BELNUC RADIOLIGAND THERAPY COURSE

BELNUC

Overview of the current treatment landscape and management of NET

Willem Lybaert MD

Oncologist VITAZ – UZA

NETwerk ENETS CoE

I have no disclosures related to this topic

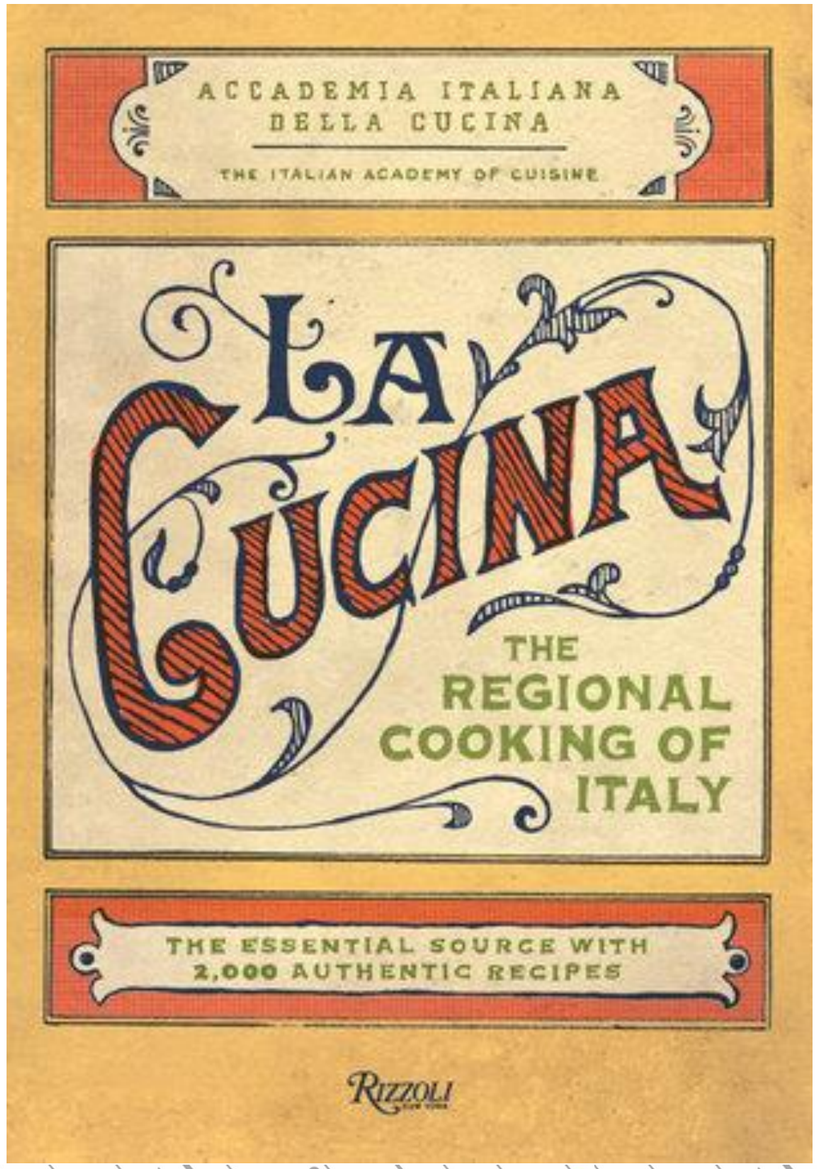
WHO 2022 CLASSIFICATION AND GRADING CRITERIA FOR GASTROENTEROPANCREATIC (GEP) NEN

Terminology	Differentiation	Grade	Mititc count mitoses/2mm²*	Ki-67 index**
G1 NET	Well differentiated	Low	< 2	< 3%
G2 NET		Intermediate	2-20	3-20%
G3 NET		High	> 20	> 20%
Small cell NEC	Poorly differentiated	High	> 20	> 20%
Large cell NEC			> 20	> 20%
MiNEN	Well or poorly differentiated	Variable	Variable	Variable

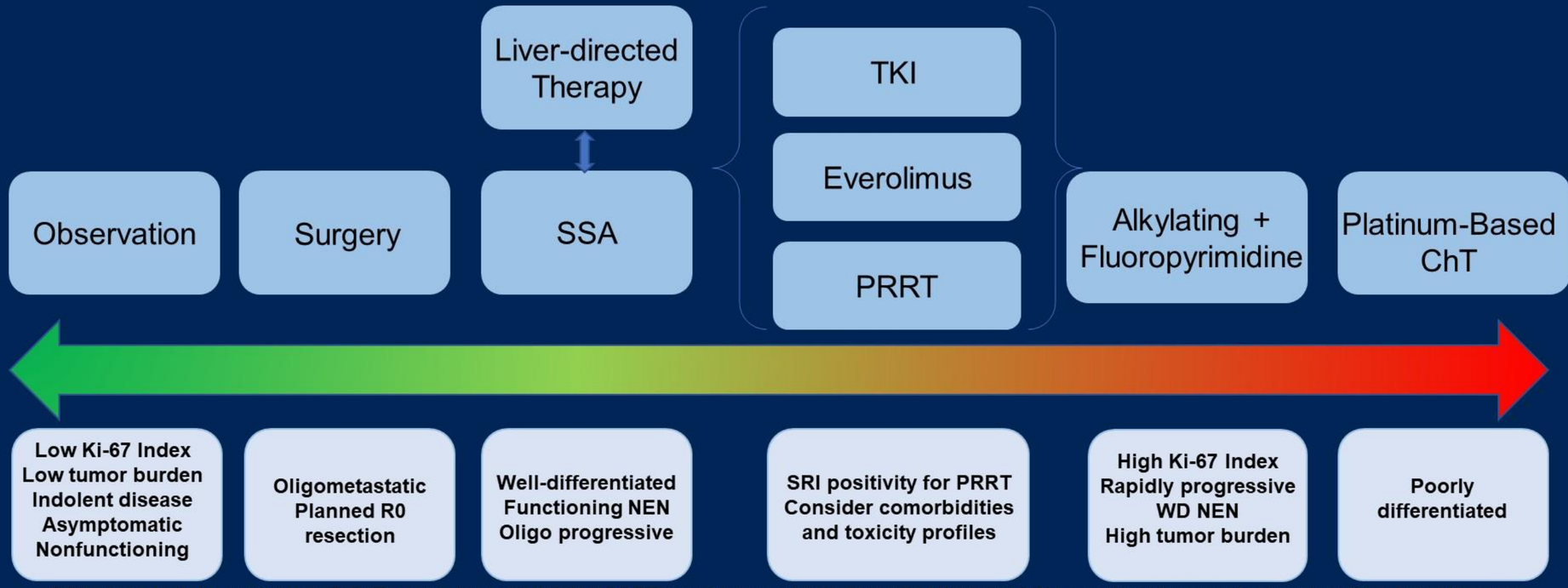
NEN = NET + NEC

- Current therapies:
  - Surgery/RFA/MWA
  - Somatostatin analogues
  - Everolimus
  - Sunitinib/surufatinib
  - PRRT
  - Chemotherapy: cisplatin/carboplatin+etoposide, CAPTEM, FOLFOX, FOLFIRI, FOLFIRINOX
  - Liver-directed therapies: bland embolisation, chemo-embolisation and SIRT
  - Studies

  - Immunotherapy: atezolizumab and durvalumab in first-line SCLC, for the other NEN unclear position: possible when lung origine and for GEP NEC…


ACCADEMIA ITALIANA
DELLA CUCINA
THE ITALIAN ACADEMY OF CUISINE
LA CUCINA
THE REGIONAL COOKING OF ITALY
THE ESSENTIAL SOURCE WITH
2,000 AUTHENTIC RECIPES
RIZZOLI

Therapeutic sequencing strategies for patients with advanced G1-2 GEP NEN

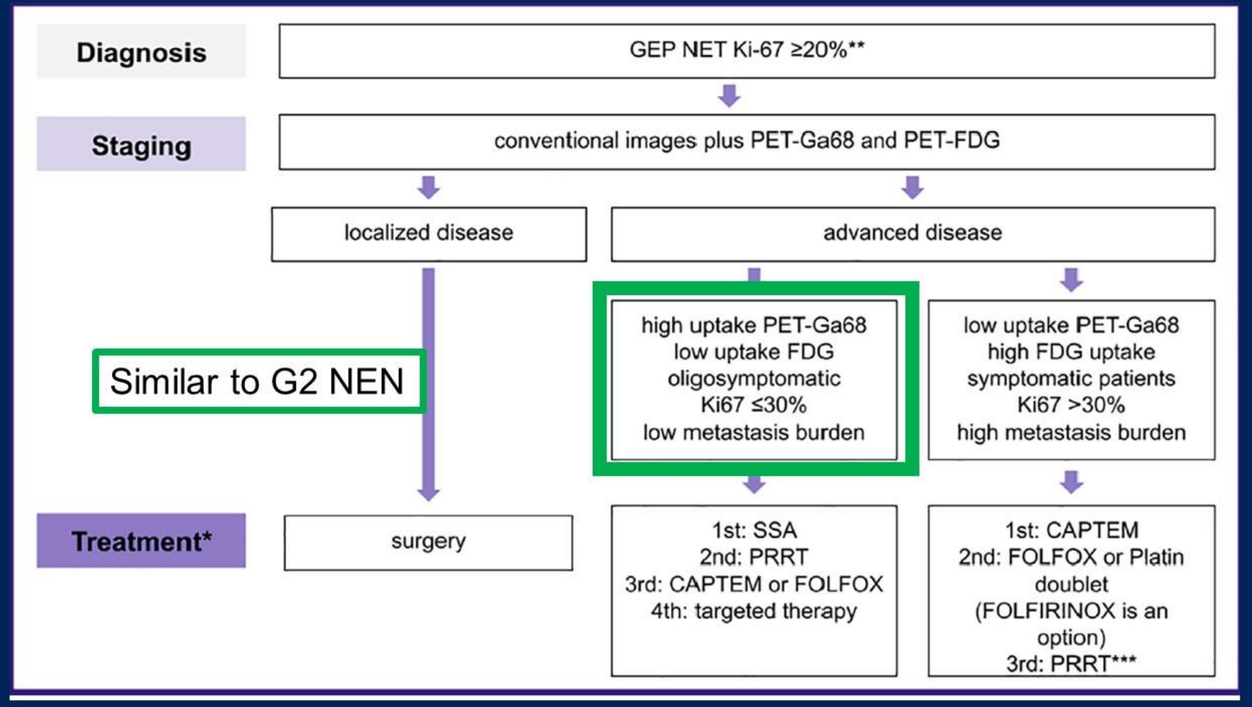


SSA: somatostatin analogues; TKI: Tyrosine kinase inhibitor; PPRT: peptide receptor radionuclide therapy; SRI: somatostatin receptor imaging; Ch: chemotherapy

Figure from the American Society of Clinical Oncology Educational Book 43. 10.1200/EDBK_389278). e389278

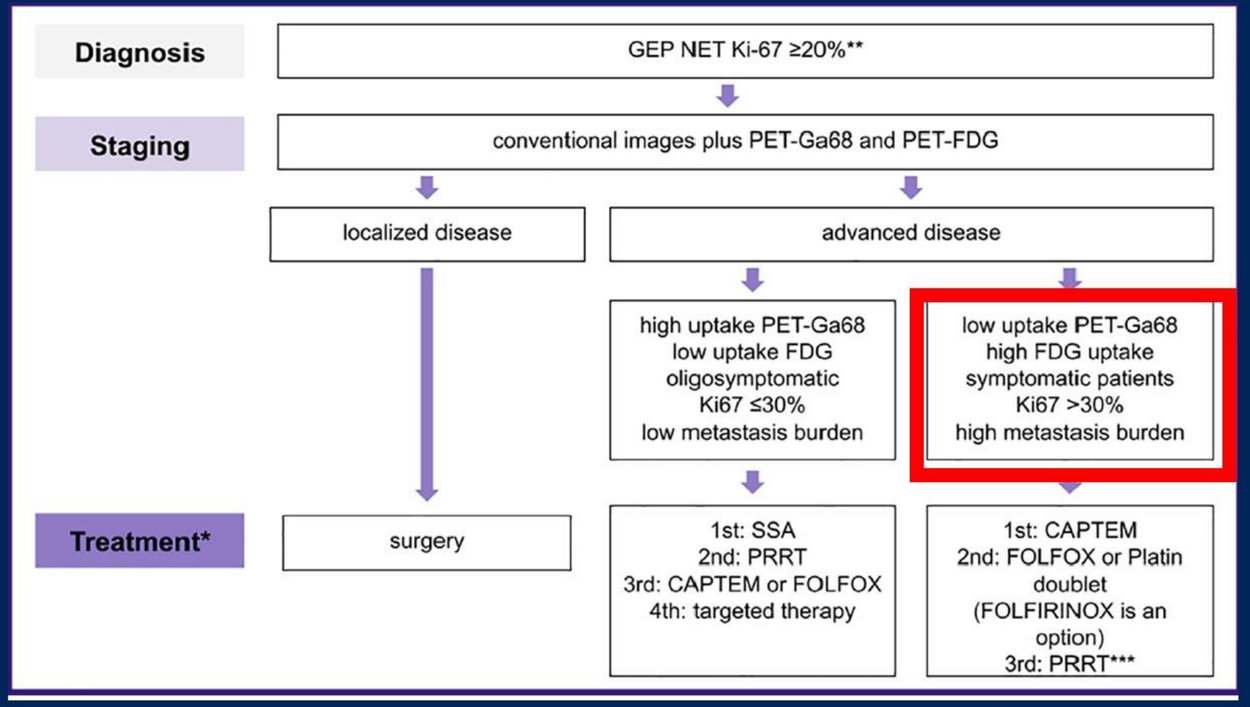
PRESENTED BY: Dr Rachel Riechelmann MD PhD

Therapeutic sequencing strategies for patients with well-differentiated G3 NEN



Donadio, Brito, Riechelmann. Ther Adv Med Oncol 2023, Vol. 15: 1

Therapeutic sequencing strategies for patients with well-differentiated G3 NEN



Not NEC

Prefer chemotherapy

Donadio, Brito, Riechelmann. Ther Adv Med Oncol 2023, Vol. 15: 1

Systemic Therapy for Tumor Control in Metastatic Well-Differentiated Gastroenteropancreatic Neuroendocrine Tumors: ASCO Guideline

Jaydira Del Rivero, MD[1]; Kimberly Perez, MD[2]; Erin B. Kennedy, MHSc[3]; Erik S. Mittra, MD, PhD[4]; Namrata Vijayvergia, MD[5]; Junaid Arshad, MD[6]; Sandip Basu, MBBS[7]; Aman Chauhan, MD[8]; Arvind N. Dasari, MD[9]; Andrew M. Bellizzi, MD[10]; Alexandra Gangi, MD[11]; Erin Grady, MD[12]; James R. Howe, MD[13]; Jana Ivanidze, MD, PhD[15]; Mark Lewis, MD[14]; Josh Mailman, MBA[16]; Nitya Raj, MD[16]; Heloisa P. Soares, MD, PhD[17]; Michael C. Soulen, MD[18]; Sarah B. White, MD, MS[19]; Jennifer A. Chan, MD, MPH[20]; Pamela L. Kunz, MD[21]; Simron Singh, MD, MPH[22]; Thorvardur R. Halfdanarson, MD[23]; Jonathan R. Strosberg, MD[24]; and Emily K. Bergsland, MD[25]

DOI https://doi.org/10.1200/JCO.23.01529

ABSTRACT

PURPOSE To develop recommendations for systemic therapy for well-differentiated grade 1 (G1) to grade 3 (G3) metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

METHODS ASCO convened an Expert Panel to conduct a systematic review of relevant studies and develop recommendations for clinical practice.

RESULTS Eight randomized controlled trials met the inclusion criteria for the systematic review.

RECOMMENDATIONS Somatostatin analogs (SSAs) are recommended as first-line systemic therapy for most patients with G1-grade 2 (G2) metastatic well-differentiated GI-NETs. Observation is an option for patients with low-volume or slow-growing disease without symptoms. After progression on SSAs, peptide receptor radionuclide therapy (PRRT) is recommended as systematic therapy for patients with somatostatin receptor (SSTR)–positive tumors. Everolimus is an alternative second-line therapy, particularly in nonfunctioning NETs and patients with SSTR-negative tumors. SSAs are standard first-line therapy for SSTR-positive pancreatic (pan)NETs. Rarely, observation may be appropriate for asymptomatic patients until progression. Second-line systemic options for panNETs include PRRT (for SSTR-positive tumors), cytotoxic chemotherapy, everolimus, or sunitinib. For SSTR-negative tumors, first-line therapy options are chemotherapy, everolimus, or sunitinib. There are insufficient data to recommend particular sequencing of therapies. Patients with G1–G2 high-volume disease, relatively high Ki-67 index, and/or symptoms related to tumor growth may benefit from early cytotoxic chemotherapy. For G3 GEP-NETs, systemic options for G1–G2 may be considered, although cytotoxic chemotherapy is likely the most effective option for patients with tumor-related symptoms, and SSAs are relatively ineffective. Qualifying statements are provided to assist with treatment choice. Multidisciplinary team management is recommended, along with shared decision making with patients, incorporating their values and preferences, potential benefits and harms, and other characteristics and circumstances, such as comorbidities, performance status, geographic location, and access to care.

Additional information is available at www.asco.org/gastrointestinal-cancer-guidelines.

ACCOMPANYING CONTENT

Appendix

Data Supplement

Accepted July 24, 2023

Published September 29, 2023

J Clin Oncol 00:1-19

View Online Article

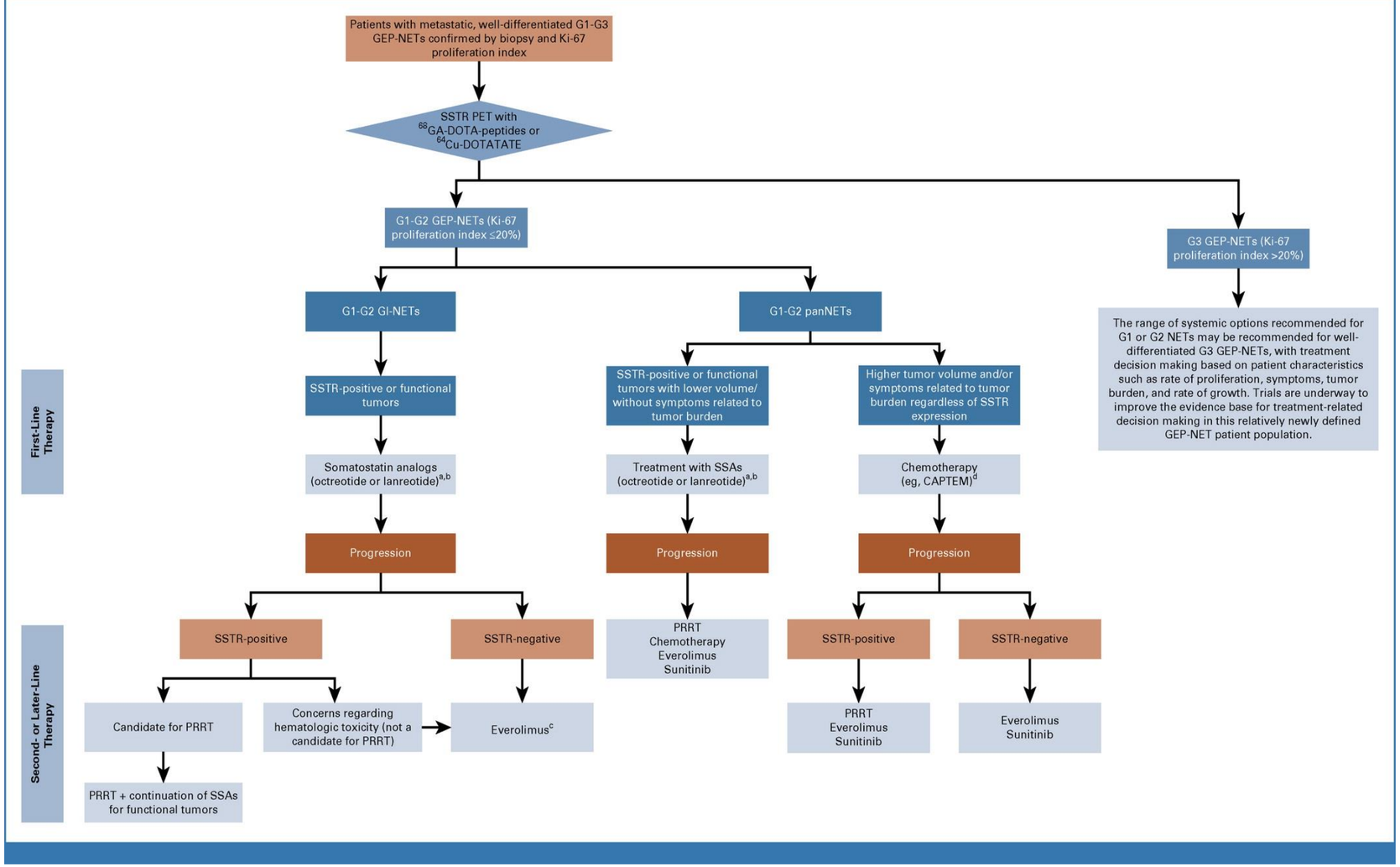


FIG 1. Systemic therapy for tumor control in well-differentiated GEP-NETs. aObservation may be considered for patients with low volume or slow growing disease, and an absence of symptoms (from tumor burden or a functional tumor). bIn the less-common circumstance of patients with SSTR-negative G1-G2 GI-NETs, everolimus may be considered as a first-line systemic treatment option. The role of SSAs in SSTR-negative tumors is uncertain. cWhile the evidence base for everolimus is in patients with nonfunctional tumors, this agent may also be considered as later-line therapy for functional tumors. dIn the rare circumstance of patients with higher-volume panNETs and/or symptoms related to tumor burden who are not candidates for chemotherapy, PRRT for patients with SSTR-positive tumors, or sunitinib or everolimus are recommended. Note: At this time, there is insufficient evidence to recommend a particular sequence of therapy options following progression for patients with G1-G2 panNETs. G, grade; GEP-NET, gastroenteropancreatic neuroendocrine tumor; panNETs, pancreatic NETs; PET, positron emission tomography; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analog; SSTR, somatostatin receptor.

Published in: Jaydira Del Rivero; Kimberly Perez; Erin B. Kennedy; Erik S. Mittra; Namrata Vijayvergia; Juniad Arshad; Sandip Basu; Aman Chauhan; Arvind N. Dasari; Andrew M. Bellizzi; Alexandra Gangi; Erin Grady; James R. Howe; Jana Ivanidze; Mark Lewis; Josh Mailman; Nitya Raj; Heloisa P. Soares; Michael C. Soulen; Sarah B. White; Jennifer A. Chan; Pamela L. Kunz; Simron Singh; Thorvardur R. Halfdanarson; Jonathan R. Strosberg; Emily K. Bergsland; *Journal of Clinical Oncology* DOI: 10.1200/JCO.23.01529

NETwerk

Tsunami of ‘treatment sequencing’ trials

SEQTOR

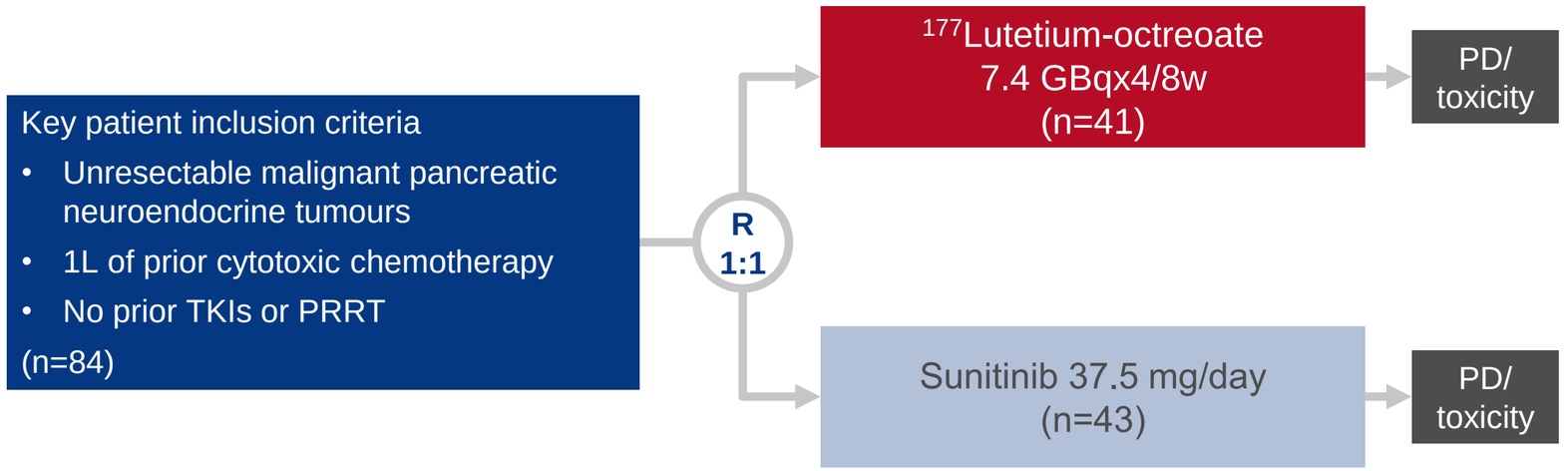
OCCLURANDOM (sunitinib vs. PRRT)

CABINET

887O: First multicentric randomized phase II trial investigating the antitumor efficacy of peptide receptor radionucleide therapy with 177Lutetium-Octreotate (OCLU) in unresectable progressive neuroendocrine pancreatic tumor: results of the OCLURANDOM trial – Baudin E, et al

Study objective

- To evaluate the efficacy and safety of peptide receptor radionucleide therapy (PRRT) with ^{177}lutetium-octreotate in patients with unresectable neuroendocrine pancreatic tumours in French centres in the phase 2 OCLURANDOM study



PRIMARY ENDPOINT

- 12-mo PFS rate

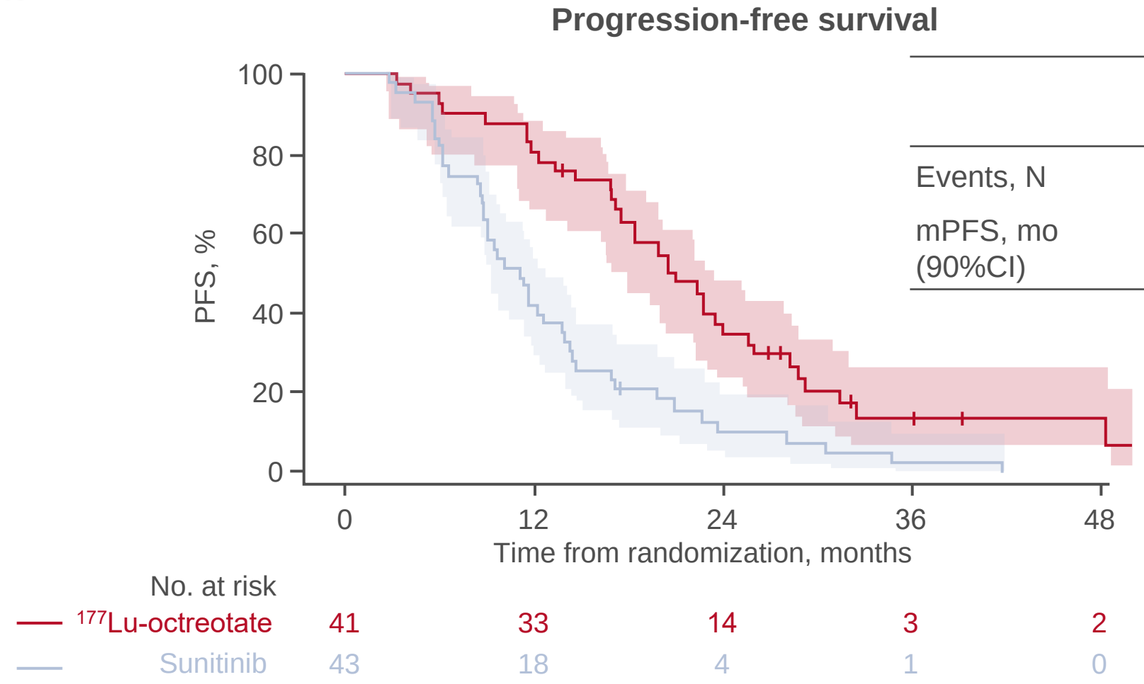
SECONDARY ENDPOINTS

- TTP, BOR, OS, QoL, safety

Presented at ESMO Congress 2022
Baudin E, et al. Ann Oncol 2022;33(suppl):abstr 887O

887O: First multicentric randomized phase II trial investigating the antitumor efficacy of peptide receptor radionucleide therapy with 177Lutetium-Octreotate (OCLU) in unresectable progressive neuroendocrine pancreatic tumor: results of the OCLURANDOM trial – Baudin E, et al

Key results



	^{177}Lu-ocreotate (n=41)	Sunitinib (n=43)
Events, N	34	42
mPFS, mo (90%CI)	20.7 (17.2, 23.7)	11.0 (8.8, 12.4)

Baudin E, et al. Ann Oncol 2022;33(suppl):abstr 887O

887O: First multicentric randomized phase II trial investigating the antitumor efficacy of peptide receptor radionucleide therapy with 177Lutetium-Octreotate (OCLU) in unresectable progressive neuroendocrine pancreatic tumor: results of the OCLURANDOM trial – Baudin E, et al

Key results

	^{177}Lu-octreotate (n=41)	Sunitinib (n=43)
12-mo PFS rate, n (%)	33 (80)	18 (42)

Grade 3–4 AEs, n (%)	^{177}Lu-octreotate (n=41)	Sunitinib (n=43)
Any	18 (44)	27 (63)
Blood	5 (12)	10 (23)
Digestive	5 (12)	9 (21)
Fatigue	3 (7)	5 (12)
Hypertension	5 (12)	8 (19)
Led to discontinuation	2 (5)	9 (21)

Conclusions

- **In patients with unresectable progressive pancreatic neuroendocrine tumours, ^{177}Lu-octreotate demonstrated promising antitumor activity and was generally well-tolerated with no new safety signals observed**

Baudin E, et al. Ann Oncol 2022;33(suppl):abstr 887O

From San Francisco to Vienna, Munich and Barcelona ✈️ 🛬

2024 ESMO GASTROINTESTINAL CANCERS

Annual Congress

FIRST-LINE EFFICACY OF [^{177}Lu]Lu-DOTA-TATE IN PATIENTS WITH ADVANCED GRADE 2 AND GRADE 3, WELL-DIFFERENTIATED GASTROENTEROPANCREATIC NEUROENDOCRINE TUMORS BY TUMOR GRADE AND PRIMARY ORIGIN: SUBGROUP ANALYSIS OF THE PHASE 3 NETTER-2 STUDY

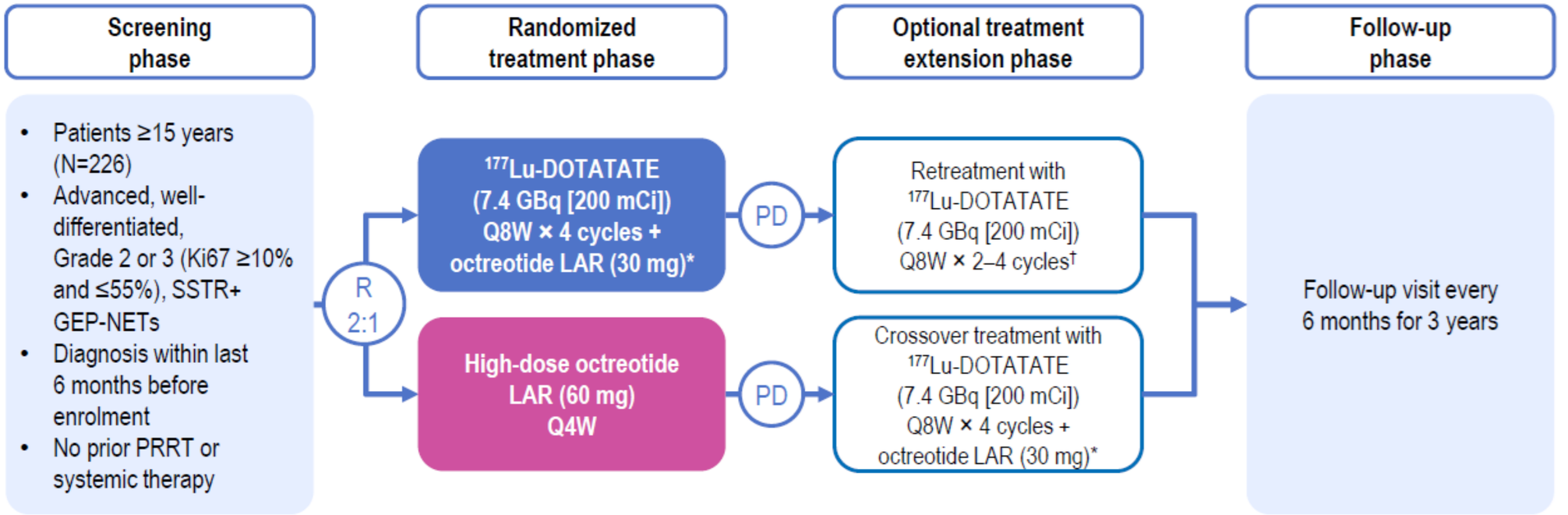
S. Singh,[1] D. Halperin,[2] S. Myrehaug,[1] K. Herrmann,[3] M. Pavel,[4] P. L. Kunz,[5] B. Chasen,[2] J. Capdevila,[6] S. Tafuto,[7] D-Y. Oh,[8] C. Yoo,[9] S. Falk,[10] T. Halfdanarson,[11] I. Folitar,[12] Y. Zhang,[13] W. W. de Herder,[14] D. Ferone[15]

[1]University of Toronto, Sunnybrook Odette Cancer Centre, Toronto, ON, Canada; [2]MD Anderson Cancer Center, Houston, TX, USA; [3]University of Duisburg-Essen, and German Cancer Consortium (DKTK)-University Hospital Essen, Essen, Germany; [4]Uniklinikum Erlangen, Friedrich Alexander University Erlangen-Nürnberg, Erlangen, Germany; [5]Yale School of Medicine, Yale University, New Haven, CT, USA; [6]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [7]Oncologia Clinica e Sperimentale Sarcomi e Tumori Rari, Istituto Nazionale Tumori IRCCS, Fondazione G. Pascale, Naples, Italy; [8]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; [9]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [10]Bristol Haematology and Oncology Centre, University Hospitals Bristol NHS Foundation Trust, Bristol, UK; [11]Mayo Clinic, Rochester, MN, USA; [12]Novartis Pharma AG, Basel, Switzerland; [13]Novartis Pharmaceuticals Corp, East Hanover, NJ, USA; [14]Erasmus MC, Rotterdam, The Netherlands; [15]Endocrinology, IRCCS Policlinico San Martino and DiMI, University of Genova, Genova, Italy

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

NETTER-2

First-line efficacy of ^{177}Lu-DOTATATE in patients with advanced, well-differentiated, Grade 2 or 3 GEP-NETs



*Q8W during ^{177}Lu-DOTATATE treatment and then Q4W; †Octreotide LAR in retreatment phase is at the investigator's discretion.
GEP-NET, gastroenteropancreatic neuroendocrine tumor; LAR, long-acting repeatable; PD, progressive disease; PRRT, peptide receptor radionuclide therapy; Q#W, every # weeks; R, randomization; SSTR, somatostatin receptor.
Singh S, et al. J Clin Oncol 2024;42(Number 3_suppl):LBA588.

NETTER-2

^{177}Lu-DOTATATE significantly improved median PFS and increased ORR versus high-dose octreotide

Primary endpoint: PFS

- ^{177}Lu-DOTATATE significantly improved median PFS by 14 months versus high-dose octreotide

	^{177}Lu-DOTATATE (n=151)	High-dose octreotide (n=75)
Median PFS, months	22.8	8.5
Stratified hazard ratio	0.276	
95% CI	0.182, 0.418	
p-value	<0.0001	

Key secondary endpoint: ORR

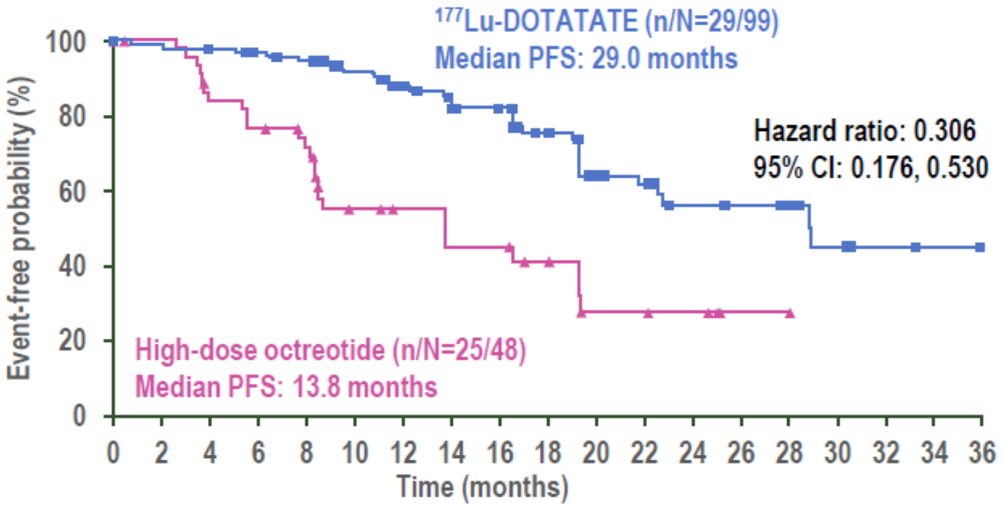
- ^{177}Lu-DOTATATE significantly improved ORR by 34% versus high-dose octreotide

	^{177}Lu-DOTATATE (n=151)	High-dose octreotide (n=75)
ORR, n (%)	65 (43.0)	7 (9.3)
Stratified odds ratio	7.81	
95% CI	3.32, 18.40	
p-value	<0.0001	

CI, confidence interval; ORR, objective response rate; PFS, progression-free survival.
Singh S, et al. J Clin Oncol 2024;42(Number 3_suppl):LBA588.

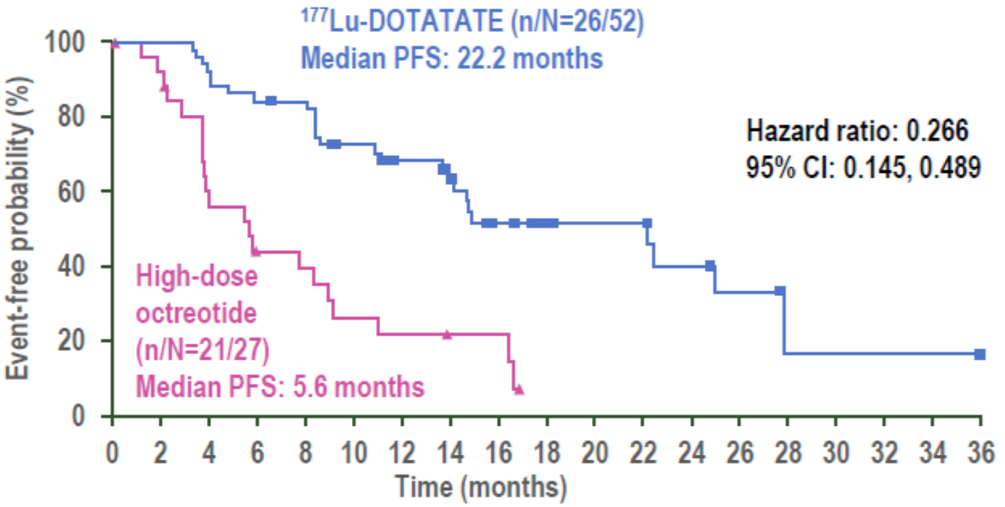
PFS BENEFIT WITH ^{177}Lu-DOTATATE WAS EVIDENT FOR PATIENTS WITH GRADE 2 AND GRADE 3 NETS

Grade 2 NET



No. at risk																			
^{177}Lu-DOTATATE	99	91	90	85	82	70	63	56	52	42	31	27	16	14	12	8	3	1	0
High-dose octreotide	48	43	35	32	28	18	16	13	13	10	5	5	4	1	1	0	0	0	0

Grade 3 NET

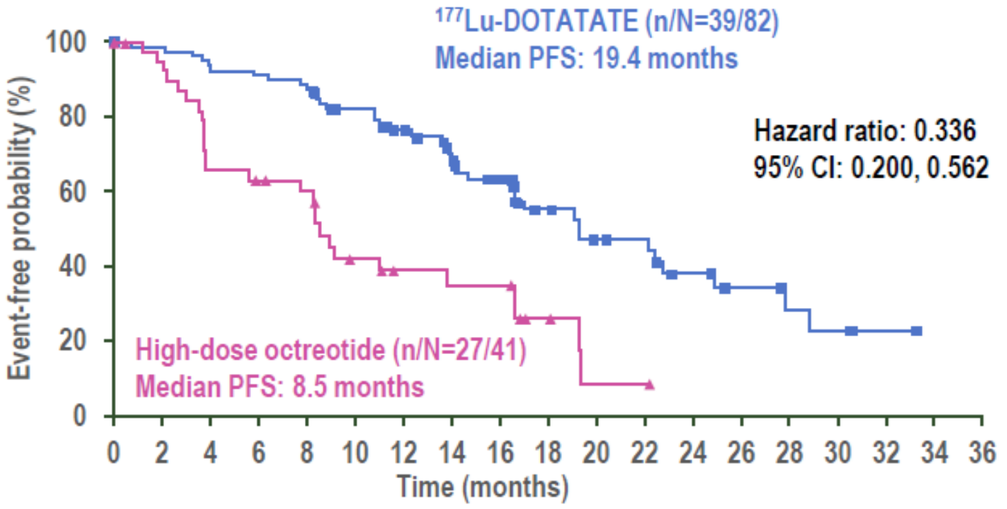


No. at risk																			
^{177}Lu-DOTATATE	52	52	48	44	43	34	29	24	16	11	10	10	7	5	1	1	1	1	0
High-dose octreotide	27	24	14	10	9	6	5	3	3	0	0	0	0	0	0	0	0	0	0

Subgroups are defined based on data from electronic case report forms.
CI, confidence interval; NET, neuroendocrine tumor; PFS, progression-free survival.

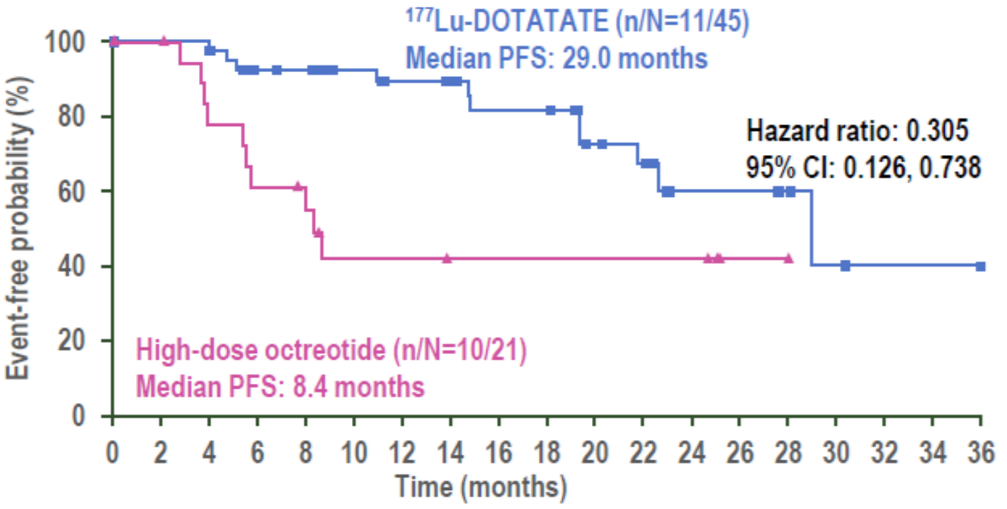
PFS BENEFIT WITH ^{177}Lu-DOTATATE WAS EVIDENT FOR PATIENTS WITH PANCREATIC AND SMALL INTESTINE NETS

Pancreatic NETs



No. at risk																		
^{177}Lu-DOTATATE	82	78	74	72	70	59	51	43	35	22	17	16	11	7	5	4	2	0
High-dose octreotide	41	36	25	23	21	13	10	9	9	4	1	1	0	0	0	0	0	0

Small intestine NETs



No. at risk																		
^{177}Lu-DOTATATE	45	41	41	35	34	28	25	24	21	21	15	13	5	5	4	2	1	1	0
High-dose octreotide	21	19	14	11	9	6	6	4	4	4	4	4	4	1	1	0	0	0	0

Subgroups are defined based on data from electronic case report forms.
CI, confidence interval; NET, neuroendocrine tumor; PFS, progression-free survival.

SUMMARY

- For PFS and ORR, a clinical benefit in favor of ^{177}Lu-DOTATATE versus high-dose octreotide was evident across all subgroups (Grade 2, Grade 3, pancreatic, and small intestine NETs)
- First-line ^{177}Lu-DOTATATE efficacy was maintained across Grade 2 and 3 NETs
  - Median PFS was 29.0 and 22.2 months, and ORR was 40.4% and 48.1%, respectively
- First-line ^{177}Lu-DOTATATE efficacy was maintained across pancreatic and small intestine NETs
  - Median PFS was 19.4 and 29.0 months, and ORR was 51.2% and 26.7%, respectively
- Time to response was similar across all subgroups
- A durable response was evident across all subgroups
- First-line ^{177}Lu-DOTATATE should be considered a standard of care for this patient population with advanced, well-differentiated, Grade 2 or 3 (Ki67 ≥10% and ≤55%), SSTR+ GEP-NETs

GEP, gastroenteropancreatic; NET, neuroendocrine tumor; ORR, objective response rate; PFS, progression-free survival; SSTR, somatostatin receptor.

First reaction: the winner nuclear medicine takes it all in the first-line treatment of NET

But time brings insights 😇

Who are these people for PRRT first-line?

- Most GEP-NET in our practice are grade 1 or grade 2 with Ki-67 ≤10%, so Ki-67 >10% population = about 20%.
- Not everyone of that 20% has the necessary SSTR expression for PRRT.
- Within that 20% population, the pNET are dominant over the small intestine NET.
- SSA in first-line also function not so badly in the NETTER-2 study and no evidence today that 'later' use of PRRT will negatively affect overall survival.
- Taking into account patient's comorbidities: renal function and hematologic reserve…
- What does our patient actually want?
  - SSA in first-line: known and safe option for a disease with a longer overall course.
  - PRRT is a more complex treatment to start the process with some more toxicities: focus on hematological consequences for therapies in later-line…
  - Apart from clinical characteristics that can influence choice, there are no good biomarkers available…
  - No quality of life data available from NETTER-2 yet…
  - What about the financial picture: cost-benefit PRRT vs. SSA?
  - If waiting time for PRRT is an issue anywhere in the world…

Fair conclusion at the moment

- **AN INDIVIDUALIZABLE standard-of-care option for the advanced, well-differentiated SSTR+ GEP-NET grade 2-3 (Ki-67 ≥10% and ≤ 55%):**
  - Higher tumor burden, when response ratio is important
  - Symptomatic disease
  - More aggressive NET disease

- **Grade 3 gastrointestinal NET (extra-pancreatic).**
- **Higher grade 2 gastrointestinal NET with symptomatic disease due to tumor burden.**

- **Symptomatic/bulky grade 3 pNET: competition from 'fast' capecitabine + temozolomide.**
- **Symptomatic/bulky higher grade 2 pNET: competition from 'fast' capecitabine + temozolomide.**
- **Quiet higher grade 2 GEP-NET (Ki-67 10-20%): competition from everolimus.**

- **Quiet GEP-NET with Ki-67 at the lower end of the 10-55% range: ‘give it a try' with SSA.**

SPINET: not big success, but clear conclusion

Society for Endocrinology

Endocrine-Related Cancer (2024) **31** e230337
https://doi.org/10.1530/ERC-23-0337

Received 11 December 2023
Accepted 24 June 2024
Available online 24 June 2024
Version of Record published 22 July 2024

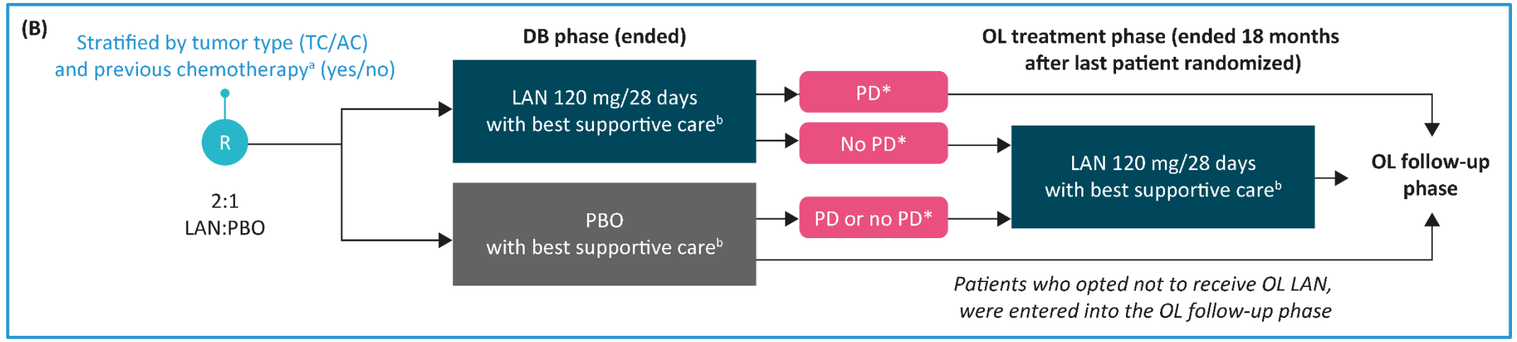
RESEARCH

Treatment of advanced BP-NETS with lanreotide autogel/depot vs placebo: the phase III SPINET study

E Baudin[1], J Capdevila[2], D Hörsch[3], S Singh[4], M E Caplin[5], E M Wolin[6], W Buikhuisen[7], M Raderer[8], E Dansin[9], C Grohe[10], D Ferone[11], A Houchard[12], X-M Truong-Thanh[13] and D Reidy-Lagunes[14] on behalf of the SPINET Study Group

Phase 3 SPINET study design

- **Protocol terminated early owing to slow accrual of patients and amended**
  - DB LAN patients without PD and all DB PBO patients could transition to OL-LAN
- **Primary endpoint (adapted):**
  - Centrally assessed median PFS in patients randomized to LAN (DB and OL-LAN phases)
- **Secondary endpoint:**
  - Changes from baseline in serum CgA levels (x ULN)
- **Exploratory endpoint:**
  - Centrally assessed TGR (% increase in target-tumor volume per month)

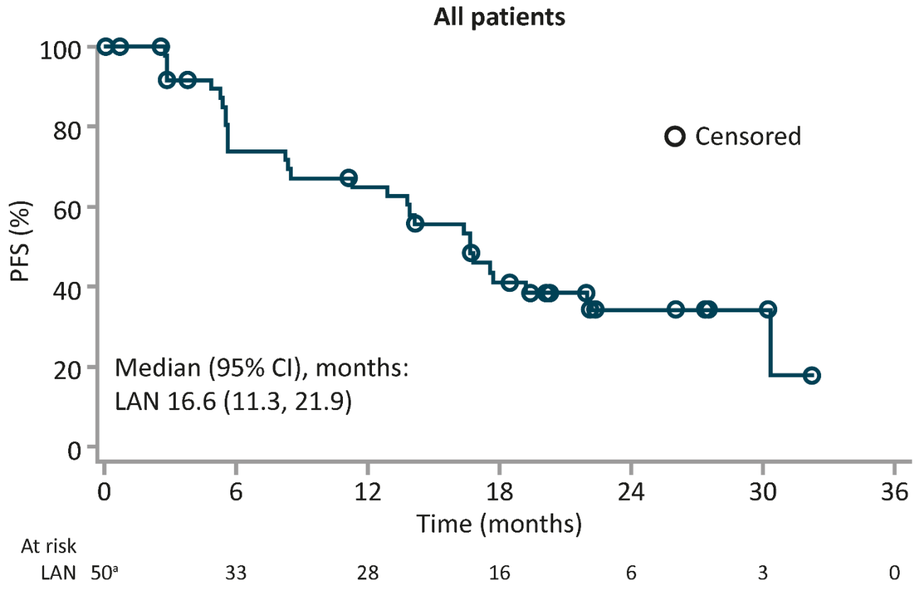


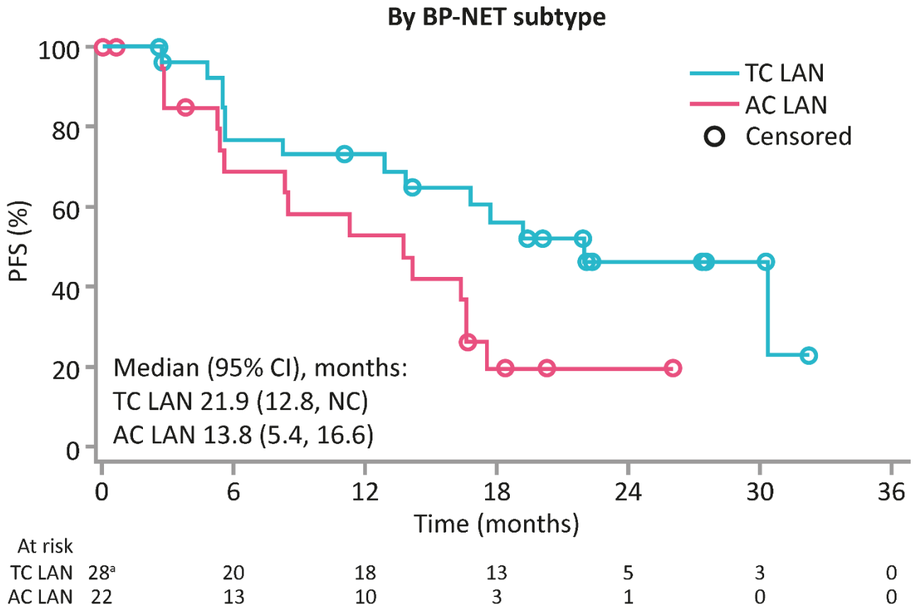
- **Patients were randomized 2:1 to LAN or PBO (planned sample size, N = 216), and stratified by tumor type and previous chemotherapy**
- **Overall, 77 patients were randomized and treated during the DB phase**
  - LAN, n = 51; Placebo, n = 26
- **In total, 40 patients from the DB phase entered the OL-LAN phase**
  - LAN/LAN, n = 21; Placebo/LAN, n = 19

*Centrally confirmed. [a]Includes cytotoxic chemotherapy, molecular targeted therapy, or interferon-alpha. [b]Symptomatic treatment for acid reflux, pain, etc
AC, atypical carcinoid; CgA, chromogranin A; DB, double blind; LAN, lanreotide autogel/depot; OL, open label; OL-LAN, open-label lanreotide autogel/depot; PBO, placebo; PFS, progression-free survival; PD, progressive disease; R, randomization; TC, typical carcinoid; TGR, tumor growth rate; ULN, upper limit of normal

Results: PFS during DB and OL-LAN phases (ITT population)

- **Median (95% CI) PFS was:**
  - **16.6** months (11.3, 21.9) in the LAN-randomized group
  - **21.9** months (12.8, NC) in TC type BP-NETs
  - **13.8** months (5.4, 16.6) in AC type BP-NETs





PFS was assessed by central review. **Analysis updated in 2022.** [a]One patient should have been censored in the PFS analysis for treatment discontinuation for toxicity or other reasons; however, the baseline central radiological assessment was performed prior to the randomization date and the patient was therefore excluded from the analysis. AC, atypical carcinoid; BP-NET, bronchopulmonary neuroendocrine tumor; CI, confidence interval; DB, double blind; ITT, intention-to-treat; LAN, lanreotide autogel/depot; NC, not calculable; OL, open label; OL-LAN, open-label lanreotide autogel/depot; PFS, progression-free survival; TC, typical carcinoid

Fair conclusion SPINET

- **Despite lower-than-target enrolment, SPINET is the largest prospective study to date of SSA therapy in SSTR-positive TC and AC. The study provides clinically important data about the activity and tolerability profile of LAN 120 mg every 28 days in unresectable and/or metastatic BP-NET.**

- **The results of SPINET provide much-needed data to support the clinical use of SSA in BP-NET, mainly TC.**

➢ **So first SSA and then everolimus in case of calm SSTR+ disease.**

➢ **Everolimus in less calm SSTR+ disease and in SSTR- disease…chemotherapy later…**

➢ **<u>Looking forward to phase 3 LEVEL trial</u>:**

177Lu-edotreotide vs. everolimus in patients with advanced NET of lung or thymic origin (treatment naïve or progressed on SSA or ≤2 additional systemic treatments)

Update SEQTOR at ESMO 2024

BARCELONA 2024 ESMO congress

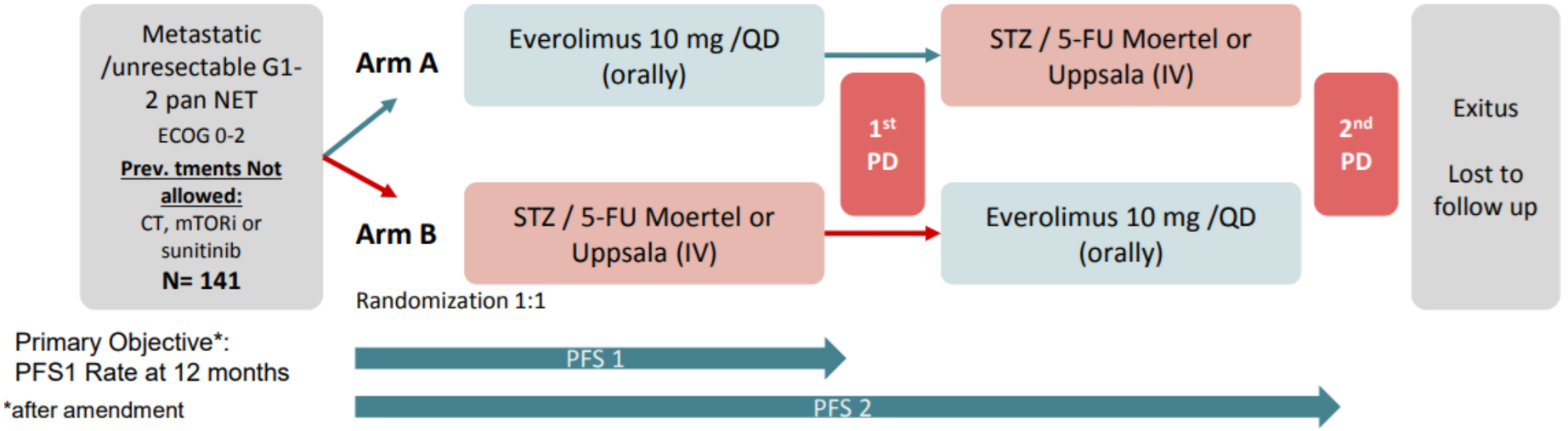
Multivariable Analysis of Streptozotocin plus 5-Fluorouracil and Everolimus Sequences in Advanced Pancreatic Neuroendocrine Tumor patients: The SEQTOR Trial (GETNE-1206)

Jaume Capdevila, Salvatore Tafuto, Merete Krogh, Alex Teulé, Rocio Garcia-Carbonero, Heinz Josef Klümpen, Birgit Cremer, Isabel Sevilla, Barbro Eriksson, Elizaveta Mitkina Tabaksblat, Jean-Philippe Metges, Nicholas Simon Reed, Joerg Schrader, Silvia Bozzarelli, Ulrich Knigge, Paula Jiménez-Fonseca, Marta Benavent Vinuales, Marino Venerito, Valentí Navarro, Ramón Salazar.

Grupo Español de Tumores Neuroendocrinos y Endocrinos (GETNE)

Update SEQTOR at ESMO 2024

STUDY DESIGN & METHODS



Today we present the multivariable analysis of PFS_1 and OS (Cox Regression) and RR (Logistic Regression) adjusted by treatment arm.

Update SEQTOR at ESMO 2024

SUMMARY & CONCLUSIONS

GETNE
Grupo Español de Tumores Neuroendocrinos y Endocrinos

Summary	❖ High tumor burden, ECOG 1/2 and sex (female) are independent poor prognostic factor. ❖ The sequence of everolimus followed by STZ/5-FU performed better in patients with grade 1 in PFS_1 and in treatment-naïve patients in OS. ❖ Upfront STZ/5-FU is more effective to obtain treatment responses in patients with grade 2 tumors.
Conclusion	❖ In the SEQTOR trial, everolimus upfront showed better outcomes in patients with treatment-naïve or grade 1 panNETs, whereas STZ/5-FU can be recommended in patients with grade 2 when tumor shrinkage is clinically relevant.

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Presented by Dr. SALAZAR in ESMO 2024

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ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

NCI National Clinical Trials Network
a National Cancer Institute program

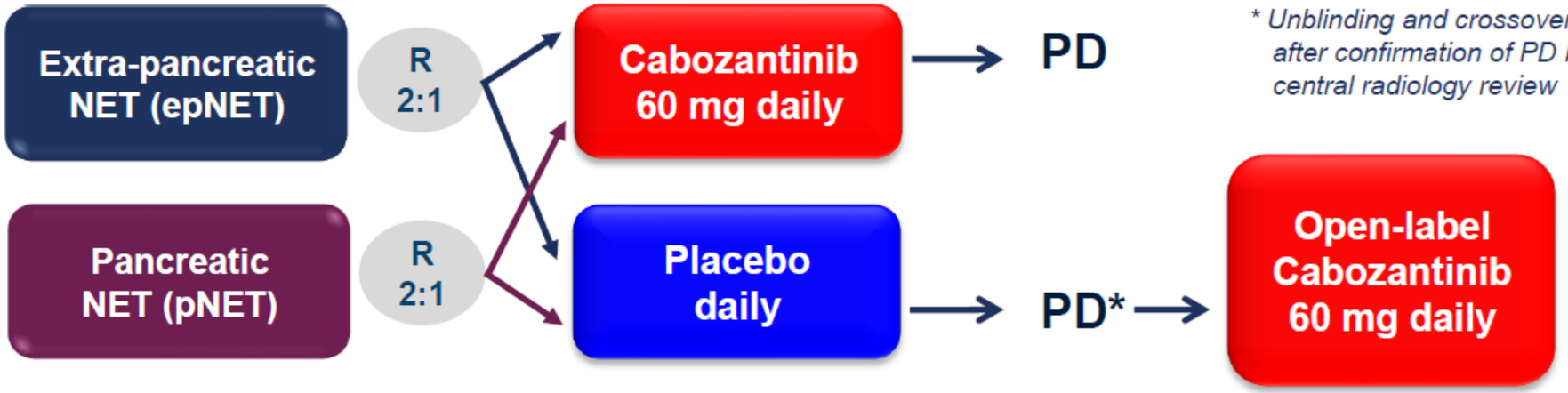
Cabozantinib Versus Placebo for Advanced Neuroendocrine Tumors after Progression on Prior Therapy (CABINET Trial/Alliance A021602)

Updated Results Including Progression Free-Survival by Blinded Independent Central Review and Subgroup Analyses

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

Update CABINET at ESMO 2024

CABINET Trial Design



Stratification factors:

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

Study Endpoints:

- **Primary Endpoint per cohort:**
  - **Progression-free survival (PFS) by blinded independent central review (BICR)**
- **Secondary Endpoint per cohort:**
  - **Overall survival (OS)**
  - **Objective response rate (ORR)**
  - **Safety and tolerability**

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Update CABINET at ESMO 2024

Key Inclusion Criteria

- Well- to moderately differentiated NET, grades 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)
  - Includes everolimus, sunitinib, or Lu-177 dotatate for pNET
  - Includes everolimus for lung NET
  - Includes everolimus or Lu-177 dotatate for GI-NET
- Concurrent SSA allowed provided stable dose for ≥ 2 months

Update CABINET at ESMO 2024

Extra-pancreatic NET: Baseline Characteristics

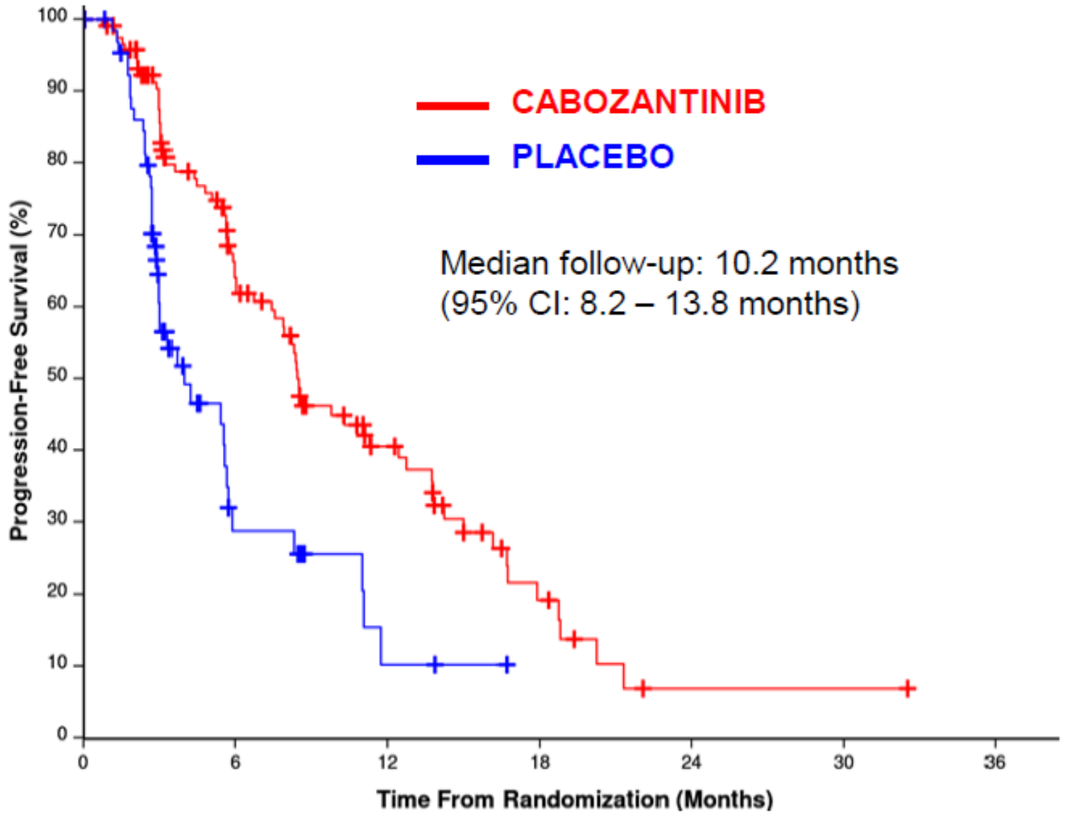
	CABOZANTINIB (N=134)	PLACEBO (N=69)
Time from diagnosis to randomization, months, median (range)	65 (10-489)	76 (13-340)
Age, years, median (range)	66 (28-86)	66 (30-82)
Female sex, n (%)	74 (55)	31 (45)
White race, n (%)	115 (86)	55 (80)
ECOG PS, n (%)		
0	49 (37)	32 (46)
1	84 (63)	36 (52)
2	1 (1)	1 (1)
Differentiation, n (%)		
Well	118 (88)	61 (88)
Moderate	6 (5)	5 (7)
Not specified	10 (8)	3 (4)
Grade, n (%)		
G1	37 (28)	15 (22)
G2	86 (64)	48 (70)
G3	8 (6)	5 (7)
Unknown	3 (2)	1 (1)

	CABOZANTINIB (N=134)	PLACEBO (N=69)
Primary tumor site, n (%)		
Gastrointestinal	70 (52)	46 (67)
Lung	27 (20)	12 (17)
Thymus	6 (5)	4 (6)
Unknown	22 (16)	2 (3)
Other	5 (4)	2 (3)
Pancreas*	4 (3)	3 (4)
Hormone syndrome present, n (%)	41 (31)	25 (36)
Concurrent SSA, n (%)	92 (69)	48 (70)
Prior SSA, n (%)	125 (93)	64 (93)
Number of prior systemic therapies, median (range)	2 (1-6)	2 (1-6)
Prior systemic therapy, n (%)		
Lu-177 dotatate	80 (60)	41 (59)
Everolimus	96 (72)	44 (64)
Temozolomide +/- capecitabine	43 (32)	20 (29)
Platinum + etoposide	11 (8)	8 (12)

**7 patients with pNET were misallocated to the epNET cohort*

Update CABINET at ESMO 2024

epNET Cohort: Progression-Free Survival
Blinded Independent Central Review



Stratified HR = 0.38
(95% CI: 0.25 – 0.59)
log-rank p<0.0001

Median PFS
Cabozantinib = 8.4 months
(95% CI: 7.6 – 12.7 months)
Placebo = 3.9 months
(95% CI: 3.0 – 5.7 months)

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Jennifer Chan, MD, MPH

Update CABINET at ESMO 2024

Pancreatic NET: Baseline Characteristics

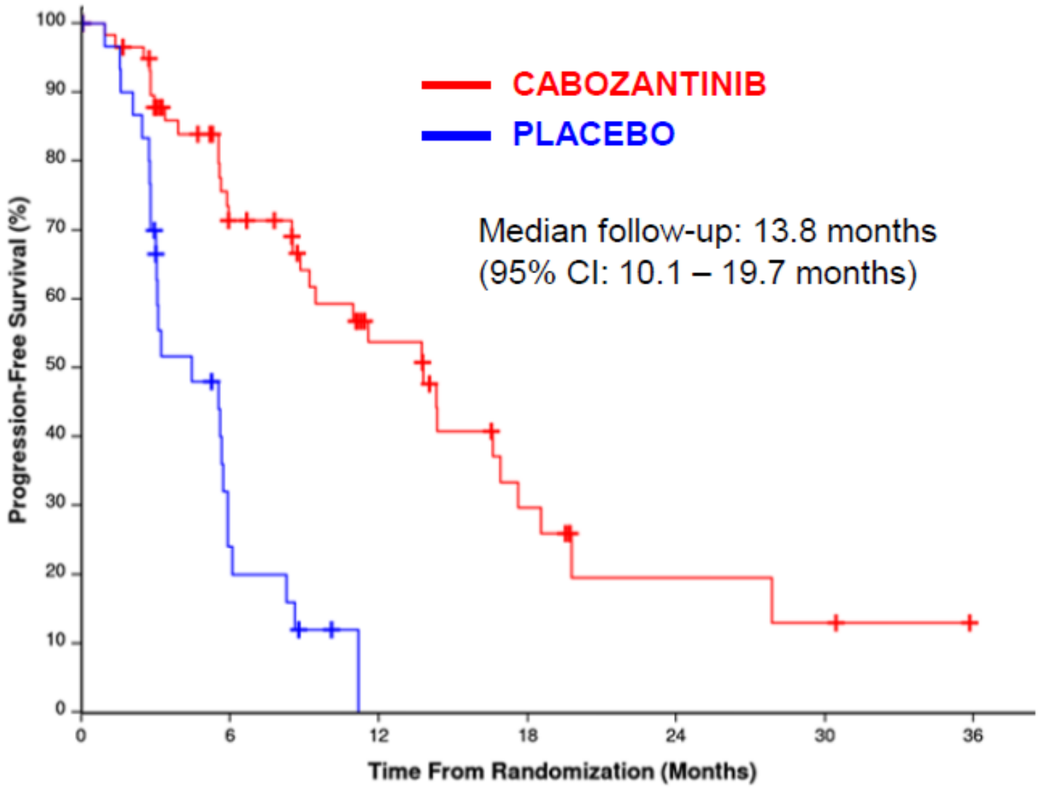
	CABOZANTINIB (N= 64)	PLACEBO (N=31)
Time from Diagnosis to Randomization, median, months (range)	71 (18-213)	73 (18-230)
Age, years, median (range)	60 (29-79)	64 (39-79)
Female sex, n (%)	27 (42)	13 (42)
White race, n (%)	54 (84)	25 (81)
ECOG PS, n (%)		
0	35 (55)	15 (48)
1	28 (44)	16 (52)
2	1 (2)	0
Differentiation, n (%)		
Well	59 (92)	30 (97)
Moderate	4 (6)	0
Not specified	1 (2)	1 (3)
Grade, n (%)		
G1	14 (22)	7 (23)
G2	39 (61)	19 (61)
G3	8 (13)	3 (10)
Unknown	3 (5)	2 (7)

	CABOZANTINIB (N= 64)	PLACEBO (N=31)
Primary tumor site		
Pancreas	62 (97)	30 (97)
Ileum*	1 (2)	0
Cecum*	0	1 (3)
Stomach*	1 (2)	0
Hormone syndrome present, n (%)	11 (17)	5 (16)
Concurrent SSA, n (%)	35 (55)	17 (55)
Prior SSA, n (%)	63 (98)	30 (97)
Number of prior systemic therapies, median (range)	3 (1-9)	2 (1-7)
Prior systemic therapy, n (%)		
Lu-177 dotatate	38 (59)	18 (58)
Everolimus	51 (80)	25 (81)
Sunitinib	18 (28)	7 (23)
Temozolomide +/- capecitabine	43 (67)	16 (52)

**3 patients with epNET were misallocated to the pNET cohort*

Update CABINET at ESMO 2024

pNET Cohort: Progression-Free Survival
Blinded Independent Central Review



Stratified HR = 0.23
(95% CI: 0.12 – 0.42)
log-rank p<0.0001

Median PFS
Cabozantinib = 13.8 months
(95% CI: 9.2 – 18.5 months)
Placebo = 4.4 months
(95% CI: 3.0 – 5.9 months)

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Jennifer Chan, MD, MPH

Update CABINET at ESMO 2024

Treatment Exposure and Patient Disposition

epNET Cohort

	CABOZANTINIB (N=132)	PLACEBO (N=67)
Duration of therapy, median (range)	5.5 months (0.2-32.4)	2.8 months (0.6-21.4)
Dose reduction required, %	66%	10%
Average daily dose, median	38.4 mg	59.0 mg
Treatment ongoing, n (%)	21 (16)	7 (10)
Off treatment, n (%)	111 (84)	60 (90)
Progressive disease	52 (47)	38 (63)
Adverse events	34 (31)	9 (15)
Withdrawn consent	7 (6)	4 (7)
Death on Study	6 (5)	3 (5)
Other reason	6 (5)	4 (7)
Alternative therapy	5 (5)	1 (2)
Other disease	1 (1)	1 (2)

pNET Cohort

	CABOZANTINIB (N=63)	PLACEBO (N=31)
Duration of therapy, median (range)	8.3 months (0.5-39.6)	2.9 months (0.5-11.2)
Dose reduction required, %	68%	19%
Average daily dose, median	37.9 mg	56.9 mg
Treatment Ongoing, n (%)	14 (22)	2 (6)
Off treatment, n (%)	49 (78)	29 (94)
Progressive Disease	28 (57)	23 (79)
Adverse Events	10 (20)	0
Withdrawn consent	5 (10)	4 (14)
Other disease	2 (4)	0
Alternative treatment	1 (2)	0
Other reason	3 (6)	2 (7)

Update CABINET at ESMO 2024

epNET: Treatment-Related Adverse Events

	CABOZANTINIB (N=132)		PLACEBO (N=67)	
	Any grade	Grades 3-4	Any grade	Grades 3-4
Any adverse event	130 (98)	82 (62)	55 (82)	18 (27)
AST increase	86 (65)	4 (3)	12 (18)	0
Fatigue	82 (62)	17 (13)	28 (42)	5 (8)
ALT increase	77 (58)	1 (1)	9 (13)	0
Diarrhea	74 (56)	14 (11)	20 (30)	3 (5)
Hypertension	70 (53)	28 (21)	13 (19)	2 (3)
Thrombocytopenia	62 (47)	1 (1)	5 (8)	1 (2)
Mucositis oral	48 (36)	5 (4)	6 (9)	0
Palmar-plantar erythrodysesthesia	48 (36)	4 (3)	5 (8)	0
Nausea	46 (35)	2 (2)	10 (15)	0
Leukopenia	46 (35)	4 (3)	2 (3)	0
Dysgeusia	45 (34)	0	1 (2)	0
Anorexia	40 (30)	2 (2)	6 (9)	0
Neutropenia	40 (30)	4 (3)	2 (3)	0
Hypothyroidism	36 (27)	0	1 (2)	0

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Grade 5 events in cabozantinib arm possibly related to study therapy:
n=1 gastrointestinal hemorrhage; n=1 cardiac arrest; n=2 death not otherwise specified

Update CABINET at ESMO 2024

pNET: Treatment-Related Adverse Events

	CABOZANTINIB (N=63)		PLACEBO (N=31)	
Adverse Event, n (%)	Any grade	Grades 3-4	Any grade	Grades 3-4
Any Adverse Event	62 (98)	41 (65)	26 (84)	7 (23)
Fatigue	47 (75)	7 (11)	10 (32)	1 (3)
AST increase	40 (63)	1 (2)	9 (29)	0
ALT increase	39 (62)	1 (2)	9 (29)	0
Diarrhea	37 (59)	4 (6)	4 (13)	0
Hypertension	36 (57)	14 (22)	7 (23)	3 (10)
Mucositis oral	30 (48)	5 (8)	1 (3)	0
Palmar-plantar erythrodysesthesia	28 (44)	6 (10)	4 (13)	0
Nausea	24 (38)	5 (8)	7 (23)	1 (3)
Thrombocytopenia	21 (33)	0	3 (10)	0
Dysgeusia	19 (30)	0	3 (10)	0
Neutropenia	17 (27)	1 (2)	2 (7)	0
Thromboembolic event	11 (18)	7 (11)	0	0

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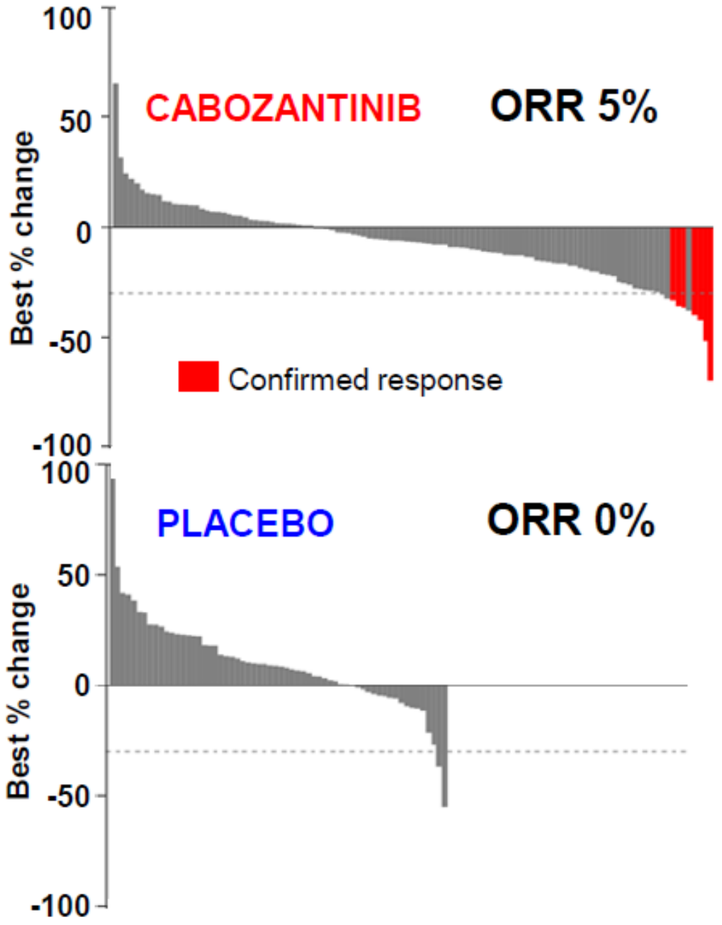
*No treatment-related Grade 5 adverse events in the pNET cohort

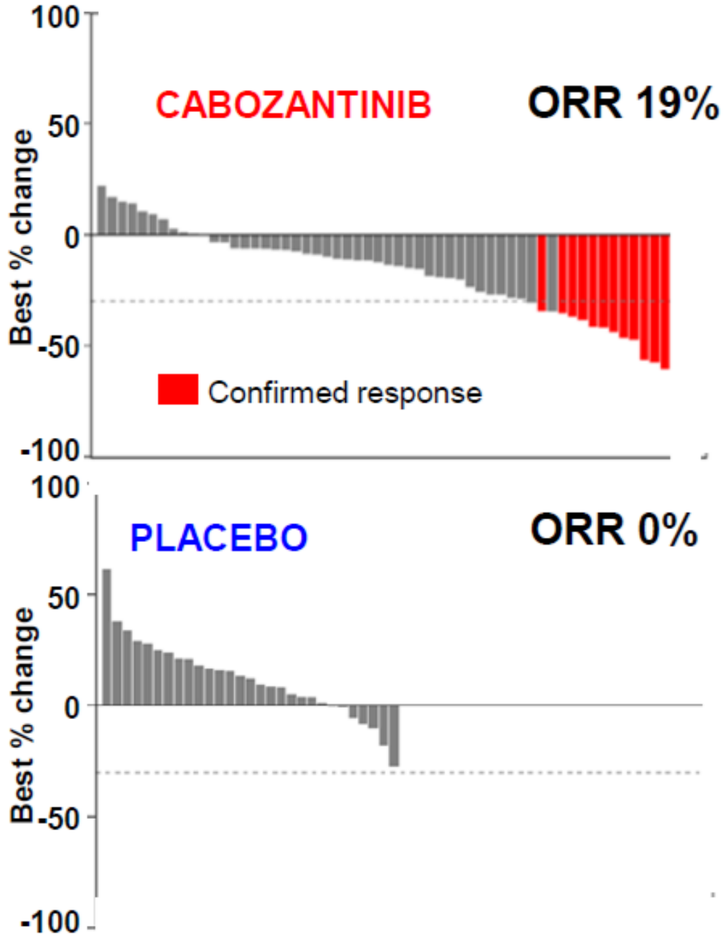
Update CABINET at ESMO 2024

Confirmed Objective Response (BICR)

epNET Cohort



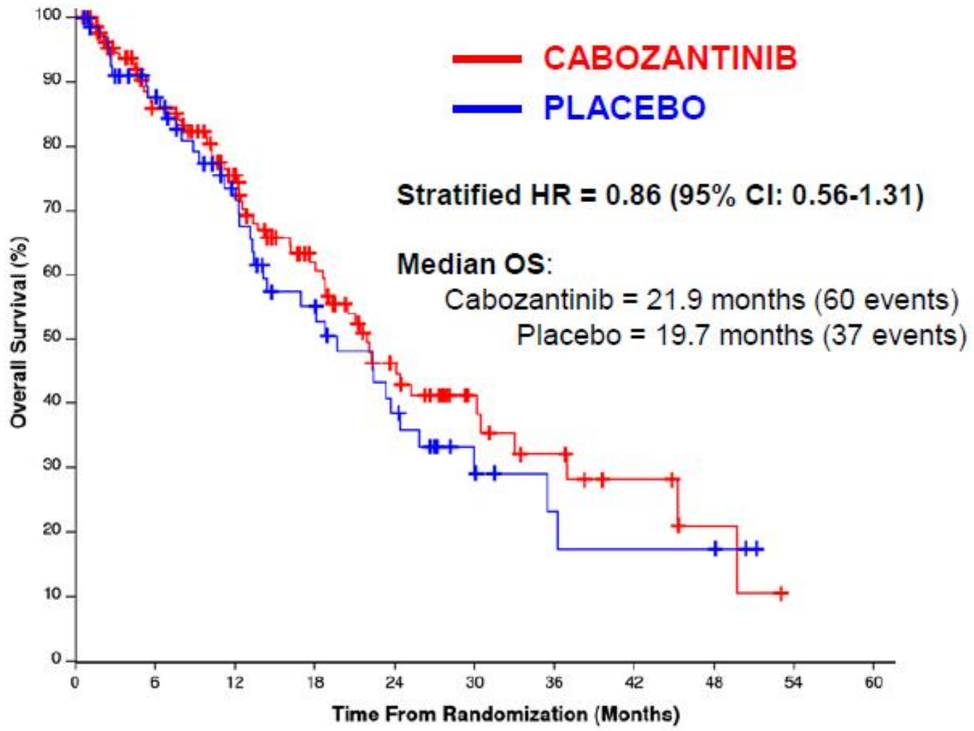
pNET Cohort



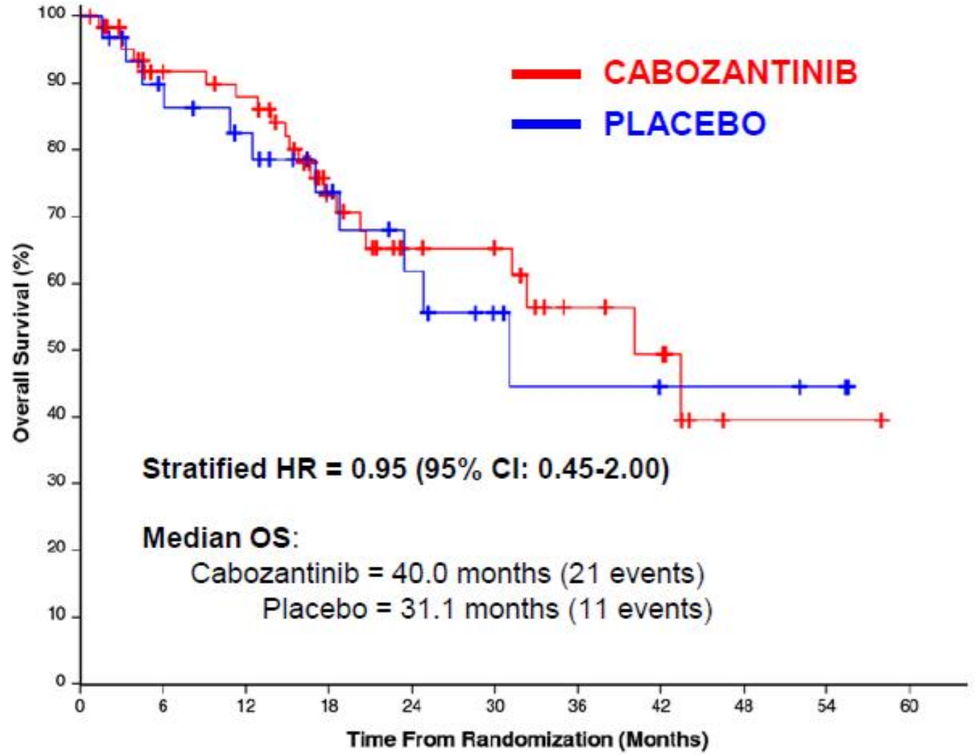
Update CABINET at ESMO 2024

Overall Survival – Interim Analysis

epNET Cohort



pNET Cohort



Update CABINET at ESMO 2024

Conclusions

- Cabozantinib significantly improves PFS in patients with previously treated, progressive extra-pancreatic or pancreatic NET
  - Subgroup analyses suggest benefits for cabozantinib across all clinical subgroups, including primary tumor site, grade, and prior anticancer therapy
- Adverse events are consistent with the known safety profile of cabozantinib
  - A majority of patients treated with cabozantinib required dose modifications or reductions to manage adverse events
- CABINET represents one of the first randomized studies specifically designed to evaluate efficacy of therapy following treatment with Lu-177 dotatate and/or targeted therapy
- Cabozantinib should be a new treatment option for patients with previously treated extra-pancreatic or pancreatic NET

Update CABINET at ESMO 2024

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of Cabozantinib to Treat Advanced Neuroendocrine Tumors

Jennifer A. Chan, M.D., M.P.H., Susan Geyer, Ph.D., Tyler Zemla, M.S., Michael V. Knopp, M.D., Ph.D., Spencer Behr, M.D., Sydney Pulsipher, M.P.H., Fang-Shu Ou, Ph.D., Amylou C. Dueck, Ph.D., Jared Acoba, M.D., Ardaman Shergill, M.D., Edward M. Wolin, M.D., Thorvardur R. Halfdanarson, M.D., Bhavana Konda, M.D., M.P.H., Nikolaos A. Trikalinos, M.D., Bernard Tawfik, M.D., Nitya Raj, M.D., Shagufta Shaheen, M.D., Namrata Vijayvergia, M.D., Arvind Dasari, M.D., Jonathan R. Strosberg, M.D., Elise C. Kohn, M.D., Matthew H. Kulke, M.D., Eileen M. O'Reilly, M.D., and Jeffrey A. Meyerhardt, M.D., M.P.H.

Questions that remain open after CABINET…

- **Where do we put cabozantinib in the treatment algorithm of NET?** After SSA and PRRT immediately cabozantinib or do we first go down the list of the other therapies that are available?

- **Given the toxicity of cabozantinib:** do we systematically start with 60 mg/day and reduce the dose in case of toxicity, or do we start with 40 mg/day and titrate the dose according to side effects?

- **What do patients think of cabozantinib?** Quality of life data? Patient-reported outcome measures?

➢ **The Food and Drug Administration (FDA) has accepted for review the supplemental New Drug Application for cabozantinib for adults with previously treated, locally advanced/unresectable or metastatic, well- or moderately-differentiated pNET, and for adults with previously treated, locally advanced/unresectable or metastatic, well- or moderately-differentiated epNET.**

EverSun trial

- **Sequential everolimus and sunitinib treatment in progressive, advanced, pancreatic NEN: real-world data from the Belgian Group of Digestive Oncology DNET & NETwerk**

- **Rationale**
  - Often sequential treatment → **optimal treatment sequence?**
  - Angelousi et al. 2017
    - Retrospective study
    - 31 patients with sequential treatment
    - Ever-Sun group vs. Sun-Ever group
    - No statistically significant differences in OS or mPFS in both groups

Sequential Everolimus and Sunitinib Treatment in Pancreatic Metastatic Well-Differentiated Neuroendocrine Tumours Resistant to Prior Treatments

Anna Angelousi[a] Kimberly Kamp[b] Maria Kaltsatou[a] Dermot O'Toole[c] Gregory Kaltsas[a] Wouter de Herder[b]

[a]Sector of Endocrinology, Department of Pathophysiology, National & Kapodistrian University of Athens, Athens, Greece; [b]Sector of Endocrinology, Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands; [c]St. Vincent's University and Department of Clinical Medicine, St. James Hospital and Trinity College, Dublin, Ireland

EverSun trial

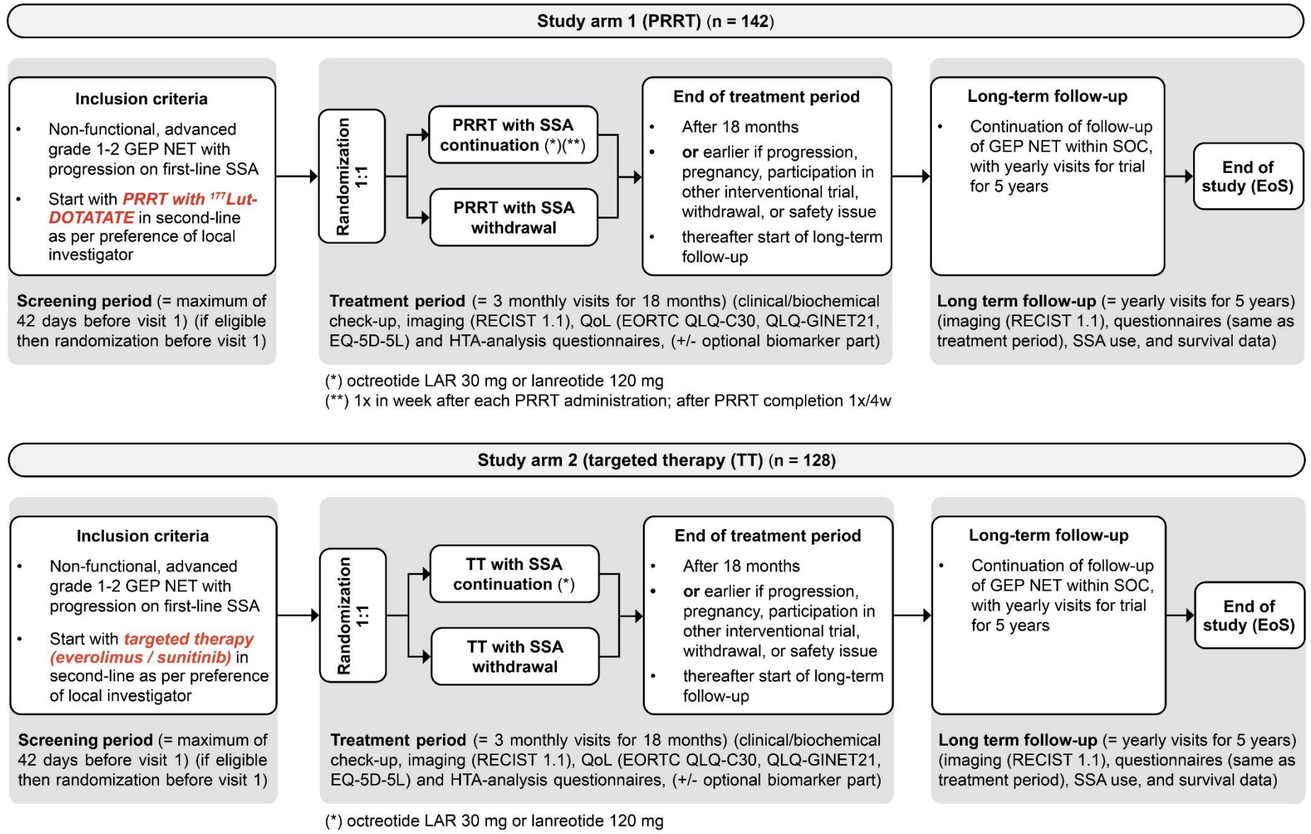
- **Conclusion:**
  - More insights into the sequential treatment of well-differentiated metastatic pNET with everolimus and sunitinib:
    - No statistically significant difference in mOS between both treatment groups.
    - No statistically significant difference in mPFS, mPFS1 and mPFS2 between both treatment groups.
    - No statistically significant difference in AEs between both groups.

➢ **Treatment modalities appear to be equivalent in both sequences.**

➢ Need for prospective studies for better insights ***that may not come***!

Update SAUNA trial

- **Upset study**

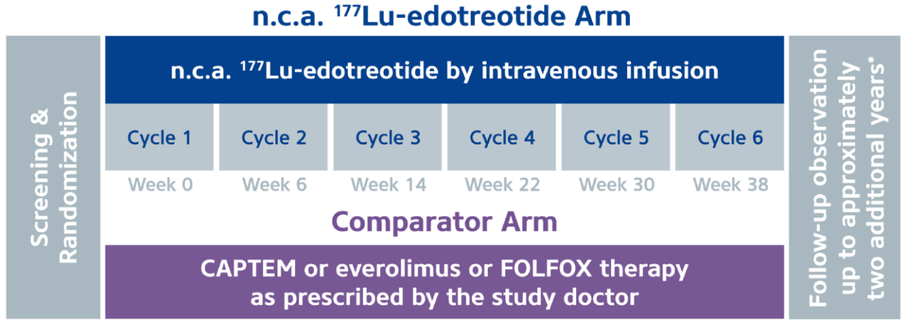


- **Status study**
  - Study running in 19 hospitals in BE/NL
  - 29 randomized patients
    - PRRT: 23
    - Targeted Therapy: 6
  - 5 End of Study patients

- **retroSAUNA**
  - Retrospective sister of SAUNA
  - Primary endpoint: OS per substudy
  - Starting up now → results in 2026
  - 10 hospitals in BE/NL/FR

COMPOSE: phase 3 trial of ^{177}Lu-edotreotide versus standard-of-care in well-differentiated (WD) aggressive grade 2 and grade 3 GEP-NET trial

- **BJ Hernando (Spain)**
  - Ongoing phase 3 trial in G2 and G3 GEP-NET exploring efficacy and safety of ^{177}Lu-edotreotide vs. eve/CAPTEM/FOLFOX. COMPOSE (NCT04919226), to extend therapeutic options for ^{177}Lu-edotreotide to high-grade NET
  - Inclusion criteria: patients aged ≥18 years; histologically confirmed diagnosis of unresectable, WD (high G2 or G3) GEP-NET; SSTR+ disease
  - Exclusion criteria: prior PRRT; major surgery within 4 weeks prior to randomization; other known malignancies; renal, hepatic, cardiovascular or hematological organ dysfunction, potentially interfering with the safety of the trial treatments
  - **Primary endpoint: PFS (RECIST v1.1), assessed every 12 weeks**
  - Secondary endpoints: OS, assessed up to 2 years after disease progression



Treatment response, tumor progression, survival data, information on further antineoplastic treatments and secondary malignancies

N=202 patients (1:1 randomization)

Recruitment started: September 2021

First patient screened in France

- **Take home messages**
  - Trial in progress
  - To provide first prospective, controlled data for ^{177}Lu-edotreotide, CAPTEM, FOLFOX and eve in treatment of patients with high G2 and G3 GEP-NET, clarifying the positioning of ^{177}Lu-edotreotide in the therapeutic algorithm

CAPTEM: capecitabine + temozolomide; eve: everolimus; FOLFOX: folinic acid, fluorouracil + oxaliplatin; G: grade; GEP-NET: gastroenteropancreatic NET; NET: neuroendocrine tumor; PFS: progression-free survival; PRRT: peptide receptor radionuclide therapy; OS: overall survival; RECIST: response evaluation criteria in solid tumors; SSTR: somatostatin receptor; WD: well-differentiated.

COMPETE phase 3 trial

COMPETE Phase III Trial – Peptide Receptor Radionuclide Therapy (PRRT) with Lutetium (^{177}Lu) Edotreotide vs. Everolimus in Patients with Progressive GEP-NETs

J.R. Strosberg,[1] A.M. Avram,[2] C.M. Aparici,[3] M.M. Wahba[4]

[1]Department of Gastrointestinal Oncology, Moffitt Cancer Center, Tampa, FL, USA; [2]University of Michigan Medical Center, Ann Arbor, MI, USA; [3]Department of Radiology, Stanford University, CA, USA; [4]Corresponding Author: ITM Isotopen Technologien Muenchen AG, Munich, Germany, Email: Mona.Wahba@itm.ag; Study sponsored by: ITM Solucin GmbH, Lichtenbergstrasse 1, 85748 Garching near Munich, Germany

Background

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are relatively rare and complex neoplasms. Their incidence and prevalence are continuously rising[1]. Current standard treatment options for metastasized GEP-NETs include somatostatin (SST) analogs (due to NETs strongly expressing SST receptors) and targeted drugs such as the mTOR inhibitor everolimus and the tyrosine kinase inhibitor sunitinib. While these treatments rarely induce objective tumor remission, disease stabilization may be achieved for a limited time, for instance, median progression free survival (mPFS) with everolimus in prospective phase III trials is 11 months[2]. Some patients may also benefit from systemic chemotherapy.

Peptide Receptor Radionuclide Therapy (PRRT) uses IV-infused radiolabeled ligands to deliver cytotoxic dose of radiation to tumor cells while sparing the surrounding tissue. This therapy is emerging as a promising option, providing more durable response and potentially higher objective response rates than currently approved therapies. PRRT with ^{177}Lu-DOTATATE has increased PFS and achieved higher response rates than high dose octreotide in patients with advanced SSTR$^+$ midgut NETs[3]. These results call for additional prospective, randomized and controlled study of other PRRTs in SSTR$^+$ NETs of the midgut and other locations.

Lutetium (^{177}Lu) edotreotide (^{177}Lu-DOTATOC), tested in the COMPETE trial, is an innovative octreotide-derived somatostatin analog containing the chelator DOTA radiolabeled with the medical radioisotope lutetium (^{177}Lu). Its favorable safety profile and promising efficacy have been demonstrated in a phase II study in 56 patients[4]. Lutetium (^{177}Lu) edotreotide PRRT in metastasized GEP-NETs achieved a median PFS of 34.5 months in patients who received ≥2 treatment cycles (Figures 1 and 2). The COMPETE trial is the first to undertake a direct comparison of PRRT vs. an approved therapeutic.

Figure 1: Kaplan-Meier estimates of PFS in the study population depending on number of lutetium (^{177}Lu) edotreotide PRRT cycles (Baum et al, 2016)

Figure 2: Kaplan-Meier estimates of OS in the study population depending on number of lutetium (^{177}Lu) edotreotide PRRT cycles (Baum et al, 2016)

Method

Trial design

COMPETE is a prospective, randomized, controlled, open-label, multi-center, phase III clinical trial to evaluate the efficacy and safety of lutetium (^{177}Lu) edotreotide PRRT compared to targeted molecular therapy with everolimus in patients with inoperable, progressive, somatostatin receptor-positive (SSTR$^+$) GEP-NETs. The study is ongoing and currently recruiting patients in at least 14 countries[5].

300 patients with progressive Grade 1 and Grade 2 GEP-NETs are being randomized: 200 patients receive up to 4 cycles of lutetium (^{177}Lu) edotreotide PRRT (7.5 GBq/cycle) every 3 months or until diagnosis of progression; 100 patients receive 10 mg everolimus until EOS or diagnosis of progression.
Study duration per patient is 30 months (Figure 3).

Treatment Schedule

* unless diagnosis of progression or EOS
** until diagnosis of progression or EOS
*** or until diagnosis of progression, whichever is earlier

Figure 3: Summary schedule of treatments and follow-up consultation

Study Objectives

Primary Objective

Progression-free survival (PFS). Diagnosis of progression will be established based on morphological imaging (MRI and/or CT) according to RECIST 1.1.

Key Secondary Objectives

Objective response rates (ORR) as best outcome; overall survival (OS); duration of disease control (DDC); safety and tolerability; health-related quality of life (HRQL); dosimetry; pharmacokinetics.

Main Inclusion Criteria

- Written informed consent
- Male or female ≥18 years of age
- Histologically and clinically confirmed diagnosis of well-differentiated NET of non-functional gastrointestinal origin (GI-NET) or both functional or non-functional pancreatic origin (P-NET), tumor grade G1 or G2 (Ki-67 ≤20%), unresectable or metastatic
- Measurable disease per RECIST 1.1, on CT/MRI scans, defined as at least 1 lesion with ≥1 cm in longest diameter and ≥2 radiological tumor lesions in total
- SSTR$^+$ disease, as evidenced by SSTR imaging within 4 months prior to randomization
- Radiological disease progression, defined as progressive disease per RECIST 1.1 criteria, evidenced by CT/MRI with ≥90 days interval during 12 months prior to randomization

Mode of Action

Lock and Key Principle

Targeted radiopharmaceuticals contain a targeting molecule and a medical radioisotope. The targeting molecule binds to the tumor specific receptor according to the lock and key principle (Figure 4). In most cases, the targeting molecule can be used for both diagnostics and therapy, only the radioisotope needs to be changed. This enables the application of theranostics in precision oncology.

Figure 4: Lock and key principle of PRRT with targeting molecule and medical radioisotope

Conclusion

COMPETE is the first pivotal study to compare PRRT with an approved therapeutic in patients with Grade 1 and Grade 2 GEP-NETs. It is expected that COMPETE will increase treatment options, including first-line therapy. Further studies with lutetium (^{177}Lu) edotreotide in patients with NETs and high unmet medical needs are under review.

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[2]Yao JC et al., Lancet 2016
[3]Strosberg et al., NEJM 2017
[4]Baum et al., Theranostics 2016
[5]Phase III Trial COMPETE

Access via QR code or find more trial information on www.compete-clinical-trial.com

Access via QR code or find more trial information on ClinicalTrials.gov NCT03049189: https://bit.ly/3uccXds

Poster #CT254 Presented at the AACR Annual Meeting 2021 (virtual meeting), April 10–15, May 17–21

NEC:
Can we really not do better?

NET grade 3 and NEC

Digestive high-grade NEN are rare with limited data on epidemiology, treatment benefit and overall survival (OS). Sorbye et al. presented the **Nordic NEC 2 study** with new data through a prospectively collected cohort. 861 cases were prospectively included between 2013 and 2017. MINEN were excluded. Centralized pathological re-evaluation was performed in 495/698 cases. All cases with Ki-67 <60% were re-evaluated. 698 high-grade digestive NEN cases were classified as 134 NET grade 3 (19%) and 564 NEC. 511 NEC and 128 NET had advanced disease. NET grade 3 with pancreatic primary in 46%. Median Ki-67 was 31% for NET grade 3 and 90% for NEC. 84% of NET grade 3 and 12% of NEC had Ki-67<55%. Palliative chemotherapy was given to 427 NEC (83% platinum+etoposide) and 115 NET grade 3 patients (39% platinum+etoposide, 57% temozolomide-based). Response rate was 34% for NEC and 28% for NET grade 3, progression at first evaluation seen in 38% of NEC and 21% of NET grade 3. Toxicity led to treatment discontinuation in 13% of NET grade 3 and 9% of NEC. PFS was 9.8 months for NET grade 3 and 6.1 months for NEC (p<0.001). Second-line chemotherapy was given to 68% of NET grade 3 and 51% of NEC. 27% developed bone metastases, 10% of NEC brain metastases. OS after first-line chemotherapy was 21.8 months for NET grade 3 and 7.4 months for NEC (p<0.001). OS for NET grade 3 was 23.7 months if Ki-67 <55% and 8.0 months if >55% (p=0.001). OS for NEC was significantly longer if Ki-67 <55% (p=0.006). Three and 5-year OS was 32% and 10% for NET grade 3 vs. 5% and 2% for NEC.

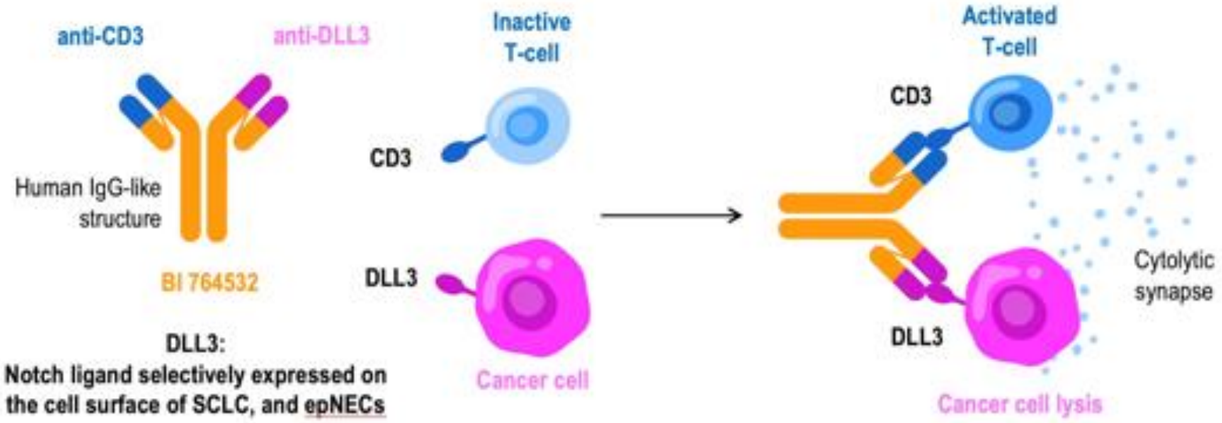
In conclusion, **in this large prospective cohort of advanced high-grade NEN patients, 1 in 3 patients had no benefit of first-line chemotherapy. Survival was <2 years for NET grade 3 and only 7.4 months for NEC.** These data are in line with the Belgian retrospective analysis from the DNET and NETwerk registry shown last year at the ENETS Conference by Islam et al. Better treatment options for this patient group are thus urgently awaited.

Sorbye H. et al. Nordic NEC 2: Characteristics and treatment outcome in a prospective cohort of 698 patients with high-grade digestive neuroendocrine neoplasms (NET G3 and NEC). Abstract presented at ENETS 2024 in Vienna.

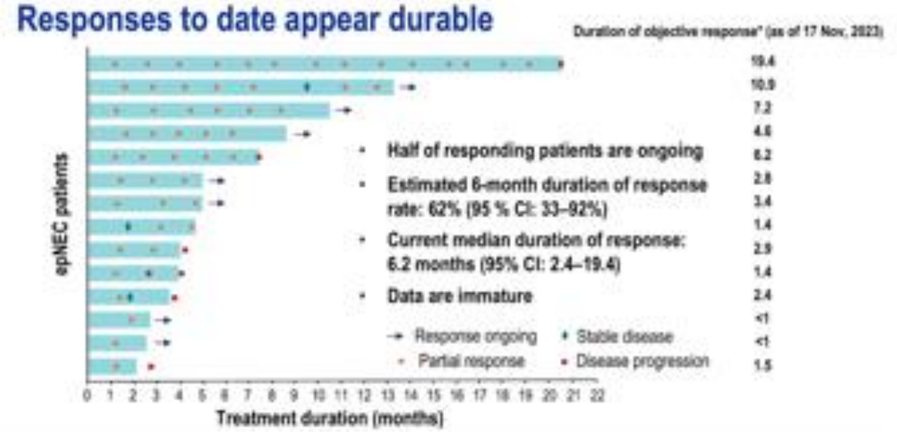
Islam O. et al. Characteristics and management of high-grade gastroenteropancreatic neuroendocrine neoplasms – A Belgian retrospective analysis from the DNET & NETwerk registry. Abstract presented at ENETS 2023 in Vienna.

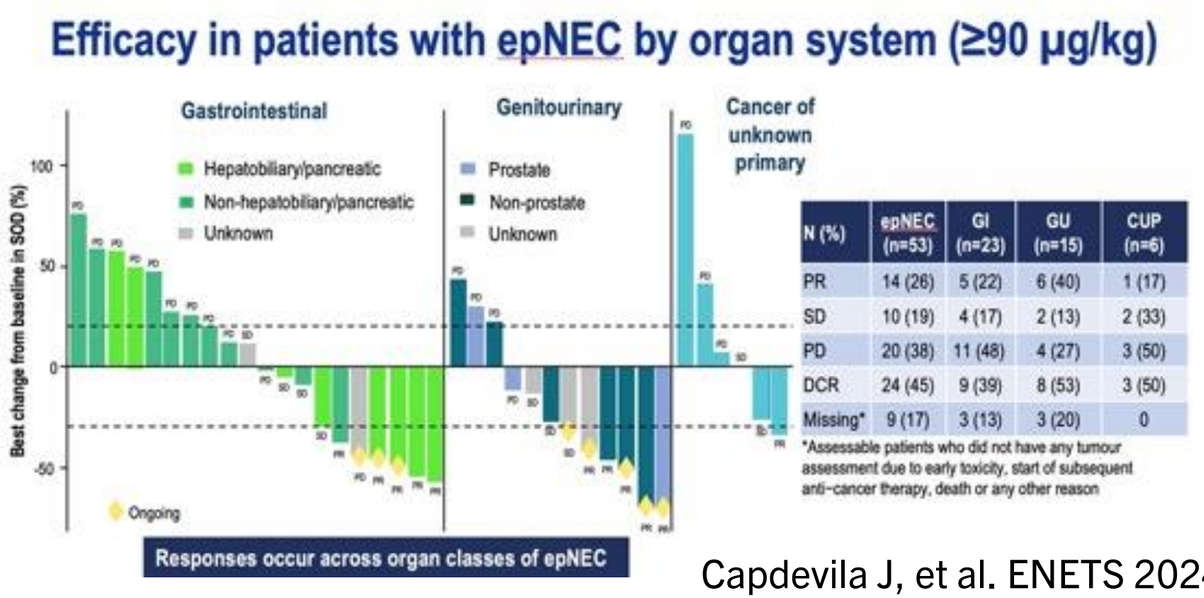
A classic car that was embellished: from rovalpituzumab tesirine to the bispecific antibodies against DLL3

Precision immunotherapy in NEN: delta-like canonical Notch ligand 3 (DLL3) therapy for NEN



- BI 764532 redirects the patient's own T-cells to lyse DLL3-expressing cancer cells
- Potent preclinical activity against DLL3-positive cells and xenograft models[1]





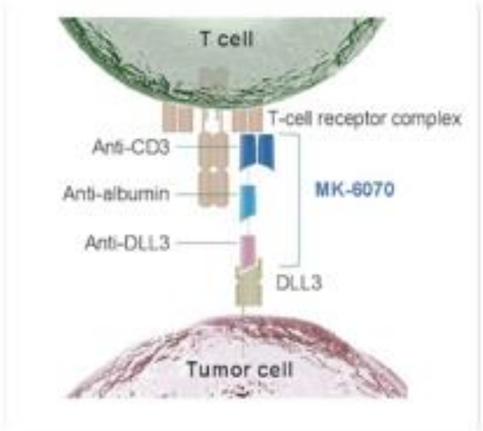
N (%)	epNEC (n=53)	GI (n=23)	GU (n=15)	CUP (n=6)
PR	14 (26)	5 (22)	6 (40)	1 (17)
SD	10 (19)	4 (17)	2 (13)	2 (33)
PD	20 (38)	11 (48)	4 (27)	3 (50)
DCR	24 (45)	9 (39)	8 (53)	3 (50)
Missing*	9 (17)	3 (13)	3 (20)	0

*Assessable patients who did not have any tumour assessment due to early toxicity, start of subsequent anti-cancer therapy, death or any other reason

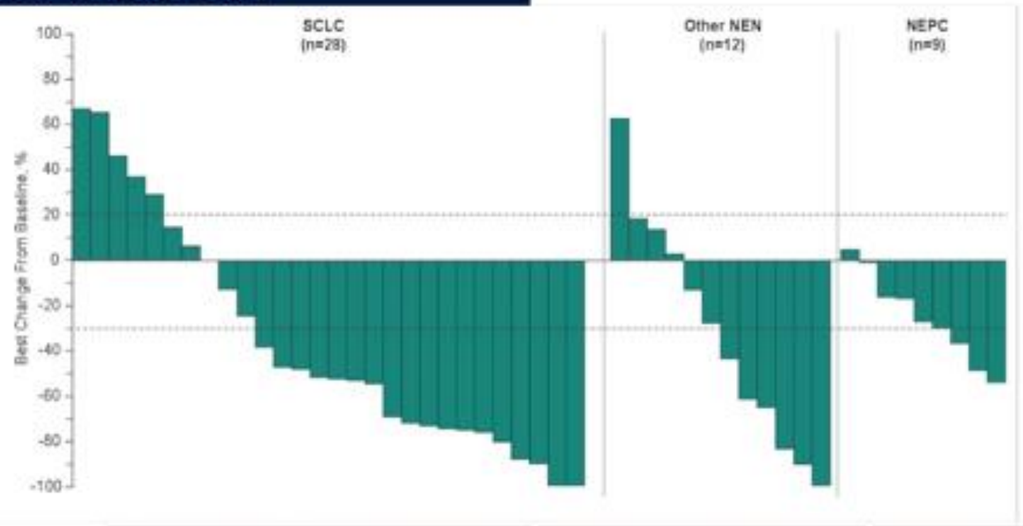
Capdevila J, et al. ENETS 2024

Precision immunotherapy in NEN: delta-like canonical Notch ligand 3 (DLL3) therapy for NEN

Updated Results From a Phase 1/2 Study of MK-6070 (HPN328), a Tri-Specific, Half-Life Extended DLL3-Targeting T-Cell Engager in Patients With Small Cell Lung Cancer and Other Neuroendocrine Cancers



Albumin: half-life extension



	SCLC n=28	Other NEN[a] n=13
RECIST v1.1		
ORR	11 (39%)	6 (46%)
DCR	20 (71%)	6 (46%)
Extracranial response per RECIST v1.1[b]		
ORR	14 (50%)	6 (46%)
DCR	21 (75%)	6 (46%)

Jaume Capdevila, MD, PhD

Beltran H, et al. ASCO 2024

Tarlatamab hits in later-line SCLC: update 08/2024

Clinical Trial Updates

Sustained Clinical Benefit and Intracranial Activity of Tarlatamab in Previously Treated Small Cell Lung Cancer: DeLLphi-300 Trial Update

Afshin Dowlati, MD[1]; Horst-Dieter Hummel, MD[2]; Stephane Champiat, MD, PhD[3]; Maria Eugenia Olmedo, MD, PhD[4]; Michael Boyer, MB, BS, PhD[5,6]; Kai He, MD, PhD[7]; Neeltje Steeghs, MD, PhD[8]; Hiroki Izumi, MD, PhD[9]; Melissa L. Johnson, MD[10]; Tatsuya Yoshida, MD, PhD[11]; Hasna Bouchaab, MD[12]; Hossein Borghaei, DO[13]; Enriqueta Felip, MD, PhD[14]; Philipp J. Jost, MD[15]; Shirish Gadgeel, MD[16]; Xi Chen, MD, PhD[17]; Youfei Yu, PhD[17]; Pablo Martinez, MD, PhD[17]; Amanda Parkes, MD[17]; and Luis Paz-Ares, MD, PhD[18]

DOI https://doi.org/10.1200/JCO.24.00553

ABSTRACT

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

Tarlatamab, a bispecific T-cell engager immunotherapy targeting delta-like ligand 3, has shown durable anticancer activity and manageable safety in previously treated small cell lung cancer (SCLC) in DeLLphi-300 phase I and DeLLphi-301 phase II trials. Here, we report extended follow-up of DeLLphi-300 (median follow-up, 12.1 months [range, 0.2-34.3]) in fully enrolled cohorts treated with tarlatamab ≥10 mg dose administered once every two weeks, once every three weeks, or once on day 1 and once on day 8 of a 21-day cycle (N = 152). Overall, the objective response rate (ORR) was 25.0%; the median duration of response (mDOR) was 11.2 months (95% CI, 6.6 to 22.3), and the median overall survival (mOS) was 17.5 months (95% CI, 11.4 to not estimable [NE]). Among 17 patients receiving 10 mg tarlatamab once every two weeks, the ORR was 35.3%, the mDOR was 14.9 months (95% CI, 3.0 to NE), the mOS was 20.3 months (95% CI, 5.1 to NE), and 29.4% had sustained disease control with time on treatment ≥52 weeks. No new safety signals were identified. In modified Response Assessment in Neuro-Oncology Brain Metastases analyses, CNS tumor shrinkage of ≥30% was observed in 62.5% of patients (10 of 16) who had a baseline CNS lesion of ≥10 mm, including in a subset of patients with tumor shrinkage long after previous brain radiotherapy. In DeLLphi-300 extended follow-up, tarlatamab demonstrated unprecedented survival and potential findings of intracranial activity in previously treated SCLC.

ACCOMPANYING CONTENT

Data Supplement

Protocol

Accepted July 22, 2024
Published August 29, 2024

J Clin Oncol 00:1-8


Warming-up

#M02

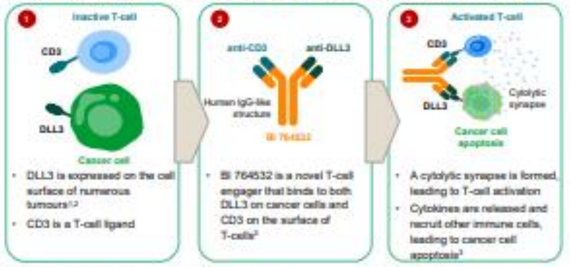
DAREON™-7: A Phase I, open-label, dose escalation and expansion cohort trial of the delta-like ligand (DLL3)-targeting T-cell engager BI 764532, plus first-line platinum-based chemotherapy in patients with DLL3-positive neuroendocrine carcinomas

Jaume Capdevila[1*], Timon Vandamme[2], Patricia Niccoli[3], Saori Mishima[4], Ken Kato[5], Yiyuan Ma[6], Ping Sun[7], Lijiang Geng[8], Ulrich M. Lauer[9]

[1]Department of Medical Oncology, Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [2]Center for Oncological Research (CORE), Integrated Personalized and Precision Oncology Network (IPPON), University of Antwerp and Department of Oncology, Antwerp University Hospital, Antwerp, Belgium; [3]Institut Paoli-Calmettes, Department of Oncology, Marseille, France; [4]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [5]Department of Head and Neck, Esophageal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; [6]Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; [7]Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA; [8]Boehringer Ingelheim (China) Investment Co., Ltd., Shanghai, China; [9]Department of Medical Oncology & Pneumology, University Hospital Tübingen, Tübingen, Germany

Introduction

Mechanism of action of BI 764532, a novel DLL3-targeting T-cell engager



- DLL3 is expressed on the cell surface of numerous tumours[1,2]
- CD3 is a T-cell ligand
- BI 764532 is a novel T-cell engager that binds to both DLL3 on cancer cells and CD3 on the surface of T-cells[3]
- A cytolytic synapse is formed, leading to T-cell activation
- Cytokines are released and recruit other immune cells, leading to cancer cell apoptosis[3]

DLL3 is highly expressed in NECs

- A large proportion of LCNEC and epNEC tumours express DLL3

~75% of LCNEC of the lung[4]

19–77% of GI epNECs depending on site of primary tumour[4]

68–81% of GU epNECs[5]

A prior Phase I study indicates that BI 764532 is effective as monotherapy in patients with pretreated NEC (NCT04429087)

- A Phase I, dose escalation and expansion study with BI 764532 is ongoing in patients with SCLC, epNEC, or LCNEC (n=107)[6,7,8]
- Promising efficacy has been seen in patients with epNEC and LCNEC of the lung. Dose optimisation is ongoing[7,8]

Rationale for DAREON™-7: to assess BI 764532 in a front-line setting combined with SoC chemotherapy

- Currently, there are limited treatment options for patients with LCNEC of the lung or epNEC, and better first-line treatment options are an unmet need
- DLL3 constitutes an attractive target, particularly in light of the BI 764532 efficacy data in NECs reported to date

CD3, cluster of differentiation 3; DLL3, delta-like ligand 3; DCR, disease control rate; epNEC, extrapulmonary NEC; GI, gastrointestinal; GU, genitourinary; IgG, immunoglobulin G; LCNEC, large cell NEC; NEC, neuroendocrine carcinoma; PR, partial response; SCLC, small cell lung cancer; SoC, standard of care
[1]ranges from 18.60% in pancreas to 77% in gastroenteropancreatic tumours

Trial design

- DAREON™-7 is a Phase I, non-randomised, open-label, multicentre dose escalation (Part A) and expansion (Part B) trial of first-line BI 764532 + SoC chemotherapy (carboplatin or cisplatin + etoposide) in patients with DLL3-positive LCNEC of the lung, epNEC, or NEC with unknown primary site (**NCT06132113**)
- In Part A, successive cohorts will receive increasing doses of BI 764532 + SoC chemotherapy until the MTD is reached, or upon decision of the Dose Escalation Committee. In Part B, two expansion cohorts will receive BI 764532 at the RDE/RP2D + SoC chemotherapy

MTD, maximum tolerated dose; RDE, recommended dose for expansion; RP2D, recommended Phase II dose

- BI 764532 will be administered IV with step-in doses followed by the target doses
- In Part A, SoC chemotherapy will be carboplatin + etoposide
- In Part B, SoC chemotherapy will be carboplatin or cisplatin + etoposide
- Dose escalation for BI 764532 will be guided by a Bayesian Logistic Regression Model with overdose control
- The trial will be conducted in approximately 20 sites across multiple countries

IV, intravenously

Objectives

Part A: Dose escalation	Part B: Dose expansion
• **Primary:** Determine the MTD and/or RDE/RP2D of BI 764532 • **Secondary:** Evaluate the BI 764532 dose-tolerability relationship	• **Primary:** Confirm safety and tolerability of BI 764532 at the RDE/RP2D + SoC chemotherapy regimens • **Secondary:** Assess the efficacy of BI 764532 + SoC chemotherapy regimens

Inclusion and exclusion criteria

Inclusion	Exclusion
Locally advanced or metastatic NEC of the following subtypes: • epNEC • LCNEC of the lung • NEC with unknown primary site	Previous treatment with T-cell engagers or cell therapies targeting DLL3
Patients who are eligible for platinum + etoposide as first-line SoC treatment	Diagnosis of Merkel cell carcinoma, medullary thyroid carcinoma or grade 3 neuroendocrine tumour, or presence of leptomeningeal carcinomatosis
At least one evaluable lesion as has been defined per RECIST 1.1	Diagnosis of immunodeficiency or systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of BI 764532
Tumour positive for DLL3 expression by IHC (central pathology review)	History of/active non-infectious pneumonitis or interstitial lung disease of any grade
Adequate liver, bone marrow and renal organ function	Significant cardiovascular or cerebrovascular diseases

IHC, immunohistochemistry; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1

Endpoints

Part A: Dose escalation	Part B: Dose expansion
• **Primary:** Occurrence of DLTs within the MTD evaluation period • **Secondary:** Occurrence of DLTs and AEs during the on-treatment period	• **Primary:** Occurrence of DLTs during the on-treatment period • **Secondary:** Objective response, defined as best overall response of CR or PR, according to RECIST v1.1; duration of response

AEs, adverse events; CR, complete response; DLTs, dose limiting toxicity

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This study is industry-sponsored. The authors were fully responsible for all content and editorial decisions, were involved at all stages of poster development and have approved the final version. The authors did not receive payment related to the development of the poster. Medical writing support for the development of this poster, under the direction of the authors, was provided by Lynn Pritchard DPhil, of Ashfield MedComms, an Inizio Company, and was industry-sponsored

Presented at the European Neuroendocrine Tumor Society (ENETS) Congress, Vienna, Austria, 13–15 March 2024

*Corresponding author email address: jcapdevila@vhio.net

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Scan this QR code or visit the URL to access the infographic summary

FDA Grants Orphan Drug Designation for ABD-147 for Neuroendocrine Carcinoma

September 5, 2024

By Ashley Gallagher, Associate Editor

News *Article*

Previously, the FDA granted fast track designation to ABD-147 (Abdera Therapeutics Inc) for extensive stage small cell lung cancer.

The FDA granted orphan drug designation to ABD-147 (Abdera Therapeutics, Inc) for the treatment of neuroendocrine carcinoma. The investigational drug is a next-generation precision radiopharmaceutical biologic that delivers Actinium-225 to solid tumors that express DLL3.

Conclusions NEN talk today 🧙‍♂️

- PRRT is advancing more and more earlier in the treatment algorithm of NET, new nuclear targets are also being added and targeted alpha-particle therapy is also showing promising results… To be continued soon! 😍
- PRRT is everywhere, but clinical factors on the Multidisciplinary Tumor Board also play an important role in the right treatment choice for the patient at the right time: doctors have to think together with the patient in their presence!
- After SSA and PRRT, there is now a whole new landscape of possibilities with not always a lot of data: cabozantinib is knocking on the door evidence-based with the beautiful CABINET study 👏 👏
- All eyes are now on DLL3-targeted therapies in NEC; immunotherapy has not turned out to be a golden treasure for NEN, future for CAR T-cell therapy? 👊
- Clinically useful biomarkers are still a major absentee in the NEN field: looking forward to thorough research projects such as FORCE, BE-FORCE, ctDNA, gut microbiome, …
- Clinical trials are very important to our patients, so INCLUDE!

Thank you for being invited to speak here as an oncologist in the territory of the nuclear lion ☺