Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

December 2024 Volume 22, Issue 10, Supplement 8

A SPECIAL MEETING REVIEW EDITION

Highlights in Neuroendocrine Tumors From the 2024 North American Neuroendocrine Tumor Society (NANETS) Multidisciplinary NET Medical Symposium

A Review of Selected Presentations From the 2024 NANETS Multidisciplinary NET Medical Symposium • November 21-23, 2024 • Chicago, Illinois

Special Reporting on:

- NET Year in Review
- The Great Debate: NETTER-2 – ^{177}Lu-Dotatate as 1st Line or 2nd+ for Ki-67 >10%
- First-Line Efficacy of ^{177}Lu-Dotatate in Gastroenteropancreatic NETs by Tumor Grade and Primary Origin: Phase 3 NETTER-2 Subgroup Analysis
- Safety of ^{177}Lu-Dotatate Treatment in Patients With Advanced NETs and Extensive/Innumerable Bone Metastases
- Cabozantinib Versus Placebo for Advanced NETs After Progression on Prior Therapy: CABINET Trial/Alliance A021602
- Preliminary Safety and Efficacy Data of [^{212}Pb]VMT-α-NET in Somatostatin Receptor 2–Expressing NETs
- Building a High-Volume Multidisciplinary NET Program
- New and Upcoming Therapeutics/Resources

PLUS Meeting Abstract Summaries

With Expert Comments by:

Namrata Vijayvergia, MD
Interim Chief, Gastrointestinal Medical Oncology
Associate Professor, Department of Hematology/Oncology
Medical Director, Medical Oncology
Member, Cancer Epigenetics Institute
Fox Chase Cancer Center
Philadelphia, Pennsylvania

ON THE WEB:
hematologyandoncology.net

Indexed through the National Library of Medicine
(PubMed/MEDLINE), PubMed Central (PMC), and EMBASE

NET Year in Review

At an educational session on Saturday, November 21, Jennifer Chan, MD, MPH, of the Dana-Farber Cancer Institute and Harvard Medical School reviewed key advances and updates over the past year in the treatment of patients with neuroendocrine tumors (NETs). She focused on progress in 4 main areas: basic and translational science, clinical trials, observational and retrospective studies, and classifications and clinical guidelines.

Basic and Translational Science

Dr Chan noted that important research has been underway to develop new models for NETs to allow for greater understanding of the biology of these malignancies. A lack of models to evaluate therapeutic efficacy has been a limitation in NETs research, but recent developments in this area could provide insights into mechanisms of the biology and inform potential therapeutic strategies.

Dayton and colleagues developed patient-derived tumor organoids and then, using drug sensitivity analyses, identified ASCL1 as a potential biomarker for response to B-cell lymphoma 2 inhibitors in a subset of pulmonary NETs and found epidermal growth factor dependency in pulmonary NET cells.[1] Davis and colleagues published results of genomic studies showing the feasibility of categorizing lung NETs into subtypes based on differentiation signals.[2] One subtype is associated with an enhancer landscape that could make these tumors more vulnerable to fibroblast growth factor inhibition. A greater understanding of regulatory networks and differentiation signals could help identify potential therapeutic strategies for lung NETs.

Hoffman and colleagues used single-cell sequencing technology to characterize gene expression in malignant gastroenteropancreatic (GEP)-NET cells.[3] They found that immunosuppressive targets such as programmed cell death protein 1 (PD-1)/programmed death ligand 1 were only sparsely expressed in tumor and lymphoid compartments, but infiltrating myeloid cell types were enriched for genes associated with other immune checkpoints such as VISTA, TIM3, Gal-9, and *SIGLEC10*, suggesting that other targets could be explored.[3]

Several recent reports provide new insights on correlations between genetic alterations and disease progression or clinical outcomes in patients with neuroendocrine neoplasms.[4,5] Dr Chan said that these studies help provide a greater understanding of the biology of NETs and may elucidate new potential therapeutic strategies.

Other studies reported on the progression of disease following treatment. Backman and colleagues assessed molecular mechanisms of disease progression in patients with metastatic low/intermediate-grade pancreatic NETs (pNETs) and found that alkylating chemotherapy may contribute to a transformation to high-grade disease.[6] Cordero-Hernandez and colleagues published a retrospective review of 152 patients with well-differentiated grade 1 or 2 NET who received peptide receptor radionuclide therapy (PRRT) with [^{177}Lu]Lu-DOTATATE (^{177}Lu-Dotatate), of whom 7 had a transformation from NET to neuroendocrine carcinoma (NEC).[7] This transformation was associated with a dismal prognosis. Researchers noted that patients with tumors in the pancreatic tail who had received prior temozolomide could be at higher risk of transformation. However, whether this transformation reflects the natural history of the disease or treatment-related factors is not well understood.

Clinical Trials: ^{177}Lu-Dotatate

The radiolabeled somatostatin analog (SSA) ^{177}Lu-Dotatate is US Food and Drug Administration (FDA)–approved for the treatment of adults and pediatric patients at least 12 years of age with somatostatin receptor (SSTR)–positive GEP-NETs, including foregut, midgut, and hindgut NETs.[8] In the phase 3 NETTER-1 trial, ^{177}Lu-Dotatate demonstrated a significant progression-free survival (PFS) benefit over high-dose octreotide long-acting repeatable (LAR) in patients with well-differentiated metastatic midgut NETs with progression after first-line SSA therapy.[9] Subsequently, the NETTER-2 trial

ABSTRACT SUMMARY A Pilot Study of Pembrolizumab and PRRT for Patients With Metastatic Grade 2/3 Well-Differentiated NETs

Fidelman and colleagues presented results from a single-arm prospective pilot study of the PD-1 inhibitor pembrolizumab plus ^{177}Lu-Dotatate in 26 patients with metastatic grade 2 or 3 well-differentiated previously treated NETs (Abstract C-27). The most common primary tumor sites were the pancreas (n=15), ileum (n=6), and lung (n=3). Patients received pembrolizumab 200 mg every 3 weeks for up to 35 doses and ^{177}Lu-Dotatate 200±20 mCi every 8 weeks for up to 4 doses. The best observed ORR was 38% and the DCR was 92%. The median PFS was 13.7 months. Grade 3 or 4 serious AEs attributed to PRRT occurring in more than 1 patient were lymphopenia (12%) and anemia (8%). Grade 3 immune-related AEs included hyperglycemia (8%) and colitis (4%); no grade 4 immune-related AEs occurred.

Table 1. Outcomes With ^{177}Lu-Dotatate Plus Octreotide LAR vs High-Dose Octreotide LAR as First-Line Therapy in NETTER-2 Trial[10,11]

Outcome	^{177}Lu-Dotatate group[a] (n=151)	Control group[b] (n=75)
Median PFS, mo (95% CI)	22.8 (19.4-not estimated)	8.5 (7.7-13.8)
Stratified HR (95% CI)	0.276 (0.182-0.418) *P*<.0001	
ORR, %	43.0	9.3
Stratified odds ratio	7.81 *P*<.0001	

[a]Intravenous ^{177}Lu-Dotatate plus intramuscular octreotide 30 mg LAR then octreotide 30 mg LAR every 4 weeks.

[b]High-dose octreotide 60 mg LAR every 4 weeks.

HR, hazard ratio; LAR, long-acting repeatable; mo, months; ORR, objective response rate; PFS, progression-free survival.

evaluated ^{177}Lu-Dotatate as first-line therapy in patients with higher grade 2 (Ki-67 ≥10% and ≤20%) and grade 3 (Ki-67 >20% and ≤55%), SSTR-positive advanced GEP-NETs.

In the NETTER-2 trial, patients were randomly assigned 2:1 to 4 cycles of intravenous ^{177}Lu-Dotatate plus intramuscular octreotide 30 mg LAR, then octreotide 30 mg LAR every 4 weeks (n=151) or high-dose octreotide 60 mg LAR every 4 weeks (n=75).[10] The trial met its primary endpoint, demonstrating a significant PFS benefit with ^{177}Lu-Dotatate over high-dose octreotide LAR (median PFS, 22.8 vs 8.5 months; stratified HR, 0.276; *P*<.0001) (Table 1).[10,11] The objective response rate (ORR) was also higher with ^{177}Lu-Dotatate vs high-dose octreotide LAR (43.0% vs 9.3%; stratified odds ratio, 7.81; *P*<.0001).[11]

Subset analyses presented at the 2024 European Society of Medical Oncology Gastrointestinal Cancers Congress and at the 2024 NANETS Multidisciplinary NET Medical Symposium demonstrated a PFS benefit with ^{177}Lu-Dotatate across NET grades and tumor locations.[12,13] AEs of any grade occurred in 93% of patients receiving ^{177}Lu-Dotatate and 95% of patients receiving high-dose octreotide LAR. The investigators concluded that ^{177}Lu-Dotatate should be considered a standard of care for these patients.

The single-arm phase 2 NEOLUPANET trial evaluated neoadjuvant ^{177}Lu-Dotatate followed by surgery in patients with nonfunctioning pNETs. Among 31 enrolled patients, 26 completed 4 cycles of ^{177}Lu-Dotatate; 18 of 31 patients (58%) attained a partial radiologic response.[14] Among 29 patients who underwent surgery, 24 had R0 resections and 4 had R1 resections. Postoperative complications developed in 21 patients and were severe in 7 patients. Dr Chan noted that longer-term follow-up is needed to better assess the role of neoadjuvant ^{177}Lu-Dotatate in patients with pNETs.

Clinical Trials: Cabozantinib

The vascular endothelial growth factor (VEGF) pathway has demonstrated activity as a therapeutic target in NETs; however, the development of resistance mechanisms including activation of MET can limit the effectiveness of VEGF inhibitors.[15] Cabozantinib is a tyrosine kinase inhibitor that has activity against multiple targets including VEGF receptor 2 (VEGFR2), MET, RET, AXL, FLT3, and c-KIT.[16]

The randomized, double-blind, phase 3 CABINET trial compared cabozantinib with placebo in patients with previously treated progressive advanced NETs.[17] The trial enrolled patients with well- to moderately differentiated grade 1-3 NETs who had received PRRT or targeted therapy or both. Patients were randomly assigned 2:1 to cabozantinib 60 mg daily or placebo daily, until progressive disease. Patients in the placebo arm could receive open-label cabozantinib 60 mg daily upon progression.

The trial met its primary endpoint, demonstrating a significant improvement in PFS by blinded independent central review (BICR) after a median follow-up of 10.2 months in the extrapancreatic NET (epNET) cohort and after a median follow-up of 13.8 months in the pNET cohort (Table 2).[18] The ORR by BICR was 5% with cabozantinib vs 0% with placebo in the epNET cohort and 19% with cabozantinib vs 0% with placebo in the pNET cohort. Common grade ≥3 adverse events (AEs) included hypertension, fatigue, diarrhea, and thromboembolic events. Dr Chan concluded that cabozantinib is an effective treatment option for patients with epNETs or pNETs.

Other Clinical Trials

The single-arm phase 2 LITESPARK-004 trial is evaluating belzutifan in patients with von Hippel-Lindau (VHL) disease–associated renal cell carcinoma and other neoplasms. Recently, Else and colleagues published results with belzutifan in patients with VHL disease–associated pancreatic lesions.[19] Of the 61 enrolled patients, all patients had at least 1 pancreatic lesion and 36% had measurable pNETs at baseline. After a median follow-up of 37.8 months, the ORR was 84% in patients with pancreatic lesions and 91% in patients with pNETs. Median duration of response (DOR) and PFS had not been reached. Grade 3 treatment-related

Table 2. Outcomes With Cabozantinib vs Placebo in the CABINET Trial[17,18]

Outcome	Patients with epNETs		Patients with pNETs	
	Cabozantinib (n=134)	Placebo (n=69)	Cabozantinib (n=64)	Placebo (n=31)
Median PFS, mo (95% CI)	8.4 (7.6-12.7)	3.9 (3.0-5.7)	13.8 (9.2-18.5)	4.4 (3.0-5.9)
Stratified HR (95% CI)	0.38 (0.25-0.59) log-rank *P*<.0001		0.23 (0.12-0.42) log-rank *P*<.0001	
ORR, %	5	0	19	0

ePNETs, extrapancreatic neuroendocrine tumors; HR, hazard ratio; mo, months; ORR, objective response rate; pNETs, pancreatic neuroendocrine tumors.

Adapted from Halfdanarson et al. Presented at: 2024 NANETS Multidisciplinary NET Medical Symposium; November 21-23, 2024; Chicago, Illinois, USA. Poster C-9.

AEs occurred in 18% of patients; there were no grade 4 or 5 treatment-related AEs. Dr Chan noted that the results of studies evaluating belzutifan in other NET populations are awaited, and the LITESPARK-004 results may translate to options for patients with VHL mutations with more advanced disease.

Other notable reports from the past year include the phase 2 ALPHAMEDIX-02 trial evaluating ^{212}Pb-Dotamtate as targeted α therapy for patients with advanced SSTR-expressing GEP-NETs,[20] a phase 2 study of the oral selective SSTR subtype 2 (SSTR2) agonist paltusotine,[21] a phase 3 trial evaluating lanreotide autogel/depot in patients with advanced bronchopulmonary NETs,[22] and the phase 2 Natalie trial of cabozantinib in patients with unresectable and progressive metastatic pheochromocytoma or paraganglioma.[23]

Dr Chan also discussed several trials recently reported in patients with NECs. The single-arm, phase 2 NICE-NEC trial evaluated carboplatin, etoposide, and nivolumab in patients with advanced grade 3 NECs of gastroenteropancreatic or unknown origin.[24] The 12-month overall survival (OS) rate of 54.1% did not meet the primary endpoint, but 37.6% of patients had an OS exceeding 2 years. The randomized phase 2/3 SWOG S2012 trial is evaluating the role of atezolizumab added to standard chemotherapy as first-line treatment in patients with poorly differentiated extrapulmonary small-cell NECs (NCT05058651).[25]

A randomized, noncomparative phase 2 trial evaluated the safety and efficacy of folinic acid, 5-fluorouracil, and irinotecan, or capecitabine plus temozolomide (FOLFIRI or CAPTEM) in patients with metastatic NECs. The trial was halted for futility, as the primary endpoint of 12-week disease control rate (DCR) was not met, showing comparable low activity with both regimens.[26]

The DeLLphi-301 trial demonstrated the activity of tarlatamab, a bispecific T-cell engager targeting δ-like ligand 3 (DLL3) and CD3, in patients with previously treated small-cell lung carcinoma (SCLC).[27] Tarlatamab demonstrated an ORR of 40% in the 10 mg group and 32% in the 100 mg group; the most common AE was cytokine release syndrome, reported in 51% and 61% of patients, respectively. In 2024, tarlatamab received FDA approval for use in patients with extensive-stage SCLC with progression on or after platinum-based chemotherapy.[28]

Observational and Retrospective Studies

Among the recent observational and retrospective studies in NETs is an analysis of a prospective carcinoid anesthesia database showing that carcinoid crisis occurred in 30% of 150 patients receiving first-line octreotide and 93% required subsequent vasopressors.[29] Patients receiving first-line vasopres-

ABSTRACT SUMMARY Once-Daily Oral Paltusotine in the Treatment of Patients With Carcinoid Syndrome: Results From a Phase 2, Randomized, Parallel-Group Study

Chauhan and colleagues presented results from a randomized, phase 2 study evaluating paltusotine, an oral selective SSTR2 agonist, in patients with carcinoid syndrome (Abstract C-5). A total of 36 patients with well-differentiated grade 1 or 2 NETs with carcinoid syndrome were enrolled and randomly assigned to once-daily paltusotine 40 mg or 80 mg for 8 weeks. Paltusotine was associated with reductions in the frequency and severity of carcinoid syndrome, including flushing and frequent/urgent bowel movements. No severe or serious treatment-related AEs were reported.

sors were significantly less likely to have multiple crises, and had a shorter crisis duration, shorter anesthesia time, and no aborted operations, vs 2% in the octreotide group (P<.05 for all). Based on the findings, vasopressors should be used as first-line treatment for intraoperative crisis.

Several recent studies evaluated bone marrow changes that could develop after PRRT. Pritzl and colleagues reported a retrospective analysis in which 14 of 346 patients (4.0%) who received ^{177}Lu-Dotatate at the Mayo Clinic developed therapy-related clonal cytopenias and neoplasms.[30] Dr Chan noted that prospective studies are needed to identify patients at risk for developing treatment-related neoplasms after PRRT. Kusne and colleagues reported a prospective study of 37 patients planning to receive ^{177}Lu-Dotatate at the Mayo Clinic.[31] Clonal hematopoiesis (CH), which was detected in 35.1% of patients, was associated with lower pretreatment baseline count and more thrombocytopenia during and after PRRT. Another recent retrospective study evaluated the association between absorbed dose of ^{177}Lu-Dotatate and tumor shrinkage in 32 patients receiving ^{177}Lu-Dotatate in a clinical trial.[32] Prospective trials are needed to determine whether individualizing PRRT dosing could improve outcomes.

Other studies evaluated biomarkers and the prevalence of germline variants in patients with NETs. Meng and colleagues published an observational study showing the feasibility of using serum chromogranin A as a biomarker in 153 patients with GEP-NETs.[33] Mohindroo and colleagues evaluated the prevalence of pathologic or likely pathologic germline variants in a high-risk pNET cohort (n=132) and an unselected cohort (n=106).[34] The prevalence of pathologic or likely pathologic germline variants was 33% in the high-risk cohort and 21% in the unselected cohort, suggesting a role for universal germline testing in patients with pNETs.

> Efforts towards development of patient-derived tumor organoids is a huge advancement as it makes it easier to test new drugs. Also exciting are targeted therapy options along with new data in lung NET, pNET, epNET, and grade 3 NET. Furthermore, testing for tumor markers in the blood may improve clinical decision making.
>
> —Namrata Vijayvergia, MD

Updates to Classifications and Guidelines

Dr Chan noted that there have been several recent updates to guidance on the staging and treatment of NETs. These include critical updates to the American Joint Committee on Cancer staging for GEP-NETs,[35] a new guidance document regarding the role of biomarkers for informing prognosis and treatment in patients with advanced GEP neuroendocrine neoplasms,[36] an American Society of Clinical Oncology guideline for systemic therapy for well-differentiated GEP-NETs,[37] a European Society for Medical Oncology guideline for the diagnosis, treatment, and follow-up of patients with rare endocrine tumors,[38] and a European Neuroendocrine Tumor Society guideline for digestive NECs.[39]

Conclusions

Dr Chan concluded that the past year has seen many advances in the understanding of the biology of NETs and in their treatment. An increasing number of tools and models have led to advances in research and in clinical care. Additional studies are needed to identify and test novel therapies and to determine optimal sequencing and predictors of benefit. Moreover, Dr Chan concluded that multidisciplinary care and collaboration are needed in the management of patients with NETs.

References

1. Dayton TL, Alcala N, Moonen L, et al. Druggable growth dependencies and tumor evolution analysis in patient-derived organoids of neuroendocrine neoplasms from multiple body sites. *Cancer Cell*. 2023;41(12):2083-2099.e9.

1. Davis E, Avniel-Polak S, Abu-Kamel S, et al. Enhancer landscape of lung neuroendocrine tumors reveals regulatory and developmental signatures with potential theranostic implications. *Proc Natl Acad Sci U S A*. 2024;121(41):e2405001121.

3. Hoffman SE, Dowrey TW, Villacorta Martin C, et al. Intertumoral lineage diversity and immunosuppressive transcriptional programs in well-differentiated gastroenteropancreatic neuroendocrine tumors. *Sci Adv*. 2023;9(39):eadd9668.

4. Elvebakken H, Venizelos A, Perren A, et al. Treatment outcome according to genetic tumour alterations and clinical characteristics in digestive high-grade neuroendocrine neoplasms. *Br J Cancer*. 2024;131(4):676-684.

5. Joseph NM, Umetsu SE, Kim GE, et al. Progression of low-grade neuroendocrine tumors (NET) to high-grade neoplasms harboring the NEC-like co-alteration of RB1 and TP53. *Endocr Pathol*. Published online November 18, 2024.

6. Backman S, Botling J, Nord H, et al. The evolutionary history of metastatic pancreatic neuroendocrine tumours reveals a therapy driven route to high-grade transformation. *J Pathol*. 2024;264(4):357-370.

7. Cordero-Hernandez IS, Ross AC, Dasari A, Halperin DM, Chasen B, Yao JC. Transformation of G1-G2 neuroendocrine tumors to neuroendocrine carcinomas following peptide receptor radionuclide therapy. *Endocr Relat Cancer*. 2024;31(4):e230203.

8. LUTATHERA® (lutetium Lu 177 dotatate) full prescribing information. Millburn, NJ: Advanced Accelerator Applications USA, Inc., a Novartis Company; October 2024.

9. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of ^{177}Lu-Dotatate for midgut neuroendocrine tumors. *N Engl J Med*. 2017;376(2):125-135.

10. Singh S, Halperin D, Myrehaug S, et al. [^{177}Lu]Lu-DOTA-TATE plus long-acting octreotide versus highdose 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. *Lancet*. 2024;403(10446):2807-2817.
11. Singh S, Halperin DM, Myrehaug S, et al. [^{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. *J Clin Oncol*. 2024;42(3 suppl):LBA588.
12. Singh S, Halperin D, Myrehaug S, et al. First-line efficacy of [177Lu]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 III NETTER-2 study. *Ann Oncol*. 2024;35(suppl 1):S94-S105.
13. Singh S, Halperin D, Myrehaug S, et al. First-line efficacy of [^{177}Lu]Lu-DOTA-TATE in gastroenteropancreatic neuroendocrine tumors by tumor grade and primary origin: phase 3 NETTER-2 subgroup analysis. Presented at: 2024 NANETS Multidisciplinary NET Medical Symposium; November 21-23, 2024; Chicago, Illinois, USA. Abstract C-31.
14. Partelli S, Landoni L, Bartolomei M, et al. Neoadjuvant ^{177}Lu-Dotatate for non-functioning pancreatic neuroendocrine tumours (NEOLUPANET): multicentre phase II study. *Br J Surg*. 2024;111(9):znae178.
15. Pozas J, San Román M, Alonso-Gordoa T, et al. Targeting angiogenesis in pancreatic neuroendocrine tumors: resistance mechanisms. *Int J Mol Sci*. 2019;20(19):4949.
16. Grüllich C. Cabozantinib: multi-kinase inhibitor of MET, AXL, RET, and VEGFR2. *Recent Results Cancer Res*. 2018;211:67-75.
17. Chan JA, Geyer S, Zemla T, et al. Phase 3 trial of cabozantinib to treat advanced neuroendocrine tumors. *N Engl J Med*. Published online September 16, 2024.
18. Halfdanarson TR, Geyer S, Zemla T, et al. Cabozantinib versus placebo for advanced neuroendocrine tumors after progression on prior therapy (CABINET Trial/Alliance A021602). Presented at: 2024 NANETS Multidisciplinary NET Medical Symposium; November 21-23, 2024; Chicago, Illinois, USA. Abstract C-9.
19. Else T, Jonasch E, Iliopoulos O, et al. Belzutifan for von Hippel-Lindau disease: pancreatic lesion population of the phase 2 LITESPARK-004 study. *Clin Cancer Res*. 2024;30(9):1750-1757.
20. Strosberg JR, Naqvi S, Cohn AL, et al. Safety, tolerability and efficacy of ^{212}Pb-DOTAMTATE as a targeted alpha therapy for subjects with unresectable or metastatic somatostatin receptor-expressing gastroenteropancreatic neuroendocrine tumors (SSTR+ GEP-NETs): A phase 2 study. *J Clin Oncol*. 2024;42(16 suppl):4020.
21. Usiskin K, Chauhan A, Mui C, et al. Interim safety and exploratory efficacy results of a phase 2, randomised, parallel-group study of oral paltusotine treatment in subjects with carcinoid syndrome. *J Neuroendocrin*. 2024;36:I29.
22. Baudin E, Capdevila J, Hörsch D, et al. Treatment of advanced BP-NETS with lanreotide autogel/depot vs placebo: the phase III SPINET study. *Endocr Relat Cancer*. 2024;31(9):e230337.
23. Jimenez C, Habra MA, Campbell MT, et al. Cabozantinib in patients with unresectable and progressive metastatic phaeochromocytoma or paraganglioma (the Natalie Trial): a single-arm, phase 2 trial. *Lancet Oncol*. 2024;25(5):658-667.
24. Riesco-Martinez MC, Capdevila J, Alonso V, et al. Nivolumab plus platinum-doublet chemotherapy in treatment-naive patients with advanced grade 3 neuroendocrine neoplasms of gastroenteropancreatic or unknown origin: the multicenter phase 2 NICE-NEC trial (GETNE-T1913). *Nat Commun*. 2024;15(1):6753.
25. Evaluating the addition of the immunotherapy drug atezolizumab to standard chemotherapy treatment for advanced or metastatic neuroendocrine carcinomas that originate outside the lung. ClinicalTrials.gov identifier: NCT05058651. Updated December 9, 2024. Accessed December 10, 2024. https://clinicaltrials.gov/study/NCT05058651
26. Bongiovanni A, Liverani C, Foca F, et al. A randomized phase II trial of Captem or Folfiri as second-line therapy in neuroendocrine carcinomas. *Eur J Cancer*. 2024;208:114129.
27. Ahn MJ, Cho BC, Felip E, et al. Tarlatamab for patients with previously treated small-cell lung cancer. *N Engl J Med*. 2023;389(22):2063-2075.
28. IMDELLTRA® (tarlatamab-dlle) full prescribing information. Thousand Oaks, CA: Amgen, Inc.; May 2024.
29. McCully BH, Kozuma K, Pommier S, Pommier RF. Comparison of octreotide and vasopressors as first-line treatment for intraoperative carcinoid crisis. *Ann Surg Oncol*. 2024;31(5):2996-3002.
30. Pritzl SL, Kusne Y, Halfdanarson TR, et al. Spectrum of therapy-related clonal cytopenias and neoplasms after exposure to Lutetium-177-Dotatate. *Leuk Res*. 2024;136:107434.
31. Kusne Y, Lasho T, Finke C, et al. Clonal hematopoiesis in patients with neuroendocrine tumor treated with Lutetium-177 and the risk of thrombocytopenia: a prospective study. *JCO Precis Oncol*. 2024;8:e2400143.
32. Warfvinge CF, Gustafsson J, Roth D, et al. Relationship between absorbed dose and response in neuroendocrine tumors treated with [^{177}Lu]Lu-Dotatate. *J Nucl Med*. 2024;65(7):1070-1075.
33. Meng QH, Halfdanarson TR, Bornhorst JA, et al. Circulating chromogranin A as surveillance biomarker in patients with carcinoids: the CASPAR study. *Clin Cancer Res*. Published online October 25, 2024.
34. Mohindroo C, Baydogan S, Agarwal P, et al. Germline testing identifies pathogenic/likely pathogenic variants in patients with pancreatic neuroendocrine tumors. *Cancer Prev Res (Phila)*. 2024;17(7):335-342.
35. Chauhan A, Chan K, Halfdanarson TR, et al. Critical updates in neuroendocrine tumors: Version 9 American Joint Committee on Cancer staging system for gastroenteropancreatic neuroendocrine tumors. *CA Cancer J Clin*. 2024;74(4):359-367.
36. Loree JM, Chan D, Lim J, et al. Biomarkers to inform prognosis and treatment for unresectable or metastatic GEP-NENs. *JAMA Oncol*. Published online October 3, 2024.
37. Del Rivero J, Perez K, Kennedy EB, et al. Systemic therapy for tumor control in metastatic well-differentiated gastroenteropancreatic neuroendocrine tumors: ASCO guideline. *J Clin Oncol*. 2023;41(32):5049-5067.
38. Hadoux J, Lamarca A, Grande E, et al. Neuroendocrine neoplasms of head and neck, genitourinary and gynaecological systems, unknown primaries, parathyroid carcinomas and intrathyroid thymic neoplasms: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *ESMO Open*. 2024;9(10):103664.
39. Sorbye H, Grande E, Pavel M, et al. European Neuroendocrine Tumor Society (ENETS) 2023 guidance paper for digestive neuroendocrine carcinoma. *J Neuroendocrinol*. 2023;35(3):e13249.

The Great Debate: NETTER-2 – ^{177}Lu-Dotatate: 1st Line or 2nd+ for Ki-67 >10%

An educational session featured a debate between 2 experts regarding the optimal sequencing of ^{177}Lu-Dotatate in the treatment of patients with GEP-NETs with a Ki-67 of 10% to 55%. The session was moderated by Daniel M. Halperin, MD, of Winship Cancer Institute of Emory University.

Arguing in favor of using ^{177}Lu-Dotatate as first-line therapy in this population was Diane Reidy-Lagunes, MD, of the Memorial Sloan Kettering Cancer Center. In her argument, Dr Reidy-Lagunes said that ^{177}Lu-Dotatate is the best drug available for these patients with respect to efficacy and safety, so administration should not be delayed. The PFS benefit demonstrated with ^{177}Lu-Dotatate over high-dose octreotide in NETTER-2 is significant, with a hazard ratio (HR) of 0.276 (P<.0001).[1] Dr Reidy-Lagunes noted that efficacy is important to consider, as patients with Ki-67 10% to 55% can potentially have a more aggressive biology and a poorer prognosis (Table 3).[2]

There are also advantages related to treatment administration and toxicity profile, Dr Reidy-Lagunes said. ^{177}Lu-Dotatate is administered via 4 doses of intravenous therapy 4 times over 8 months, avoiding the need for daily oral therapies or intensive intravenous chemotherapy regimens.[3]

Table 3. 5-Year Overall Survival Rates in Patients With Localized, Regional, and Metastatic pNETs: SEER Database Analysis[2]

pNETs		5-year overall survival, %
Localized	**Overall**	**83.19**
	Grade 1	87.28
	Grade 2	79.69
	Grade 3	46.24
Regional	**Overall**	**67.36**
	Grade 1	80.99
	Grade 2	72.49
	Grade 3	38.19
Metastatic	**Overall**	**28.13**
	Grade 1	51.03
	Grade 2	45.16
	Grade 3	12.37

pNETs, pancreatic neuroendocrine tumors.

^{177}Lu-Dotatate is also associated with a lower risk of chronic toxicities, such as low-grade fatigue and diarrhea, associated with some therapies, thereby maintaining patients' quality of life.

^{177}Lu-Dotatate is associated with a risk for bone marrow damage and myelodysplastic syndromes, which are rare but serious AEs. Emerging evidence suggests that the risk of bone marrow damage may be higher after alkylating therapies. In the study by Kusne and colleagues reporting a baseline CH rate of 35% among 37 patients planning ^{177}Lu-Dotatate, 30% of patients had received alkylating agents.[4]

Dr Reidy-Lagunes concluded that using ^{177}Lu-Dotatate first-line makes sense, as it is the most effective drug, avoids the potential risks of using PRRT in patients who have received other therapies, and increases the likelihood that patients will be able to receive ^{177}Lu-Dotatate at all by administering it when blood counts are sufficiently high and patients have not received liver-directed therapies that could also preclude its use.

The con for first-line ^{177}Lu-Dotatate was given by Guillaume Pegna, MD, of Oregon Health & Science University. Dr Pegna argued that ^{177}Lu-Dotatate is an important tool in the treatment of GEP-NETs, but a one-size-fits-all approach may not be optimal. NETs encompass multiple diseases with different severities, and patients can differ in symptomatology and disease aggressiveness, even within a single pathologic grade.

He also noted that the use of high-dose octreotide as a control arm for NETTER-2 in patients with higher-grade pNETs was appropriately designed at the time, but today chemotherapy regimens such as CAPTEM or folinic acid, 5-fluorouracil, and oxaliplatin may be more commonly used and are in line with guidelines.[5] In the ECOG-ACRIN 2211 trial, CAPTEM was associated with a median PFS of 22.7 months and an ORR of 39.7% in patients with advanced pNETs.[6] Although data are limited regarding the efficacy of chemotherapy in patients with grade 3 disease, in a phase 2 single-arm trial, chemotherapy was associated with a

ABSTRACT SUMMARY ACTION-1 Phase 1b/3 Trial of RYZ101 in GEP-NETs Progressing After ^{177}Lu Somatostatin Analogue Therapy: Phase 1b Safety/Efficacy

The α-emitting radiopharmaceutical therapy ^{255}Ac-Dotatate (RYZ101) is being developed for the treatment of SSTR2-positive solid tumors. Daniel Halperin, MD, and colleagues presented results from the ACTION-1 trial, which is evaluating RYZ101 in patients with SSTR2-positive, grade 1 or 2, well-differentiated, inoperable, advanced GEP-NETs with progression after 2 to 4 cycles of ^{177}Lu SSA therapy (Abstract C-17). The phase 1b part of the trial evaluated decreasing doses of RYZ101 administered every 8 weeks for up to 4 cycles, with lysine and arginine co-infused for renal protection. As of the data cutoff, 17 patients had received RYZ101 at the starting dose. After a median follow-up of 12.3 months since enrollment, no dose-limiting toxicities were noted, and no dose de-escalation had been employed. Dose reductions were required in 4 patients owing to grade 2 thrombocytopenia (n=3) and grade 3 anemia (n=1). Fifteen patients received the 4 planned doses; 2 patients discontinued because of disease progression. The most frequent treatment-related grade 3 or greater adverse events were anemia (17.6%), lymphocyte count decrease (17.6%), and creatinine clearance decrease (11.8%). The confirmed ORR was 29.4%, including 1 complete response and 4 partial responses; stable disease was attained in 7 patients (41.2%). The phase 3 portion of the trial, currently enrolling, is comparing RYZ101 every 8 weeks for 4 cycles vs standard of care in patients with advanced SSTR2-positive GEP-NETs progression following prior ^{177}Lu-labeled SSAs.

The NETTER-2 trial prospective data reveals that in the first-line setting, ^{177}Lu-Dotatate is very effective and an option for patients who are Ki-67 10% to 55%. But the heterogeneous nature of this disease necessitates additional considerations.

PRRT may be specially considered in functional tumors as it does a really good job of providing long-term control of both the symptoms and the tumor. I also consider PRRT in patients with higher tumor burden who are not acutely symptomatic over chemotherapy.

In retrospective sequencing studies, ^{177}Lu-Dotatate is associated with better response and less toxicity. So, I use ^{177}Lu-Dotatate over everolimus and sunitinib in most patients with higher risk disease, and especially in the older frail patients, and where I need a response. The answer to whether ^{177}Lu-Dotatate should be given before SSA or after SSA is nuanced and individualized.

—Namrata Vijayvergia, MD

median PFS of 9.3 months in patients with grade 3 pNETs with Ki-67 less than 55%.[7]

Looking ahead, several trials are comparing chemotherapy with PRRT in this population, including the phase 2 ComPareNET trial (NCT05247905) of CAPTEM vs ^{177}Lu-Dotatate in patients with advanced pNETs and the phase 3 COMPOSE trial (NCT04919226) of ^{177}Lu-Edotreotide vs best standard of care in patients with well-differentiated aggressive grade 2 and 3 GEP-NETs.[8,9]

Dr Pegna also posed the question of whether other therapies could be considered for patients who are older or who have less symptomatic or more indolent disease. He noted that in the NETTER-2 trial, octreotide 60 mg LAR every 4 weeks was associated with a median PFS of 8.5 months and has a highly favorable toxicity profile, and thus could be a reasonable treatment option in selected patients with GEP-NETs. Dr Pegna also discussed cost differences between different therapies, which could also be a consideration.

Dr Pegna concluded that GEP-NETs are heterogeneous and there are multiple disease-specific and patient-specific factors to consider, and thus, although ^{177}Lu-Dotatate has changed the treatment paradigm, it should be considered only 1 tool in the toolbox of GEP-NET therapies.

References

1. Singh S, Halperin D, Myrehaug S, et al. [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. *Lancet*. 2024;403(10446):2807-2817.
2. Sonbol MB, Mazza GL, Mi L, et al. Survival and incidence patterns of pancreatic neuroendocrine tumors over the last 2 decades: a SEER database analysis. *Oncologist*. 2022;27(7):573-578.
3. LUTATHERA® (lutetium Lu 177 dotatate) full prescribing information. Millburn, NJ: Advanced Accelerator Applications USA, Inc., a Novartis Company; October 2024.
4. Kusne Y, Lasho T, Finke C, et al. Clonal hematopoiesis in patients with neuroendocrine tumor treated with Lutetium-177 and the risk of thrombocytopenia: a prospective study. *JCO Precis Oncol*. 2024;8:e2400143.
5. National Comprehensive Cancer Network® (NCCN) clinical practice guidelines in oncology: neuroendocrine and adrenal tumors. Version 2.2024. August 1, 2024. Accessed December 4, 2024. https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf
6. Kunz PL, Graham NT, Catalano PJ, et al. Randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors (ECOG-ACRIN E2211). *J Clin Oncol*. 2023;41(7):1359-1369.
7. Jeong H, Shin J, Jeong JH, et al. Capecitabine plus temozolomide in patients with grade 3 unresectable or metastatic gastroenteropancreatic neuroendocrine neoplasms with Ki-67 index <55%: single-arm phase II study. *ESMO Open*. 2021;6(3):100119.
8. Comparing capecitabine and temozolomide in combination to ^{177}Lu-Dotatate in patients with advanced pancreatic neuroendocrine tumors. ClinicalTrials.gov identifier: NCT05247905. Updated October 26, 2024. Accessed December 5, 2024. https://clinicaltrials.gov/study/NCT05247905
9. ^{177}Lu-Edotreotide versus best standard of care in well-differentiated aggressive grade-2 and grade-3 gastroenteropancreatic neuroendocrine tumors (GEP-NETs): COMPOSE. ClinicalTrials.gov identifier: NCT04919226. Updated August 12, 2024. Accessed December 5, 2024. https://clinicaltrials.gov/study/NCT04919226

First-Line Efficacy of ^{177}Lu-Dotatate in Gastroenteropancreatic NETs by Tumor Grade and Primary Origin: Phase 3 NETTER-2 Subgroup Analysis

The randomized, phase 3 NETTER-2 trial evaluated ^{177}Lu-Dotatate in the first-line setting in patients with advanced grade 2 or 3 well-differentiated GEP-NETs. This open-label, parallel-group superiority trial enrolled patients at least 15 years of age with newly diagnosed higher-grade 2 (Ki-67 ≥10% and ≤20%) and grade 3 (Ki-67 >20% and ≤55%) SSTR-positive advanced GEP-NETs. Patients were randomly assigned 2:1 to receive 4 cycles of intravenous ^{177}Lu-Dotatate plus intramuscular octreotide 30 mg LAR, then octreotide 30 mg LAR every 4 weeks (n=151) or high-dose octreotide 60 mg LAR every 4 weeks (n=75).

As previously reported, the trial met its primary endpoint, demonstrating a significant improvement in PFS with ^{177}Lu-Dotatate over high-dose octreotide LAR (median PFS, 22.8 vs 8.5 months; stratified HR, 0.276; 95% CI, 0.182-0.418; *P*<.0001).[1] At 2024 NANETS Multidisciplinary NET Medical Symposium, Simron Singh, MD, and colleagues presented subgroup analyses from NETTER-2, reporting outcomes based on tumor grade and tumor site.[2]

> Until now, grade 3 NET has been treated as an orphan disease. So, the most important aspect of NETTER-2's subgroup analysis was that the grade 3 tumor group was associated with an impressive and significant improvement in PFS. The difference in PFS for groups with pNET vs small intestinal NET was as expected. However, the much better response rates of around 50% in both the pNET group and grade 3 group has given me a lot of confidence in using ^{177}Lu-Dotatate in both these groups.
>
> —Namrata Vijayvergia, MD

The primary tumor site and tumor grade were well balanced between arms. The most common primary tumor sites were the pancreas (54.4%) and small intestine (29.2%). Tumors were grade 2 in 65.0% of patients, with a median Ki-67 of 13.0% (range, 10%-20%),

Table 4. PFS in NETTER-2 Based on NET Grade and Site of Origin[2]

Subgroup		Median PFS, mo		HR (95% CI)
		^{177}Lu-Dotatate group[a]	Control group[b]	
Grade	2	29.0	13.8	0.306 (0.176-0.530)
	3	22.2	5.6	0.266 (0.145-0.489)
Site of origin	Pancreas	19.4	8.5	0.336 (0.200-0.562)
	Small intestine	29.0	8.4	0.305 (0.126-0.738)

[a]Intravenous ^{177}Lu-Dotatate plus intramuscular octreotide 30 mg LAR then octreotide 30 mg LAR every 4 weeks.

[b]High-dose octreotide 60 mg LAR every 4 weeks.

HR, hazard ratio; LAR, long-acting repeatable; mo, months; PFS, progression-free survival.

Adapted from Singh et al. Presented at: 2024 NANETS Multidisciplinary NET Medical Symposium; November 21-23, 2024; Chicago, Illinois, USA. Poster C-31.

Table 5. Objective responses in NETTER-2 Based on NET Grade and Site of Origin[2]

Subgroup		ORR, %		Odds ratio for response (95% CI)	Median time to response among responders to ^{177}Lu-Dotatate, mo	Median duration of response to ^{177}Lu-Dotatate, mo
		^{177}Lu-Dotatate group[a]	Control group[b]			
Grade	2	40.4	10.4	5.83 (2.12-16.00)	5.73	24.9
	3	48.1	7.4	11.57 (2.48-53.97)	5.82	19.3
Site of origin	Pancreas	51.2	12.2	7.56 (2.70-21.19)	5.85	18.4
	Small intestine	26.7	4.8	7.27 (0.88-60.24)	5.78	Not estimable

[a]Intravenous ^{177}Lu-Dotatate plus intramuscular octreotide 30 mg LAR then octreotide 30 mg LAR every 4 weeks.

[b]High-dose octreotide 60 mg LAR every 4 weeks.

LAR, long-acting repeatable; mo, months; ORR, objective response rate.

Adapted from Singh et al. Presented at: 2024 NANETS Multidisciplinary NET Medical Symposium; November 21-23, 2024; Chicago, Illinois, USA. Poster C-31.

and were grade 3 in 35.0% of patients, with a median Ki-67 of 30.0% (range, 21%-50%).

Efficacy analyses showed a significant improvement in median PFS with ^{177}Lu-Dotatate over high-dose octreotide LAR in patients with grade 2 NETs (29.0 vs 13.8 months; HR, 0.306; 95% CI, 0.176-0.530) and in patients with grade 3 NETs (22.2 vs 5.6 months; HR, 0.266; 95% CI, 0.145-0.489) (Table 4). The PFS benefit with ^{177}Lu-Dotatate over high-dose octreotide LAR was also observed whether the tumor originated in the pancreas (median PFS, 19.4 vs 8.5 months; HR, 0.336; 95% CI, 0.200-0.562) or in the small intestine (median PFS, 29.0 vs 8.4 months; HR, 0.305; 95% CI, 0.126-0.738).

Objective responses were higher with ^{177}Lu-Dotatate compared with high-dose octreotide LAR across tumor grade and site (Table 5). Time to response was similar across subgroups, and responses also appeared durable across subgroups. Investigators concluded that ^{177}Lu-Dotatate should be considered a first-line standard of care for patients with advanced well-differentiated grade 2 or 3 SSTR-positive GEP-NETs.

References

1. Singh S, Halperin D, Myrehaug S, et al. [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. *Lancet*. 2024;403(10446):2807-2817.
2. Singh S, Halperin D, Myrehaug S, et al. First-line efficacy of [^{177}Lu]Lu-DOTA-TATE in gastroenteropancreatic neuroendocrine tumors by tumor grade and primary origin: phase 3 NETTER-2 subgroup analysis. Presented at: 2024 NANETS Multidisciplinary NET Medical Symposium; November 21-23, 2024; Chicago, Illinois, USA. Abstract C-31.

Safety of ^{177}Lu-Dotatate Treatment in Patients With Advanced NETs and Extensive/Innumerable Bone Metastases

Osama M. Mosalem, MD, and colleagues presented results of a retrospective study evaluating the safety of ^{177}Lu-Dotatate in patients with extensive bone metastases.[1] The analysis included 48 patients from Mayo Clinic centers who had either extensive (73%) or confluent/near-confluent (27%) bone metastases. The incidence of hematologic toxicities was 50%, including 23.5% grade 3 or 4 events. The most frequent hematologic toxicities were anemia (50%; 14.5% grade 3/4), thrombocytopenia (33%; 19% grade 3/4), and neutropenia (17%; 10% grade 3/4). Prolonged cytopenias (≥6 months posttreatment) developed in 21%. Treatment-related myelodysplastic syndrome developed in 1 patient (2%), and treatment-related clonal cytopenias developed in 2 patients (4%).

The researchers noted that the incidence of hematologic toxicities

ABSTRACT SUMMARY *MEN1/DAXX* Alterations Are Associated With Improved Overall Survival in Patients With pNETs

Gujarathi and colleagues presented results of a retrospective chart review assessing the potential role of alterations in 2 genes, *MEN1* and *DAXX*, for predicting outcomes in patients with pNETs (Abstract O-4). The analysis included 62 patients who had received care at a specialized NET center between 2013 and 2024. *MEN1/DAXX* alterations were present in 45% of patients (n=28). Patients with *MEN1/DAXX* alterations were significantly less likely than patients with wild-type *MEN1/DAXX* to have grade 3 tumors (7.1% vs 35.3%; *P*=.01) but other clinical factors were similar between arms, including the presence of metastases, extrahepatic metastases, and bone metastases, and elevated baseline chromogranin A level.

Among patients who had received ^{177}Lu-Dotatate, the presence of deleterious alterations in *MEN1* or *DAXX* was associated with significantly longer PFS (median PFS, 26.5 months vs 12.9 months among patients with wild-type *MEN1/DAXX*; *P*=.01). No significant differences in PFS based on *MEN1/DAXX* status were noted for patients who had received CAPTEM or surgical debulking for metastatic disease. Altered *MEN1/DAXX* was also associated with a significant improvement in OS from diagnosis (median OS, not reached vs 53.8 months with wild-type *MEN1/DAXX*; log-rank *P*=.049). The investigators cautioned that this was a retrospective single-center study. External validation and prospective studies are needed to further investigate these findings and determine the prognostic and predictive value of *MEN1/DAXX* alterations in pNETs.

was higher than prior reports in this population.[2] However, most hematologic toxicities were transient. They emphasized the importance of monitoring and assessment of hematologic parameters when considering ^{177}Lu-Dotatate in patients with extensive or innumerable bone metastases.

References

1. Mosalem OM, Kamatham V, Sonbol MB, et al. Safety of lutetium-177 dotatate treatment in patients with advanced neuroendocrine tumors and extensive/innumerable bone metastases. Presented at: 2024 NANETS Multidisciplinary NET Medical Symposium; November 21-23, 2024; Chicago, Illinois, USA. Abstract C-19.

2. Alsadik S, Gnanasegaran G, Chen L, et al. Safety and efficacy of 177 Lu-Dotatate in neuroendocrine tumor patients with extensive bone disease. *Clin Nucl Med*. 2023;48(8):667-672.

This retrospective study talks about the slightly higher risk of hematologic toxicities associated with ^{177}Lu-Dotatate in patients with bone metastases, but I have not seen this in my practice. ^{177}Lu-Dotatate is a very effective therapy in patients with bone metastases. What is more worrisome for me than patients with bone metastases is when we have patients treated with prior chemotherapy and in quick succession with ^{177}Lu-Dotatate or ^{177}Lu-Dotatate followed by chemotherapy which increases the risk of long-term myelotoxicity. —Namrata Vijayvergia, MD

Cabozantinib Versus Placebo for Advanced NETs After Progression on Prior Therapy: CABINET Trial/Alliance A021602

Thor R. Halfdanarson, MD, and colleagues presented results from the CABINET trial, focusing on subset analyses including by tumor site, grade, and prior therapy. The CABINET trial enrolled 203 patients with epNETS and 95 patients with pNETS.[1]

Subset analyses showed a significant improvement in PFS with cabozantinib over placebo in most subgroups, including in patients with well-differentiated and moderately differentiated NETs and across tumor grades (aside from the small subset of 8 patients with grade 3 epNETs), and regardless of primary tumor site or prior treatment with everolimus or ^{177}Lu-Dotatate.

The safety profile of cabozantinib was similar to prior reports.[2] The most common grade 3/4 AEs observed with cabozantinib were fatigue, diarrhea, hypertension, palmar-plantar erythrodysesthesia, and venous thromboembolism (Table 6). Dose reductions were required for 66% to 68% of patients receiving cabozantinib, compared with 10% to 19% of patients receiving placebo.

Investigators noted that OS data are not yet available. They concluded that the CABINET trial was one of the first prospective randomized trials to evaluate a therapy in patients already treated with PRRT, chemotherapy, and

Table 6. Selected Grade 3 or 4 AEs Reported With Cabozantinib and Placebo in the CABINET Trial[1]

Grade 3/4 AE	Patients with epNETs, %		Patients with pNETs, %	
	Cabozantinib (n=134)	Placebo (n=69)	Cabozantinib (n=64)	Placebo (n=31)
Any	62	27	65	23
Fatigue	62	8	11	3
Diarrhea	11	5	6	0
Hypertension	21	3	22	10
Mucositis	4	0	8	0
PPE	3	0	10	0
VTE	0	0	11	0

AE, adverse event; ePNETs, extrapancreatic neuroendocrine tumors; pNETs, pancreatic neuroendocrine tumors; PPE, palmar-plantar erythrodysesthesia; VTE, venous thromboembolism.

Adapted from Halfdanarson et al. Presented at: 2024 NANETS Multidisciplinary NET Medical Symposium; November 21-23, 2024; Chicago, Illinois, USA. Poster C-9.

targeted therapy, and that the findings indicate that cabozantinib is an effective option for these patients.

References

1. Halfdanarson TR, Geyer S, Zemla T, et al. Cabozantinib versus placebo for advanced neuroendocrine tumors after progression on prior therapy (CABINET Trial/Alliance A021602). Presented at: 2024 NANETS Multidisciplinary NET Medical Symposium; November 21-23, 2024; Chicago, Illinois, USA. Abstract C-9.
2. Chan JA, Geyer S, Zemla T, et al. Phase 3 trial of cabozantinib to treat advanced neuroendocrine tumors. *N Engl J Med*. Published online September 16, 2024.

I think that cabozantinib is a welcome addition to the oncologist's toolkit as it is supposed to have widespread applicability—from grade 1 NET to NET from any site of origin. However, cabozantinib-associated toxicities, though mostly reversible, are a concern and efficacy data doesn't seem as good as that of ^{177}Lu-Dotatate.

I would probably use cabozantinib before everolimus, given the exciting data in pancreatic NET, lung NET, grade 3 NET, and in heavily pretreated population. It would also have a role in patients who cannot get ^{177}Lu-Dotatate due to various reasons—disease progression on ^{177}Lu-Dotatate, kidney dysfunction, lack of receptors, extremely small burden of disease, etc.
—Namrata Vijayvergia, MD

Preliminary Safety and Efficacy Data of [^{212}Pb]VMT-α-NET in Somatostatin Receptor 2–Expressing NETs

Richard L. Wahl, MD, presented preliminary results of a phase 1 study evaluating the novel α radionuclide therapy [^{212}Pb]VMT-α-NET in patients with advanced SSTR2-expressing NETs with progression on prior therapy who had not previously received PRRT.[1] The first-in-human study included 4 dose-escalation cohorts, with the first 2 cohorts incorporating dosimetry evaluations with a therapeutic surrogate ([^{203}Pb]VMT-α-NET) before receiving up to 4 cycles of [^{212}Pb]VMT-α-NET at one of 2 doses

(92.5 MBq or 185 MBq) coadministered with renal protective amino acids.

Among 9 patients who had received treatment at the time of analysis, no dose-limiting toxicities, grade ≥4 or serious AEs, or declines in renal function were observed, and no dysphagia was reported. The most frequent toxicities were grade 1 or 2 fatigue (77%), grade 1 alopecia (66%), grade 1 or 2 lymphocyte count reduction (66%), grade 1 or 2 nausea (66%), grade 1 or 2 anemia (55%), and grade 1, 2, or 3 diarrhea (66%). In the preliminary report of antitumor activity, durable control of disease was observed in 8 of 9 patients (89%) and investigators noted signs of clinical activity. The dose escalation study is ongoing, with the goal of defining a recommended phase 2 dose.

These preliminary safety and efficacy data are promising and present an exciting future but answers to many questions are yet to be determined to assess the clinical relevance: How the PFS and the OS benefits are going to hold? What is the duration of response? What does the long-term toxicity profile look like?
—Namrata Vijayvergia, MD

Reference

1. Wahl RL, Anthony L, Solnes LB, et al. Preliminary safety and efficacy data of [^{212}Pb]VMT-α-NET in somatostatin receptor 2 (SSTR2) expressing neuroendocrine tumors (NETs). Presented at: 2024 NANETS Multidisciplinary NET Medical Symposium; November 21-23, 2024; Chicago, Illinois, USA. Abstract C-37.

Building a High-Volume Multidisciplinary NET Program

At an educational session, experts from the University of Chicago shared their experience building and running a high-volume multidisciplinary NET program.[1] The program is codirected by medical oncologist Chih-Yi "Andy" Liao, MD, and surgical oncologist Xavier Keutgen, MD, who joined forces to build a dedicated program for patients with NETs.

The program, which was first established in 2019, has grown to be the top NET program in the area, with more than 1000 patient clinic visits each year. The program holds the top

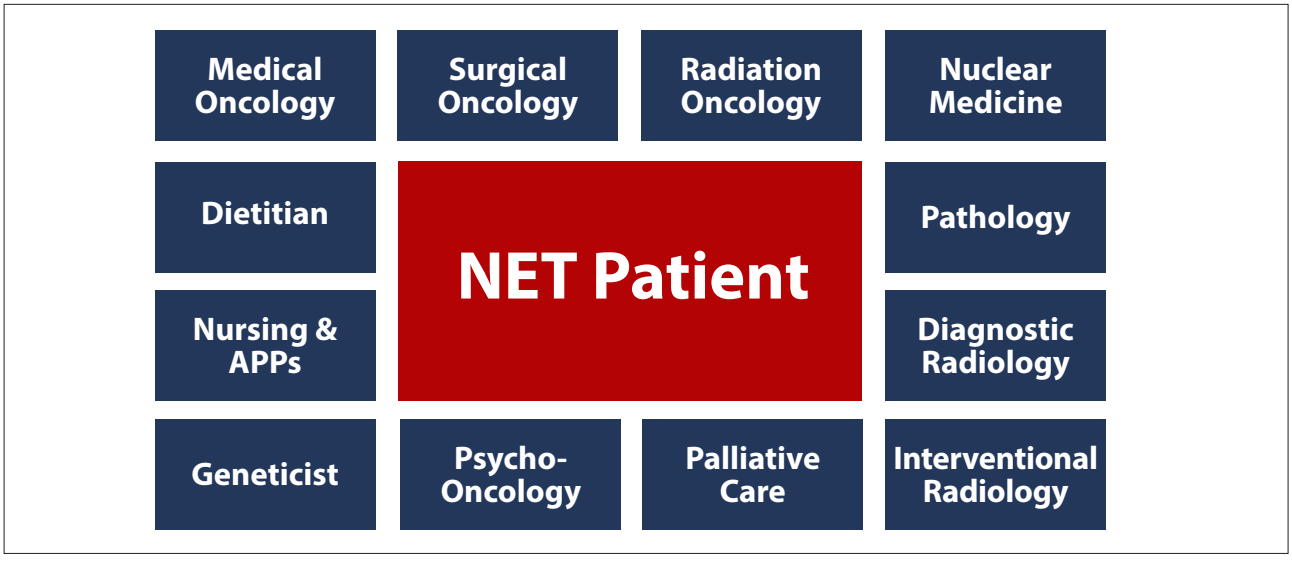

Figure 1. Components of the multidisciplinary NET program at the University of Chicago.

Courtesy of Andy Liao, MD

APP, advanced practice provider; NET, neuroendocrine tumor.

Adapted from Keutgen et al. Presented at: 2024 NANETS Multidisciplinary NET Medical Symposium; November 21-23, 2024; Chicago, Illinois, USA.

A multidisciplinary NET program is critical to successful NET management. Given the range of treatments—surgery, liver-directed therapies, nuclear medicine therapies, radiation, and medical therapies—and requirement for symptom management necessitate having specialists from surgery, nuclear medicine, radiation oncology, interventional radiology, medical oncology, gastroenterology, endocrinology, genetics, etc. on the multidisciplinary NET team. Presenting NET cases at multidisciplinary conferences along with active research built into a high-volume program helps further treatment and develop clinical trials, as has been my center's experience.
—Namrata Vijayvergia, MD

market share in the region, caring for 12.6% of patients with NETs, and this margin continues to widen, Dr Liao said. Research is another important component of the program, which aims to bring forward innovative clinical trials and team science.

The multidisciplinary clinic includes oncology subspecialties (medical oncology, surgical oncology, radiation oncology, nuclear medicine), pathology, a dedicated nurse navigator, and clinical support staff (Figure 1). In the clinic, patients are seen by the oncologist and the surgeon at the same time to enhance communication, facilitate comanagement, minimize treatment delays, and present a united front for patients. The program also includes a synchronized clinical research team to enable clinical trial recruiting. The multidisciplinary team meets monthly via tumor boards.

Dr Liao said that to build the program, they created a business plan and presented it to their cancer center leadership, demonstrating that with modest investments they could become regional leaders and transform the care of patients with NETs.

Reference

1.Keutgen X (moderator). Building a high-volume multidisciplinary NET program presented by The University of Chicago. Presented at: 2024 NANETS Multidisciplinary NET Medical Symposium; November 21-23, 2024; Chicago, Illinois, USA.

New and Upcoming Therapeutics/Resources

At an educational session moderated by Thor R. Halfdanarson, MD, of the Mayo Clinic, researchers discussed potential future strategies in development for the treatment of patients with NETs.

Targeting DLL3 in NETs

Valentina Gambardella, MD, PhD, of the Hospital Clínico Universitario de Valencia, discussed the potential role of DLL3 as a therapeutic target in NETs. DLL3 is expressed on approximately 70% to 80% of NETs with specificity.[1] Among the DLL3-targeted therapies in development is obrixtamig, a DLL3/CD3 T-cell engager. In a phase 1 trial, obrixtamig showed preliminary antitumor activity in patients with DLL3-positive large-cell neuroendocrine car-

ABSTRACT SUMMARY Imaging, Clinical, and Safety Outcomes in Metastatic NET Patients Treated With PRRT in the Midwestern USA

Sriwastwa and colleagues presented a retrospective study evaluating outcomes with ^{177}Lu-Dotatate in patients with metastatic NETs receiving care in a tertiary referral center in the midwestern United States (Abstract C-20). A total of 42 patients had received at least 1 dose and had at least 12 months of follow-up. The most common tumors were gastrointestinal NETs (64.3%), followed by pancreatic (31%), and bronchial (4.8%). Tumors were World Health Organization grade 1 or 2 (Ki-67 <20%) in 41 patients (98%). After a median follow-up of 40 months, the ORR was 9.5% (all PRs) and the stable disease rate was 59.5%. Disease progression occurred in 13 patients (31%), of whom 12 patients (29%) had died. The median PFS and OS had not been reached. Grade 1 or 2 AEs developed in 92.6% of patients; transient lymphopenia occurred in 33 patients (78.6%) and transient hyperglycemia occurred in 25 patients (59.5%). Factors significantly associated with risk of disease progression included having a grade 3 AE (P=.025) and having a higher posttreatment chromogranin A level (P=.033). Primary or metastatic disease site and pretreatment chromogranin A levels were not significantly associated with disease progression.

ABSTRACT SUMMARY Corticosteroid Prophylaxis Did Not Decrease Tumor Flare Reaction in High-Risk NET Patients Treated With ^{177}Lu-Dotatate

Cass and colleagues at Vanderbilt-Ingram Cancer Center presented results of an analysis evaluating outcomes in 41 patients with NETs who were treated with ^{177}Lu-Dotatate at their institution and had received corticosteroids for the prevention of tumor flare reaction owing to a high burden of disease, significant peritoneal or mesenteric disease, or disease involvement of critical structures (Abstract C-33). The most common site of primary disease was the small intestine (75.6%) followed by the pancreas (4.8%), lung (4.8%), and other sites (14.6%). A history of tumor flare reaction was reported in 12.1% of patients. Overall, tumor flare developed in 32% of patients. The incidence of small bowel obstructions was 10%; 27% of patients had increased pain and 2% had vision changes. Corticosteroid-associated AEs occurred in 20% of patients; the most frequent AEs were hyperglycemia and insomnia. One patient developed gastrointestinal bleeding requiring hospitalization and intervention. The researchers concluded that short-course prophylactic corticosteroids did not decrease the incidence of tumor flare reactions in high-risk patients with NETs receiving ^{177}Lu-Dotatate.

cinoma of the lung.[2] Responses have also been observed across organ classes in patients with extrapulmonary neuroendocrine carcinoma.[3] Tarlatamab, a bispecific T-cell engager that binds DLL3 and CD3, has demonstrated antitumor activity in a phase 1 study in patients with neuroendocrine prostate cancer and recently demonstrated favorable survival outcomes in a phase 2 study in patients with previously treated SCLC.[4,5] Cytokine release syndrome is a key AE with tarlatamab.

HPN328 is a trispecific antibody that incorporates anti-DLL3, anti-CD3, and anti-albumin for half-life extension. HPN328 has demonstrated preliminary antitumor activity and tolerability in patients with NECs.[6] Dr Gambardella noted that there are many open questions regarding the potential role of T-cell engagers related to patient selection, class-specific toxicities, and the sequencing of these agents.

Developing CAR-T Therapy for NETs

Xianxin Hua, MD, PhD, of the University of Pennsylvania and the Abramson Family Cancer Research Institute, discussed a novel chimeric antigen receptor (CAR) T-cell therapy that he and his colleagues are developing. The researchers identified a cell-surface adhesion protein, CDH17, which is upregulated in gastrointestinal cancers and NETs.[7] This supported the development of the CDH17-targeting CAR T-cell therapy CHM-2101, which has been shown to eradicate CDH17-expressing NETs in preclinical models without harming normal intestinal epithelial cells.[7] A phase 1/2 study evaluating CHM-2101 in patients with advanced gastrointestinal cancers is ongoing.

Exploring Fluorescence-Guided Surgery

Ali Azhdarinia, PhD, of McGovern Medical School at UTHealth Houston, reviewed his research into high-contrast detection of SSTR2 for fluorescence-guided surgery in patients with pNETs. This technology aims to reduce the likelihood of incomplete resection by systemically administering a tumor-targeting fluorescent compound. Dr Azhdarinia and colleagues have published preclinical studies showing the feasibility of detecting SSTR2 with a fluorescent tag, with high specificity for pNET tissues.[8] A first-in-human trial is planned.

References

1. Frizziero M, Kilgour E, Simpson KL, et al. Expanding therapeutic opportunities for extrapulmonary neuroendocrine carcinoma. *Clin Cancer Res*. 2022;28(10):1999-2019.
2. Wermke M, Gambardella V, Kuboki Y, et al. Phase I trial of DLL3/CD3 IgG-like T-cell engager BI 764532 in patients with DLL3-positive tumors: patients with LCNEC. Presented at: 2024 World Conference on Lung Cancer; September 7-10, 2024; San Diego, California, USA. Abstract OA10.05.
3. Capdevila J, Gambardella V, Kuboki Y, et al. Updated phase 1 data for the DLL3/CD3 IgG-like T-cell engager BI 764532 in DLL3-positive tumors: focus on extrapulmonary neuroendocrine carcinoma. Presented at: 2024 NANETS Multidisciplinary NET Medical Symposium; November 21-23, 2024; Chicago, Illinois, USA. Abstract C-12.
4. Aggarwal RR, Rottey S, Bernard-Tessier A, et al. Phase 1b study of tarlatamab in de novo or treatment-emergent neuroendocrine prostate cancer (NEPC). *J Clin Oncol*. 2024;42(16 suppl):5012.
5. Sands J, Cho BC, Ahn MJ, Reck M, et al. Tarlatamab sustained clinical benefit and safety in previously treated SCLC: DeLLphi-301 phase 2 extended follow-up. *J Thorac Oncol*. 2024;19(10 suppl):S30-S31.
6. Beltran H, Johnson ML, Jain P, et al. Updated results from a phase 1/2 study of HPN328, a tri-specific, half-life (T1/2) extended DLL3-targeting T-cell engager in patients (pts) with small cell lung cancer (SCLC) and other neuroendocrine cancers (NEC). *J Clin Oncol*. 2024;42(16 suppl):8090.
7. Feng Z, He X, Zhang X, et al. Potent suppression of neuroendocrine tumors and gastrointestinal cancers by CDH17CAR T cells without toxicity to normal tissues. *Nat Cancer*. 2022;3(5):581-594. [published correction appears in *Nat Cancer*. 2024;5(4):691.]
8. AghaAmiri S, Estrella JS, Vargas SH, et al. Translational potential of a contrast agent for FGS applications in pNETs. *Mol Imaging Biol*. 2024;26(2):191-194.

Combination therapies, targeted therapies (DLL3 and CAR-T), potential oral therapies (an important quality of life consideration), fluorescence-guided surgery potentially reducing the likelihood of incomplete resection are all exciting areas of research.
—Namrata Vijayvergia, MD