

Executive Summary

National Cancer Institute Gastrointestinal Steering Committee

Neuroendocrine Tumor Clinical Trials Planning Meeting:

Treatment in the Era of Peptide Receptor Radionuclide Therapy

March 8-9, 2021

Meeting Co-Chairs: Thomas Hope, M.D., Pamela Kunz, M.D., and Simron Singh M.D., M.P.H., with Wolf Lindwasser, Ph.D. and Elise C. Kohn, M.D.

Meeting Description

The National Cancer Institute (NCI) Gastrointestinal Steering Committee (GISC) convened the Clinical Trials Planning Meeting for Neuroendocrine Tumors: Treatment in the Era of Peptide Receptor Radionuclide Therapy (PRRT) on March 8-9, 2021. Meeting attendees included GISC members, members of the GISC Neuroendocrine Tumor Task Force (NET TF), physicians, new investigators, researchers, patient advocates, NCI staff, and invited representatives from industry. The purpose of the meeting was to identify clinical trial strategies to help define the treatment of patients with neuroendocrine tumors (NETs) in the era of PRRT.

Background

Important progress has been made over the last decade in the classification, imaging, and treatment of NETs, with several new agents approved for use. Refinements of the pathologic classification reflect recognition of the value of Ki67/mitotic rate (WHO 2010)¹ and the presence of a well differentiated G3 entity (WHO 2017)². In addition, our understanding of the molecular underpinnings of well-differentiated pancreatic NETs (panNETs) has advanced considerably³⁻⁵. Telotristat was approved for symptom control in patients with refractory carcinoid syndrome.⁶ The antitumor activity of somatostatin analogs, mTOR, and VEGFR inhibition has been established, leading to the approval of lanreotide (for gastroenteropancreatic NETs [GEP-NET])⁷, everolimus (gastrointestinal, lung, and panNETs)^{8,9} and sunitinib (panNETs)¹⁰. Capecitabine and temozolomide has become the de facto standard of care chemotherapy in recurrent panNET based on retrospective data¹¹ and the results of E2211¹². Somatostatin receptor (SSTR) PET imaging (⁶⁸Ga-DOTATATE, ⁶⁸Ga-DOTATOC and ⁶⁴Cu-DOTATATE) has emerged as a common imaging modality both for staging and selecting patients for PRRT, replacing SSTR-based scintigraphy¹³. Perhaps the biggest development over the last decade has been the approval of ¹⁷⁷Lu-DOTATATE PRRT therapy for treatment of GEP-NETs¹⁴.

While the treatment options available for patients with well differentiated NETs have greatly expanded, the rapidly changing landscape has left us with a number of unanswered questions about how best to optimize, sequence, and individualize therapy. In particular, the approval by FDA of ¹⁷⁷Lu-DOTATATE in SSTR-positive GEP-NETs has attracted great enthusiasm (HR 0.21, median PFS not reached vs. 8 months compared to high dose octreotide LAR, p<0.001)¹⁴. Treatment is associated with the longest progression-free survival (PFS) reported in somatostatin analog-refractory midgut NETs, although the radiographic response rate is low (18%). Limited retrospective data suggest ¹⁷⁷Lu-DOTATATE is associated with higher response rates in panNETs, but prospective studies are needed¹⁵. Furthermore, ¹⁷⁷Lu-DOTATATE appears to be associated with a small but significant risk of myelodysplastic syndrome or acute myeloid leukemia (2.7% at 2 years¹⁶), a clinically-relevant toxicity in patients with a median overall survival (OS) measured in years (6 years for stage IV panNET, 10+ years for small bowel NETs)¹⁷.

Consensus & Recommendations

Neuroendocrine neoplasms are a heterogeneous set of diseases for which either separate trials should be conducted by primary site for bronchial, midgut, panNETs; alternatively, stratification by primary site should be considered if separate trials are not feasible. Additionally, stratification for grade and differentiation should be built into study designs. Consideration should also be made for both the number and types of prior therapies. Investigators should attempt to harmonize the definition of SSTR positivity and account for intratumoral heterogeneity in expression in designing SSTR-based therapy trials.

The recent advances in the field also led to the recognition that questions remain around optimal sequencing of PRRT relative to other therapeutic options, the role of retreatment with PRRT, and whether or not PRRT can be further optimized, refined or decrease toxicity by using PRRT combination therapy and/or an individualized approach to dosing. There was consensus that answering these questions via clinical trials must be considered in the context of the life cycle of the disease and by grade of disease and extent and location of disease (see figure 1).

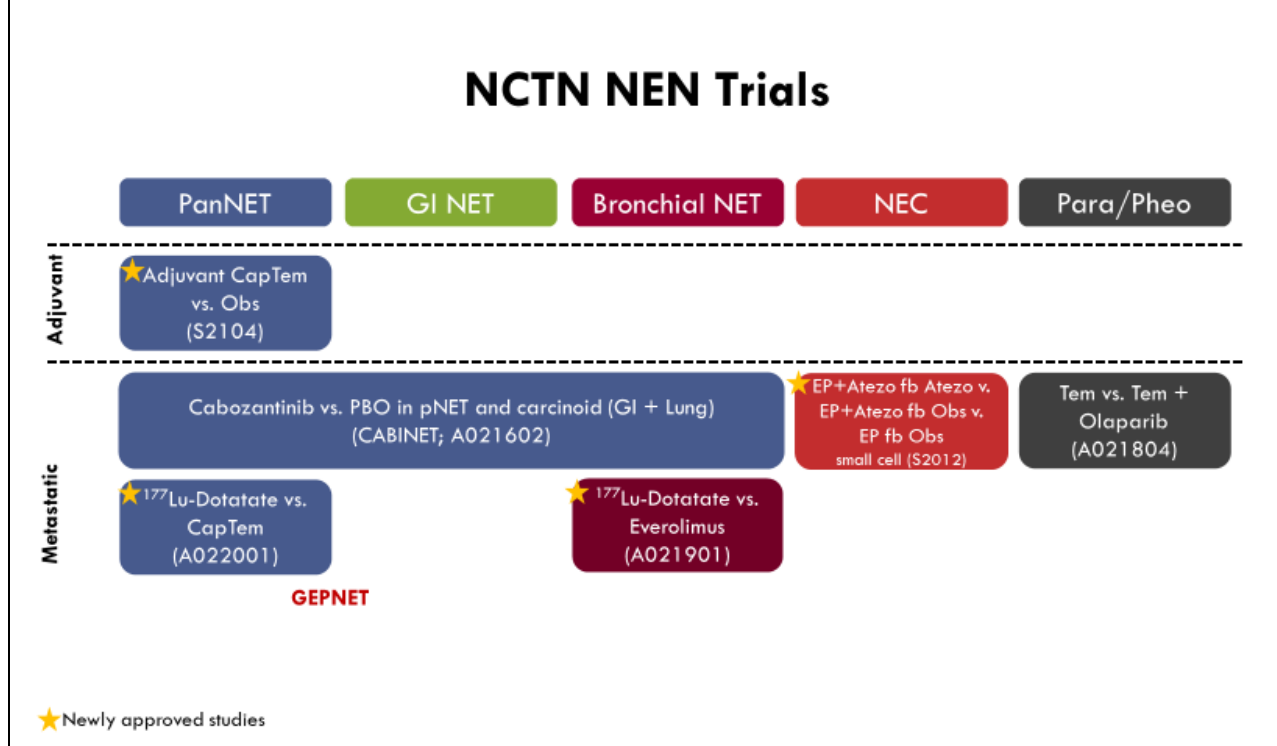
Detailed discussions on trial opportunities were initiated two years before the CTPM, which was delayed a year due to the COVID-19 pandemic. Topics for which published and ongoing studies were evaluated included:

- a) mechanisms to enhance efficacy, role and response to PRRT;
- b) timing, sequencing and dosimetry;
- c) the role of subsequent therapy in both PRRT resistant and PRRT sensitive populations; and,
- d) tenets/principles of care and trial design in the new era of discriminants for types of NET and treatment opportunities.

Note: Immediately following the March 2021 CTPM, the concept, A022001, *a Phase II randomized, prospective trial of Lu-177 dotatate PRRT versus capecitabine and temozolomide in well-differentiated pancreatic neuroendocrine tumors*, was approved by the GISC. This information of approval was NOT available at the CTPM and discussions were exclusive of this concept.

This study will be open to all well-differentiated panNET patients, all grades, with eligibility to be modified to remove overlap with CABINET (A021602) by requiring a change to enroll only symptomatic patients, or those with large tumor burdens (to be defined). As such, accrual to this new concept/protocol is likely to have an impact on the advancement of new potential studies in the **panNET** clinical space, with the exception of phase 1 and signal-finding studies.

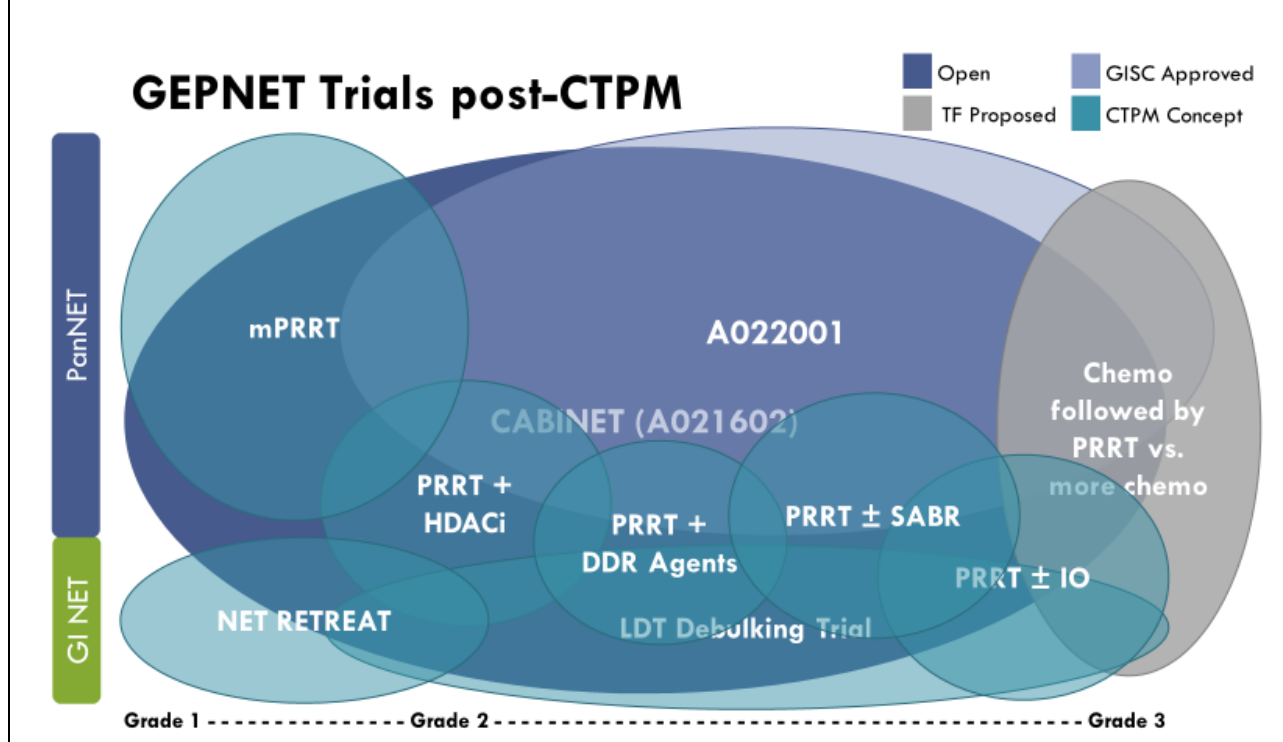
Figure 1. National Clinical Trials Network (NCTN) trials for neuroendocrine neoplasms (NENs). Abbreviations used in the figure: NEC (neuroendocrine carcinoma), Para (paraganglioma), Pheo (pheochromocytoma), CapTem (capecitabine and temozolomide), Obs (observation), Atezo (atezolizumab), fb (followed by), EP (etoposide and platinum [carboplatin or cisplatin]), PBO (placebo).



Proposed Concepts

The following concepts were developed by working groups prior to the CTPM and further refined during the meeting (see figure 2). They were then prioritized by which were deemed feasible to undertake concept development immediately (high priority), consideration for an intermediate timeline for development due to requirement for further data or data maturation, and a final category where it was concluded there was a need for preclinical data, clinical data and/or other advances to be made.

Figure 2. NCTN trials in metastatic GEP-NETs, including open trials, trials under development (“pending”), and trials proposed at the CTPM. Additional abbreviations used in the figure: DDR (DNA damage response), HDACi (histone deacetylase inhibitor), IO (immuno-oncology agent), LDT (liver-directed therapy), SABR (stereotactic ablative radiation). Trial acronyms are explained in the text (see Proposed Concepts).



Immediate term:

- NET RETREAT (SWOG/CCTG): Randomized phase 2 study of repeat ¹⁷⁷Lu-DOTATATE vs. everolimus in previously PRRT-treated midgut NET
 - Metastatic, WD, G1-2, midgut, at least 12 months durable response after initial PRRT
 - Will provide key prospective clinical data regarding retreatment benefit, cumulative toxicity and myelotoxicity risks
- Modified PRRT (mPRRT): “Standard” PRRT (4 cycles) vs. mPRRT (2-8 cycles with goal of 80-130 Gy total dose in lesions > 3cm)
 - *Overlaps patient population eligible for A022001*
 - Metastatic, WD, G1-2, panNET, RECIST progression in last 12 months, SSTR+, 2 lesions ≥ 3cm, no prior PRRT
 - Could be done front line or incorporated into RETREAT

Medium term (awaiting near-term data):

- Immunotherapy Combination Trial: ¹⁷⁷Lu-DOTATATE ± PD-1 inhibitor
 - Metastatic WD, aggressive G2/3, GEP NET, SSTR+, any line
 - Awaiting preclinical or other clinical data to support development
 - Phase 1 lead-in/randomized phase 2 design
 - Will form working group to support development
 - *Risk of overlap patient population eligible for A022001*
- DNA Damage Repair Combination Trial: Randomized “pick the winner design” Phase 2/3 study of ¹⁷⁷Lu-DOTATATE with DNA damage repair (DDR)
 - Patients randomized 1:1:1:1 to triapine, olaparib, or peposertib + ¹⁷⁷Lu-DOTATATE, or ¹⁷⁷Lu-DOTATATE alone
 - Metastatic, WD G2/3, Ki67 between 5-55%, GEP-NETs, SSTR+, any line, progressive disease within 12 months of enrollment.
 - Awaiting data from ETCTN 10388, 10450, and CCR/NCI studies
 - Will form working group to support development

Needs more development/long term:

- SABR trial: PRRT +/- stereotactic ablative radiation (SABR) for heterogeneous metastatic WD high-risk limited metastases NETs
 - Metastatic, WD G2/3, Ki67 between 10-55%, GEP-NETs, SSTR+, any line
 - Will form working group to support development
- Debulking trial: ¹⁷⁷Lu- DOTATATE vs. LDT followed by ¹⁷⁷Lu- DOTATATE
 - Metastatic, WD G1-3, SBNETs, SSTR+
 - Testing role and timing of LDT and PRRT
 - Need to identify optimal patient population and design
- ENHANCE PRRT: Escalating Neuroendocrine Therapy for Incomplete Responders to PRRT: Randomized phase 2 study of ¹⁷⁷Lu- DOTATATE + Cape vs. ¹⁷⁷Lu- DOTATATE + Atezo
 - Metastatic, WD G1-3, GEPNETs, SSTR+, PD within 12 months after completion of prior PRRT
 - Needs further work on design
- Window of opportunity trial: ¹⁷⁷Lu- DOTATATE + HDAC inhibitor
 - Awaiting preclinical data

This Executive Summary presents the consensus arising from the CTPM. These recommendations are not meant to address all clinical contexts, but rather represent priorities for publicly funded clinical research.

Anticipated Actions

- Multidisciplinary, diverse, and inclusive working groups will be formed to foster the development of several proposed trials.
- We encourage involvement of multiple NCTN groups and partnerships between junior investigators (i.e., no prior NCTN trial leadership) and senior mentors.
- A paper will be prepared for documentation of meeting outcomes and recommendations.

References

1. Bosman FT, World Health Organization., International Agency for Research on Cancer. *WHO classification of tumours of the digestive system*. 4th ed. Lyon: International Agency for Research on Cancer; 2010.
2. Ohike N, Adsay NV, La Rosa S. *WHO Classification of Tumours of Endocrine Organs, 4th ed*. Lyon IARC Press; 2017.
3. Jiao Y, Shi C, Edil BH, et al. DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. *Science*. 2011;331(6021):1199-1203.
4. Raj N, Shah R, Stadler Z, et al. Real-Time Genomic Characterization of Metastatic Pancreatic Neuroendocrine Tumors Has Prognostic Implications and Identifies Potential Germline Actionability. *JCO Precis Oncol*. 2018;2018.
5. Scarpa A, Chang DK, Nones K, et al. Whole-genome landscape of pancreatic neuroendocrine tumours. *Nature*. 2017;543(7643):65-71.
6. Kulke MH, Horsch D, Caplin ME, et al. Telotristat Ethyl, a Tryptophan Hydroxylase Inhibitor for the Treatment of Carcinoid Syndrome. *J Clin Oncol*. 2017;35(1):14-23.
7. Caplin ME, Pavel M, Cwikla JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014;371(3):224-233.
8. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6):514-523.
9. Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2016;387(10022):968-977.
10. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6):501-513.
11. Strosberg JR, Fine RL, Choi J, et al. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. *Cancer*. 2010.
12. Kunz PL, Catalano PJ, Nimeiri H, et al. A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: A trial of the ECOG-ACRIN Cancer Research Group (E2211). *J Clin Oncol*. 2018;36(15).
13. FDA approves new diagnostic imaging agent to detect rare neuroendocrine tumors (<https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm504524.htm>) [press release]. 2016.
14. 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.

15. Brabander T, van der Zwan WA, Teunissen JJM, et al. Long-Term Efficacy, Survival, and Safety of [(177)Lu-DOTA(0),Tyr(3)]octreotate in Patients with Gastroenteropancreatic and Bronchial Neuroendocrine Tumors. *Clin Cancer Res.* 2017;23(16):4617-4624.
16. Lutathera Prescribing information. 2018;
https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208700s000lbl.pdf.
17. Dasari A, Shen C, Halperin D, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol.* 2017;3(10):1335-1342.

NCI Neuroendocrine Tumor Clinical Trials Planning Meeting

Treatment in the Era of PRRT

March 8-9, 2021

AGENDA

Monday, March 8 – Day 1

10:00 – 10:15 am ET Welcome and Introduction (Wolf Lindwasser, Elise Kohn, Tom Hope, Pam Kunz, Simron Singh)
Outline of the process, goals and deliverables

10:15 – 10:30 Disease life cycle considerations and Trial development (Pam Kunz, Simron Singh)

Session 1: Enhancing Efficacy and Increasing Response of PRRT (Moderator: Pam Kunz)

10:30 – 10:45 Improving the affinity and modulating SSTRs – Brian Untch

10:45 – 11:00 Enhancing response in immunotherapy and radiation – Sandra Demaria

11:00 – 11:15 Combination Therapy – Aman Chauhan

11:15 – 11:30 Role of Alpha emitters – Robert Hobbs

11:30 – 11:45 Discussion

11:45 – 12:30 pm Break

Session 2: Timing, Sequencing and Dosimetry (Moderator: Tom Hope)

12:30 – 12:45 Practical experience of dosimetry trials in PRRT – Rebecca Wong

12:45 – 1:00 Timing, Freq and role of Repeat PRRT – Lisa Bodei

1:00 – 1:15 Minimizing and preventing Toxicity in PRRT - Andrew Kennedy

1:15 – 1:30 Cytoreductive therapy and sequencing of PRRT – Emily Bergsland

1:30 – 1:45 Discussion

Session 3: Industry Presentations (Moderator: Simron Singh)

1:45 – 1:50	ITM – Mona Wahba
1:50 – 1:55	Exelixis – Stephen Salatan
1:55 – 2:00	Novartis – Geromo Gericke, Antonio Nakasoto
2:00 – 2:05	Ipsen – Sandy McEwan, Tom Beveridge
2:05 – 2:40	Discussion
2:40	Recuse Industry Partners from Open Session of Meeting
2:40 – 2:50	Break

Session 4: Concept Presentations and Discussion (Moderator: Tom Hope)

2:50 – 3:05	Group 1 – Simron Singh, Jennifer Chan
3:05 – 3:20	Group 2 – Pam Kunz, Heloisa Soares
3:20 – 3:35	Group 3 – Tom Hope, David Bushnell
3:35 – 4:30	Discussion

Breakout Session 1: Assessing the Proposed Concepts

4:30 – 5:30	Breakout Group 1 (Co-leaders: Singh, Chan)
	Breakout Group 2 (Co-leaders: Kunz, Soares)
	Breakout Group 3 (Co leaders: Hope, Bushnell)
5:30	End of Day 1
5:30 – 6:30	CTPM Co-Chairs Meeting (Closed)

Tuesday, March 9 – Day 2

10:00 – 10:10 am ET Welcome to Day 2, Day 1 overview – CTPM co-chairs

Session 5: Clinical Trial Design (Moderator: Simron Singh)

- 10:10 – 10:25 Appropriate endpoints in PRRT trials and biomarker assessment/correlatives (Primary and Secondary) – Marianne Pavel
- 10:25 – 10:40 Using Phase 2 trial designs to inform Phase 3/ standardizing eligibility criteria – Daniel Halperin
- 10:40 – 10:55 Innovative Trial designs for potential PRRT trials (e.g., adaptive trial design) – Fang-Shou Ou
- 10:55 – 11:10 Assessing Imaging and endpoints in PRRT trials – Frank Lin
- 11:10 – 11:25 Discussion

Session 6: Principles of Clinical Trial Design (Moderators: Simron Singh/Jen Chan)

- 11:25 – 12:20 pm Discussion
- 12:20 – 1:00 Break
- 1:00 – 1:10 Navigating Next Steps – Elise Kohn

Session 7: Finalizing the Concepts (Moderator: Tom Hope)

- 1:10 – 2:20 Discussion
- 2:10 – 2:30 Wrap up and Adjourn – Co-chairs
- 2:30 – 3:30 Executive Planning Committee meeting (Closed)

NCI Neuroendocrine Tumor CTPM: Treatment in the Era of PRRT Participant List

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