest advances in immunotherapy for NETs, despite the disappointing activity of immune checkpoint inhibitors as monotherapy, are also highlighted in this report. Here, the combination of tislelizumab plus surufatinib showed encouraging antitumor activity, while the future of oncolytic viruses appears potentially promising, as indicated by preliminary data from early-phase trials and preclinical studies presented at NANETS. Other novel immunotherapies presented include anti-SSTR CAR T cells, a survivin-targeting vaccine, and a hormone-based BiTE.

Finally, this report focuses on the importance of finding reliable biomarkers that can predict the response to standard treatments. In *MEN1*-mut/*DAXX*-wt pancreatic NET patients, the *MEN1* mutation was positively associated with CAPTEM response compared to other genomic profiles. Moreover, a novel



method, known as optical genome mapping (OGM) that allows for the identification of genomic structural variants in metastatic NETs was presented. Of note, OGM combined with short-read sequencing technologies, may be a promising tool to improve the molecular characterization of NETs.

Once again, the NANETS Symposium highlighted the importance of multidisciplinary and collaborations for accelerating cutting-edge NET research – establishing new standards of care with an eye to even better outcomes for diagnosing and treating NET patients.

We hope you enjoy reading this special memo in Oncology issue.

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SSTR-positive neuroendocrine tumors: peptide receptor radionuclide therapy

Real-world insights into re-treatment with the FDA-approved β -emitter ^{177}Lu -DOTATATE

^{177}Lu -DOTATATE was approved by the FDA in 2018 following the encouraging results from the NETTER-1 trial, where a regimen of 4 doses was shown to improve both progression-free survival (PFS) and overall survival (OS) com-

pared to somatostatin analog (SSA) therapy in patients with advanced gastroenteropancreatic neuroendocrine tumors (GEP-NETs) [1]. However, the progression of advanced NETs is inevitable and there is currently a lack of available treatment options for these patients. A retrospective chart review at a single US center evaluated the real-world effectiveness and safety of

re-treatment with ^{177}Lu -DOTATATE on progression [2].

Thirty-one patients with advanced NETs who received initial treatment with up to 4 doses of ^{177}Lu -DOTATATE and who were re-treated with ≥ 1 additional dose following disease progression and a period of ≥ 6 months since the end of initial treatment, were evaluated. Patients received a median of 6 doses (4 initial

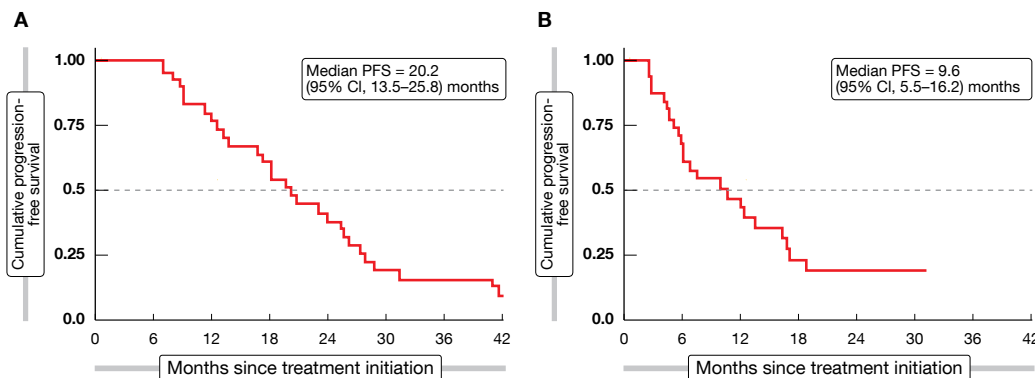


Figure 1: Progression-free survival observed from the start of initial treatment (A) and re-treatment with ^{177}Lu -DOTATATE (B)

doses and 2 re-treatment doses) and the average administered activity considering all stages of treatment was 41.9 ± 4.4 GBq. Best responses of partial response and stable disease were observed in 11 patients (35%) and 20 patients (65%) after initial treatment, and in 7 patients (23%) and 14 patients (45%) after re-treatment, respectively. Median progression-free survival (PFS) was 20.2 and 9.6 months after initial and re-treatment (Figure 1), respectively, and median OS was 42.6 months from the start of initial treatment and 12.6 months from the start of re-treatment. Although hematological parameters decreased significantly during both initial and re-treatment, they recovered with no significant difference between the values prior to initial treatment and prior to re-treatment. Only 1 grade 3 hematological adverse event (AE) occurred during initial treatment (neutropenia), while during re-treatment 4 grade 3 AEs were noted (1 leukopenia, 1 anemia, 2 thrombocytopenia). Clinically significant hematotoxicity occurred in 1 and 3 patients following initial and re-treatment, respectively. No grade 3 or 4 nephrotoxicity was observed at any time.

This real-world study provided early evidence supporting re-treatment with ^{177}Lu -DOTATATE, which appeared to be well tolerated and offered disease control in patients with progressive NETs following initial ^{177}Lu -DOTATATE treatment.

COMPOSE: ^{177}Lu -edotreotide, an alternative β -emitter

Well-differentiated aggressive grade 2 and 3 GEP-NETs frequently develop into metastatic disease [4]. The radiolabeled somatostatin analog ^{177}Lu -edotreotide (^{177}Lu -DOTATOC), a peptide receptor radionuclide treatment (PRRT), has

shown potential to expand the treatment landscape for these patients beyond current standard therapies, as it previously demonstrated promising efficacy and a favorable safety profile. In a retrospective study, two or more cycles of ^{177}Lu -edotreotide had been shown to provide a median PFS of nearly 30 months in metastatic GEP-NET patients [3]. The COMPOSE trial, a randomized, open-label, multicenter, phase III study, was designed to provide prospective data on the efficacy (PFS and OS) and safety of first- or second-line treatment with ^{177}Lu -edotreotide in patients with SSTR-positive GEP-NETs [5].

Recruitment of patients started in September 2021 and currently includes 29 sites across the globe. At least 202 patients are planned to be randomized 1:1 to either up to six cycles of ^{177}Lu -edotreotide (7.5 GBq per cycle administered intravenously at 6- to 8-week intervals) or an active comparator (capecitabine and temozolomide (CAPTEM) or folinic acid + fluorouracil + oxaliplatin (FOLFOX) chemotherapy, or everolimus according to investigator's choice). Interestingly, the authors noted that results from the control arm would provide prospective data on the efficacy of CAPTEM chemo-

therapy in grade 2 and 3 GEP-NETs, which is currently lacking too.

Expanding the range of PRRT options: promising results with α -emitters

PRRT with the β -particle emitter ^{177}Lu -DOTATATE is currently considered the standard of care (SoC) for patients with SSTR-positive GEP-NETs [6]. Despite the demonstrated benefits of ^{177}Lu -DOTATATE, there is a growing interest in α -emitter therapy with isotopes such as ^{212}Pb and ^{225}Ac , which have higher linear energy transfer (80–100 keV/ μm) and a shorter path length (40–100 μm) than β -emitters. As such, they have the potential to improve both the efficacy and safety of PRRT by causing irreversible DNA damage (i.e., double-strand breaks) in cancer cells as well as less collateral damage in healthy tissues, which should reduce the toxicity of the treatment [7].

In a preclinical study presented by Schultz et al., the efficacy of the novel α -emitter ^{212}Pb -PSC-PEG2-TOC was evaluated and compared to ^{177}Lu -DOTATATE in a mouse model. Single or fractionated doses of ^{212}Pb -PSC-PEG2-TOC (total ac-

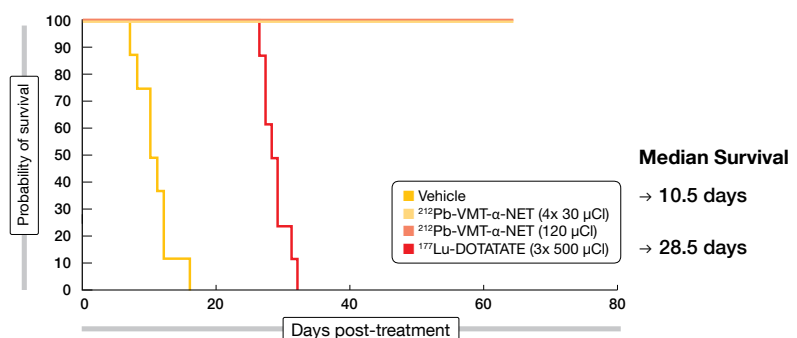


Figure 2: Overall survival benefit with ^{212}Pb -PSC-PEG2-TOC compared to ^{177}Lu -DOTATATE in a preclinical mouse model

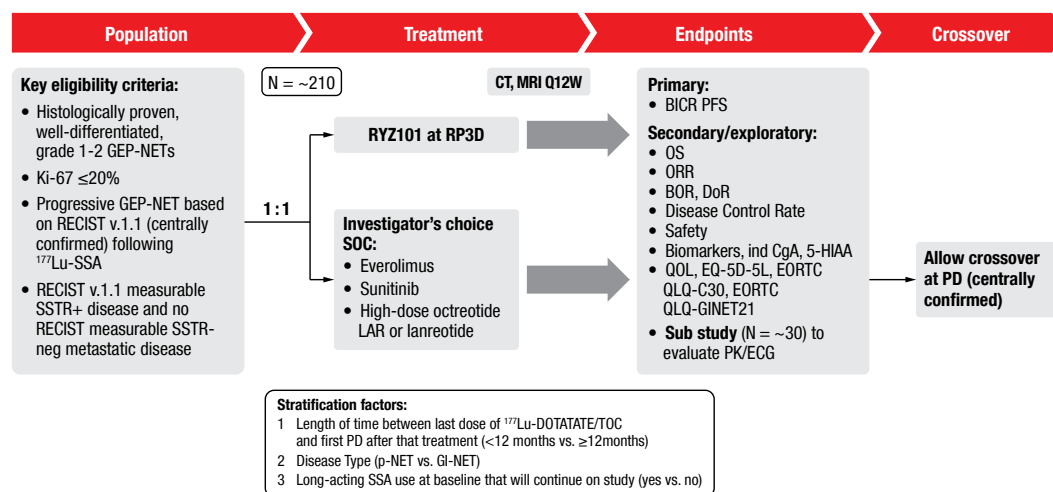


Figure 3: Study design of the part 2 (Phase 3) of the ACTION-1 trial

tivity at 4.44 MBq) were intravenously injected in tumor-bearing mice and 100% complete tumor responses were achieved (as of day 65 post-therapy initiation). ^{212}Pb -PSC-PEG2-TOC was well tolerated in comparison with ^{177}Lu -DOTATATE, which resulted in an improved OS compared to the vehicle cohort (28.5 days vs. 10.5 days) but no complete responses were observed (**Figure 2**) [8]. The promising efficacy of ^{212}Pb -PSC-PEG2-TOC demonstrated in this preclinical setting warrants further investigation in SSTR-positive NETs.

In line with these data, preliminary results from a phase I dose-escalation trial evaluating the α -emitter ^{212}Pb -DOTAMTATE in SSTR-positive NET patients were also presented at NANETS 2022. Metastatic NET patients with histologically confirmed tumors from any primary site were included in the study and treated with the recommended phase 2 dose (RP2D) of 4 cycles of 2.50 MBq/kg administered intravenously at 8-week intervals. An objective radiological response was observed in 10 out of 12 PRRT-naïve patients, while 6 out of 10 patients who had progressed after prior PRRT therapy with ^{177}Lu -DOTATATE demonstrated an objective response (ORR 60%). The treatment was well tolerated in all patients, with the most common treatment-emergent adverse events (TEAEs) being nausea, fatigue and alopecia. There were no serious drug-related TEAEs, and no dose reductions or treatment delays were required [9].

The authors concluded that ^{212}Pb -DOTAMTATE demonstrated promising efficacy and a favorable safety profile.

Enrolment in a phase II trial aiming to confirm the safety and efficacy of ^{212}Pb -DOTAMTATE in a larger cohort of patients with advanced NETs was ongoing at the time of presentation.

ACTION-1: α -emitter ^{225}Ac -DOTATATE after progression on ^{177}Lu -based PRRT

^{225}Ac -DOTATATE (RYZ101), another α -emitter, is currently being investigated for the treatment of SSTR-positive well-differentiated GEP-NETs. The ACTION-1 study is a randomized, open-label phase 1b/3 trial designed to first determine the safety, pharmacokinetics and recommended phase 3 dose (RP3D) of ^{225}Ac -DOTATATE (Phase 1b). In the second part of this study (Phase 3), its efficacy at the RP3D compared to the SoC (everolimus, sunitinib, or high-dose long-acting SSAs) will be assessed in patients with advanced GEP-NETs who have progressed following 2-4 cycles of prior PRRT with ^{177}Lu -labeled SSAs.

Enrolment in ACTION-1 part 1 is ongoing and currently includes about 6 sites across the US. The starting dose planned for this study is 120 kBq/kg administered intravenously every 8 weeks for up to 4 cycles, which will be de-escalated if necessary. Upon end of part 1, ~210 patients will be recruited at around 60 international sites and randomized 1:1 to receive either ^{225}Ac -DOTATATE at the previously established RP3D or investigator's choice of SoC. The primary endpoint of this study will be PFS by RECIST v1.1 (**Figure 3**) [10].

Exploring combination treatments to enhance PRRT

18-30% of patients do not respond to ^{177}Lu -DOTATATE [1]. Upgrading of the tumor and loss of SSTR expression through diverse epigenetic mechanisms, as well as the increased activity of DNA repair pathways that prevent radiation from inducing DNA damage, have been proposed as potential causes of PRRT refractory disease [11]. Several preclinical studies presented

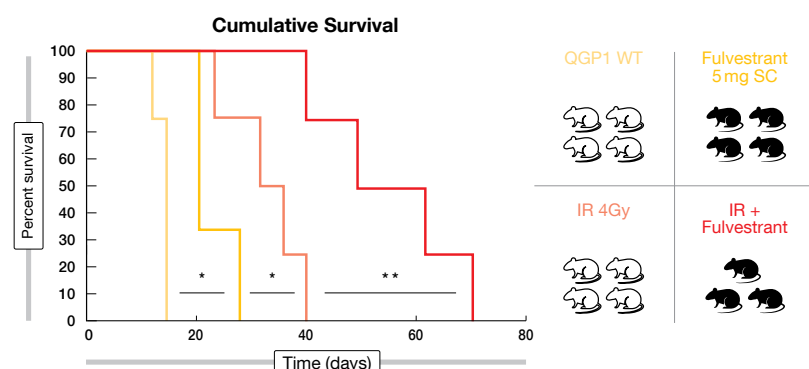


Figure 4: Cumulative survival results for Fulvestrant plus IR compared to Fulvestrant or IR alone in QGP1 tumor-bearing mice

at NANETS 2022 evaluated the combination of PRRT with other targeted therapies to improve its efficacy. On the one hand, two studies have shown that SSTR2 expression can be increased in NET cells by targeting various epigenetic enzymes that negatively control its expression, including DNA-methyltransferase (DNMT) and histone deacetylases (HDACs) [12, 13]. In line with this, enhanced uptake of ^{68}Ga -DOTATATE was observed in NET cells treated with VPA (HDAC inhibitor) and decitabine (DNMT inhibitor), as compared with either single drug [13]. Moreover, both fulvestrant (ESR1 inhibitor) and ATRA (Pin1 inhibitor) have been shown to radiosensitize NET cells by significantly decreasing expression of DNA repair genes such as BRCA1 and RAD51, and to delay tumor growth and

extend survival in a mouse xenograft model when combined with radiation (Figure 4) [14, 15].

CALR: a novel target for PRRT in pNETs

Current theranostic techniques have taken advantage of the common overexpression of SSTR2 in well-differentiated GEP-NETs by targeting them with radiolabeled SSAs. However, approximately 25% of low-grade, as well as most high-grade, pancreatic NETs (pNETs) are reported to lack SSTR expression and thus will not benefit from available therapies. Thus, alternative targets are required to provide new treatment options for these patients [16].

Preliminary results from a preclinical study presented at NANETS 2022 high-

lighted the potential of calreticulin (CALR) as an alternative diagnostic and therapeutic target for pNET patients with low expression of SSTRs. CALR is usually located in the endoplasmic reticulum and can transiently translocate to the cell membrane in response to certain stimuli [17]. In this study, surface translocation of CALR was induced in pNET cells to be detected by a novel radiolabeled peptide (^{68}Ga -CALR). In mice, ^{68}Ga -CALR was shown to be rapidly cleared via the kidneys and no significant uptake was seen in vital organs when injected at 3 MBq [18]. The authors concluded that these data strongly support the potential of CALR-radiolabeled peptides as new tools for the diagnosis and treatment of a subset of pNET patients. ■

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Advances in immunotherapy for neuroendocrine tumors

Limited activity of checkpoint inhibitors as monotherapy

Chemotherapy is currently the SoC first-line treatment for high-grade neuroendocrine neoplasms (HG-NENs), even though it only provides modest benefits in OS and PFS [1]. Given the lack of therapeutic options for metastatic NEN patients and the promising

antitumor activity of immunotherapy demonstrated across several solid cancer types, the efficacy of pembrolizumab monotherapy was investigated in an open-label, nonrandomized phase II study in patients with metastatic extra-pulmonary HG-NEN (Ki67 >20%) [2].

Six patients who had progressed upon platinum- or temozolomide-based

chemotherapy were included in the study and received at least 1 dose of pembrolizumab. The authors reported that one patient had stable disease, which was maintained for 8.3 months, while the remaining 5 had progressive disease at 6 weeks (Figure 1, Table 1). The treatment was well tolerated and only one AE of grade ≥ 3 was considered to be related to the drug.

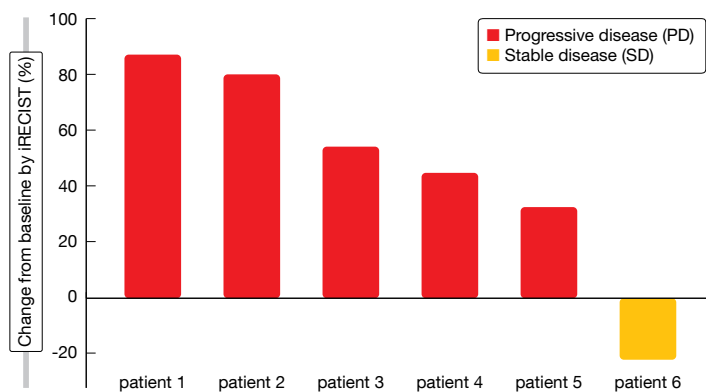


Figure 1: Percent change in target tumor size from baseline at 6 weeks of pembrolizumab monotherapy

TABLE 1 Treatment response by iRECIST at 6 weeks (N=6)	
Best overall response	N (%)
Complete response (CR)	0 (0%)
Partial response (PR)	0 (0%)
Stable disease (SD)	1 (17%)
Progressive disease (PD)	5 (53%)

Despite the small number of patients, these results already indicated that pembrolizumab has limited activity as monotherapy in HG-NENs. These findings were consistent with previously published studies assessing pembrolizumab's efficacy in metastatic grade 3 NENs [3, 4].

Conflicting results of different combinations of ICIs with TKIs: tislelizumab plus surufatinib...

As outlined above, the efficacy of immune checkpoint inhibitors (ICIs) as monotherapy in NETs has been disappointing [2-4]. However, the combination with tyrosine kinase inhibitors (TKIs), which has proven effective in other cancers such as endometrial cancer or renal cell carcinoma [5, 6], remains to be further explored in NETs. The inhibition of angiogenesis together with the stimulation of an immune response may have a synergistic effect and enhance overall antitumor activity.

The open-label, phase 1b/2 dose escalation/expansion study presented by Eads et al. explored the preliminary antitumor activity of tislelizumab, an anti-PD-1 monoclonal antibody, plus surufatinib, a TKI, in thoracic- and GEP-NETs. Twenty-nine NET patients who had received prior anticancer treatment were enrolled in the expansion

study, where they received 300 mg of surufatinib orally, once daily (RP2D established in escalation), and 200 mg of tislelizumab intravenously every 3 weeks. No patient demonstrated a complete response. However, partial responses were observed in five patients (17.2%), and 10 patients had stable disease (34.5%) (**Figure 2**). The reported ORR was 11.1% for the thoracic NET cohort and 20% for the GEP-NET cohort (**Table 2**). While at least one TEAE of any grade occurred in all 29 patients, TEAEs of grade ≥ 3 were noted in 20 patients (69%). The most common TEAEs were increased aspartate aminotransferase (AST) (51.7%), nausea and hypertension (44.8% each), decreased appetite and fatigue (41.4% each), and increased alanine aminotransferase (ALT) (34.5%). One case each of increased AST and ALT led to dose reductions in the GEP-NET cohort [7].

The authors concluded that surufatinib plus tislelizumab demonstrated encouraging anti-tumor activity and manageable safety in pre-treated patients with NETs.

...and pembrolizumab plus lenvatinib

In contrast with the previous findings, the combination of pembrolizumab

with the multitargeted TKI lenvatinib assessed in an open-label phase II trial presented at NANETS 2022 did not demonstrate sufficient response in patients with advanced gastrointestinal and thoracic NETs [8]. This prospective study included patients with well-differentiated NETs who had received at least two prior lines of systemic treatment and showed evidence of disease progression within 8 months of study entry. Study participants were administered 20 mg of lenvatinib orally daily and 200 mg of pembrolizumab intravenously every three weeks until unacceptable toxicity or progressive disease.

In an interim analysis of the first 20 patients enrolled in the study, only two reached a partial response (10%). The median PFS was 9 months. Probably- or definitely-associated grade 3 AEs were reported by 12 patients (60%), and 14 patients (70%) required dose reductions or discontinued one of the treatments. Since not even 4 ORs were reached, further enrolment was not warranted.

Potential of oncolytic viruses to sensitize tumors to checkpoint inhibitors: early-phase trials and preclinical data

It has been proposed that the limited activity of ICIs in NENs may be due to a non-inflamed phenotype of their tumor microenvironment [9]. Based on this assumption, several studies started to explore the potential of oncolytic viruses to convert NENs to a highly inflamed phenotype, which would sensitize them to ICI therapy [10, 11].

An engineered Vesicular stomatitis virus-based oncolytic virus (VSV-IFN β -NIS) is currently being tested in combination with pembrolizumab in a phase 1/2 trial in neuroendocrine carcinoma (NEC) patients who have progressed on at least one prior line of systemic therapy. As reported at NANETS 2022 by McGarrath et al., the safety run-in phase of the study has been completed and the enrolment of patients for the dose expansion cohort was ongoing at the time of presentation. Twelve NEC patients of any primary tumor site will be included in the study and treated with the RP2D of VSV-IFN β -NIS on day 1, followed by pembrolizumab on day 8 and then every 3 weeks until progression of disease or

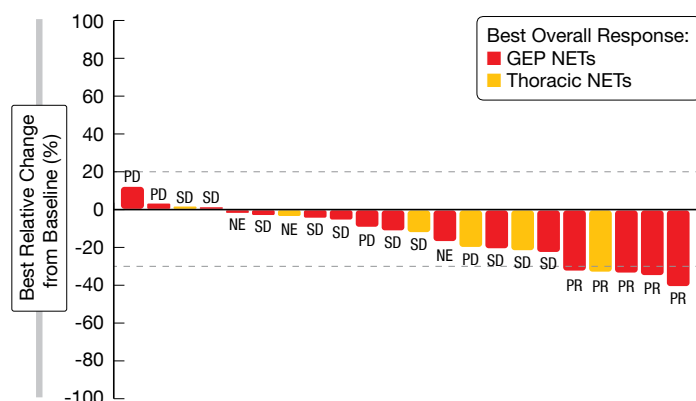


Figure 2: Best percent change in target lesion diameter with tislelizumab plus surufatinib in thoracic and GEP NETs

TABLE 2 Antitumor Activity		
	Thoracic NETs (N=9)	GEP NETs (N=20)
Best overall response, n (%)		
Complete response (CR)	0	0
Partial response (PR)	1 (11.1)	4 (20.0)*
Stable disease (SD)	3 (33.3)	7 (35.0)
Progressive disease (PD)	1 (11.1)	4 (20.0)
Not evaluable	1 (11.1)	2 (10.0)
Missing	3 (33.3)	3 (15.0)
Objective response rate, n (%) (95% CI)	1 (11.1) (0.3, 48.2)	4 (20.0)* (5.7, 43.7)
Disease control rate, n (%) (95% CI)	4 (44.4) (13.7, 78.8)	11 (55.0) (31.5, 76.9)

* Includes 1 unconfirmed PR at data cutoff

unacceptable toxicity, for up to 2 years. The primary endpoint will be ORR by RECIST v1.1, and if at least one objective response is observed and safety is confirmed, the study regimen will be considered for further investigation [10].

The Seneca Valley virus (SVV), on the other hand, is a naturally occurring oncolytic virus found to have selectivity for NETs. In a preclinical study presented at NANETS 2022, the efficacy of SVV in combination with ICIs was evaluated using an ICI-resistant mouse model. SVV was intratumorally injected along with systemic ICIs (anti-PD-1 and/or anti-CTLA4). Complete responses were observed in 5 out of 6 (>83%) tumor-bearing mice within 44 days of injection of SVV+anti-PD-1+anti-CTLA4, and these animals remained tumor-free for >160 days. In contrast, control-treated mice were all sacrificed by day 70 (median survival <50 days)

due to tumor burden, with transient tumor regressions observed only in those treated with anti-PD-1 plus anti-CTLA4. In addition, tumors from mice injected with the combination of SVV+ICIs showed the highest levels of CD3+ and CD8+ T-cell infiltration, which indicates conversion to an inflamed phenotype. This study provided evidence that SVV is able to reverse resistance to ICIs and enhance their efficacy. Based on these promising preclinical data, a first-in-human phase I trial of SVV oncolytic virotherapy combined with ICIs is expected to start enrolling NEN patients in the first quarter of 2023 [11].

Novel immunotherapies in the NET setting: from CAR T-cells...

Adoptive cell therapy using chimeric antigen receptor (CAR) T-cells has proven

remarkably effective in patients with B-cell malignancies, but there is a lack of data regarding solid tumors, including NETs [12]. Results from preclinical studies presented at NANETS 2022 showed that an anti-SSTR CAR construct, which was developed to direct T-cells against SSTR-positive NETs by incorporating the SSA octreotide in the extracellular domain, demonstrated promising cytotoxic activity both in vitro and in vivo [13]. The design of a clinical trial to evaluate its toxicity is currently under development. Since the potential for toxicities and side effects associated with CAR T-cells is very high, the authors underlined that even if no toxicities of the construct were observed in SSTR-expressing organs in mice, only patients who have progressed after previous lines of treatment and who have exhausted all other options will be included in the clinical trial.

... to a survivin-targeting vaccine...

SurVaxM is a novel immunotherapy based on a peptide vaccine that targets survivin, a cell-survival protein expressed in 95% of glioblastomas and many other cancers, including NETs [14]. A subset of NET patients with survivin-expressing tumors could potentially benefit from a survivin-targeting therapy, as survivin expression has been shown to correlate with poorer outcomes in NETs (OS 8.5 years vs. 18.3 years) [15].

An ongoing phase I trial is currently assessing the safety and immunogenicity of SurVaxM in patients with survivin-positive (>1% by immunohistochemistry) metastatic NETs. With enrolment still ongoing at the time of presentation, 4 patients had completed the treatment (4 doses every 2 weeks), and the observed PFS reported at NANETS 2022 was 10.9 months [16].

... and a somatostatin-based bispecific T-cell engager

Another novel immunotherapy currently under development for NETs is based on bispecific antibodies, which are designed to target a specific tumor-associated antigen as well as to engage and activate tumor-infiltrating lymphocytes [17].

With the aim of targeting well-differentiated NETs, Pelle et al. investigated a hormone-based bispecific T-cell engager (BiTE) composed of two molecules of somatostatin-14 linked with a single-chain variable fragment-based anti-CD3. In a preclinical setting,

this BiTE-like molecule was shown to specifically engage the T-cell receptor CD3 (>85% of T-cells bound at a concentration of 100 nM) and to efficiently induce a high level of SSTR-specific T-cell activation, as indicated by the significantly increased secretion of

IFN- γ detected in the presence of SSTR-expressing cells ($p < 0.0001$) [18]. Based on these promising results, further studies will be aimed at determining the efficacy of the BiTE *in vivo*. ■

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Biomarkers: predicting response to treatment

Better PFS with CAPTEM in *MEN1*-mut/*DAXX*-wt pNET patients

pNETs frequently contain mutations in *MEN1*, *ATRX*, *DAXX*, and the *PI3K/AKT/mTOR* pathway [1]. However, more data are needed to determine whether this information can predict response to standard treatments, such as CAPTEM.

At NANETS 2022, Hendifar et al. presented retrospective data on 25 patients with well-differentiated grade 1 and 2 pNETs who had received CAPTEM as first- or second-line treatment and whose tumors had been molecularly characterized through next-generation sequencing (NGS). As reported by the authors, *MEN1* mutations were posi-

tively associated with CAPTEM response. However, this effect was less pronounced in the subset of patients with co-occurring *DAXX* mutations, which are commonly found together with *MEN1* alterations. PFS with CAPTEM was significantly longer, regardless of line of therapy, in *MEN1*-mut/*DAXX*-wt pNET patients compared to other genomic profiles (Figure 1) [2]. The correlation of this novel genomic signature with response to CAPTEM in pNETs should be validated in a prospective and larger cohort.

PRRT-predictive quotient predicts response to PRRT

Another treatment strategy commonly used in the management of NETs is

PRRT [3]. However, there is also a lack of reliable molecular biomarkers predicting its clinical efficacy. Data regarding a PRRT-predictive-quotient (PPQ) was presented at NANETS 2022 and may be a promising non-invasive tool to improve the management of NET patients undergoing PRRT.

PPQ is a blood-based genomic assay that integrates circulating levels of NET-specific gene transcripts with tumor grade (as determined by Ki67 staining) to provide information on tumor radiosensitivity and PRRT responsiveness (PPQ+ = predicted PRRT responder). In a previous study on three independent cohorts of ¹⁷⁷Lu-PRRT-treated lung and GEP-NET patients, PPQ was shown to predict response to PRRT in a specific manner and with an

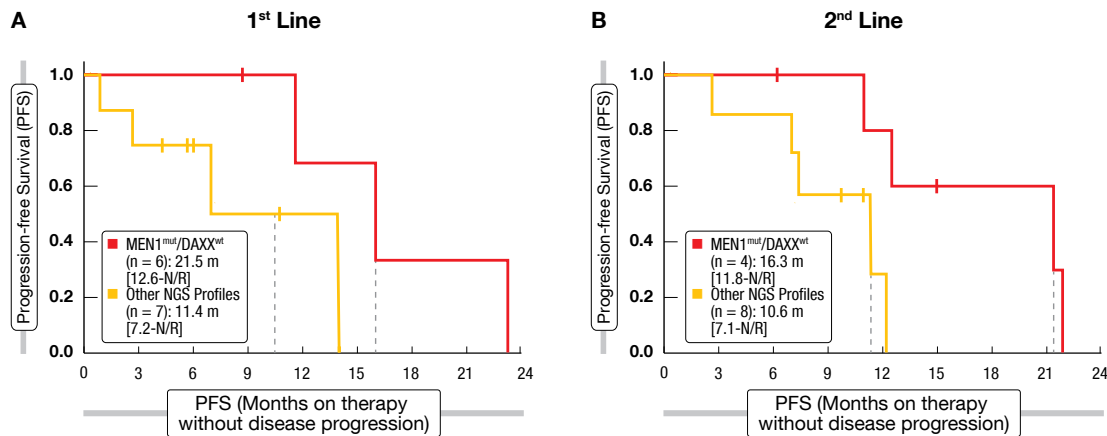


Figure 1: Progression-free survival outcomes with first (A) or second (B) line CAPTEM in pNET subgroups defined by their *MEN1/DAXX* mutational status

accuracy of >95% (compared to an accuracy of only 50% in SSA-treated cohorts) [4, 5]. The efficacy of PPQ as a predictive marker of PRRT response is currently being validated in a prospective cohort of metastatic NET patients in the US, where the potential of PPQ to predict the toxicity of PRRT will also be evaluated [6].

Immune-related effects as biomarkers of SSA response

Treatment with SSAs such as lanreotide is considered standard of care in advanced NETs. SSAs exert an inhibitory effect on tumor cells through binding to the overexpressed SSTR2 [7]. However, the effect of SSAs on immune cells, which have also been shown to differentially express *SSTR1-5*, is not well understood.

To identify potential biomarkers that would predict response to SSA, Maguire et al. investigated the effects of lanreotide on different subsets of T-cells sorted from a cohort of SSA-treated NET patients (9 responders and 8 non-responders). According to the results from gene and protein expression analysis presented at NANETS 2022, a basal (pre-treatment) upregulation of T-cell receptor and interferon signaling in CD4+ and CD8+ cells, respectively, indicated a greater immunological competence of responders compared to non-responders. Three months after SSA treatment, downregulation of cytokine and chemokine signaling as well as upregulation of ubiquitination and proteasome degradation-associated genes

was observed in responders [8]. This study underscored the relevance of immune effects associated with SSA therapy. Based on these data, the clinical utility of the differentially expressed genes in responders vs. non-responders as predictive markers of SSA response may be determined.

New strategies for molecular profiling of NETs

Optical genome mapping (OGM) was presented at NANETS 2022 as a novel method for the identification of genomic structural variants that may drive the progression of metastatic NETs [9]. NETs have generally been thought to have a low mutation burden [1, 10]. Considering that genetic profiling is usually performed with short-read sequencing technologies, which are able to detect single nucleotide variants but might miss large structural variants [11], the addition of OGM would provide complementary information and contribute to a better molecular characterization of NETs.

A proof-of-concept study evaluated OGM using biopsy samples from 16 metastatic NET patients of different grade and primary site. The authors reported a mean of 48 ± 43 and a median of 32 structural variants identified in each sample. On average, deletions accounted for 44% of variants, insertions for 21%, inversions for 2%, inter-chromosomal translocations for 15%, and intra-chromosomal translocations for 18% (Table 1). OGM not only identified structural variants in all samples, but

also found trends towards differences between tumors of different grade and primary site of origin [9]. New variants identified by OGM could be further correlated with clinical data and outcomes to identify potential biomarkers that may help improve the clinical management of NETs.

An alternative strategy for the molecular profiling of pNENs that may help provide better tailored treatments for these patients was presented by Lou et al. Based on an analysis of 318 NEN cases from which histological grade annotation as well as NGS and WTS data were available, a threshold of *MKI67* expression able to differentiate low grade (LG) from high grade (HG) NENs was defined. This *MKI67* threshold was then validated in a larger cohort of NEN patients ($n=1768$). The differences between the mutational landscapes of HG- vs. LG-NENs observed in pathology-based cohorts were recapitulated in the HG and LG cohorts inferred from *MKI67* expression, including *TP53*, *KRAS* and *RBI*. These molecular alterations were more frequent in HG-NENs than in LG (Δ prevalence = 44.31%, 24.09% and 25.61%, respectively; $q < 0.05$), while LG-NENs were found to have higher expression of *SSTR1-3* (1.12-fold, 1.77-fold and 1.06-fold, respectively; $q < 0.05$). In contrast, *SSTR4* was significantly higher in HG-NENs (3.87-fold, $q < 0.05$). Subsequently, the prevalence of each mutation was assessed according to the expression levels of each SSTR subtype. In HG-NENs, *MEN1*, *ATRX* and *TSC2* were increased among *SSTR1-2*-high

TABLE 1

Sample	Grade	Ki-67	Primary	Deletions	Insertions	Inversions	Inter-chromosomal translocations	Intra-chromosomal translocations	All mutations
1	2	12	lung	22	10	0	0	3	35
2	2	18	pancreas	34	10	2	21	1	68
3	3	40	pancreas	46	24	3	67	46	186
4	3	64	pancreas	36	16	5	6	21	84
5	2	7	rectum	17	14	0	0	3	34
6	2	6	rectum	19	8	0	0	2	29
7	1	1	SB	9	7	0	2	0	18
8	2	7	SB	17	8	0	0	0	25
9	2	6	SB	24	7	0	7	36	74
10	2	13	SB	14	8	0	0	0	22
11	2	12	SB	9	7	0	2	0	18
12	2	12	SB	16	8	1	8	15	48
13	2	7	SB	10	4	0	0	0	14
14	2	6	SB	33	14	3	2	9	61
15	2	5	SB	22	5	0	0	1	28
16	3	28	SB	9	16	0	4	1	30

cases, while *KRAS* and *RB1* were more frequent in *SSTR1-2*-low tumors [12]. The authors concluded that transcriptomics could be leveraged to predict pNEN grade and to identify the mole-

cular profiles associated with the expression of each *SSTR* subtype. Thus, routinely assessing *SSTR* subtype expression and incorporating molecular profiling might help to improve clinical

decision-making, e.g., the identification of patients eligible for PRRT among other therapies. ■

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