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Clinical outcomes in patients with baseline renal dysfunction in the NETTER-1 Study: ^{177}Lu-DOTATATE vs. high dose octreotide in progressive midgut neuroendocrine tumors

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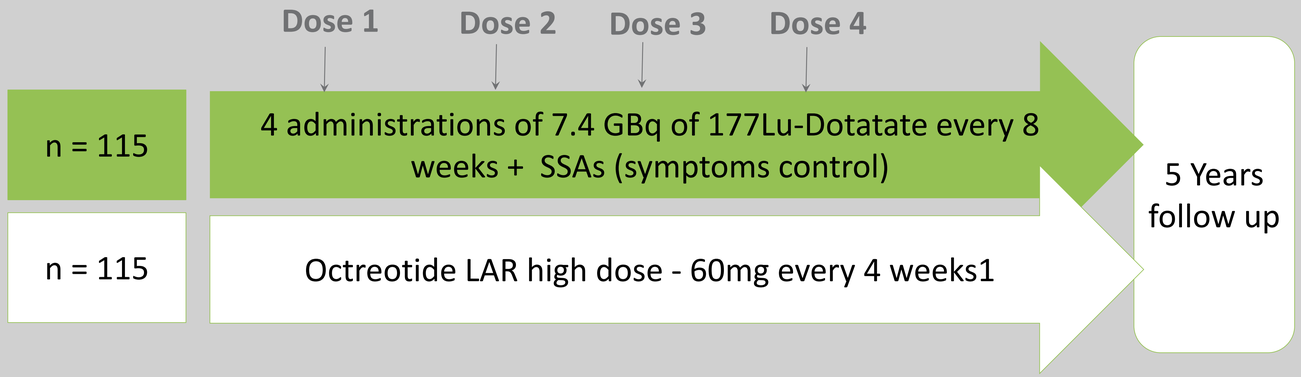
Intro

- **Does ^{177}Lu-DOTATATE compromise kidney function ?**
- **Are patients with renal impairment eligible for ^{177}Lu-DOTATATE treatment ?**

NETTER-1 study design

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

Treatment and Assessments
Progression free survival (RECIST criteria) every 12 weeks



1. FDA and EMA recommendation

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Method

- Nephrotoxicity and treatment efficacy assessed in the two study arms (^{177}Lu-DOTATATE vs. high-dose octreotide LAR 60 mg)
- Baseline normal renal function ≥ 60 ml/min
- Impaired renal patients < 60 ml/min
- Primary endpoints in both arms : PFS, creatinine clearance, adverse effects, hematotoxicity as measured by platelet count

Arm	Normal renal function	Impaired renal function (CrCl<60)
^{177}Lu-DOTATATE	93	24
Octreotide LAR 60 mg	85	25

p = 0.41825
for imbalance between the two study arms

Safety and Tolerability - All Grades (Safety Set; n=221)

Maximal Severity, number of episodes	^{177}Lu-DOTATATE (n=111)	Octreotide LAR 60mg (n=110)
Grade 1 (mild)	938	494
Grade 2 (moderate)	370	178
Grade 3 (severe)	98	56
Grade 4 (threatening / disabling)	5	6
Grade 5 (death)	5	8

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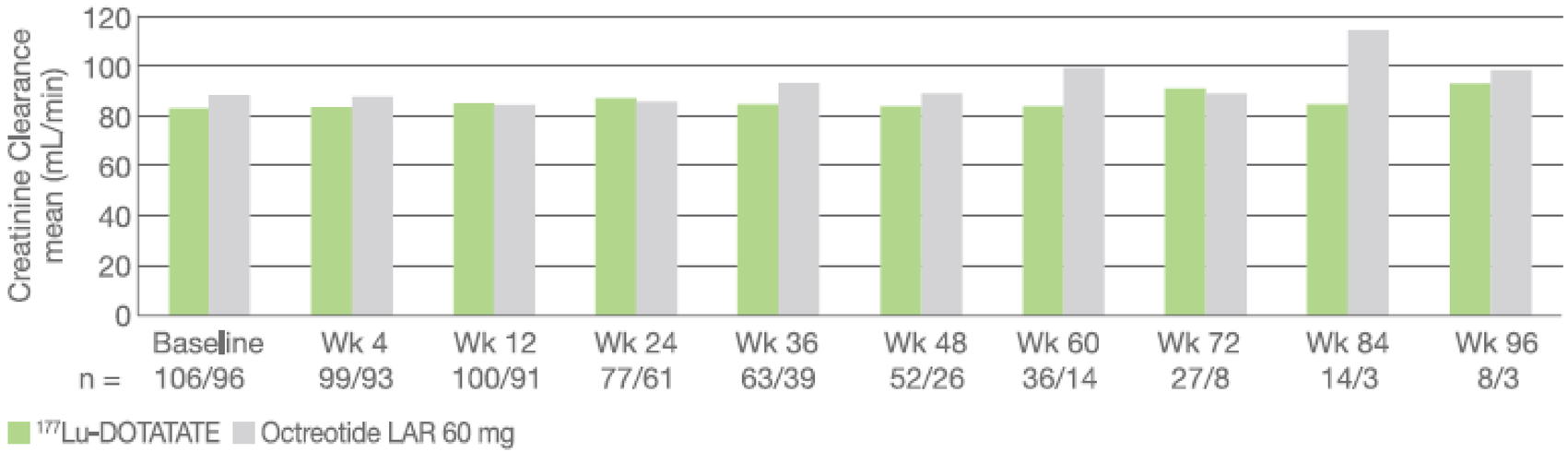
Creatinine clearance

	^{177}Lu-DOTATATE (n=111)	Octreotide LAR 60 mg (n=110)
	Grade 3/4	Grade 3/4
Creatinine increased	0%	0%



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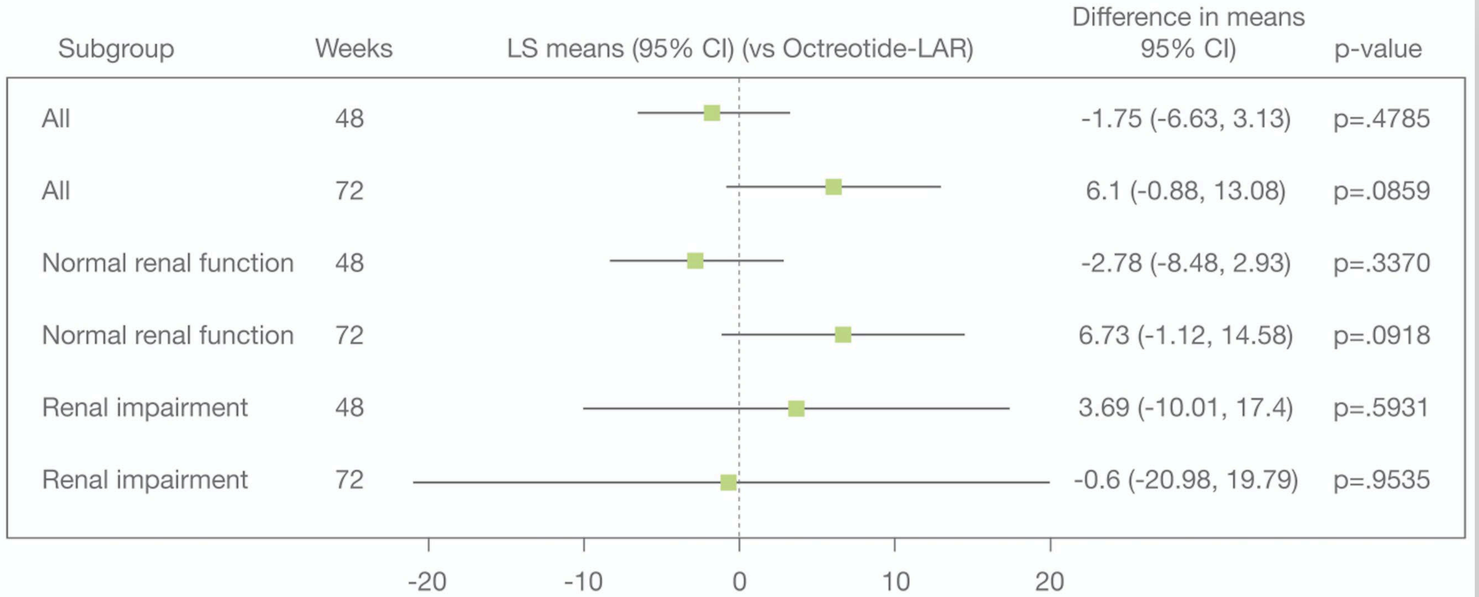
Creatinine clearance MMRM results by impairment subgroups Safety Analysis Set

Subgroup	Weeks	Difference in means 95% CI	p-value
All	48	-1.75 (-6.63, 3.13)	p=.4785
All	72	6.1 (-0.88, 13.08)	p=.0859
Normal renal function	48	-2.78 (-8.48, 2.93)	p=.3370
Normal renal function	72	6.73 (-1.12, 14.58)	p=.0918
Renal impairment	48	3.69 (-10.01, 17.4)	p=.5931
Renal impairment	72	-0.6 (-20.98, 19.79)	p=.9535



MMRM analysis uses all data when estimating the difference between treatments at a certain week in terms of change from baseline. The p-value gives the probability of observing a greater difference by chance (under the assumption that the true difference equals zero).

In all subjects, ^{177}Lu-DOTATATE treatment was associated with non-significant trend towards improved creatinine clearance compared to high-dose octreotide LAR 60 mg

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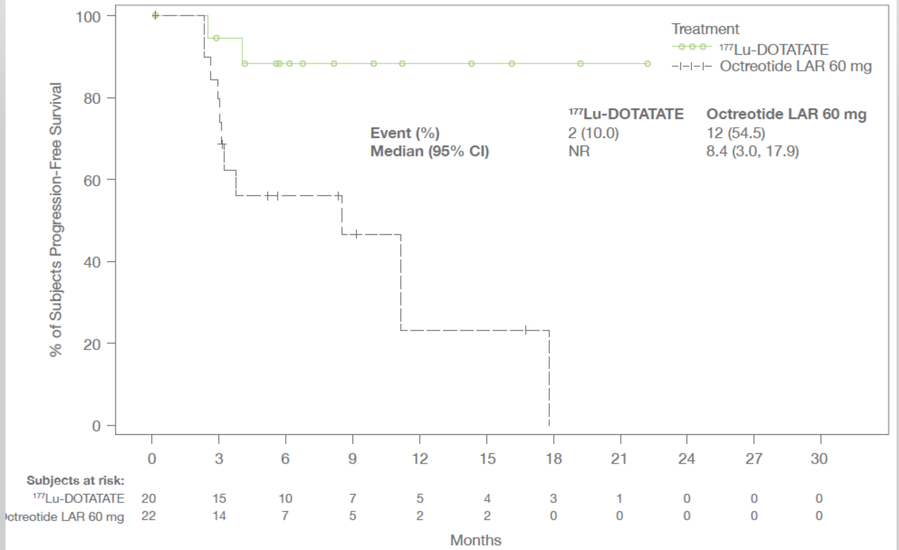
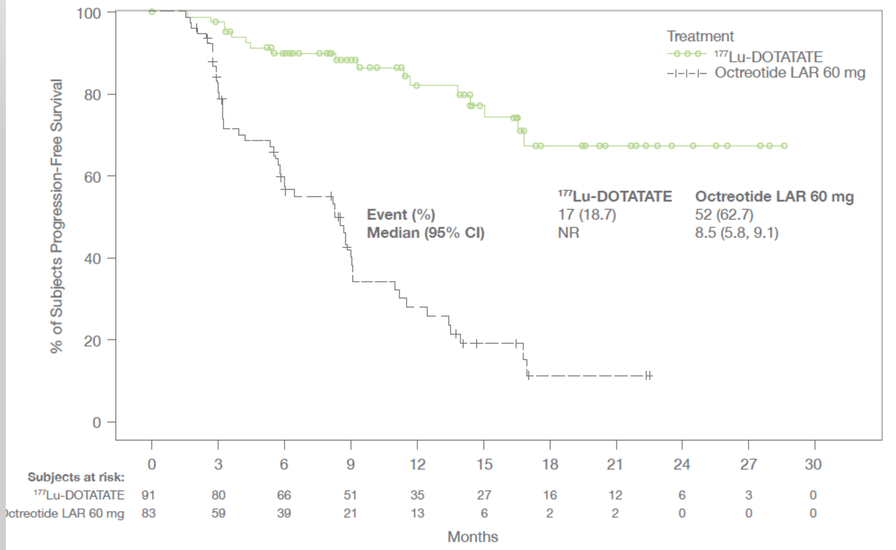
Kaplan-Meier Plot of Progression-Free Survival for patients with renal impaired function at baseline - Central Review Data Full Analysis Set



p-values were obtained from the Log-Rank test; HR=Hazard Ratio; obtained from the Cox-regression model; NR=Not Reached; CI=Confidence Interval.
Data cutoff date: 24 July 2015.

Kaplan-Meier Plot of Progression-Free Survival for patients with normal renal function at baseline - Central Review Data Full Analysis Set



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Conclusions

The NETTER-1 study did not show any evidence of nephrotoxicity associated with ^{177}Lu-DOTATATE treatment, even among patients with impaired renal function

Treatment with ^{177}Lu-DOTATATE resulted in a markedly longer progression-free survival regardless of whether baseline renal function was normal or impaired.