INTRODUCTION

The NETTER-1 study, a phase 3 trial in patients with midgut NETs, demonstrated that treatment with 177Lu-DOTATATE led to a clinically and statistically significant improvement in PFS as a primary endpoint (HR, 0.18 [95% CI: 0.11, 0.29]; p < 0.0001). In a sensitivity analysis using the RPSFT method, which adjusted survival of those patients in the treatment arms who crossed over to radioligand therapy after disease progression, the adjusted HR for OS was 0.30 (two-sided). The adjusted HR for OS was 0.84 (95% CI: 0.30, 2.30; p = 0.73) in the control arm. The results of the study were consistent for patients with non-functional midgut NETs and for patients with functional midgut NETs.

Methods

- **Patient eligibility criteria:** NETTER-1 has been previously described. Briefly, adults with advanced, irrefractory, well-differentiated (G1/G2) midgut NETs with positive 18F-fluorodeoxyglucose uptake on all target lesions and disease progression while receiving a fixed dose of long-acting somatostatin analogue (SMA) were included.
- **Population:** In the NETTER-1 study, 111 patients were randomized 1:1 to treatment with 177Lu-DOTATATE or 90Y-DOTATOC, respectively. The primary endpoint was PFS, with a median follow-up of 76.3 months (range, 0.1–95.0 months) in the 177Lu-DOTATATE arm and 76.5 months (range, 0.1–92.3 months) in the control arm.
- **Endpoints:** The study was also designed to assess OS as a key secondary endpoint. The authors performed a prespecified analysis of the RPSFT method, which adjusted survival of the patients in the control arm who crossed over to radioligand therapy (36%) after disease progression with additional cycles of 177Lu-DOTATATE.
- **To account for the impact of ‘cross-over’ to subsequent radioligand therapy, a rank-preserving structural failure time (RPSFT) analysis was performed in a statistical analysis plan amendment before the data lock.**
- **No serious adverse events were deemed related to 177Lu-DOTATATE and adverse events impacting on patient’s quality of life were rarely reported.**

**KEY FINDINGS & CONCLUSIONS**

- In the phase 3 NETTER-1 study, with a median follow-up of more than 6 years, the prespecified final analysis of OS (secondary endpoint) in the ITT population did not reach statistical significance (HR, 0.84 [95% CI: 0.30, 2.30]; p = 0.73), but was statistically impacted by a high rate of cross-over (36%) of patients in the control arm versus 6% in the 177Lu-DOTATATE arm.
- Median OS was 48 months in the 177Lu-DOTATATE arm and 36 months in the control arm.
- Two types of 177Lu-DOTATATE-treated patients (1.8%) developed MDS, consistent with previous reports: no cases of MDS or acute leukemia were reported during long-term follow-up.
- No new safety signals emerged during long-term follow-up.
- In overall conclusion, the NETTER-1 study demonstrated that treatment with 177Lu-DOTATATE led to a clinically and statistically significant improvement in PFS as a primary endpoint (HR, 0.18 [95% CI: 0.11, 0.29]; p < 0.0001) as well as a clinically meaningful improvement in median OS of 11.7 months versus high-dose long-acting octreotide.

**METHODS**

- **Patient eligibility criteria:** NETTER-1 has been previously described. Briefly, adults with advanced, irrefractory, well-differentiated (G1/G2) midgut NETs with positive 18F-fluorodeoxyglucose uptake on all target lesions and disease progression while receiving a fixed dose of long-acting somatostatin analogue (SMA) were included.
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**RESULTS**

**Patients and treatments**

- **Patient disposition shown in Figure 1:** In total, 111 patients were randomized 1:1 for treatment.
- **Demographic and baseline characteristics:** were balanced between the treatment groups: Median time since diagnosis of midgut NET was shorter in the 177Lu-DOTATATE arm than in the control arm (6.8 years versus 5.3 years).
- **Of the 111 patients who received 177Lu-DOTATATE treatment, 84 (75.7%) received the planned four cycles.**

**Figure 1.** Patient disposition and subsequent treatment long-term follow-up in NETTER-1 study

**Figure 2.** Kaplan-Meier analysis of overall survival in the intention-to-treat population

**Figure 3.** Kaplan-Meier analysis of overall survival accounting for cross-over to radioligand therapy in the control arm (RPSFT method)

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**First author disclosures**

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