Clinical Trials: The Latest and Greatest

NEUROENDOCRINE CANCER FOUNDATION

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February, 2026

Disclosures

Advisory Board/Consulting Role for:

- Ipsen, ITM, Exelixis, Novartis, Curium, Boehringer Ingelheim, Sanofi, Tersera

Job Description:

- Medical Oncologist and Clinical Trialist

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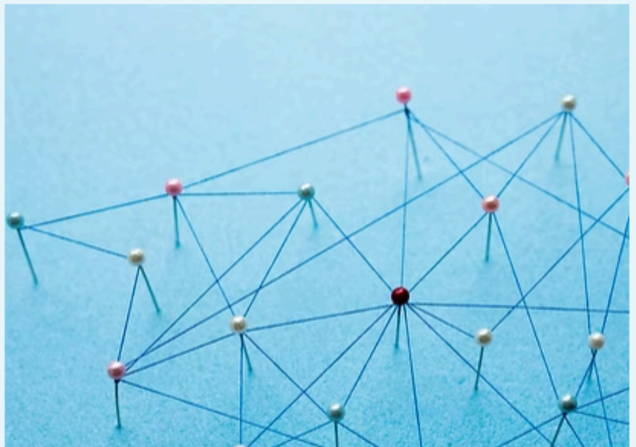
Learning About Clinical Trials

NCF.net/clinical-trials/additional-resources



Learning About Clinical Trials

NCF.net/clinical-trials/additional-resources

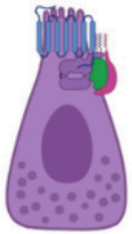
"Navigating Clinical Trials: Expectations vs Realities" with Taymeyah Al-Toubah, MPH - August 2023 LACNETS Patient Educational Event

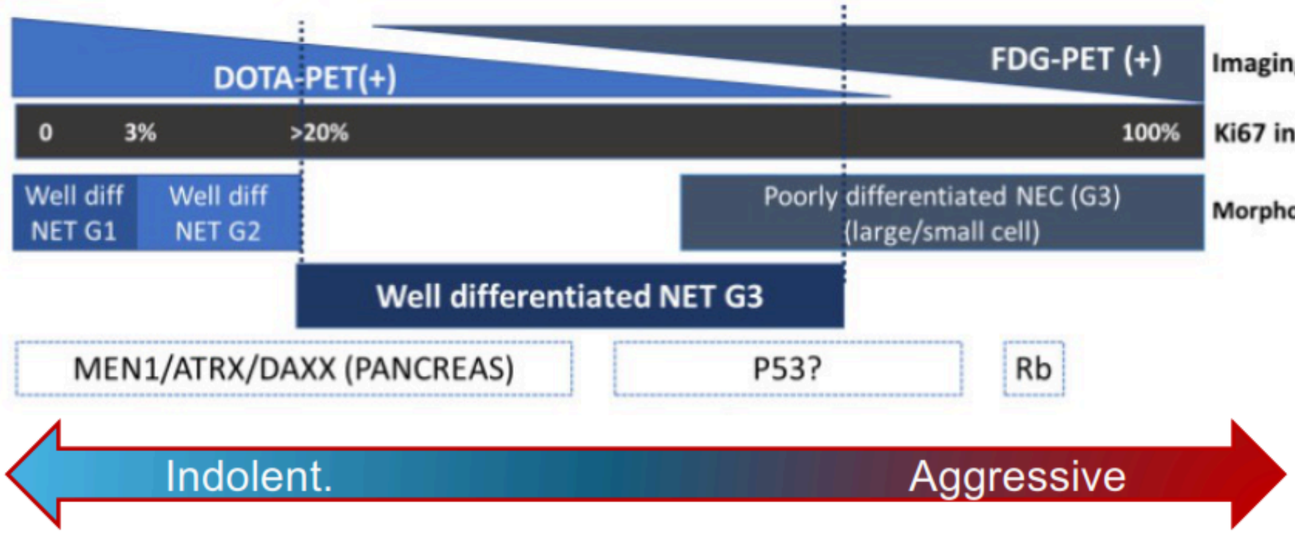
"Clinical Trials: Why, What & How" - 2023 LACNETS Patient Education Conference

Neuroendocrine Neoplasms: One Name: Many Diseases

- Neuroendocrine neoplasms are a very heterogeneous disease
- Increasing in incidence and prevalence
- Different classifications
- Distinct behavior → treatments are based on differentiation, grade and site of origin

Neuroendocrine Tumor (NET)





Neuroendocrine carcinoma (NEC)

Varghese DG et al: Cancers (Basel). 2023 Jul 21;15(14):3712. PMID: 37509373

Clinical Trials in Neuroendocrine Cancer

Understanding the Goal of a Study

- The type of clinical trial offered depends on where you are in your cancer journey.
- Some trials aim to make surgery possible.
- Others try to prevent recurrence, control spread, or improve how you feel.

NEOADJUVANT TRIALS

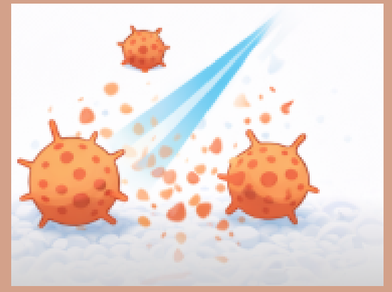
"Shrink Before Surgery"

Used before surgery to shrink the tumor and make surgery safer.

ADJUVANT TRIALS

"The Safety Net"

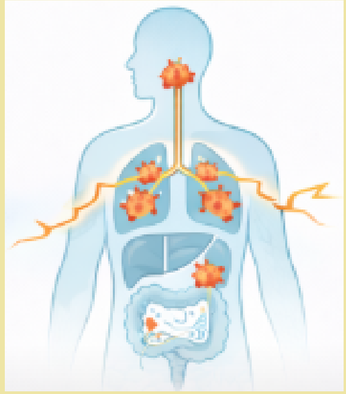
Used after surgery to kill microscopic cancer cells that may remain.



METASTATIC TRIALS

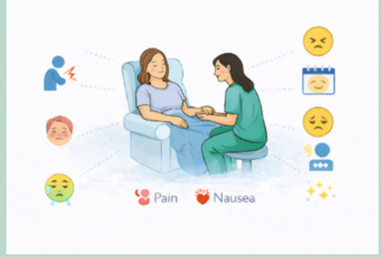
"Advanced Control"

Used when cancer has spread.
These treatments work throughout the body to shrink tumors, stop growth, and help patients live longer.



SYMPTOM CONTROL & SUPPORTIVE CARE TRIALS

Focused on improving quality of life.
These studies help manage fatigue, pain, flushing, nausea, mood, and other symptoms.



Well-Differentiated NETs & Trials That Are Enrolling

ADJUVANT STUDY

S2104 Trial
ClinicalTrials.gov NCT05040360

Improving Treatment After Pancreatic NET Surgery

The Problem

- Even after successful surgery, **some patients with high-risk pancreatic neuroendocrine tumors (pNETs)** can still have their cancer return.
- Scans may show no evidence of disease, but **microscopic cancer cells may still be present.**
- **Currently**, there is no proven way to lower this risk after surgery.

Current Approach

After surgery for high-risk pNETs:

- Most patients are placed under “observation”
  - This means regular scans and follow-up visits.
- No additional treatment is routinely given.

There is **no established standard adjuvant therapy** (treatment given after surgery to reduce recurrence).

Doctors are monitoring—but not actively treating.

Trial Rationale

CAPTEM (capecitabine + temozolomide) is an oral chemotherapy combination that:

- Has shown effectiveness in advanced pancreatic NETs
- Can shrink **tumors** or stabilize disease
- Is generally manageable as an oral treatment

Key Question:

If CAPTEM works in advanced disease, could it also work earlier, after surgery, to prevent the cancer from coming back?

Trial Goal

- Test whether adjuvant **CAPTEM** can improve outcomes after surgery
- Increase time patients remain cancer-free
- Reduce recurrence risk
- Improve long-term outcomes in high-risk pNET patients

S2104 Trial (Continued)

ClinicalTrials.gov NCT05040360

Question

Does adding CAPTEM (capecitabine + temozolomide) after surgical removal of high-grade pancreatic NETs **improve patient outcomes** compared with observation alone?

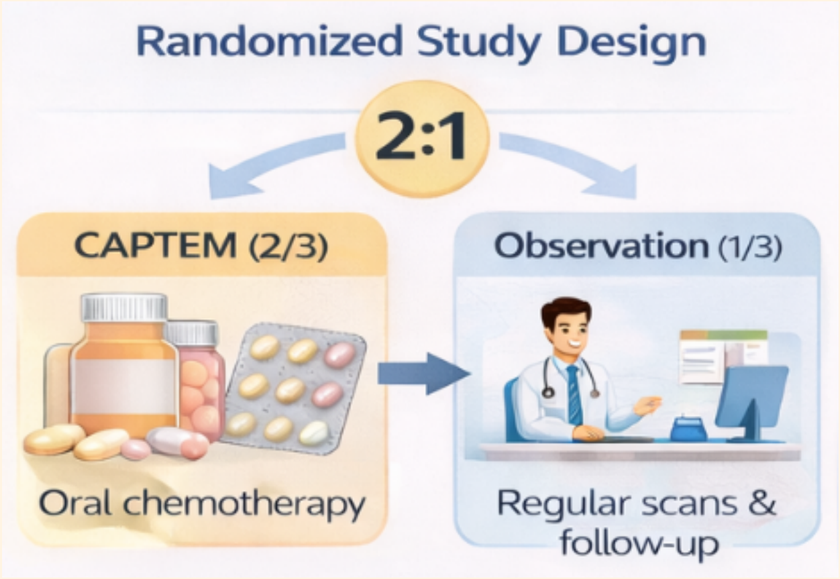
Can chemotherapy after surgery help patients live longer and stay cancer-free longer?

Who Can Enroll?

- ✓ Adults over 18 years
- ✓ High-grade, well-differentiated pancreatic NET
- ✓ Tumor completely removed by surgery

Study Design

Patients will be randomly assigned 2:1 to either receive the chemotherapy drugs capecitabine and temozolomide (CAP/TEM) or to **observation** with regular monitoring.



Outcomes

Will the chemotherapy drugs added after surgery extend the time with no evidence of disease?

Recurrence-free survival

- Time patients remain cancer-free after treatment

SYMPTOM CONTROL

CAREFNDR Trial: Carcinoid Syndrome Trial

ClinicalTrials.gov NCT07087054

The Challenge: Current Treatment Limitations

Monthly injections:
May be painful, inconvenient
flushing & diarrhea return between doses

Daily Unpredictability

The Solution: Once-Daily Paltusotine

Oral pill daily

Steady Control & Consistent Symptom Relief

Why This Matters

Phase 2 Success:

63%

Flushing decreased

Diarrhea decreased

Trial Goal: Improve patient quality of life with more consistent & convenient symptoms control.

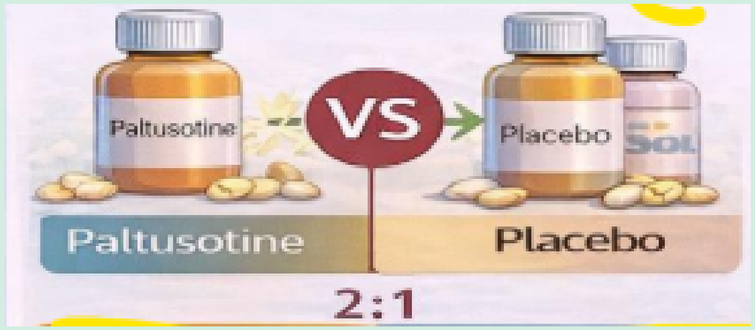
Phase 3 Goal: Long-term safety & relief confirmed in more patients.

CAREFNDR Trial: Carcinoid Syndrome Trial (Continued)

ClinicalTrials.gov NCT07087054

Question	Who May Qualify?	End Point
Can a daily oral pill replace monthly hormone injections to control the symptoms of carcinoid syndrome?	• Age 18 years or older • Well-Differentiated NET Grades 1 & 2 • Currently taking monthly injections • Carcinoid syndrome with flushing & with or without diarrhea	How well does daily Paltusotine control the symptoms of carcinoid syndrome? ✅ **Primary:** Change in daily flushing episodes from baseline to 12 weeks ✅ **Key Secondary:** Change in daily bowel movements from baseline to 12 weeks **Phase 3 Goal:** Long-term safety & symptom relief confirmed in more patients.

Study Design



Tumor Control For Advanced or Metastatic Cancer

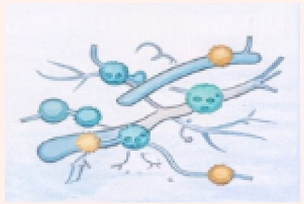
STELLAR-311 Trial

ClinicalTrials.gov NCT06943755

Can a new drug, zanzalintinib, delay cancer growth better than everolimus?

Trial Rationale: Why This Study?

Researchers are testing zanzalintinib because many patients with advanced neuroendocrine tumors (NETs) need more effective options after their first treatment stops working.



- Targeted Growth Blocking: Zanzalintinib is a “next-generation” targeted therapy. It works by blocking multiple pathways (like VEGF receptors) that tumors use to grow and form vessels.
- A “Head-to-Head” Comparison: Everolimus is already a standard, FDA-approved pill for NETs. This trial aims to prove if zanzalintinib is more powerful or better tolerated than this existing option.
- Simplifying Treatment: Both drugs are pills taken once daily at home, which is more convenient than treatments requiring hospital visits.

Who May Qualify?

- Adults (18+) with advanced or metastatic Grade 1, 2, or 3 NETs originating in the pancreas or other organs.
- Must have had their tumor grow after receiving up to one previous treatment

Study Design

Randomized Open-Label:
Participants are assigned by a computer (like a coin flip) to Group A: Zanzalintinib or Group B: Everolimus

Special Feature: The Crossover Option

- If a participant in Group B (Everolimus) has their tumor start to grow again, they may be allowed to switch over and start taking the experimental drug, zanzalintinib.

Main Goal

- Progression-Free Survival (PFS): To measure how long patients live without their cancer worsening.

Other Goals:

- Tracking how many tumors shrink (response rate)
- Overall survival, and patient quality of life

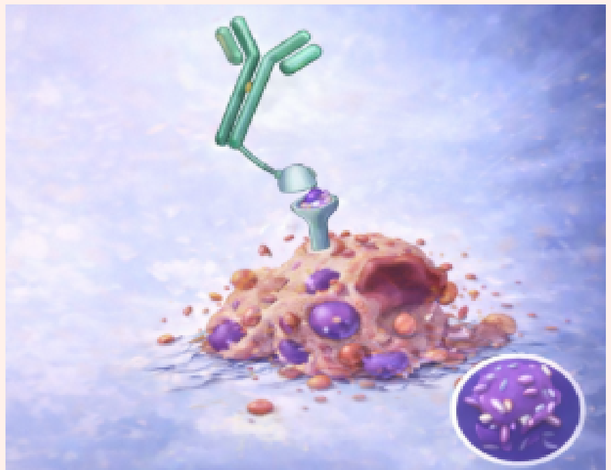
BRAVESST2 Trial

ClinicalTrials.gov NCT07129252

This trial is testing CRN09682, a first-in-class nonpeptide drug conjugate (NDC).

Targeted Tumor Killing Without Radiation

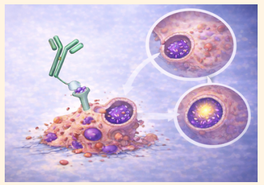
While current treatments like PRRT use radiation to kill cancer cells, CRN09682 uses a potent cytotoxic drug (MMAE). It is designed to act like a “guided missile,” binding specifically to the SST2 receptors.



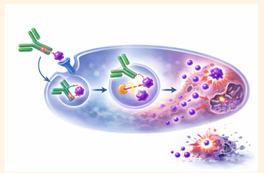
How the Drug Works

Selective Binding
A first-in-class NDC that selectively binds to somatostatin receptor 2 (SST2) receptors on tumor cell.

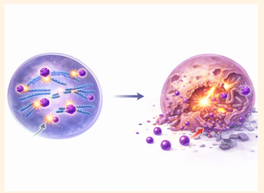
Internalization
Receptor “swallows” the MMAE drug, bringing it inside the tumor cell.



Release of Payload
Inside the cell, natural enzymes break the link, releasing the MMAE toxin.



Cell Death
The MMAE toxin disrupts the cell’s microtubules, stopping the tumor cell from growing and causing it to die.



Improved Tumor Penetration

- Because CRN09682 is a small molecule (nonpeptide), it is much smaller than traditional antibody-drug conjugates (ADCs).
- This smaller size is intended to help the drug penetrate deeper into tumors and be cleared from the body faster, potentially reducing side effects.

Simplified Manufacturing

Unlike radioactive therapies or complex biological drugs, NDCs are made using traditional chemical synthesis.

BRAVESST2 Trial (Continued)

ClinicalTrials.gov ID:NCT07129252

The Big Question

Is the new investigational drug CRN09682 safe, and how well does it work at different doses to stop the growth of tumors that have **“docking stations”** (SST2 receptors) on their surface?

CRN0982 + MMAE
Potent Cytotoxic Drug

Who May Qualify?

- **Adults with advanced** or metastatic neuroendocrine tumors (NET), neuroendocrine carcinomas (NEC), or other solid tumors that have grown recently (confirmed by scans).
- **Patients** whose tumors show up on somatostation receptor (SSR) scan

Study Design

- **Phase 1 & 2 Study**
  This is a two part trial. This first part finds the best dose, and the second part tests that dose in more people.
- **Treatment**
  The drug is given as an intravenuous (IV) infusion once every 21 days (one “cycle”).

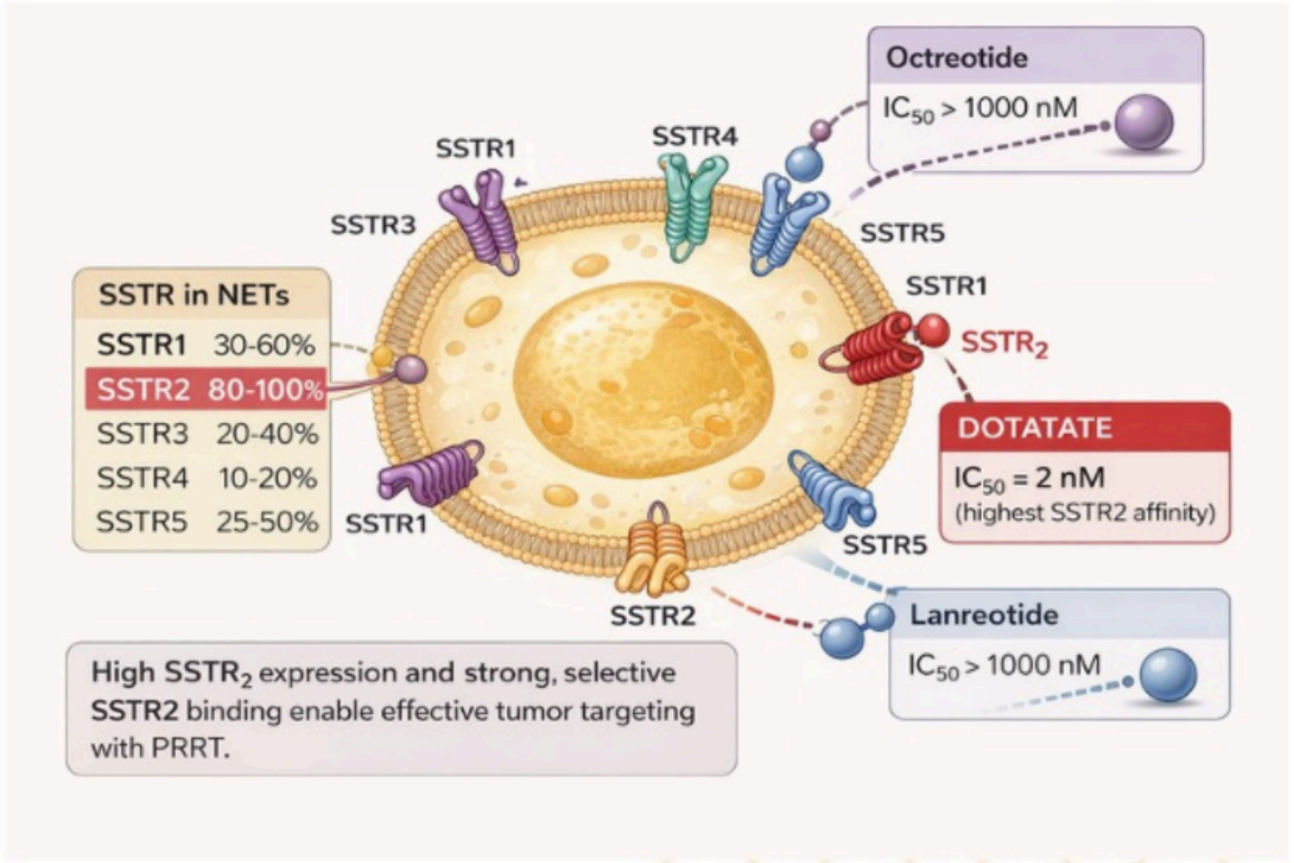
End Point

- **Main Goal:**
  To evaluate the safety of the drug and determine the most effective dose.
- **Secondary Goal:**
  To see how many tumors shrink or stay the same size.

Note: You may not qualify if your cancer got worse while you were receiving PPRT or within 6 months of finishing it.

Theranostics in NETs: Why This Works

- Somatostatin receptor (SSTR) overexpression in NETs
- High prevalence of SSTR2/SSTR5 expression
- Typically, well-differentiated biology with an indolent course, allowing radiation-based strategies.
- Same molecular target for diagnosis and therapy.



Hu Y, et al: 2021. Front. Endocrinol. 12:679000.
PMID: 34093445

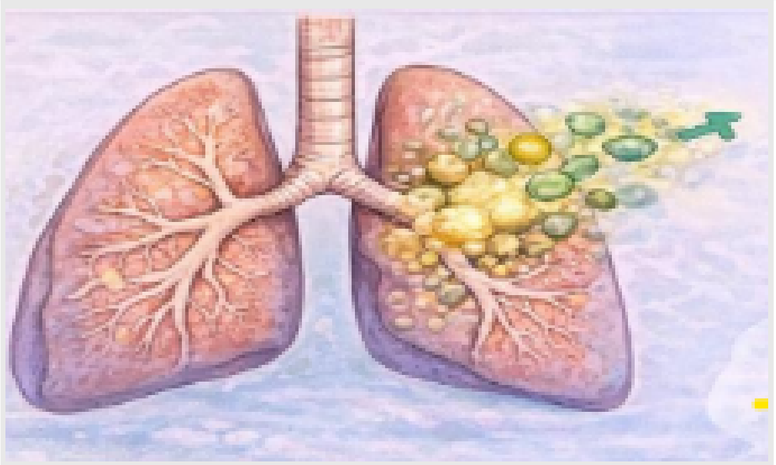
Schematic illustration for educational use

B-LuRE (Bronchial Neuroendocrine Cancer)

ClinicalTrials.gov ID:NCT04665739

Randomized Phase II Trial of Lutetium Lu 177 DOTATATE Versus Everolimus in Somatostatin Receptor Positive Bronchial NETs

Lung NETs are rare, slow-growing tumors that form in the lungs. They often make too much of the hormone serotonin, which can cause flushing, diarrhea, and other symptoms.



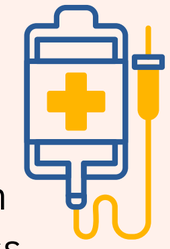
Question

Can targeted radiation therapy (Lutetium Lu 177 DOTATATE) help control somatostatin receptor-positive lung (bronchial) neuroendocrine tumors better than the oral drug Everolimus?

Which treatment keeps the cancer from growing for a longer period of time?

Current Treatment Options

Chemotherapy



Chemotherapy can stop or slow the growth of the NETs (but it is less commonly effective in Lung NETs).

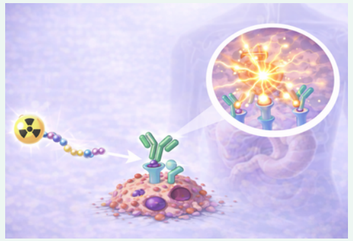
SSA Injections

Somatostatin analog (SSA) injections given monthly can help block hormone production and slow tumor growth.

Oral Everolimus

Everolimus is a daily pill that targets a growth pathway inside NET cells, helping to slow down tumor growth and keep the cancer under control for longer.

PRRT



Peptide Receptor Radionuclide Therapy (PRRT) targets receptors (SSTR) on NETs & delivers radiation.

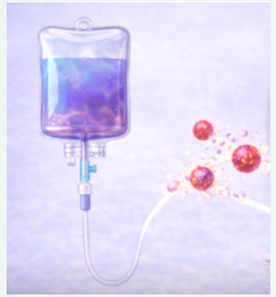
B-LuRE (Continued)

ClinicalTrials.gov ID:NCT04665739

Who May Qualify

- Age 18 years or older
- Somatostatin receptor-positive bronchial NETs
- Advanced disease that has spread or grown
- No prior PRRT or Everolimus treatment
- Able to undergo treatment and imaging tests

Design



Lutetium Lu 177 DOTATATE

VS

Everolimus

- IV infusion every 8 weeks x 4 cycles
- Allows for crossover

End Point

Primary Goal:

Progression-Free Survival (PES) Time until the cancer worsens, compared between the two groups

Secondary Outcomes:

- Overall survival
- Tumor response rate
- Side effects & safety

NET RETREAT Trial

ClinicalTrials.gov ID:NCT05773274

A Phase II Trial of Lu-177 Retreatment vs. Oral Pills for Gastrointestinal NETs.
This trial will compare retreatment with Lutathera (177Lu-DOTATATE) to switching to an oral medication like everolimus, sunitinib or cabozantinib to find out which option is better at keeping the cancer from growing.

Treatment Effectiveness

Can “retreating” with more Lutathera (Lu-177 DOTATATE) be more effective than switching to a different medication?

Targeting Tumor Biology

PRRT targets specific receptros (SSTR) on NET cells, delivering radiation directly to the tumors.

If these receptors are still present after initial treatment, more Lutathera (177Lu-DOTATATE) could continue to be effective.

Keep targeting receptors on NET cells with minimal damage to healthy cells.

Comparison to Standard of Care

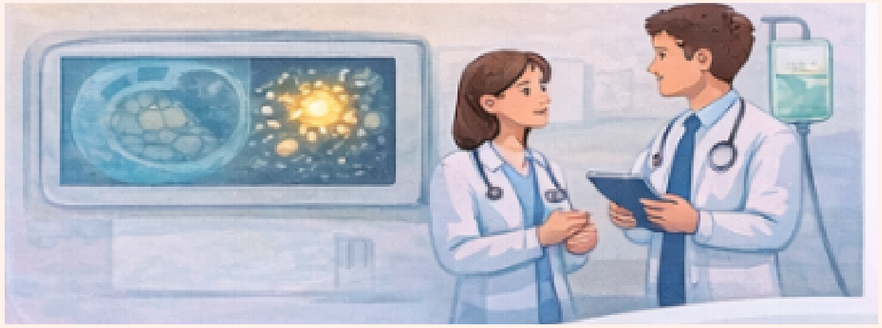
The “usual approach” after Lutathera stops working is to try oral pills called TKIs (Sunitinib & Cabozantinib). These medications block proteins that help tumors grow.

NET RETREAT Trial (Continued)

ClinicalTrials.gov ID:NCT05773274

Question

Is it better to give more Lu-177 DOTATATE (retreatment) or switch to an oral pill (TKI) after Lutetium-177 DOTATATE has stopped controlling gastrointestinal tumors NETs?



Who May Qualify?

Patients will be randomly assigned 2:1 to receive either additional Lu-177 DOTATATE (retreatment) or one of the standard therapies.

*Allows for crossover at time of confirmed progression

End Point

Which treatment is better at preventing the cancer from growing?

Progression-Free Survival:
Longer time before cancer grows or spreads.

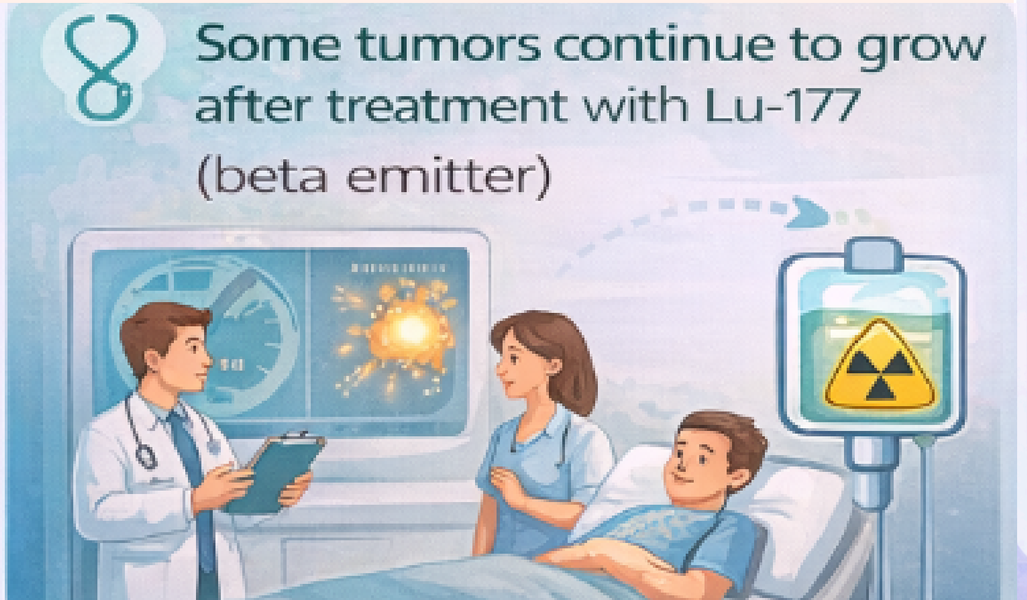
ACTION-1 Trial

ClinicalTrials.gov ID:NCT05477576

A Retreatment Study for GEP-NETs After Lu-177

Question

Can treatment with the investigational therapy RYZ101 (Actinium-225 DOTATATE) help patients live longer without their gastroenteropancreatic neuroendocrine tumors (GEP-NETs) growing or spreading again after Lutetium-177 DOTATATE (Lu-177)?



An Alpha Emitter (Actinium-225) may work when a beta emitter stops working.

ACTION-1 Trial (Continued)

ClinicalTrials.gov ID:NCT05477576

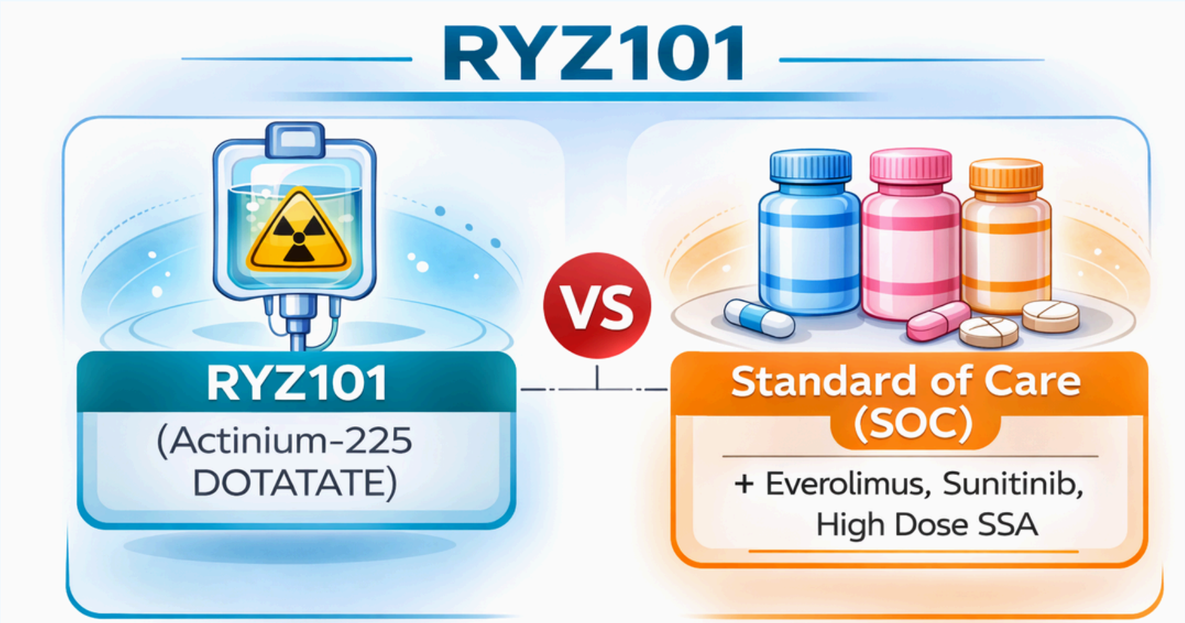
A Retreatment Study for GEP-NETs After Lu-177

Who May Qualify?

- 18 years old or older
- Grade 1 - 2, well-differentiated GEP-NETs shown on pathology
- Disease control from 2-4 Lu-177 DOTATATE doses and disease progression afterward
- No prior external beam radiation

Study Design

Patients will be randomly assigned 1:1 to either receive the investigational treatment RYZ101 (Actinium-225 DOTATATE) or to continue standard of care (Everolimus, Sunitinib, High Dose SSA)



End Point

Will patients receiving RYZ101 live longer without their cancer growing (Progression-Free Survival)?

212Pb-VMT-α-NET Trial

ClinicalTrials.gov ID:NCT05636618

First-in-Human Trial of Targeted Alpha Therapy for Advanced Neuroendocrine Tumors

The Goal of the Study

Is the new targeted alpha therapy drug safe and what is the best dose for treating advanced NETs?

Targeted Alpha Therapy

[212Pb] VMT-α-NET Targeted Alpha-Particle Therapy is designed to act as a heat-seeking missile, finding cancer cells that have a specific "docking station."

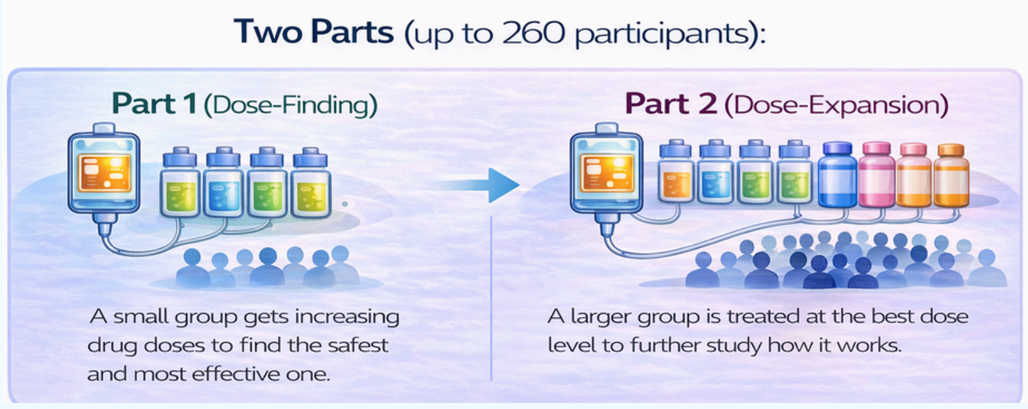
Potential Benefits:
Researchers hope to kill cancer cells more effectively while reducing damange to nearby healthy tissue.

Who May Qualify?

- **Diagnosis:**
  - Advanced/metastatic NETs that cannot be removed by surgery
- **Receptor Positive:**
  - Tumors show SSTR2 receptor by PET scan (such as the DOTATATE scan)
- **Prior Treatment:**
  - No previous radioactive "peptide" therapies (e.g., Lutathera)

What to Expect

- **Treatment:** The medicine is given as an infusion into a vein.
- **Protective Measures:** To protect kidneys, "reno-protective" amino acides given through an IV.



End Point

- Does the new targeted alpha therapy drug slow or halt the growth of NETs?
- Is the treatment safe, and what are the side effects?

RYZ401 Trial

ClinicalTrials.gov ID: NCT07165132

Study of RYZ401 in Subjects With Solid Tumors Expressing Somatostatin Receptors

Question

Can a new radiopharmaceutical therapy called RYZ401—which uses targeted alpha radiation—**be safe and potentially helpful** in treating people with neuroendocrine tumors (NETs) and other solid tumors that express somatostatin receptors (SSTR)?

This study is exploring whether RYZ401 should be developed further for patients.

Who May Qualify

- Are 18 years or older
- Have a confirmed **NET or other solid tumor** that has somatostatin receptors (SSTR+) on imaging.
- Have advanced, unresectable, or metastatic disease.
- Have adequate organ function.
- Have **not previously received radiopharmaceutical therapy** (RPT) such as Lutetium-177 based PRRT.

Design

- **Phase 1, first-in-human study**—the earliest stage of research to test a new therapy in people.
- **Two parts:**
  - **Dose-escalation:** Small groups receive increasing amounts of RYZ401.
  - **Dose-expansion:** Larger group receives that recommended dose to learn more about how it effects tumors.

End Point

- **Primary Goals:**
  - Find the best dose to use in future studies
  - Understand **how safe and tolerable** RYZ401 is for participants
- **Secondary Observations:**
  - Preliminary signs of whether tumors shrink or stop growing
  - How to body process the drug
  - Safety and side effects

Watch Dr. Chauhan's Presentation

The Latest on Immunotherapy for Neuroendocrine Cancer

Available at

NCF.net/events/dec2025

Take Home Message

- Exciting progress in the Neuroendocrine Cancer field
- Several ongoing clinical trials that might be a good fit for you!

Thank you!

@helops79

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