Inside the Issue: Optimizing the Diagnosis and Treatment of Neuroendocrine Tumors

A CME/MOC-Accredited Live Webinar

Thursday, August 29, 2024
5:00 PM – 6:00 PM ET

Faculty

Pamela Kunz, MD
Simron Singh, MD, MPH

Moderator

Neil Love, MD

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Faculty

Pamela Kunz, MD
Associate Professor of Medicine/Oncology
Division Chief, GI Oncology
Director, Center for GI Cancers
Yale School of Medicine and Yale Cancer Center
New Haven, Connecticut

Simron Singh, MD, MPH
Professor, University of Toronto
Susan Leslie Clinic for Neuroendocrine Tumours
Odette Cancer Centre
Sunnybrook Health Sciences Centre
Toronto, Ontario, Canada

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

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Survey Participants

Daniel M Halperin, MD
Consulting Medical Oncologist
Atlanta, Georgia

Heloisa P Soares, MD, PhD
Medical Director, Clinical Trials Office
Leader, University of Utah NET Destination Care Program
Associate Professor, Division of Oncology
Huntsman Cancer Institute, University of Utah
Salt Lake City, Utah

Daneng Li, MD
Associate Professor
Department of Medical Oncology and Therapeutics Research
City of Hope Comprehensive Cancer Center
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Jonathan Strosberg, MD
Professor, Dept of GI Oncology
Moffitt Cancer Center
Tampa, Florida

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Dr Love — Disclosures

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Dr Kunz — Disclosures
Faculty

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Contracted Research	Novartis, RayzeBio
Speaker	Bristol Myers Squibb, Foundation Medicine

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Dr Singh — Disclosures
Faculty

Advisory Committees	Ipsen Biopharmaceuticals Inc, Novartis

Dr Halperin — Disclosures
Survey Participant

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Contracted Research	Camurus, ITM Isotope Technologies Munich SE, Novartis, RayzeBio
Data and Safety Monitoring Board/Committee	RadioMedix Inc

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Dr Li — Disclosures
Survey Participant

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Speakers Bureau	Ipsen Biopharmaceuticals Inc

Dr Soares — Disclosures
Survey Participant

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Contracted Research	Bristol Myers Squibb, ITM Isotope Technologies Munich SE, Novartis

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Dr Strosberg — Disclosures
Survey Participant

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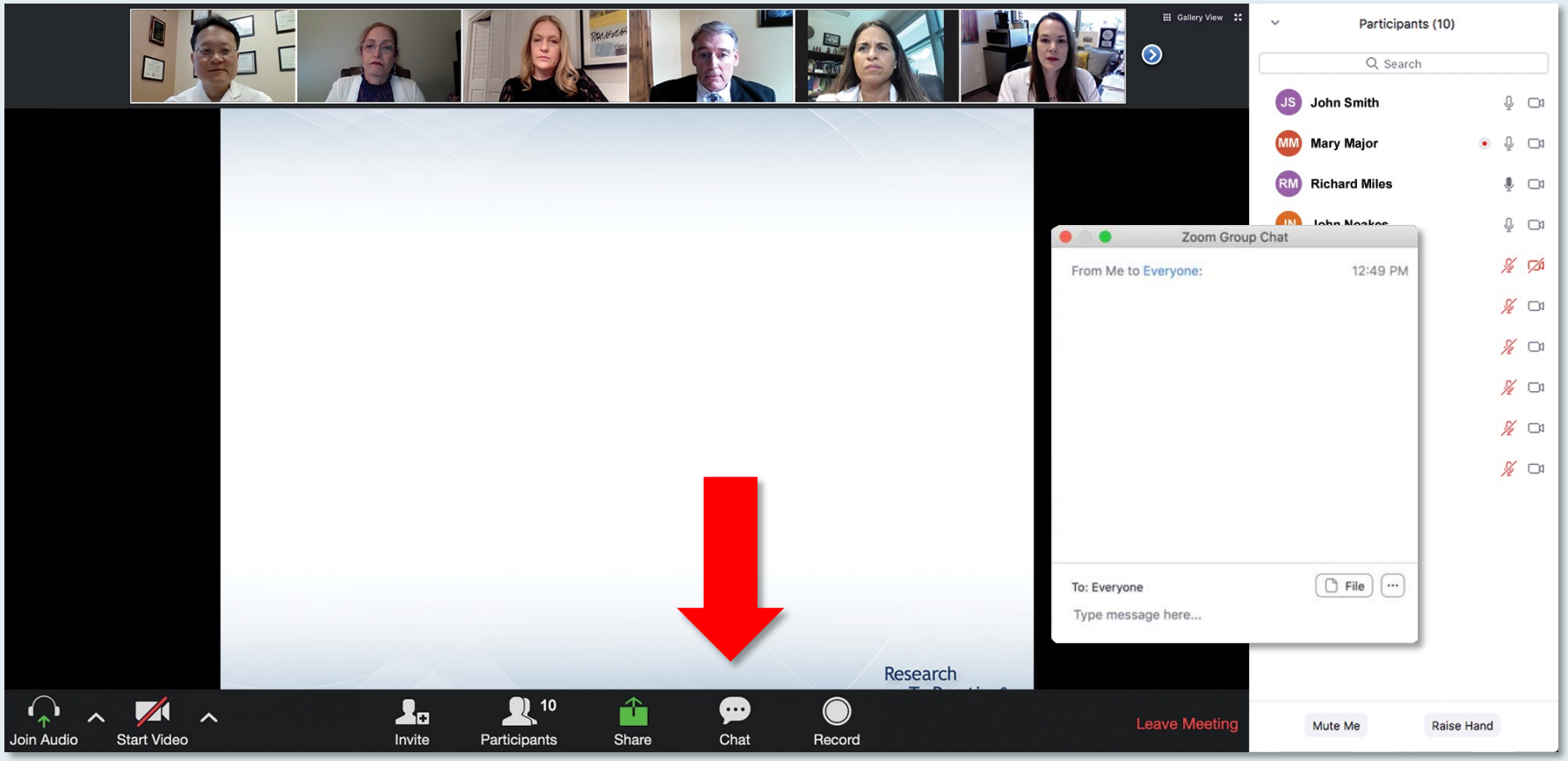

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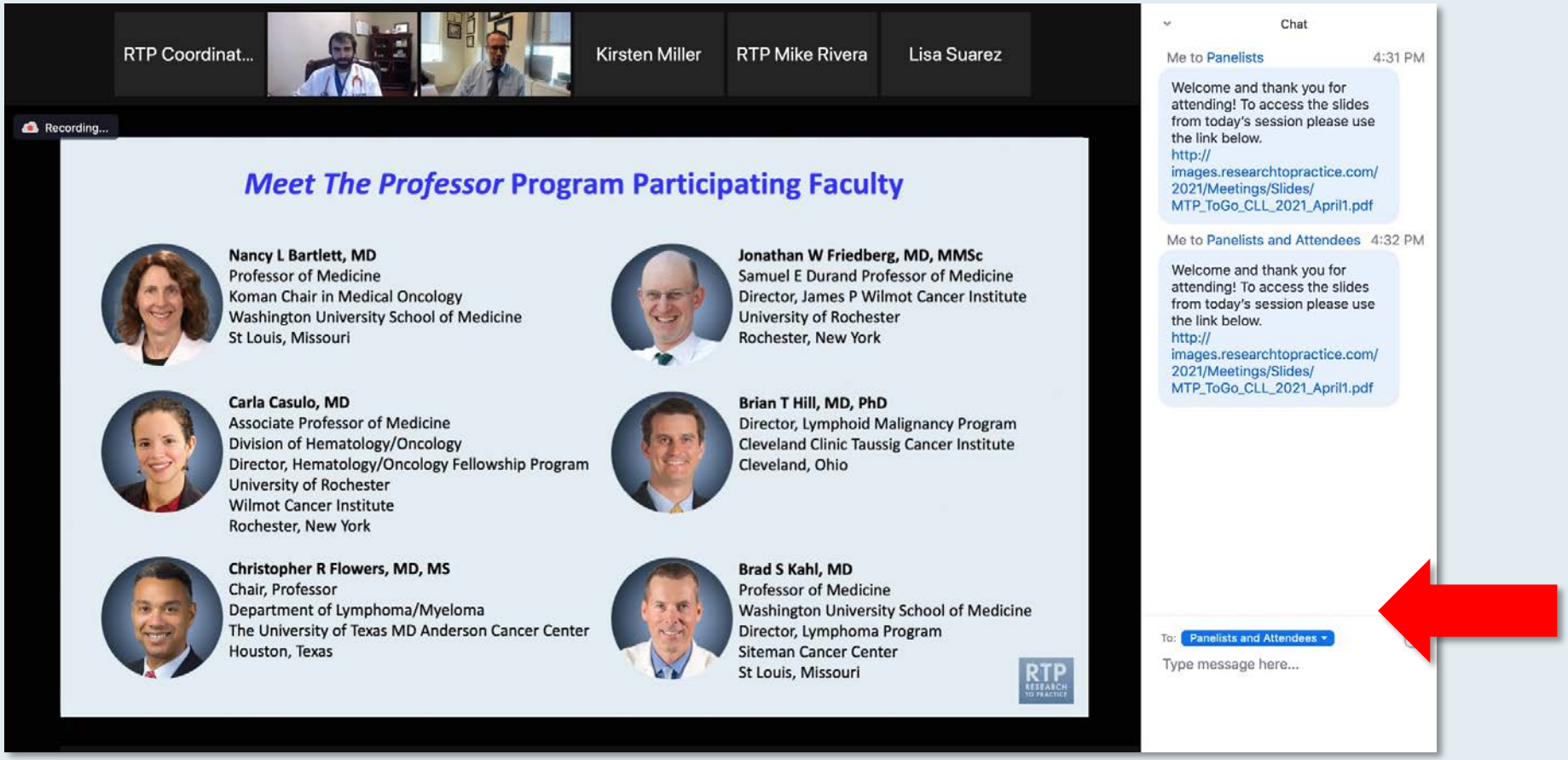

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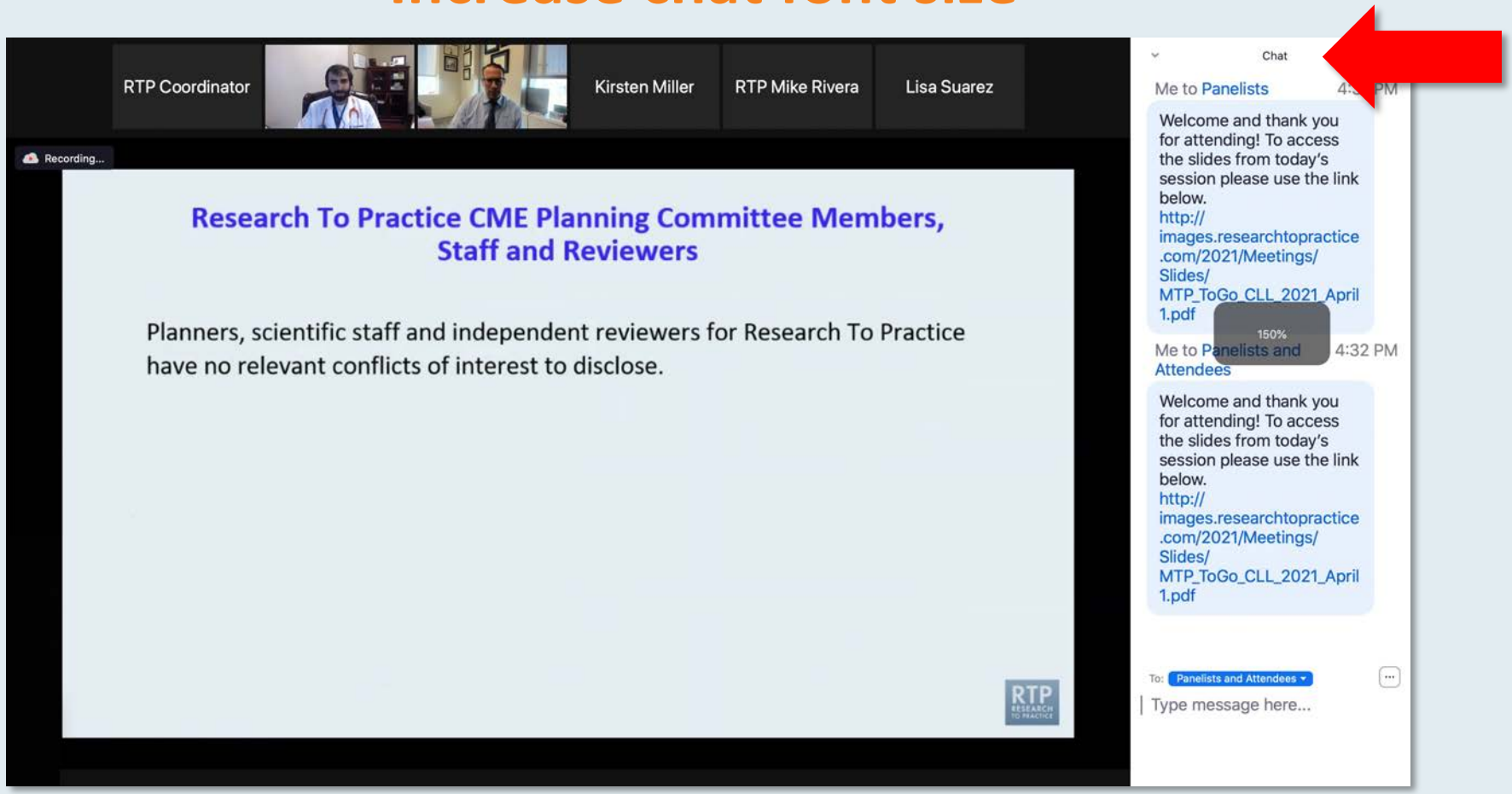

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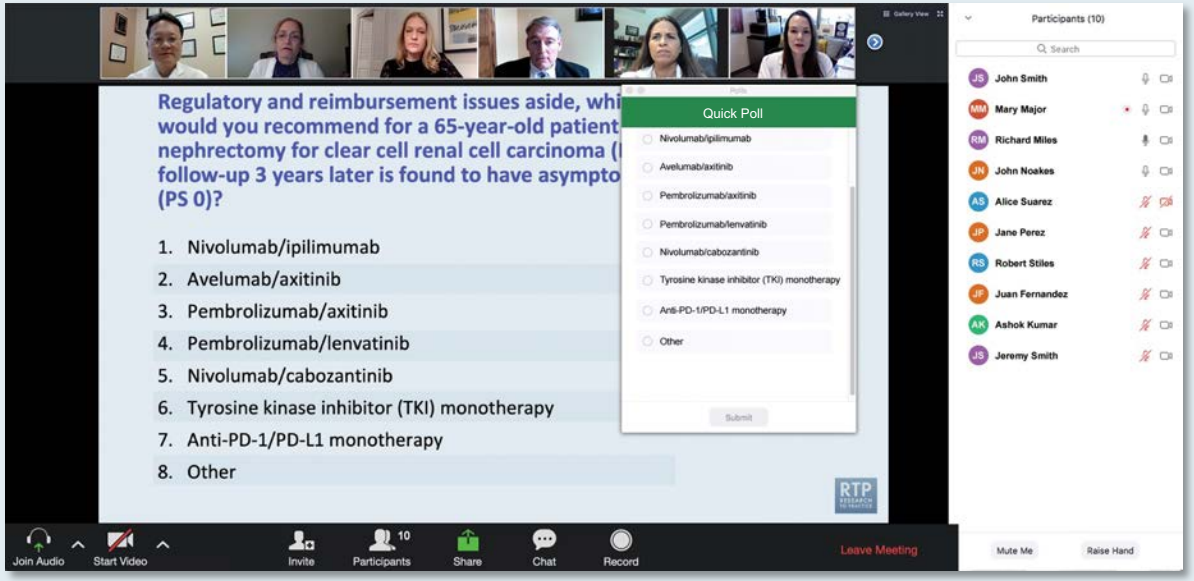

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Neuroendocrine Tumors

DR PAMELA KUNZ
YALE CANCER CENTER

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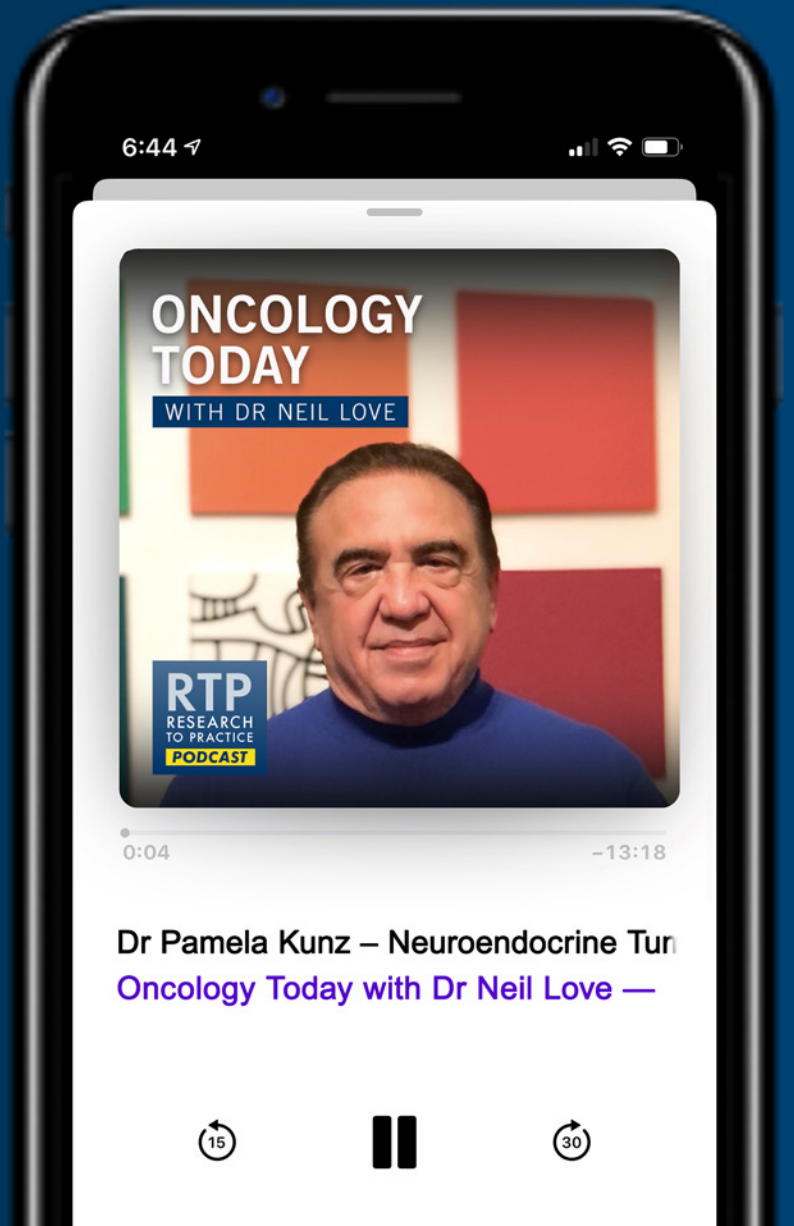

Data + Perspectives: Clinical Investigators Discuss the Role of CAR T-Cell Therapy for Patients with Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia

Part 1 of a 2-Part CME Satellite Symposium Series During the Society of Hematologic Oncology 2024 Annual Meeting

Wednesday, September 4, 2024
11:46 AM – 12:46 PM CT

Faculty

Joshua Brody, MD
Jason Westin, MD, MS

Moderator

Matthew Lunning, DO

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Laurie H Sehn, MD, MPH

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Christopher R Flowers, MD, MS

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Ibiayi Dagogo-Jack, MD

Additional faculty to be announced.

Moderator

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Meet The Professor: Optimizing the Management of Chronic Lymphocytic Leukemia

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Matthew S Davids, MD, MMSc

Moderator

Neil Love, MD

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What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Hematologic Cancers

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Faculty

Professor Andreas Hochhaus

B Douglas Smith, MD

Moderator

Michael J Mauro, MD

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Faculty

Farrukh T Awan

Bita Fakhri, MD, MPH

Kerry A Rogers, MD

William G Wierda, MD, PhD

Moderator

Jeff Sharman, MD

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What Clinicians Want to Know: Addressing Current Questions and Controversies in the Use of CAR T-Cell Therapy and Bispecific Antibodies in the Management of Lymphoma

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Friday, December 6, 2024

11:30 AM – 1:30 PM PT (2:30 PM – 4:30 PM ET)

Faculty

Jennifer Crombie, MD

Martin Hutchings, MD, PhD

Matthew Lunning, DO

Tycel Phillips, MD

Moderator

Jeremy S Abramson, MD, MMSc

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What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Myelofibrosis

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Faculty

Prithviraj Bose, MD

Angela G Fleischman, MD, PhD

Abdulraheem Yacoub, MD

Moderator

Andrew T Kuykendall, MD

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What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Acute Myeloid Leukemia

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Friday, December 6, 2024

3:15 PM – 5:15 PM PT (6:15 PM – 8:15 PM ET)

Faculty

Alexander Perl, MD

Richard M Stone, MD

Eunice S Wang, MD

Andrew H Wei, MBBS, PhD

Moderator

Eytan M Stein, MD

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What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Multiple Myeloma

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Faculty

Professor Philippe Moreau, MD
Robert Z Orlowski, MD, PhD
Noopur Raje, MD
Paul G Richardson, MD

Moderator

Sagar Lonial, MD

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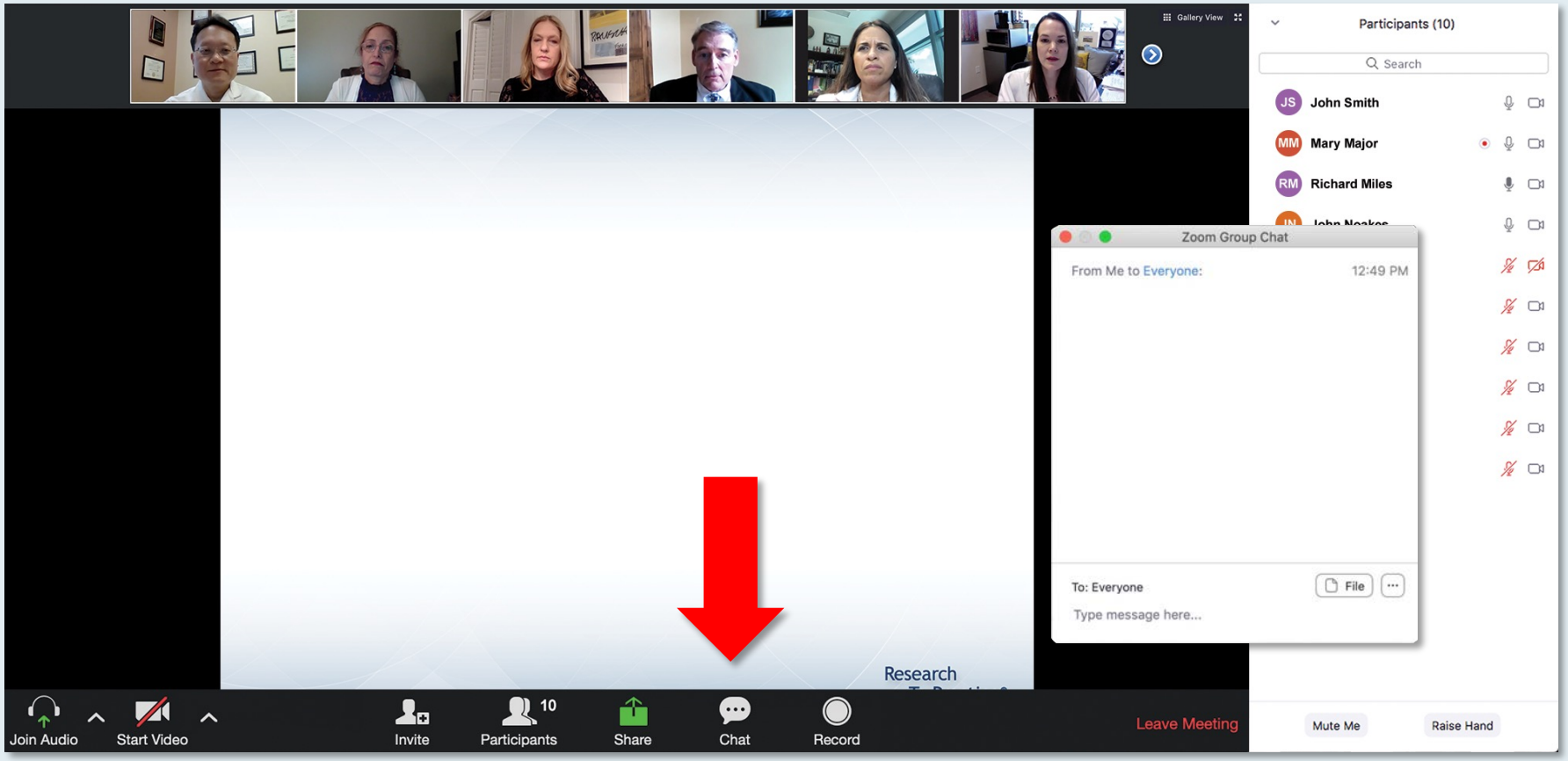

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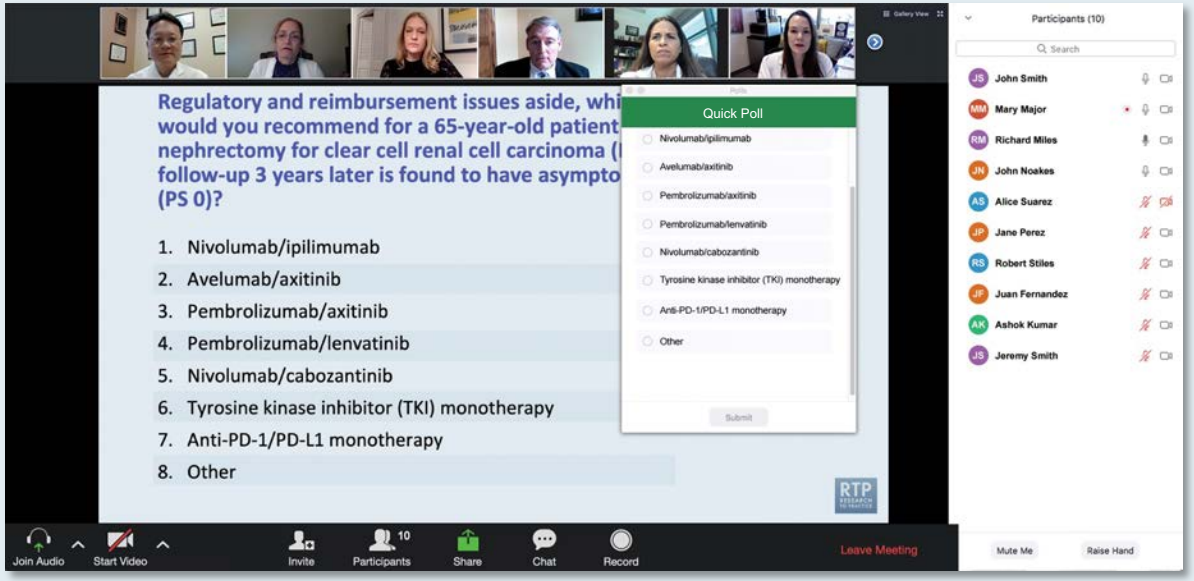

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Neuroendocrine Tumors

DR PAMELA KUNZ
YALE CANCER CENTER

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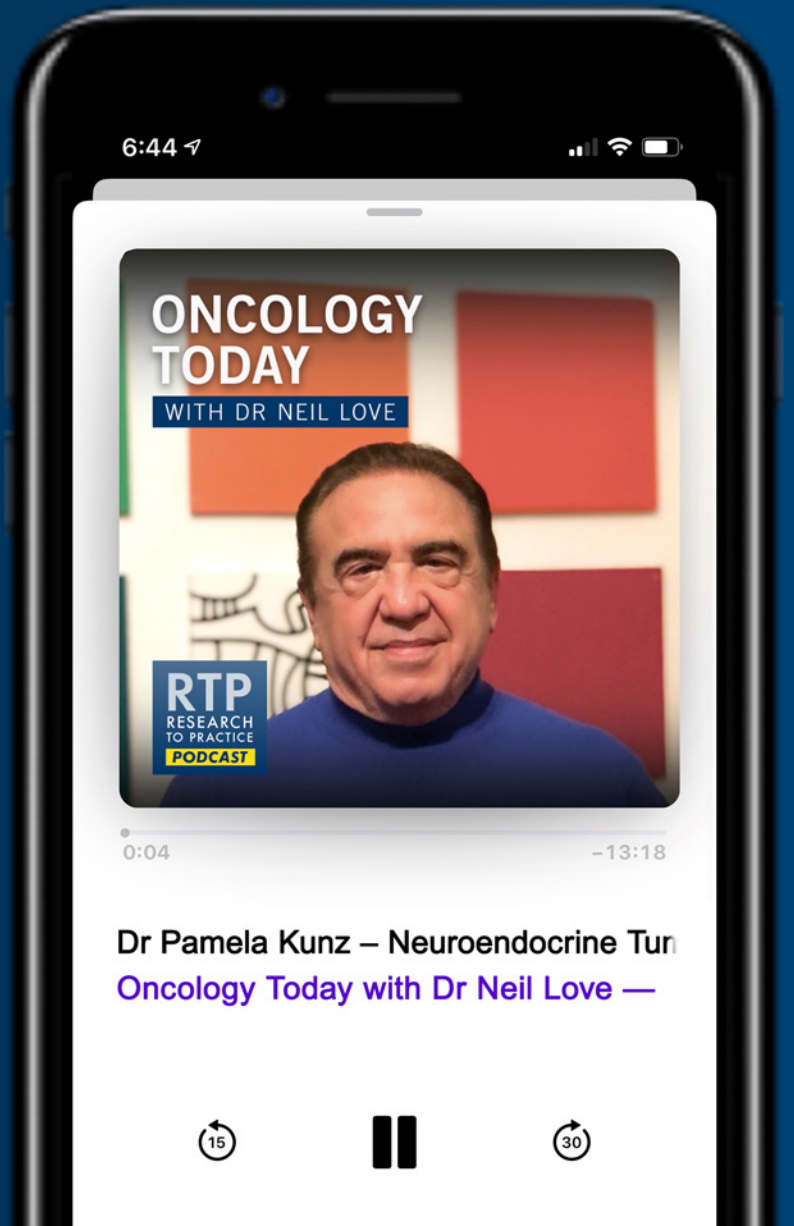

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Dr Kunz — Disclosures
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First Line Therapy of Neuroendocrine Cancers (NETs)

Research To Practice Seminar
Aug, 2024

Simron Singh, MD. MPH. FRCPC.

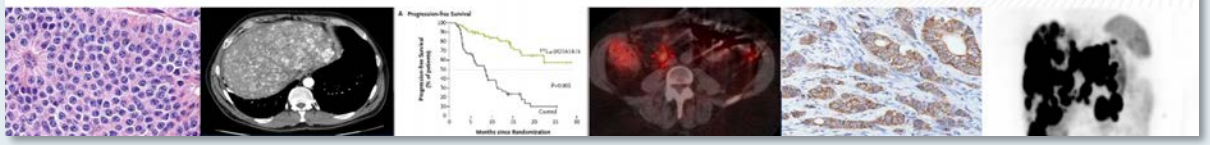
Professor of Medicine, University of Toronto
Susan Leslie Clinic for Neuroendocrine Tumours, Sunnybrook Odette Cancer Center
Provincial Lead, Cancer Care Ontario, Person Centered Care

The Susan Leslie Clinic for Neuroendocrine Tumours

Later-Line Treatment for Advanced NETs

Pamela L. Kunz, MD
Associate Professor of Medicine / Oncology
Director, Center for Gastrointestinal Cancers
Chief, Division GI Medical Oncology
Yale School of Medicine, Yale Cancer Center

Research To Practice ~ August 2024



Agenda

Module 1: Overview

Module 2: Peptide Receptor Radionuclide Therapy for Neuroendocrine Tumors (NETs)

Module 3: Multitarget Tyrosine Kinase Inhibitors for the Treatment of NETs

Module 4: Other New Advances in the Management of NETs

Striving for Consensus: Optimizing the Current and Future Management of Biliary Tract Cancers — A Clinical Investigator Think Tank

Friday, August 23, 2024

12:00 PM – 3:00 PM ET

Faculty

Lipika Goyal, MD, Mphil

James J Harding, MD

Milind Javle, MD

Robin (Katie) Kelley, MD

Moderator

Neil Love, MD

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Common Questions for Neuroendocrine Tumors

Initial Evaluation

Should patients with a diagnosis of a NET be evaluated by a center of excellence for NETs, either in person or through virtual communication?

What are common clinical presentations of metastatic NET? What is the current chance of 5-year survival for patients presenting with metastatic disease?

What imaging modality/modalities do you use for initial staging?

How do differentiation and tumor grade factor into your treatment decisions?

Which patients with metastatic disease do you elect to observe instead of initiating therapy?

Common Questions for Neuroendocrine Tumors

Initial Treatment Selection

How do you decide whether to use local therapy (surgery) for a patient with metastatic disease?

What is the current role of adjuvant chemotherapy for patients who have undergone resection? What ongoing trials are evaluating this strategy?

Globally, how would you indirectly compare the major treatment modalities available for NETs in terms of efficacy (eg, response rates) and toxicities/risks?

Common Questions for Neuroendocrine Tumors

Somatostatin Analogs

What factors do you consider when selecting between the available somatostatin analogs (SSAs) for your patients? What information do you discuss with your patients regarding SSA therapy?

Are there any clinical situations in which you would recommend an SSA to an asymptomatic patient with low tumor burden somatostatin receptor (SSTR)-positive disease?

Are there notable differences between octreotide and lanreotide in terms of efficacy and tolerability profiles?

In a patient with clear-cut disease progression on an SSA, in what situations, if any do you continue the SSA or intensify the dose of the SSA?

How common is it to observe transformation of low-grade NETs to high-grade NETs?

Common Questions for Neuroendocrine Tumors

Somatostatin Analogs (Continued)

What imaging modality/modalities do you use for initial staging and to follow a patient's response to treatment?

What imaging modality do you use to look for recurrences in patients with a history of NET with completely resected disease? Will a regular CT scan with contrast suffice in these cases or is a PET dotatate scan necessary?

Do you encounter issues with insurance approval of PET dotatate scans?

Common Questions for Neuroendocrine Tumors

Genetic Testing

Do you routinely order genetic testing for all patients with NET or for only select patients?

What aspects of a patient's familial or medical history would suggest to you an inherited predisposition to NETs and prompt genetic testing?

What specific gene mutations do you look for? What is the significance of genetic alterations in Rb or TP53 for NETs?

What testing platform(s) do you use (germline-only blood test, broad-based NGS for germline and somatic gene mutations)?

Common Questions for Neuroendocrine Tumors

Tumor Markers

In patients with fully resected disease, do you check tumor markers at each follow-up visit, and if so, which ones?

What tumor markers do you use to follow a patient's response to treatment in the metastatic setting?

Are there any biomarkers you follow to assess the extent of a patient's disease?

Is there a role for minimal residual disease assessment or measuring levels of circulating tumor DNA?

Should patients with a diagnosis of a NET be evaluated by a center of excellence for NETs, either in person or through virtual communication?

 Dr Kunz	Yes, all patients
 Dr Singh	Yes, all patients
 Dr Halperin	Yes, all patients
 Dr Li	Yes, all patients
 Dr Soares	Yes, all patients
 Dr Strosberg	Yes, some patients, depending on comfort of local physician and circumstances

What clinical and biological factors do you consider when deciding to initiate systemic therapy for patients with gastroenteropancreatic NETs (GEP-NETs)?

 Dr Kunz	Primary site, grade, Ki-67, symptoms, pace of growth, SSTR status
 Dr Singh	Primary site, stage, differentiation, Ki-67, symptoms, tumor growth rate, disease bulk, functional vs not, performance status
 Dr Halperin	Disease volume, cadence of progression, pathological differentiation, primary site and tumor grade
 Dr Li	Grade, disease volume, labs, performance status
 Dr Soares	Grade, disease volume, Ki-67, symptoms
 Dr Strosberg	Tumor grade, SSTR expression, tumor burden, tumor aggressiveness

SSTR = somatostatin receptor

Are there any clinical situations in which you would recommend a somatostatin analog (SSA) to an asymptomatic patient with low tumor burden somatostatin receptor (SSTR)-positive disease?

 Dr Kunz	Yes, if patient prefers to start treatment
 Dr Singh	Yes, for GI NETs with Ki-67 <10%
 Dr Halperin	Yes, if patient prefers
 Dr Li	Yes, if functional tumor
 Dr Soares	Yes, if patient prefers
 Dr Strosberg	Yes, if patient prefers to start treatment

RTP RESEARCH TO PRACTICE

Based on your clinical experience and knowledge of available data, what do you estimate to be the proportion of patients receiving the SSAs below who experience the following treatment-related adverse events?

	Gallstones		Hypothyroidism	
	Octreotide	Lanreotide	Octreotide	Lanreotide
 Dr Kunz	~50%	~50%	~30%	~30%
 Dr Singh	10%	5%	Minimal	Minimal
 Dr Halperin	10%	15%	10%	10%
 Dr Li	15%	15%	1%	1%
 Dr Soares	70%	70%	5%	5%
 Dr Strosberg	15%	15%	<1% clinically significant	<1% clinically significant

Based on your clinical experience and knowledge of available data, what do you estimate to be the proportion of patients receiving the SSAs below who experience the following treatment-related adverse events?

	Hypoglycemia		Hyperglycemia	
	Octreotide	Lanreotide	Octreotide	Lanreotide
 Dr Kunz	<10%	<10%	~50%	~50%
 Dr Singh	Minimal	Minimal	10%	10%
 Dr Halperin	3%	3%	30%	30%
 Dr Li	10%	10%	30%	30%
 Dr Soares	5%	5%	50%	50%
 Dr Strosberg	<1% clinically significant	<1% clinically significant	5% clinically significant	5% clinically significant

GEPNETs: Treatment options beyond SSA

Small bowel NET

Systemic therapy options
- Everolimus
- ^{177}Lu-Dotatate [SSTR+]
- Cytotoxic chemotherapy

Locoregional therapy options
- Liver-directed therapy

Pancreatic NET

Systemic therapy options
- Everolimus
- Sunitinib
- Capecitabine/Temozolomide
- ^{177}Lu-Dotatate [SSTR+]

Locoregional therapy options
- Liver-directed therapy

Optimal sequence of therapies is unknown

Adapted from the NCCN Neuroendocrine Tumor Guidelines v 1.2023

GEPNETs: Treatment in 2024

Small bowel NET

Systemic therapy options

- Everolimus
- ^{177}Lu-Dotatate [SSTR+] 2nd line G1/G2
- ^{177}Lu-Dotatate [SSTR+] 1st line G2/G3*
- Cytotoxic chemotherapy
- Cabozantinib*

Locoregional therapy options

- Liver-directed therapy

Pancreatic NET

Systemic therapy options

- Everolimus
- Sunitinib
- Capecitabine/Temozolomide
- Other cytotoxic chemotherapy
- ^{177}Lu-Dotatate [SSTR+] 2nd line G1/G2
- ^{177}Lu-Dotatate [SSTR+] 1st line G2/G3*
- Cabozantinib*

Locoregional therapy options

- Liver-directed therapy

Optimal sequence of therapies is unknown

Adapted from the NCCN Neuroendocrine Tumor Guidelines v 1.2023; * = not yet FDA approved

Selecting treatment: A balancing act

- Patient characteristics
- Treatment Outcomes: Stabilization vs. Response
- Side Effects: Minimal vs. moderate

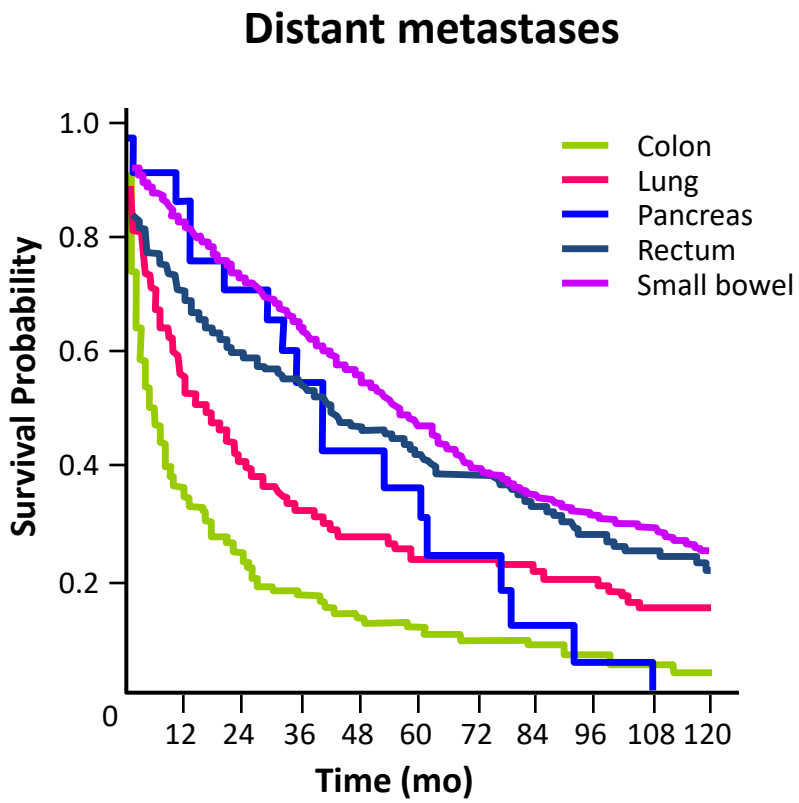
Peptide Receptor Radionuclide Therapy (PRRT)	Somatostatin Analogues	Targeted Therapies	Cytotoxic Chemotherapy
Moderate response	Stability	Stability	Best response
Well-tolerated	Well-tolerated	Moderate Side Effects	Moderate Side Effects

Courtesy of Pamela Kunz, MD

Correlation of Primary Tumour Site With Survival

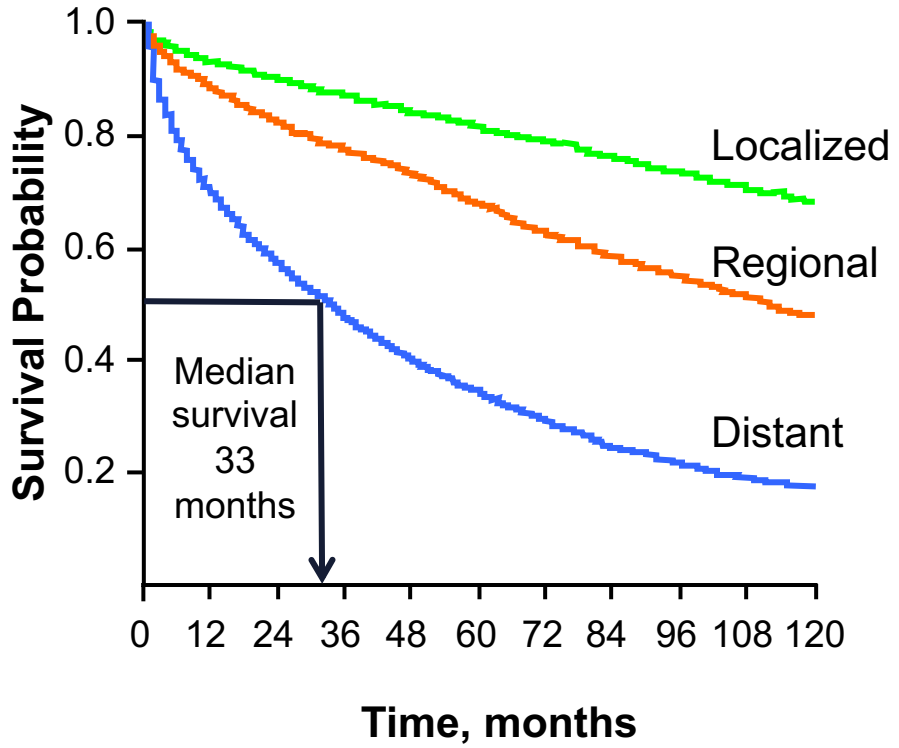
- Known prognostic factors include:
  - **Location of primary tumour**
  - Tumour stage
  - Extent of disease
  - Degree of differentiation/ Tumour grade
  - Patient age
  - Performance status

65% of patients with advanced NET will not be alive in 5 yr



Yao JC, Hassan M, Phan A, et al. *J Clin Oncol*. 2008;26:3063-3072.

33-Month Median Survival for Patients With Distant Metastatic NET



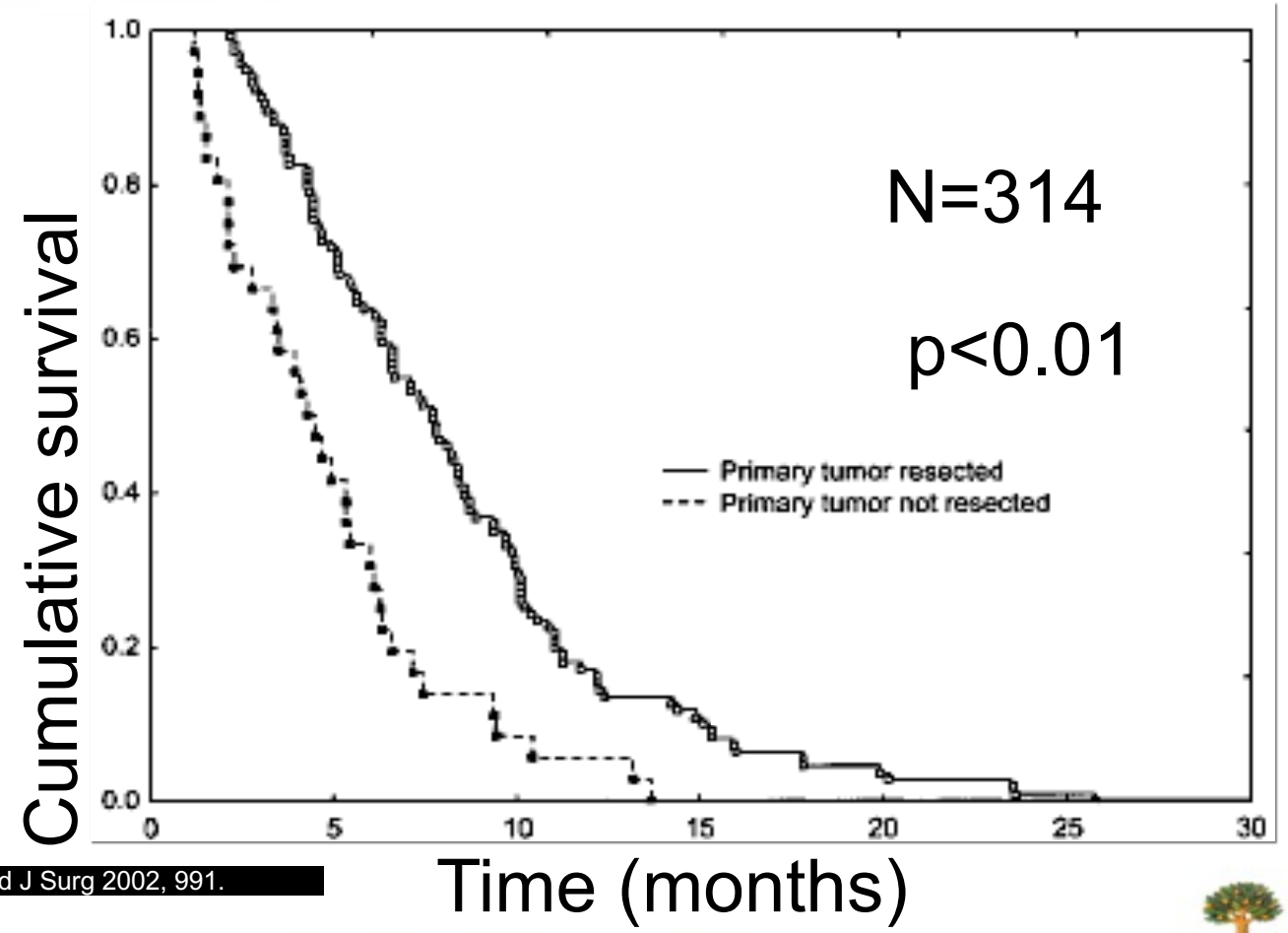
	Median Survival	
	Months	95% CI
Localized	223	208-238
Regional	111	104-118
Distant	33	31-35

CI, confidence interval.

Data from an analysis of 35,825 cases of NET identified in the SEER registries

Yao JC et al. *J Clin Oncol.* 2008;26:3063-3072.

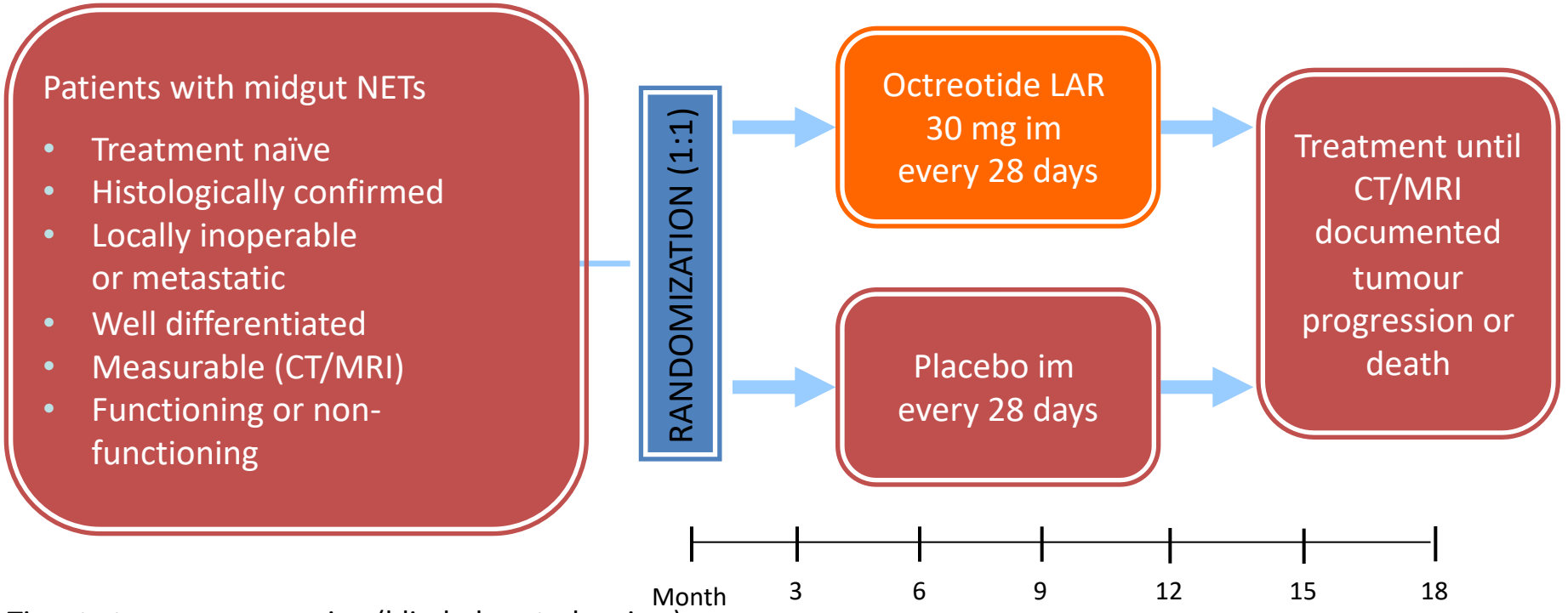
Removing the primary … helps – just do the right surgery!



Hellman P et al. World J Surg 2002, 991.

PROMID: Evaluation of the Antiproliferative Effect of Octreotide LAR

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



- Primary endpoint: Time to tumour progression (blinded central review)
- Secondary endpoints: objective response rate, survival, quality of life, safety

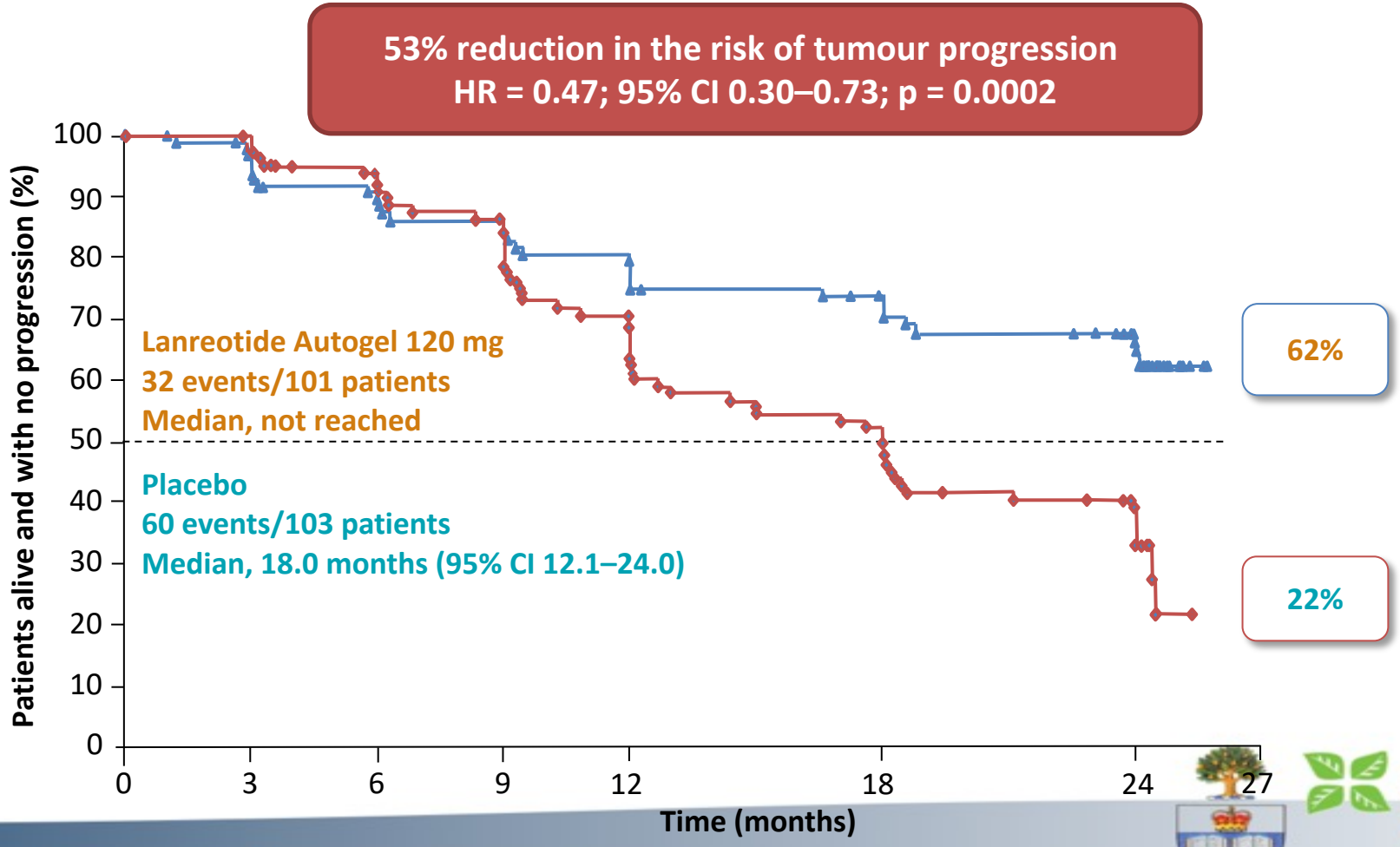
Rinke A *et al*. *J Clin Oncol* 2009;27:4656–4663

Courtesy of Simron Singh, MD, MPH

Tumour control in NET:

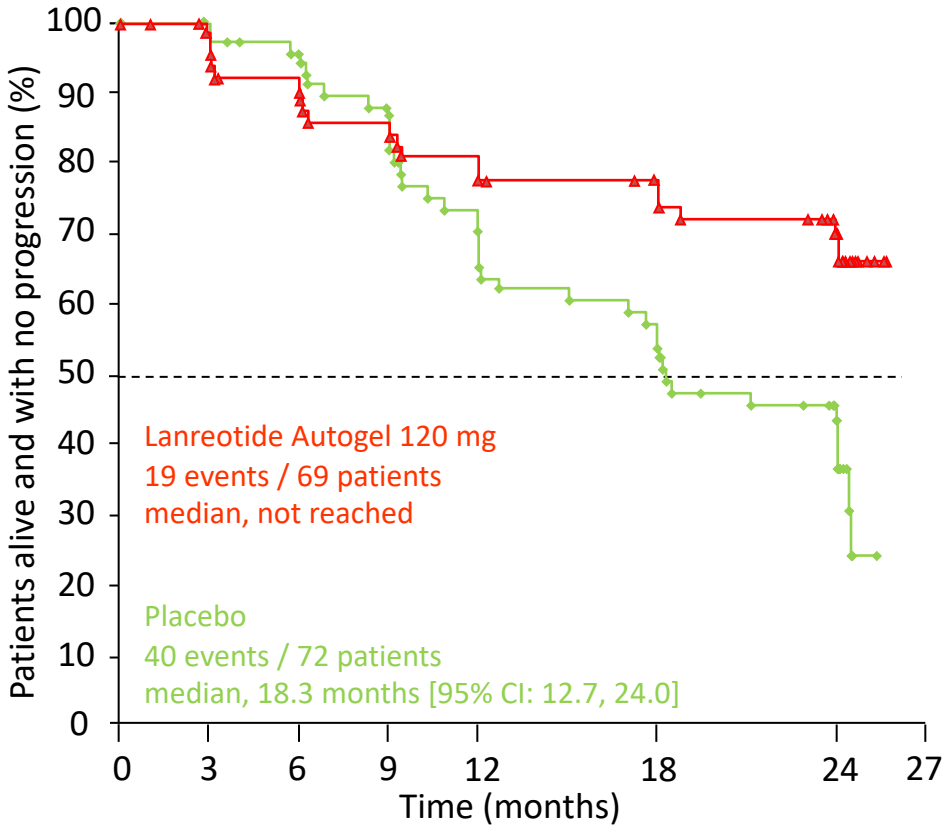
Lanreotide Autogel significantly prolongs PFS

CLARINET: well-/moderately differentiated non-functioning GEP NET

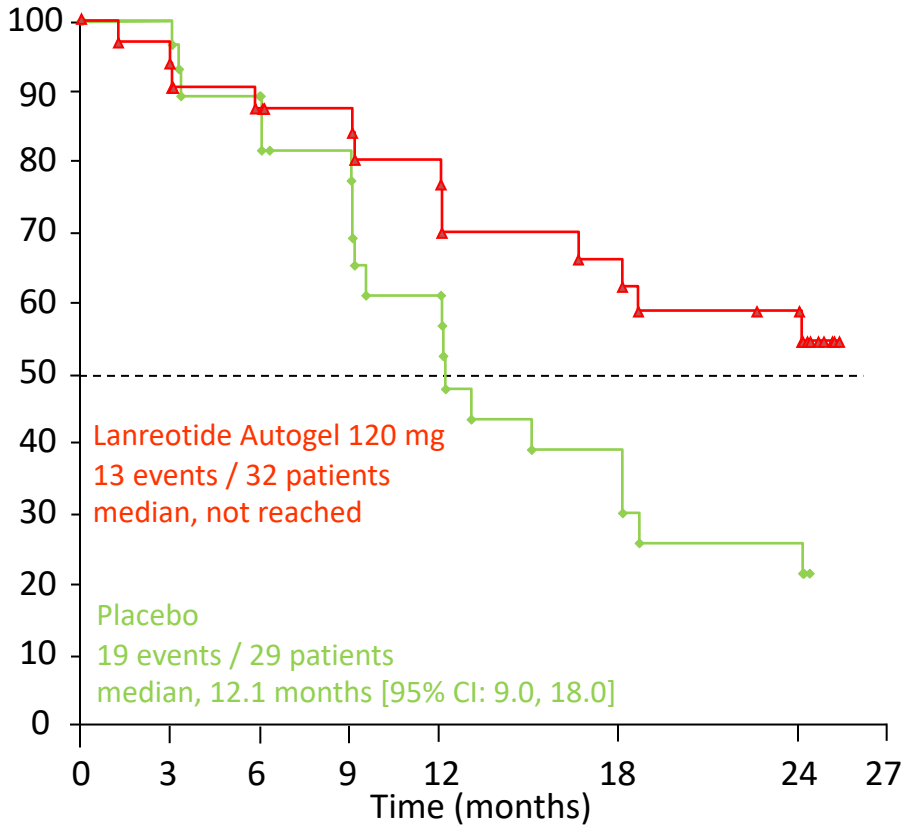


Caplin et al. NEJM 2014.

Lanreotide Subgroup Analysis (ITT): Effect of Tumour Grade



G1 tumours (n = 141)
Lanreotide Autogel vs placebo
p = 0.0016, HR = 0.43 (95% CI: 0.25, 0.74)



G2 tumours (n = 61)
Lanreotide Autogel vs placebo
p = 0.0235, HR = 0.45 (95% CI: 0.22, 0.91)

HR, hazard ratio; ITT, intention-to-treat. p value derived from log-rank test, HR derived from Cox proportional hazard model

Agenda

Module 1: Overview

Module 2: Peptide Receptor Radionuclide Therapy for Neuroendocrine Tumors (NETs)

Module 3: Multitarget Tyrosine Kinase Inhibitors for the Treatment of NETs

Module 4: Other New Advances in the Management of NETs

Common Questions for Neuroendocrine Tumors

Peptide Receptor Radionuclide Therapy

What is the difference between alpha-emitting and beta-emitting radionuclides?

How does the extent of SSTR positivity factor into your treatment decision-making?

How often do you see oligometastases and how do you manage them with local therapy?

What are common side effects that may be observed with lutetium Lu 177 dotatate? What strategies do you use to prevent or manage these effects?

Do the side effects differ when administered in combination with an SSA?

How commonly do you observe renal toxicity secondary to lutetium Lu 177 dotatate therapy? What is the role of amino acid infusions to address this side effect?

Common Questions for Neuroendocrine Tumors

Peptide Receptor Radionuclide Therapy (Continued)

Are there any radiation protection precautions that should be taken with lutetium Lu 177 dotatate therapy? Do these precautions pose any challenges?

What is the incidence of secondary malignancies such as myelodysplastic syndrome after lutetium Lu 177 dotatate? What is the lag time between treatment and the development of secondary cancers?

How often do you observe the development of neuroendocrine hormonal crisis with lutetium Lu 177 dotatate treatment? Are there any factors that predispose a patient to its development?

What other radioligand therapies are currently under clinical investigation?

A 60-year-old man with no past medical history presents to a local emergency department for kidney stones. Routine CT scan and MRI reveal a large pancreatic mass and numerous bulky liver metastases. ^{68}Ga-dotatate PET imaging shows strong SSTR uptake. Regulatory and reimbursement issues aside, which systemic treatment would you recommend if biopsy of the liver demonstrated a well differentiated …?

	Grade 1 NET	Grade 2 NET	Grade 3 NET
 Dr Kunz	Lutetium Lu 177 dotatate or Capecitabine/temozolomide	Lutetium Lu 177 dotatate or Capecitabine/temozolomide	Capecitabine/temozolomide or Other chemotherapy
 Dr Singh	SSA	SSA if low grade, chemotherapy if bulky or neoadjuvant or PRRT	Lutetium Lu 177 dotatate + octreotide
 Dr Halperin	Capecitabine/ temozolomide	Capecitabine/ temozolomide	Lutetium Lu 177 dotatate
 Dr Li	SSA	Lutetium Lu 177 dotatate + octreotide	Capecitabine/ temozolomide
 Dr Soares	Capecitabine/ temozolomide	Capecitabine/ temozolomide	Capecitabine/ temozolomide
 Dr Strosberg	SSA	SSA	Lutetium Lu 177 dotatate + octreotide

SSA: octreotide or lanreotide; PRRT = peptide receptor radionuclide therapy

To approximately how many patients with previously untreated GEP-NETs have you administered lutetium Lu 177 dotatate with or without an SSA on or off protocol?

 Dr Kunz	0
 Dr Singh	20
 Dr Halperin	5
 Dr Li	100
 Dr Soares	6
 Dr Strosberg	3

RTP RESEARCH TO PRACTICE

In the literature or your personal experience, what have you observed regarding the efficacy and tolerability of lutetium Lu 177 dotatate in combination with an SSA?

 Dr Kunz	Very well tolerated
 Dr Singh	No difference in personal experience
 Dr Halperin	Very effective and highly tolerable
 Dr Li	Good disease control and tolerability, less ORR than clinical trial results
 Dr Soares	Good, but unclear if better than SSA alone as there is no randomized trial
 Dr Strosberg	Addition of SSA does not impact toxicity, and unclear whether SSA contributes to efficacy in patients who already had disease progression on SSA

RTP RESEARCH TO PRACTICE

A 60-year-old woman with a well differentiated Grade 2 (Ki-67 3%) SSTR-positive pancreatic NET with low-volume liver metastases receives octreotide and maintains stable disease for 2 years. A recent follow-up CT scan reveals 5 new lesions in the liver that are subsequently deemed unresectable. Regulatory and reimbursement issues aside, which systemic therapy would you recommend for this patient?

 Dr Kunz	Lutetium Lu 177 dotatate or capecitabine/temozolomide
 Dr Singh	Capecitabine/temozolomide
 Dr Halperin	Everolimus
 Dr Li	Everolimus
 Dr Soares	Lutetium Lu 177 dotatate
 Dr Strosberg	Lutetium Lu 177 dotatate

RTP RESEARCH TO PRACTICE

Based on your clinical experience and knowledge of available data, what are the top 3 side effects patients experience when receiving lutetium Lu 177 dotatate?

 Dr Kunz	Fatigue, cytopenias, MDS (rare)
 Dr Singh	Fatigue, decreased blood counts, MDS
 Dr Halperin	Fatigue, lymphopenia, thrombocytopenia
 Dr Li	Fatigue, lymphopenia, hair thinning
 Dr Soares	Fatigue, cytopenias, mild kidney impairment
 Dr Strosberg	Fatigue, cytopenias, nausea

MDS = myelodysplastic syndromes

How concerned are you about the risk of secondary cancer such as myelodysplastic syndromes or acute leukemia for your patients receiving lutetium Lu 177 dotatate?

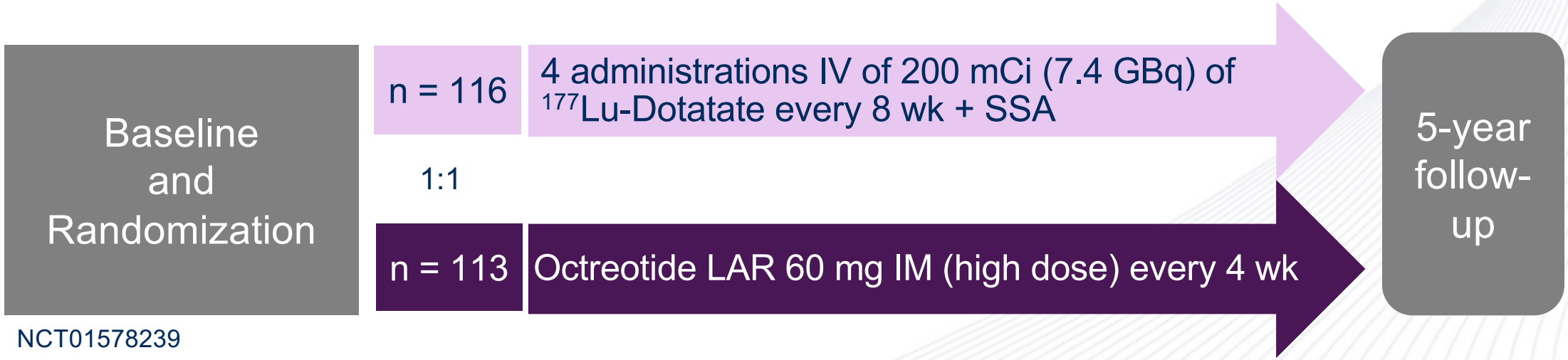
 Dr Kunz	Minimally concerned
 Dr Singh	Minimally concerned
 Dr Halperin	Moderately concerned
 Dr Li	Highly concerned
 Dr Soares	Moderately concerned
 Dr Strosberg	Moderately concerned

RTP
RESEARCH TO PRACTICE

Phase III ^{177}Lu-Dotatate (NETTER-1)

Aim	Evaluate efficacy and safety of ^{177}Lu-Dotatate + SSAs compared to octreotide LAR 60 mg in inoperable, somatostatin receptor-positive, midgut NET, progressive under octreotide LAR 30 mg
Design	International, multicenter, randomized, comparator-controlled, parallel group

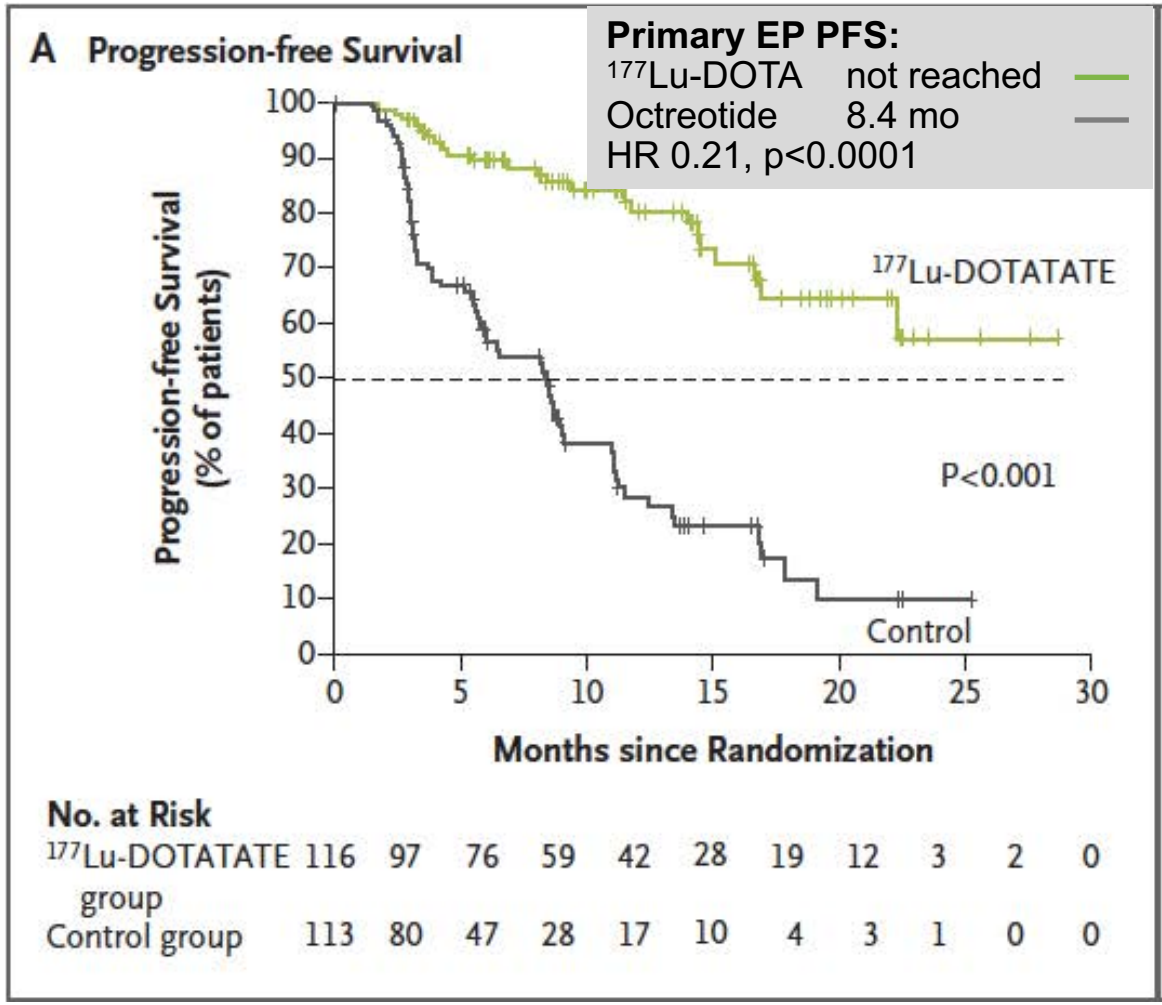
Treatment and Assessments: Progression-free survival (by RECIST) every 12 wk; Primary EP PFS

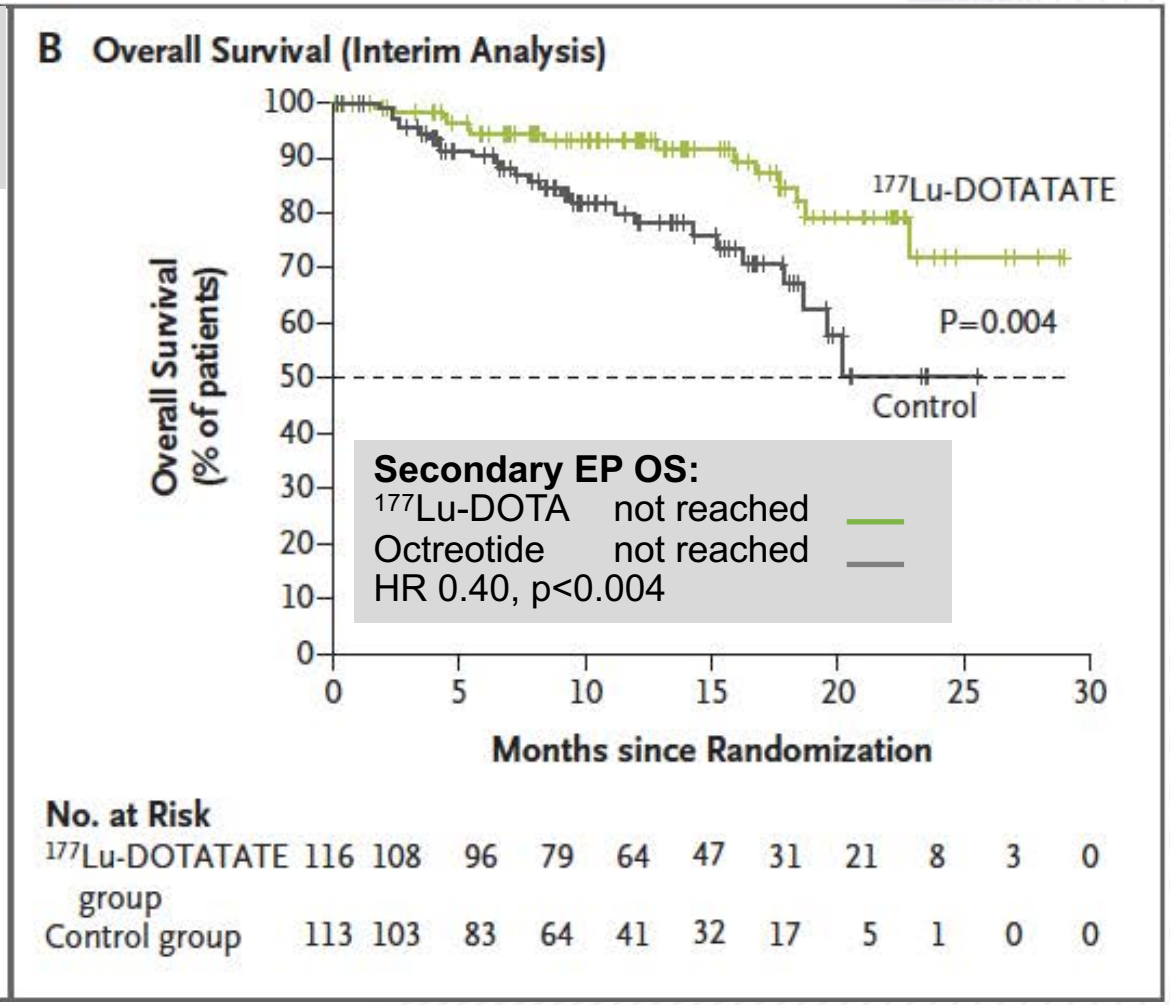


NCT01578239

Courtesy of Pamela Kunz, MD

NETTER-1: PFS and OS

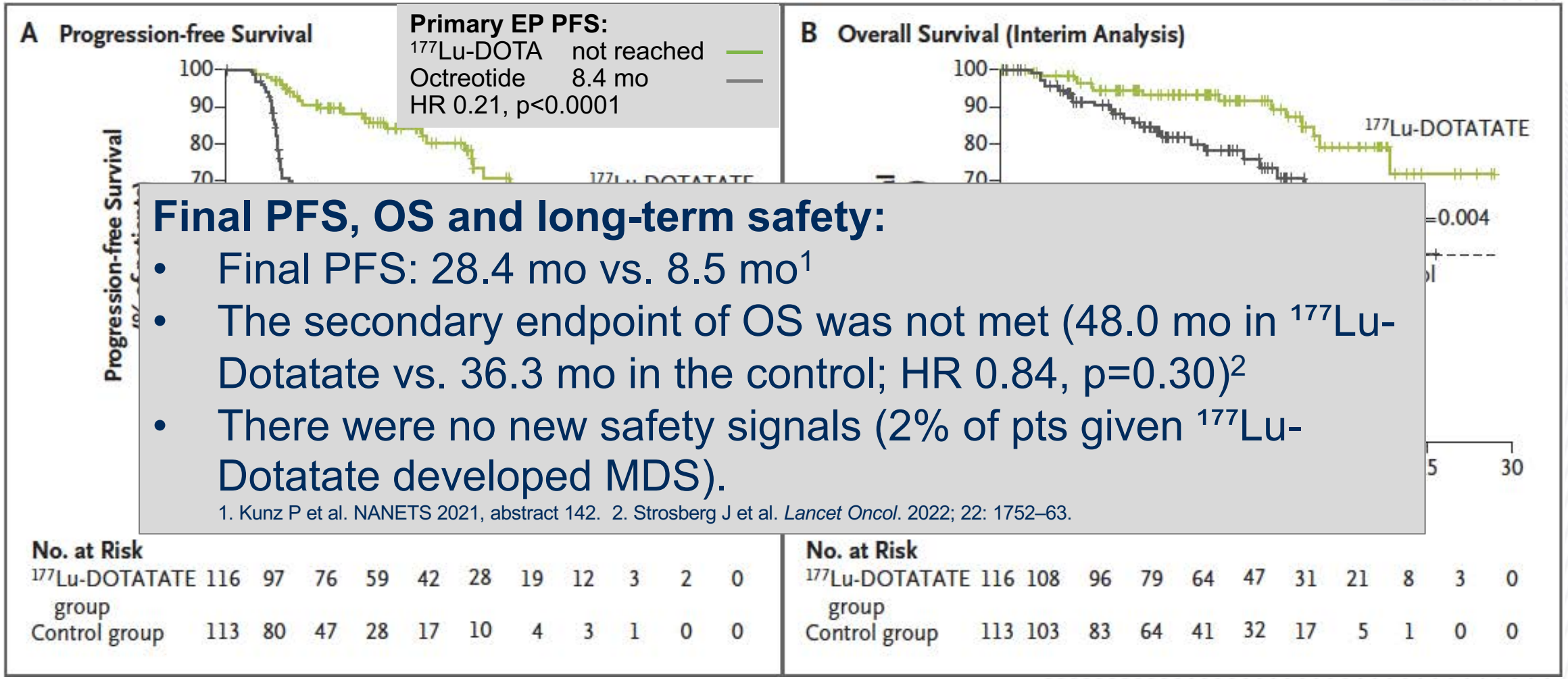




^{177}Lu-Dotatate FDA-Approved for GEP NETs (2018)

1. Strosberg J et al. *N Engl J Med.* 2017;376(2):125-135.

NETTER-1: PFS and OS



Final PFS, OS and long-term safety:

- Final PFS: 28.4 mo vs. 8.5 mo[1]
- The secondary endpoint of OS was not met (48.0 mo in ^{177}Lu-Dotatate vs. 36.3 mo in the control; HR 0.84, p=0.30)[2]
- There were no new safety signals (2% of pts given ^{177}Lu-Dotatate developed MDS).

1. Kunz P et al. NANETS 2021, abstract 142. 2. Strosberg J et al. *Lancet Oncol*. 2022; 22: 1752–63.

^{177}Lu-Dotatate FDA-Approved Jan 2018

Strosberg J et al. *N Engl J Med.* 2017;376(2):125-135.

Courtesy of Pamela Kunz, MD

NETTER-1: Response Rates

Table 2. Objective Tumor Response.*

Response Category	^{177}Lu-Dotatate Group (N = 101)	Control Group (N = 100)	P Value†
Complete response — no. (%)	1 (1)	0	
Partial response — no. (%)	17 (17)	3 (3)	
Objective response			
No. with response	18	3	
Rate — % (95% CI)	18 (10–25)	3 (0–6)	<0.001

Strosberg J et al. *N Engl J Med.* 2017;376(2):125-135.

Courtesy of Pamela Kunz, MD

NETTER-1: Adverse Events

Table 3. Overview of Adverse Events (Safety Population).*

Event	^{177}Lu-Dotatate Group (N=111)	Control Group (N=110)	P Value†
	number of patients (percent)		
Adverse event			
Any	106 (95)	95 (86)	0.02
Related to treatment	95 (86)	34 (31)	<0.001
Serious adverse event			
Any	29 (26)	26 (24)	0.76
Related to treatment	10 (9)	1 (1)	0.01
Withdrawal from trial because of adverse event			
Because of any adverse event	7 (6)	10 (9)	0.46
Because of adverse event related to treatment	5 (5)	0	0.06

Most common AEs: cytopenias, nausea, vomiting, fatigue (MDS 2%-3%)

Strosberg J et al. *N Engl J Med.* 2017;376(2):125-135.

Trials to Watch - RLT in GEPNET

Study	Design	Indication	Drugs	N
COMPETE NCT03049189	Randomized, Ph III (2:1)	Well-diff, G1/2 GEP NET, SSTR+, after SSA	**^{177}Lu-Edotreotide** vs. everolimus	300 Accrual complete
COMPOSE NCT04919226	Randomized, Ph III (2:1)	Well-diff, G2/3, met GEPNET, SSTR+, any line	**^{177}Lu-Edotreotide** vs. PI choice (everolimus, CapTem, FOLFOX)	202
A022001 NCT05247905 PIs: Hobday/Soares	Randomized Ph II (1:1)	Well-diff, G1-3, met pNET, 1st line for symptomatic G2/3, 2nd line+ for others	**^{177}Lu-Dotatate** vs. CapTem	198
ACTION-1 NCT05477576	Randomized Ph 1b/III (1:1)	Well-diff, G1/2, met GEPNET, SSTR+, PD after ^{177}Lu-Dota	**^{225}Ac-Dotatate** vs. investigator's choice	218
CCTG-NE1 NET RETREAT NCT05773274	Randomized Ph II (1:1)	Well-diff, G1/2, met midgut NET, SSTR+, PD after ^{177}Lu-Dota	**^{177}Lu-Dotatate x 2** vs. Everolimus	100

Courtesy of Pamela Kunz, MD

Courtesy of Simron Singh, MD, MPH

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[177Lu]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, MD • Daniel Halperin, MD • Sten Myrehaug, MD • Ken Herrmann, MD • Prof Marianne Pavel, MD • Pamela L Kunz, MD • et al. Show all authors • Show footnotes

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[177Lu]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**

ASCO® Gastrointestinal Cancers Symposium

Efficacy and Safety of [^{177}Lu]Lu-DOTA-TATE in Newly Diagnosed Patients with Advanced Grade 2 and Grade 3, Well-Differentiated Gastroenteropancreatic Neuroendocrine Tumors: Primary Analysis of the Phase 3 Randomized NETTER-2 Study

Simron Singh MD, MPH,[1] Daniel Halperin MD,[2] Sten Myrehaug MD,[1] Ken Herrmann MD,[3,4] Marianne Pavel MD,[5] Pamela L. Kunz MD,[6] Beth Chasen MD,[2] Jaume Capdevila MD, PhD,[7] Salvatore Tafuto MD,[8] Do-Youn Oh MD, PhD,[9] Changhoon Yoo MD, PhD,[10] Stephen Falk MD,[11] Thorvardur Halfdanarson MD,[12] Ilya Folitar MD,[13] Yufen Zhang PhD,[14] Paola Santoro MS,[14] Paola Aimone MD,[13] Wouter W. de Herder MD, PhD,[15] Diego Ferone MD,[16] on behalf of all the NETTER-2 Trial Investigators

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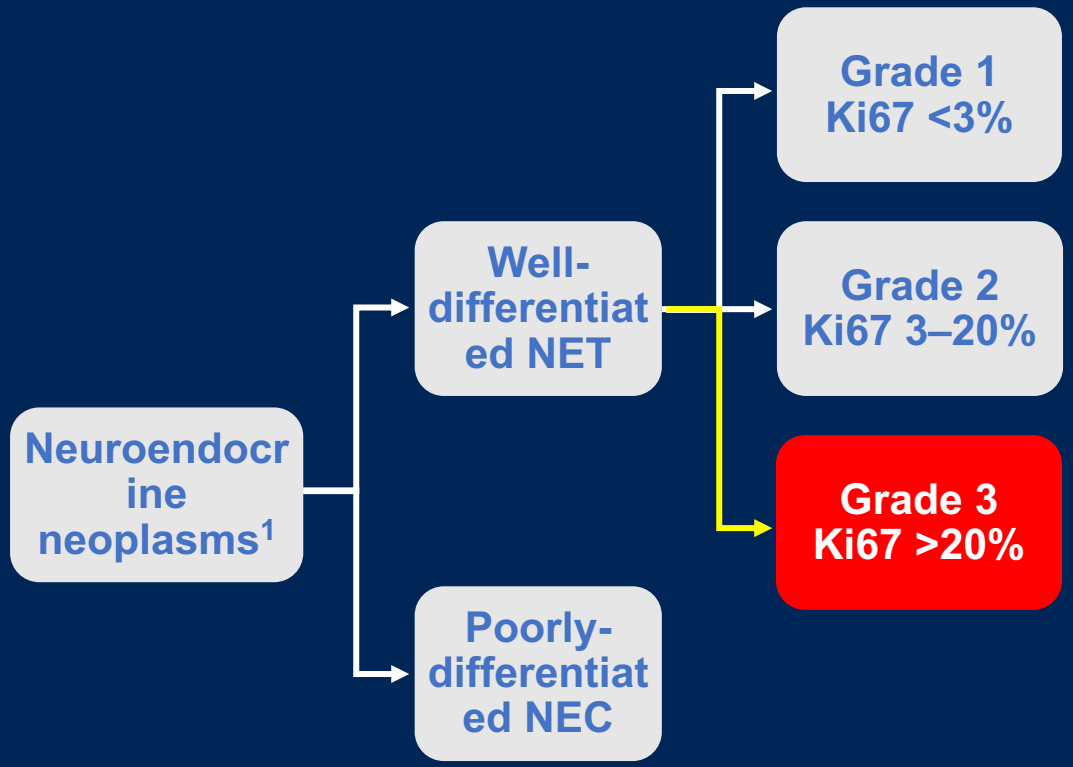
Simron Singh

Courtesy of Simron Singh, MD, MPH

Standard of care is undefined for newly diagnosed high G2 and G3 GEP-NETs



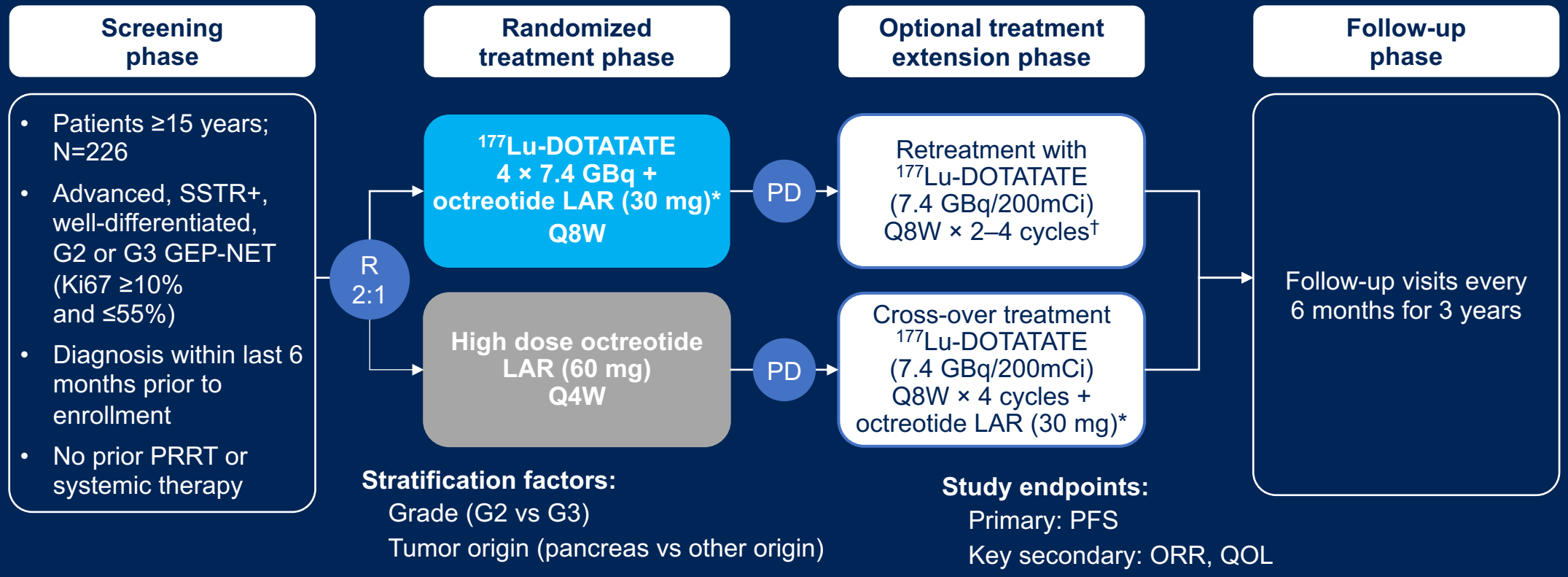
- Well-differentiated G3 NETs are a relatively new classification[2]
- No randomized studies have investigated the most appropriate first-line treatment strategy for high G2 / G3 GEP-NETs[3,4]

G, grade; GEP-NET, gastroenteropancreatic neuroendocrine tumor; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor.

1. Nagtegaal ID, et al. Histopathology 2020;76:182–188; 2. Rindi G, et al. Mod Pathol 2018;31:1770–86; 3. Del Rivero J, et al. J Clin Oncol 2023;41:5049–67; 4. Eads JR, et al. Endocr Relat Cancer 2023; 30:e220206.

Courtesy of Simron Singh, MD, MPH

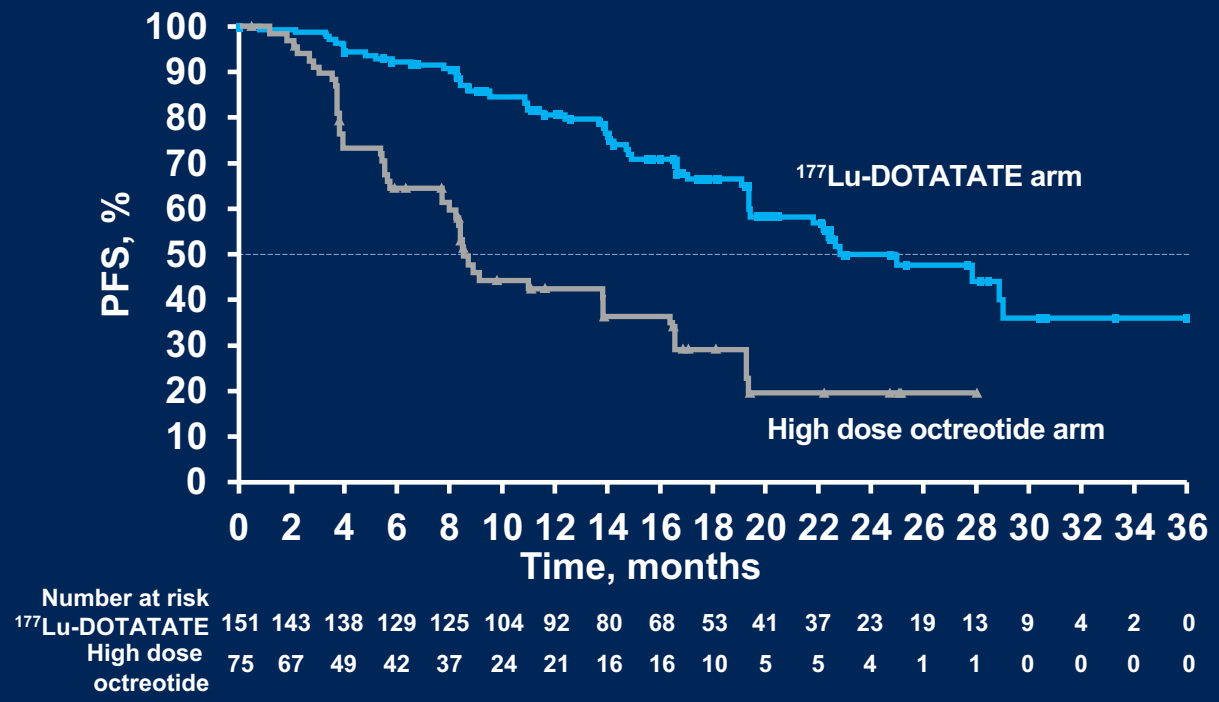
NETTER-2 (NCT03972488) is the first randomized trial to evaluate RLT as 1L treatment in any solid tumor



*Q8W during ^{177}Lu-DOTATATE treatment then Q4W; †Octreotide LAR in retreatment phase is at discretion of investigator.
1L, first line; G, grade; GEP-NET, gastroenteropancreatic neuroendocrine tumor; LAR, long-acting repeatable; ORR, objective response rate; PD, progressive disease; PRRT, peptide receptor radionuclide therapy;
QnW, every n weeks; QOL, quality of life; R, randomization; RLT, radioligand therapy; SSTR, somatostatin receptor.

Courtesy of Simron Singh, MD, MPH

^{177}Lu-DOTATATE showed significant improvement in primary PFS endpoint



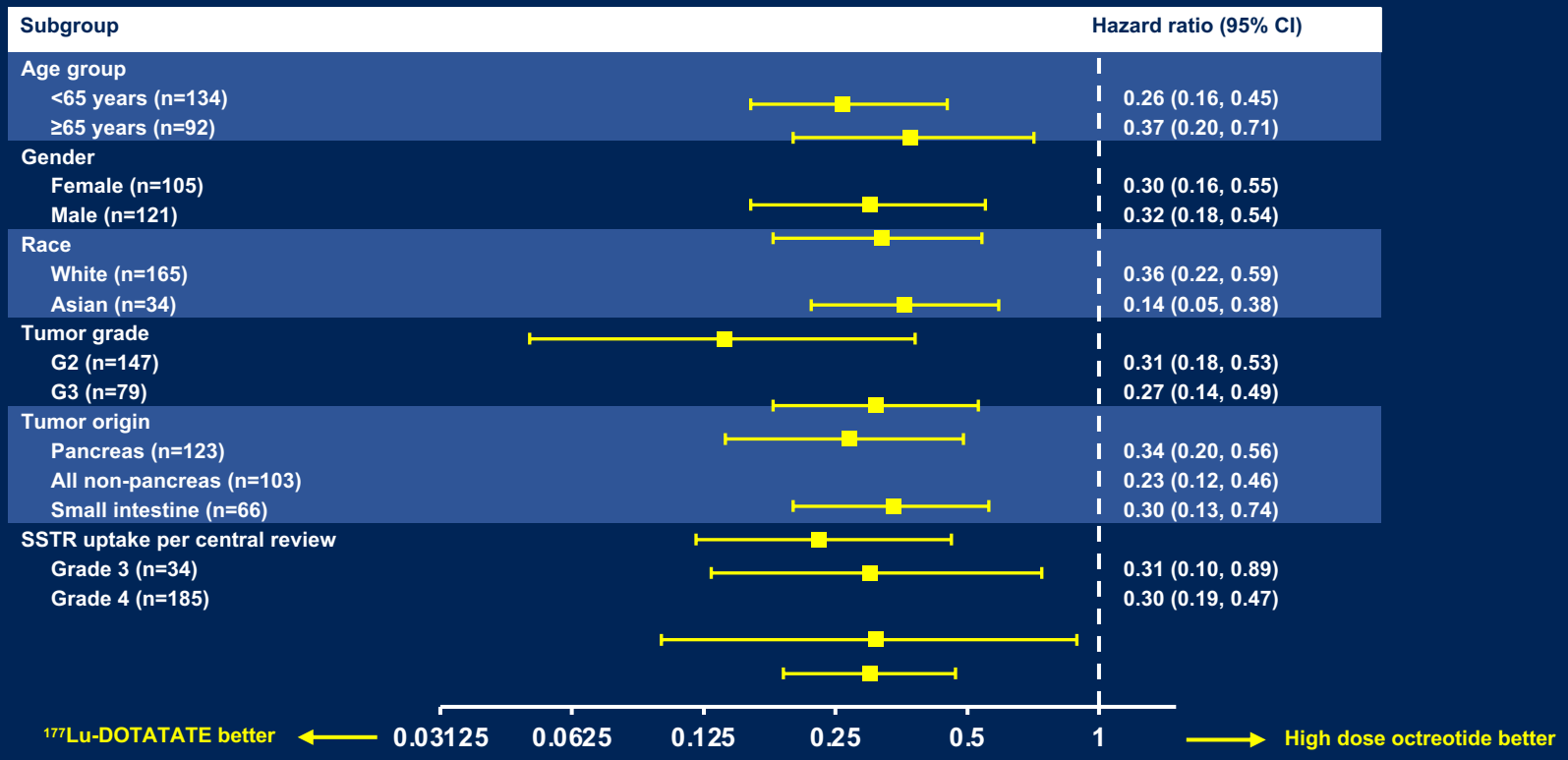
	^{177}Lu-DOTATATE arm n=151	High dose octreotide arm n=75
PFS median, months (95% CI)	**22.8** (19.4, NE)	**8.5** (7.7, 13.8)
Stratified HR (95% CI)	0.276 (0.182, 0.418)	
p-value	<0.0001	
Number of events, n (%)	55 (36)	46 (61)
Progression	47 (31)	41 (55)
Death	8 (5)	5 (7)

72% reduction in the risk of disease progression or death in the ^{177}Lu-DOTATATE arm versus the high dose octreotide arm

PFS centrally assessed according to RECIST 1.1
CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Courtesy of Simron Singh, MD, MPH

PFS benefit was consistent across prespecified subgroups



CI, confidence interval; G, Grade; PFS, progression-free survival; SSTR, somatostatin receptor

ORR was significantly higher for ^{177}Lu-DOTATATE

	^{177}Lu-DOTATATE arm n=151	High dose octreotide arm n=75
Best overall response, n (%)		
CR	8 (5.3)	0 (0)
PR	57 (37.7)	7 (9.3)
SD	72 (47.7)	42 (56.0)
Non-CR / Non-PD	0 (0)	1 (1.3)
PD	8 (5.3)	14 (18.7)
Unknown	6 (4.0)	11 (14.7)
ORR*, n (%)	65 (43.0)	7 (9.3)
[95% CI]	[35.0, 51.3]	[3.8, 18.3]
Stratified odds ratio (95% CI)	7.81 (3.32, 18.40)	
p-value	<0.0001	
Responders, n	65	7
Duration of response median (95% CI), months	23.3 (18.4, NE)	NE (2.3, NE)

*CR+PR (central review, RECIST 1.1; confirmation of response was not required)
CI, confidence interval; CR, complete response; NE, not estimable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Courtesy of Simron Singh, MD, MPH

Safety was in line with the established profiles of ^{177}Lu-DOTATATE and octreotide LAR

	^{177}Lu-DOTATATE group n=147	High dose octreotide group n=73
Any AE / AE related to treatment (all grades), n (%)	136 (93) / 101 (69)	69 (95) / 43 (59)
Any AE / AE related to treatment (Grade ≥3), n (%)	52 (35) / 23 (16)	20 (27) / 3 (4)
Most common all grade AEs (>20%), n (%)		
Nausea	40 (27.2)	13 (17.8)
Diarrhea	38 (25.9)	25 (34.2)
Abdominal pain	26 (17.7)	20 (27.4)
Most common grade ≥3 AEs (>3%), n (%)		
Lymphocyte count decreased	8 (5.4)	0 (0)
GGT increased	7 (4.8)	2 (2.7)
Small intestinal obstruction	5 (3.4)	0 (0)
Abdominal pain	4 (2.7)	3 (4.1)
Secondary hematologic malignancies, n (%)	1 (0.7)	0 (0)

AE, adverse event; GGT, gamma-glutamyl transferase; LAR, long-acting repeatable

Courtesy of Simron Singh, MD, MPH

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]

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Courtesy of Simron Singh, MD, MPH

Agenda

Module 1: Overview

Module 2: Peptide Receptor Radionuclide Therapy for Neuroendocrine Tumors (NETs)

Module 3: Multitarget Tyrosine Kinase Inhibitors for the Treatment of NETs

Module 4: Other New Advances in the Management of NETs

Common Questions for Neuroendocrine Tumors

Multitarget Tyrosine Kinase Inhibitors

Which tyrosine kinase inhibitors have been studied for the treatment of NETs? How do they compare to everolimus in terms of their efficacy and tolerability?

Which tyrosine kinases are targeted by cabozantinib?

Does the site of the primary NET have any effect on responses observed to cabozantinib?

What is known about the efficacy of cabozantinib, including response rates?

What are the main side effects are observed with cabozantinib? How often are dose adjustments necessary?

Have you administered or would you administer cabozantinib outside of a clinical trial to a patient with an advanced NET and progressive disease?

Have you administered or would you administer cabozantinib outside of a clinical trial to a patient with an advanced NET and progressive disease? To approximately how many such patients have you done so?

	Cabozantinib outside of a clinical trial?	Number of patients
 Dr Kunz	I have	2
 Dr Singh	I have	10
 Dr Halperin	I have	5
 Dr Li	I have	5
 Dr Soares	I have	10
 Dr Strosberg	I have	12

In the literature or your personal experience, what have you observed regarding the efficacy of cabozantinib?

 Dr Kunz	Similar to published results
 Dr Singh	Effective
 Dr Halperin	Excellent disease control, rare response
 Dr Li	Consistent with clinical trial results in terms of disease control and less ORR
 Dr Soares	Efficacious, and patients can have symptomatic response
 Dr Strosberg	Probably slightly better than everolimus or sunitinib; mostly disease stabilization

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In the literature or your personal experience, what have you observed regarding the tolerability of cabozantinib?

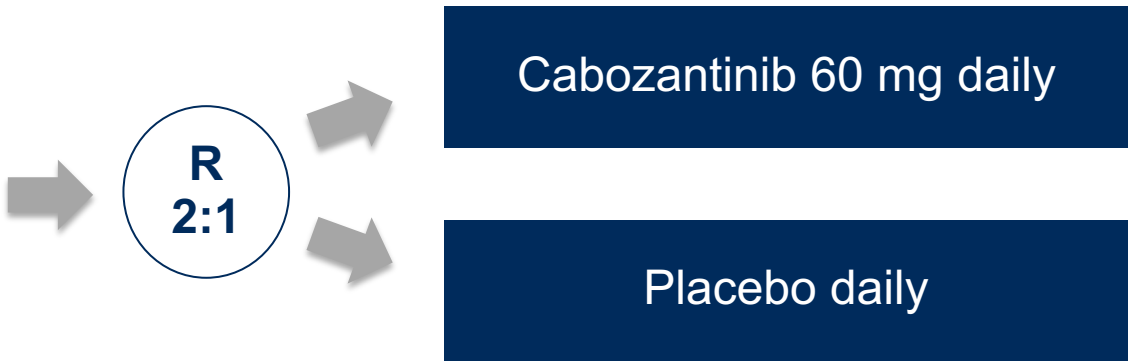
 Dr Kunz	Fatigue, diarrhea — I usually start with a 40-mg dose
 Dr Singh	Well tolerated
 Dr Halperin	More challenging, fatigue and diarrhea
 Dr Li	Needs good weekly management when starting, to control side effects
 Dr Soares	Fatigue and HTN issues better at reduced dose, such as 40 mg
 Dr Strosberg	Most patients require dose reductions from starting dose of 60 mg, many all the way down to 20 mg

NEW

Targeted Therapy: Cabozantinib

cMET, VEGFR2, AXL, RET

CABINET (A021601): Phase III Study of Cabozantinib vs. Placebo (PI: Chan)



1° Endpoint : PFS (Central Review)

2° Endpoints: OS, RR, Safety, Tolerability

*Crossover allowed at PD

Key inclusion criteria:

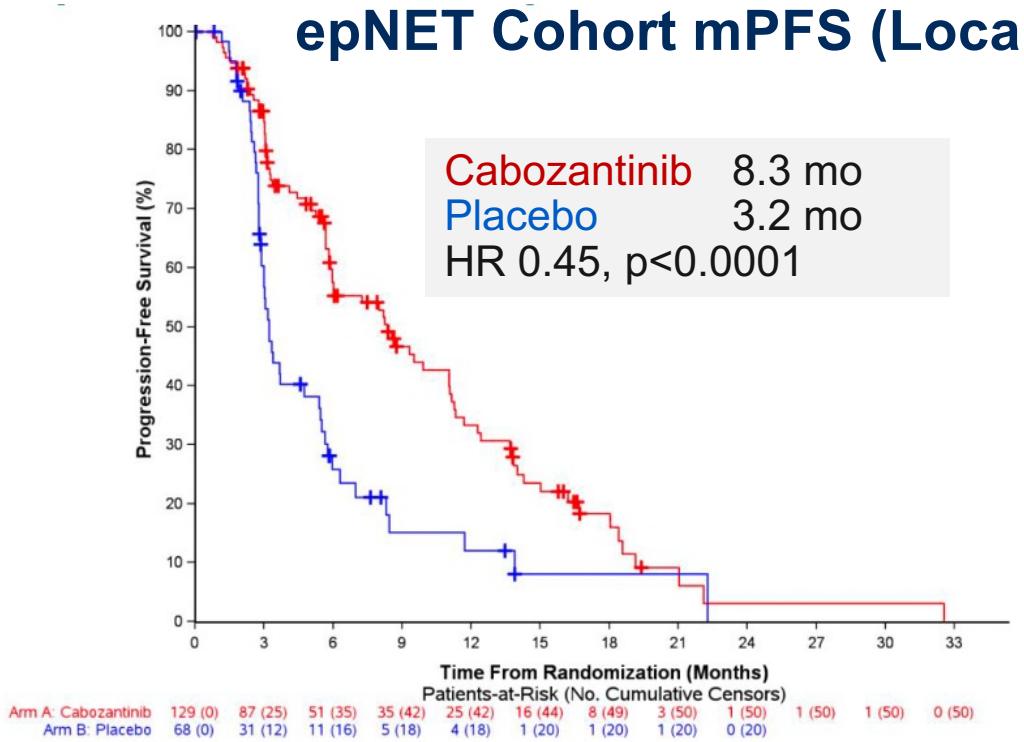
- Well- to moderately differentiated NET, functional and non-functional
- Any radiographic progression within 12 mo prior to randomization
- Progression on at least 1 prior FDA-approved systemic therapy, not including SSA
- Concurrent SSA allowed provided stable dose for ≥ 2 mo

Chan JA, et al. ESMO 2023, LBA53.

CABINET: Primary Endpoint PFS

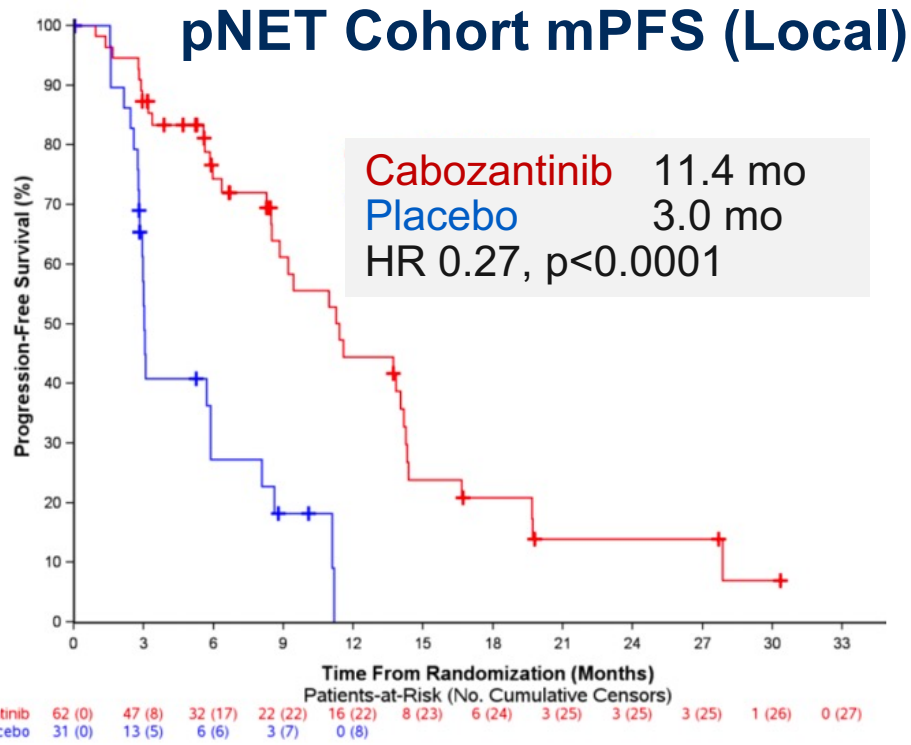
cMET, VEGFR2, AXL, RET

epNET Cohort mPFS (Local)



Cabozantinib 8.3 mo
Placebo 3.2 mo
HR 0.45, p<0.0001

pNET Cohort mPFS (Local)



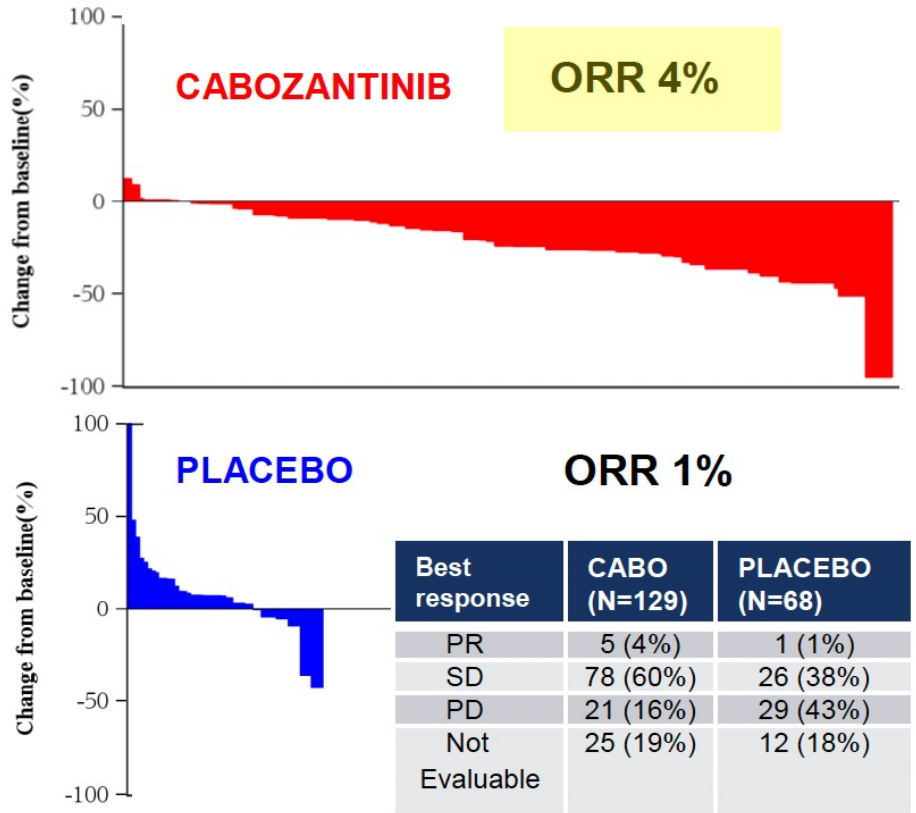
Cabozantinib 11.4 mo
Placebo 3.0 mo
HR 0.27, p<0.0001

Chan JA, et al. ESMO 2023, LBA53.

CABINET: Response Rates

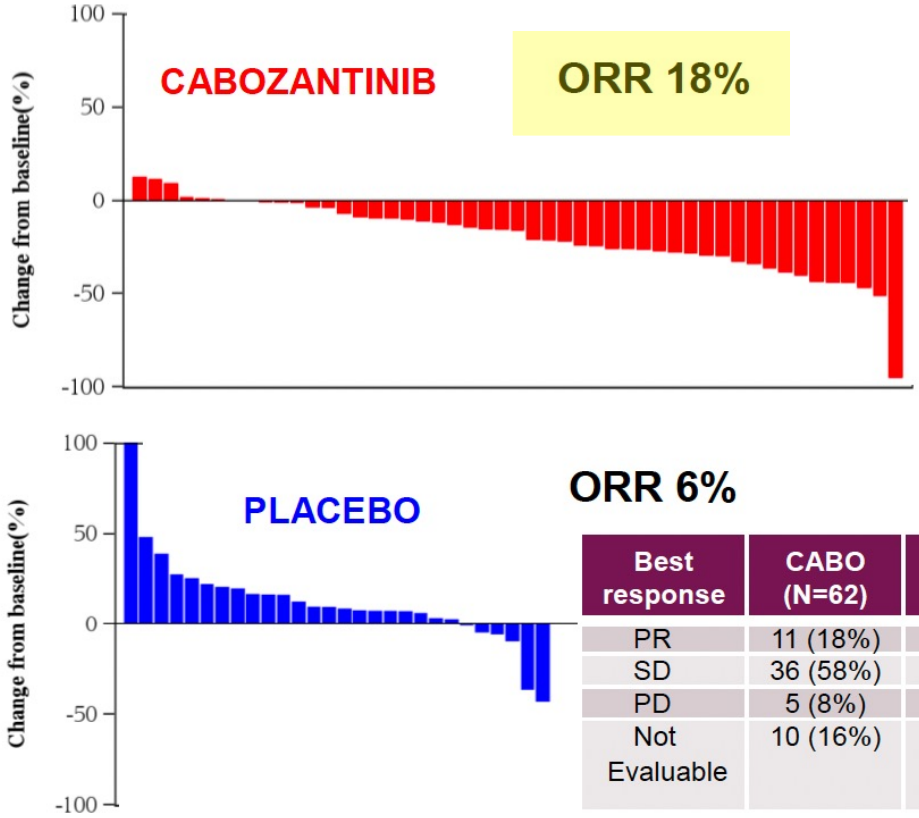
cMET, VEGFR2, AXL, RET

epNET Cohort



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 Cohort



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%)

Chan JA, et al. ESMO 2023, LBA53.

Courtesy of Pamela Kunz, MD

CABINET: Adverse Events

epNET Cohort

	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 Cohort

	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

Chan JA, et al. ESMO 2023, LBA53.

Courtesy of Pamela Kunz, MD

The trail of other TKIs…

Drug	Target 🎯	Indication	Primary Endpoint	Status
Pazopanib[1]	VEGF, PDGFR, c-KIT, FGF	Advanced carcinoid	PFS 11.6 vs. 8.5 mo (p=0.0005)	Company decision to not purse Ph III
Surufatinib[2,3]	VEGFR-1, VEGFR-2, VEGFR-3, FGFR1, CSFR1	Pancreatic, Extra-pancreatic NET	pNET: PFS 10.9 vs 3.7 mo; (p=0.0011) epNET: PFS 9.2 vs. 3.8 mo; (*p* <0.0001)	FDA approval denied (2022)
Axitinib[4]	VEGFR1-3	Extrapancreatic NETs	PFS 17.2 vs. 12.3 mo (p = 0.169)	Negative trial (but high RR)
Lenvatinib[5]	VEGFR-1-3, FGFR 1-4, PDGFRα, PDGFRβ, c-KIT, RET	GI and pNET	RR pNET: 44% RR GI NET: 17%	High RR, however, non-randomized

1. Bergsland. ASCO 2019, Ab 4005. 2. Xu J et al. *Lancet Oncol*. 2020;21(11):1489-1499; 3. Xu J et al. *Lancet Oncol*. 2020;21(11):1500-1512. 4. Garcia-Carbonero, et al. ASCO 2021, abstract 360. 5. Capdevila, J Clin Oncol 2021; 39:2304-2312

Courtesy of Pamela Kunz, MD

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Common Questions for Neuroendocrine Tumors

New Advances in the Management of NETs

For which of your patients with NETs do you test for a germline von Hippel-Lindau (VHL) gene alteration?

Is belzutifan being investigated for cancers not associated with VHL gene mutations? (Sounds like renal cell carcinoma!)

For patients with a NET who harbor a VHL gene mutation, where in your treatment algorithm do you incorporate belzutifan?

How often do you observe anemia secondary to belzutifan? Is there any role for erythropoiesis-stimulating agents?

Do you test for a germline VHL gene alteration in your patients with NETs?

 Dr Kunz	Yes, at diagnosis
 Dr Singh	No
 Dr Halperin	No
 Dr Li	Yes, at diagnosis
 Dr Soares	Yes, if clinical suspicion for germline VHL mutation
 Dr Strosberg	No, unless suggestive family history

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

Belzutifan for von Hippel–Lindau Disease: Pancreatic Lesion Population of the Phase 2 LITESPARK-004 Study

Tobias Else[1], Eric Jonasch[2], Othon Iliopoulos[3], Kathryn E. Beckermann[4], Vivek Narayan[5], Benjamin L. Maughan[6], Stephane Oudard[7], Jodi K. Maranchie[8], Ane B. Iversen[9], Cynthia M. Goldberg[10], Wei Fu[10], Rodolfo F. Perini[10], Yanfang Liu[10], W. Marston Linehan[11], and Ramaprasad Srinivasan[11]

Clin Cancer Res 2024;30(9):1750-7.

LITESPARK-004: Belzutifan in von Hippel–Lindau (VHL) Disease – Pancreatic Lesions and Pancreatic NETs Cohort

Characteristic	Pancreatic lesions *N* = 61	pNETs *N* = 22
Age, median (range; y)	41 (19–66)	42 (19–66)
Sex, *n* (%)		
Male	32 (52)	11 (50)
Female	29 (48)	11 (50)
ECOG PS, *n* (%)		
0	50 (82)	20 (91)
1	10 (16)	2 (9)
2	1 (2)	0
VHL disease subtype, *n* (%)		
1	51 (84)	17 (77)
2A	2 (3)	1 (5)
2B	6 (10)	3 (14)
2C	0	0
Missing	2 (3)	1 (5)
Prior surgeries[a], *n* (%)		
Total number of patients who had ≥1 prior surgery	59 (97)	22 (100)
Pancreatic lesions[b]	9 (15)	2 (9)
Size of target lesions, median (range; mm)	19 (10–61)[c]	19 (10–52)[d]

Else T et al. *Clin Cancer Res* 2024;30(9):1750-7.

Courtesy of Pamela Kunz, MD

LITESPARK-004: Belzutifan in VHL-Associated Pancreatic NETs — Response Data

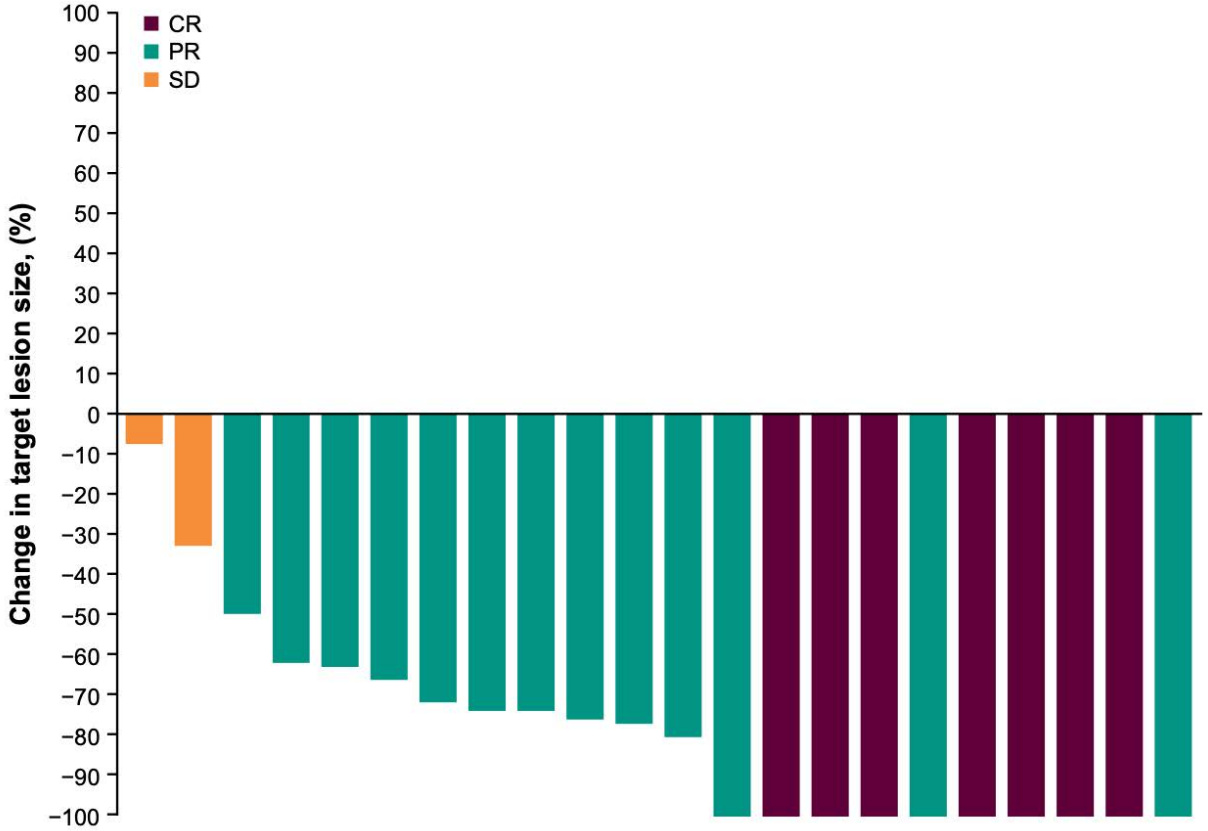


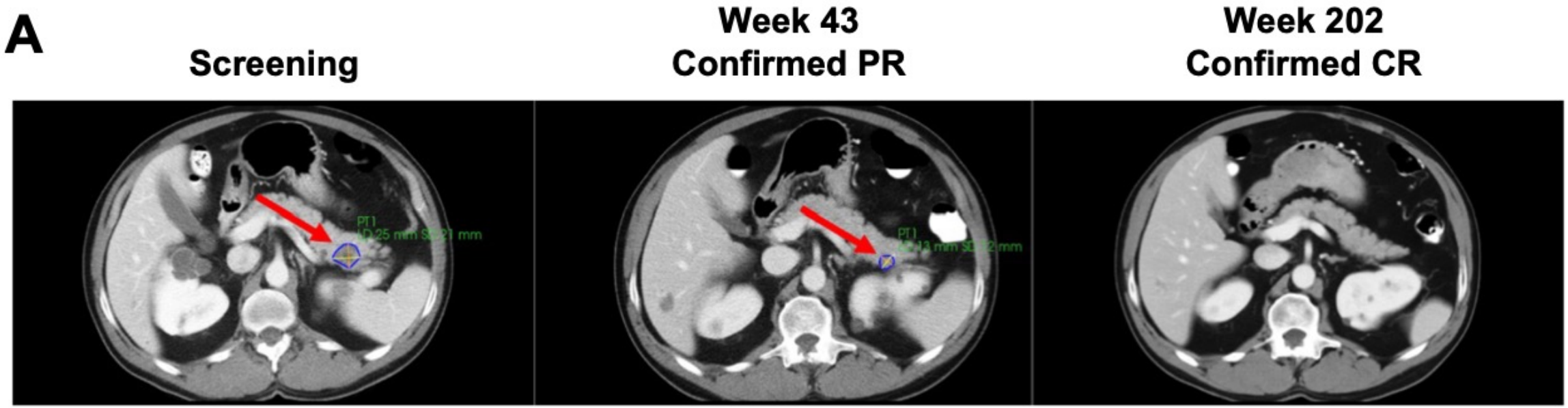
Table 2. Response in VHL disease–associated pancreatic neoplasms.

	Pancreatic lesions ***N*** **= 61**	**pNETs** ***N*** **= 22**
ORR, *n* (%; 95% CI)	51 (84) (71.9–91.8)	20 (91) (70.8–98.9)
Best overall response, *n* (%)		
CR	17 (28)	7 (32)
PR	34 (56)	13 (59)
Stable disease	9 (15)	2 (9)
Progressive disease	0	0
Not evaluable	1 (2)	0
TTR, median (range; mo)	8.3 (2.5–32.9)	8.2 (2.5–16.4)
DOR, median (range; mo)	NR (2.6+ to 37.3+)	NR (11.0+ to 37.3+)

Else T et al. *Clin Cancer Res* 2024;30(9):1750-7.

Courtesy of Pamela Kunz, MD

LITESPARK-004: Belzutifan in VHL-Associated Pancreatic NETs — Durability of Response



Else T et al. *Clin Cancer Res* 2024;30(9):1750-7.

Courtesy of Pamela Kunz, MD

Data + Perspectives: Clinical Investigators Discuss the Role of CAR T-Cell Therapy for Patients with Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia

Part 1 of a 2-Part CME Satellite Symposium Series During the Society of Hematologic Oncology 2024 Annual Meeting

Wednesday, September 4, 2024
11:46 AM – 12:46 PM CT

Faculty

Joshua Brody, MD
Jason Westin, MD, MS

Moderator

Matthew Lunning, DO

RTP RESEARCH TO PRACTICE

Thank you for joining us!

Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open for 5 minutes after the meeting ends.

Information on how to obtain CME, ABIM MOC and ABS credit is provided in the Zoom chat room. Attendees will also receive an email in 1 to 3 business days with these instructions.

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