Is First-Line PRRT in GEP-NETs the Standard of Care

2024 Debates and Didactics

Haematology and Oncology

Olumide Gbolahan

Assistant Professor

GI Oncology

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

Disclosures

Advisory role: Boston Scientific, Jazz, JnJ. AstraZeneca
Research Support: AstraZeneca, Astella Pharmaceuticals, Ipsen, Merck, Eisai, Jazz, SeaGen
No off- label uses of drugs will be presented.

Is First-Line PRRT in GEP-NETs the Standard of Care

Or

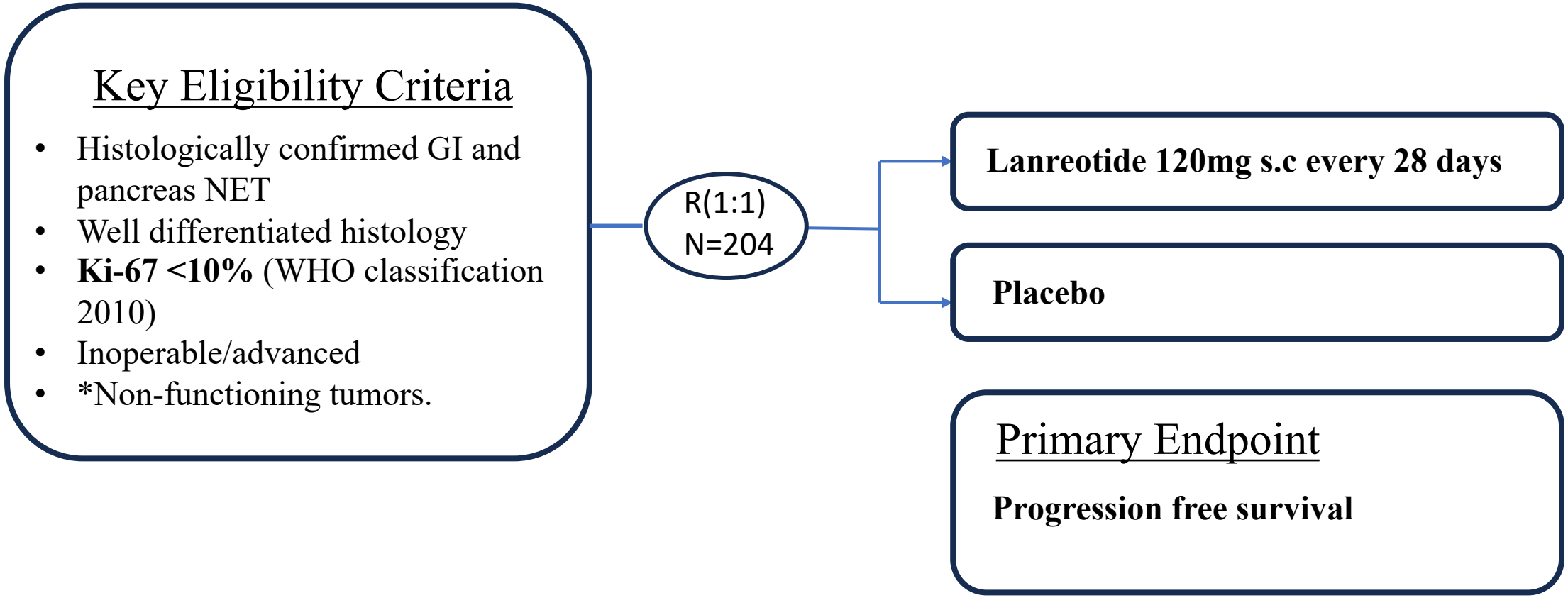
Shall we apply NETTER-2 to all GEP-NETs

First line treatment of GEP-NET is complicated by tumor biology

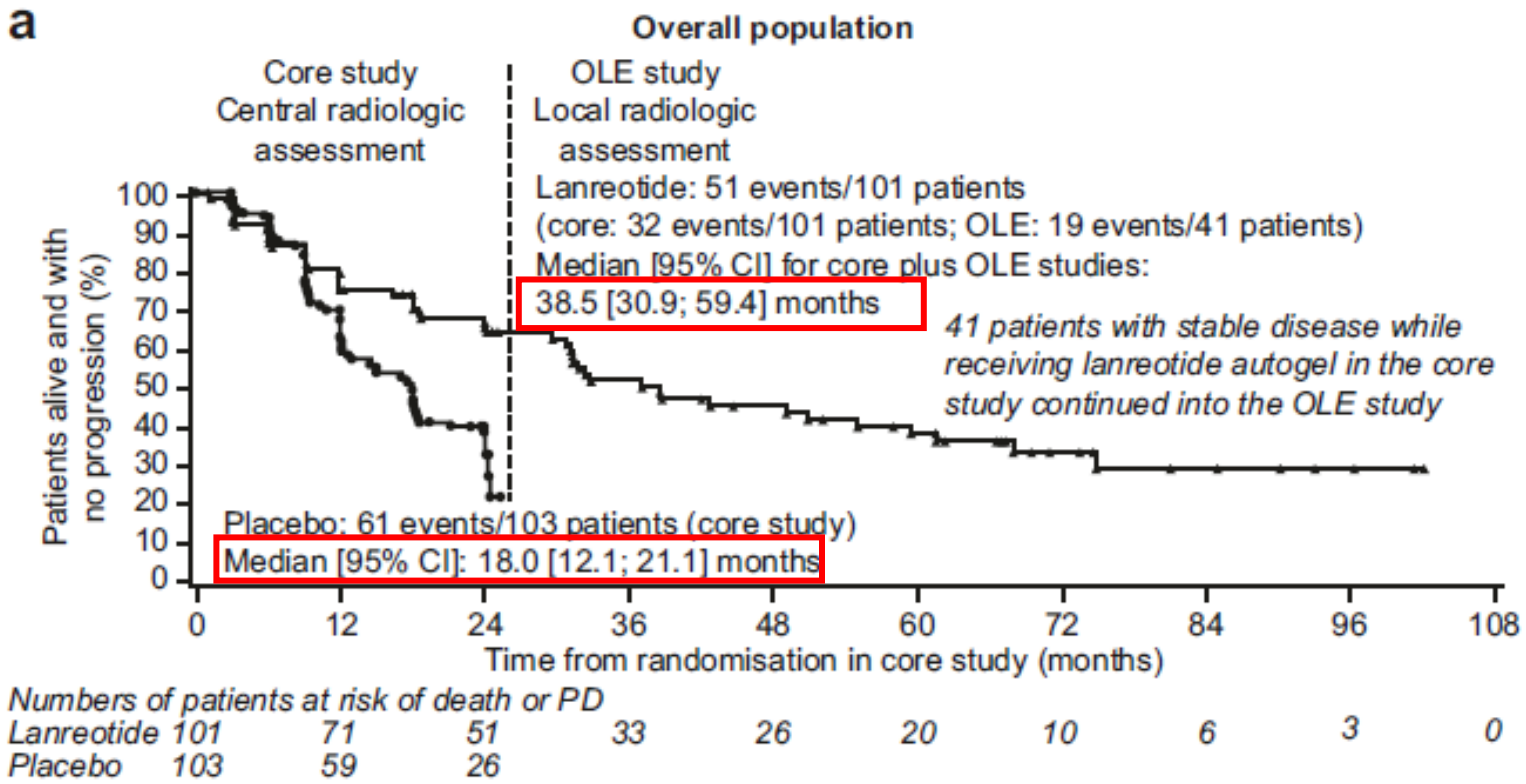
- Presence of Somatostatin receptors
- Tumor grade: Grade 1 and 2 (single digit Ki67) vs grade 2 (double digit Ki 67) and grade 3
- Primary site: Pancreas vs gastrointestinal lumen
- Options for treatment- W&W, octreotide, PRRT, other

CLARINET study

Phase III randomized double-blind, placebo-controlled study.



CLARINET – (Open-label extension) results



Endocrine. 2021; 71(2): 502–513.

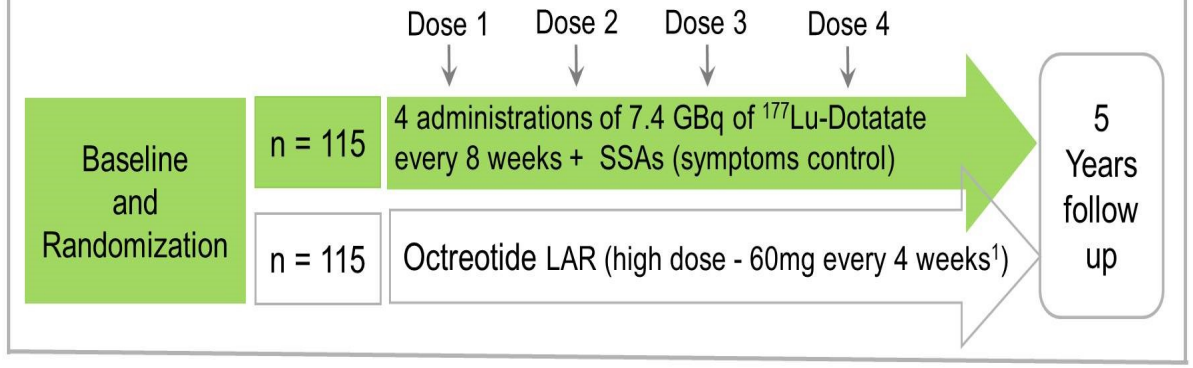
PRRT is effective in the second line for G1 and G2 NET

NETTER -1 Study Objectives and Design

Aim	Evaluate the efficacy and safety of ^{177}Lu-Dotatate + SSAs (symptoms control) compared to Octreotide LAR 60mg (off-label use)[1] 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



[1] FDA and EMA recommendation

Main Inclusion Criteria

- Patients ≥18 years of age
- Metastatic or locally advanced, inoperable, histologically proven, midgut NET
- Ki67 index ≤ 20% (Grade 1-2)
- Progressive disease (RECIST Criteria 1.1 centrally confirmed) on uninterrupted fixed dose of octreotide LAR (20-30 mg every 3-4 weeks)
- Somatostatin receptor positive disease
- Karnofsky Performance Score ≥ 60
- Including functioning and non-functioning

J Clin Oncol 34, 2016 (suppl; abstr 4005)

PRRT is effective in the second line for G1 and G2 NET

Advanced Accelerator Applications

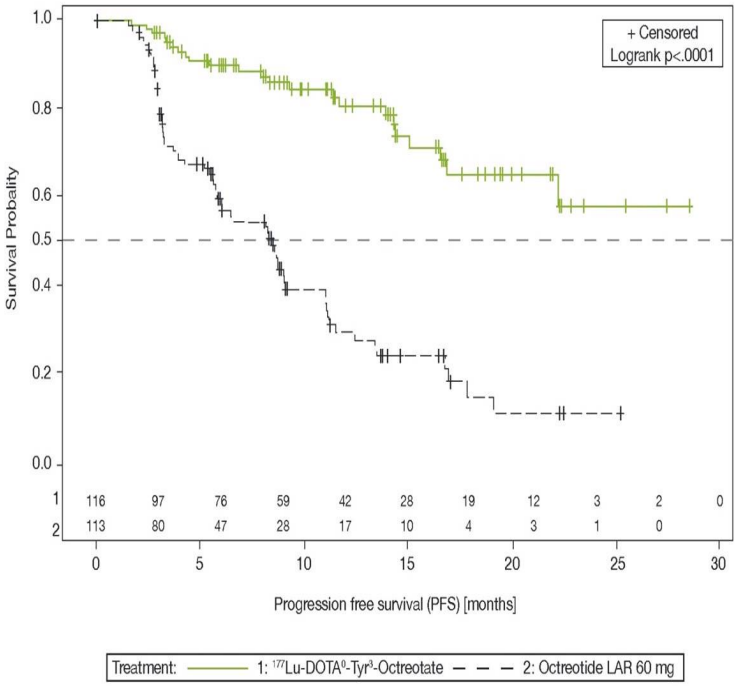
N = 229 (ITT)
Number of events: 91
^{177}Lu-Dotatate: 23
Oct 60 mg LAR: 68

Hazard ratio: **0.21**
[0.13 – 0.33]
p < 0.0001

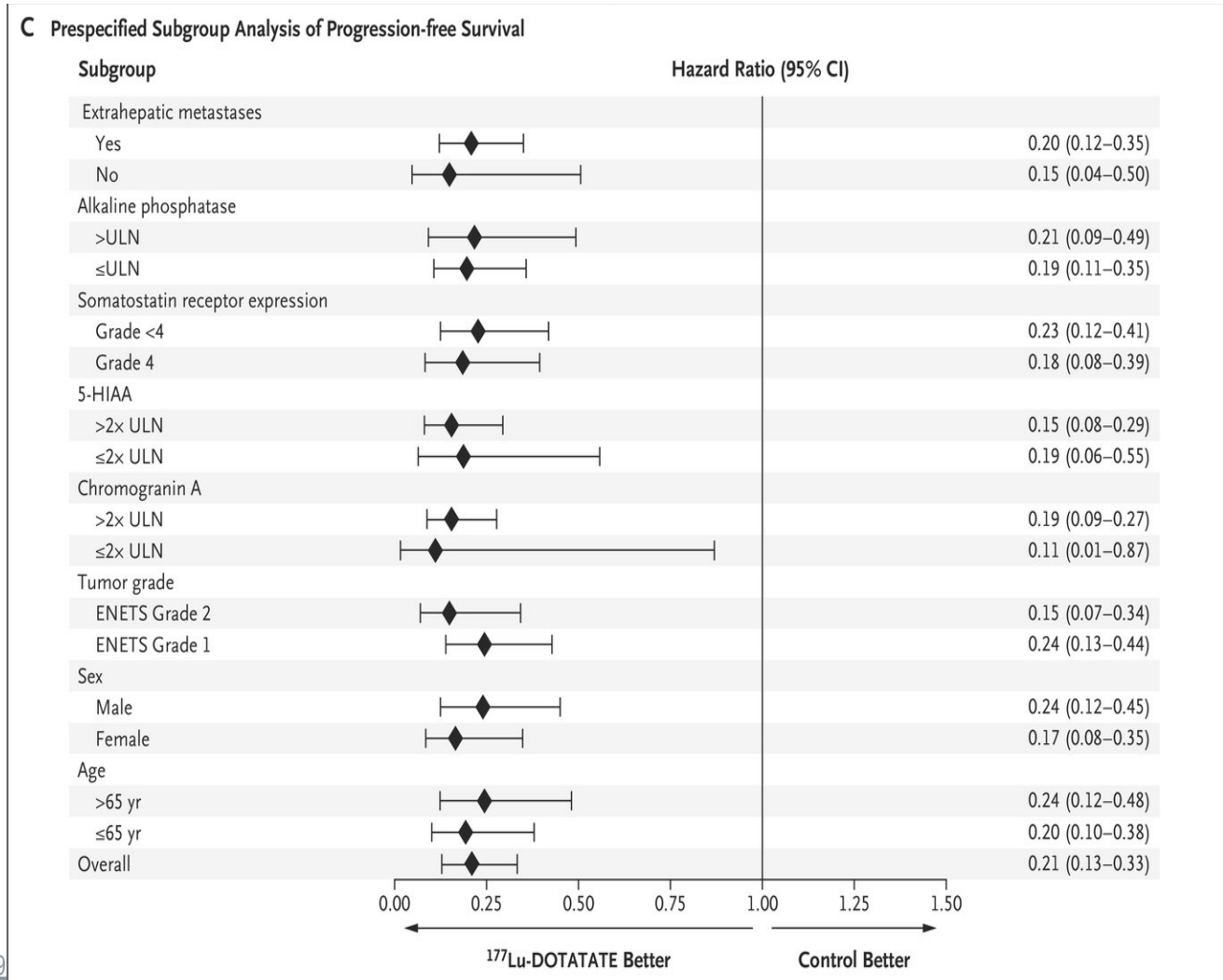
79% reduction in the risk of disease progression/death

Estimated Median PFS in the Lu-DOTATATE arm ≈ 40 months

Progression-Free Survival



All progressions centrally confirmed and independently reviewed for eligibility (SAP)



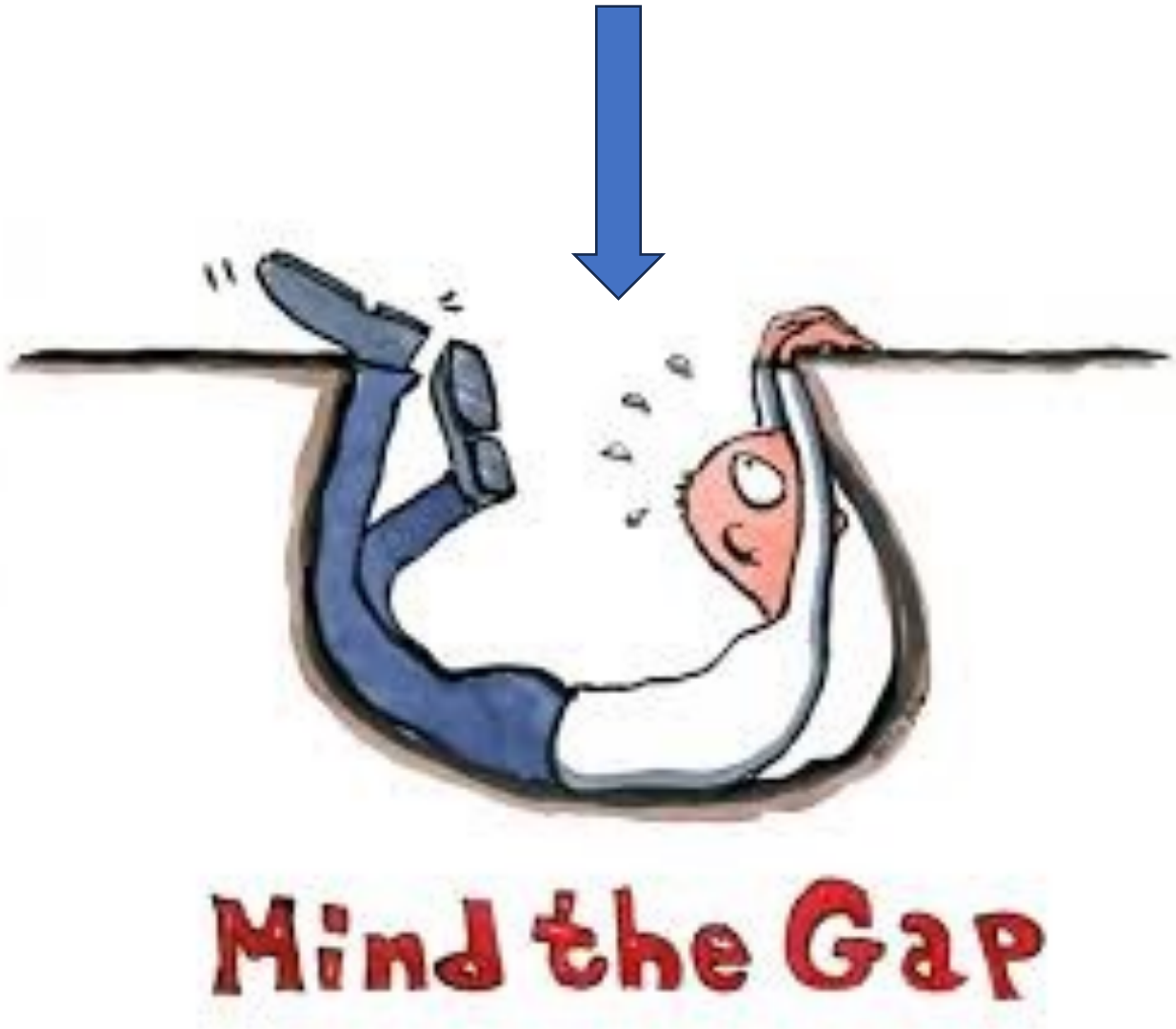
J Clin Oncol 34, 2016 (suppl; abstr 4005)

N Engl J Med 2017;376:125-135

For Grade 1-2 WD NET

- **Lanreotide provides mPFS of 38.5 months vs 18 months for G1 and some G2 NET**
- **There are no prospective data for PRRT in the 1st line for G1 and G2 NET (Ki 67 up to 10%)**
- **NETTER-1 is compelling for 2nd line PRRT for G2 NET**
- **Considering the biology of this disease, and the AE profile of PRRT**
- **PRRT CANNOT be the 1st line option in this group.**

Grade 3 Neuroendocrine tumors



Drawing and art text by Frits Ahlefeldt

First line management of advanced G2- G3 NET

[^{177}Lu]Lu-DOTA-TATE plus long-acting octreotide versus high-dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2–3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study

Simron Singh, Daniel Halperin, Sten Myrehaug, Ken Herrmann, Marianne Pavel, Pamela L Kunz, Beth Chasen, Salvatore Tafuto, Secondo Lastoria,

We have a conflict of interest ☺

The problems with NETTER-2.

Methods

	^{177}Lu-Dotatate plus octreotide 30 mg LAR (n=151)	High-dose octreotide 60 mg LAR (control group; n=75)	All patients (n=226)
Neuroendocrine tumour grade at diagnosis			
Grade 2 (Ki67 ≥10% and ≤20%)	99 (66%)	48 (64%)	147 (65%)
Grade 3 (Ki67 >20% and ≤55%)	52 (34%)	27 (36%)	79 (35%)
Ki67 index	17% (12–25)	16% (12–25)	16% (12–25)

→ This is the population in need

	^{177}Lu-Dotatate plus octreotide 30 mg LAR (n=151)	High-dose octreotide 60 mg LAR (control group; n=75)	All patients (n=226)
Time since initial diagnosis, months	1·8 (1·2–3·7)	2·1 (1·4–3·9)	1·9 (1·3–3·7)

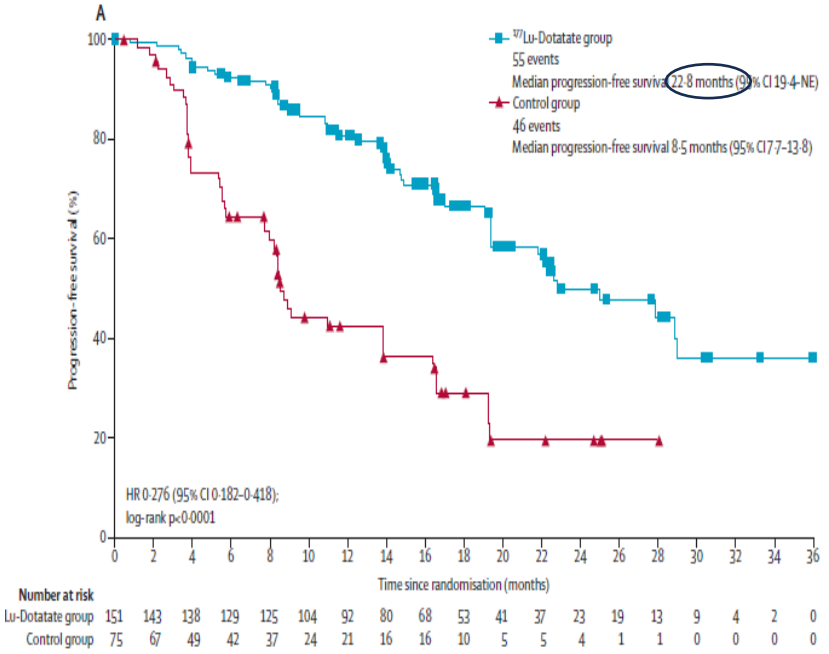
→ Is this appropriate?

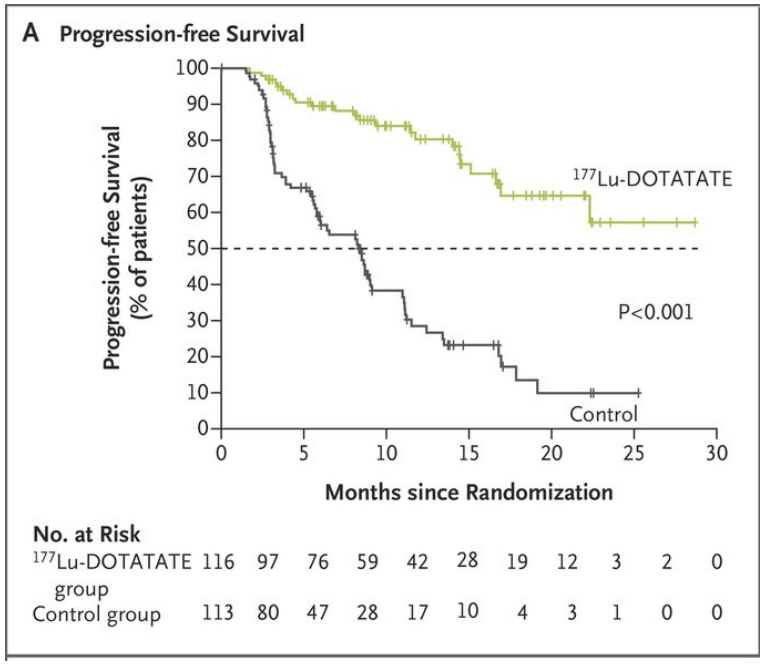
→ Indolent disease

Karnofsky Performance Scale score at baseline			
60	0	1 (1%)	1 (<1%)
70–80	28 (19%)	10 (13%)	38 (17%)
90–100	123 (81%)	64 (85%)	187 (83%)

→ Where did the sick go?

Results





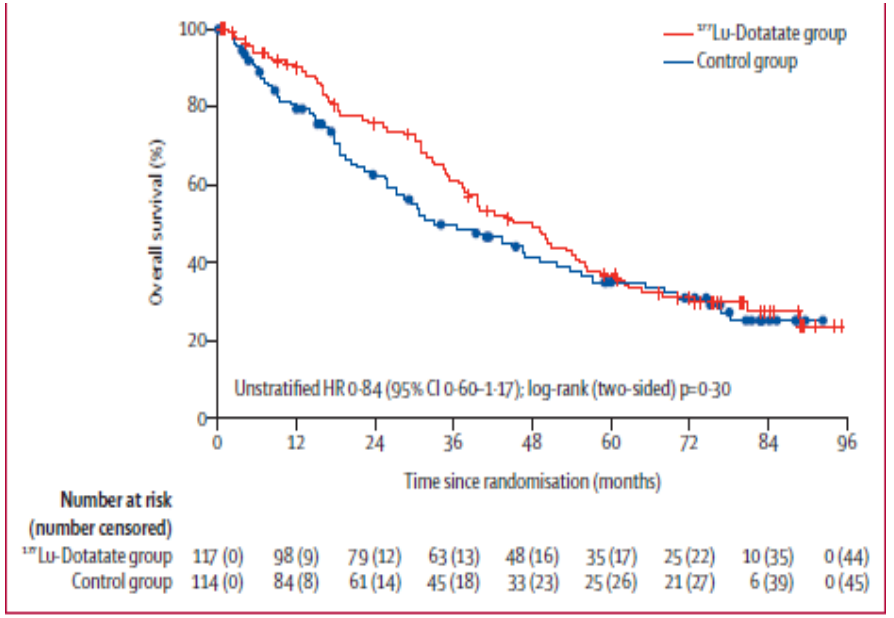
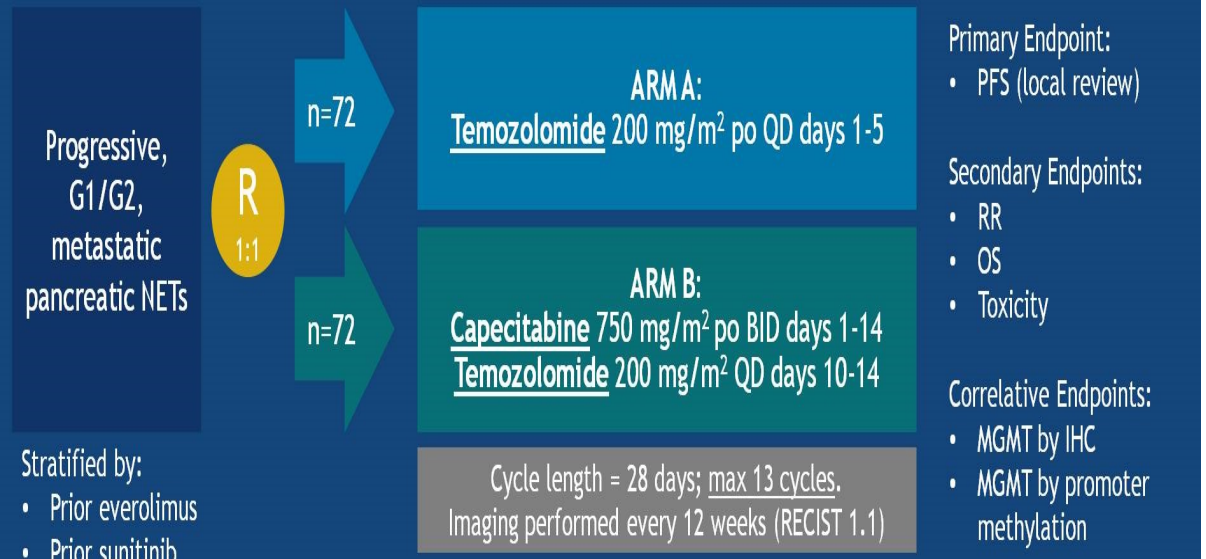


Figure 2: Overall survival

Capecitabine Temozolomide as the alternative for G2 pNET

E2211 Study Design



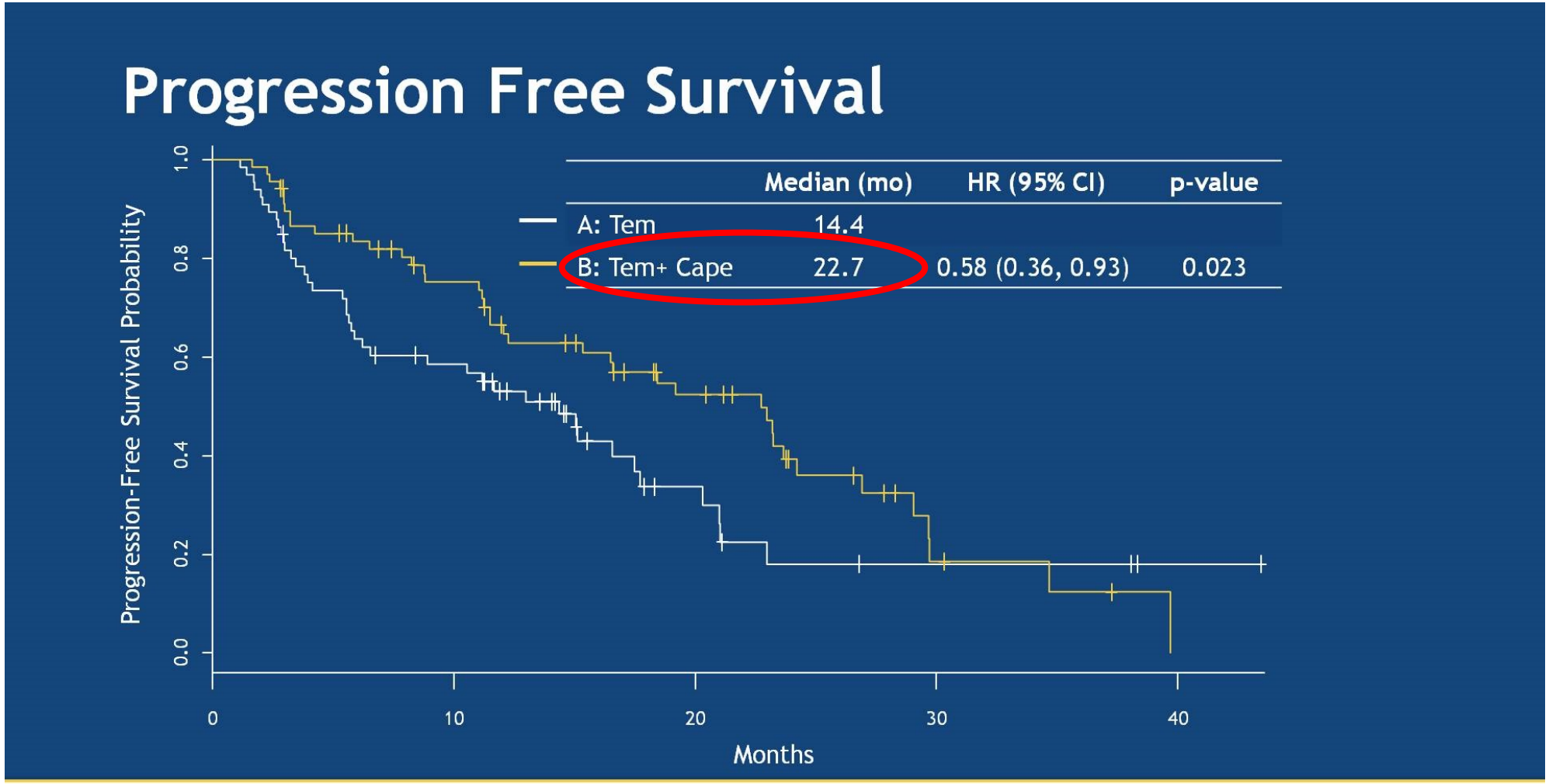
NCT01824875

Baseline characteristics (2)

	Temozolomide (N=72)	Temozolomide + Capecitabine (N=72)
Time from Diagnosis (months)	24.4 mo	34.0 mo
*WHO Grade		
Low (Grade 1)	45.1%	68.1%
Intermediate (Grade 2)	54.9%	31.9%
Sites of Metastasis		
Liver	93.1%	93.1%
Bone	12.5%	11.1%
Lung	6.9%	13.9%
Peritoneum	5.6%	9.7%
**Prior Treatment		
Everolimus	34.7%	36.1%
Sunitinib	12.5%	11.1%
**Concurrent SSA	54.2%	52.8%

* Imbalance (p=0.013); ** Stratification factor.

Capecitabine Temozolomide as the alternative for G2 pNET



PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Pamela L. Kunz, MD Abstract #4004

Summary of 1st line treatment

Variable	Score
1st line randomized	2
Phase 3	2
Phase 2	1
Clinical experience	1

	Octreotide LA	PRRT	Cap/Tem
G1 Ki 67 < 3%			
G2 Ki 67 3-10 %			
G2 Ki 67 10-19%			
G3 Ki 67 20-55%			

Key
Green: 4 and above
Amber:3
2: Red

Is First-Line PRRT in GEP-NETs the Standard of Care

- Absolutely not.
- Grade 1 and 2 NET should be treated with Octreotide unless very symptomatic/large disease burden
- In which case consider PRRT
- Capecitabine and temozolomide may have a role in the 1st line especially for pNET
- PRRT should be first-line SoC for Grade 3 NET