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Establishing content validity of patient-reported outcome (PRO) measures in extrapulmonary neuroendocrine carcinomas (epNEC): A cognitive debriefing interview study

Marianne Pavel[1], Stephen Ijioma[2], Thomas Boerner[2], Julia Koevi[2], Nicholas Liu[3], Maarten Voorhaar[2], Claudia Carulla[4], Simona Sgarbi[4], Agnes Williams[5]

1. Uniklinikum Erlangen, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany; 2. Boehringer Ingelheim, International GmbH, Ingelheim am Rhein, Germany; 3. Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA; 4. IQVIA, Madrid, Spain, 5. IQVIA, London, United Kingdom

CONCLUSIONS

epNEC is reported to impose a substantial and heterogeneous symptom burden, encompassing both systemic and tumor location-specific symptoms

Despite substantial symptom heterogeneity, physical functioning (PF) consistently emerge as a key and meaningful impact of epNEC across clinicians, patient advocates, and patients

Findings support the content validity (understanding, relevance, ease of answering, recall period) of the QLQ-C30 PF domain and IL46. The remaining QLQ-C30 items were relevant to epNEC and easy to understand. Selected PRO-CTCAE items were also well understood and easy to answer. In contrast, the EORTC QLQ-GI.NET21 showed limited relevance in patients with epNEC due to biological and symptomatic differences between NETs and NECs.

Together, these findings support the use of QLQ-C30, IL46 and PRO-CTCAE items as part of a fit-for-purpose PRO assessment strategy for future epNEC clinical studies

Introduction

- epNEC is a rare and highly aggressive group of neoplasms arising outside the lungs, associated with rapid disease onset, limited treatment options, poor prognosis and significant quality of life burden [1-3]. Incidence is similar in men and women[4]
- A recent concept elicitation study of 27 patients with epNEC[5] identified heterogeneous symptoms and burdensome impacts on physical functioning
- No well-defined, content-valid PRO instruments are currently available for epNEC
- While PRO measures used in patients with neuroendocrine tumors (NETs) could be applicable in epNEC, differences in biological behavior, tumor differentiation, and hormone production may limit the content validity of these PROs in epNEC
- Further evaluation is needed to determine the content validity of existing PRO measures in patients with epNEC to ensure that meaningful and interpretable patient experience data is captured in clinical trials

Objectives

To evaluate the **content validity** of select PRO instruments in patients with epNEC, generating evidence to inform a **fit-for-purpose PRO measurement strategy** for future clinical trials

Methods

- Non-interventional, cross-sectional, qualitative interview study

Selected PROs to assess in this study

EORTC QLQ-C30: EORTC Quality of Life Questionnaire-Core Questionnaire

EORTC QLQ-GI.NET21: EORTC Gastro-intestinal Neuroendocrine Tumor module

EORTC IL46: EORTC Item Library 46 single item (assesses overall side effect burden)

PRO-CTCAE: PRO of the Common Terminology Criteria for Adverse Events
- Taste changes
- Rash
- Numbness and tingling
- Dizziness
- Headache
- Hair loss
- Chills

- Following the ISPOR PRO Good Research Practices guidance and given the rarity of epNEC and difficulty identifying patients with epNEC a three-step systematic approach was used:

Clinician interviews
- 3 oncologists experienced in treating epNEC with obrixtamig in ongoing trials
- 45-min interviews exploring:
  - Signs, symptoms, and impacts of epNEC
  - Obrixtamig side effects
  - Relevance of PRO-CTCAE items selected for obrixtamig

Focus group
- 4 patient representatives and two additional oncologists
- 150-min focus group confirming key epNEC signs, symptoms, and impacts, and evaluating the relevance of EORTC QLQ-C30, IL46, and QLQ-GI.NET21 items in epNEC

Patient interviews
- 6 patients with epNEC
- 45-min cognitive debriefing interviews assessing item understanding, relevance, ease of completion, and recall periods of the selected PRO instruments

Findings

Across all phases, **physical functioning (PF)** was consistently identified as central to the patient experience with epNEC

1 Clinician interviews

- Three experienced clinicians from different countries participated

	Clinician 1	Clinician 2	Clinician 3
Country	Germany	Spain	Japan
Specialty	Oncologist	Oncologist	Oncologist
Years treating epNEC	30	20	>20
epNEC patients/year	60	50	3-4
Main sites treated	GI, GU, GY	GI, GU (except prostate), unknown primary*	GI, unknown primary*

* Site of origin is not possible to determine due to metastasized tumor at the time of diagnosis

- Symptom presentation varied substantially across primary tumor sites, highlighting the need for PRO measures that capture a broad range of patient experiences
- Physical functioning (PF) was identified as a key aspect of epNEC affected by both disease and chemotherapy

Affected PF areas mentioned: difficulty taking **long walks**, **climbing stairs**, **exercising**, inability to **self-care**, needing **breaks**

- Most commonly reported treatment-specific adverse events associated with obrixtamig were cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and fatigue

PRO-CTCAE: Chills, dizziness, rash and taste changes were confirmed as relevant PRO-CTCAE concepts. Hair loss was reported only when combined with chemotherapy. Headaches and numbness/tingling were not reported by clinicians

2 Focus group

- Four patient representatives and two clinicians participated

Participants	Countries	Experience
n=4 patient representatives	US, US, UK, Germany	Leading epNEC patient support group, leading NEC/NET hotline, attending webinars/ conferences, providing patient resources
n=2 clinicians	US, Germany	Medical oncologists specializing in NECs

All participants (n=6) confirmed:
- The relevance of signs/symptoms and daily life impacts of epNEC listed in the conceptual model developed in a recent qualitative study with 27 patients[5]
- The key importance of physical impacts, driven by fatigue, weakness, and pain
- The burden associated with transition from independence to dependence

Affected PF areas mentioned: difficulty **getting out of bed**, **walking**, **playing with children**, **household** activities, needing **rest breaks** in between tasks, needing a **lie down** during the day, inability to **exercise**, **loss of independence** and needing to develop **coping mechanisms**

EORTC QLQ-C30: All items were considered relevant to epNEC

EORTC IL46: Item was considered relevant to assess side effects

EORTC QLQ-GI.NET21: This NET-specific PRO was considered to have limited relevance in patients with epNEC, due to biological and symptomatic differences between NETs and NECs. Therefore, this PRO was excluded from debriefing with patients

3 Patient interviews

- Six adult patients from US (n=3), Germany (n=2), and Italy (n=1)
- Predominantly female (n=5), white (n=6), with a mean age of 56 years (SD=11.1). Half were retired (n=3)
- Diverse educational background from secondary/high school to Master's degree
- Most had gastrointestinal epNEC (n=4), with varied primary sites and disease stages (I-IV)

Table: Cognitive debriefing of selected PROs

	Relevance	Understanding	Ease of answering	Recall period
EORTC QLQ-C30 PF domain	✓	✓	✓	✓
EORTC IL46	✓	✓	✓	✓
Other QLQ-C30 domains	✓	–	–	✓
PRO-CTCAE	–	✓	✓	–

✓ Positive feedback from ≥4 of 6 participants for most items; ✓ Suggestions received from half of participants for most items; – Attribute not assessed; only selected attributes were formally debriefed, given the established use of these instruments in oncology

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; EORTC, European Organisation for Research and Treatment of Cancer; IL46, Item Library 46 single item; PRO, Patient-reported outcome; QLQ-C30, Quality of Life Questionnaire-Core Questionnaire

In-depth content validity assessment of priority PROs:

EORTC QLQ-C30 PF domain (5 items)
- Highly relevant to the epNEC patient experience
- Well understood and easy to answer; minor wording and translation feedback did not affect participants' ability to respond
- No defined recall period in the PF domain; interpretation varied

EORTC IL46 (single item)
- Relevant for assessing treatment side effects
- Well understood and easy to answer; minor wording concerns
- Some noted that the 1-week recall period may be too short due to side effect fluctuations across treatment cycles

Content validity assessment of other PROs: selected attributes assessed*

Other QLQ-C30 domains (25 items)
- All items relevant to all or nearly all participants
- No difficulties understanding the items
- No issues answering based on the past week, however some suggested a longer recall period

PRO-CTCAE (selected items)
- Selected items (see Methods) were well understood and easy to answer by the participants who completed debriefing (n=2)

*These instruments are well established across multiple cancer populations and were therefore assessed only for selected attributes

Abbreviations
CRS, Cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; epNEC, Extrapulmonary neuroendocrine carcinoma; EORTC, European Organisation for Research and Treatment of Cancer; GI, Gastrointestinal; GU, Genitourinary; GY, gynecological; ICANS, Immune effector cell-associated neurotoxicity syndrome; IL46, Item Library 46 single item; NET, Neuroendocrine tumor; PF, Physical functioning; PRO, Patient-reported outcome; QLQ-C30, Quality of Life Questionnaire-Core Questionnaire; QLQ-GI.NET21, Gastrointestinal Neuroendocrine Tumor module

References
1. Stumpo, S. et al. *Extrapulmonary Neuroendocrine Carcinomas: Current Management and Future Perspectives*. J Clin Med. 2023;12:7715. 2. Frizziero et al. *Expanding Therapeutic Opportunities for Extrapulmonary Neuroendocrine Carcinoma*. Clin Cancer Res. 2022;28:1999–2019. 3. Del Olmo-García et al. *Nutritional status and quality of life of patients with advanced gastroenteropancreatic neuroendocrine neoplasms in Spain*. The Oncologist. 2025;30:oyae343. 4. Dasari et al. *Comparative study of lung and extrapulmonary poorly differentiated neuroendocrine carcinomas*. Cancer. 2018;124:807–815. 5. Zhou Y, Ijioma S, Liu N, et al. Exploring symptoms, impacts, and bothersomeness in patients with extrapulmonary neuroendocrine carcinoma (epNEC). ENETS 2026, Abstract H25.

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