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PRRT IN GI-NET
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PRRT BACKGROUND

- **Neuroendocrine tumours overexpress SSR** and the presence and rate of expression of these receptors is **used for diagnosis and therapeutic purposes**
- **PRRT has shown considerable promise** for the treatment of **advanced, well-differentiated NETs**, the majority of which express high levels of SSRs to which somatostatin analogues bind
- In **PRRT, a SSA is combined with a therapeutic dose of radionuclides**, e.g. Yttrium 90 (Y-90), Lutetium 177 (Lu-177) and Gallium 68 (Ga-68)
- This targeted form of systemic radiotherapy **allows the delivery of radionuclides directly to tumour cells**

NET, neuroendocrine tumours; PRRT, Peptide Receptor Radionuclide Therapy; SSA, somatostatin analogue; SSR, somatostatin receptors

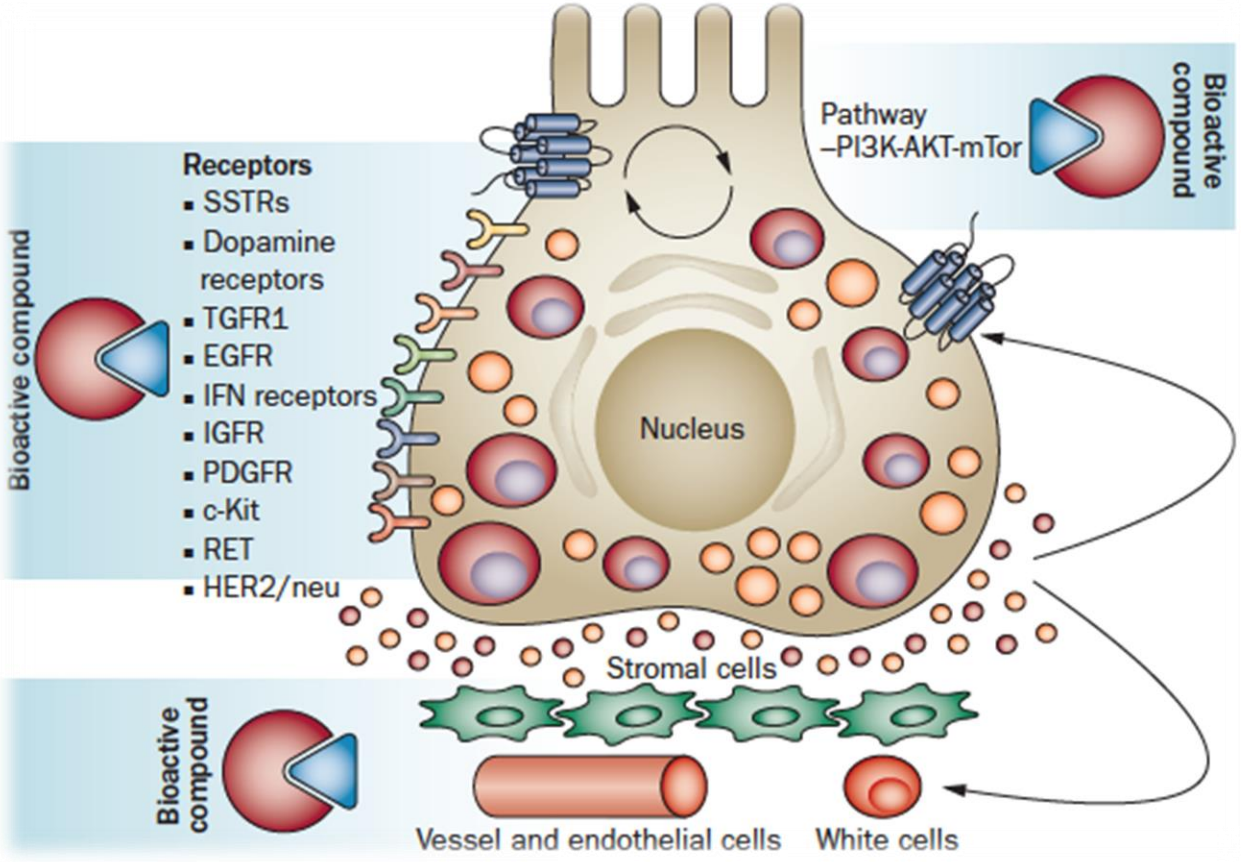
RADIOPEPTIDE THERAPY: RATIONALE AND BASIS

Biotherapeutics:
SSA, IFN, PRRT

Chemotherapeutics:
STZ, TMZ, Platinum-based

Small molecules:
Everolimus, Sunitinib, Cabozantinib, Lenvatinib

Biological molecules:
Bevacizumab



IFN, interferon; PRRT, Peptide Receptor Radionuclide Therapy; SSA, somatostatin analogues; STZ, streptozocin; TMZ, temozolomide

Rindi G & Wiedenmann B. Nature Reviews Endocrinology, 2012;8:54-64

RADIOPEPTIDE THERAPY: RATIONALE AND BASIS

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LIGAND-BINDING AFFINITIES OF SRIF-BASED RADIOCHEMICALS

	SST1	SST2	SST3	SST4	SST5	Approvals
In-DTPA-OC	>10,000	22 ± 3.6	182 ± 13	>1,000	237 ± 52	FDA approved
Y-DOTA-TOC	>10,000	11 ± 1.7	389 ± 135	>1,000	114 ± 29	Phase II studies
Ga-DOTA-TOC	>10,000	2.5 ± 0.5	613 ± 140	>1,000	73 ± 2	EMA approved
Ga-DOTA-TATE	>10,000	0.2 ± 0.04	>1,000	300 ± 140	377 ± 18	FDA approved
Lu-DOTATATE	>1,000	2.0 ± 0.8	162 ± 16	>1,000	>1,000	EMA approved
Ga-DOTA-NOC	>10,000	1.9 ± 0.4	40.0 ± 5.8	260 ± 74	7.2 ± 1.6	Phase II studies

DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; DOTA-TATE, DOTA-Tyr3-ocreotate (Ga=gallium, Lu=Lutetium); DOTA-TOC, DOTA-D-Tyr^3-ocreotide (y=yttrium, Ga=gallium); Ga-DOTA-NOC, Gallium-DOTA-D-Nal^3-ocreotide; In-DTPA-OC, Indium-diethylenetriamine pentaacetic acid-ocreotide; SRIF, somatotropin-release inhibitory factor; SST, somatostatin receptor

Günther T, et al. Pharmacol Rev 2018; 70:763–835

NETTER-1 PHASE III TRIAL

STUDY DESIGN

Aim	Evaluate the efficacy and safety of ^{177}Lu-Dotatate (Lutathera®) plus Octreotide30 mg compared to Novartis Octreotide LAR 60mg (off-label use) in patients with inoperable, somatostatin receptor positive, midgut NET, progressive under Octreotide LAR 30mg (label use)
Design	International, multicenter, randomized, comparator-controlled, parallel-group

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

Dose 1 Dose 2 Dose 3 Dose 4

Baseline and Randomization

- n = 115 → 4 administrations of 7.4 GBq of ^{177}Lu-Dotatate every 8 weeks + Octreotide30 mg
- n = 115 → Octreotide LAR 60mg every 4 weeks

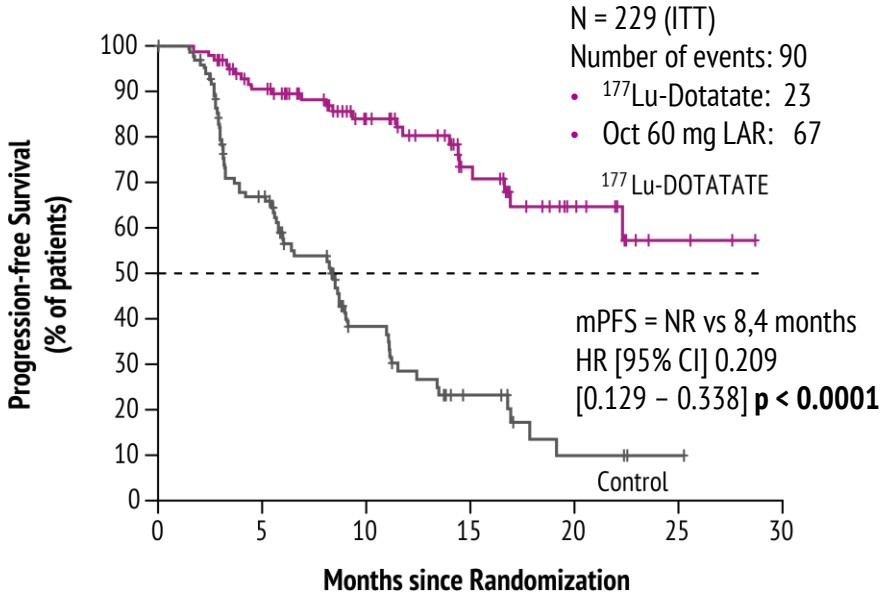
→ 5 Years follow up

GBq, gigabecquerels; LAR, long acting release; Lu, lutetium

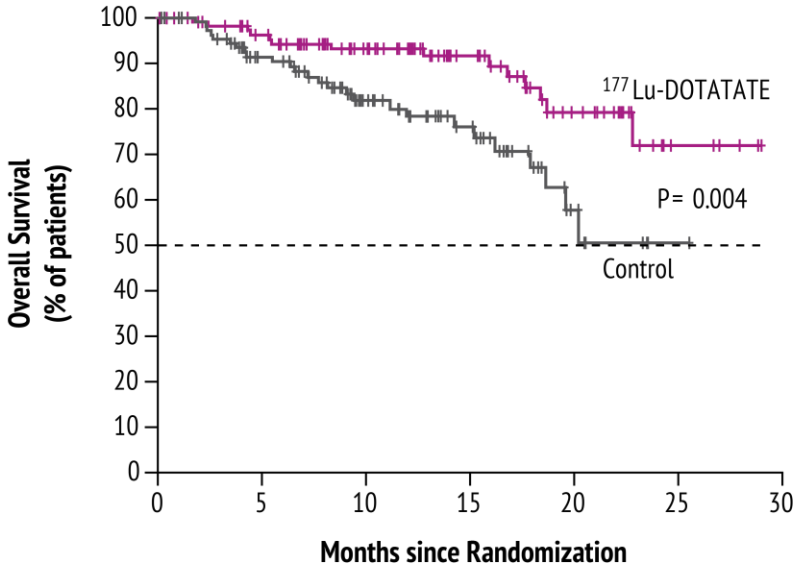
Strosberg, J. NEJM 2017; 376:125-35

NETTER-1 PHASE III TRIAL

SURVIVAL OUTCOMES



No. at Risk											
177Lu-DOTATATE group	116	97	76	59	42	28	19	12	3	2	0
Control group	113	80	47	28	17	10	4	3	1	0	0

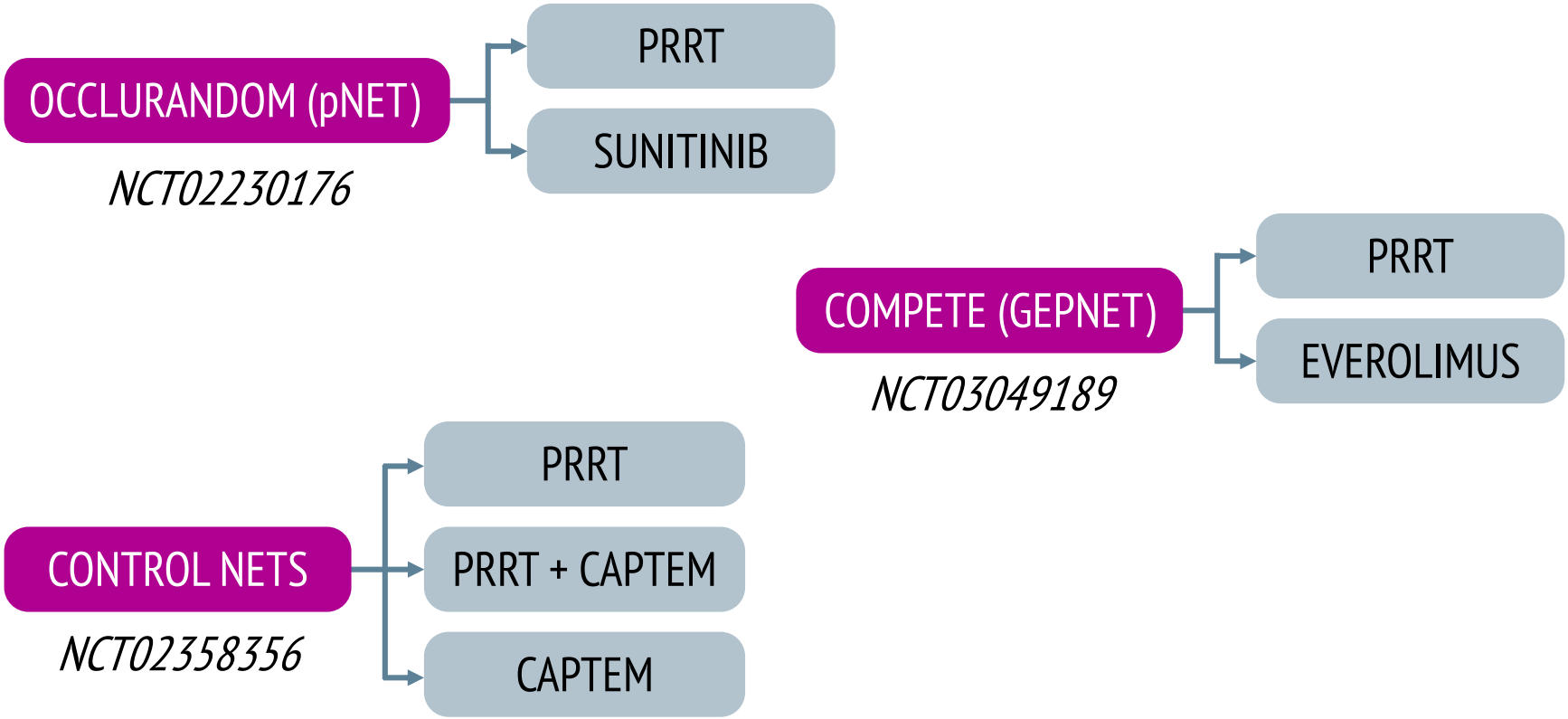


No. at Risk											
177Lu-DOTATATE group	116	108	96	79	64	47	31	21	8	3	0
Control group	113	103	83	64	41	32	17	5	1	0	0

HR, hazard ratio; LAR, long acting release; mPFS, median progression free survival; NR, not reported; LAR, long acting release; Lu, lutetium; Oct, ocreotide

Strosberg, J. NEJM 2017;376:125-35

CURRENTLY ONGOING PRRT TRIALS



CAPTEM, capecitabine and temozolomide; GEPNET, gastroenteropancreatic neuroendocrine tumours; pNET, pancreatic neuroendocrine tumour; NET, neuroendocrine tumour; PRRT, peptide receptor radionuclide Therapy; RCT, randomised clinical trial

https://clinicaltrials.gov

SUMMARY

- There is now **evidence from a RCT** of the **benefit of PRRT** in patients with NETs
- **Ongoing clinical trials** will provide **further evidence** of the effect of PRRT both **alone and in combination with other treatments**
- This will provide a better understanding of the **most effective way to use PRT in the therapeutic algorithm of patients** with NETs

NET, neuroendocrine tumour; PRRT, peptide receptor radionuclide Therapy; RCT, randomised clinical trial

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