Oncology Today with Dr Neil Love — Thyroid Cancer and Neuroendocrine Tumors

A CME/MOC-Accredited Virtual Event

Wednesday, January 25, 2023
5:00 PM – 6:00 PM

Faculty

Jonathan Strosberg, MD
Lori J Wirth, MD

Moderator

Neil Love, MD

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Faculty

Jonathan Strosberg, MD
Professor, Dept of GI Oncology
Moffitt Cancer Center
Tampa, Florida

Lori J Wirth, MD
The Elizabeth and Michael Ruane Chair of Endocrine Oncology
Associate Professor
Harvard Medical School
Medical Director, Head and Neck Oncology
Massachusetts General Hospital
Boston, Massachusetts

Live Moderator
Neil Love, MD
Research To Practice

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ONCOLOGY TODAY

WITH DR NEIL LOVE

Thyroid Cancer

DR ERIC SHERMAN

MEMORIAL SLOAN KETTERING CANCER CENTER

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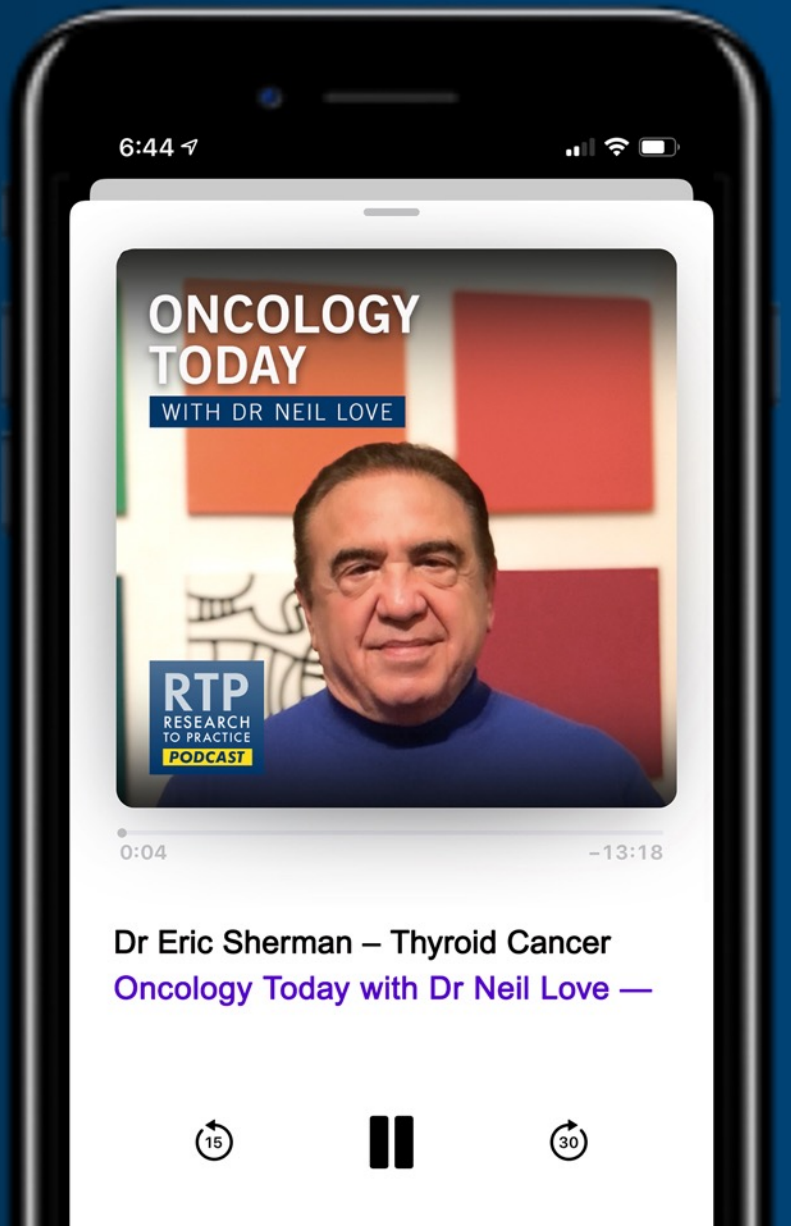

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WITH DR NEIL LOVE

Neuroendocrine Tumors

DR PAMELA KUNZ
YALE CANCER CENTER

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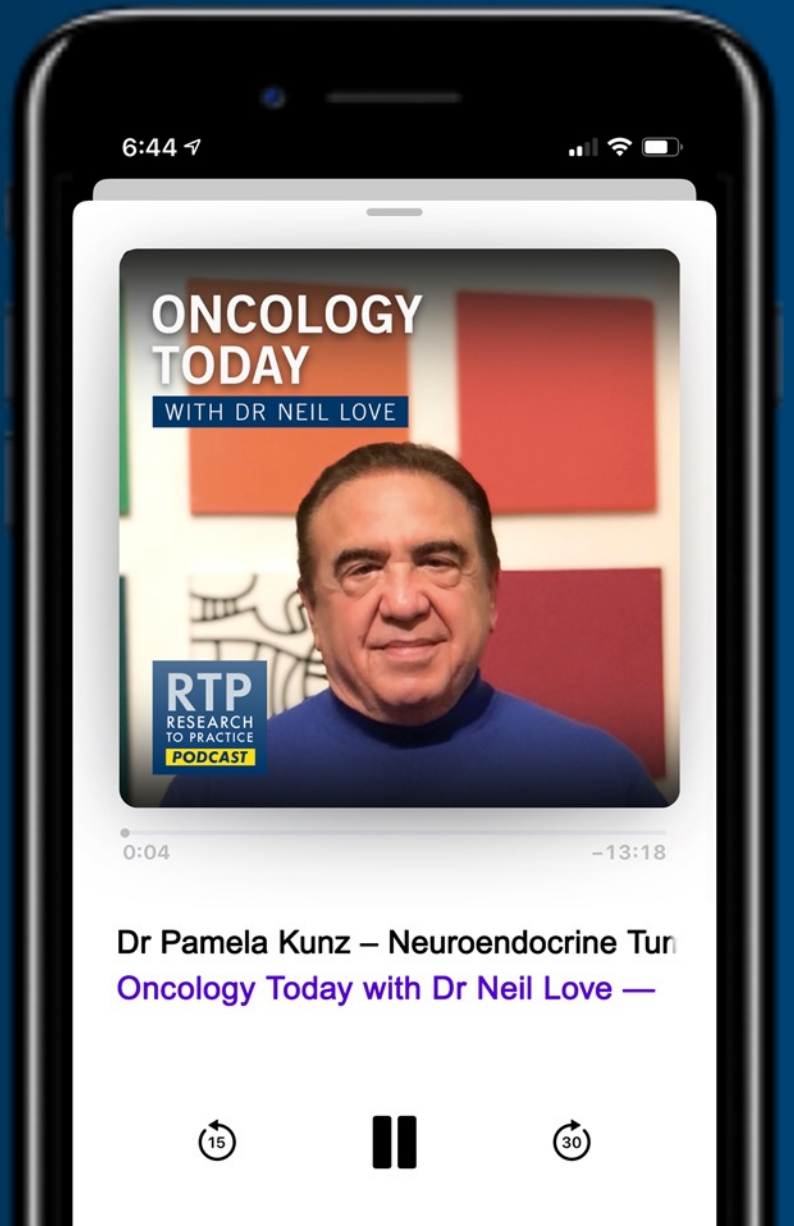

Meet The Professor

Optimizing the Management of Multiple Myeloma

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Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

A Multitumor CME/MOC-Accredited Live Webinar Series

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Laurie H Sehn, MD, MPH

Moderator

Neil Love, MD

RTP Year in Review 2023

Inside the Issue — Optimizing the Management of Adverse Events Associated with BTK Inhibitors

A CME/MOC-Accredited Virtual Event

Thursday, February 2, 2023
5:00 PM – 6:00 PM ET

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Kerry A Rogers, MD

Moderator

Neil Love, MD

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Inside the Issue — Exploring the Current Role of Ovarian Suppression in the Management of Breast Cancer

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Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Renal Cell Carcinoma

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Prof Karim Fizazi, MD, PhD

Maha Hussain, MD, FACP, FASCO

Matthew R Smith, MD, PhD

Moderator

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Dr Strosberg — Disclosures

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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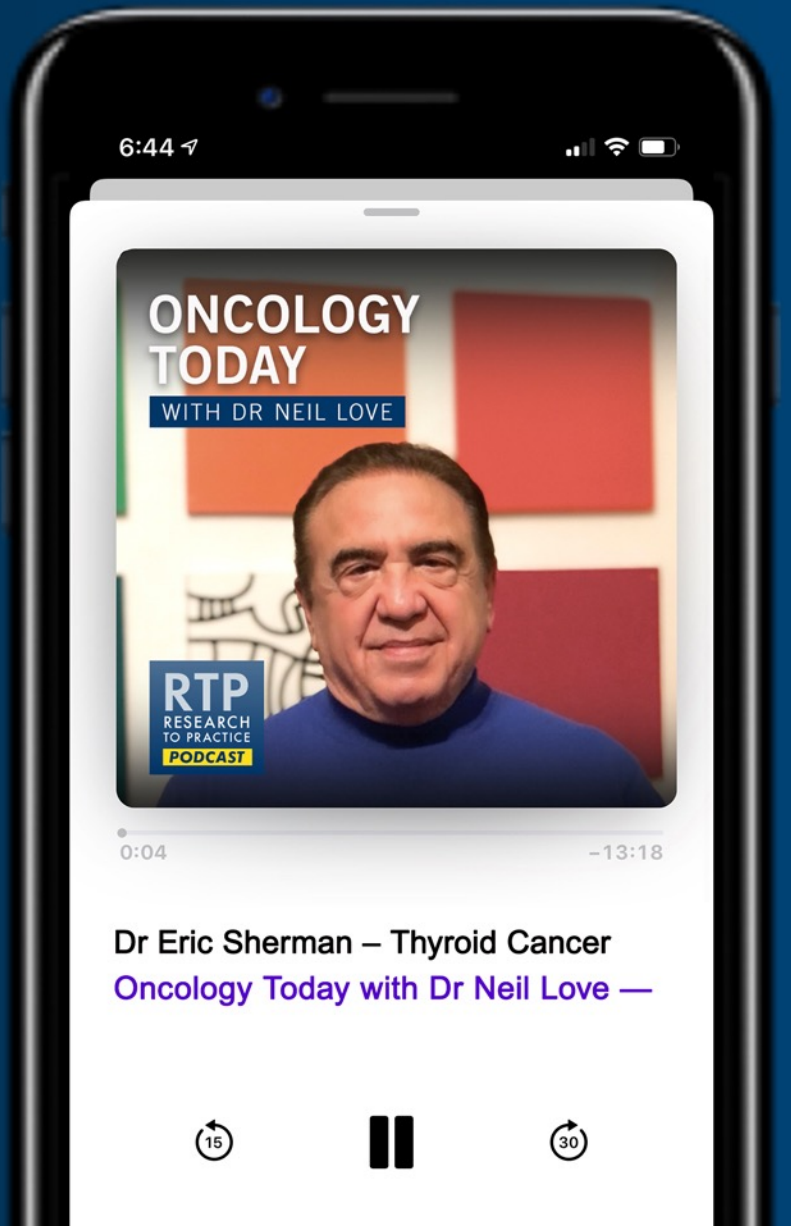

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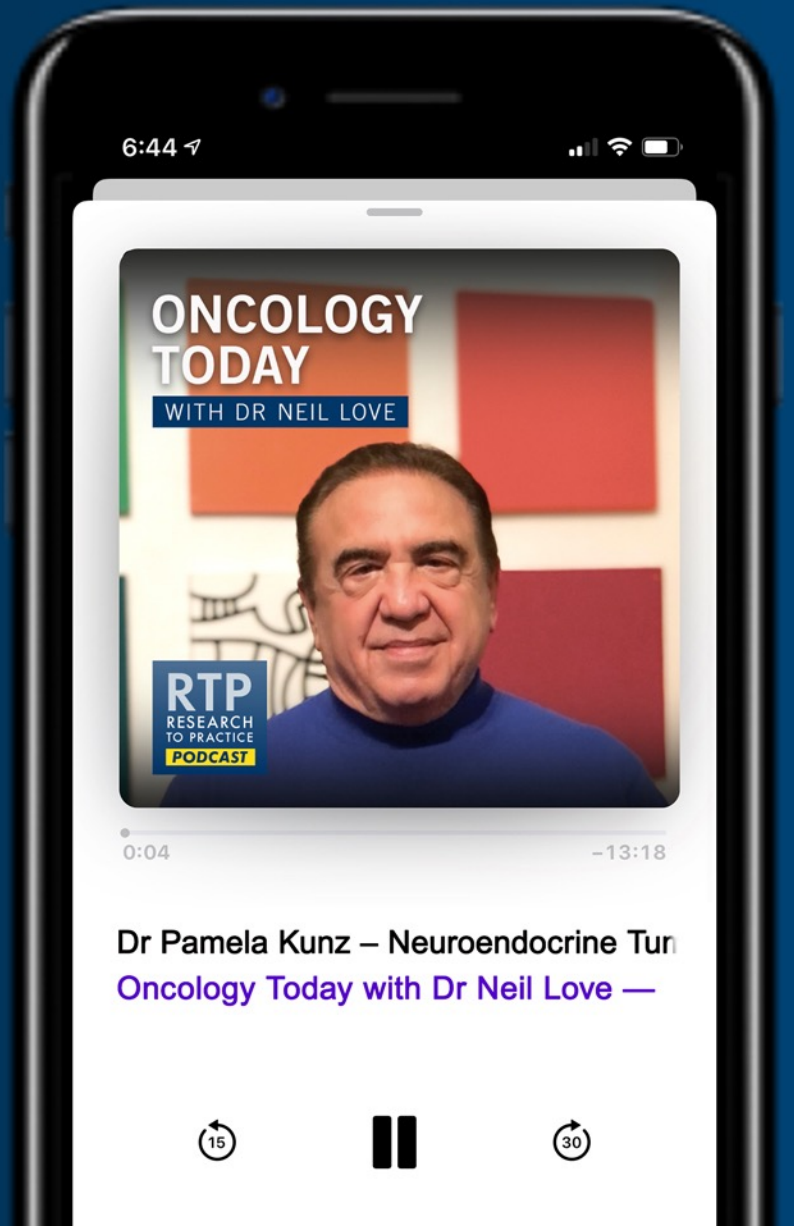

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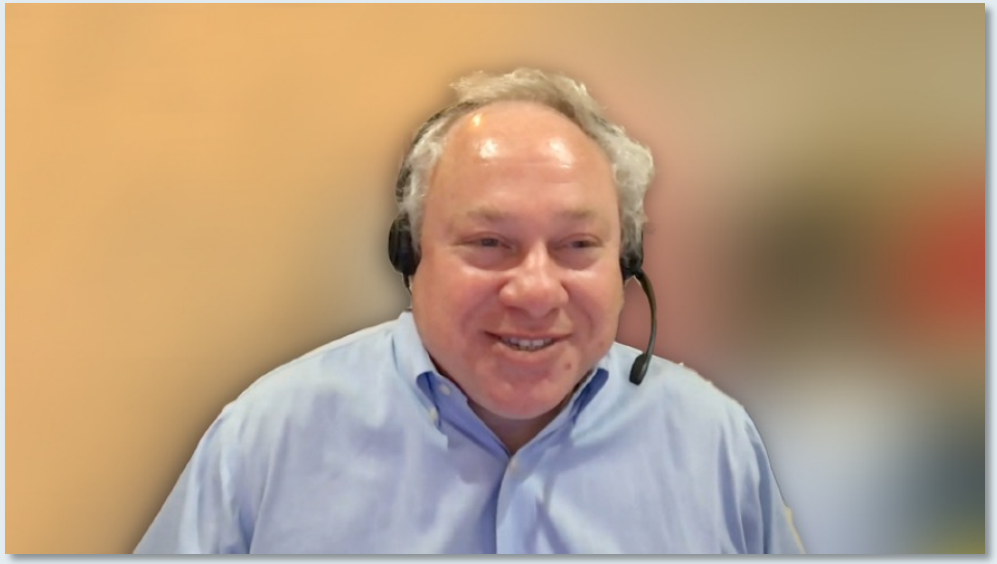
Pamela Kunz, MD
Yale Cancer Center
New Haven, Connecticut



Eric Sherman, MD
Memorial Sloan Kettering Cancer Center
New York, New York

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Oncology Today with Dr Neil Love — Thyroid Cancer Edition: A CME Series Focused on Research and Management Issues Across the Oncology Continuum.

Eric Sherman, M.D.
Associate Attending Physician
Head and Neck Cancer Service
Memorial Sloan-Kettering Cancer Center

Neuroendocrine Tumors

Pamela L. Kunz, MD
Associate Professor of Medicine / Oncology
Director, Center for Gastrointestinal Cancers
Vice Chief, Diversity Equity and Inclusion, Section of Medical Oncology
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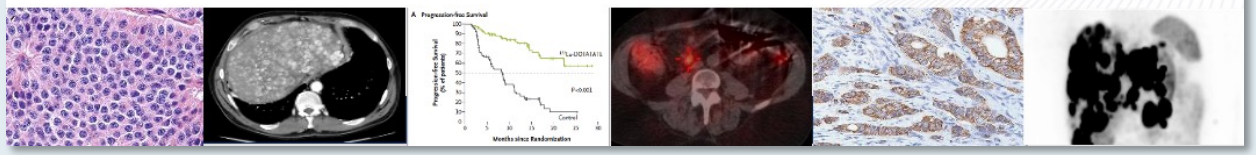

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MODULE 2: NTRK Fusions

MODULE 3: RET Mutations/Fusions

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- Dr Wirth: 69-year-old woman with poorly differentiated thyroid cancer initially treated with lenvatinib

MODULE 2: NTRK Fusions

- Dr Sherman: 61-year-old woman with metastatic papillary thyroid cancer and an NTRK fusion who received repotrectinib
- Dr Wirth: 62-year-old with metastatic papillary thyroid cancer with NTRK fusion who received larotrectinib

MODULE 3: RET Mutations/Fusions

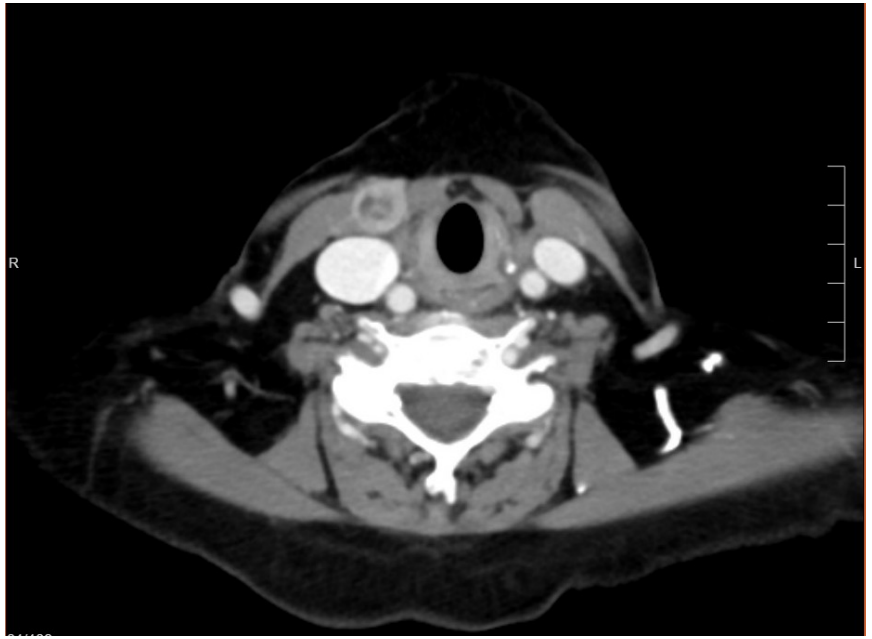
- Dr Sherman: 41-year-old man who presents with metastatic medullary thyroid cancer and a RET mutation
- Dr Wirth: 43-year-old man with metastatic medullary thyroid cancer and a RET mutation who received selpercatinib

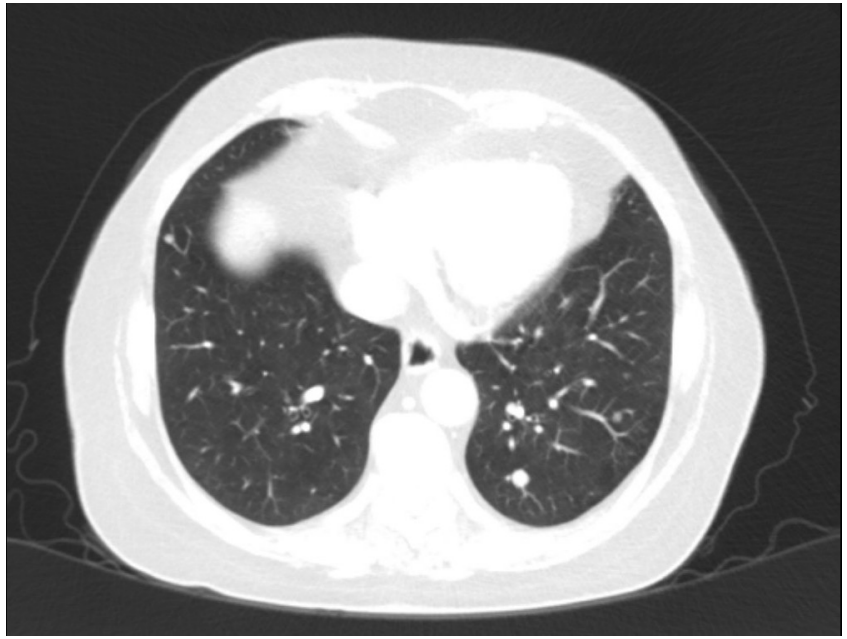
Dr Wirth: 69-year-old woman with poorly differentiated thyroid cancer initially treated with lenvatinib

- 69-year-old woman
  - Radiation in infancy for enlarged thymus
  - Hashimoto thyroiditis, multinodular goiter, anal cancer (2010)
  - New neck mass noted in 2018
    - FNA – suspicious for follicular neoplasm
    - Afirma GSC suspicious for malignancy
  - Underwent total thyroidectomy
    - Pathology – Poorly differentiated thyroid carcinoma, 2.8 cm, insular type, widely invasive, marked vascular invasion, including large vessels, extrathyroidal extension. 9 mitoses in 10 high-powered fields. Tumor necrosis present.
  - I-131, 125 mCi
    - WBS – uptake in R>L thyroid bed only

Dr Wirth: 69-year-old woman with poorly differentiated thyroid cancer initially treated with lenvatinib (continued)

- June, 2020 – rising Tg prompted N/C CT
  - R supraclavicular neck mass within SCM & lung nodules
    RAI-refractory disease

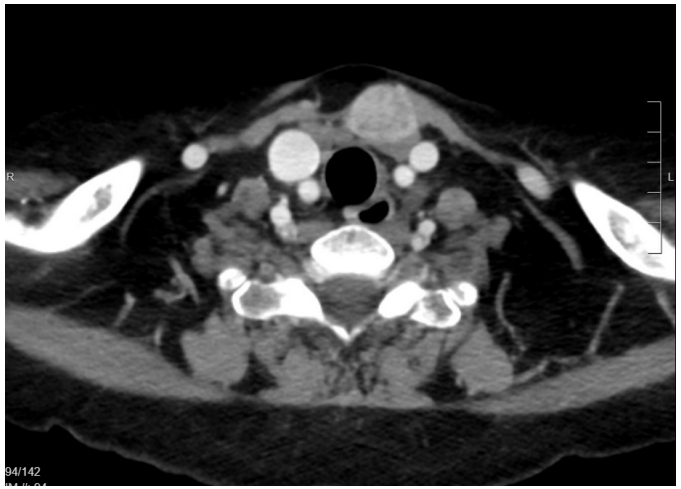


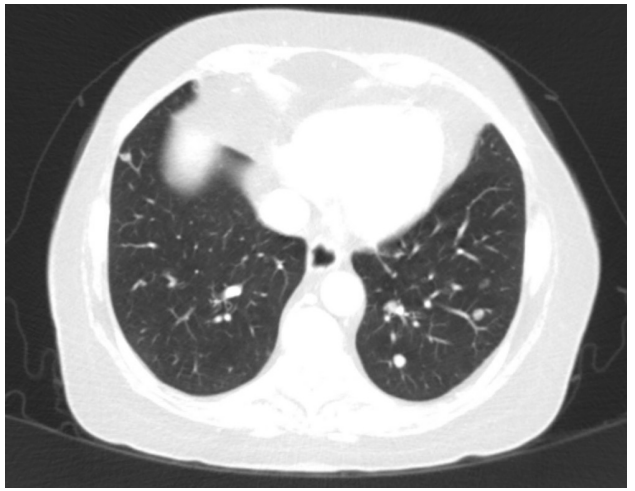


  - Underwent revision neck surgery
    - Pathology – 1.5-cm intramuscular PDTC, 7 R cervical nodes negative

Dr Wirth: 69-year-old woman with poorly differentiated thyroid cancer initially treated with lenvatinib (continued)

- Molecular diagnostics
  - TERT promoter mutation (C228T)
  - THADA–IGF2BP3 fusion
    - Not previously described, classified as of unknown significance →IGF2 protein expression?
- Jan, 2021 disease progression R neck > lung nodules

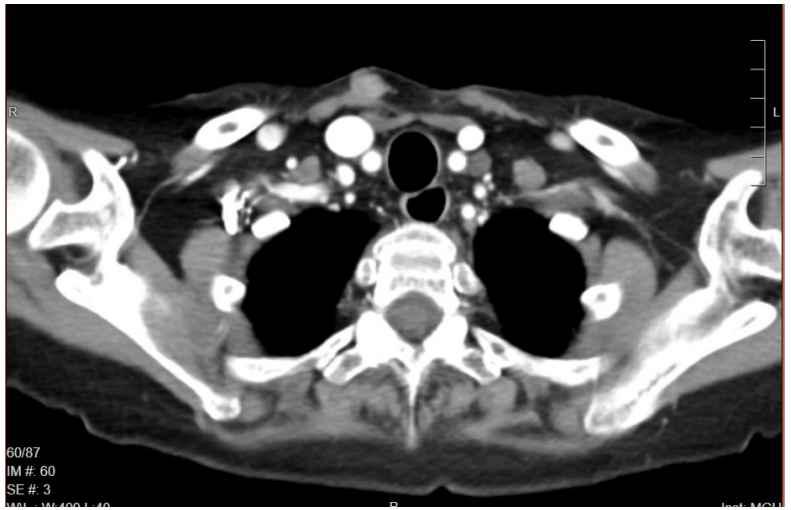




  - 2nd revision neck surgery

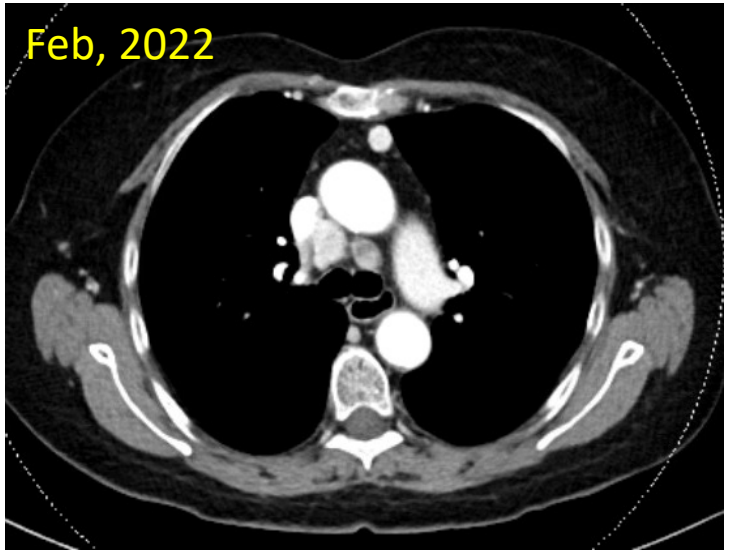
Dr Wirth: 69-year-old woman with poorly differentiated thyroid cancer initially treated with lenvatinib (continued)

- Feb, 2021
  - Lenvatinib 24 mg QD initiated
  - Treatment-emergent (TE) HTN, lisinopril started
  - TE diarrhea, lenvatinib reduced to 20 mg QD
    - Proctitis, hydrocortisone, lidocaine, sitz baths, GI consult + further dose reduction to 14 mg QD
- April, 2021 restaging – decrease in lung nodules, decrease in Tg
- Aug, 2021 – PD, new R lower neck nodule & Tg increasing
  - Lenvatinib discontinued after 6 mos
  - 3rd revision neck surgery
  - IMRT to neck

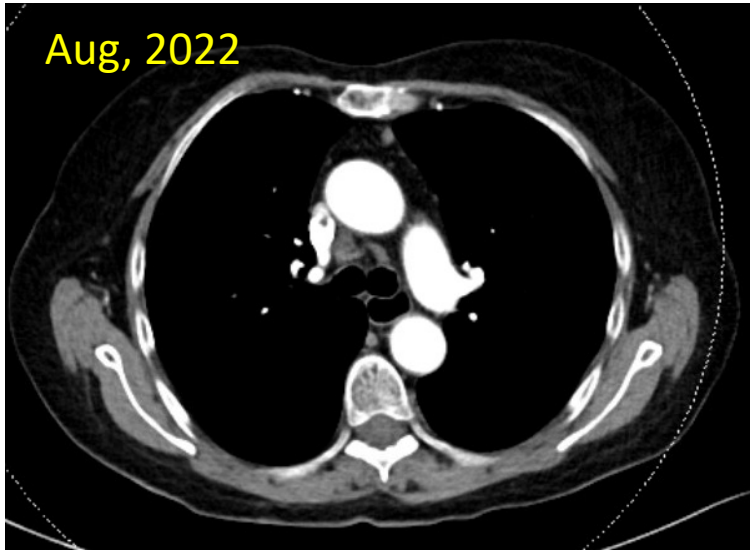


Dr Wirth: 69-year-old woman with poorly differentiated thyroid cancer initially treated with lenvatinib (continued)

- March 2022 – progressive lung nodules, mediastinal & hilar adenopathy
  - Cabozantinib 40 mg QD initiated (reduced d/t toxicity prev experienced on lenvatinib)
    - TE mild–moderate diarrhea, mild HFS, no HTN



Tg = 504 ng/mL



Tg = 7.0 ng/mL

As of Jan, 2023 remains in partial response (@ 10 mos), tolerating cabozantinib 40 mg QD fairly well

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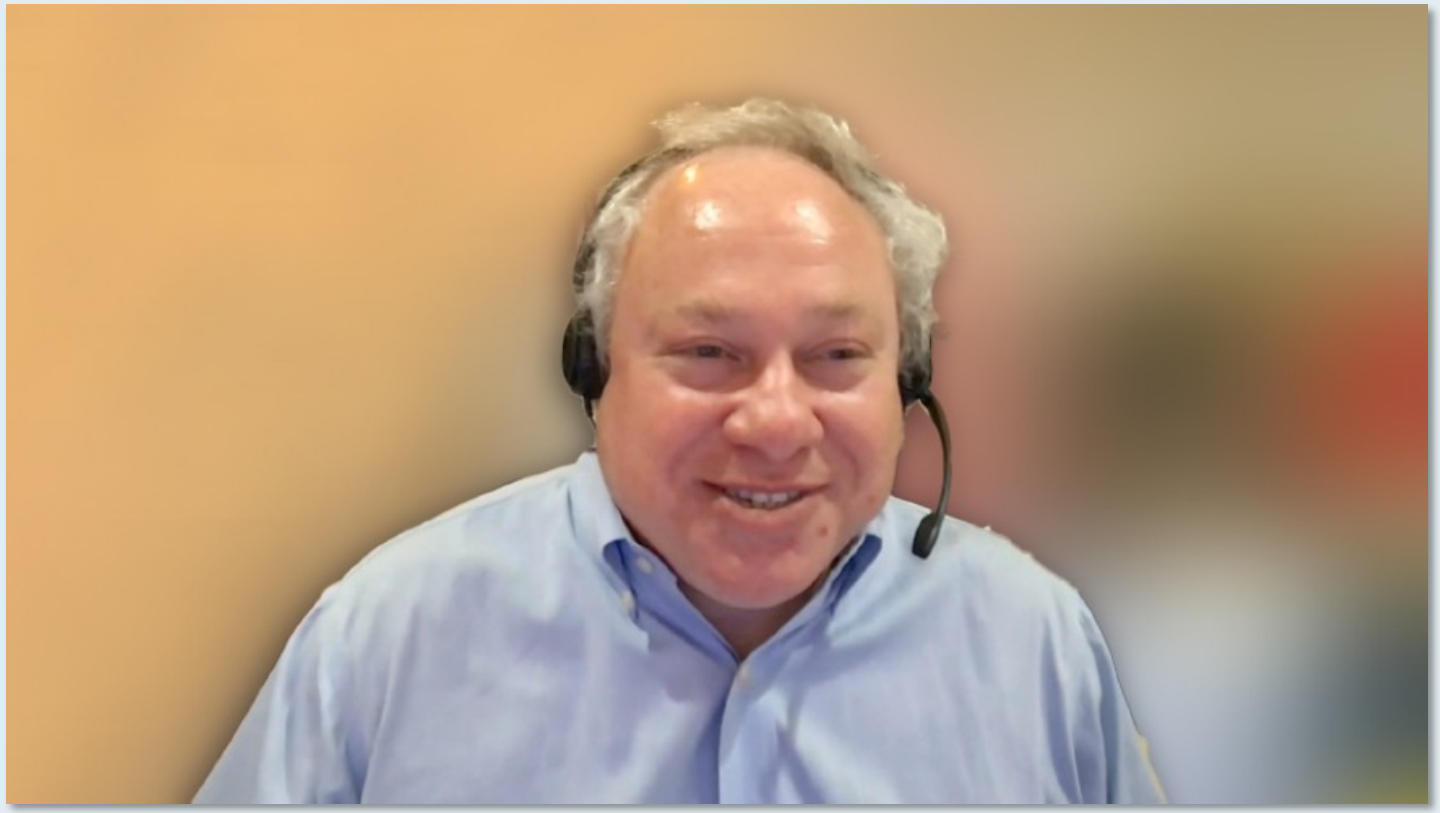
Case Presentation: 61-year-old woman with metastatic papillary thyroid cancer and an NTRK fusion who received repotrectinib



Eric Sherman, MD (New York, New York)

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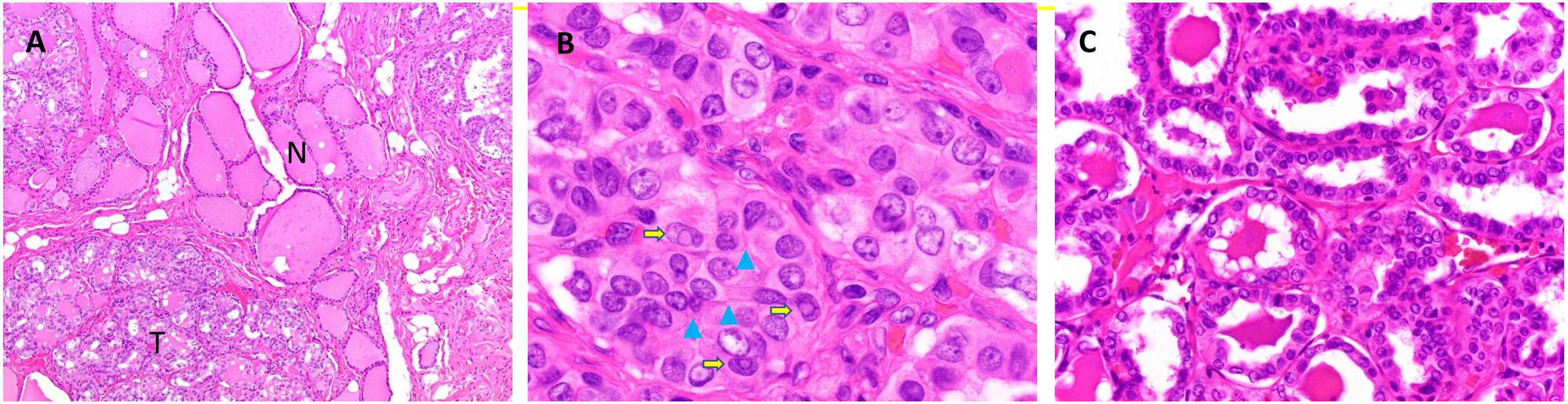
Dr Wirth: 62-year-old with metastatic papillary thyroid cancer with NTRK fusion who received larotrectinib

- 62-year-old neurologist
  - Paratracheal mass found incidentally on chest CT, 2013
  - Thoracoscopic resection: papillary thyroid carcinoma (PTC)
  - Total thyroidectomy and central/lateral neck dissection

Path: PTC, diffuse sclerosing variant



- Tumor invasive throughout thyroid, ETE into soft tissue, multifocal LVI including extrathyroidal LV1, no PNI. Numerous + LNs, with ENE, largest 3.2 cm
- A: Higher power (100X) H&E: distinct tumor clusters (T) amongst normal thyroid follicles (N)
- B: Oil immersion (1000X): squamoid features notable in diffuse sclerosing variant, prominent pink desmosomes separating the cells (blue arrowheads), nuclear clearing and distinct intranuclear pseudoinclusions (yellow arrows)
- C: Typical follicular architecture (400X). This pattern, when seen in combination with other patterns (solid growth, classic papillary growth and squamous features) is practically diagnostic of a kinase fusion-related carcinoma

Images courtesy of Peter Sadow MD, PhD.; Chu YH, et al. *Mod Pathol* 2020;33:2458–72.

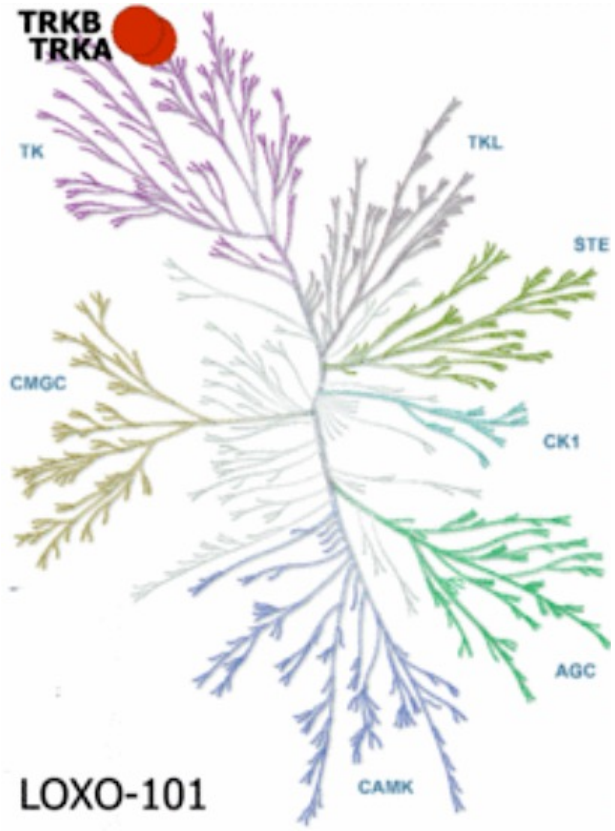
Dr Wirth: 62-year-old with metastatic papillary thyroid cancer with NTRK fusion who received larotrectinib (continued)

- Our in-house genotyping SNaPshot v1.0: Negative for mutations in K/H/N RAS & BRAF
- Received 125 mCi I-131, post-treatment WBS – uptake in thyroid bed only
- November, 2016 PET/CT: Multiple new & increasing lung nodules
- In-house fusion assay v. 1ß ordered: Targeted RNA NGS using Anchored Multiplex PCR (AMP)
  - No reportable fusion transcripts involving ALK/RET/ROS1/BRD4/NUTM1/

  EGFR/EWSR1 rearrangements and MET exon 14 skipping
  - **PPL** Exon22 (ENST00000345988) and **NTRK1** Exon13 (ENST00000524377) **fusion** found, confirmed by FISH

Dr Wirth: 62-year-old with metastatic papillary thyroid cancer with NTRK fusion who received larotrectinib (continued)

- December, 2016: Enrolled in Phase II basket trial of LOXO-101

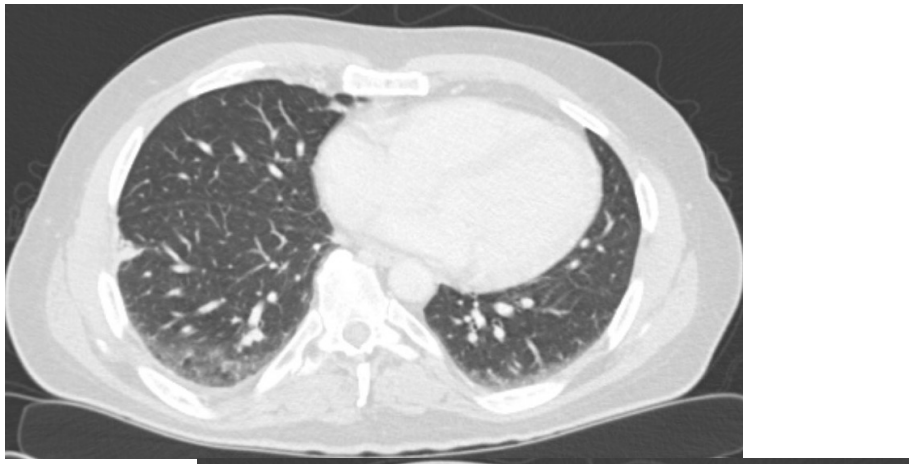


Larotrectinib

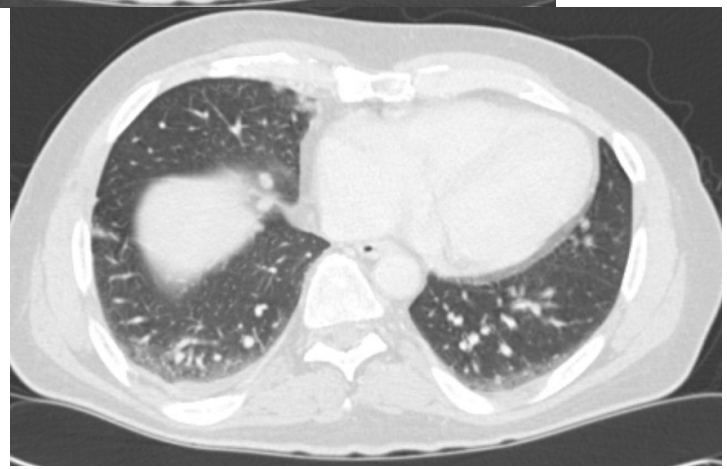
- First-in-class highly selective small molecule TRK 1/2/3 inhibitor
- First gene-specific, tissue agnostic FDA approval in oncology

Scott LJ. *Drugs* 2019;79:201–6.

Dr Wirth: 62-year-old with metastatic papillary thyroid cancer with NTRK fusion who received larotrectinib (continued)

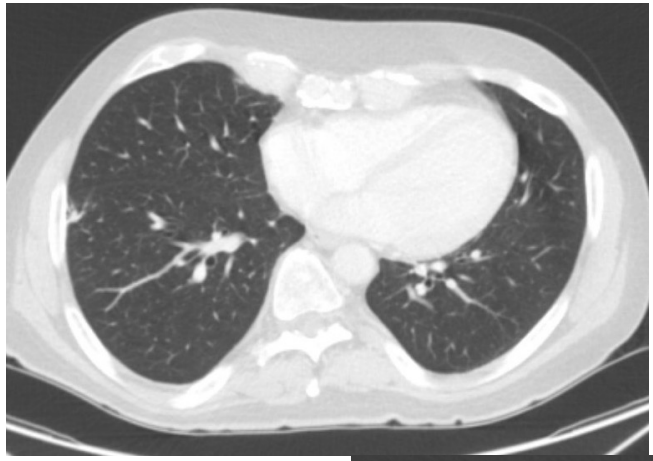


Tg = 1185

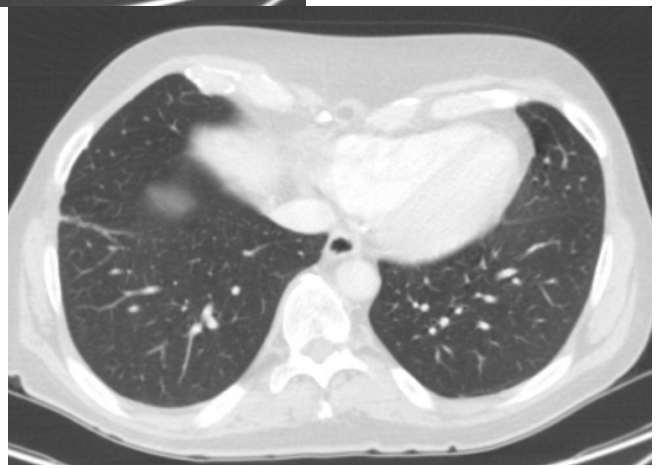


4 mos

March, 2017



Tg = 66



Complete response

- AEs: Gr 1 fatigue
- **Today** still on study, in CR
- Tg = 33

Agenda

Thyroid Cancer

MODULE 1: Nontargeted Treatment

- Dr Wirth: 69-year-old woman with poorly differentiated thyroid cancer initially treated with lenvatinib

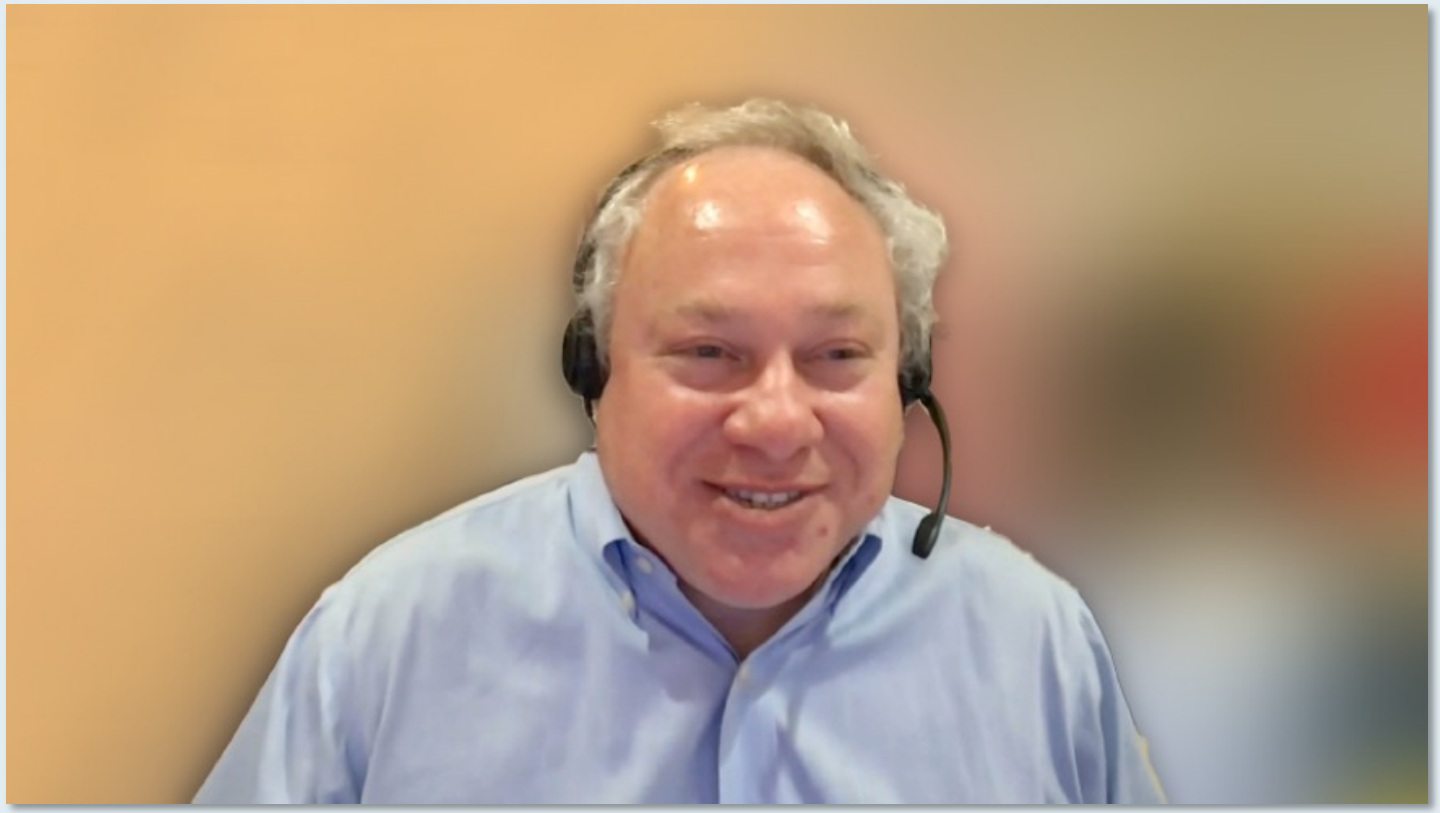
MODULE 2: NTRK Fusions

- Dr Sherman: 61-year-old woman with metastatic papillary thyroid cancer and an NTRK fusion who received repotrectinib
- Dr Wirth: 62-year-old with metastatic papillary thyroid cancer with NTRK fusion who received larotrectinib

MODULE 3: RET Mutations/Fusions

- Dr Sherman: 41-year-old man who presents with metastatic medullary thyroid cancer and a RET mutation
- Dr Wirth: 43-year-old man with metastatic medullary thyroid cancer and a RET mutation who received selpercatinib

Case Presentation: 41-year-old man who presents with metastatic medullary thyroid cancer and a RET mutation



Dr Eric Sherman (New York, New York)

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Dr Wirth: 43-year-old man with metastatic medullary thyroid cancer and a RET mutation who received selpercatinib

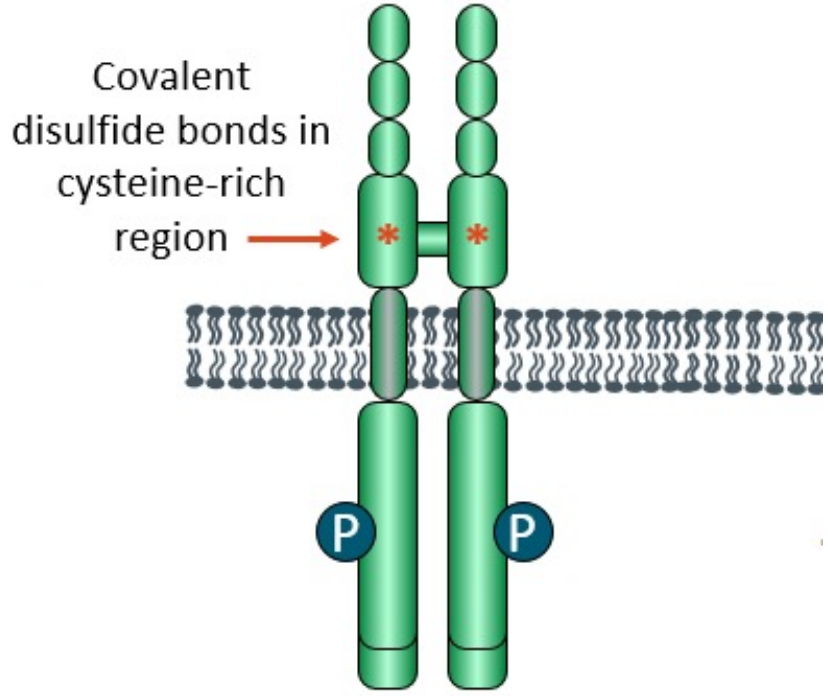
- 2014, 43-year-old man
  - Presented with a progressive neck mass not previously addressed d/t lack of health insurance
  - FNA – suspicious for medullary thyroid cancer (MTC)
  - No family history of endocrine malignancy
  - Pre-op plasma metanephrines/normetanephrines WNL
  - Pre-op calcitonin (Ct) = 32,143, CEA = 1241
- Aug, 2014 – thyroidectomy and neck dissection
  - Path – 2.2 cm R MTC with extrathyroidal extension, satellite nodules in isthmus and left lobe, C cell hyperplasia as present. 11/11 nodes +, largest 2.5 cm.
  - Germline RET testing negative for MEN2A/B

Dr Wirth: 43-year-old man with metastatic medullary thyroid cancer and a RET mutation who received selpercatinib (continued)

- Dec, 2014 – 2nd R neck dissection
  - Path –MTC with extranodal extension
- Feb, 2015 – 3rd surgery to clear mediastinum attempted as only site of radiographically evident disease
  - Ct = 26,048; CEA = 989.7
- Oct, 2016
  - PET/CT – FDG + supraclavicular nodes extending into thoracic inlet, bilateral mediastinal R>L nodes in continuity with a large right mediastinal mass, all increased in size since Feb 2015
- Cabozantinib initiated @ 140 mg QD
  - Experienced PR, lasting 2½ yrs

Dr Wirth: 43-year-old man with metastatic medullary thyroid cancer and a RET mutation who received selpercatinib (continued)

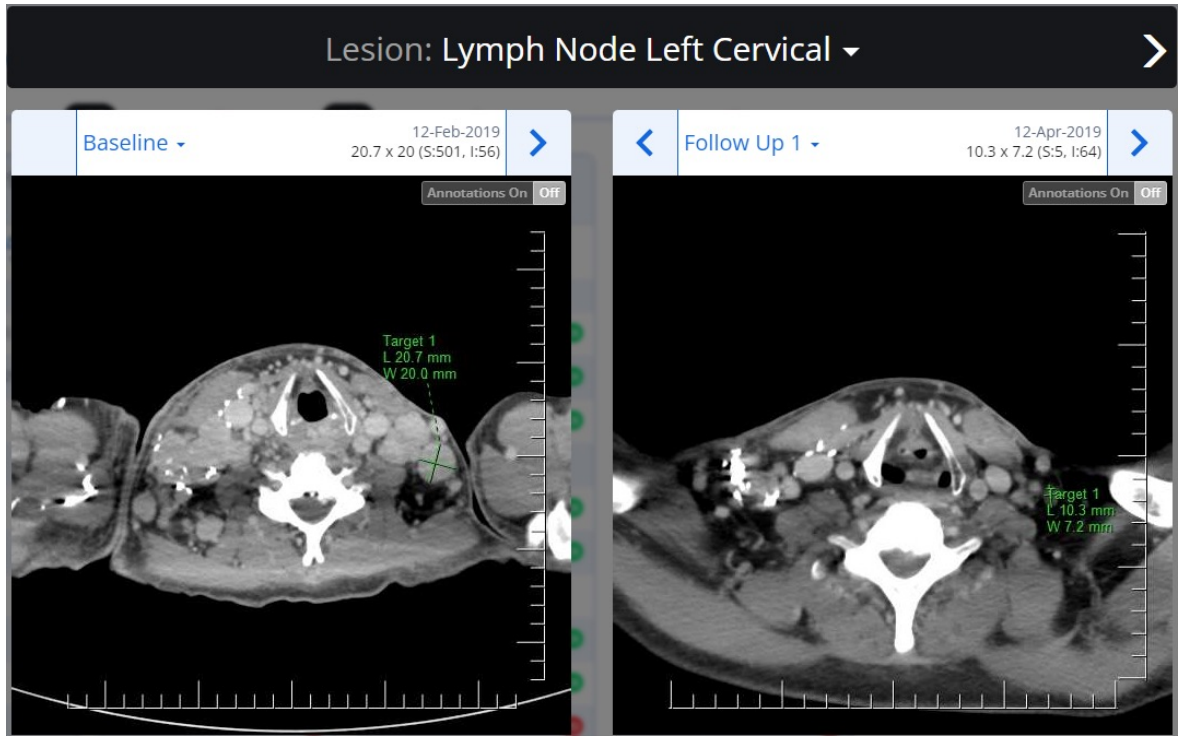
- Tumor molecular diagnostics:
  - *RET* Leu629_Ile638delinsCysAsp
- Feb, 2018
  - Enrolled on Phase I/II LIBRETTO-001 trial
  - Selpercatinib 160 mg BID

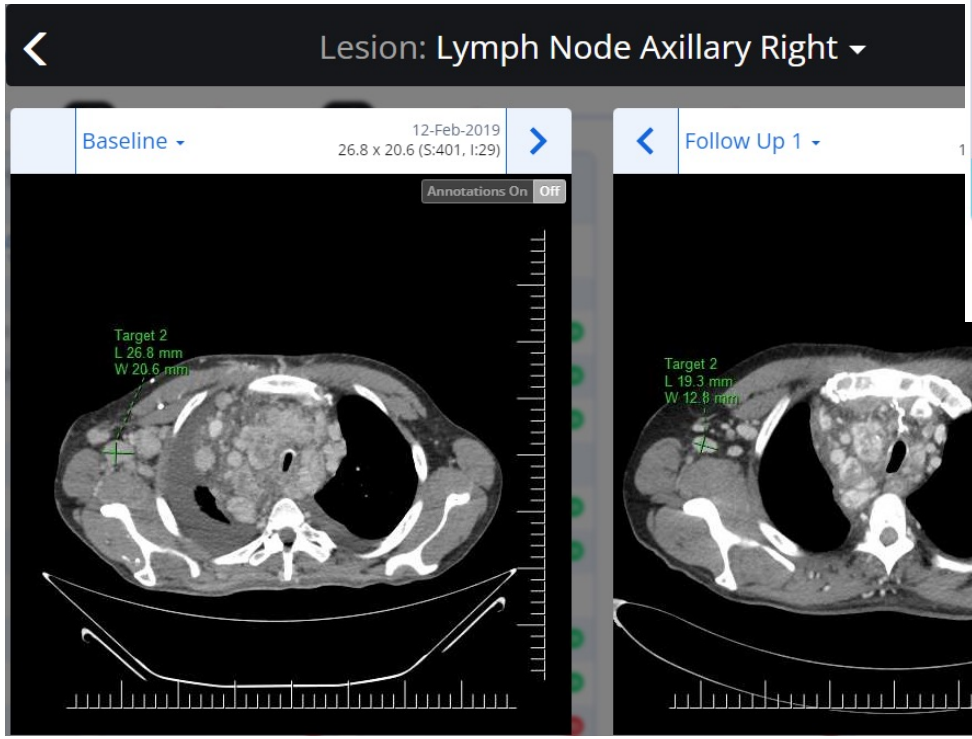


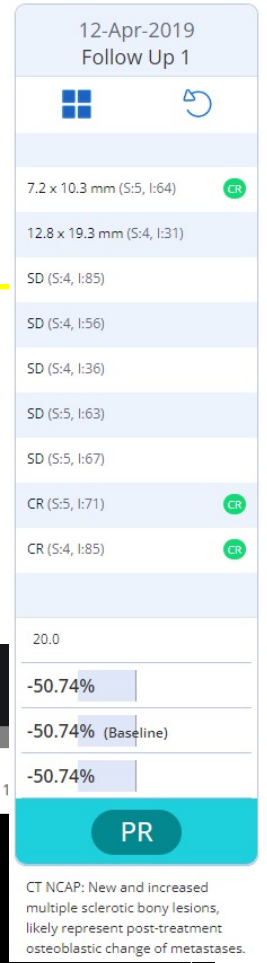
Activation of RET kinase domain by ligand-independent dimerization

Dr Wirth: 43-year-old man with metastatic medullary thyroid cancer and a RET mutation who received selpercatinib (continued)

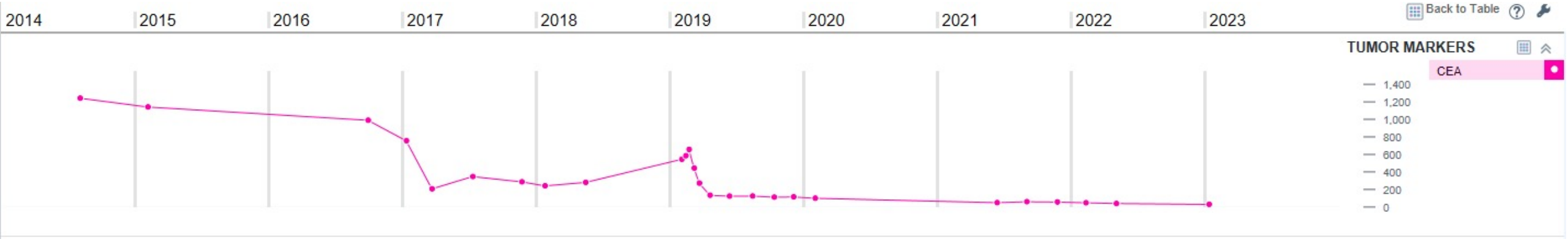
- On study, no AEs
  - In fact, energy, appetite & diarrhea all improved
  - Gained weight
  - Cont. working full-time job in retail





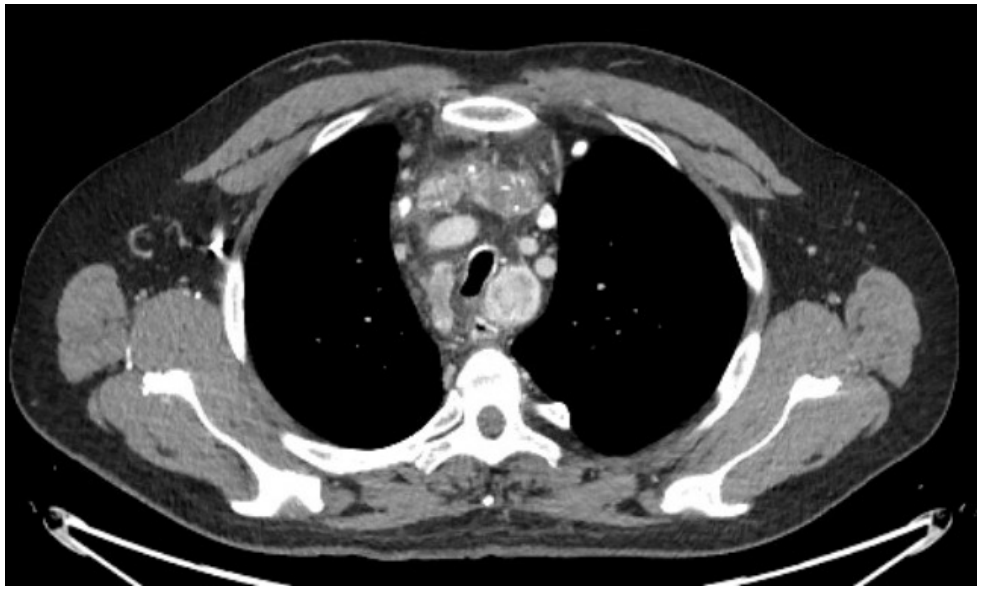


- Tumor markers
  - Ct & CEA



Dr Wirth: 43-year-old man with metastatic medullary thyroid cancer and a RET mutation who received selpercatinib (continued)

- Feb, 2022
  - 4 yrs on selpercatinib
  - L paratracheal oligoprogression
  - EBUS biopsy – MTC confirmed
    - Molecular diagnostics



```
Single nucleotide variants:
RET ENSP00000347942.3:p.Leu629Pro (ENST00000355710.3:c.1886T>C)
KRAS ENSP00000308495.3:p.Gly13Asp (ENST00000311936.3:c.38G>A)

Insertions/deletions:
RET ENSP00000347942.3:p.Glu632_Ile638del
(ENST00000355710.3:c.1895_1915delAGCTGTGCCGCACGGTGATCG)
```

- Selpercatinib held May – June, 2022
- IMRT to bilateral mediastinum

Dr Wirth: 43-year-old man with metastatic medullary thyroid cancer and a RET mutation who received selpercatinib (continued)

- June, 2022
  - Remained on LIBRETTO-001
  - Selpercatinib resumed
- Jan, 2023
  - Remains “in response” outside of radiated mediastinum
  - Ct = 457; CEA = 29.9
  - Feels great

Agenda

Neuroendocrine Tumors (NET)

MODULE 4: Somatostatin Analogs

- Dr Kunz: 50-year-old woman with newly well-differentiated small bowel NET and low-volume liver metastases

MODULE 5: Management of Carcinoid Syndrome

- Dr Strosberg: 60-year-old man who received telotristat ethyl for carcinoid syndrome diarrhea
- Dr Kunz: 60-year-old man with well-differentiated small bowel NET with stable disease on octreotride who is now experiencing increasing diarrhea

MODULE 6: Von Hippel-Lindau-Associated Pancreatic NETs

- Dr Strosberg: 48-year-old woman with von Hippel-Lindau syndrome and a pancreatic NET who received belzutifan
- Dr Kunz: 60-year-old man with symptomatic, well-differentiated hypervascular pancreatic NET with bulky liver metastases
- Dr Strosberg: 72-year-old woman with a low-grade NET of the terminal ileum with numerous hepatic lesions and a mesenteric mass treated with lanreotide

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Case Presentation: 50-year-old woman with newly well-differentiated small bowel NET and low-volume liver metastases

Pamela Kunz, MD (New Haven, Connecticut)

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Dr Strosberg – 60-year-old man who received telotristat ethyl for carcinoid syndrome diarrhea

- A 60-year-old man presented in 2/2016 with small bowel obstruction.
- CT scan showed transition point in the distal small intestine and multiple liver tumors.
- He underwent right hemicolectomy along with biopsy of a liver tumor.
- Pathology revealed metastatic low-grade neuroendocrine tumor (ki-67 <2%) with 5 tumors in the small intestine (largest 4cm) and 8/10 involved LNs.
- An OctreoScan showed avid uptake in the liver and retroperitoneal LNs.
- Urine 5-HIAA was mildly elevated at 22mg.
- Patient denied any flushing or diarrhea.

Dr Strosberg – 60-year-old man who received telotristat ethyl for carcinoid syndrome diarrhea (continued)

- The patient was started on octreotide LAR 30mg.
- Disease remained stable.
- He developed mild diarrhea, palliated with pancreatic enzymes.
- In 2018, he underwent a series of hepatic arterial embolizations for mildly progressive hepatic metastases. Scans showed minor response to treatment.
- In 6/2021, he complained of increased diarrhea over 3 months to about 6 times a day. Urine 5-HIAA had increased to 51mg. He also had mild worsening of chronic renal insufficiency (creatinine 1.6, baseline 1.3). CT scan was stable compared to a year earlier.

Dr Strosberg – 60-year-old man who received telotristat ethyl for carcinoid syndrome diarrhea (continued)

- Telotristat 250mg tid was prescribed.
- On follow-up visit 1 month later, patient reported improvement in diarrhea to about 3 times daily.
- Echocardiogram revealed mild-moderate tricuspid regurgitation.
- Urine 5-HIAA 3 months later had improved to 40mg.
- He remains on telotristat and octreotide LAR. Scans are stable.
- Echocardiogram is monitored yearly: screening for carcinoid heart disease.

Case Presentation: 60-year-old man with well-differentiated small bowel NET with stable disease on octreotride who is now experiencing increasing diarrhea

Dr Pamela Kunz (New Haven, Connecticut)

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Case Presentation: 60-year-old man with well-differentiated small bowel NET with stable disease on octreotride who is now experiencing increasing diarrhea (continued)

Dr Pamela Kunz (New Haven, Connecticut)

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Neuroendocrine Tumors (NET)

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Dr Strosberg – 48-year-old woman with von Hippel-Lindau syndrome and a pancreatic NET who received belzutifan

- A 48-year-old woman presented in 2003 with cervical and lumbar spinal hemangioblastomas and developed a 2cm left renal lesion in 2007. Partial nephrectomy revealed clear cell RCC.
- Tested positive for VHL mutation. Family history was positive for the disease.
- In 2017, she developed abdominal pain. CT revealed 4.1cm pancreatic uncinate mass, and several renal lesions measuring up to 3.4cm.
- FNA of the pancreatic mass revealed well-differentiated NET, with insufficient tissue for grading.
- ^{68}Ga-Dotatate PET scan showed uptake in the pancreatic mass.

Dr Strosberg – 48-year-old woman with von Hippel-Lindau syndrome and a pancreatic NET who received belzutifan (continued)

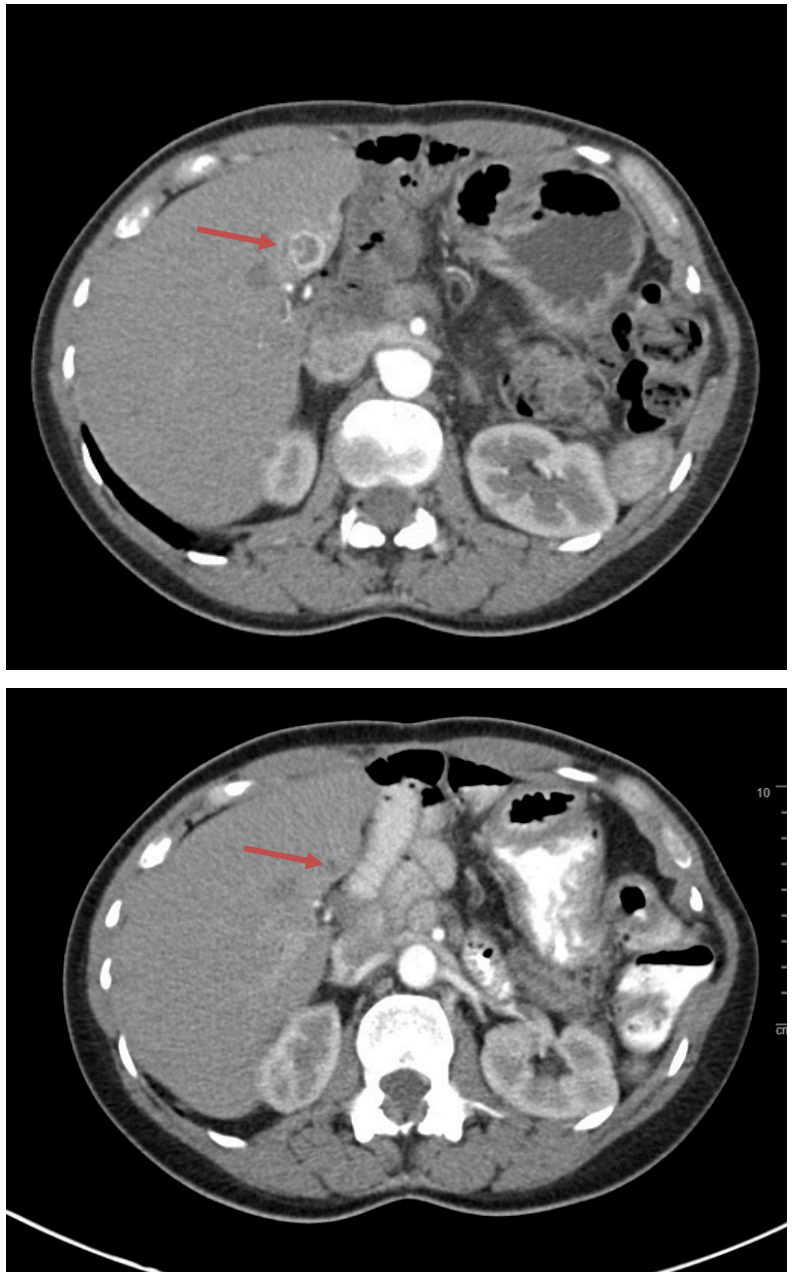
- The pancreatic tumor was considered locally advanced (unresectable)
- Patient began neoadjuvant lanreotide and sunitinib (the latter selected for its antiangiogenic properties in vHL-associated disease)
- Minor response observed on CT.
- Neoadjuvant treatment switched to capecitabine/temozolomide in 6/2018 with further minor response after 4 months.

Dr Strosberg – 48-year-old woman with von Hippel-Lindau syndrome and a pancreatic NET who received belzutifan (continued)

- Whipple surgery in 11/2018 revealed a 3.1cm grade 2 NET with 10/25 involved LNs and ki-67 index of 18%.
- She developed a small ^{68}Ga-Dotatate positive liver metastasis in 11/2019.
- The lesion was ablated percutaneously, and she began octreotide LAR.
- CT in 2/2020 showed multiple new liver lesions and she resumed sunitnib.
- Disease progressed in 2/2021 and she began everolimus.

Dr Strosberg – 48-year-old woman with von Hippel-Lindau syndrome and a pancreatic NET who received belzutifan (continued)

- She progressed further in 8/2021 and began belzutifan, an oral small molecule inhibitor of HIF-2α.
- Side effects consisted of mild fatigue and headaches, which resolved after 2 weeks, as well as grade 2 anemia.
- MRI performed 3 weeks after treatment onset showed significant partial response, and subsequent CT scans have shown near-complete response, both of her hepatic metastases and renal tumors.



Liver metastasis before (top) and after (bottom) initiation of belzutifan

Case Presentation: 60-year-old man with symptomatic, well-differentiated hypervascular pancreatic NET with bulky liver metastases

Dr Pamela Kunz (New Haven, Connecticut)

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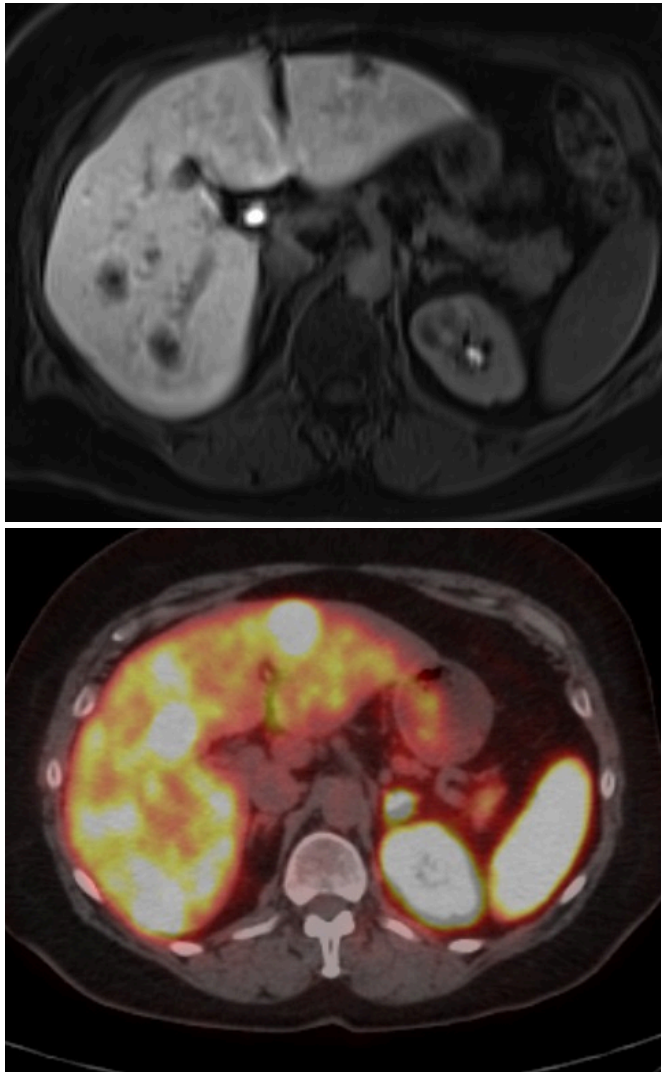
Dr Strosberg – 72-year-old woman with a low-grade NET of the terminal ileum with numerous hepatic lesions and a mesenteric mass treated with lanreotide

- A 72-year-old woman presented with abdominal pain and nausea in 2014. Scans showed evidence of bowel obstruction and she underwent segmental ileocecectomy in 8/2014.
- Pathology revealed low-grade neuroendocrine tumor involving the terminal ileum and cecum with 2 of 4 involved LNs.
- MRI with Eovist contrast in 2017 showed a stable 12mm mesenteric LN and multiple small new liver lesions.
- A ^{68}Ga-Dotatate PET showed uptake in numerous liver lesions as well as mesenteric mass.



MRI (top) and 68Ga-Dotatate PET showing somatostatin receptor avid liver metastases

Dr Strosberg – 72-year-old woman with a low-grade NET of the terminal ileum with numerous hepatic lesions and a mesenteric mass treated with lanreotide (continued)

- Urine 5-HIAA was normal at 14mg (nl <15). She had mild flushing and no diarrhea.
- She began lanreotide 120mg in 2/2018. Flushing resolved. Side effects consisted of mild abdominal cramping with first injection.
- She progressed in the liver in 3/2020 and received 4 cycles of ^{177}Lu-Dotatate between 4/2020 and 10/2020.
- She continued lanreotide 2 hours after each ^{177}Lu-Dotatate cycle (holding injection 4 weeks later). She remained on lanreotide after completion of ^{177}Lu-Dotatate therapy.
- She progressed in the liver in 7/2022. Also developed mild diarrhea. Urine 5-HIAA increased to 24mg .

Dr Strosberg – 72-year-old woman with a low-grade NET of the terminal ileum with numerous hepatic lesions and a mesenteric mass treated with lanreotide (continued)

- She underwent a series of bland hepatic arterial embolizations with partial response.
- Diarrhea resolved.
- She remains on lanreotide.

Meet The Professor

Optimizing the Management of Multiple Myeloma

Thursday, January 26, 2023
5:00 PM – 6:00 PM ET

Faculty

Noopur Raje, MD

Moderator

Neil Love, MD

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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