Poster# **1735TiP**

Dr Simron Singh | simron.singh@sunnybrook.ca

# Trial in progress: NETTER-3: A Phase III study of [$^{177}$Lu]Lu-DOTA-TATE in patients with newly diagnosed, Grade 1 and Grade 2 (Ki-67 <10%) advanced gastroenteropancreatic neuroendocrine tumors and high disease burden

Simron Singh,[1] Jaume Capdevila,[2] Thorvardur R. Halfdanarson,[3] Daniel Halperin,[4] Ken Herrmann,[5] Marianne E. Pavel,[6] Jiapan Xu,[7] Dhrubajyoti Pathak,[8] Pamela L. Kunz[9]

[1]University of Toronto, Sunnybrook Odette Cancer Center, Toronto, ON, Canada; [2]Medical Oncology Department, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [3]Division of Medical Oncology, Mayo Clinic, Rochester, MN, USA; [4]Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA, USA; [5]Department of Nuclear Medicine, University of Duisburg-Essen, and German Cancer Consortium (DKTK)-University Hospital Essen, Essen, Germany; [6]Department of Medicine 1, Uniklinikum Erlangen, Friedrich Alexander University Erlangen-Nuernberg, Erlangen, Germany; [7]Advanced Quantitative Sciences, China Novartis Institutes for Biomedical Research, Shanghai, China; [8]Clinical Development, Novartis Pharma AG, Basel, Switzerland; [9]Yale School of Medicine, Yale University, New Haven, CT, USA

## SUMMARY

- Patients with G1 and G2 (Ki-67 <10%) advanced GEP-NETs and with high disease burden are at a higher risk of rapid deterioration and disease progression.
- For patients with newly diagnosed, advanced G1 and G2 GEP-NETs and with high disease burden, the optimal treatment is unknown.
- The Phase III NETTER-3 trial will assess the efficacy and safety of $^{177}$Lu-DOTATATE in combination with octreotide LAR in patients with newly diagnosed, G1 and G2 advanced GEP-NETs and high disease burden.

Scan to obtain:
- Poster

https://tinyurl.com/SimronSingh1735TiP



This study is sponsored by Novartis Pharmaceuticals.
Poster presented at ESMO 2025, Berlin, Germany, 17–21 October 2025.

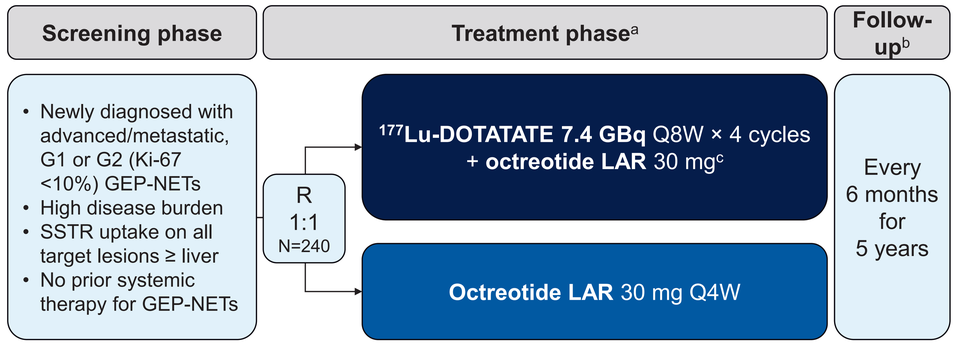
## INTRODUCTION

- Patients with newly diagnosed, Grade 1 (G1) and 2 (G2), somatostatin receptor (SSTR)-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are typically treated with somatostatin analogs (SSAs).[1] However, the approval of SSAs was based on the PROMID[2] and CLARINET[3] studies, which primarily enrolled patients with Ki-67 <10% and did not specifically recruit patients with high disease burden.
- Patients with G1 and G2 advanced GEP-NETs and with high disease burden, such as high tumor load,[4] elevated alkaline phosphatase,[4–6] the presence of bone and peritoneal metastases,[7,8] and/or tumor- or hormone excess-related symptoms,[7] are at a higher risk of rapid deterioration and disease progression.
- The optimal treatment for patients with newly diagnosed, advanced G1 and G2 GEP-NETs and with high disease burden is unknown due to limited prospective clinical data.
- The radioligand therapy [$^{177}$Lu]Lu-DOTA-TATE ($^{177}$Lu-DOTATATE) plus octreotide long-acting release (LAR) significantly prolonged median progression-free survival (PFS) versus high-dose octreotide LAR in patients with:
  - Advanced, progressive, well-differentiated (G1 and G2), SSTR-positive midgut NETs (not reached vs 8.5 months; hazard ratio [HR] 0.18; 95% confidence interval [CI] 0.11, 0.29; p<0.0001).[9]
  - Newly diagnosed, advanced, well-differentiated, higher G2 and G3 (Ki-67 10–55%), SSTR-positive GEP-NETs (22.8 vs 8.5 months; HR 0.28, 95% CI 0.18, 0.42; p<0.0001).[10]
- NETTER-3 (NCT06784752[11]) will evaluate the efficacy and safety of $^{177}$Lu-DOTATATE plus octreotide LAR versus octreotide LAR alone in patients with newly diagnosed, G1 and G2 (Ki-67 <10%) advanced GEP-NETs and with high disease burden.

## STUDY DESIGN

- NETTER-3 is a multi-center, Phase III, open-label, randomized study.
- The primary objective is to demonstrate the superiority of $^{177}$Lu-DOTATATE plus octreotide LAR versus octreotide LAR alone for prolonging PFS, based on blinded central review.
- Approximately 240 patients will be randomized in a 1:1 ratio, assigned to the experimental arm or the control arm (**Figure 1**):
  - Experimental arm: $^{177}$Lu-DOTATATE (7.4 GBq administered every 8±1 weeks for a total of 4 administrations) plus octreotide LAR (30 mg administered every 8 weeks during treatment with $^{177}$Lu-DOTATATE, then every 4 weeks thereafter until disease progression).
  - Control arm: Octreotide LAR (30 mg every 4 weeks until disease progression).
- Randomization will be stratified by NET grade (G1 vs G2) and tumor origin (pancreatic vs other).

**Figure 1. Study design**

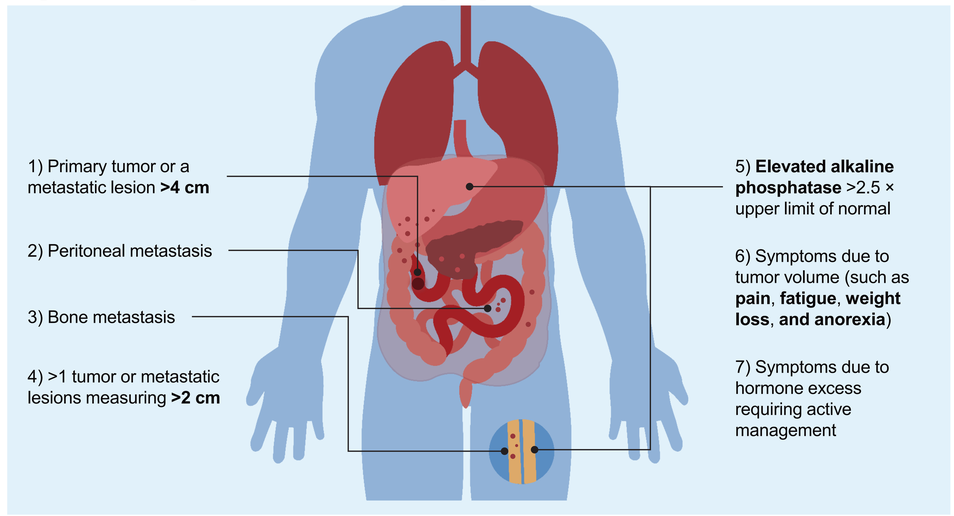



[a]Continues until disease progression or is limited to 76 weeks for patients who have not progressed after the primary PFS analysis; tumor assessments will be performed at 16±1 weeks, 24±1 weeks, and then every 12±1 weeks thereafter from randomization until disease progression; [b]During the long-term follow-up phase, all serious AEs (treatment related), AEs of renal toxicity, and AEs of secondary malignancies (including hematological [e.g. MDS] and solid tumors) will be reported; [c]Octreotide LAR 30 mg every 8±1 weeks during treatment with $^{177}$Lu-DOTATATE, then Q4W thereafter.
AE, adverse event; G, Grade; GEP-NET, gastroenteropancreatic neuroendocrine tumor; LAR, long-acting release; MDS, myelodysplastic syndrome; PFS, progression-free survival; Q4W, every 4 weeks; Q8W, every 8 weeks; R, randomized; SSTR, somatostatin receptor.

## STUDY POPULATION

- Patients (≥12 years old) with: metastasized or locally advanced, unresectable, histologically confirmed, well-differentiated G1 or G2 (Ki-67 <10%) GEP-NET diagnosed ≤6 months before screening; SSTR uptake on all target lesions, as assessed by locally approved radioligand imaging agents ≤3 months prior to randomization; and high disease burden as determined by the investigator (**Figure 2**).
- Prior systemic therapy is not permitted (except ≤4 prior cycles of SSAs without disease progression).

**Figure 2. Guiding criteria for determining high disease burden**




High disease burden will be determined by the investigator using these criteria as a guide; participants are not required to meet all criteria.

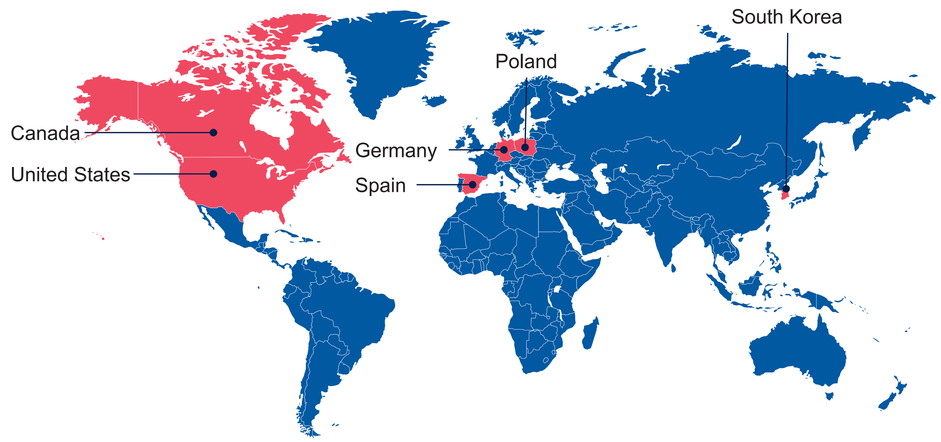
## ENDPOINTS

- Primary: PFS assessed by Blinded Independent Review Committee (BIRC) as per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
- Key secondary: Time to deterioration (TTD; from randomization) for selected quality-of-life domains based on the European Organization for Research and Treatment of Cancer Quality of Life questionnaires (EORTC QLQ), including the EORTC QLQ-GI.NET21 and EORTC QLQ-C30.
- Secondary:
  - Efficacy (per RECIST v1.1): Investigator-assessed PFS; BIRC- and investigator-assessed objective response rate, disease control rate, duration of response, and overall survival.
  - Safety and tolerability: Incidence and severity of adverse events (AEs) and serious AEs; changes in laboratory values, vital signs, and electrocardiogram; and dosage interruptions, discontinuations, and reductions.
  - Quality of life: TTD for other domains of the EORTC QLQ-GI.NET21 and EORTC QLQ-C30; and absolute change from baseline in all EORTC QLQ-GI.NET21 and EORTC QLQ-C30 domains and the EuroQol 5-Dimension 5-Level (EQ-5D-5L) index at each time point.
  - Pharmacokinetics and dosimetry (assessed in a subset of patients): area under the curve, clearance, distribution volume, and half-life; and absorbed dose.

## CURRENT STATUS

- This study is currently recruiting patients in the countries shown in **Figure 3**.
- For more details about the study or to contact the Sponsor, please see: https://clinicaltrials.gov/study/NCT06784752.

**Figure 3. Countries currently recruiting patients**




### References

**1.** Riechelmann RP *et al.* Am Soc Clin Oncol Educ Book 2023;43:e389278; **2.** Rinke A *et al.* J Clin Oncol 2009;27:4656–63; **3.** Caplin ME *et al.* N Engl J Med 2014;371:224–33; **4.** Pandrowala SA *et al.* J Gastrointest Cancer 2024;55:1220–8; **5.** Clancy TE *et al.* Dig Dis Sci 2006;51:877–84; **6.** Fairweather M *et al.* Ann Surg Oncol 2017;24:2319–25; **7.** Carmona-Bayonas A *et al.* J Clin Oncol 2019;37:2571–80; **8.** Scopel M *et al.* Endocr Connect 2022;11:e210568; **9.** Lutathera SmPC, Apr 2025. Available at: https://www.ema.europa.eu/en/documents/product-information/lutathera-epar-product-information_en.pdf. Accessed 18 Sep 2025; **10.** Singh S *et al.* Lancet 2024;403:2807–17; **11.** https://clinicaltrials.gov/study/NCT06784752. Accessed 18 Sep 2025.

### Acknowledgments

Medical writing support was provided by Andrea Luengas, PhD, at Aspire Scientific Ltd. (Manchester, UK) under the guidance of the authors, with funding from Advanced Accelerator Applications, a Novartis Company, and in accordance with Good Publication Practice 2022 guidelines (https://www.ismpp.org/gpp-2022).

### Disclosures

Dr. Singh declares a research grant from Novartis (paid to his institution); financial compensation for advisory board participation, consulting, and speaking engagements from Camurus, Ipsen, and Novartis; and financial compensation from Ipsen and Novartis for travel/attending meetings.
The corresponding abstract for this poster presentation includes full disclosure information for all authors.