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Accepted manuscript

# UNMET MEDICAL NEEDS IN METASTATIC LUNG AND DIGESTIVE NEUROENDOCRINE NEOPLASMS.

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## ABSTRACT

Unmet medical needs are not infrequent in oncology and these needs are usually of higher magnitude in rare cancers. The field of neuroendocrine neoplasms (NENs) has evolved rapidly during the last decade and currently a new WHO classification is being implemented and several treatment options are available in metastatic setting after the results of prospective phase III clinical trials. However, several questions are still unanswered and decisions in our daily clinical practice should be made with limited evidence. In the 2016 meeting of the advisory board of the European Neuroendocrine Tumor Society (ENETS) the main unmet medical needs in metastatic NENs setting were deeply discussed and several proposals to try to solve them are presented in this article, including biomarkers, imaging and therapy.

## INTRODUCTION

The treatment landscape of advanced neuroendocrine neoplasms (NENs) has dramatically evolved over the last decade. Somatostatin analogs, targeted drugs (everolimus and sunitinib) and more recently peptide receptor radionuclide therapy (PRRT) have been approved for distinct subtypes of NENs (1-5). Other treatment options are available, including loco-regional therapies in liver-predominant disease and systemic chemotherapy in more aggressive NENs(6). Given the heterogeneity of the disease, therapy selection is still a challenge, even with approved drugs. Predictive markers are still lacking. While some treatments are safe, other treatments might be disadvantageous for patients not only for a lack of activity but deleterious side effects. The better knowledge of tumor heterogeneity, behavior, and prognosis of NENs has allowed a more precise classification and drug development plan in the metastatic setting. However, several issues are unresolved in the field of biomarkers, tools to best assess therapy response, and therapeutic choices.

The advisory board of the European Neuroendocrine Tumor Society (ENETS) discussed in their annual meeting which topics covering the unmet medical needs should be addressed in the metastatic setting and suggested several clinical and translational studies to solve these limitations.

The current article summarizes the urgent limitations in different fields of NENs setting including biomarkers, disease behavior, imaging, and therapy.

## UNMET NEEDS IN THE BIOMARKER FIELD

The search for biomarkers in oncology is mandatory to optimize therapy and to define prognostic tools for a better treatment management. General prognostic biomarkers are routinely used in clinical practice to guide treatment strategies in NENs, including differentiation and proliferation (measured by Ki67 index or mitotic count), tumor burden, hormone related syndromes or circulating biomarkers such

as chromogranin A or 5-HIAA (table 1). These tools are mainly used to define prognosis but their utility to predict efficacy of therapies is limited.

Prospective validation of promising novel biomarkers such as of circulating tumor cells (CTCs) (7) and circulating tumor DNA (ctDNA) regarding their prognostic value is needed before implementing these tools in clinical practice. Feasibility of ctDNA compared to CTCs probably will position this approach for liquid biopsy in the near future (8). The increasing use of circulating transcripts analysis (NETest) is showing additional data on different tumor types and therapies, even the real value compared with routine biomarkers, such as CgA, has been validated in small prospective cohorts and is investigated in ongoing clinical trials.

Proliferation and differentiation have also been assessed with the combination of tracers in the nuclear medicine theragnosis. Tumor heterogeneity is frequently shown by combining PET tracers, such as 18FDG and 68Ga-DOTA-SSA. The correlation of molecular tumor changes and translation to nuclear imaging could help to better define tumor heterogeneity and potentially guide therapeutic decisions.

The panel suggested several study proposals to define the possible role of new biomarkers in NENs, and the main ones are summarized in table 2.

## UNMET NEEDS IN THE IMAGING FIELD

The natural history of well-differentiated NETs, with a usual, slowly growing behavior, and the richness of vascularity as well as disease stabilization as best response to most therapies have always created a challenge in tumor assessment and response to therapy. The application of RECIST criteria assessing objective response in tumors with shrinkage of at least 30% of the tumor volume seems too rigorous for slowly growing NET. Patients may benefit from targeted therapies even if best response is stabilization of the disease. Reevaluation of the sunitinib phase 2 and phase 3 clinical trial data recently suggested a 10% cut-off value for objective response as a better predictor of durable progression-free survival(11).

However this threshold needs to be validated prospectively including other types of treatment. The use of Choi criteria has been discussed since tumor shrinkage is combined with tumor attenuation measures and may depict some of the morphological changes that may occur with the use of targeted drugs such as necrosis. Occurrence of large areas of hypodensity and or necrosis has been described with the use of sunitinib and everolimus(12). First data indicate that Choi criteria may add to early response prediction in advanced GEP NENs treated with sunitinib(13); Recent data from the phase IV study of sunitinib in pan-NETs showed a better estimation of PFS and ORR compared with RECIST (14). However, the value of Choi criteria needs to be validated prospectively in an integrated approach using modified RECIST criteria and Choi criteria.

The velocity of tumor growth has been defined as a prognostic tool and a critical value for decision of initiation of systemic therapy with targeted agents or chemotherapy. The concept of tumor growth rate (TGR) has been retrospectively suggested as a valuable prognostic biomarker and the changes of TGR also have been related with prolonged benefit to somatostatin analogs (15-17).

For the panel, two main issues should be urgently assessed regarding imaging procedures. Firstly, the TGR should be better defined by tumor type, location of metastases, and prediction of survival and response to therapy irrespective of the type of therapy. And secondly, radiological characteristics regardless of TGR should be uniformly standardized to avoid misunderstandings in tumor evaluation under specific therapies. The creation of clear criteria for tumor evaluation and different thresholds to predict response to each specific therapy should be of great interest. Table 3 summarizes a proposal for a retrospective study to validate TGR in different scenarios and radiological features to predict response and survival.

## UNMET NEEDS IN LOCOREGIONAL AND SYSTEMIC THERAPIES

The natural history of the vast majority of NETs with high liver tropism of systemic disease has allowed during decades the combination or sequential application of locoregional liver therapies with systemic treatments. The limitation of active schedules to treat advanced disease has probably reinforced the intensive liver-directed approaches to reduce tumor volume, decrease hormone release and impact on the survival of patients. Fortunately, during the last decade the armamentarium to treat systemic disease has significantly increased based on positive results of phase III clinical trials, and in advanced NETs, the use of several systemic therapies including somatostatin analogs, targeted agents and PRRT, has demonstrated significant benefit in progression-free survival in different NETs locations.

It remains unclear if a loco-regional therapy may impact the outcome of a patient to the same extent as a systemic therapy. Similarly, it is not clarified if a sequential selection of specific drugs is superior to another sequence of drugs. None of the trials has shown overall survival benefit, but this finding is probably confounded by a high cross over rate in randomized placebo-controlled trials. Given the fact that none of the therapies provides cure, novel treatments are warranted. Thus, the panel discussion was focused on three main issues: the role of locoregional liver therapies compared with systemic treatments, the optimal sequence of available systemic therapies and the future of new drugs in NENs setting.

The experience of liver directed therapies has been quite extensive during the last three decades with several reports showing radiological responses and clinical benefit. However, the lack of well-designed prospective and randomized clinical trials has limited the level of evidence of locoregional liver therapies in NETs. The arrival of new drugs in this setting based on positive results of phase III studies has increased the doubts of optimal indication of liver directed therapies and we urgently need to create new evidence of the best scenarios for this treatment approach. Table 4 summarizes the main proposals discussed by the panel that could help to reduce the unmet needs in locoregional treatments.

Currently, systemic treatment options for advanced NENs are based on the results of prospective clinical studies in most of the indications. Regarding pancreatic origin, in addition to the streptozotocin-based chemotherapy approved for this indication in the US, somatostatin analogs, everolimus and sunitinib have demonstrated significant impact in controlling tumor progression compared with placebo in phase III studies. Recently, for small intestinal origin, everolimus and <sup>177</sup>lutetium DOTATATE have shown significant improvement of progression-free survival in advanced stages and also everolimus has been the first drug to demonstrate an impact on progression-free survival in a phase III clinical trial including lung neuroendocrine tumors. All these approved therapies need to be placed with other non-standardized options, such as temozolomide-based chemotherapy or PRRT for primary tumors outside the small intestine, that exponentially increase the complexity of sequential therapies in advanced Pan-NETs or lung carcinoids.

One of the phase III clinical trials in NENs setting that is recruiting patients nowadays is the SEQTOR study, an academic trial with the primary goal is to assess the sequence of established systemic therapies for pancreatic NETs (streptozotocin-based chemotherapy and everolimus). Another trial comparing everolimus with PRRT in GEP-NET is the COMPETE study that recently started recruitment as well as the French multicenter trial comparing PRRT and sunitinib in Pan-NETs (OCCLURANDOM). Several studies are comparing different treatment options for advanced disease, however, the real impact on survival of sequential therapies that do not follow a rigorous scheme but may be highly variable depending on accessibility of drugs and patient-related factors and comorbidities could only be assessed by prospective data or big data analysis from current clinical practice. Table 5 summarizes the proposal of the panel for a high-quality assessment of real-world data of sequential therapies in NETs.

And last, but not least, classical unmet need in oncology arrives when patients experience disease progression after all available treatment strategies have been



employed. We are currently in the precision oncology era but NENs are not the paradigm for this ambitious approach. The lack of clearly identified driver mutations has jeopardized the development of targeted agents with the same efficacy observed in other tumor types, such as lung cancer or melanoma. But not only new drug development in refractory setting is urgently needed, but a better understanding of drug combinations is especially necessary for the NET field, where somatostatin analogues are probably too frequently used in combination with targeted agents or even with chemotherapy, with the lack of benefit demonstrated in prospective trials(18). Some retrospective reports have suggested at least an additive effect of octreotide or lanreotide with everolimus or sunitinib (19), even this data has not been validated prospectively. Several clinical trials are currently recruiting patients and may clarify this issue in the near future. To the panel, five main unmet needs were profoundly discussed regarding the value of currently available drugs, drug combinations and future development and are summarized in table 6.

Finally, the drug development has not been equally dedicated to all neuroendocrine tumors types or situations. Nowadays, for lung carcinoids, everolimus is the only drug approved so far, based on the results of a phase III clinical trial(20). However, the most frequent first approach to treat advanced lung carcinoids is the use of somatostatin analogs, even in the absence of prospective data in this setting and based only in retrospective cohorts that suggest a promising benefit of somatostatin analogs mainly in typical carcinoids (21). The SPINET (Lanreotide vs Placebo) study is currently recruiting patients to answer this important question, however the recruitment is significantly lower than expected mainly because most patients receive somatostatin analogues “off label” upfront. The recommendation of the panel to solve this problem comes from two different points. Firstly, to prioritize the recruitment of patients in the SPINET study to clearly define the role of SSA in this setting, and secondly, foreseeing the long duration of expected recruitment and the time gap to make prospective data available, a high quality data collection of patients with lung carcinoids treated with somatostatin analogs outside of a clinical trial, could help in the final interpretation

of the real value of this therapy. Further, chemotherapy (e.g. temozolomide) is frequently used as an additional treatment option, particularly in atypical carcinoids. Although a prospective phase 2 study is ongoing (ATLANT) gathering retrospective high-quality data may help to understand the value of chemotherapy in lung carcinoids. On the same way, PRRT has only retrospective data in lung carcinoids and its use cannot be widely recommended until a confirmatory prospective clinical trial will be available, so a global retrospective approach evaluating the activity of PRRT in this setting together with the best way to assess the somatostatin receptor expression in lung carcinoids should be a priority for the scientific community (22).

The new WHO classification 2017 has included the expected group of G3 NETs, based on evidence of a clearly different behavior and response to chemotherapy compared with G3 NECs. This discrimination of subgroups within the NEN G3 will be expanded to other anatomical sites in the near future. This new classification has clearly created a new orphan disease within NENs and treatment strategy for this new group is urgently needed. Data coming from prospective clinical trials will be very limited and again high-quality data from routine practice would be extremely useful.

## CONCLUSIONS

Unmet needs are frequent in medicine, and especially in oncology, and even more in a complex, heterogeneous and multidisciplinary disease like NENs. The panel acknowledges the limitations of selecting some unmet needs and not others and to create several proposals to try to resolve them. The field of discussion, advanced disease, is too broad to go into detail of all currently unmet needs, but efforts have been focused on six aspects that include the development of prognostic and predictive biomarkers, an optimization of the imaging assessment, a better understanding of the complexities of the disease, the development of high quality retrospective studies that may complement the prospective ongoing trials and achieve faster results, an optimization of the available drugs and the design of

future prospective trials, and finally a more accurate estimation of patients' quality of life and overall survival impact.

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Table 1: Biomarkers in NEN

	<b>Established</b>	<b>Exploratory (optional)</b>
<b>Tissue</b>	Ki67	PTEN, TSC-2 expression
	Mitotic count	DAXX, ATRX
	Morphology	TP53, RB
<b>Circulating markers and metabolites</b>	CgA	NETest
	NSE	CTCs
	Peptide hormones*	ctDNA
	5-HIAA**	miRNAs
<b>Functional Imaging</b>	111In Octreoscan; 68Ga-SR-PET/CT FDG-PET***	68Ga-NODAGA-JR11 or 68Ga-OPS202 (imaging); 177Lu-DOTA-JR11 or 177Lu-OPS201 (therapy) 18F-Fluorothymidin-PET

\*In functioning tumors: gastrin, insulin, glucagon, vasoactive intestinal peptide

\*\* 5-HIAA; 5-hydroxyindoleacetic acid in 24h urine, metabolic breakdown product of serotonin

\*\*\* in poorly differentiated NEN and as a prognostic tool in all NENs(9, 10)

Table 2: Novel Biomarkers in NEN and potential applications

<b>Study objective</b>	<b>Setting</b>	<b>Biomarker</b>	<b>Goal</b>
Definition of new prognostic biomarkers	PanNET G2  PanNET G3 and NECs	Histological markers, such as DAXX/ ATRX  TP53, RB  DAXX/ ATRX	Establishment of prognostic markers in metastatic disease to facilitate therapy onset / choices;  Improved discrimination of NETG2/ NEN G3;  Establishment of a molecular classification
Comparison of CgA with novel circulating biomarkers	GEP-NET G1/ G2 and lung carcinoids	CTCs, NETest microRNAs	Establishment of biomarkers with higher sensitivity and more accurate information on recurrence and/or progression
Explore tumor heterogeneity	GEP-NET G1/ G2/ G3	18FDG and 68Ga-SSA-PET-CT/MRI; “Omics” in biopsies;  Validation of circulating biomarkers;  nomogram	Facilitate appropriate therapy selection;  Define patients with possibility of response to PRRT (specific score)
Impact of molecular profiling on	All NENs	Molecular profiling, including	New target identification;  Precision medicine for

therapy selection and outcome		genomics, gene and protein expression.	optimized therapeutic management
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Table 3: Preferred trial proposal to assess tumor response with targeted drugs

	Inclusion criteria	Main evaluations & objectives
	<p>Metastatic Pan-NETs &amp; GI NETs with liver involvement (G1/G2)</p> <p>Cohort 1: Treated patients (for response evaluation/prediction/TGR)</p> <p>Cohort 2: Therapy naïve patients under surveillance (for TGR prognostic value)</p>	<p>Central radiology review</p> <p>Characterization of liver metastases (size, contrast enhancement, vascularization, TGR)</p> <p>Create clear criteria for tumor evaluation under different conditions (SSA, antiangiogenics, mTOR, PRRT, chemotherapy)</p> <p>Create a threshold to predict response to treatment</p> <p>Create a prognostic value of TGR in Pan-NETs and GI-NETs (and at different times of the evolution of the disease)</p> <p>Correlation with PFS</p>

		based on RECIST & OS
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Table 4: Trial proposal to establish the role of locoregional and ablative therapies in NEN

STUDY	SETTING	OBJECTIVES
Debulking liver surgery	Pan-NETs and SI NETs Limited liver disease	Define the optimal % of tumor resection to impact on outcome
Role of surgery in potentially resectable liver metastases	PanNETs and SINETs Liver disease only	Compare systemic therapies upfront vs full resection of liver metastases; define Ki67 cut-off value for resection and identification of other prognostic markers for benefit of surgery
Role of liver-directed embolization	Pan-NETs and SI-NETs Predominant liver disease	Compare systemic therapies vs liver embolization in specific endpoints, such as liver-disease progression
Role of radioembolization in NETs	Pan-NETs and SI-NETs Predominant liver disease	Comparison of TAE/TACE and radioembolization
Evaluation of intraarterial PRRT liver infusion	PanNETs and SI-NETs Predominant liver disease	Comparison of intraarterial PRRT liver infusion vs systemic PRRT; assess toxicity, QoL, and outcome (PFS)

SI-NET, small intestinal neuroendocrine tumors

Table 5: Sequential therapies in NETs study proposal

Setting	Pan-NETs and SI-NETs G1/ G2/ G3	Special remarks
Main objective	Overall survival with respect to each sequential therapy strategy	
Objectives per each treatment line	Median PFS Objective response rate Improvement of symptoms Quality of life	Response rate evaluated by central radiology review
Additional objectives	Accessibility of therapies Real world data of therapies administered to NET patients Personal and economic status Differences between countries	
Main inclusion criteria	At least three sequential therapies Balance between known prognostic factors; separation by primary tumor site (pancreatic vs. small intestinal NET)	Clustering of same treatment algorithms

Table 6. Unmet needs in drug development for NETs

Main issue	Available data	Proposal
Define the correct drug dose	Studies ongoing (CLARINET forte) and results of completed studies (control arm NETTER-1, phase III pasireotide)	Studies with pasireotide at different dose levels  Retrospective data of high doses of octreotide/ lanreotide for symptom and tumor control
Define the continuation of SSAs beyond progression	CALGB; SWOG	Prospectively collected data of continuation of SSAs and combination with targeted agents
Drug combinations to revert prior resistance	CALGB (everolimus+bevacizumab)	Design of prospective clinical trials for drug combination and new drugs with different targets to revert resistance
Exploration of serotonin synthesis inhibition by telotristat ethyl	Lack of evidence of the drug impact in reduction of progression of carcinoid heart disease (or prevention of recurrence after bioprosthetic valve replacement) and mesenteric fibrosis	Translational research  Real world data (prevalence of CHD in patients treated with TE vs. patients not having access to the drug) when drug will be widely used for symptom control; preferable study



		design is to assess recurrence of endocardial fibrosis after heart valve surgery
Definition of immune landscape of NENs and best approach for immunotherapy	Keynote 028 subset of NET; Keynote 158 (ongoing)  PDR001 study	Design of prospective clinical trials with optimized drug combinations, e.g. PRRT and checkpoint inhibitor

TE telotristat ethyl, CHD carcinoid heart disease

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