ORIGINAL ARTICLE

# Phase 3 Trial of $^{177}$Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators*

## ABSTRACT

### BACKGROUND

Patients with advanced midgut neuroendocrine tumors who have had disease progression during first-line somatostatin analogue therapy have limited therapeutic options. This randomized, controlled trial evaluated the efficacy and safety of lutetium-177 ($^{177}$Lu)–Dotatate in patients with advanced, progressive, somatostatin-receptor–positive midgut neuroendocrine tumors.

### METHODS

We randomly assigned 229 patients who had well-differentiated, metastatic midgut neuroendocrine tumors to receive either $^{177}$Lu-Dotatate (116 patients) at a dose of 7.4 GBq every 8 weeks (four intravenous infusions, plus best supportive care including octreotide long-acting repeatable [LAR] administered intramuscularly at a dose of 30 mg) ($^{177}$Lu-Dotatate group) or octreotide LAR alone (113 patients) administered intramuscularly at a dose of 60 mg every 4 weeks (control group). The primary end point was progression-free survival. Secondary end points included the objective response rate, overall survival, safety, and the side-effect profile. The final analysis of overall survival will be conducted in the future as specified in the protocol; a prespecified interim analysis of overall survival was conducted and is reported here.

### RESULTS

At the data-cutoff date for the primary analysis, the estimated rate of progression-free survival at month 20 was 65.2% (95% confidence interval [CI], 50.0 to 76.8) in the $^{177}$Lu-Dotatate group and 10.8% (95% CI, 3.5 to 23.0) in the control group. The response rate was 18% in the $^{177}$Lu-Dotatate group versus 3% in the control group (P<0.001). In the planned interim analysis of overall survival, 14 deaths occurred in the $^{177}$Lu-Dotatate group and 26 in the control group (P=0.004). Grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia occurred in 1%, 2%, and 9%, respectively, of patients in the $^{177}$Lu-Dotatate group as compared with no patients in the control group, with no evidence of renal toxic effects during the observed time frame.

### CONCLUSIONS

Treatment with $^{177}$Lu-Dotatate resulted in markedly longer progression-free survival and a significantly higher response rate than high-dose octreotide LAR among patients with advanced midgut neuroendocrine tumors. Preliminary evidence of an overall survival benefit was seen in an interim analysis; confirmation will be required in the planned final analysis. Clinically significant myelosuppression occurred in less than 10% of patients in the $^{177}$Lu-Dotatate group. (Funded by Advanced Accelerator Applications; NETTER-1 ClinicalTrials.gov number, NCT01578239; EudraCT number 2011-005049-11.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Strosberg at the Moffitt Cancer Center, 12902 Magnolia Dr., Tampa, FL 33612, or at jonathan.strosberg@moffitt.org.

*A complete list of investigators in the Neuroendocrine Tumors Therapy (NETTER-1) trial is provided in the Supplementary Appendix, available at NEJM.org.

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