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Impact of Liver Tumor Burden on Therapeutic Effect of ^{177}Lu-DOTATATE Treatment in NETTER-1

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Abstract

Background

The aim of this study was to assess Progression Free Survival (PFS), Safety and Quality of Life (QoL) in subgroups of varying hepatic burden in the NETTER-1 study population.

Methods

Patients (pts) were randomized to receive either ^{177}Lu-DOTATATE (Lu)(n=117) or high-dose octreotide (Oct) (n=114). The liver tumor burden (LTB) was defined as tumor volume/total liver volume by CT, and categorized as low (<25%), moderate (25-50%), and high (>50%). PFS, QoL and hepatotoxicity were assessed based on baseline LTB.

QoL was analysed using EQRTC QLQC 30 and G.I. NET 21 questionnaires completed at baseline and every 12 weeks thereafter for low and moderate/high LTB subgroups. Deterioriation was defined if the score decreased by ≥10 points at any time point after baseline. Time to deterioration (TTD) was defined as the time from randomization to the first QoL deterioration.

Results

Median PFS (months) in Lu vs Oct was 28.35 vs 11.04 in low (HR= 0.218, 95% CI 0.120 to 0.394); Not Reached (NR) vs 8.67 in moderate (HR=0.202, 95% CI 0.077 to 0.525); 19.38 vs 5.52 in high LTB (HR= 0.193, 95% CI 0.079 to 0.474), respectively. Median TTD (months) for Global Health Status was 28.81 vs 6.11 in low (HR = 0.376, 95% CI 0.196 to 0.720); NR vs 5.98 in moderate/high LTB (HR=0.453, 95% CI 0.178 to 1.152). Table 1 summarizes the results of PFS and TTD for multiple clinically relevant QoL domains. In Lu arm, Grade 3/4 (CTCAE v 4.03) AST and ALT toxicities occurred in the low LTB in 2 and 3 patients, and in the high LTB group in 3 and 1 patients, respectively. Grade 3/4 hyperbilirubinemia occurred in one patient from the low LTB and one from the moderate LTB group. All liver function tests abnormalities were resolved without sequela. There were no high grade ALT, AST and Biliriubin toxicities in Oct arm.

Conclusions

^{177}Lu-DOTATATE treatment demonstrated significant PFS improvement regardless of the extent of baseline liver tumor burden in patients with well-differentiated, metastatic midgut NET. Clinically significant liver function test abnormalities were rare, were not associated with high liver tumor burden, and resolved without sequela. The analysis shows that ^{177}Lu-DOTATATE treatment also provides quality of life benefit regardless of baseline liver tumor burden.

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Impact of Liver Tumor Burden on Therapeutic Effect of ^{177}Lu-DOTATATE Treatment in NETTER-1

Background

- Metastases are found predominantly in the liver in patients with small intestinal NET,[4] and patients with high liver tumor loads have worse prognoses than patients with few liver metastases[5,6]
- It is unclear whether the extent of liver tumor burden before treatment will influence clinical response to ^{177}Lu-DOTATATE

NETTER-1 study objectives and design[1,3]

Aim: Evaluate the efficacy and safety of ^{177}Lu-DOTATATE + SSA compared with high-dose long-acting octreotide in patients with inoperable, locally advanced or metastatic, somatostatin receptor positive, midgut NET with radiologic PD under a standard dose of long-acting octreotide (20–30 mg q3–4w)

Design: International, multicenter, randomized, comparator-controlled, parallel-group

Treatment and Assessments
- Progression-free survival (central RECIST) every 12 weeks
- Safety (NCI CTCAE v4.03) every 2–12 weeks
- Quality of life (EORTC QLQ-C30 and GI.NET21) every 12 weeks

Dose 1 ↓ Dose 2 ↓ Dose 3 ↓ Dose 4 ↓

Randomization
Stratified by:
- Highest tumor uptake by SRS (Krenning scale: grade 2, 3, or 4)
- Duration of constant dose long-acting octreotide (≤6 or >6 months)

n = 117: 4 administrations of 7.4 GBq of ^{177}Lu-DOTATATE (q8w) + SSA (long-acting octreotide 30 mg q4w)

n = 114: Octreotide LAR 60 mg q4w (high dose)

5 years, follow-up

SSA, Somatostatin analogs; CTCAE, Common Terminology Criteria for Adverse Events; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; GI, gastrointestinal; LAR, long-acting release; NCI, National Cancer Institute; NET, neuroendocrine tumors; q3-4w, every 3-4 weeks; q4w, every 4 weeks; q8w, every 8 weeks; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors; SRS, somatostatin receptor scintigraphy.

- Median PFS was 28.4 months (95% confidence interval [CI] 28.4–not evaluable) for those receiving ^{177}Lu-DOTATATE and 8.5 months (95% CI 5.8–11.0) for those receiving octreotide long-acting release (LAR) 60 mg (hazard ratio [HR] 0.214; 95% CI 0.139–0.331)[2]
- Time to deterioration (TTD) in quality of life (QoL) (≥10-point decrease from baseline) was significantly longer in the ^{177}Lu-DOTATATE treatment arm than in patients receiving octreotide LAR 60 mg domains of global health status, physical functioning, role functioning, diarrhea, pain, fatigue in the domains of body image and disease-related worries

Objective

- To assess PFS, QoL, and liver function abnormalities in subgroups with varying baseline liver tumor burden in the NETTER-1 population

Methods

- Baseline liver tumor burden was defined as baseline liver tumor volume/total liver volume by computed tomography (CT); patients were categorized as having low (<25%), moderate (25%–50%), or high (>50%) liver tumor burden
- Kaplan–Meier plots of PFS were generated by (1) treatment arm and subgroups with low, moderate, and high baseline liver tumor burden, (2) subgroups with elevated or normal baseline levels of alkaline phosphatase (ALP), and (3) subgroups with presence or absence of a large (>30 mm diameter) lesion at baseline
- Kaplan–Meier plots of TTD were generated in EORTC-QLQ-C30 domains of global health status, physical functioning, role functioning, diarrhea, pain, and fatigue and the EORTC-QLQ-GI.NET21 flushing domain according to treatment arm and subgroups with low or moderate/high baseline liver tumor burden
- Grade 3 or 4 (National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 [NCI CTCAE v4.03]) liver function test abnormalities (aspartate aminotransferase [AST], alanine aminotransferase [ALT], ALP, albumin, and bilirubin) were assessed according to treatment arm and subgroups with low, moderate, and high baseline liver tumor burden

Results

- Significant prolongation in median PFS was evident with ^{177}Lu-DOTATATE compared with octreotide LAR 60 mg, regardless of baseline liver tumor burden (Table 1; Figure 2)
- ^{177}Lu-DOTATATE was associated with an ~80% reduction in the estimated risk of tumor progression or death compared with octreotide LAR 60 mg across the patient subgroups with low, moderate, or high baseline liver tumor burden

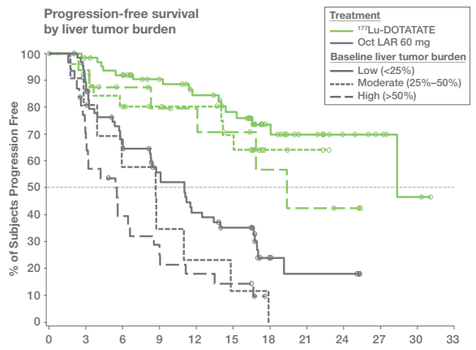
Table 1. Median PFS in Patients Receiving ^{177}Lu-DOTATATE + SSA or Octreotide LAR 60 mg by Low (<25%), Moderate (25%–50%), or High (>50%) Baseline Liver Tumor Burden

Baseline liver tumor burden	Treatment arm	N	Events, n (%)	Median PFS, months	Hazard ratio (95% CI)	P
<25%	^{177}Lu-DOTATATE	71	16 (22.5)	28.35	0.218 (0.120–0.394)	<0.0001
	Oct LAR 60 mg	70	43 (61.4)	11.04		
25%–50%	^{177}Lu-DOTATATE	27	8 (29.6)	NR	0.202 (0.077–0.525)	0.001
	Oct LAR 60 mg	13	9 (69.2)	8.67		
>50%	^{177}Lu-DOTATATE	19	6 (31.6)	19.38	0.193 (0.079–0.474)	0.0003
	Oct LAR 60 mg	31	26 (83.9)	5.52		

NR, not reached.

Medians are generated using Kaplan–Meier estimates. HRs, their corresponding 95% CIs, and *P* values are estimated using a Cox regression model with randomized treatment, liver tumor burden at baseline (<25%, 25%–50%, or >50%) and (liver tumor burden at baseline*randomized treatment interaction term) as covariates.

Figure 2.

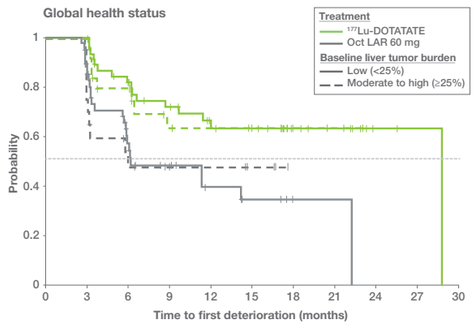


Number at risk:

Low (<25%) baseline liver tumor burden	^{177}Lu-DOTATATE	71	63	58	49	42	36	20	13	8	5	2	0
	Oct LAR 60 mg	70	57	41	30	22	16	5	3	3	0	0	0
Moderate (25%–50%) baseline liver tumor burden	^{177}Lu-DOTATATE	27	23	20	17	16	13	3	2	0	0	0	0
	Oct LAR 60 mg	13	8	5	3	2	1	0	0	0	0	0	0
High (>50%) baseline liver tumor burden	^{177}Lu-DOTATATE	19	15	12	10	9	7	4	3	2	0	0	0
	Oct LAR 60 mg	31	20	11	8	5	4	0	0	0	0	0	0

- ^{177}Lu-DOTATATE was associated with an ~59% reduction in the estimated risk for deterioration of QoL domain global health status compared with octreotide LAR 60 mg in patients with low or moderate/high baseline liver tumor burden (Figure 3; Table 2)

Figure 3.



Number at risk:

Low (<25%) baseline liver tumor burden	^{177}Lu-DOTATATE	71	46	34	28	20	19	9	7	2	1	0	
	Oct LAR 60 mg	70	38	20	13	8	4	1	1	0	0	0	
Moderate to high (≥25%) baseline liver tumor burden	^{177}Lu-DOTATATE	46	26	18	11	10	9	4	2	0	0	0	
	Oct LAR 60 mg	44	16	8	6	5	3	0	0	0	0	0	

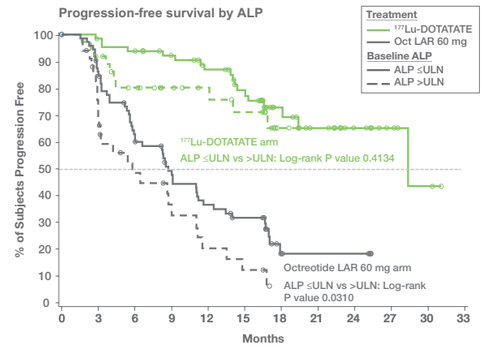
Table 2. Median TTD of QoL Domains in Patients Receiving ^{177}Lu-DOTATATE + SSA or Octreotide LAR 60 mg by Low (<25%) or Moderate to High (≥25%) Baseline Liver Tumor Burden

Baseline liver tumor burden	Treatment arm	N	Median TTD, months						
			EORTC QLQ-C30 domains						GI.NET21 domain
			Global health status	Physical functioning	Role functioning	Diarrhea	Fatigue	Pain	Flushing
<25%	^{177}Lu-DOTATATE	71	28.81	25.20	14.72	NR	8.97	13.01	11.76
	Oct LAR 60 mg	70	6.11	11.47	11.30	NR	5.98	11.20	14.23
	Hazard ratio (95% CI)		0.376 (0.196–0.720)	0.512 (0.264–0.994)	0.651 (0.362–1.170)	0.438 (0.206–0.930)	0.550 (0.318–0.951)	0.663 (0.367–1.199)	0.967 (0.512–1.827)
≥25%	^{177}Lu-DOTATATE	46	NR	NR	NR	NR	5.88	NR	NR
	Oct LAR 60 mg	44	5.98	11.56	11.56	11.89	5.78	11.10	16.72
	Hazard ratio (95% CI)		0.453 (0.178–1.152)	0.526 (0.207–1.335)	0.425 (0.161–1.120)	0.500 (0.192–1.301)	0.764 (0.366–1.596)	0.411 (0.156–1.080)	0.751 (0.255–2.210)

NR, not reached.

- In the overall patient population (pooled from both treatment arms), no significant difference was detected in median PFS stratified by normal or elevated levels of baseline ALP (16.69 vs 12.09 months; log-rank P = 0.1177)
- No difference was observed in median PFS with ^{177}Lu-DOTATATE in patients with normal compared with elevated baseline ALP (28.35 months vs not reached), whereas patients with elevated baseline ALP had shorter median PFS with octreotide LAR 60 mg than those with normal baseline ALP (5.78 vs 8.74 months) (Figure 4)

Figure 4.

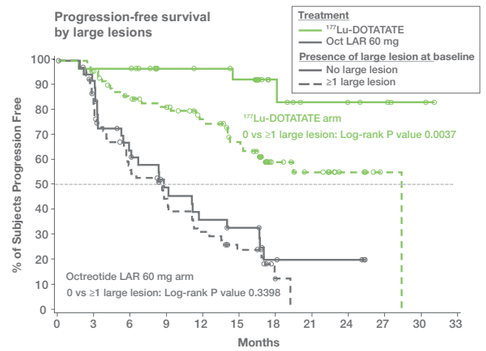


Number at risk:

ALP ≤ULN	^{177}Lu-DOTATATE	72	64	61	54	48	40	20	12	6	3	2	0
	Oct LAR 60 mg	76	61	43	31	23	17	4	3	3	0	0	0
ALP >ULN	^{177}Lu-DOTATATE	41	33	26	21	18	15	7	6	4	2	0	0
	Oct LAR 60 mg	37	23	13	9	5	3	0	0	0	0	0	0

- The majority (70%) of large (>30 mm diameter) lesions were located in the liver
- In the overall patient population (pooled from both treatment arms) no significant difference was detected in median PFS stratified by the presence or absence of a large lesion at baseline (13.83 vs 18.07 months; log-rank P = 0.0622)
- ^{177}Lu-DOTATATE was superior to octreotide LAR 60 mg in terms of median PFS regardless of whether a large lesion was present at baseline (Figure 5)
- No large lesion: HR 0.069 (95% CI 0.021–0.233; Cox regression P < 0.0001)
- ≥1 large lesion: HR 0.266 (95% CI 0.165–0.429; Cox regression P < 0.0001)
- In the ^{177}Lu-DOTATATE treatment arm, patients with no large lesion at baseline had significantly longer median PFS than those with ≥1 large lesion (not reached vs 28.35 months)
- The presence or absence of a large baseline lesion did not influence the PFS of patients receiving octreotide LAR 60 mg (8.74 months vs 8.44 months)

Figure 5.



Number at risk:

No large lesion	^{177}Lu-DOTATATE	37	32	32	24	23	21	10	6	5	4	2	0
	Oct LAR 60 mg	39	33	22	15	11	9	4	3	3	0	0	0
≥1 large lesion	^{177}Lu-DOTATATE	80	69	58	52	44	35	17	12	5	1	0	0
	Oct LAR 60 mg	75	52	35	26	18	12	1	0	0	0	0	0

- Grade 3 or 4 liver function abnormalities were rare and were not associated with baseline liver tumor burden (Table 3)

Table 3. Frequency of Grade 3 or 4 Liver Function Test Abnormalities in the Safety Population by Treatment Arm and Low (<25%), Moderate (25%–50%), or High (>50%) Baseline Liver Tumor Burden

Baseline liver tumor burden	Treatment arm	N	Grade 3 or 4 liver function test abnormalities, n				
			↑ AST	↑ ALT	↑ ALP	↓ Albumin	↑ Bilirubin
<25%[a]	^{177}Lu-DOTATATE	68	2	3	4	0	1
	Oct LAR 60 mg	70	0	0	3	0	0
25%–50%	^{177}Lu-DOTATATE	25	0	0	0	0	1
	Oct LAR 60 mg	12	0	0	0	0	0
>50%	^{177}Lu-DOTATATE	18	3	1	2	0	0
	Oct LAR 60 mg	30	0	0	7	0	0

NCI CTCAE v4.03 grade 3/4 increases in AST, ALT, and ALP are defined as >5× ULN; grade 3/4 increase in bilirubin is defined as >3× ULN; grade 3/4 decrease in albumin is defined as <2 g/dL.
These data are from the safety population.
aIn the low baseline liver tumor burden subgroup, one patient was randomly assigned to receive ^{177}Lu-DOTATATE but instead received octreotide LAR 60 mg.

- All liver function abnormalities resolved without sequelae

Conclusion

- ^{177}Lu-DOTATATE demonstrated significant prolongation in median PFS compared with octreotide LAR 60 mg regardless of the extent of baseline liver tumor burden, elevated baseline ALP, or the presence of a large (>30 mm diameter) lesion at baseline in patients with advanced, progressive midgut NET
- Clinically significant liver function test abnormalities were rare and were not associated with high baseline liver tumor burden
- ^{177}Lu-DOTATATE provides clinically relevant QoL benefit regardless of baseline liver tumor burden

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