ENETS – NANETS Webinar

PARTS 1 & 2:
Highlights of PRRT & drug development abstracts

Wednesday, 26 June 2024, 18:00 – 19:35 CEST

Live poll question:
Getting to know the audience

In which medical discipline are you trained and/or work in?

Please click on this button above the video: Select the medical discipline you are trained and/or work in (before webinar)

1. Oncology
2. Gastroenterology
3. Endocrinology
4. Pathology
5. Radiology
6. Nuclear medicine
7. Surgery
8. Tumor & cell biology
9. Other

Tonight's faculty – Part 1

Moderator & Panel:

Rocio GARCIA-CARBONERO

Hospital Universitario Doce de Octubre
Madrid, Spain
Oncology

Speaker & Panel:

Francesca SPADA

European Institute of Oncology (IEO)
Milan, Italy
Oncology

Alejandro GARCIA ALVAREZ

Vall d'Hebron Institute of Oncology
Barcelona, Spain
Medical Oncology

Panel – Part 1:

Eric BAUDIN

Institut Gustave Roussy
Villejuif (Paris), France
Endocrinology

Jennifer CHAN

Dana-Farber Cancer Institute
Boston, Massachusetts, USA
Medical Oncology

Daniel HALPERIN

The Univ. of Texas MD Anderson Cancer Center
Houston, Texas, USA
Oncology

Frank LIN

National Cancer Inst., Center for Clinical Research
Bethesda, Maryland, USA
Nuclear Medicine

Emil LOU

The University of Minnesota
Minneapolis, Minnesota, USA
Hematology, Oncology, Transplant

Erik MITTRA

Oregon Health & Science University (OHSU)
Portland, Oregon, USA
Nuclear Medicine & Radiology

Stefano PARTELLI

Vita-Salute University-San Raffaele
Milan, Italy
Surgery

Tonight's agenda – Part 1

Nuclear medicine / PRRT abstracts | Time: 12:00 – 12:45 EDT / 18:00 – 18:45 CEST

Moderator: Rocio GARCIA-CARBONERO

18:00 - 18:02 CEST: Opening – **Rocio GARCIA-CARBONERO**

18:02 - 18:22 CEST: Current trials

- 18:02 - 18:12 CEST: NETTER 2 trial – **Francesca SPADA**
- 18:12 - 18:17 CEST: Phase 2 Trial of Lu-177-DOTATATE in Metastatic or Inoperable Pheochromocytoma/Paraganglioma: Interim Analysis Results – **Alejandro GARCIA ALVAREZ**
- 18:17 - 18:22 CEST: Neoadjuvant PRRT in pNET (NeoLuPaNET) – **Alejandro GARCIA ALVAREZ**

18:22 - 18:42 CEST: Discussion Panel speakers: **Eric BAUDIN, Jennifer CHAN, Daniel HALPERIN, Rocio GARCIA-CARBONERO, Frank LIN, Emil LOU, Erik MITTRA, Stefano PARTELLI + presenters**

18:42 - 18:45 CEST: Closing – **Rocio GARCIA-CARBONERO**

18:45 - 19:50 CEST: ***BREAK***

NETTER-2

Francesca Spada, M.D. Ph.D.

Division of GI & NET - European Institute of Oncology (IEO), IRCCS (Milano)

IEO ENETS Center of Excellence

DISCLOSURE INFORMATION

Personal financial interests:
Advisory board, public speaking, travel: Advanced Accelerator Applications, Hutchmed, Ipsen, Novartis, MSD/Merck, Pfizer

Institutional financial interests:
Clinical trials (P.I.): GETNE, Hutchmed, Incyte, MSD/Merck

Non-financial interests:
AIOM: coordinator of Neuroendocrine Neoplasms Guidelines

ESMO: member of the NETs and Endocrine Tumors Faculty

ITANET: member of the Scientific Board

Background

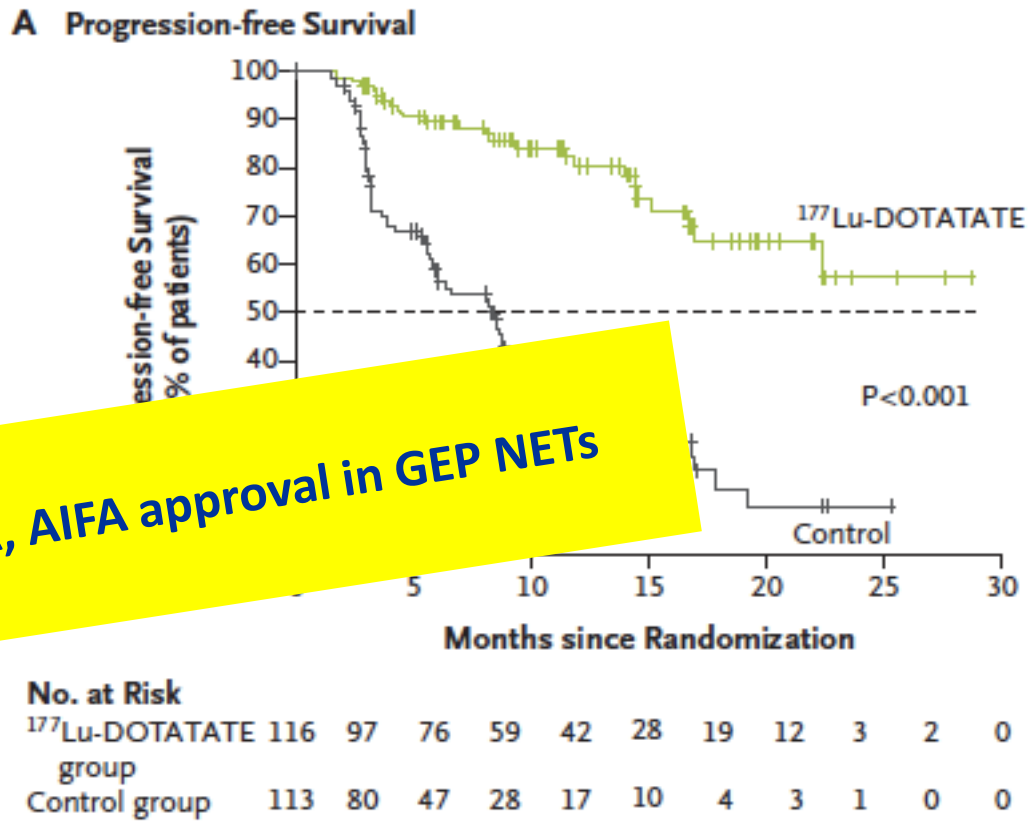
- ✓ Radioligand therapy delivers **cytotoxic radiation directly to the tumour** reducing systemic adverse events
- ✓ [^{177}Lu]Lu-DOTA-TATE (^{177}Lu-Dotatate) **binds SSTR used diagnostically and therapeutically** for decades
- ✓ International guidelines recommend **SSAs as first line therapy for advanced G1-G2 GEP-NETs** based on PROMID and CLARINET
- ✓ **Platinum/Etoposide is generally accepted for advanced G3 NENs with Ki67 > 55%** based on low-quality evidence
- ✓ There is **no universally accepted standard of care** for newly diagnosed advanced "high G2" and G3 GEP-NETs

Sgouros G. et al, Nat Rev Drug Discov 2020; de Jong M. et al, Int J Cancer 2001; Reubi JC et al, trends Pharmac Sci 2013; Rinke A. et al, JCO 2009; Caplin M. et al, N Engl J Med 2014; Del Rivero J. et al, JCO 2023; Eads JR et al, End Relat Cancer 2023; Sorbye H. et al, J Neuroendocrinol 2023

NETTER-1: Multicenter, open-label, randomised, phase III trial

- ✓ **Midgut primary tumours only (31% G2 NETs),** locally advanced or metastatic
- ✓ **Progressive on OCT LAR 20-30 mg q. 3-4 w over the last 3 years (34% progressive** on previous systemic therapy **other than SSAs**)
- ✓ Primary endpoint **PFS fully reached (HR 0.**
- ✓ Cor
  sub
- ✓ **QoL preserved**

[^{177}Lu]Lu-DOTA-TATE (^{177}Lu-Dotatate) FDA, EMA, AIFA approval in GEP NETs



Strosberg J. et al, NEJM 2017

NETTER-1

But we always thought it had to go second or later!!!

NETTER-2

[^{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, Jaume Capdevila, Amparo García-Burillo, Do-Youn Oh, Changhoon Yoo, Thorvardur R Halfdanarson, Stephen Falk, Ilya Folitar, Yufen Zhang, Paola Aimone, Wouter W de Herder, Diego Ferone, on behalf of all the NETTER-2 Trial Investigators**

Singh S. et al, Lancet 2024

NETTER-2: Study design

ENETS GUIDELINES (2023)
G1-G2 NET / G3 NET
(no spec. cut-off of Ki67)

?

ESMO GUIDELINES (2020)
G2 NET Ki67 > 10% - 15%
G3 NET Ki67 > 15 <50%

Screening phase

- Patients ≥15 years; N=226
- Advanced, SSTR+, well-differentiated, G2 or G3 GEP-NET (Ki67 ≥10% and ≤55%)
- Diagnosis within last 6 months prior to enrollment
- No prior PRRT or systemic therapy

Randomized treatment phase

R 2:1

- **^{177}Lu-DOTATATE 4 × 7.4 GBq + octreotide LAR (30 mg)* Q8W**
- **Octreotide control**
  High-dose octreotide LAR (60 mg) Q4W

PD

Optional treatment extension phase

- Retreatment with ^{177}Lu-DOTATATE (7.4 GBq/200mCi) Q8W × 2–4 cycles†
- Cross-over treatment ^{177}Lu-DOTATATE (7.4 GBq/200mCi) Q8W × 4 cycles + octreotide LAR (30 mg)*

Follow-up phase

Follow-up visits every 6 months for 3 years

Stratification factors:
- Grade (G2 vs G3)
- Tumor origin (pancreas vs other origin)

Study endpoints:
- Primary: PFS
- Key secondary: ORR, QOL

Histological confirmation and Ki67 assessment were done locally by each study site!!!

Singh S. et al, Lancet 2024

NETTER-2: Statistical plan

- ✓ **PFS primary analysis at 101 progression-free survival events**
- ✓ **Based on the NETTER-1 results,** a doubling PFS from an assumed **15 months** for the control group **(OCT LAR 60 mg)** to 30 months for the [^{177}Lu]Lu-DOTA-TATE (^{177}Lu-Dotatate) group will be expected (alternative hypothesis)
- ✓ **To have a 90% probability of rejecting the null hypothesis, approximately 222 pts would need to be randomly assigned in a 2:1 ratio to a** [^{177}Lu]Lu-DOTA-TATE (^{177}Lu-Dotatate) group **vs. control group.**

Hypothesis
PFS primary analysis

Hp (PFS): from 15 to 30 months (HR: 0.50)

1-beta: 90%

99 PFS events required

Alpha: 2,5%

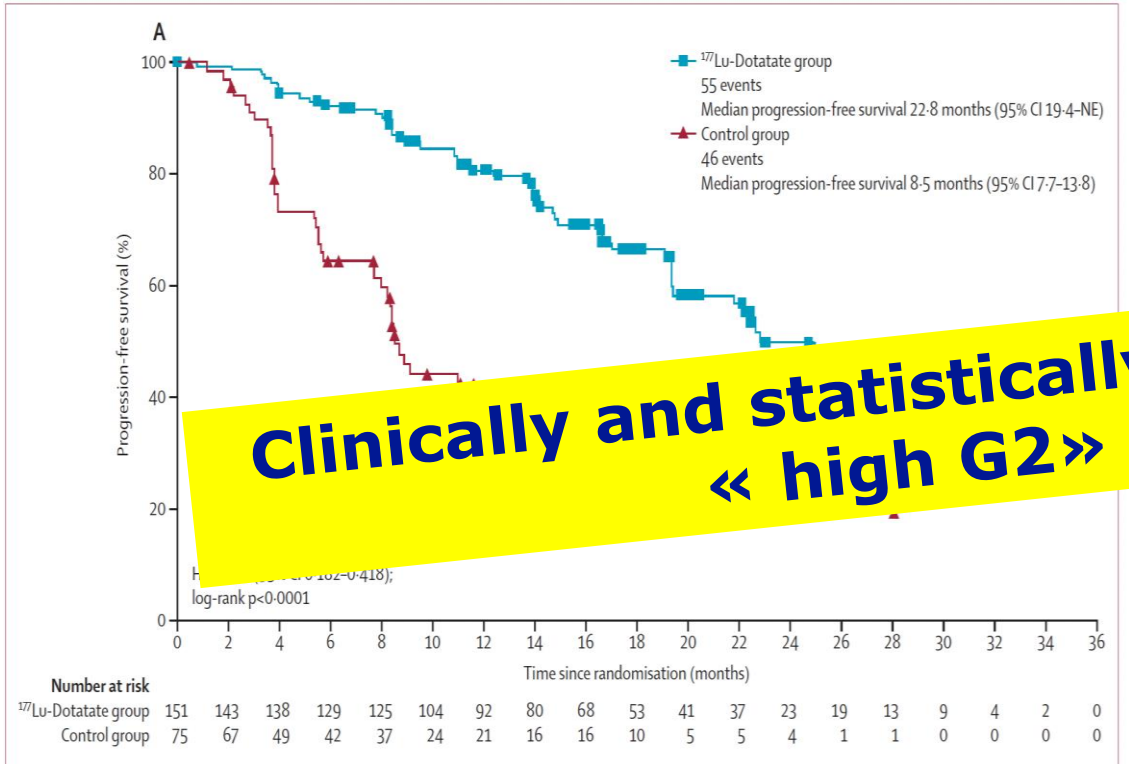
22,2 months enrolment

15% dropout

*Estimation of the survival distribution of **PFS performed using the Kaplan-Meier method**, and the **CIs of the median PFS using a stratified Cox model**.*
Objective response rate** between treatment groups and the odds ratio along with 95% Cis calculated using the stratified **Cochran-Mantel-Haenszel method

Singh S. et al, Lancet 2024

^{177}Lu-DOTATATE + OCT LAR high doses showed significant improvement in primary PFS* endpoint



	^{177}Lu-DOTATATE group (n=151)	OCT LAR control group (n=75)
PFS median, months (95%CI)	22,8 (19.4, NE)	8,5 (7.7, 13.8)
Stratified HR (95% CI)		

Clinically and statistically relevant in newly diagnosed « high G2» and G3 GEP-NETs

Lu-DOTATATE group vs. OCT LAR control group

- **Benefit across all the pre-specified subgroups (PANCREAS = OTHER!!!)**
- **Safety in line with known for both arms**

*centrally assessed according RECIST 1.1

Singh S. et al, Lancet 2024

^{177}Lu-DOTATATE + OCT LAR high doses showed significantly activity

65 ORR (43%) ^{177}Lu-DOTATATE vs. 7 ORR (9.3%) (OCT LAR 60 mg control group) (p-value <0.0001)

	^{177}Lu-DOTATATE arm n=151	Control arm n=75
Best overall response, n (%)		
CR		
PR		7 (9.3)
SD	72 (47.7)	42 (56.0)

Clinically and statistically active in newly diagnosed « high G2» and G3 GEP-NETs

Phase II trial of capecitabine + temozolomide vs. temozolomide in G1-G2 PanNET (p-value 0.59):

- 27 ORR (CR + PR) = 39,7% capecitabine + temozolomide arm
- 22 ORR (CR + PR) = 33,8% temozolomide arm

Singh S. et al, Lancet 2024; Kunz P. et al, JCO 2022

NETTER-2

Well-conducted study, clearly positive for its primary endpoint!!!

BUT some questions still remain…

1. Should Ki67 have an absolute value?

Ki67 > 20% identified a very aggressive subset of well differentiated NETs

- ✓ This has not panned out to be clearly true (lack of repeatability among observers and methods used to quantify; spread vs. «hotspot»)
- ✓ Morphology seems to surpass Ki67 in terms of tumour behaviour
- ✓ Lack of evidence on effect of approved therapies in GEP-NET G3 (6% of GEP NETs)
- ✓ **Importance of centralised histological and Ki67 confirmation by expert pathologist as in NETTER-1**

Scarpa A. et al. Nature 2017; Luchini C. et al. Modern Pathol 2022;
Li L. et al. Diagnostic Pathol 2022; Owens R. et al. Histopath.2020; Coriat R. et al The Oncologist 2016

2. Can we propose ^{177}Lu-Dotatate SAFELY to ALL the newly diagnosed advanced "high G2" and G3 GEP-NETs?

YES

- ✓ Neither treatment was particularly toxic
- ✓ TTD in QoL **(global health status, diarrhoea, fatigue, pain)** was similar between arms

EVEN IF ^{177}Lu-Dotatate arm is a **combination arm (^{177}Lu-Dotatate + OCT LAR)**

BUT…

- ✓ If QoL is affected by **functional status** and not by treatments is not so clear
- ✓ If QoL is affected by **tumour growth** and not by treatments is not so clear

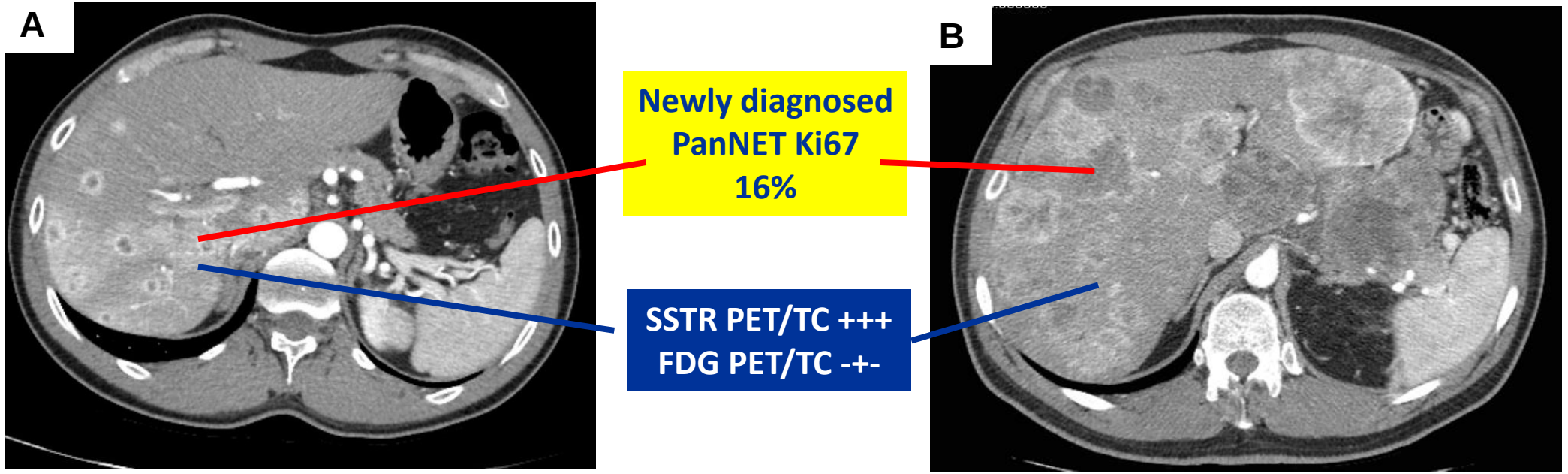
Singh S. et al, Lancet 2024 (appendix-1)

3. Would I propose OCT LAR 60 mg, considering the type of study-population?

NETTER-2	^{177}Lu-DOTATATE group (n=151)	OCT LAR control group (n=75)
PFS median, months (95%CI)	22,8 (19.4, NE)	8,5 (7.7, 13.8)
Stratified HR (95% CI) p-value	0.276 (0.182, 0,418) <0.0001	

REGISTRATIVE STUDIES	N° pts	PRIMARY SITE	PFS / TTP (months)	PLACEBO (months)
PROMID (A. Rinke, JCO 2009)	**85**	**midgut**	**14,3**	**6**
RADIANT-3 (J.C. Yao, NEJM 2011)	410	PanNET	11	4,6
SUN1111 (Raymond, NEJM 2011)	171	PanNET	11,4	5,5
CLARINET (M.E. Caplin, NEJM 2014)	204	GEP	N.R.	18
RADIANT-4 (J.C. Yao, Lancet 2016)	302	not-PanNET	11	3,9
NETTER-1 (J. Strosberg, NEJM 2017)	229	midgut	N.R.	8,4

Clinical cases: From theory to clinical practice



- Not syndromic
- Sporadic
- Multiple liver metastases
- **Asymptomatic**
- **PD over the last 6 months**

PROBABLY YES

- Not syndromic
- Sporadic
- Multiple liver metastases
- **Symptomatic for tumour burden**
- **PD over the last 2 months**

PROBABLY NO

4. Would I propose 177Lu-DOTATATE to all the newly diagnosed advanced «high G2» and G3 GEP-NETs since we have NETTER-2 evidence?

4. What do we need for treatment-decision in clinical practice?

Recommendations

General Recommendations for G1-G3 GEP-NETs

Recommendation 1.1. Selection of initial treatment options and sequencing of treatments following progression should consider patient and tumor characteristics such as hormone status, primary site, grade, extent and burden of disease, growth rate, comorbidities, and somatostatin receptor (SSTR) positivity, and should be discussed within a multidisciplinary team (MDT) when possible (Type: Informal consensus; benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Strong).

Del Rivero J et al, ASCO Guidelines, JCO 2023

Conclusion at a Glance

- ✓ NETTER-2 is the **first phase III study to evaluate radioligand therapy** in the **first-line setting** for any metastatic solid tumour
- ✓ NETTER-2 is the **first phase III study in patients with newly diagnosed «high G2» and G3 GEP-NETs**
- ✓ **NETTER-2 provided a very good evidence-based option in newly diagnosed «high G2» and G3 GEP-NETs**
- ✓ Waiting for predicting factors, clinical features of the patients and disease and multidisciplinary discussions remain our best friends

Live Poll Question:

High liver tumor burden, advanced PanNET Ki67 19%, symptomatic, SSTR+++, FDG-PET/TC +++.

What would you suggest as first-line systemic treatment?

1) PRRT

2) Alkylating-based chemotherapy

3) TKI

4) EVEROLIMUS

The IEO NET multidisciplinary group, ENETS CoE

Safety and Efficacy of Lu-177-DOTATATE in Metastatic or Inoperable Pheochromocytoma/ Paraganglioma – An Interim Analysis

Alejandro Garcia Alvarez, MD MsC

Gastrointestinal and Endocrine Tumor Unit

Vall d'Hebron University Hospital

DISCLOSURE SLIDE

- **Alejandro Garcia-Alvarez declares:**
  - **To participate in speakers' bureau for:** Angelini Pharma España, Eisai Europe, and Eisai.
  - **To receive travel & accommodation expenses from**: Pfizer, Ipsen, Eisai Europe, Advanz, Amgen, Advanz Pharma, and Advanced Accelerator Applications / Novartis.

Lu-177-DOTATATE in PPGL

Clinical Trial Characteristics

- Open-label, single-arm, single center (NCI), **phase II study**.

- Patients were **eligible** if:
  - Biopsy-proven PPGL.
  - SSTR PET scan positive.
  - RECIST progression with 12 months.

- **Two cohorts** of patients: SDHx mutated and Sporadic PPGLs.

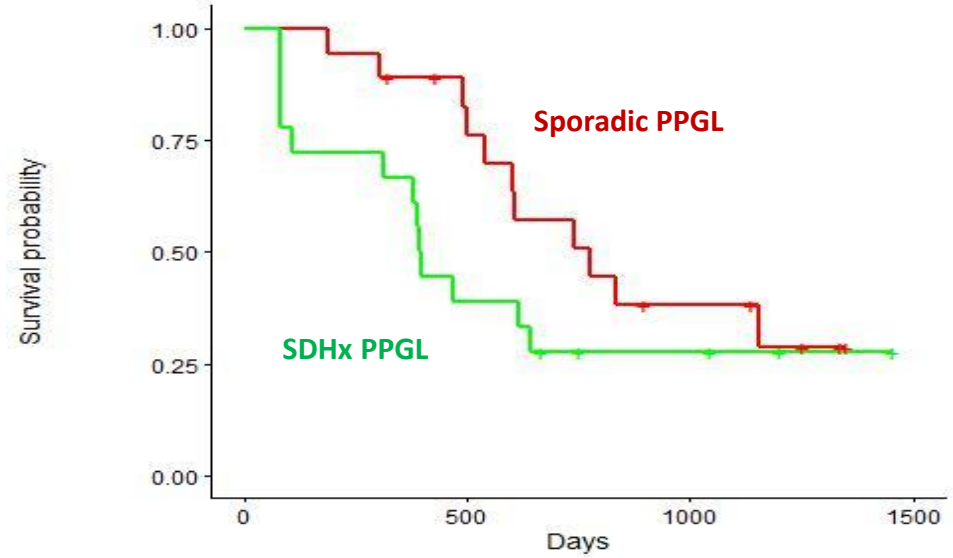
- **Primary endpoint**: Improve PFS rate at 6 months after starting treatment from 55% (natural history) to 75%

- **Treatment**: Four cycles of Lu-177-DOTATATE.

Lu-177-DOTATATE in PPGL

Efficacy Results

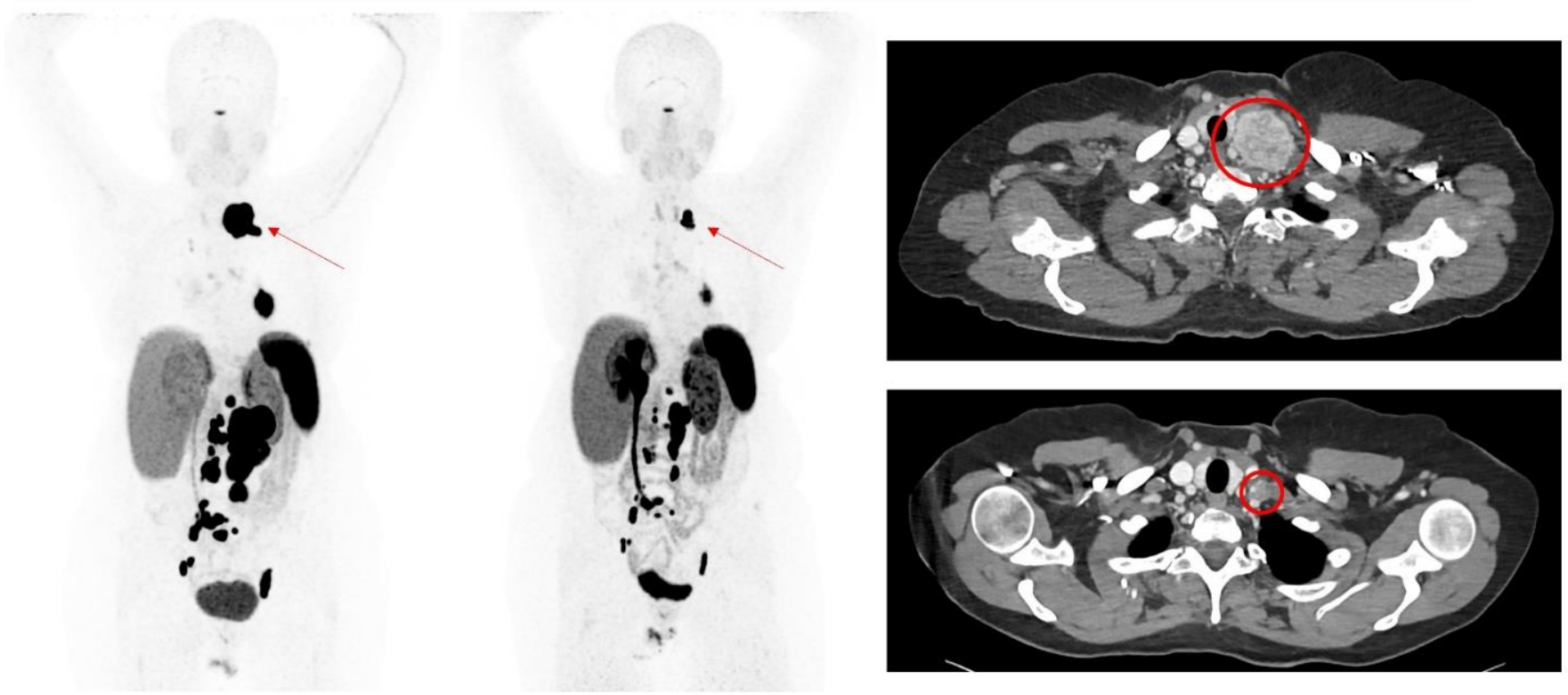
Overall Response	SDHx (n=18)	Sporadic (n=18)	Total (n=36)
Partial Response	3 (17%)	2 (11%)	5 (14%)
Stable Disease	10 (55%)	16 (89%)	26 (72%)
Progression	5 (28%)	0 (0%)	5 (14%)



	Median PFS
SDHx (n=18)	395 days
Sporadic (n=18)	775 days; HR 1.8 (p=0.154)
Total (n=36)	607 days (95% CI: 467-1153 days)

Lu-177-DOTATATE in PPGL

Imaging Response by PET and RECIST



Ga-68-DOTATATE PET: 2/9/2018

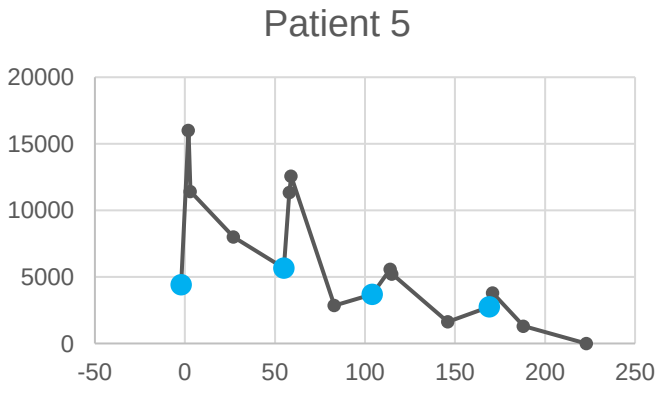
11/5/2019

Lu-177-DOTATATE in PPGL

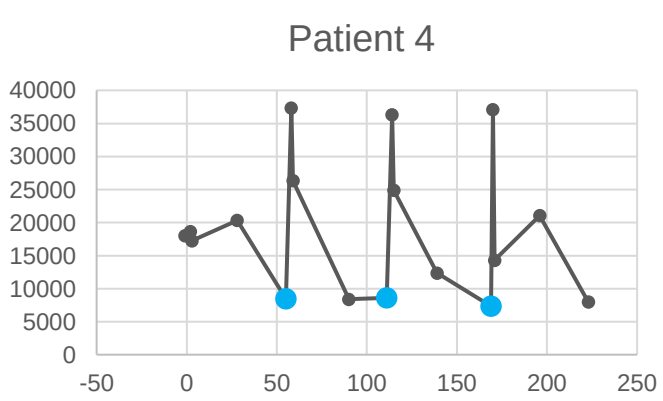
Catecholamine Release Syndrome

- Can start during Lu-177-DOTATATE infusion and last days to weeks (peak incidence within 24-48 hours).
- Some require ICU care (phentolamine, nicardipine drip).
- Pattern of increase in catecholamine levels may have meaning.

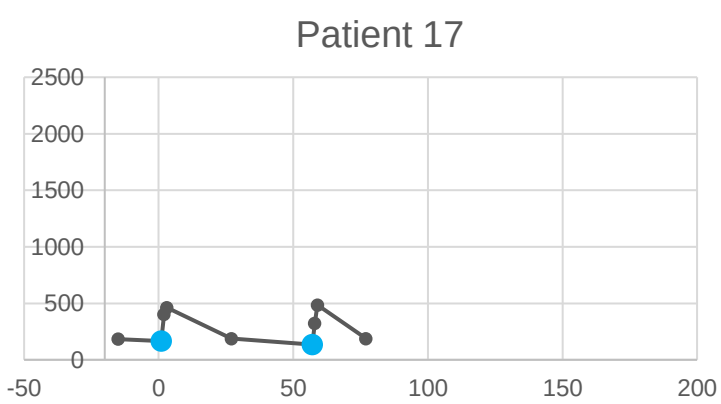
Responder



Stable Disease



Progression



Lu-177-DOTATATE in PPGL

Conclusions

- Lu-177-DOTATATE is efficacious, data comparable to those seen in GEP-NET patients.
- Genetic subtype (SDHx) impacts clinical outcomes.
- Lu-177-DOTATATE treatment in PPGL is safe, with AE profile similar to previously reported.
- CRS risk highest in first 24-48 hours – need to be prepared.

A Prospective Phase II Single-arm Trial On Neoadjuvant PRRT With 177Lu-DOTATATE Followed By Surgery For Resectable Pancreatic Neuroendocrine Tumors: NeoLuPaNET Study

Alejandro Garcia Alvarez, MD MsC

Gastrointestinal and Endocrine Tumor Unit

Vall d'Hebron University Hospital

NeoLuPaNET Study

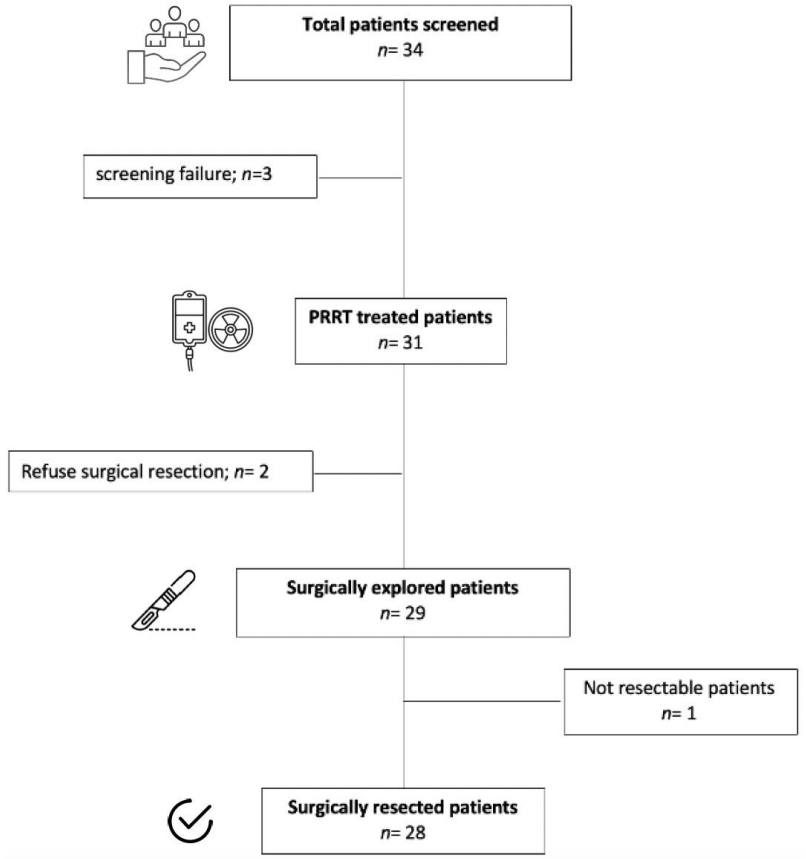
Clinical Trial Characteristics

- Open-label, single-arm, multicentric, **phase II study**.
- Patients were **eligible** if they had histologically confirmed resectable and SSTR-PET scan positive NF-PanNET with at least one of the following **"high risk" features**:
  - Radiological tumour size > 40mm,
  - Well differentiated G2 NF-PanNETs with Ki67 > 10%,
  - Presence of nearby organs involvement,
  - Vascular invasion (excluding SMV/PV > 180° and/or CT/SMA invasion),
  - Mesenteric and/or portal and/or splenic vein thrombosis,
  - Presence of a single resectable liver metastasis,
  - Presence of enlarged hypervascularised lymph nodes at imaging, positive at 68Ga-DOTATOC PET.
- **Primary endpoints**:
  - Post-operative 90-day morbidity and mortality
  - Radiological response to PRRT according to RECIST criteria (version1.1)
- **Treatment**: Four cycles of Lu-177-DOTATATE.

NeoLuPaNET Study

Treatment Administration and Flowchart

- A total of 34 patients were screened and 31 patients were enrolled between 2000 and 2023.
- **Week 0**: Enrolment.
- **Weeks 1-25**: PRRT administration.
- **Week 38** (3 months after last PRRT administration): CT and 68Ga-PET Evaluation and Restaging.
- **Week 40** (3,5 months after last PRRT administration): Surgery.



NeoLuPaNET Study

Efficacy Results

Pre-PRRT vs Post-PRRT

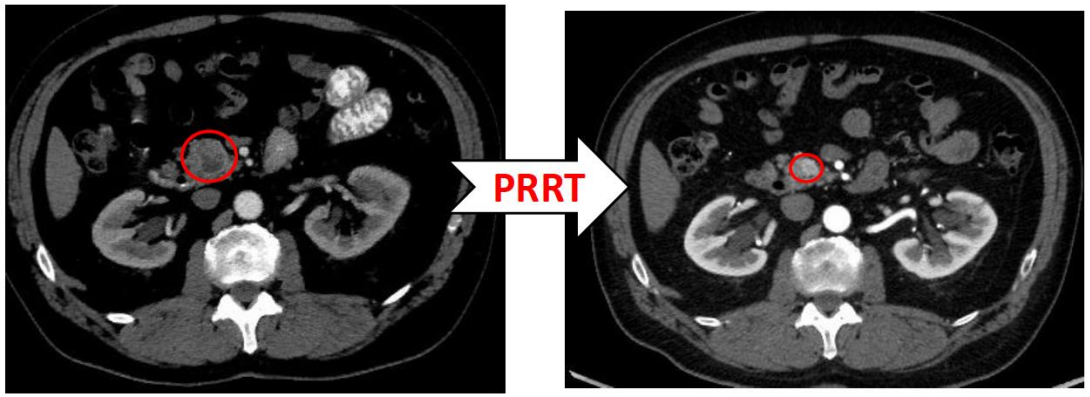
Variable	n (% or ±SD or IQR)
Pre-PRRT 68Ga-PET, SUV max	65.5 (42.5-112.8)
18-FDG PET Positive	23 (74%)
18-FDG PET, SUV max	8.55 (5.6–11.95)
Number of PRRT cycles	
- 2 cycles	2 (6)
- 3 cycles	3 (10)
- 4 cycles	26 (84)
RECIST criteria	
- Progressive disease	0 (0)
- Stable disease	13 (42)
- Partial response	18 (58)
- Complete response	0 (0)

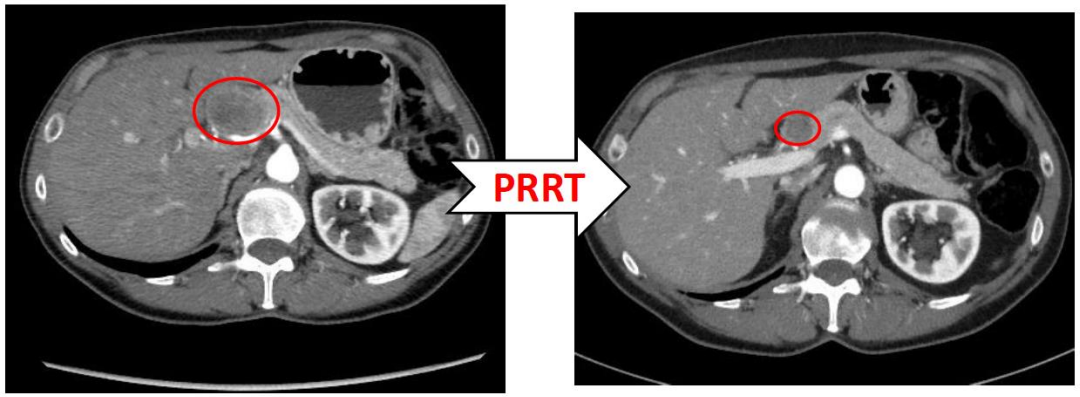
Perioperative Details

Variable	n (% or ±SD or IQR)
Resectable disease	28 (97%)
Post-operative complications	21 (72%)
Severity of complications	
- Clavien-Dindol	4 (14%)
- Clavien-Dindo II	10 (34%)
- Clavien-Dindo III	7 (24%)
POPF	
- Biochemical leak	1 (3%)
- CR-POPF	10 (34%)
Length of hospital stay	10 (7–23)
90 days mortality	0 (0%)

NeoLuPaNET Study

Imaging Response by CT Scan





NeoLuPaNET Study

Conclusions

- Neoadjuvant PRRT demonstrated to be a **safe** and **effective** therapeutic option for patients with high-risk NF-PanNETs.
    - An objective **radiological response** was observed in the majority of treated patients.
    - No negative impact on postoperative **morbidity** and **mortality**.

ENETS – NANETS Webinar

PART 2:
Multikinase inhibitors / Drug development

Wednesday, 26 June 2024, 18:50 – 19:35 CEST / 12:50 – 13:35 EDT

Tonight's faculty – Part 2

Moderator & Panel:

Emil LOU

The University of Minnesota
Minneapolis, Minnesota, USA
Hematology, Oncology, Transplant

Speaker & Panel:

Shagufta SHAHEEN

Stanford University
Stanford, California, USA
Medical Oncology

Panel – Part 2:

Eric BAUDIN

Institut Gustave Roussy
Villejuif (Paris), France
Endocrinology

Jennifer CHAN

Dana-Farber Cancer Institute Boston,
Massachusetts, USA
Medical Oncology

Rocio GARCIA-CARBONERO

Hospital Universitario Doce de Octubre
Madrid, Spain
Oncology

Camilo JIMENEZ

The University of Texas MD Anderson Cancer Center
Houston, Texas, USA
Oncology

Tonight's agenda – Part 2

Multikinase Inhibitors / Drug development | Time: 12:50 – 13:35 ET / 18:50 – 19:35 CEST

Moderator: Emil LOU

18:50 - 18:52 CEST: Introduction – **Emil LOU**

18:52 - 19:12 CEST: Current trials – **Shagufta SHAHEEN**

- 18:52 - 19:00 CEST: CABINET trial
- 19:00 - 19:08 CEST: NATALIE in Pheo/para
- 19:08 - 19:12 CEST: (Combination MKI trials) Everolimus + Lenvatinib (ENETS) and CABATEN trial

19:12 - 19:32 CEST: Discussion – Panel speakers: **Eric BAUDIN, Jennifer CHAN, Rocio GARCIA-CARBONERO, Camilo JIMENEZ, Emil LOU + presenter**

19:32 - 19:35 CEST: Closing – **Emil LOU**

Multikinase Inhibitors/Drug Development

Neuroendocrine Tumors (NETs)
Pheochromocytoma and Paraganglioma(PPGL)
Neuroendocrine Neoplasms(NENs)

Shagufta Shaheen, MD (she/her)

Clinical Assistant Professor (Medicine/Oncology)
Stanford University

DISCLOSURE INFORMATION

- Crinetics Pharmaceuticals (steering committee).
- Exelixis (advisory board, honoraria)
- Bristol Myers Squibb Foundation (Grant recipient)
- Lexicon (advisory board)
- Ipsen (advisory board)
- Natera (advisory board)

Outline

CABINET TRIAL: Pancreatic and extra-pancreatic NET

NATALIE TRIAL: Pheochromocytoma and Paraganglioma

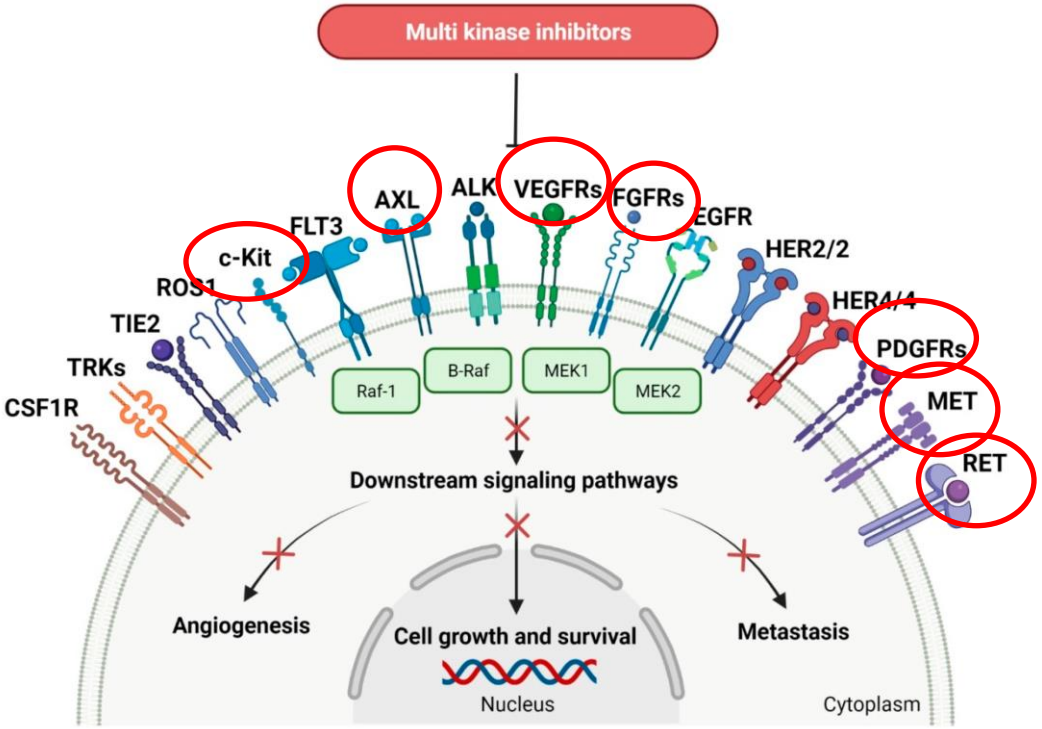
Everolimus and Lenvatinib: Extra-pancreatic NET

Cabozantinib plus Atezolizumab: Neuroendocrine Neoplasms(NENs)- CABATEN

Multikinase Inhibitors

- Tyrosine Kinase: catalyses the transfer of phosphate group

- Regulate fundamental cellular functions, i.e. growth, differentiation, survival, migration, cell death.



Molecules **2022**

CABINET TRIAL: Pancreatic and extra-pancreatic NET

Alliance A021602: Phase III, Double-Blinded Study of Cabozantinib Versus Placebo for Advanced Neuroendocrine Tumors (NET) After Progression on Prior Therapy (CABINET)

Jennifer A Chan, Susan Geyer, Fang-Shu Ou, Michael V Knopp, Spencer Behr, Tyler Zemla, Jared Acoba, Ardaman Shergill, Edward M Wolin, Thorvardur R Halfdanarson, Nikolaos A Trikalinos, Bhavana Konda, Namrata Vijayvergia, Arvind Dasari, Jonathan R Strosberg, Elise C Kohn, Matthew H Kulke, Eileen M O'Reilly, Jeffrey A Meyerhardt

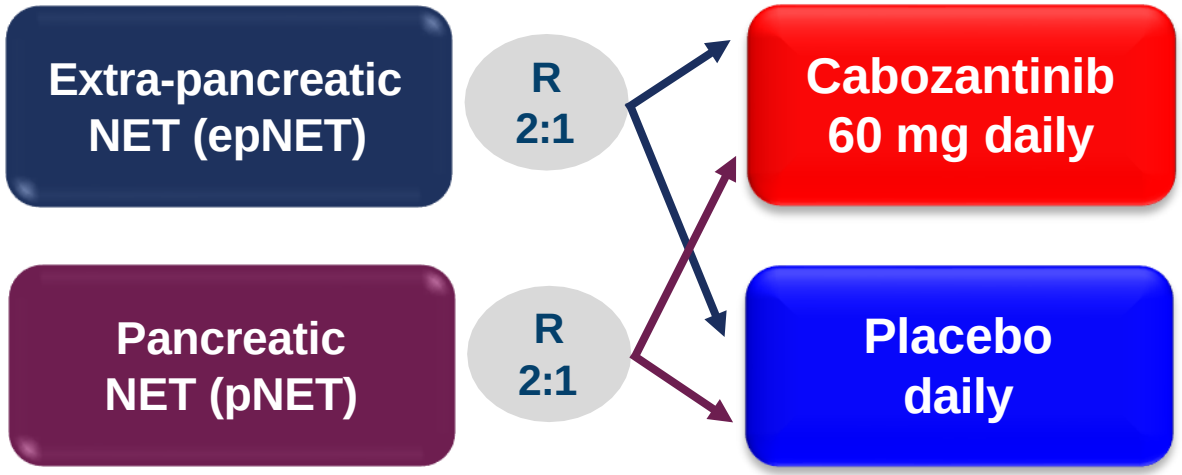
Presented by Dr Jennifer Chan: ESMO Congress 2023

Background

- **Cabozantinib:** oral multikinase inhibitor
  - VEGF-R, c-MET, AXL, and RET

- **CABINET (Alliance A021602)**
  - Efficacy of cabozantinib in patients with advanced extra pancreatic neuroendocrine tumor (epNET) and pancreatic neuroendocrine (pNET)
    - Well to moderately differentiated NET (Grade 1-3)
    - Disease progression by RECIST within 12 months prior to randomization
    - Progression or intolerance of at least 1 prior FDA-approved systemic therapy, not including somatostatin analogs (SSA)
    - Concurrent SSA allowed provided stable dose for ≥ 2 months

CABINET TRIAL Study Design



** Unblinding and crossover allowed after confirmation of PD by central radiology review*

Interim analyses in both cohorts demonstrate statistically significant and clinically meaningful improvement in PFS by local radiology review in patients treated with cabozantinib

DSMB voted unanimously to stop accrual to the trial, unblind patients and allow cross-over from placebo to cabozantinib

Stratification factors:

- epNET: Concurrent SSA & Primary site (midgut GI/unknown vs. non-midgut GI/lung/other)
- pNET: Concurrent SSA & Prior sunitinib

Study End

- **Primary**
  - **Prog**
    by bli
- **Seconda**
  - **Overall survival**
  - **Objective response rate**
  - **Safety and tolerability**

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Presented by Dr Jennifer Chan: ESMO Congress 2023

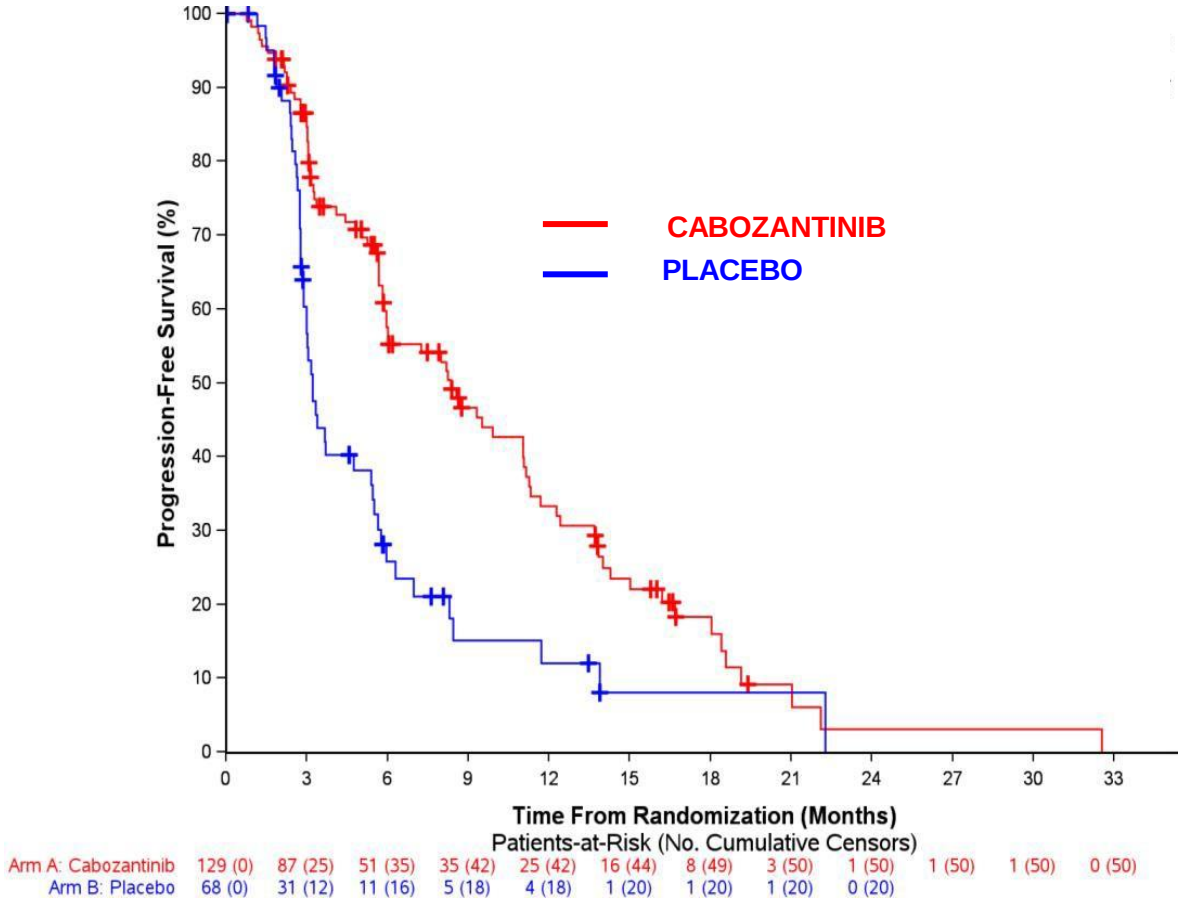
Baseline Characteristics: Extra-pancreatic NET

	CABOZANTINIB (N=129)	PLACEBO (N=68)
Time from Diagnosis to Randomization, months, median (range)	87 (10-489)	83 (13-340)
Age, years, median (range)	66 (28-86)	66 (30-82)
Gender (female)	74 (57%)	31 (46%)
ECOG PS		
0	44 (34%)	30 (45%)
1	83 (64%)	35 (52%)
2	1 (1%)	1 (2%)
Differentiation		
Well	101 (79%)	56 (84%)
Moderate	7 (6%)	5 (8%)
Poor	2 (2%)	0
Not specified	18 (14%)	6 (9%)
Grade		
G1	35 (27%)	14 (21%)
G2	80 (63%)	44 (66%)
G3	7 (6%)	6 (9%)
Unknown	6 (5%)	3 (5%)

	CABOZANTINIB (N=129)	PLACEBO (N=68)
Primary tumor site		
GI	64 (50%)	45 (66%)
Lung	27 (21%)	12 (18%)
Unknown	20 (16%)	1 (1%)
Other	18 (14%)	10 (15%)
Hormone syndrome present	39 (31%)	24 (36%)
Concurrent SSA	80 (62%)	44 (65%)
Prior SSA	118 (91%)	59 (87%)
Prior systemic therapy		
Median # (range)	2 (1-7)	2 (1-6)
Everolimus	91 (71%)	42 (62%)
Lu-177 dotatate	75 (58%)	40 (59%)
Tem +/- Capecitabine	42 (33%)	19 (28%)
Platinum based chemo	11 (9%)	9 (13%)
Other TKI	7 (5%)	4 (6%)

Presented by Dr Jennifer Chan: ESMO Congress 2023

epNET Cohort: Progression Free Survival (Local Review)



Stratified HR = 0.45
(95% CI: 0.30 – 0.66)
log-rank p<0.0001

Median PFS:
Cabozantinib = 8.3 months
Placebo = 3.2 months

Median follow-up: 13.9 months

Presented by Dr Jennifer Chan: ESMO Congress 2023

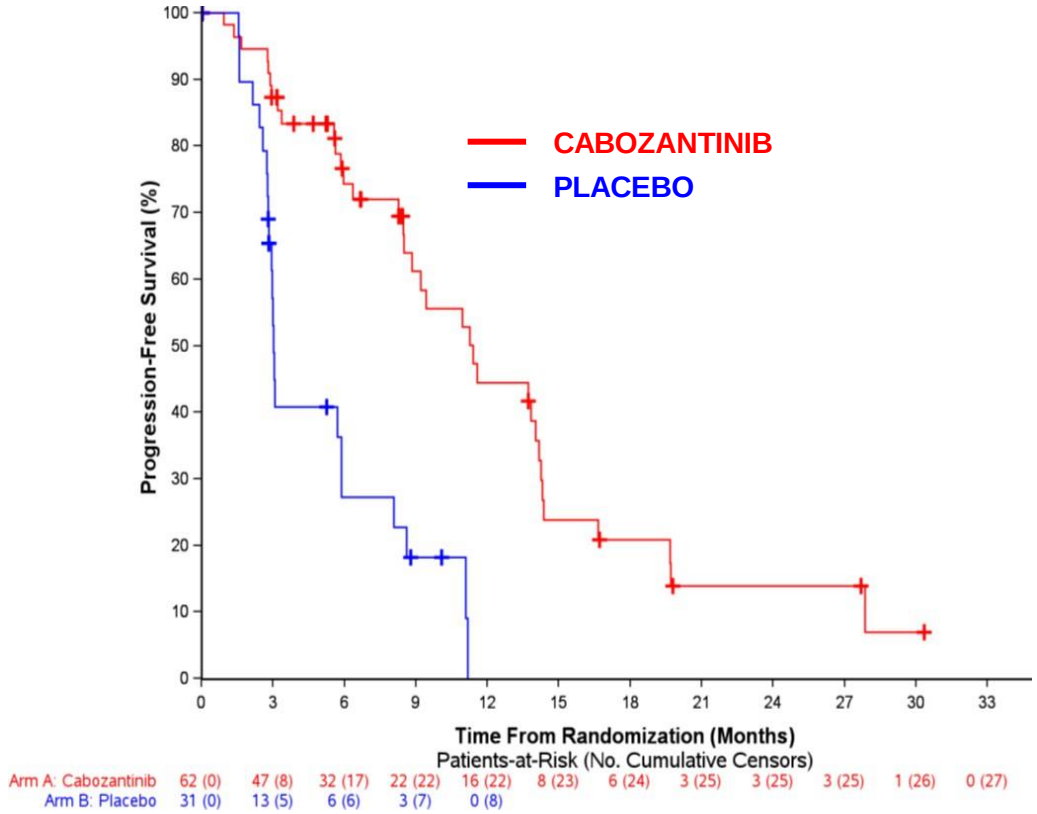
Baseline Characteristics: Pancreatic NET

	CABOZANTINIB (N= 62)	PLACEBO (N=31)
Time from Diagnosis to Randomization, median, months (range)	84 (1-213)	83 (18-197)
Age, years, median (range)	60 (29-79)	64 (39-79)
Gender (female)	44	42
ECOG PS		
0	33 (53%)	14 (47%)
1	28 (45%)	16 (53%)
2	1 (2%)	0
Differentiation		
Well	56 (90%)	29 (97%)
Moderate	4 (7%)	0
Not specified	2 (3%)	1 (3%)
Grade		
G1	14 (23%)	5 (17%)
G2	39 (63%)	19 (63%)
G3	6 (10%)	3 (10%)
Unknown	3 (5%)	3 (10%)

	CABOZANTINIB (N= 62)	PLACEBO (N=31)
Hormone syndrome present	11 (18%)	4 (13%)
Concurrent SSA	37 (45%)	17 (44%)
Prior SSA	60 (97%)	29 (94%)
Prior systemic therapy		
Median # (range)	3 (1-9)	2 (0-7)
Everolimus	51 (82%)	24 (77%)
Lu-177 dotatate	34 (55%)	18 (58%)
Sunitinib	18 (29%)	7 (23%)
Tem +/- Capecitabine	42 (68%)	16 (52%)

Presented by Dr Jennifer Chan: ESMO Congress 2023

pNET Cohort: Progression Free Survival (Local Review)



Stratified HR = 0.27
(95% CI: 0.14 – 0.49)
log-rank p<0.0001

Median PFS:
Cabozantinib = 11.4 months
Placebo = 3.0 months

Median follow-up: 16.7 months

Presented by Dr Jennifer Chan: ESMO Congress 2023

Adverse Events

epNET

	CABOZANTINIB (N=124)	PLACEBO (N=63)
Grade 3 AE	74 (59.7%)	21 (33.3%)
Grade 4 AE	9 (7.3%)	1 (1.6%)
Grade 5 AE	11 (8.9%)	5 (7.9%)
Commonly Occurring Grade 3+ AEs (≥ 10%)		
Hypertension	34 (27.4%)	3 (4.8%)
Fatigue	17 (13.7%)	5 (7.9%)
Diarrhea	12 (10%)	2 (3%)

Grade 5 AEs in Cabozantinib Arm:

- Unrelated/unlikely related in 8 pts
- Possibly related in 3 pts (hemorrhage in 1 pt; NOS in 2 pts)

pNET

	CABOZANTINIB (N=60)	PLACEBO (N=30)
Grade 3 AE	34 (56.7%)	13 (43.3%)
Grade 4 AE	5 (8.3%)	0
Grade 5 AE	2 (3.3%)	0
Commonly Occurring Grade 3+ AEs (≥ 10%)		
Hypertension	16 (26.7%)	6 (20.0%)
Fatigue	8 (13.3%)	1 (3.3%)
Hyperglycemia	5 (8.3%)	3 (10.0%)
Thromboembolic event	7 (11.7%)	0
Hand-foot syndrome	6 (10.0%)	0

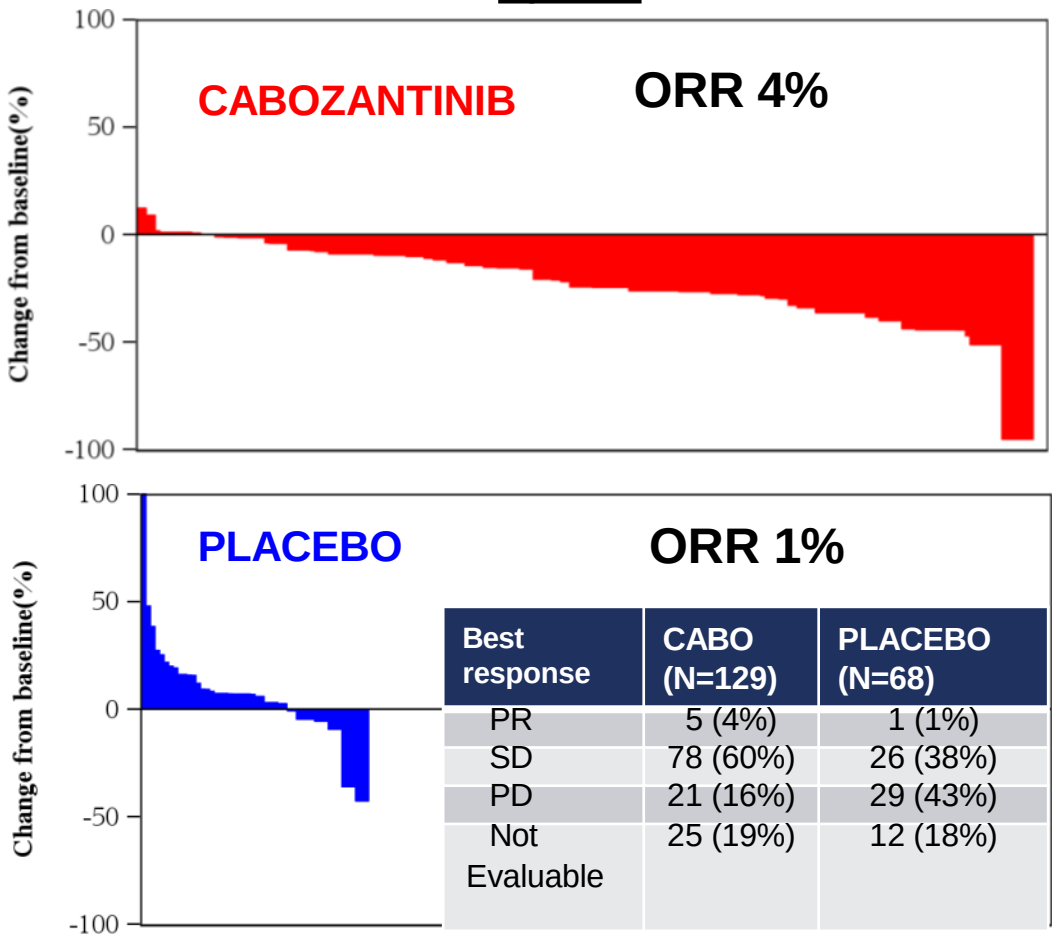
Grade 5 AEs in Cabozantinib Arm:

- Unrelated in 2 pts

Presented by Dr Jennifer Chan: ESMO Congress 2023

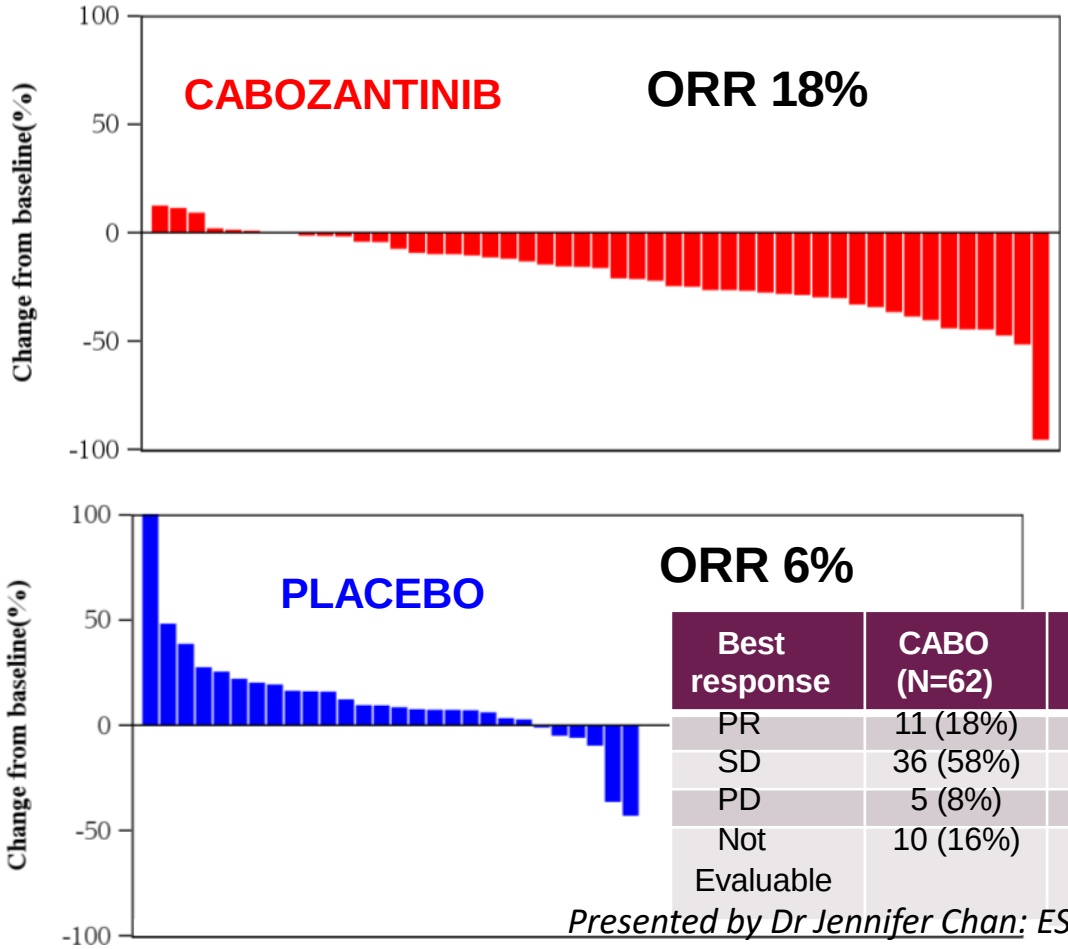
Best Overall Response (Local Review)

epNET



Best response	CABO (N=129)	PLACEBO (N=68)
PR	5 (4%)	1 (1%)
SD	78 (60%)	26 (38%)
PD	21 (16%)	29 (43%)
Not Evaluable	25 (19%)	12 (18%)

pNET

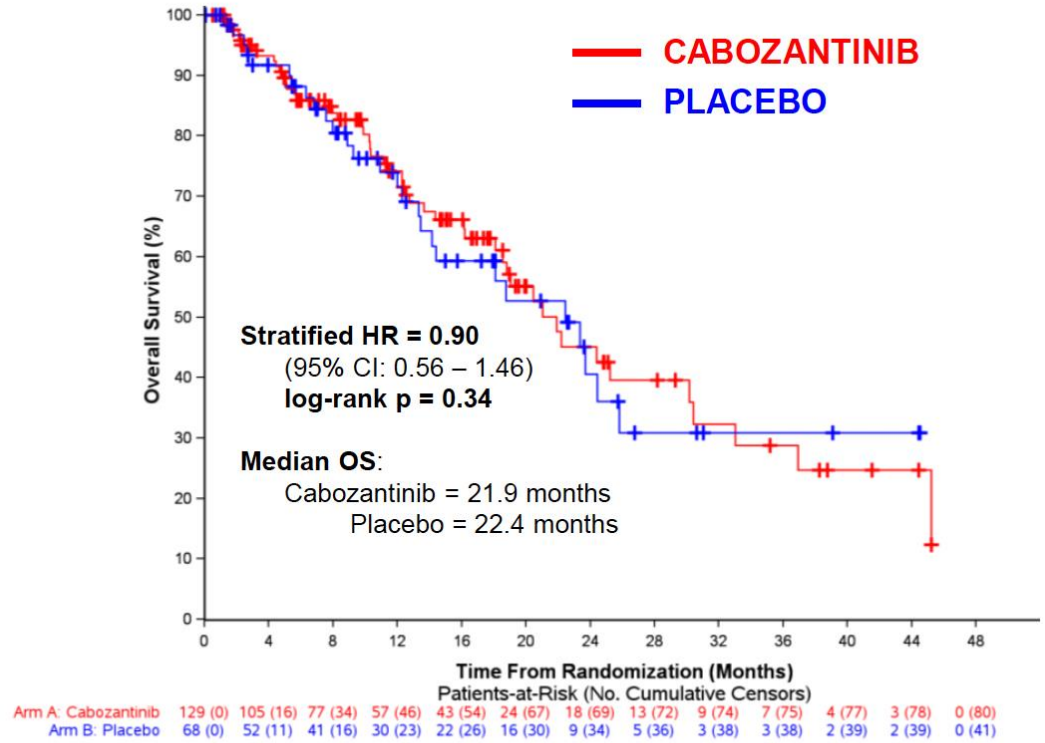


Best response	CABO (N=62)	PLACEBO (N=31)
PR	11 (18%)	2 (6%)
SD	36 (58%)	12 (39%)
PD	5 (8%)	14 (45%)
Not Evaluable	10 (16%)	3 (10%)

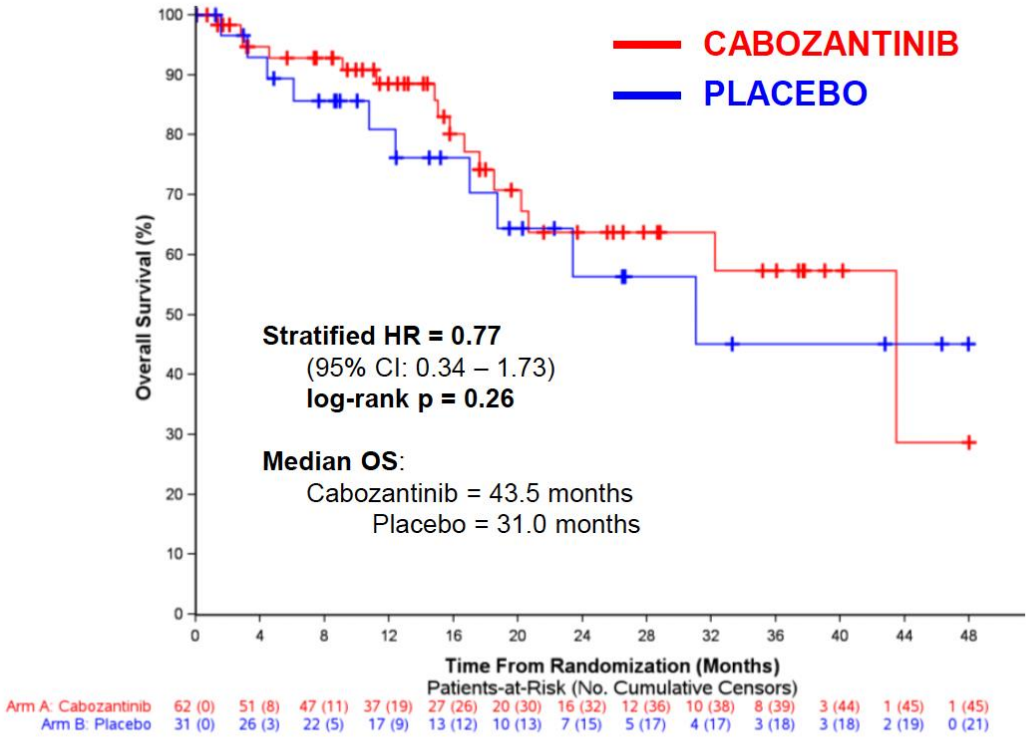
Presented by Dr Jennifer Chan: ESMO Congress 2023

Overall Survival

epNET



pNET



Presented by Dr Jennifer Chan: ESMO Congress 2023

Conclusions

- Cabozantinib significantly improves PFS in patients with previously treated extra-pancreatic and pancreatic NET
- Adverse events are consistent with the known safety profile of cabozantinib
- Is this clinically significant: Yes
- Is this practice changing: Yes (pending FDA approval)

NATALIE TRIAL: Pheochromocytoma and Paraganglioma(PPGL)

Cabozantinib in patients with unresectable and progressive metastatic phaeochromocytoma or paraganglioma (the Natalie Trial): a single-arm, phase 2 trial

Camilo Jimenez, Mouhammed Amir Habra, Matthew T Campbell, Gina Tamsen, Damaris Cruz-Goldberg, James Long, Roland Bassett, Robert Dantzer, Vania Balderrama-Brondani, Jeena Varghese, Yang Lu

Presented by Dr Jimenez: NANETS 2023

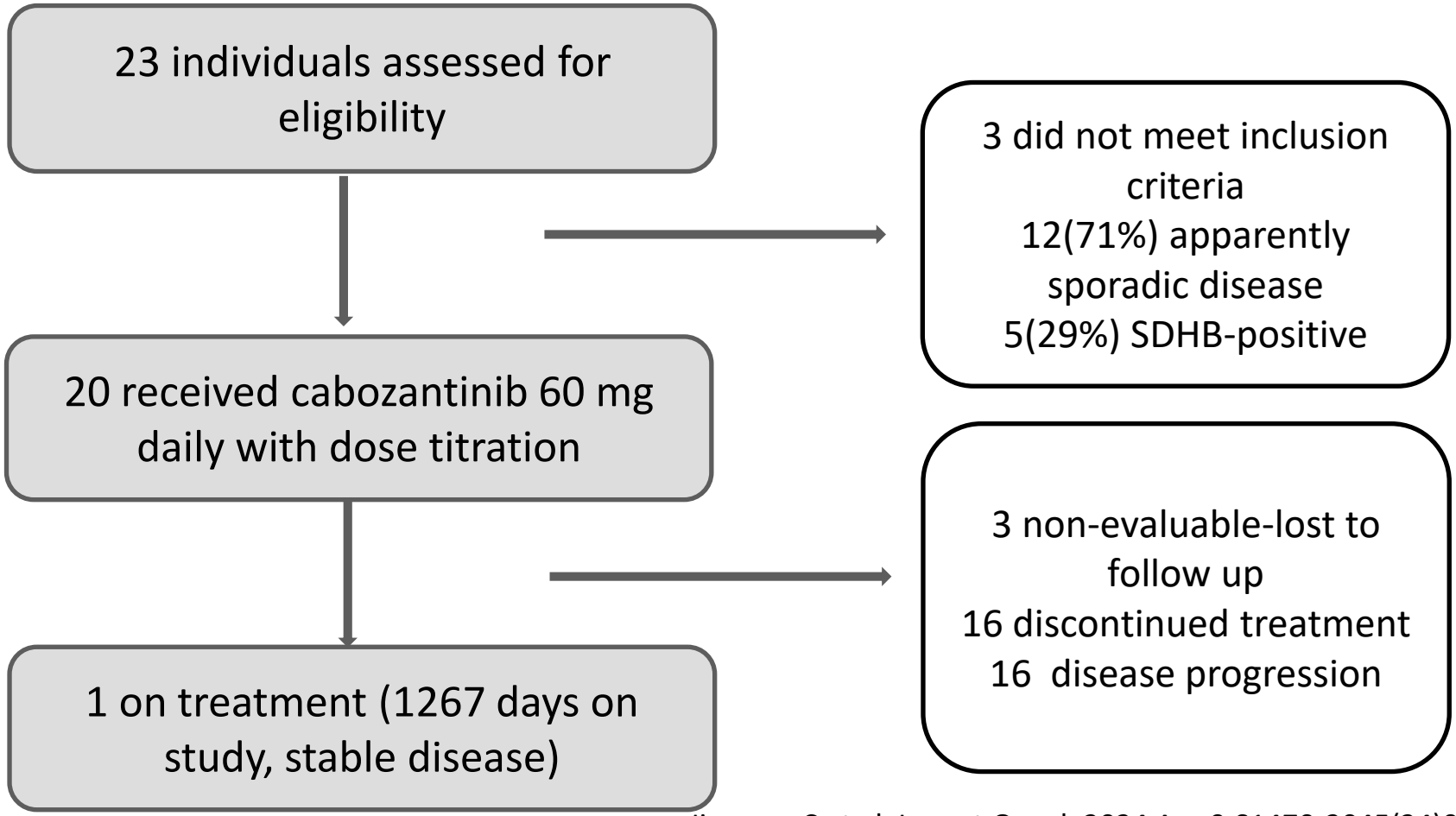
Jimenez C et al. Lancet Oncol. 2024 Apr 9:S1470-2045(24)00133-5.

Trial Profile

Primary end point:
Overall response rate

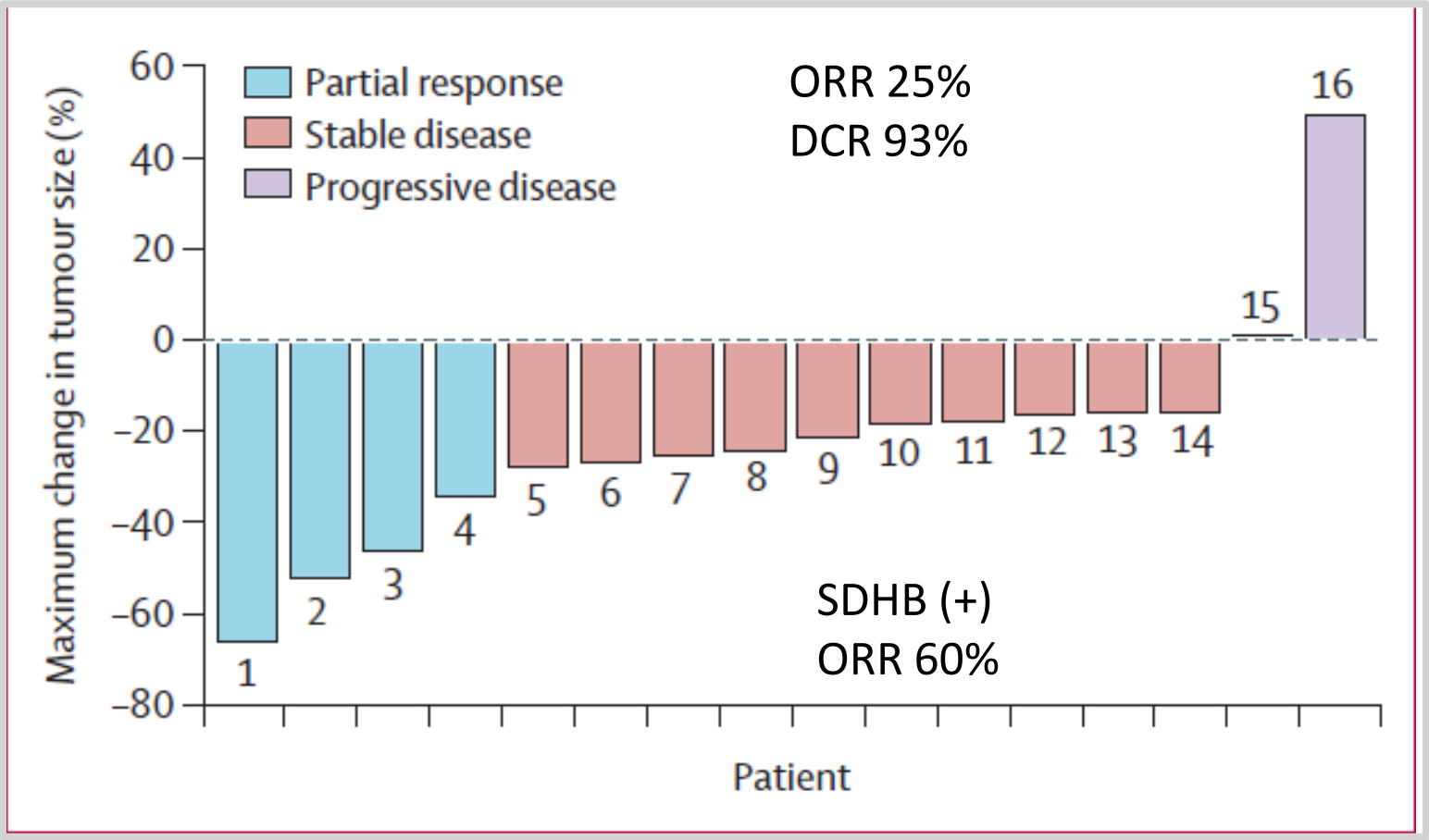
Secondary endpoints:
Progression free survival
Overall survival
Safety
Blood pressure control

RECIST progression within 12 months before enrolment



Jimenez C et al. Lancet Oncol. 2024 Apr 9:S1470-2045(24)00133-5.

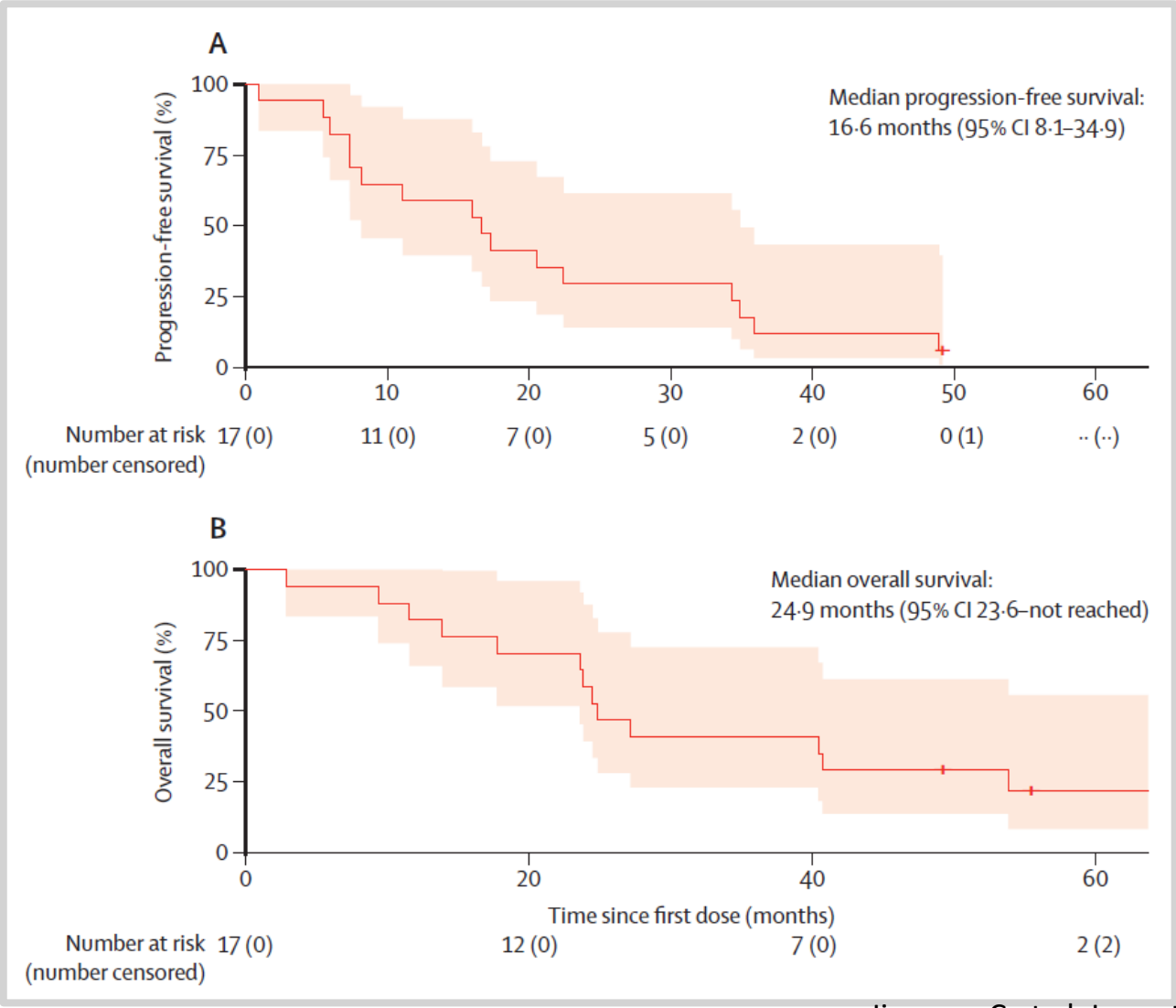
Overall Response Rate



80% of patients exhibited blood pressure improvement relative to baseline

Jimenez C et al. Lancet Oncol. 2024 Apr 9:S1470-2045(24)00133-5.

Progression Free Survival/Overall Survival



Jimenez C et al. Lancet Oncol. 2024 Apr 9:S1470-2045(24)00133-5.

Adverse Events

	Grade 1	Grade 2	Grade 3
Laboratory abnormalities			
Increased ALT or AST	15 (88%)	0	0
Increased alkaline phosphatase	7 (41%)	2 (12%)	0
Increased amylase or lipase	2 (12%)	1 (6%)	2 (12%)
Increased creatinine	6 (35%)	1 (6%)	0
Hypomagnesaemia	3 (18%)	0	1 (6%)
General disorders			
Dysgeusia	12 (71%)	0	0
Hand-and-foot syndrome	7 (41%)	3 (18%)	1 (6%)
Mucositis	8 (47%)	2 (12%)	0
Fatigue	7 (41%)	9 (53%)	0
Weight loss	8 (47%)	2 (12%)	0
Hypertension	4 (24%)	11 (65%)	1 (6%)
Diarrhoea	7 (41%)	0	0
Nausea	8 (47%)	0	0
Arthralgia or myalgia	6 (35%)	0	0
Primary hypothyroidism	4 (24%)	8 (47%)	0
Anorexia	7 (41%)	4 (24%)	0
Hoarseness	4 (24%)	0	0
Rectal fistula	0	0	1 (6%)
QT interval prolongation	0	0	1 (6%)
Grey hair or skin hypopigmentation	7 (41%)	0	0
Peripheral oedema	2 (12%)	0	0

96% of treatment related adverse events were grade 1-2

G3 Adverse events: 2 pts had elevated pancreatic enzymes
HFS, HTN, rectal fistula, qt interval prolongation

No Grade 4 or 5 Adverse events were reported

Jimenez C et al. Lancet Oncol. 2024 Apr 9:S1470-2045(24)00133-5.

Conclusion

- Cabozantinib is an effective systemic therapy for adult patients with metastatic pheochromocytoma and paraganglioma irrespective of the primary tumor origin and genotype.
- Patients with hormonally active tumors exhibited improved blood pressure relative to baseline
- Is this clinically significant: Yes
- Is this practice changing: potentially, an option in this rare disease group

Everolimus and Lenvatinib: Extra-pancreatic NET

A Phase II Study of Lenvatinib and Everolimus in Advanced Extra Pancreatic Neuroendocrine Tumors

Arvind Dasari[1], Wei Qiao[2], Daniel Halperin[1], Venkat Surabhi[3], Nir Stanietzky[3], Mackenzie Phillips[1], Divya Sakamuri[1], Kaye Wilson[1], Michael Leung[4], Makenna Smack[4], James Yao[1]

1: Department of Gastrointestinal Medical Oncology; 2: Department of Biostatistics; 3: Department of Abdominal Imaging; 4: Pharmacy Clinical Programs
The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Background

- Lenvatinib is a potent VEGF pathway inhibitor with activity against multiple tyrosine kinases including RET, KIT, PDGFR, VEGFR1-3, PDGFRα and FGFR1-4
- Combined inhibition of **VEGF and FGF** axes has been shown to be an effective way to reverse resistance to antiangiogenic agents
- Everolimus is a mTOR inhibitor (mechanistic target of rapamycin)
- Concomitant inhibition of **the mTOR and VEGF** pathways has been shown to be synergistic

Dr Dasari: ENETS 2024

Matsui, Clin Cancer Res. 2008; 14: 5459-5465; Matsui, Int J Cancer. 2008; 122: 664-671; Motzer, Lancet Oncol 2015;16:1473-1482; Casanovas, Cancer Cell 8:299-309, 2005; Lenvatinib package insert

Study Design

32 patients with advanced
well-differentiated extra-pancreatic NETs

Lenvatinib 18 mg po daily plus Everolimus 5 mg dose reduced to
Lenvatinib 14 mg po daily plus Everolimus 5 mg

Primary end point:
Overall Response Rate

Secondary endpoints:
Progression free survival
safety

Patient Characteristics (N = 32)

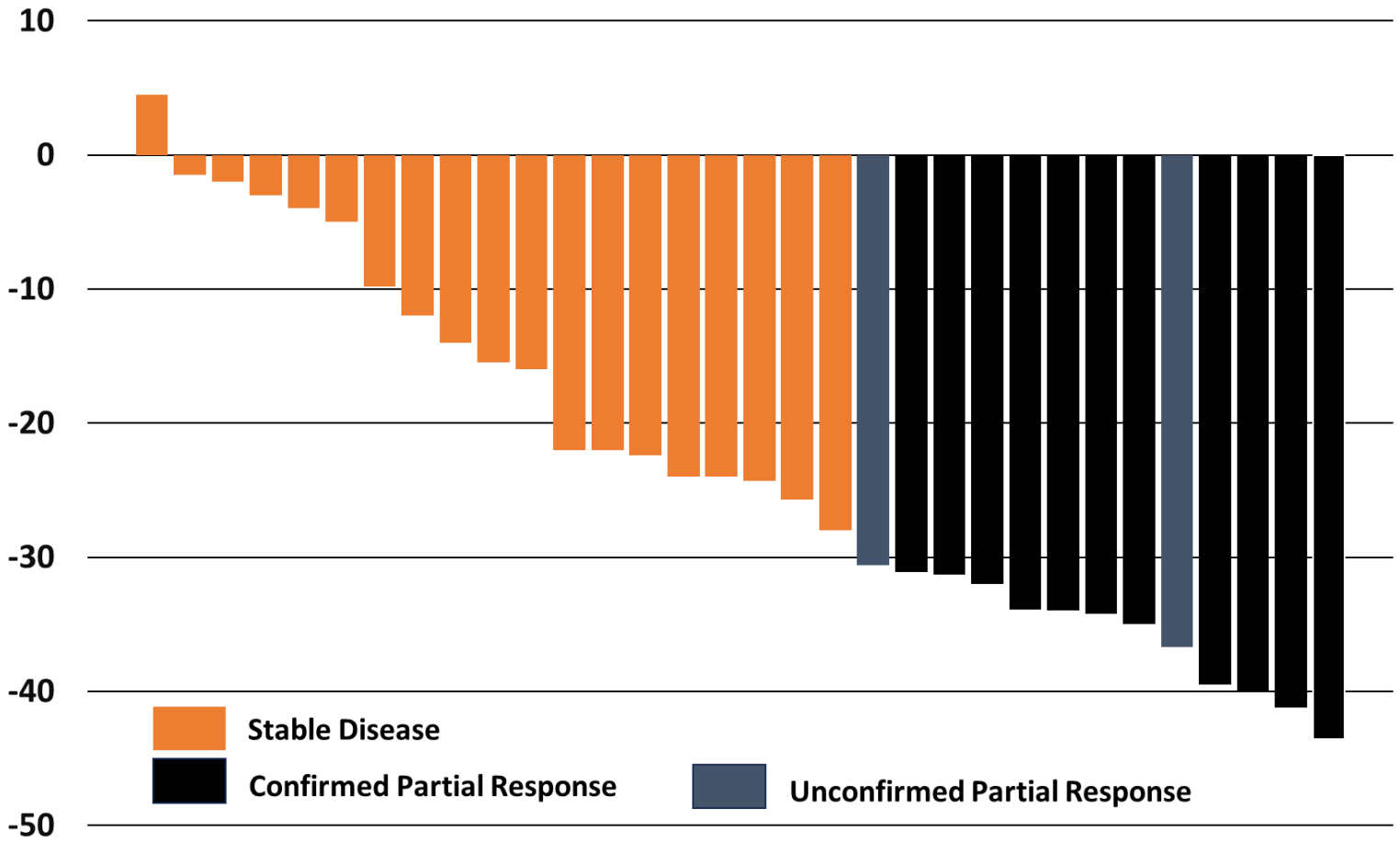
Event	Distribution
Age, median (range)	59 (33-76) years
Gender, M/F	59/41%
Ki-67, median (range)	8 (1-40)%
Functional tumors, n (%)	11 (34%)
Time from diagnosis to study entry, median	29 months
Primary Site, n (%)	
Small bowel	19 (59%)
Lung & Thymus	5 (16%)
Unknown Primary	5 (16%)
Colon & rectum	3 (9%)
Prior Systemic Therapies, median (range)	2 (0-3)

2-stage statistical design

≥ 3 responses were needed for the study to be positive

Dr Dasari: ENETS 2024

Primary Endpoint: ORR

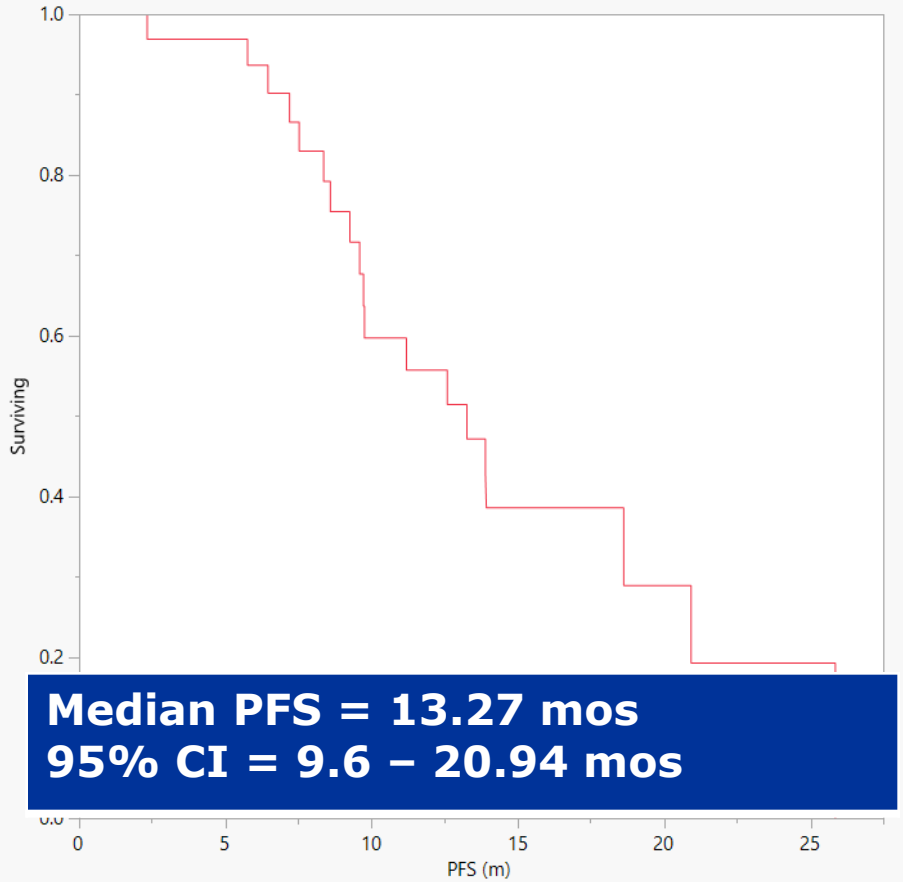


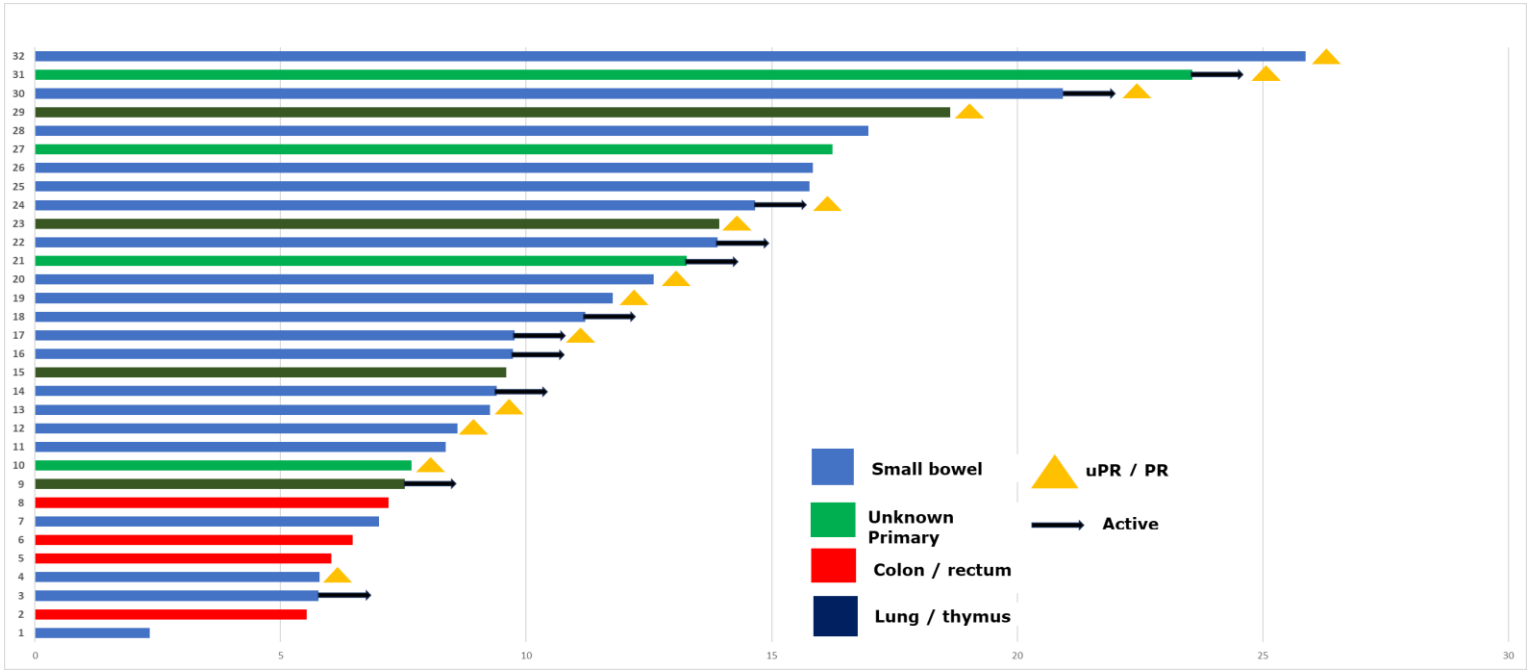
ORR = 40.7%
(95% CI = 23.7% – 59.4%)

Confirmed PR	**34.4%**
Unconfirmed PR	**6.3%**

Dr Dasari: ENETS 2024

Secondary Endpoint: Progression Free Survival





11 patients still on study as of data cutoff

Dr Dasari: ENETS 2024

Secondary Endpoint: Adverse Effects

Grade ≥ 3 Events

Event	All pts	After dose reduction
	# of pts (%)	# of pts (%)
Elevated LFTs	8 (25%)	3 (11%)
HTN	6 (18.7%)	4 (12.5%)
Thrombocytopenia	4 (12.5%)	3 (11%)
Myocardial Infarction	1 (3.1%)	-
Neutropenia	1 (3.1%)	-
Hypertriglyceridemia	1* (3.1%)	1* (3.7%)
Fatigue	1 (3.1%)	1 (3.7%)
Mucositis	1 (3.1%)	-
Weight Loss	1 (3.1%)	-

*Only Grade 4 event;
No Grade 5 events

Any grade:
fatigue (66%)
proteinuria (56%)
diarrhea (53%)

Dr Dasari: ENETS 2024

Conclusions

- Lenvatinib 14 mg + Everolimus 5 mg shows promising activity in patients with epNETs with
  - *ORR 40.7% (95% CI 23.7 – 59.4%)*
  - *PFS 13.27 mos (95% CI 9.6 – 20.94 mos)*

- TALENT Trial*: Ph II trial of Lenvatinib 24 mg orally daily in grade 1 and 2 pancreatic and GI-NET
  - ORR: 16.3% in giNETs
  - PFS: 15.7 m (95% CI 11.5-19.4)

- Lenvatinib + Everolimus: Benefit was noted across all primary sites

- Is this clinically significant: potentially

- Is this practice changing: No (not at this time)
  - Future randomized trials are needed to evaluate impact of combination therapy against sequential treatment

**Capdevila et al; JCO 2021*

Cabozantinib plus Atezolizumab: Neuroendocrine Neoplasms(NENs)
CABATEN

GETNE S2109 CABATEN

Responses to Cabozantinib plus Atezolizumab in a wide population of Advanced and Progressive neuroendocrine neoplasms (NENs): A prospective multi-cohort Basket Phase II Trial (CABATEN / GETNE-T1914)

Javier, Molina-Cerrillo, Enrique Grande, Marta Benavent Viñuales, Rocio Garcia-Carbonero, Alex Teule, Ana Custodio, Paula Jimenez-Fonseca, Cinta Hierro, Carlos López, Isabel Sevilla, Marta Llanos, Jaume Capdevila

Dr. Javier Molina Cerrillo

Medical Oncology Department
Hospital Universitario Ramón y Cajal
Madrid, Spain

ENETS-NANETS Webinar | 26 June 2024
Highlights of PRRT and drug development abstracts

Background

- Experience with Immune-checkpoint inhibitors (ICIs) is scarce in Neuroendocrine Neoplasms (NENs) and early results are discouraging [1-2]
- Angiogenesis plays a key role in development and progression of NENs
- Synergy is observed with antiangiogenics and PD-1/PD-L1 inhibitors and combinations are approved in several tumor types. [3-5]
- Atezolizumab is a PD-L1 inhibitor
- Cabozantinib is a multikinase inhibitor: VEGF-R, c-MET, AXL, and RET

1. Dasari A, et al. JAMA Oncol. 2017
2. Capdevila J, et al. Nat. Comm. 2023
3. Shrimali RK, et al. Cancer Res. 2010
4. Rizzo A, et al. Eur. Urol. Focus. 2022
5. Stefanini B, et al. Expert Rev. Anticancer. Ther. 2023

Study design

CABATEN is an academic, prospective, multicenter, phase II single arm basket trial that recruited patients with neuroendocrine & endocrine neoplasms in 6 cohorts including:

- **Well-differentiated lung NET (WHO G1-2)**
- Anaplastic thyroid carcinoma (ATC)
- Adrenocortical carcinoma (ACC)
- **Pheochromocytoma and paraganglioma (PPGL)**
- **Well-differentiated GEP-NET (WHO G1-2)**
- **Poorly differentiated EP-NEN (WHO G3)**

Screening

Primary objective: Objective Response Rate (ORR)

Secondary objectives: Progression-Free Survival (PFS), Overall Survival (OS), Safety Duration of Response (DoR), Biomarkers, Quality of Life (QoL)

Atezolizumab 1200 mg IV every 3 weeks (one cycle) + Cabozantinib 40 mg/day PO → **Follow-up**

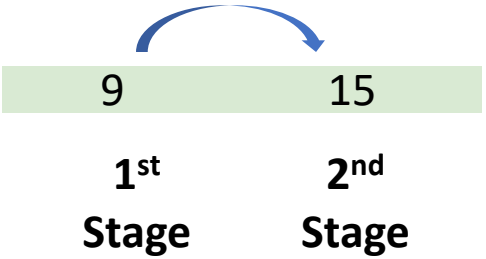
PFS evaluated every 12W

OS

Progression or toxicity

Simon II optimal two-stage design

- H_0: ORR = 5% (historical cohorts)
- H_1: ORR = 20%
- α= 0.1 (unilateral)
- β= 0.2
- 9 patients in 1st stage



1 response/ 9 patients at 1st stage to continue accrual in a 2nd stage, for a total of 24 patients.
3 responses/24 patients in 2nd stage to consider the study positive for the cohort ACC.

Presented by Dr Cerrillo: ENETS 2024

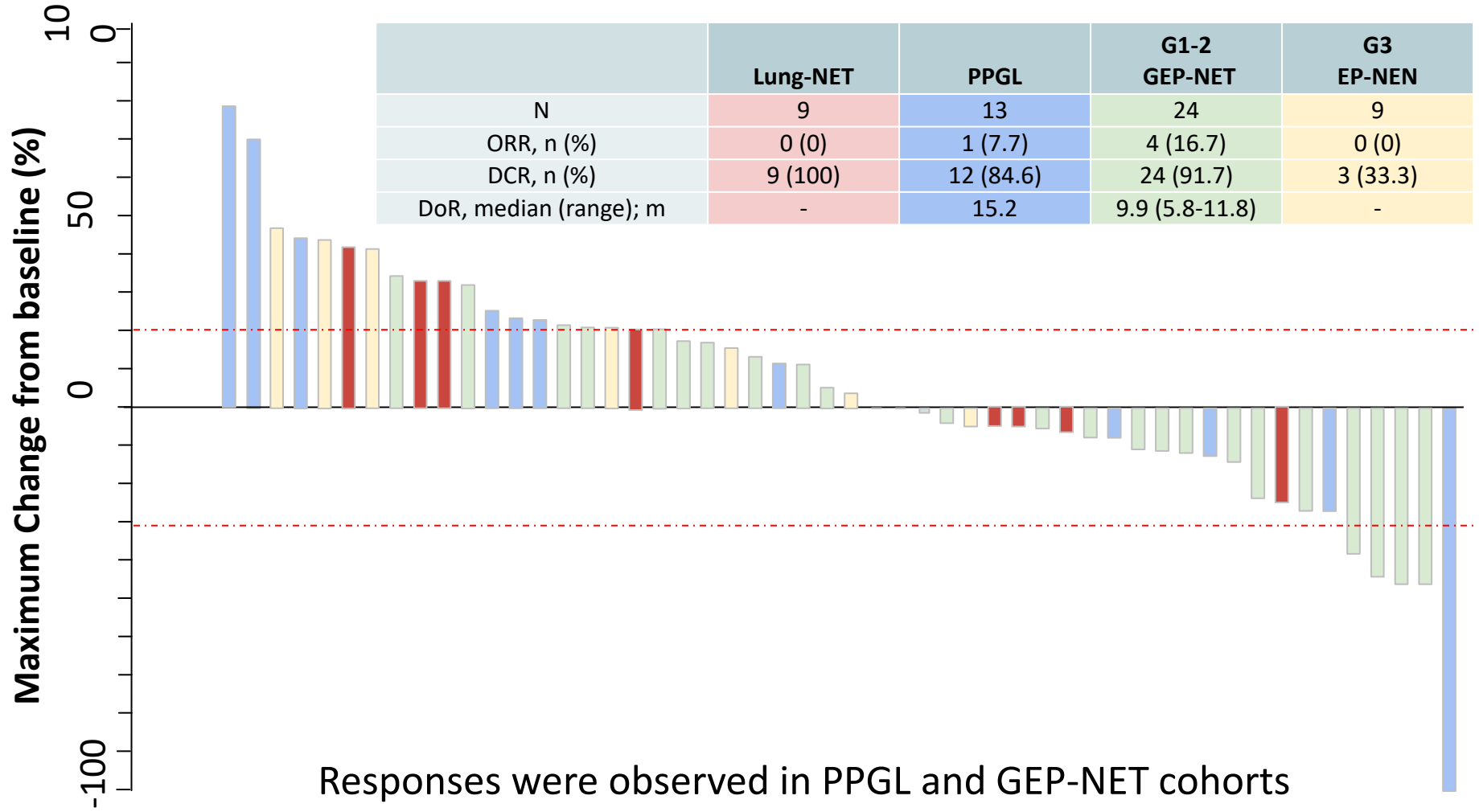
Baseline Characteristics

Characteristics		Lung NET N = 9	PPGL N = 13	G1-2 GEP-NET N = 24	G3 EP-NEN N = 9
Age, years	Median (range)	63 (31-81)	48 (36-67)	60 (31-77)	62 (38-73)
Gender, n (%)	Male	5 (55.6)	10 (76.9)	13 (54.2)	6 (66.7)
WHO grade, n (%)	1	1 (11.1)	-	7 (29.2)	0 (0)
	2	8 (88.9)	-	17 (70.8)	0 (0)
	3	0 (0)	-	0 (0)	9 (100)
Number of metastasis sites, n (%)	0	2 (22.2)	1 (7.7)	1 (4.2)	0 (0)
	1	0 (0)	0 (0)	0 (0)	0 (0)
	≥ 2	7 (77.8)	12 (92.3)	23 (95.8)	9 (100)
Metastasis locations, n (%)	Liver	5 (55.6)	4 (30.8)	20 (83.3)	8 (88.9)
	Nodes	5 (55.6)	2 (15.4)	10 (41.7)	5 (55.6)
	Bone	2 (22.2)	6 (46.2)	7 (29.2)	2 (22.2)
	Lung	3 (33.3)	3 (23.1)	2 (8.3)	0 (0)
Previous treatments, n (%)	0	0 (0)	2 (15.4)	0 (0)	0 (0)
	1	2 (22.2)	3 (23.1)	10 (41.7)	4 (44.4)
	≥ 2	7 (77.8)	8 (61.5)	14 (58.3)	5 (55.6)
	SSA	7 (77.8)	3 (27.3)	20 (83.3)	0 (0)
Previous treatment type, n (%)	Chemotherapy	5 (55.6)	7 (63.6)	7 (29.2)	9 (100)
	TKIs	7 (77.8)	2 (18.2)	11 (45.8)	0 (0)
	PRRT	1 (11.1)	3 (27.3)	4 (16.7)	0 (0)
	Mitotane	0 (0)	1 (9.1)	0 (0)	0 (0)
	Other	1 (11.1)	0 (0)	0 (0)	0 (0)

Presented by Dr Cerrillo: ENETS 2024

Efficacy: ORR

	Lung-NET	PPGL	G1-2 GEP-NET	G3 EP-NEN
N	9	13	24	9
ORR, n (%)	0 (0)	1 (7.7)	4 (16.7)	0 (0)
DCR, n (%)	9 (100)	12 (84.6)	24 (91.7)	3 (33.3)
DoR, median (range); m	-	15.2	9.9 (5.8-11.8)	-



Responses were observed in PPGL and GEP-NET cohorts

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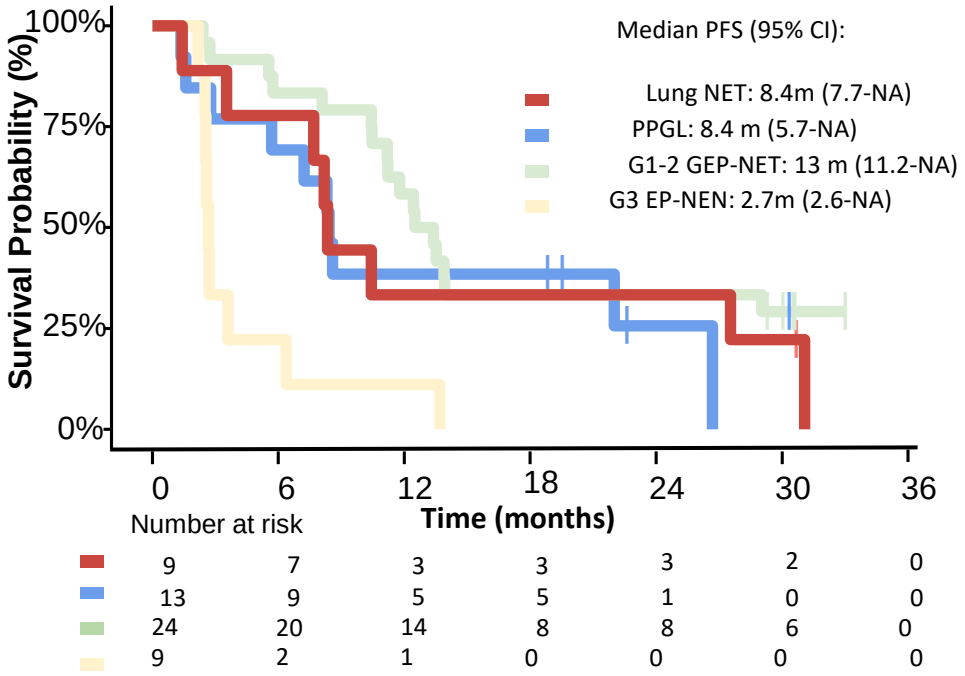
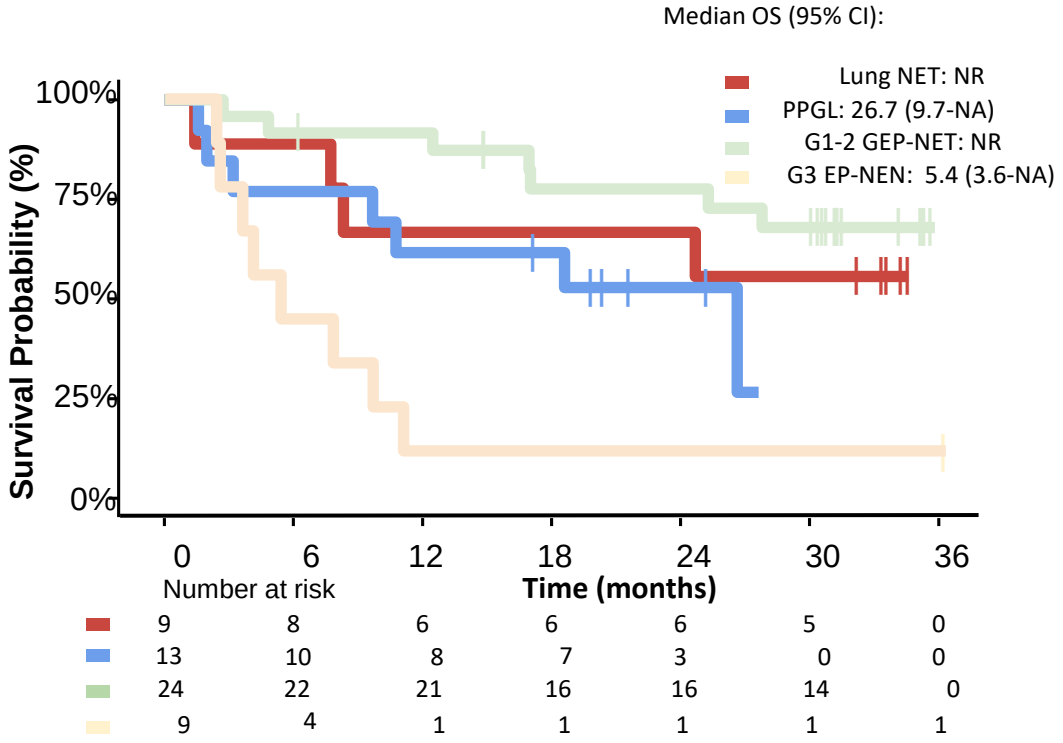
Efficacy (Kaplan Meier)

PFS



12m PFS rate	% (95 CI)
Lung NET	33.3 (13.2-84)
PPGL	38.5 (19.3-76.5)
G1-2 GEP-NET	58.3 (41.6-81.8)
G3 EP-NEN	11.1 (1.8-70.5)

OS



12m OS rate	% (95 CI)
Lung NET	66.7 (42-100)
PPGL	61.5 (40.4-94.6)
G1-2 GEP-NET	91.7 (81.3-100)
G3 EP-NEN	11.1 (1.8-70.5)

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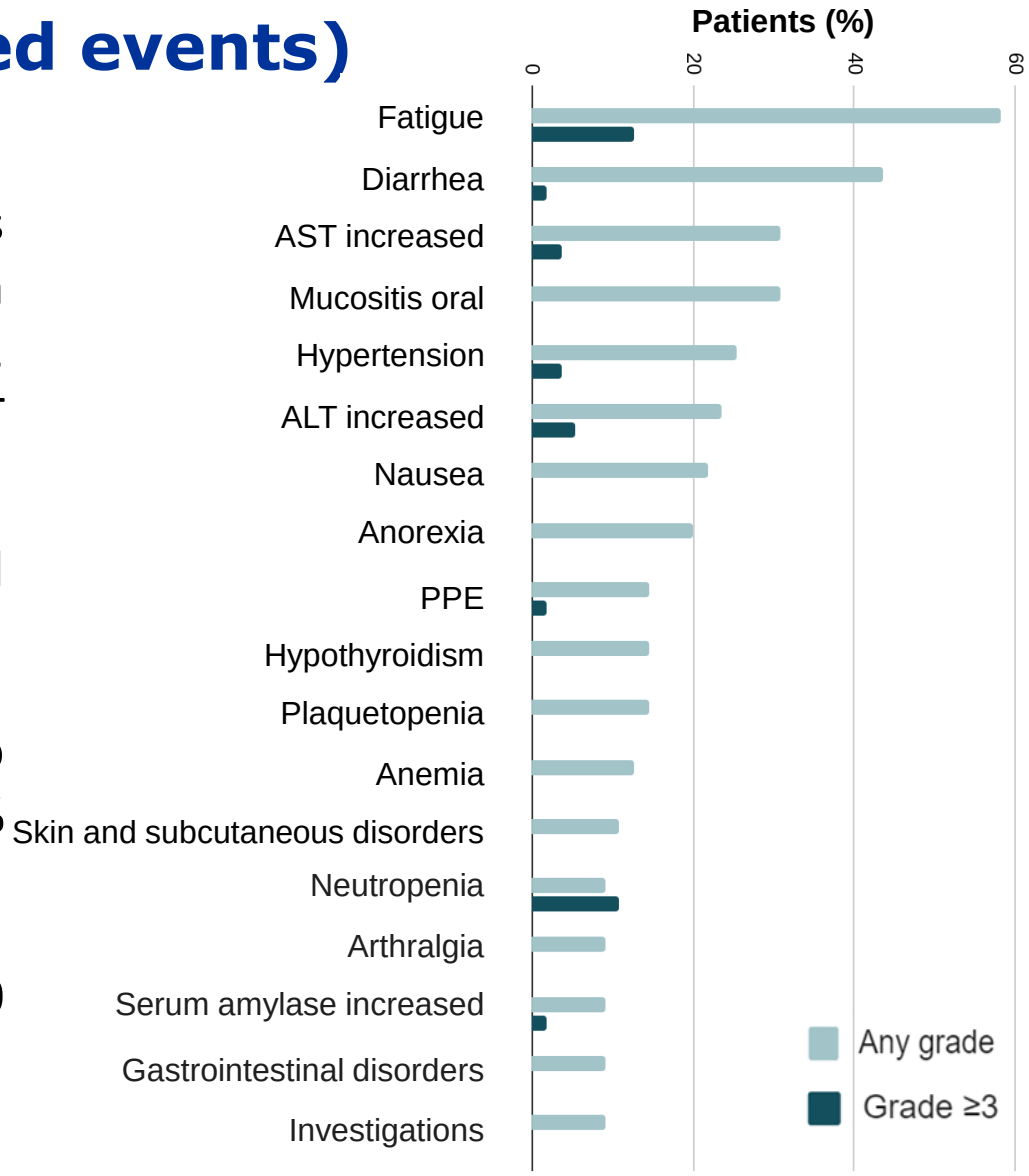
Safety (treatment-related events)

- Most frequent grade ≥3 toxicities were fatigue (12.7%), neutropenia (10.9%) and liver enzyme increase, ALT increased (5.4%) and AST increased (3.6%)
- One patient died due to drug-related (Grade 5) pancreatitis.
- Cabozantinib and atezolizumab treatment was interrupted in **80 %** and **41.8%** of patients respectively
- Cabozantinib was reduced to 20 mg/day in **52.7%** of patients.



CABATEN: Study design

- **CABATEN is a prospective, multicenter, phase II single arm basket trial that recruited patients with neuroendocrine & endocrine neoplasms in 6 cohorts, including ACC**

Well-differentiated lung NET

Anaplastic thyroid carcinoma

Adrenocortical carcinoma (ACC)
- after progression to chemotherapy and/or mitotane with no prior exposure to any TKI or ICI
- ECOG 0-1
- No limit to prior lines of treatment

Pheochromocytoma and paraganglioma

Well-differentiated GEP-NET

Poorly differentiated EP-NEN

ACC: N=24

Primary objective: Objective response rate (ORR)

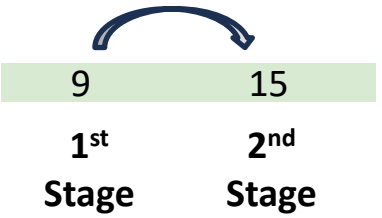
Secondary objectives: Progression-free Survival (PFS), Overall Survival (OS), Safety Duration of Response (DoR), Biomarkers

Atezolizumab 1200 mg IV
every 3 weeks
+
Cabozantinib 40 mg/day PO

Simon II optimal two-stage design

- H_0: ORR = 5% (historical cohorts)
- H_1: ORR = 20%
- α= 0.1 (unilateral)
- β= 0.2
- 9 patients in 1st stage

1 response/ 9 patients at 1st Stage to continue accrual in a 2nd stage, for a total of 24 patients. **3 responses/24 patients in 2nd stage to consider the study positive for the cohort ACC.**



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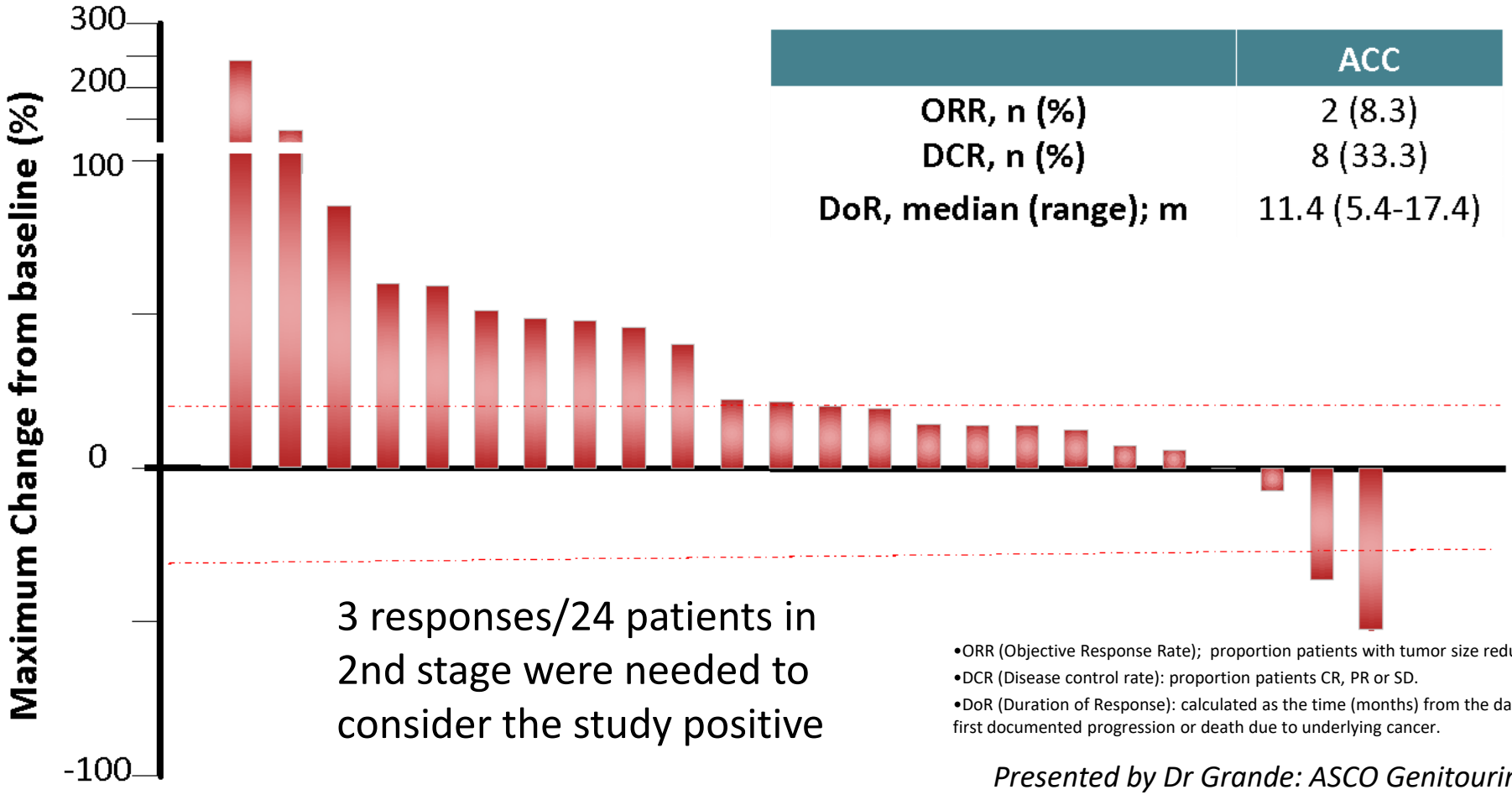
CABATEN: Overall response rate in ACC



	ACC
ORR, n (%)	2 (8.3)
DCR, n (%)	8 (33.3)
DoR, median (range); m	11.4 (5.4-17.4)

3 responses/24 patients in 2nd stage were needed to consider the study positive

- ORR (Objective Response Rate); proportion patients with tumor size reduction (CR o PR)
- DCR (Disease control rate): proportion patients CR, PR or SD.
- DoR (Duration of Response): calculated as the time (months) from the date of first documented CR or PR to the first documented progression or death due to underlying cancer.

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Conclusions

- The combination of cabozantinib and atezolizumab showed limited efficacy in the CABATEN NEN cohorts
- Responses were observed in PPGL and GEP-NET cohorts, but not in Lung NET, G3 EP-NEN and ACC regardless of dose intensity of cabozantinib
- Safety was conditioned by cabozantinib toxicity profile, that needed frequent dose reductions/discontinuations.

Summary

- Cabozantinib demonstrates efficacy across all grades (G1-3) and primary sites of neuroendocrine tumors (NETs) as well as in pheochromocytoma/paraganglioma (PPGL)
- Cabozantinib an effective treatment option in NETs and PPGL, offering therapeutic benefits irrespective
- Sequencing antinib earlier given high response rate and PFS
- Combination TKI and Everolimus might be beneficial in some patients, i.e when goal of therapy is response, and is worth exploring further

Future directions: Combination novel TKIs and novel ICI??

Acknowledgments

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Closing comments

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- ✓ YOU, the participants

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Part 3 of the ENETS-NANETS webinar will take place on
Wednesday, 10 July from 12:00 – 12:45 EDT / 18:00 – 18:45 CEST:
New insights, directions & signals

For updates, please check our website:

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