Peptide receptor radionuclide therapy in G3 gastroenteropancreatic neuroendocrine tumors: a missed opportunity for European patients?

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Neuroendocrine neoplasms (NENs) are classified as rare cancers.[1] According to the WHO 2022 classification, gastroenteropancreatic well-differentiated NENs (GEP-NETs) are stratified into grade 1 (Ki-67 < 3%), grade 2 (3–20%), and grade 3 (>20%).[2] While most GEP-NETs are grade 1 or lower-grade 2 (Ki-67 3–10%), both the incidence of these cancers and the availability of effective treatments decline as Ki-67 increases.

High-level evidence supporting the use of peptide receptor radionuclide therapy (PRRT) in patients with GEP-NETs first emerged following the NETTER-1 trial, which compared ^{177}Lu-dotatate versus high-dose octreotide in patients with grade 1 and 2 small bowel NETs progressing on standard-dose octreotide.[3] More recently, the phase 3 NETTER-2 trial compared ^{177}Lu-dotatate plus standard-dose octreotide versus high-dose octreotide as first-line therapy in patients with advanced, SSTR-positive GEP-NETs with higher grade 2 and grade 3 tumors (Ki-67 10–55%).[4] NETTER-2 demonstrated a significant extension of the median PFS (22.8 months versus 8.5 months; HR: 0.28, $p < 0.0001$) and a marked improvement of the objective response rate (43% versus 9.3%) in patients treated with ^{177}Lu-dotatate. At the time of the primary analysis, no significant difference was seen between ^{177}Lu-dotatate and high-dose octreotide in terms of overall survival (OS). This is a frequent event in NET clinical trials and is thought to be the consequence of high rates of crossover from the control to the investigational arm.

Based on the NETTER-2 trial, the scientific community was poised to welcome ^{177}Lu-dotatate as a new first-line therapeutic option for patients with higher grade 2 and grade 3 GEP-NETs. The anticipation was particularly strong for grade 3 tumors, a subgroup for which treatment options are poorly supported by high-quality evidence. ^{177}Lu-dotatate was expected to represent a major advance, offering patients a therapeutic strategy grounded on robust clinical data.

Given the results of the NETTER-2 trial, an application was filed by Novartis to the European Medicine Agency (EMA) to extend the indications of ^{177}Lu-dotatate to patients with newly diagnosed, unresectable or metastatic, higher grade 2 or grade 3 GEP-NETs. However, the manufacturer withdrew the application on May 9, 2025.[5] In its letter notifying EMA of the withdrawal, the company stated that the decision was not related to the quality, efficacy or safety of ^{177}Lu-dotatate.[5] Before the withdrawal, EMA had completed an initial evaluation, raised formal questions, and reviewed the company's responses. Despite these steps, several issues remained unsolved, leading EMA to provide a provisional negative opinion. Among the key concerns expressed by EMA were the lack of OS prolongation observed in the NETTER-2 trial and the possibly unfavourable risks (e.g. second primary malignancies, hematological and renal toxicities and cancer hyper-progression) in a treatment-naïve population. As a result, the current EMA approval for ^{177}Lu-dotatate remains limited to advanced, progressive, grade 1 and grade 2 GEP-NETs,[6] and it currently unclear whether a new submission will be filed by Novartis.

The unease of EMA reviewers with the use of PFS as a primary endpoint to justify first-line use of ^{177}Lu-dotatate over a somatostatin analog is understandable. Octreotide and lanreotide are both low risk drugs with few toxicities. Without any evidence of OS benefit, it is hard to determine whether early use of ^{177}Lu-dotatate in treatment-naïve patients is justified.

Nevertheless, the failure to approve ^{177}Lu-dotatate for European patients with G3 tumors in any line of therapy is lamentable. The activity of somatostatin

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analogs in this population is minimal at best. Unapproved chemotherapy regimens such as capecitabine and temozolomide are commonly used in patients with pancreatic primaries but few, if any therapies, are of proven benefit in gastrointestinal G3 NETs. In this context, ^{177}Lu-dotatate therapy would fill a critical gap.

The concerns expressed by EMA and the subsequent decision to withdraw the application for extending the indications of ^{177}Lu-dotatate raise several pressing questions. How can trial sponsors better collaborate with regulatory agencies to ensure validity of primary endpoints prior to study initiation? How should European scientific societies reconsider and update their recommendations for clinical guidelines, which had already begun to incorporate the potential use of ^{177}Lu-dotatate beyond its current indication?

For now, it appears that European patients with grade 3 GEP-NETs will be denied access to ^{177}Lu-dotatate. The scientific community, regulatory authorities and pharmaceutical industry must partner to foster access to effective treatments in the right settings.

Contributors

FP, MC, JS: conceptualization, writing–original draft, writing–review and editing. All Authors contributed equally.

Declaration of interests

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