The recent European approval of lutetium (^{177}Lu) oxodotreotide increases treatment options for gastroenteropancreatic neuroendocrine tumors

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“Lutetium (^{177}Lu) oxodotreotide is the very first registered PRRT to be brought to the European NET patient community, providing an alternative option by targeting tumors with radiolabeled molecules that bind to specific receptors expressed by the tumor.”

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The recent European Approval of Lutetium (^{177}Lu) oxodotreotide has meant the introduction of another new therapy option to treat gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Lutetium (^{177}Lu) oxodotreotide is a ^{177}Lu -labeled somatostatin analog peptide for the treatment of unresectable or metastatic, progressive, well-differentiated (G1 and G2), somatostatin receptor-positive GEP-NETs in adults. It belongs to an emerging form of treatment called peptide receptor radionuclide therapy (PRRT), which involves targeting tumors with radiolabeled molecules that bind to specific receptors expressed by the tumor.

The European approval of Lutetium (^{177}Lu) oxodotreotide allows for its marketing in all 28 European Union member states, as well as Iceland, Norway and Liechtenstein. This approval is based on the results of a randomized pivotal Phase III study, NETTER-1, in midgut NET patients; and efficacy and safety data from a Phase I/II trial conducted by Erasmus Medical Center in more than 1200 patients with a wide range of NET indications [1].

The challenges associated with GEP-NETs

There are numerous challenges associated with GEP-NETs, and these include the side effects and symptoms of the condition based mainly on the location of the tumors. GEP-NETs, are a group of tumors derived from the neuroendocrine cells, which can occur anywhere along the GI tract [2]. GEP-NETs are also rare diseases, for example, in USA, the estimated incidence of NETs in gastroenteropancreatic sites is 3.56 per 100,000, including 0.48 per 100,000 persons in the pancreas [3]. However, the prevalence of NETs is relatively high, despite the low incidence, as they are often slow growing (171,321 per 100,000 persons in USA) [3,4].

Symptomatology can vary widely, complicating accurate diagnosis. In many cases, NETs may be nonfunctioning tumors with no secretion of actively symptomatic hormones. As a result of this, nonfunctioning NETs can remain clinically silent in the early years of the disease process, often delaying the diagnosis in many patients [5]. Some patients with NETs develop symptoms arising from the excessive production of hormones by neuroendocrine tumor cells, such patients are said to have functioning tumors [6]. The secretion by GEP-NETs of peptides and neuroamines can cause distinct clinical syndromes, including carcinoid syndrome due to the secretion of serotonin [7]. Symptoms of the condition vary, however, the majority includes diarrhea, abdominal pain, flushing, fatigue or heart problems [8]. Other commonly experienced symptoms can also include weight loss, anorexia, nausea and intra-abdominal mass effects [9]. However, the condition can often be misdiagnosed, as with nonfunctioning tumors, there can be either a lack of symptoms or symptoms of a nonspecific nature. The most common misdiagnoses for NETs include irritable bowel syndrome, allergies, Crohn's disease, anxiety and menopause [10].

Once diagnosed, optimal management of NETs is required and this usually involves a multidisciplinary effort employing medical, surgical, imaging and pathology specialties [11]. Surgery is often the first line therapy for treating early stage NETs. However, many patients with NETs are diagnosed once metastases have already occurred,

limiting the curative ability of surgical approaches. NETs of the intestine commonly metastasize to the mesentery, peritoneum and liver. Patients with NETs have a 9.3 years mean overall survival time [3]. However, for pancreatic NETs, median overall survival is 3.6 years in advanced disease [3]. In dedicated centers, the 5-year survival rate for metastatic pancreatic NETs is above 60% [12].

What does Lutetium (^{177}Lu) oxodotreotide offer based on the NETTER-1 trial results?

PRRT, Lutetium (^{177}Lu) oxodotreotide now provides the clinical community with an alternative solution. The approval of this novel treatment was based on the results of a randomized pivotal Phase III study, NETTER-1 that compared treatment using Lutetium (^{177}Lu) oxodotreotide with a 60 mg dose of Octreotide LAR (double dose standard of care) and overexpressing somatostatin receptors as well as efficacy and safety data from the Erasmus Phase I/II trial conducted in more than 1200 patients, with a wide range of NET indications including foregut (including bronchial and pancreatic), midgut and hindgut [1].

An update of the NETTER-1 efficacy results was requested by the European Medicines Agency with a cut-off date of 30 June 2016 and these results were consistent with previously published results in *The New England Journal of Medicine* [1]. The NETTER-1 study met its primary end point, showing a reduction of risk of progression or death of 79% using Lutetium (^{177}Lu) oxodotreotide compared with octreotide LAR 60 mg. The current update (after 71 cumulative deaths), also confirmed the favorable trend of 28 deaths in the Lutetium (^{177}Lu) oxodotreotide arm versus 43 in the octreotide LAR 60 mg arm. Additionally, the median overall survival in the octreotide LAR arm was 27.4 months, but was still not reached in the Lutetium (^{177}Lu) oxodotreotide arm after 42 months, with a hazard ratio of 0.536, meaning a reduction of risk of death of 46% using lutetium (^{177}Lu) oxodotreotide compared with octreotide LAR 60 mg [13].

How does the introduction of Lutetium (^{177}Lu) oxodotreotide impact the treatment landscape for GET-NETs?

The NETTER-1 trial has now meant that Lutetium (^{177}Lu) oxodotreotide has received orphan drug designation from the European Medicines Agency and the US FDA.

In terms of other therapies for treating GEP-NETs, there are limited other approved and effective treatments currently available. Systemic therapies including somatostatin analogs (SSA) encompassing octreotide LAR and lanreotide autogel are recommended as first-line therapy in midgut and pancreatic NETs to control tumor growth, however the Ki-67 threshold, based on the CLARINET study, is $\text{Ki-67} \leq 10\%$ [14,15].

IFN- α is another option and a second-line therapy in neuroendocrine neoplasms, previously considered for more functionally active tumors, often as an add-on therapy to SSA. It might be considered an antiproliferative option, however the toxicity of IFN- α is limiting in its own right [14].

Novel targeted drugs everolimus and sunitinib are the third available treatment option, and are approved for pancreatic NETs based on the results of two placebo-controlled trials on progressive pancreatic NETs [16,17]. These are considered first-line therapies, when SSA is not a viable option, and usually prior to the consideration of systematic chemotherapy. Everolimus can also be recommended in advanced NET of nonpancreatic origin in case of disease progression. This recommendation is based on the results of the RADIANT-4 trial that reached its primary end point and demonstrates superior progression-free survival with everolimus compared with placebo in nonfunctional NET of intestinal or lung origin [18].

Systematic chemotherapy is a further option indicated in progressive pancreatic NETs for progressive or large volume G1, G2 and well-differentiated G3 tumors. Chemotherapy regimens include cytotoxic combinations STZ/5-FU. This form of treatment is however only recommended in patients with higher tumor burden or in patients with significant tumor progression in $\leq 6\text{--}12$ months [14]. Temozolomide/capecitabine has increased in popularity, being considered a first-line therapy; however, it is not categorically recommended due to current limited data for temozolomide. Platinum-based chemotherapy is also recommended as a first-line therapy in G3 NEC [14].

Finally, PRRT, which encompasses Lutetium (^{177}Lu) oxodotreotide, is recommended after the failure of other medical therapies [14]. Lutetium (^{177}Lu) oxodotreotide is the very first registered PRRT to be brought to the European NET patient community, providing an alternative option by targeting tumors with radiolabeled molecules that bind to specific receptors expressed by the tumor. The NETTER-1 quality of life analysis provides evidence of benefit in key domains that are pertinent to midgut NETs, including global health and diarrhea. This suggests that treatment with Lutetium (^{177}Lu) oxodotreotide not only maintains, but improves, quality of life [19,20].

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References

1. Strosberg J, El-Haddad G, Wolin E *et al*. Phase III trial of ¹⁷⁷Lu-dotatate for midgut neuroendocrine tumors. *N. Engl. J. Med.* 376, 125–135 (2017).
2. Díez M, Teulé A, Salazar R. Gastroenteropancreatic neuroendocrine tumors: diagnosis and treatment. *Ann. Gastroenterol.* 26(1), 29–36 (2013).
3. Dasari A, Shen C, Halperin D *et al*. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol.* 3(10), 1335–1342 (2017).
4. Geschwind Jean-Francois H, Soulen Michael C. *Interventional Oncology: Principles and Practice of Image-Guided Cancer Therapy*. Geschwind Jean-Francois H, Soulen Michael C. (Eds). (2nd Ed.) Cambridge University Press, Cambridge, UK (2016).
5. O'Connor JM, Marmissolle F, Bestani C *et al*. Observational study of patients with gastroenteropancreatic and bronchial neuroendocrine tumors in Argentina: results from the large database of a multidisciplinary group clinical multicenter study. *Mol. Clin. Oncol.* 2(5), 673–684 (2014).
6. Oladejo AO. Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) - approach to diagnosis and management. *An. Ib. Postgrad. Med.* 7(2), 29–33 (2009).
7. Modlin IM, Oberg K, Chung DC *et al*. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol.* 9(1), 61–72 (2008).
8. Kaupp-Roberts S, Srirajaskanthan R, Ramage JK. Symptoms and quality of life in gastroenteropancreatic neuroendocrine tumours. *EMJ Oncol.* 3(1), 34–40 (2015).
9. Gut P, Czarnywojtek A, Bączek M *et al*. Clinical features of gastroenteropancreatic tumours. *Prz. Gastroenterol.* 10(3), 127–134 (2015).
10. Carcinoid.org. Could you have a neuroendocrine tumor? (2018). www.carcinoid.org/wp-content/uploads/2015/07/NET-Cancer-infographic-Nov-2016.pdf
11. Singh S, Asa SL, Dey C *et al*. Diagnosis and management of gastrointestinal neuroendocrine tumors: an evidence-based Canadian consensus. *Cancer Treat. Rev.* 47, 32–45 (2016).
12. Öberg K, Knigge U, Kwekkeboom D, Perren A. Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 23(Suppl. 7), vii124–vii130 (2012).
13. Advanced Accelerator Applications. Lutathera® (lutetium (¹⁷⁷Lu) oxodotreotide) Summary of Product Characteristics (SmPC). (2017). http://ec.europa.eu/health/documents/community-register/2017/20170926138665/anx_138665_en.pdf
14. Pavel M, O'Toole D, Costa F *et al*. ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (nen) and nen of unknown primary site. *Neuroendocrinology* 103, 172–185 (2016).
15. Caplin M, Pavel M, Ćwikła JB *et al*. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N. Engl. J. Med.* 371, 224–233 (2014).
16. Yao J, Shah MH, Ito T *et al*. RAD001 in advanced neuroendocrine tumors, third trial (RADIANT-3) study group. Everolimus for advanced pancreatic neuroendocrine tumors. *N. Engl. J. Med.* 364(6), 514–523 (2011).
17. Raymond E, Dahan L, Raoul JL *et al*. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N. Engl. J. Med.* 364, 501–513 (2011).
18. Yao J, Fazio N, Singh S *et al*. RAD001 in advanced neuroendocrine tumours, fourth trial (RADIANT-4) study group. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, Phase 3 study. *Lancet* 387(10022), 968–977 (2016).
19. Strosberg J, Wolin EM, Chasen B *et al*. Improved time to quality of life deterioration in patients with progressive midgut neuroendocrine tumors treated with ¹⁷⁷Lu-DOTATATE: the NETTER-1 Phase III Trial. Presented at: ESMO 2017 Congress. 11 September 2017. *Ann. Oncol.* 28(Suppl. 5) (2017).
20. Strosberg J, Wolin E, Chasen B *et al*. QOL Improvements in NETTER-1 Phase III Trial in patients with progressive midgut neuroendocrine tumors. NANETS 2017, Abstract C-33. (2018) <https://nanets.net/abstracts-archive/2017/554-c33-qol-improvements-in-netter-1-phase-iii-trial-in-patients-with-progressive-midgut-neuroendocrine-tumors/file>