Fondazione IRCCS Istituto Nazionale dei Tumori

Sistema Socio Sanitario Regione Lombardia

UNIVERSITÀ DEGLI STUDI DI MILANO

# 5th Milan NET Conference

A live and web multimodal meeting among active Italian NET Centers

Wednesday June 12th, 2019
Milan

# PRRT alone or in combination with other drugs ?

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# DISCLOSURE

- **Personal financial interests:** Novartis, Ipsen, Pfizer, Merck Serono, Advanced Accelerator Applications, MSD (Advisory board,public speaking)

- **Institutional financial interests:** Novartis, Ipsen, Merck Serono, MSD, Pharmacyclics, Incyte, Halozyme, Roche, Astellas, Pfizer (Clinical trial or research projects: principal investigator, steering committee member)

- **Non-financial interests:**
  - ESMO: Coordinator of the Neuroendocrine, Endocrine neoplasms and CUP Faculty
  - ENETS: advisory board chairman
  - AIOM: coordinator for ITALIAN NEN guidelines
  - ITANET: Scientific committee member

# Outline

- PRRT + SSA
- PRRT + radiosensitizing agents
- PRRT + Chemotherapy (double systemic treatment)
- PRRT + molecular targeted therapy

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# Phase 3 Trial of $^{177}$Lu-Dotatate for Midgut Neuroendocrine Tumors

**TRIAL DESIGN**

In this open-label, phase 3 trial, we randomly assigned patients, in a 1:1 ratio, to receive $^{177}$Lu-Dotatate plus best supportive care, consisting of octreotide LAR at a dose of 30 mg every 4 weeks for symptom control ($^{177}$Lu-Dotatate receive high-dose octreotide LAR, 60 mg every 4 weeks) or best supportive care, consisting of octreotide LAR at a dose of 30 mg every 4 weeks for symptom control. Patients in the control group who had disease progression were permitted to receive $^{177}$Lu-Dotatate. Patients continued to receive treatment with octreotide LAR, which was administered intramuscularly at a dose of 30 mg approximately 24 hours after each infusion of $^{177}$Lu-Dotatate and then monthly after completion of all four treatments. In the control group,

- No information about the number of functioning vs. non functioning NETs
- It is not clear if non functioning NET pts received a concomitant OCT LAR

*Strosberg et al., NEJM 2017*

Health-Related Quality of Life in Patients With Progressive Midgut Neuroendocrine Tumors Treated With $^{177}$Lu-Dotatate in the Phase III NETTER-1 Trial

***Random Assignment and T***

Patients wer… Lu-Dotatate (200 mCi… followed by octreotide long-acting … high-dose octreotide (60 mg every 4 weeks).

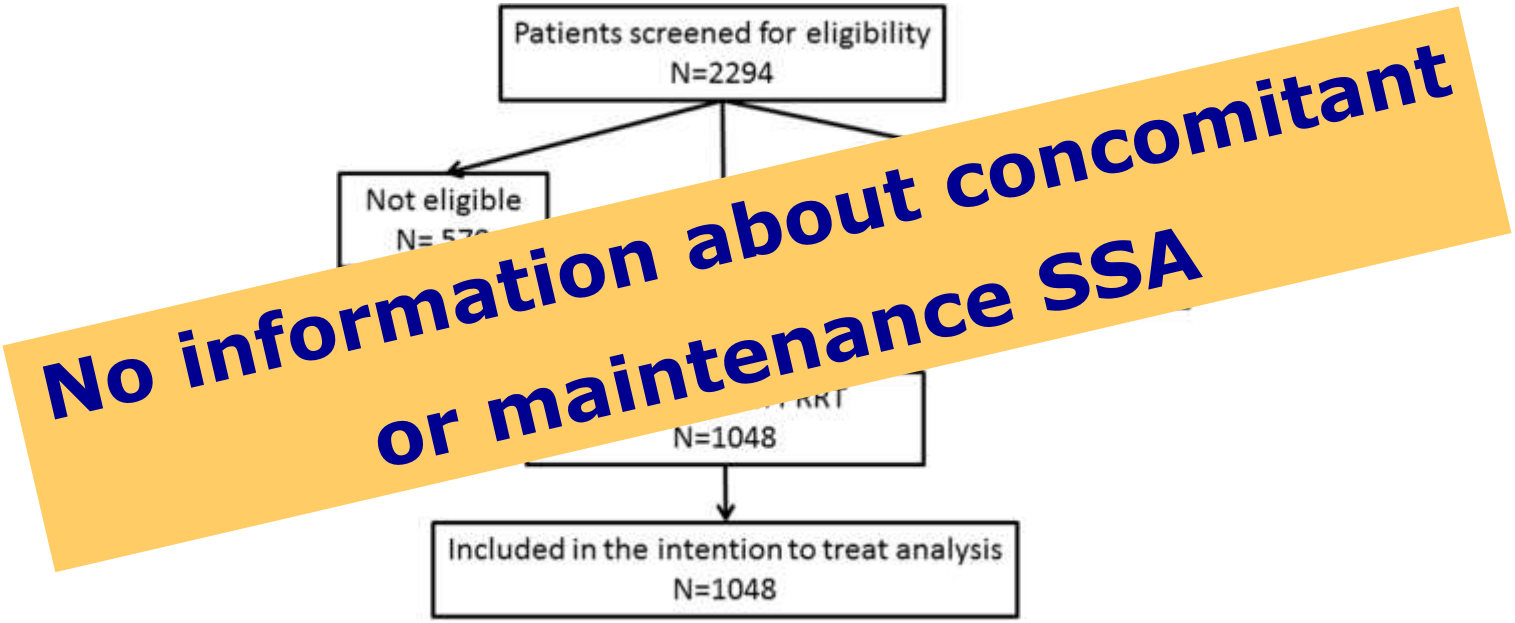
No information about the number of functioning vs. non functioning NETs

*Strosberg et al., J Clin Oncol 2018*

# Results and adverse events of personalized peptide receptor radionuclide therapy with $^{90}$Yttrium and $^{177}$Lutetium in 1048 patients with neuroendocrine neoplasms

Richard P. Baum[1], Harshad R. Kulkarni[1], Aviral Singh[1], Daniel Kaemmerer[2], Dirk Mueller[1], Vikas Prasad[3], Merten Hommann[2], Franz C. Robiller[4], Karin Niepsch[1], Holger Franz[5], Arthur Jochems[6], Philippe Lambin[6,7] and Dieter Hörsch[8]

Oncotarget, 2018, Vol. 9, (No. 24), pp: 16932-16950

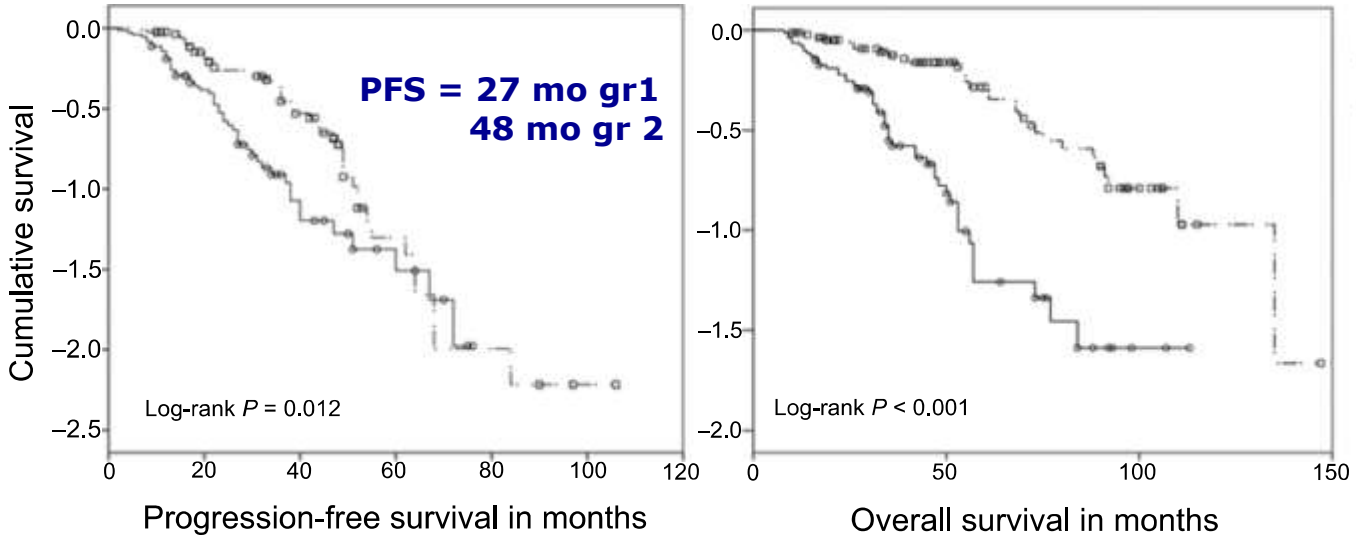



**No information about concomitant or maintenance SSA**

# PRRT
# + concomitant and/or maintenance SSA

Group 1 (81 pts): PRRT alone
Group 2 (87 pts): PRRT+SSA (77% OCT, 23% LAN) → SSA as maintenance
or PRRT → SSA (65% OCT, 31% LAN)

| | |
|---|---|
| Functioning | 59 % |
| Non functioning | 41 % |

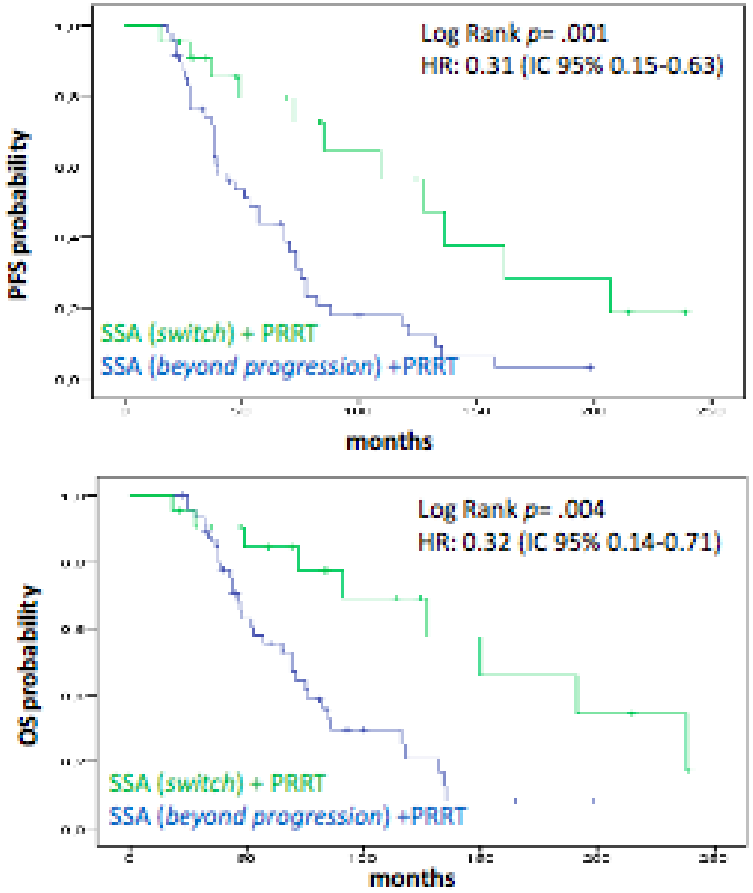



Survival benefit was seen in both functioning and non functioning NETs

*Yordanova et al, Clin Cancer Res 2018*

# PRRT + SSA after PD on SSA

- ✓ **S1**, pts who kept the same SSA treatment beyond first PD;
- ✓ **S2,** pts who switched the SSA with another SSA after first PD.




In the S1 (SSA beyond PD) group PRRT was associated with OCT in 74.5% and LAN in 25.5% of pts. In the S2 group (SSA switched with other SSA) PRRT was associated with OCT in 27.3% and LAN in 72.7% of pts (**Table 1**).

*Prinzi et al, ESMO 2018 Poster display session*

# ENETS 2019 – PRELUDE trial

(H18) - SELECTED FOR POSTER WALKS
Tumour Growth Rate (TGR) to Monitor Growth/Predict Response to Lanreotide Autogel (LAN) Use before, during and after Peptide Receptor Radionuclide Therapy (PRRT) in Advanced Gastroenteropancreatic Neuroendocrine Tumours (GEP-NETs): Data from PRELUDE

*Prasad V[A], Srirajaskanthan R[B], Grana CM[C], Baldari S[D], Shah T[E], Lamarca A[F], Courbon F[G], Scheidhauer K[H], Baudin E[I], Truong Thanh XM[J], Houchard A[J], Bodei L[K];*

$^{177}$Lu-DOTATATE/TOC + LAN → LAN alone

G1-G2 SSTR-2++ GEP(23)/Lung(1) NETs

ORR = 27%

Baseline TGR predictive cut-off = 1.18%/0.33%

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- **PRRT + radiosensitizing agents**
- PRRT + Chemotherapy (double systemic treatment)
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Eur J Nucl Med Mol Imaging (2008) 35:743–748
DOI 10.1007/s00259-007-0688-7

OpenAccess

ORIGINAL ARTICLE

# Report on short-term side effects of treatments with $^{177}$Lu-octreotate in combination with capecitabine in seven patients with gastroenteropancreatic neuroendocrine tumours

Martijn van Essen · Eric P. Krenning · Boen L. Kam · Wouter W. de Herder · Maarten O. van Aken · Dik J. Kwekkeboom

7 pts with GEP NETs

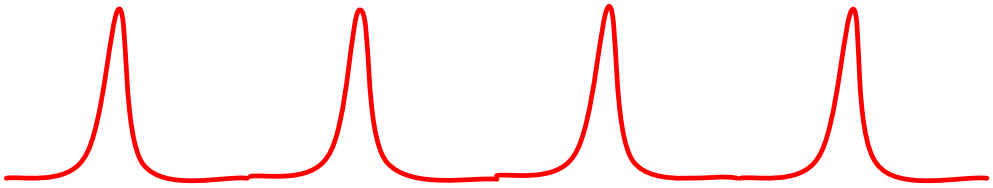
$^{177}$Lu-octreotate 7.4 GBq + CAP 1650 mg/sm/day

- The combination was safe (1 G3 anemia, 1 G3 thrombocytopenia)
- A randomised trial got started

In 2010 an academic study with $^{177}$Lu-Dotatate + metronomic CAP in pts with SSTR-2 positive and **FDG-positive** GEP NET.

*Lisa Bodei, Giovanni Paganelli, Chiara Grana*

**"CONVENTIONAL"**



**Maximum Tolerated Dose (MTD)**

**"METRONOMIC"**

**Continuative low dose**

**Oral daily**
(e.g. CTX, capecitabine, UFT)

**I.V. weekly**
(e.g. taxanes, antracyclines)

**I.V. protracted continuous infusion**
(e.g. 5-FU)



*Lambrescu et al., Canc Treat Rev 2017*

# $^{177}$Lu-Octreotate-based PRRT + radiosensitizing fluoropyrimidines in NET patients

25 pts PRRT + **c.i. 5-FU**

2 pts PRRT + **CAP**

PRRT + Fluoropyrimidines was **safe** and well-tolerated for pts who have previously been treated with $^{111}$In-pentetreotide

However, caution is recommended in patients with **bone metastases** due to a possible higher bone marrow toxicity.

*Hubble et al., Eur J Nucl Med 2010*

# PRRT radiosensitization with 5-FU and epigenetic modifier

Peptide Receptor ChemoRadionuclide Therapy
(PRCRT)

| NET cell lines | 5-FU alone |
| --- | --- |
| BON-1 and QGP1 | 5-FU + Decitabine or Tacedinaline |

SSTR-2 expression and $^{68}$Ga-Dotatoc uptake by means of western blot and radioligand binding assay

Results:
5-FU alone or in combination:

- ✓ *Radiosensitized tumor cells*
- ✓ *Upregulated SSTR-2 expression in tumor cells*
- ✓ *Increased radioligand binding of $^{68}$Ga-Dotatoc to tumor cells*

*Jin et al., J Nulc Med 2019*

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# Phase I-II Study of Radiopeptide $^{177}$Lu-Octreotate in Combination with Capecitabine and Temozolomide in Advanced Low-Grade Neuroendocrine Tumors

35 pts with progressive NET (mainly GEP)

*Treatment toxicity*

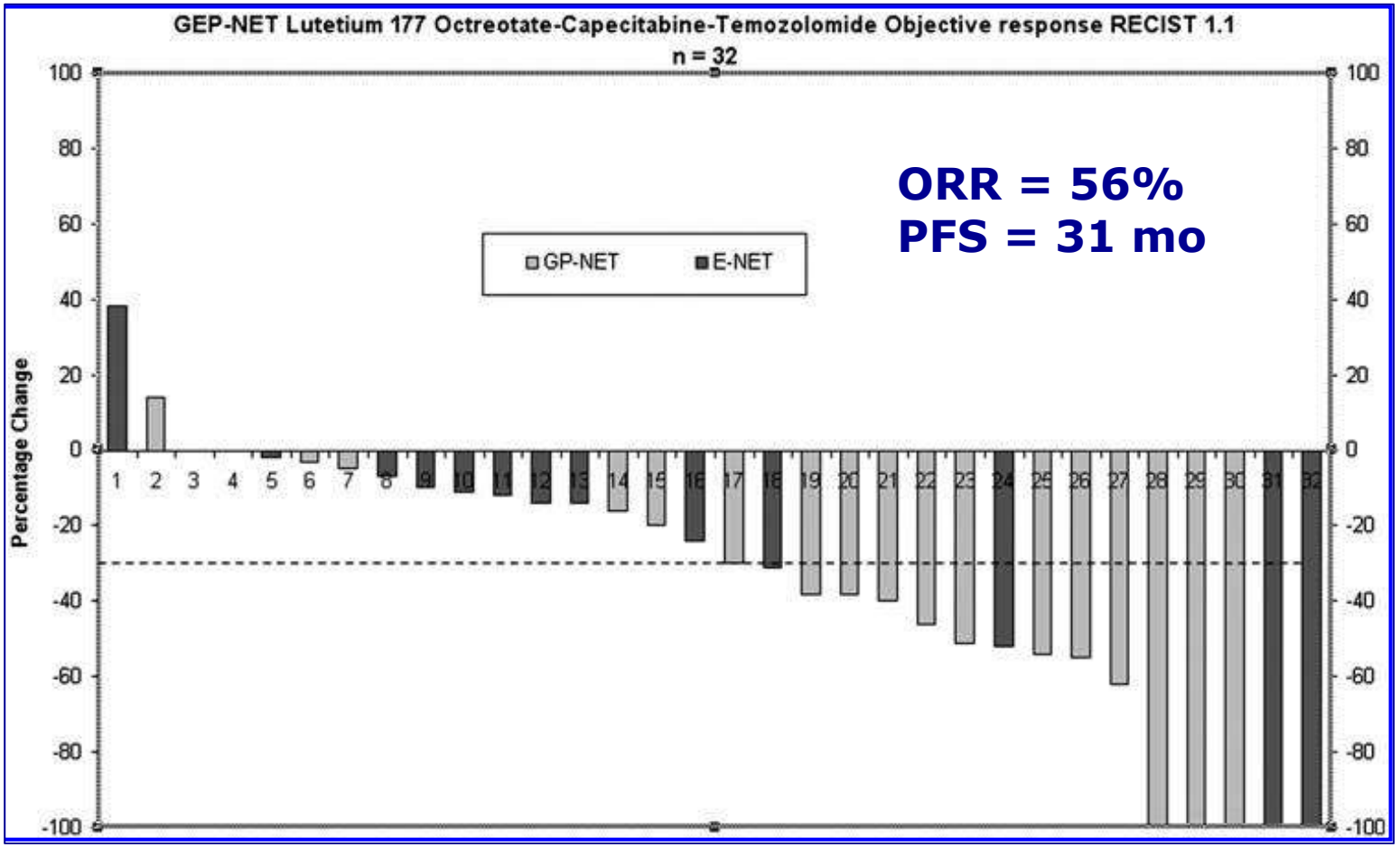
| Adverse event | Grade 1–2 | Grade 3 |
|---|---|---|
| Nausea/vomiting | 10 (36%) | 1 (3%) |
| Neutropenia | 5 (18%) | 2 (6%) |
| Anemia | 3 (11%) | 0 (0%) |
| Thrombocytopenia | 8 (29%) | 0 (0%) |
| Angina | — | 2 (6%) |

The combination was safe.

The recommended regimen was:

CAP 1500 mg/sm days 1-14 + TEM 200 mg/sm days 10-14 + $^{177}$Lu-Octreotate 7.8 GBq starting day 5, every 8 weeks

*Claringbold et al., Cancer Bioth Radiopharm 2012*




*Claringbold et al., Cancer Bioth Radiopharm 2012*

# Hematological toxicity of combined $^{177}$Lu-octreotate PRRT + CAP+/-TEM chemotherapy in GEP NET patients Long-term follow-up

65 pts **monitored for 5 years**:

- 28 PRRT + CAP
- 37 PRRT + CAP-TEM

*With a long-term F-up of a median of 36 months the short-term bone marrow toxicity of PRRT was not significantly increased by the addition of CAP +/- TEM*

*Kesavan et al., Neuroendocrinology 2014*

# PRRT beyond alkylating-based chemotherapy: is it safe?

**High risk of myelodysplastic syndrome and acute myeloid leukemia after $^{177}$Lu-octreotate PRRT in NET patients heavily pretreated with alkylating chemotherapy**

20 pts treated with $^{177}$Lu between 2005 and 2013

**<u>Delayed</u> G3-4 hem. Tox. in 30% of pts**

*Brieau et al., Res Letter 2016*

No difference in tumor/organ **dosimetry** between
$^{177}$Lu-Dotatate +/- concomitant CAP-TEM

10 pts PRRT + CAP-TEM
10 pts PRRT alone

Radiation absorbed dose for kidney, liver, spleen, bone marrow and tumor

**No significant difference** between the two groups

*Thakral et al., Br J Radiol 2018*

# PRRT + Chemo in NETs progressing on PRRT or Chemo alone

All NETs (mainly pancreatic)
were "high grade" (9 G2/ 6 G3)
or FDG-PET positive (8)

15 pts treated with $^{177}$Lu-Octreotate
**+ TEM-CAP (12) or TEM (3)**
**11 pts received concomitant SSA**

Disease control in 38-55% of progressive NETs

*Yordanova et al, Clin Nucl Med 2019*

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# ENETS 2019

(O04) - SELECTED FOR Case report
Controlling Severe Hypoglycemia with Everolimus plus 177Lu-DOTATATE in Metastatic Insulinoma: Two Cases

*Bernardo YM[A], Crona J[A], Welin S[A], Fröss-Baron K[A], Granberg D[A], Eriksson B[A];*
*[A]ENETs Centre of Excellence of Uppsala, University Hospital, Uppsala, Sweden*

- 2 pts with progressive insulinoma added PRRT to EVE 10 mg/day
- It was safe (reported thrombocytopenia in 1 case)

# EVE beyond PRRT: is it safe?

High toxicity for EVE in pts pre-treated with PRRT and chemo

*Panzuto et al., Oncologist 2014*

EVE well tolerated after PRRT

*Kamp et al., End Rel Cancer 2013*

# CONCLUDING REMARKS

- SSA combination with PRRT remains controversial, particularly in non functioning NETs
- Radiosensitizing monochemotherapy was well defined, mainly with CAP
- PRRT + CAP-TEM was reported safe and active
- Prospective randomised trials comparing single PRRT with combination are warranted

European Institute of Oncology, IEO, Milan, Italy

**ENETS Center of Excellence for GEP NETs**

Istituto Europeo di Oncologia

## IEO NET multidisciplinary team