# Novel Targeted Therapies in Neuroendocrine Cancers

**Rohit Thummalapalli, MD**

Gastrointestinal Medical Oncologist, Assistant Attending Physician
Memorial Sloan Kettering Cancer Center

March 2, 2026

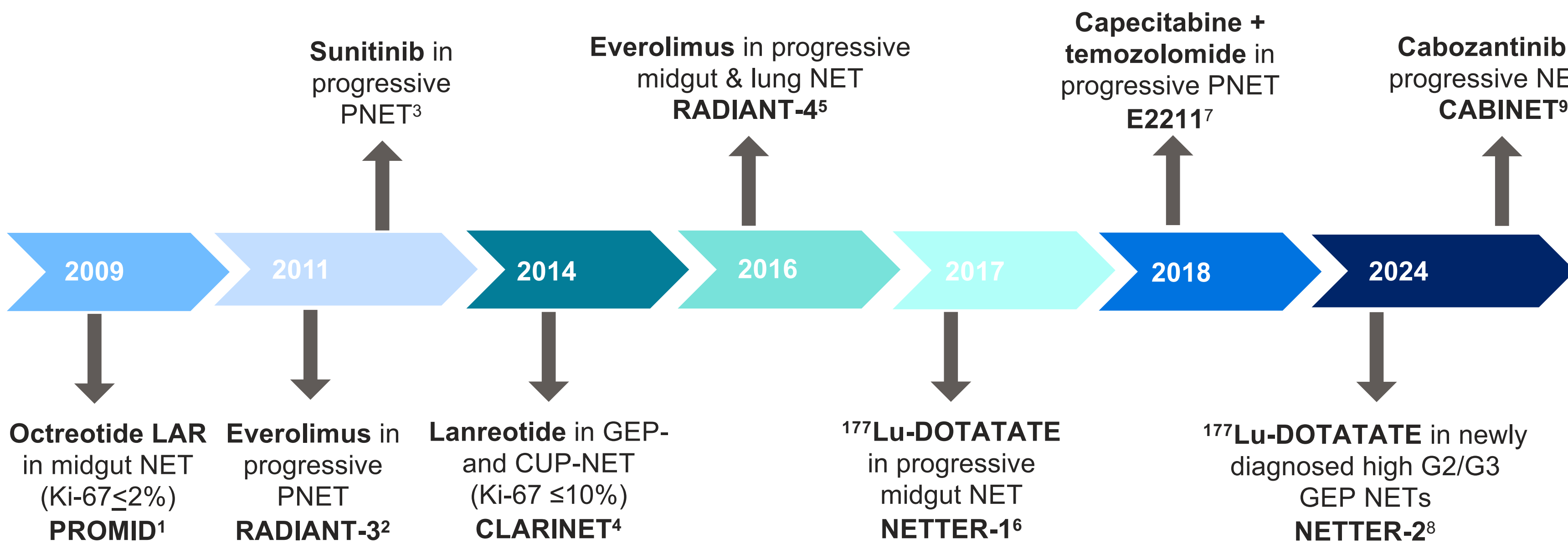
Memorial Sloan Kettering
Cancer Center

# WHO 2022 classification of neuroendocrine neoplasms (NENs)

**Increasing aggressiveness** ↓

| Grade | Differentiation | Mitotic Count/Ki-67 |
|---|---|---|
| NET: Grade 1 (Low) | Well differentiated | <2 mitoses/10 HPF<br><3% Ki-67 index |
| NET: Grade 2 (Intermediate) | Well differentiated | 2-20 mitoses/10 HPF<br>3-20% Ki-67 index |
| NET: Grade 3 (High) | Well differentiated | >20 mitoses/10 HPF<br>>20% Ki-67 index |
| Neuroendocrine carcinoma (NEC) | Poorly differentiated<br>Small cell<br>Large cell<br>Non-small cell<br>Mixed (MiNEN) | >20 mitoses/10 HPF<br>>20% Ki-67 index |

# Modern therapeutic paradigm for NETs




PNET = pancreatic neuroendocrine tumor | (1) Rinke A, et al. *J Clin Oncol*. 2009;27(28):4656-4663. (2) Yao JC, et al. *N Engl J Med*. 2011;364:514-523. (3) Raymond E, et al. *N Engl J Med*. 2011;364(3):501-513. (4) Caplin ME, et al. *N Engl J Med*. 2014;371:224-233. (5) Yao JC, et al. *Lancet* 2016;387(10022): 968-977. (6) Strosberg J, et al. *N Engl J Med*. 2017;376:125-135. (7) Kunz, et al. *J Clin Oncol*. 2023;41(7):1359-1370. (8) Singh,et al. *Lancet* 2024;403(10446): 2807-2817. (9) Chan JA, et al. *N Engl J Med*. 2024;392(7):653-665.

# Modern therapeutic paradigm for extrapulmonary poorly differentiated NECs

1L / 2L

**Etoposide + carboplatin/cisplatin**

**+ ICI?** (NICE-NEC [2]; SWOG S2012 [3] ongoing)

? (FOLFIRINEC [1], ongoing)

**mFOLFIRINOX (GEP NECs)**

→

Later line

Dual ICI therapy (e.g. nivolumab/ipilimumab): DART SWOG S1609 [4, 5], NIPINEC [6]

Pembrolizumab (MSI-H, dMMR – **rare**; TMB-H – unclear efficacy)

Matched targeted therapies in **rare subsets:**

- BRAF/MEK inhibitors for *BRAF V600E*-mutant disease (~10% of colorectal NECs [7], case report levels of efficacy [7, 8])
- TRK/RET inhibitors for *NTRK, RET* fusion-positive (exceptionally rare, < 0.5%)

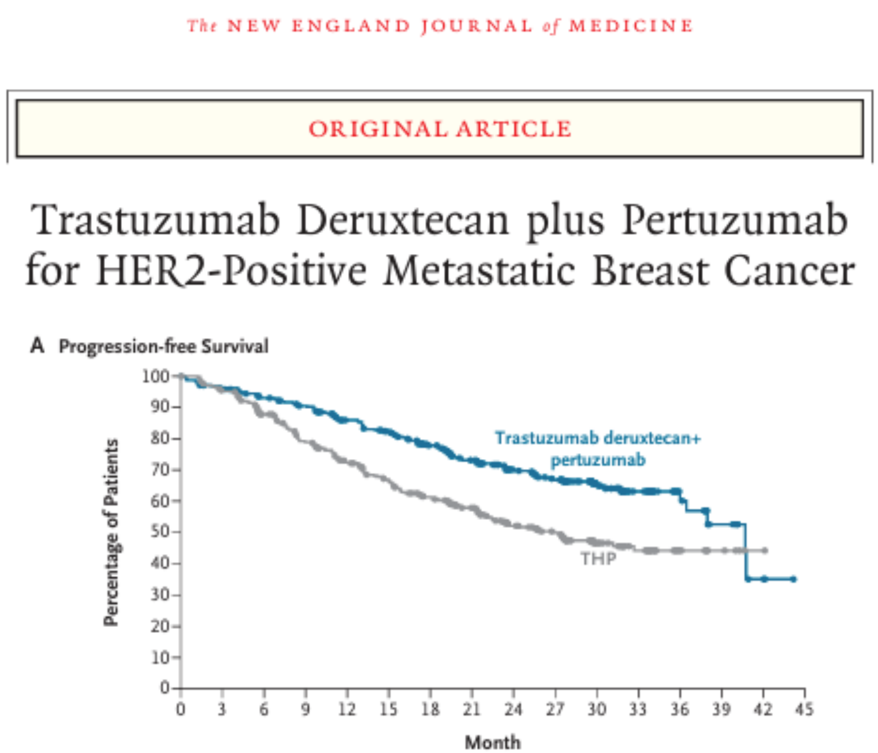
(1) Hadoux, et al. *Dig Liv Dis* 2021. (2) Riesco-Martinez, et al. *Nature Communications* 2024. (3) Zhen, et al. ASCO 2022. (4) Patel, et al. *CCR* 2020. (5) Patel, et al. *Cancer* 2021. (6) Girard, et al. ESMO 2021. (7) Klempner, et al. *Cancer Discovery* 2016. (8) Falkman, et al. *Ups J Med Sci* 2024.

# What are targeted therapies?

- No one right answer
- **Some define:** therapies targeting individual biologic pathways tumors depend on
  - mTOR pathway inhibitors: e.g. everolimus in NETs
  - Angiogenesis (tumor blood vessel) inhibitors: e.g. cabozantinib in NETs
- **Others define:** a therapy specifically designed against a biomarker present in a tumor
  - At the moment in NENs, generally **none** apart from SSAs/SSTR-targeted RLTs, and belzutifan for VHL-associated disease

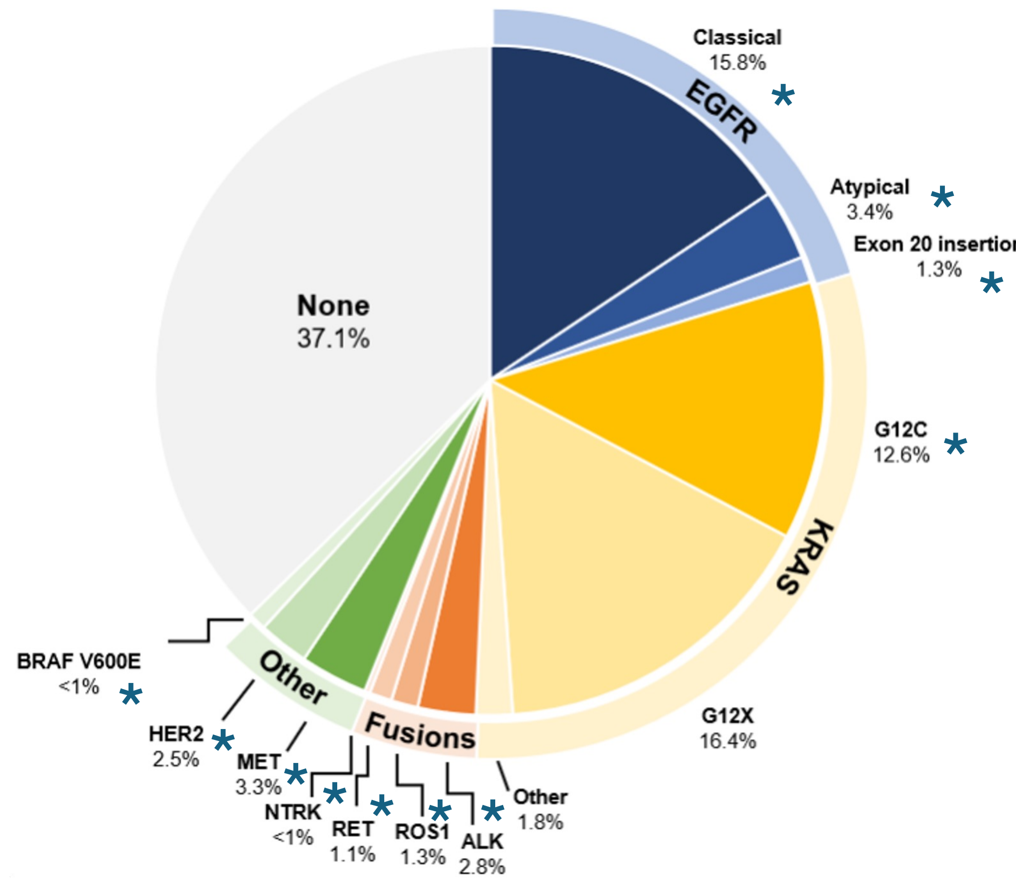
# Targeted therapies across solid tumor oncology

HER2+ breast cancer




Tolaney, et al. *NEJM* 2025

Lung adenocarcinoma




Choudhury, et al. *Clinical Cancer Research* 2023

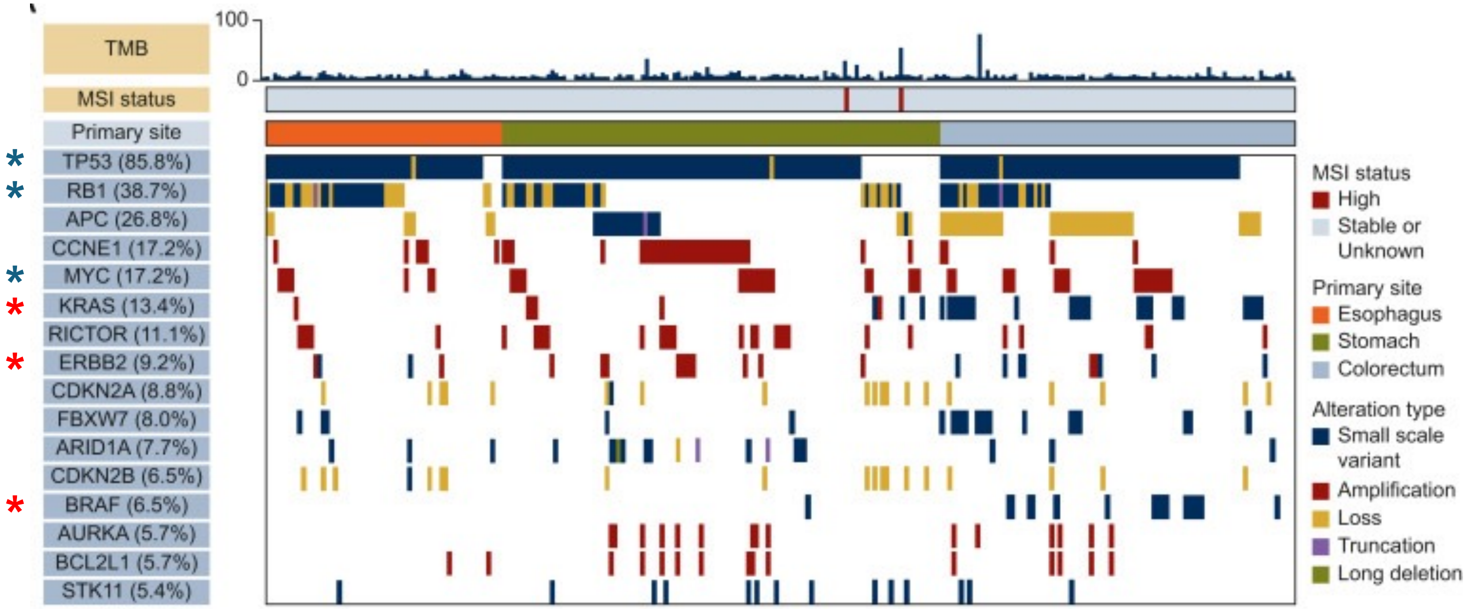
# What make NETs different than other cancers with more defined targeted therapies?

- **Small bowel NETs:**
  - Exceptionally low mutation frequencies [1]
  - Recurrent chromosomal rearrangements
  - Likely an **epigenetically** driven disease (widespread DNA methylation changes, alterations in chromosomal remodeling enzymes) [2]
- **Pancreatic NETs:**
  - Mainly **tumor suppressor** alterations: *ATRX/DAXX, MEN1, TSC2* [3, 4]
  - Highly aneuploid tumors: common large chromosomal gains and losses [4]

(1) Banck, et al. *JCI* 2013. (2) Patte, et al. *Nature Communications* 2025. (3) Jiao, et al. *Science* 2011. (4) Raj, et al. *JCO PO* 2018.

# What make NECs different than other cancers with more defined targeted therapies?

- **NECs:** largely driven by **tumor suppressors** (*TP53, RB1*), and difficult to target oncogenes (*MYC*)
- Role for targeting drivers associated with **site-specific adenocarcinomas** (*ERBB2, KRAS, BRAF*) remains uncertain; are these tumors still dependent?




Ozato, et al. *ESMO GI* 2025

# We have had to think differently to develop targeted therapies in NENs!

- Understand biological pathways conferring tumor cell dependence, not specifically tied to tumor genetics
  - mTOR pathway → everolimus

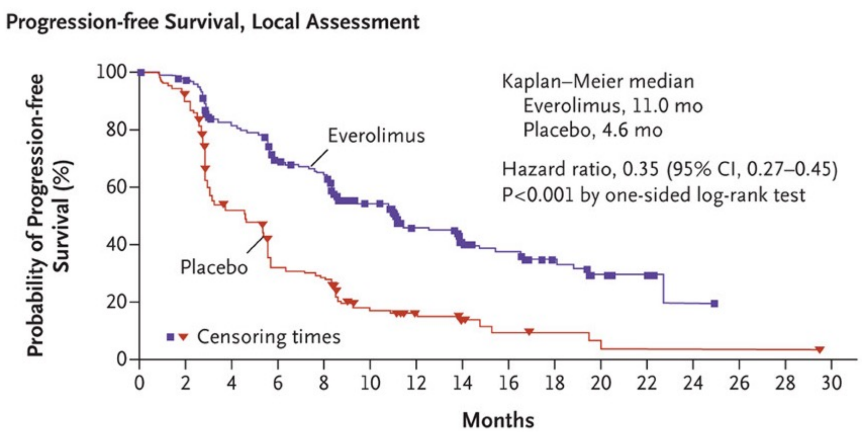
- Target the tumor microenvironment:
  - Angiogenesis supporting NEN tumor cell growth → multi-targeted TKIs (e.g. cabozantinib)
  - Immune-based vulnerabilities → role for ICI + TKI combination therapies?

- Identify unique vulnerabilities tied to neuroendocrine cell lineage/identity
  - Particular focus on new cell surface protein targets → DLL3, SEZ6, DLK1, and others

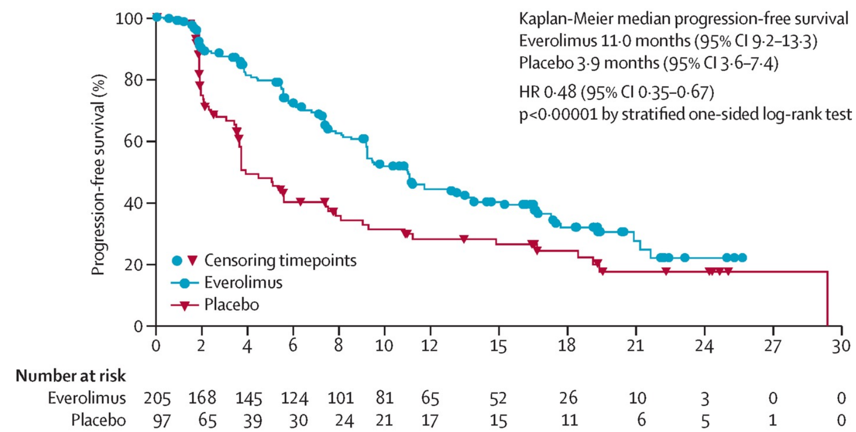
- Future: new synthetic lethality opportunities? Epigenetic therapies/tumor suppressor targeting? Therapies for more intractable oncogenes (e.g. KRAS, MYC)?

# Everolimus in pancreatic and lung/GI NETs

**RADIANT-3: PanNETs**



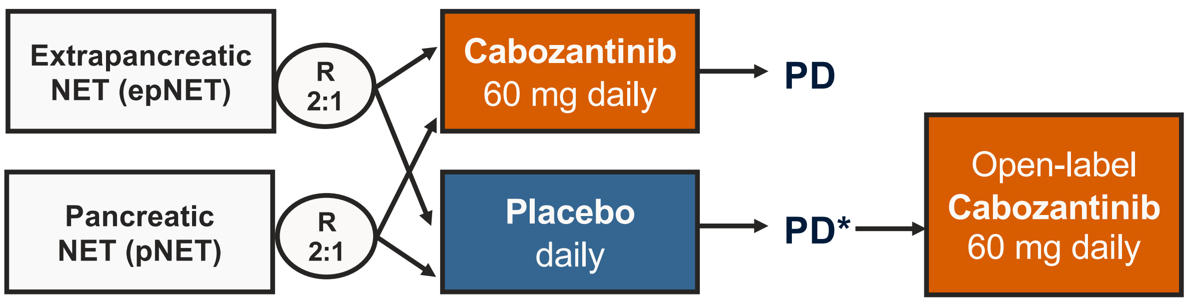

**RADIANT-4: NF lung and GI NETs**




- PFS benefit in RADIANT-3 [1] (no OS benefit; 85% crossover [2])
- PFS benefit and numerical OS benefit in RADIANT-4 (no crossover allowed [3])
- Common AEs: stomatitis, rash, diarrhea, edema, pneumonitis, hyperglycemia, asthenia; 59% dose adjustments [1]
- RADIANT trials in “well-moderately differentiated” NET population (pre-WHO 2017 definitions): likely almost exclusively modern G1/G2 NETs
- Role for everolimus in G3 NETs remains uncertain, and mainly limited to retrospective series [4]

(1) Yao, et al. *NEJM* 2011. (2) Pommier, et al. *Gastrointest Cancer Res* 2014. (3) Yao, et al. *Lancet* 2016. (4) Panzuto, et al. *Pancreas* 2017.

# CABINET: Phase 3 Cabozantinib vs. Placebo Previously-Treated, Extrapancreatic or Pancreatic NET




** Unblinding and crossover allowed after confirmation of PD by central radiology review*

**Primary Endpoints**

- Primary per cohort: Progression-free survival (PFS) by blinded independent central review

**Key Secondary Endpoints per cohort**

- Overall survival
- Objective response rate
- Safety and tolerability

**Key inclusion criteria:**

- Well- to moderately differentiated NET, **grades 1-3**
- Functional and nonfunctional included
- Disease progression by RECIST within 12 months prior to randomization
- Progression or intolerance of **at least 1 prior FDA-approved systemic therapy**, not including somatostatin analogs (SSA)
  - ➢ Includes everolimus, sunitinib, or $^{177}$LU-DOTATATE for pNET
  - ➢ Includes everolimus for lung NET
  - ➢ Includes everolimus or $^{177}$Lu-DOTATATE dotatate for GI-NET
- Concurrent SSA allowed provided stable dose for ≥ 2 months

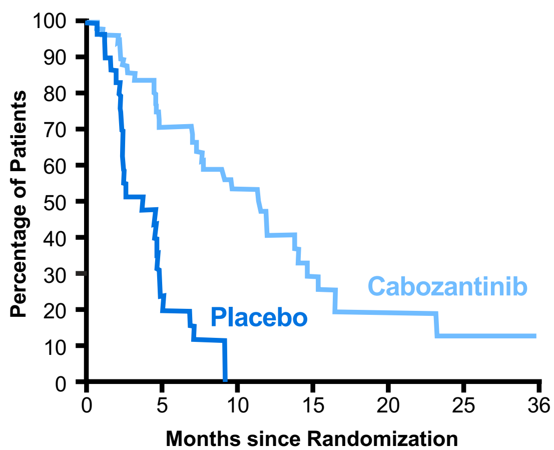
| Characteristic | Extrapancreatic NET Cohort | | Pancreatic NET Cohort | |
|---|---|---|---|---|
| | Cabozantinib (N = 134) | Placebo (N = 69) | Cabozantinib (N = 64) | Placebo (N = 31) |
| **Previous systemic therapy, no. (%)** | | | | |
| Somatostatin analogue | 125 (93) | 64 (93) | 63 (98) | 30 (97) |
| $^{177}$Lu-DOTATATE | 80 (60) | 41 (59) | 38 (59) | 18 (58) |
| Everolimus | 96 (72) | 44 (64) | 51 (80) | 25 (81) |
| Temozolomide with or without capecitabine | 43 (32) | 20 (29) | 438 (67) | 16 (52) |
| Cisplatin or carboplatin plus etoposide | 11 (8) | 8 (12) | NA | NA |
| Sunitinib | NA | NA | 18 (28) | 7 (22) |

NET = neuroendocrine tumor; Chan JA, et al. *N Engl J Med*. 2025;392:653-665.

# CABINET: cabozantinib significantly improves PFS in pNET and epNET

## PFS in the Pancreatic NET Cohort

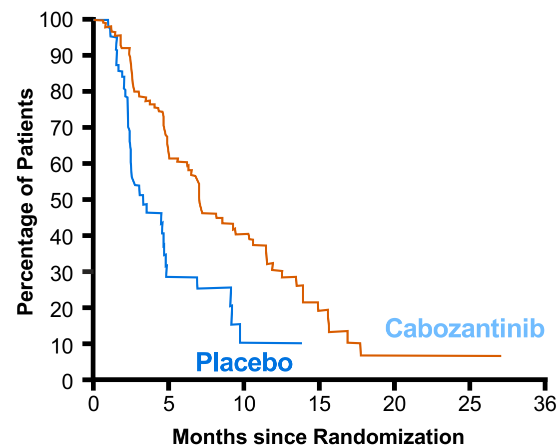
| | Cabozantinib | Placebo |
|---|---|---|
| **Events/Total No.** | **32/64** | **25/31** |
| **Median PFS,** mo (95% CI) | **13.8** (9.2-18.5) | **4.4** (3.0-5.9) |
| **HR for disease progression or death** (95% CI) | **0.23** (0.12-0.42) | |
| ***P* value** by log-rank test | **< 0.001** | |




| No. at risk (no. censored) | | | | | | | |
|---|---|---|---|---|---|---|---|
| Cabozantinib | 64 (0) | 33 (16) | 18 (24) | 8 (27) | 3 (30) | 2 (30) | 0 (32) |
| Placebo | 31 (0) | 6 (4) | 0 (6) | | | | |

## PFS in the Extrapancreatic NET Cohort

| | Cabozantinib | Placebo |
|---|---|---|
| **Events/Total No.** | **71/134** | **40/69** |
| **Median PFS,** mo (95% CI) | **8.4** (7.6-12.7) | **3.9** (3.0-5.7) |
| **HR for disease progression or death** (95% CI) | **0.38** (0.25-0.59) | |
| ***P* value** by log-rank test | **< 0.001** | |

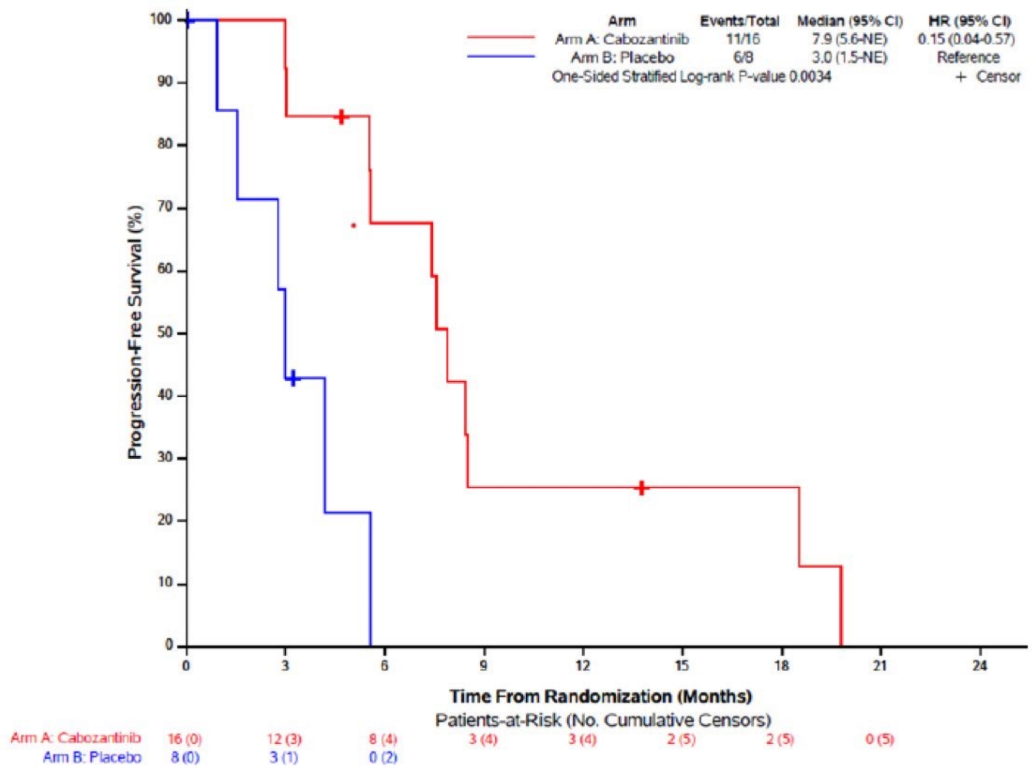



| No. at risk (no. censored) | | | | | | | |
|---|---|---|---|---|---|---|---|
| Cabozantinib | 134 (0) | 58 (39) | 26 (52) | 8 (59) | 1 (62) | 1 (62) | 0 (63) |
| Placebo | 69 (0) | 9 (24) | 2 (27) | 0 (29) | | | |

Mo = months; no = number; OS = overall survival; PFS = progression-free survival; Chan JA, et al. *N Engl J Med*. 2025;392:653-665.

# CABINET: G3 NET subgroup analysis

- 24 patients in CABINET with G3 disease (including both pancreatic and extrapancreatic cohorts)
  - mPFS 7.9 vs 3.0 months
  - ORR 25% vs 0%
  - *P* = 0.003




Strosberg, et al. *Endocrine Related Cancer* 2026

# CABINET (pNET cohort): Toxicity and Dose Reductions

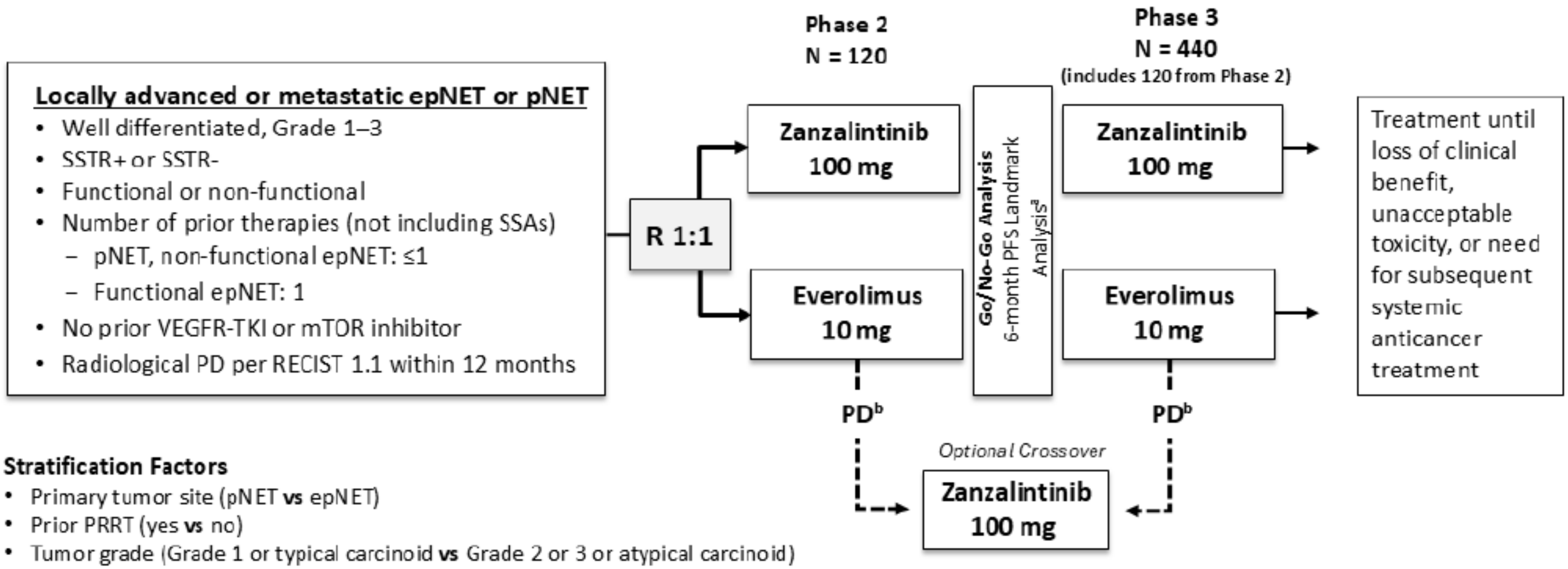
Grade 3/4 TRAEs = 65% with cabozantinib; HTN (22%), fatigue (11%), thromboembolic events (11%)

Dose reductions occurred in 68% of patients receiving cabozantinib and 19% with placebo

Average daily dose was **37.9 mg** of cabozantinib, 56.9 mg of placebo

Chan JA, et al. *N Engl J Med*. 2025;392:653-665.

# STELLAR-311: zanzalintinib vs everolimus




- NCT06943755 (recruiting)

# ICI + TKI combination studies in NENs

- Lenvatinib + pembrolizumab for GI/thoracic NETs [1]
  - 10% RR, mPFS 8 months (reference: lenvatinib RR 15% in GETNE1509 [2])
- CABATEN/GETNE-T1914: cabozantinib + atezolizumab in endocrine/NE malignancies [3]
  - G1/G2 GEP NET: RR 17%, mPFS 13 mo
  - G3 epNEN: (G3 NET = 2, PDNEC = 7): RR 0%, mPFS 2.7 mo
- CABOAVENEC: cabozantinib + avelumab in chemorefractory high grade NENs [4]
  - 19 pts to date (12 G3 NET, 7 NEC): response rate 21%, mPFS 11 months
- Lenvatinib + pembrolizumab for G3 NETs: NCT05746208 (recruiting)
- Cabozantinib + ipi/nivo in epNECs: NCT04079712 (completed)

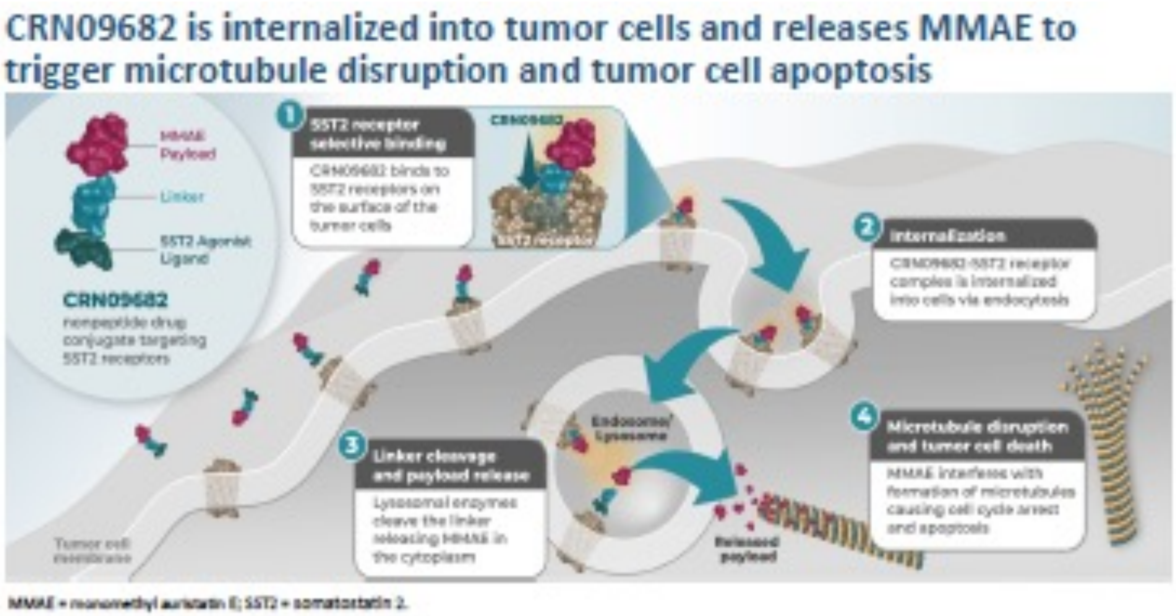
(1) Al-Toubah, et al. *ESMO Open* 2024. (2) Capdevila, et al. *JCO* 2021. (3) Capdevila, et al. *CCR* 2025. (4) Weber, et al. ESMO 2023.

# Belzutifan for VHL-associated PanNETs and PPGLs

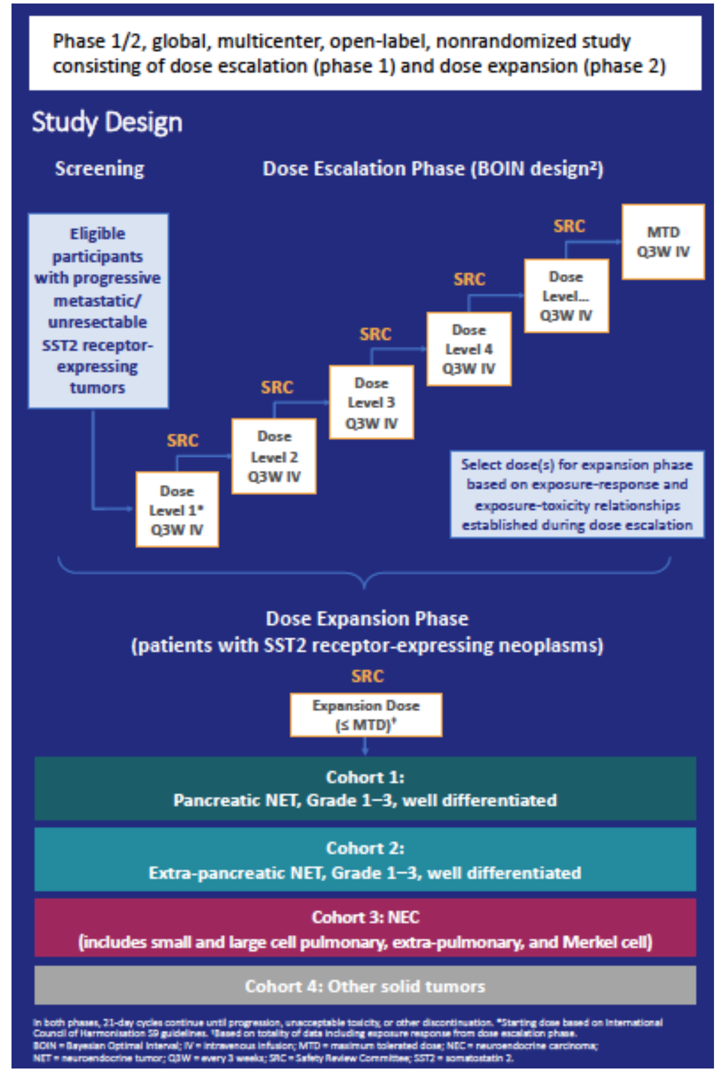
- VHL syndrome [1]: ~1/30,000; type 1 vs type 2 depending on VHL subtype
  - 10-20% of VHL syndrome patients will develop PanNET: typically more indolent, multifocal tumors
  - 15-30% develop pheochromocytoma or paraganglioma (30-60% in type 2)
  - Lead to activation of HIF-2α; inhibited by belzutifan [2]
- Belzutifan in ccRCC [2]
  - 22 patients with VHL-associated pancreatic NETs on study: ORR 91% (20/22)
- LITESPARK-015: Cohort A2 (PanNETs) [3]
  - RR 10%
  - Trial not restricted to VHL population, responses seen in VHL and non-VHL patients
- LITESPARK-015: PPGL [4]
  - RR 26%, median DOR 20.4 months, median PFS 22.3 months

(1) Kaelin, et al. JCI 2022. (2) Jonasch, et al. *NEJM* 2021. (3) Capdevila, et al. ESMO 2025. (4) Jimenez, et al. *NEJM* 2025.

# CRN09682: novel SSTR2-targeted non-peptide drug conjugate (NDC)



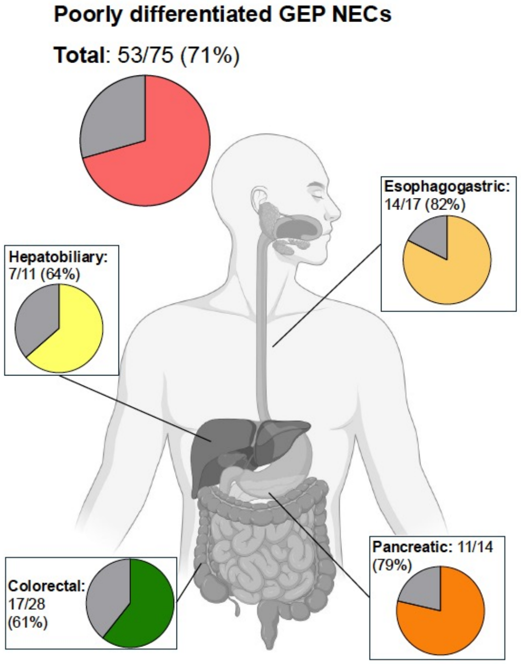

- NCT07129252 (recruiting)



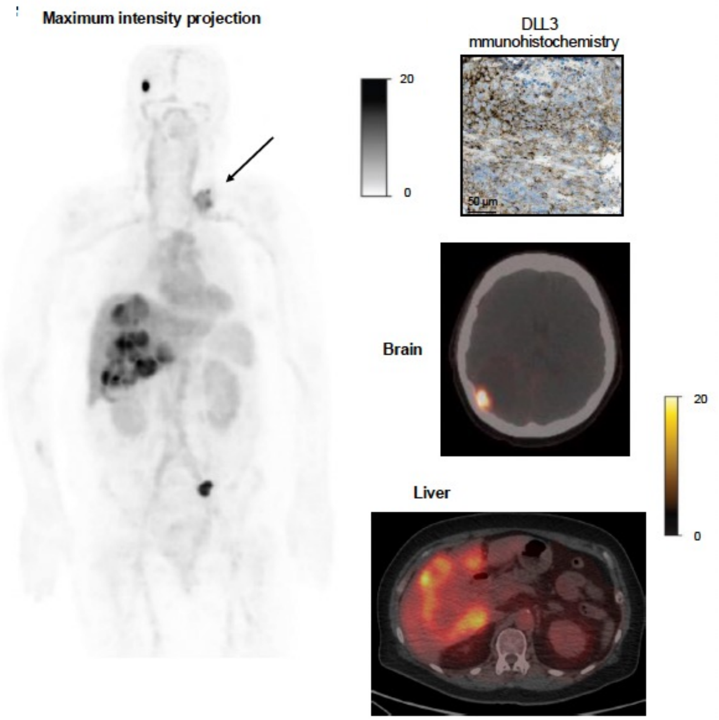

Li, et al. NANETS 2025

# DLL3: an emerging target in poorly differentiated NECs

- Negative regulator of Notch signaling, target of ASCL1 (neuroendocrine TF)
- Expressed in ~80% of small cell lung cancer (SCLC)
- Recently, we have learned DLL3 is also expressed in ~70-80% of epNECs, including GEP NECs

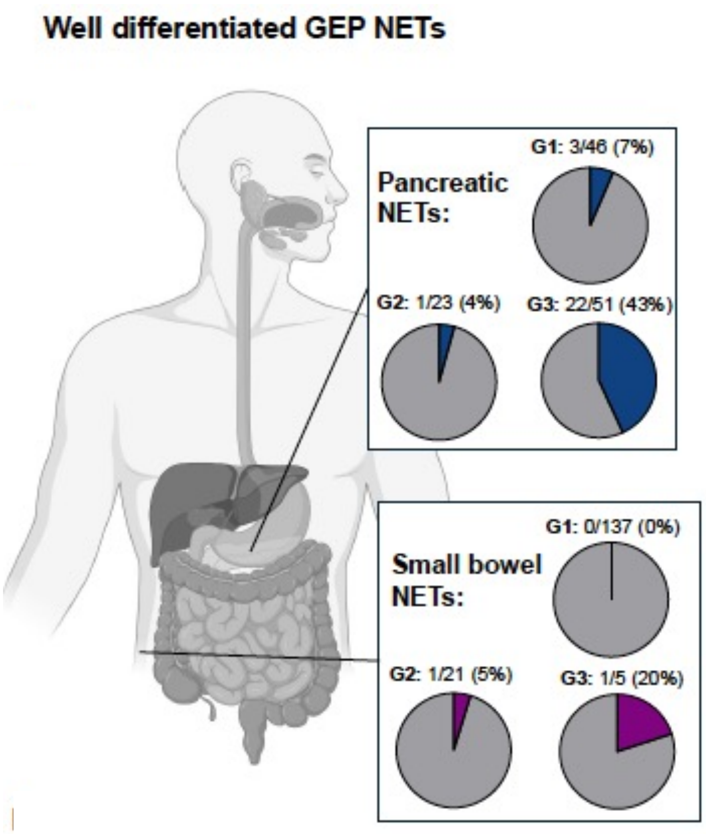


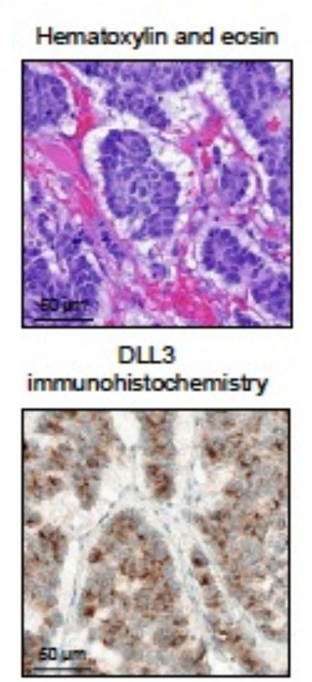

Gallbladder NEC



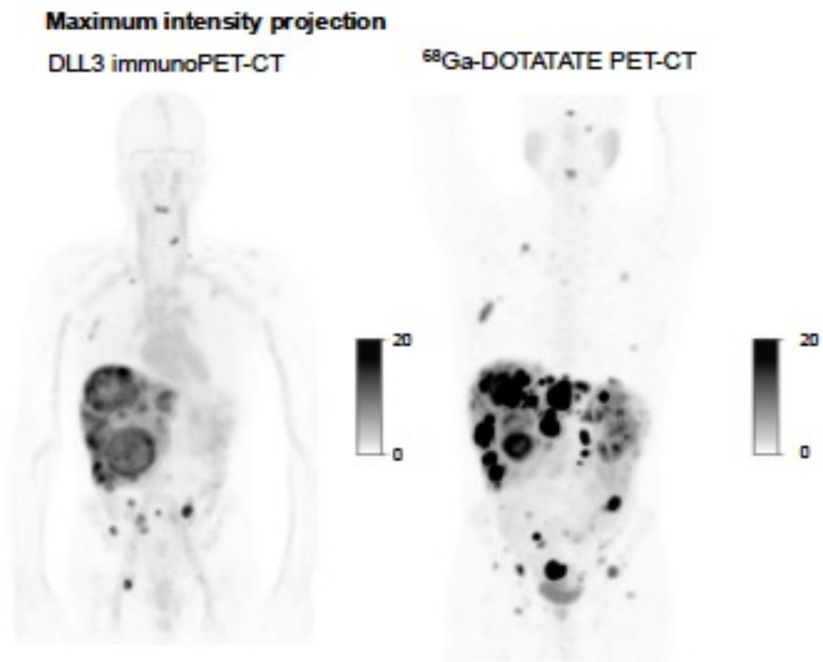

Thummalapalli, et al. *JCO PO* 2025

# DLL3 expression in high grade (grade 3) NETs




G3 pancreatic NET




Thummalapalli, et al. *JCO PO* 2025

# Landscape of DLL3 targeted therapy development across classes

**CD3 T cell engagers (TCEs)**
- Tarlatamab
- Obrixtamig
- RO7616789
- MK-6070 (formerly HPN-328)

**CD47 bispecific:**
- PT217

**Antibody-drug conjugates:**
- ZL-1310
- IBI-3009
- IDE849

**CAR T cells:**
- AMG 119
- LB2102

**Radioligand therapies:**
- ABD-147 ($^{225}$Ac)
- Novartis [225Ac]Ac-ETN029

As of 3/2026:
**SCLC and/or NEPC only**
**Open to epNECs**
**Dedicated GEP NEC cohorts**

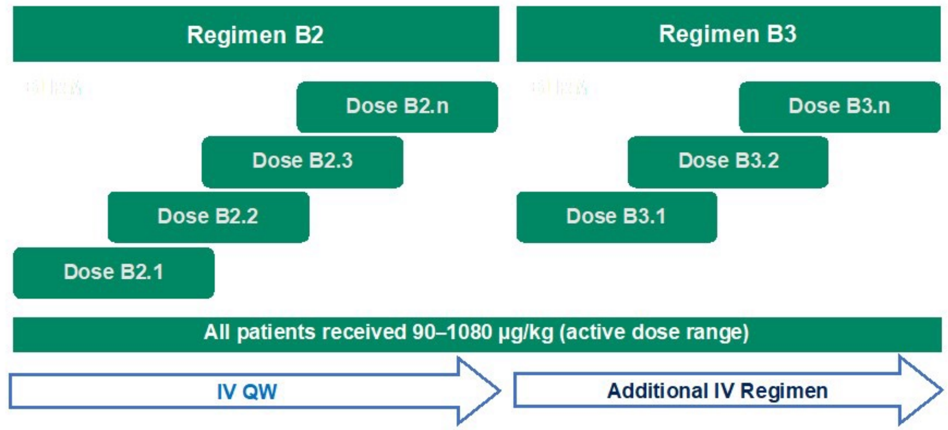
## Abstract 3004: Efficacy and safety of the DLL3/CD3 T-cell engager obrixtamig in patients with extrapulmonary neuroendocrine carcinomas with high or low DLL3 expression: results from an ongoing Phase I trial

Jaume Capdevila,[1] Valentina Gambardella,[2] Yasutoshi Kuboki,[3] Olatunji B. Alese,[4] Daniel Morgensztern,[5] Cyrus Sayehli,[6] Miguel F. Sanmamed,[7] Edurne Arriola,[8] Matus Studeny,[9] Mohamed Bouzaggou,[10] Zhiheng Chen,[11] Valeria Lifke,[12] Jürgen Wolf,[13] Martin Wermke[14]

### Key inclusion criteria

- Advanced SCLC, **epNEC**, or LCNEC-L
- DLL3-positive according to central review
- Failed/ineligible for available standard therapies
- Adequate liver, bone marrow, and renal function

**Patients with epNECs treated in Regimen B2 and B3 are reported here**




Primary endpoint: MTD - DLTs in the MTD evaluation period

All patients were required to have DLL3-positive tumors (>0% of TC with moderate-to-strong staining with DLL3 investigational assay (SP347; Roche Diagnostics)

- 165 (83%) of 200 patients

DLL3 testing was performed at the Roche CDx CAP/CLIA Laboratory

Tumors were categorized as either DLL3-high (≥50% TC) or DLL3-low

- (>0% to <50% TC) – 30 (50%) and 30 (50%)

# Abstract 3004: Safety

## Baseline characteristics

| | DLL3$^{high}$ n=30 | DLL3$^{low}$ n=30 |
|---|---|---|
| Median age, years (range) | 69 (36–81) | 61 (33–77) |
| Sex, n (%) | | |
| Female | 13 (43) | 4 (13) |
| Male | 17 (57) | 26 (87) |
| ECOG PS, n (%)* | | |
| 0 | 10 (33) | 14 (47) |
| 1 | 17 (57) | 13 (43) |
| Primary site of disease, n (%) | | |
| GI | 14 (47) | 18 (60) |
| GU | 12 (40) | 8 (27) |
| CUP | 4 (13) | 3 (10) |
| Other | 0 | 1 (3)† |
| Prior lines of therapy, n (%)‡ | | |
| 1 | 10 (33) | 6 (20) |
| 2 | 11 (37) | 8 (27) |
| >2 | 9 (30) | 15 (50) |

## Safety

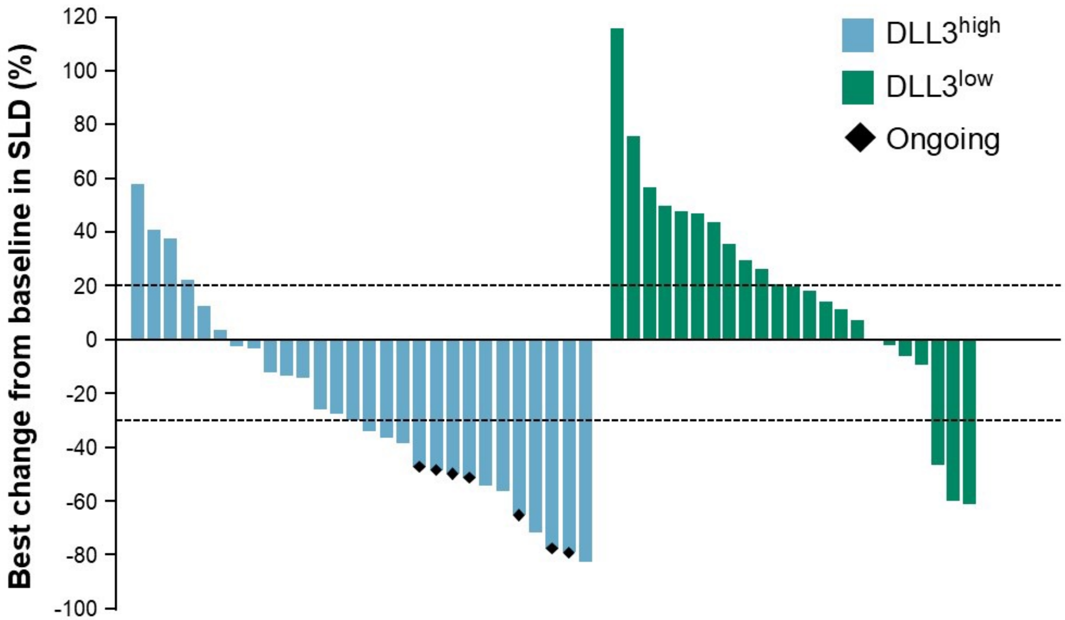
| | All N=60 | | DLL3$^{high}$ n=30 | | DLL3$^{low}$ n=30 | |
|---|---|---|---|---|---|---|
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Any TRAE, n (%)* | 57 (95) | 13 (22) | 30 (100) | 7 (23) | 27 (90) | 6 (20) |
| Cytokine release syndrome | 39 (65) | 2 (3) | 21 (70) | 1 (3) | 18 (60) | 1 (3) |
| Pyrexia | 19 (32) | 0 | 12 (40) | 0 | 7 (23) | 0 |
| Dysgeusia | 15 (25) | 0 | 11 (37) | 0 | 4 (13) | 0 |
| Asthenia | 14 (23) | 1 (2) | 6 (20) | 0 | 8 (27) | 1 (3) |
| Fatigue | 11 (18) | 0 | 7 (23) | 0 | 4 (13) | 0 |
| Decreased appetite | 10 (17) | 0 | 4 (13) | 0 | 6 (20) | 0 |
| Lymphocyte count decreased | 9 (15) | 7 (12) | 7 (23) | 5 (17) | 2 (7) | 2 (7) |
| Potential neurological adverse events, including ICANS, n (%) | 8 (13) | 3 (5) | 5 (17) | 2 (7) | 3 (10) | 1 (3) |

Capdevila, et al. ASCO 2025

# Efficacy: overall and by DLL3 expression

**Patients with $DLL3^{high}$ tumors had a high ORR and DCR**

| Confirmed response | All N=60 | $DLL3^{high}$ n=30 | $DLL3^{low}$ n=30 |
|---|---|---|---|
| **ORR, %** (95% CI) | 22 (13–34) | 40 (25–58) | 3 (1–17) |
| PR, n (%) | 13 (22) | 12 (40) | 1 (3) |
| **DCR, %** (95% CI) | 47 (35–59) | 67 (49–81) | 27 (14–44) |
| SD, n (%) | 15 (25) | 8 (27) | 7 (23) |
| PD, n (%) | 23 (38) | 8 (27) | 15 (50) |
| NE, n (%)* | 9 (15) | 2 (7) | 7 (23) |

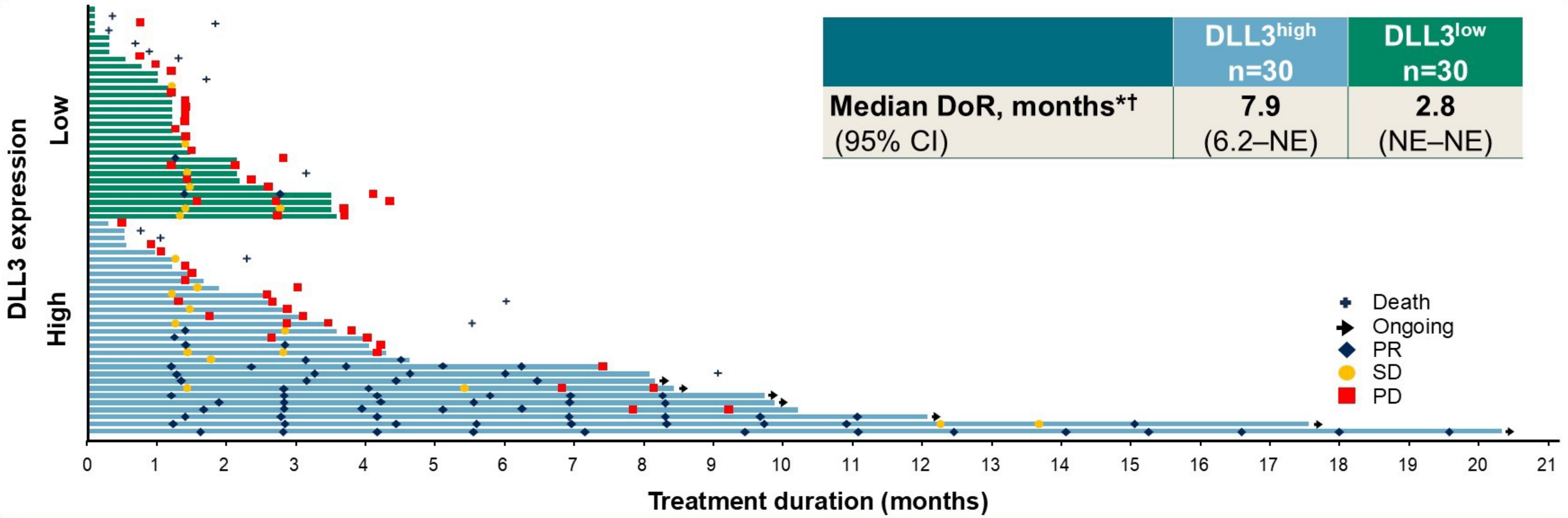



Data cut-off: June 21, 2024
*9 patients discontinued treatment before first imaging and were NE. Reasons for discontinuation were: clinical disease progression (n=6), adverse event, withdrawal by patient and other (all n=1)
CI, confidence interval; DCR, disease control rate; DLL3, delta-like ligand 3; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; SLD, sum of lesion diameter

Capdevila, et al. ASCO 2025

# Duration of response by DLL3 expression

**Obrixtamig demonstrated durable efficacy in patients with DLL3$^{high}$ epNEC**




| | DLL3$^{high}$ n=30 | DLL3$^{low}$ n=30 |
|---|---|---|
| **Median DoR, months*†** (95% CI) | **7.9** (6.2–NE) | **2.8** (NE–NE) |

- 7 of 30 (23%) DLL3$^{high}$ patients remained on treatment at the time of data cut-off

Data cut-off: June 21, 2024
*Confirmed; †median follow-up: 9.7 months (95% CI: 6.5–13.9)
CI, confidence interval; DLL3, delta-like ligand 3; DoR, duration of response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease

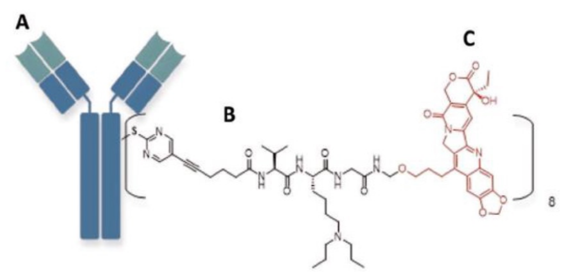
Capdevila, et al. ASCO 2025

ENA 2024
EORTC NCI AACR
36th Symposium

# ZL-1310: Novel Delta-Like Ligand 3 (DLL3) Targeting ADC

- DLL3 is a neuroendocrine-specific antigen that is a validated target and is highly expressed in SCLC, an indication with a high unmet medical need[1-3]
- ZL-1310 is a novel ADC that employs the TMALIN® (Tumor Microenvironment Activable LINker-payload) platform and targets DLL3 with an anti-DLL3 monoclonal antibody linked to a topoisomerase I inhibitor payload via a protease-cleavable linker[4]

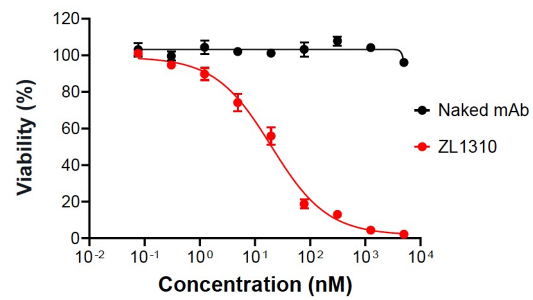
## Structure of ZL-1310[4]



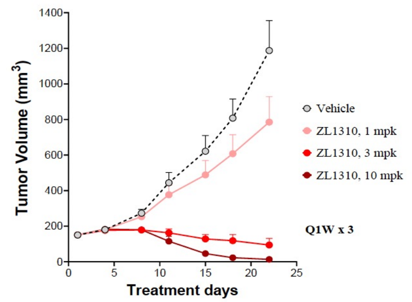

A: Humanized anti-DLL3 IgG1 mAb
B: Cleavable tripeptide-based linker
C: Camptothecin derivative payload, C24; DAR=8

## ZL-1310 Preclinical Activitiy[4]

ZL-1310-mediated cytotoxicity in DLL3+ NCI-H69 SCLC Cells




ZL-1310-mediated significant TGI in human SCLC LU5215 (DLL3[low]) PDX Model

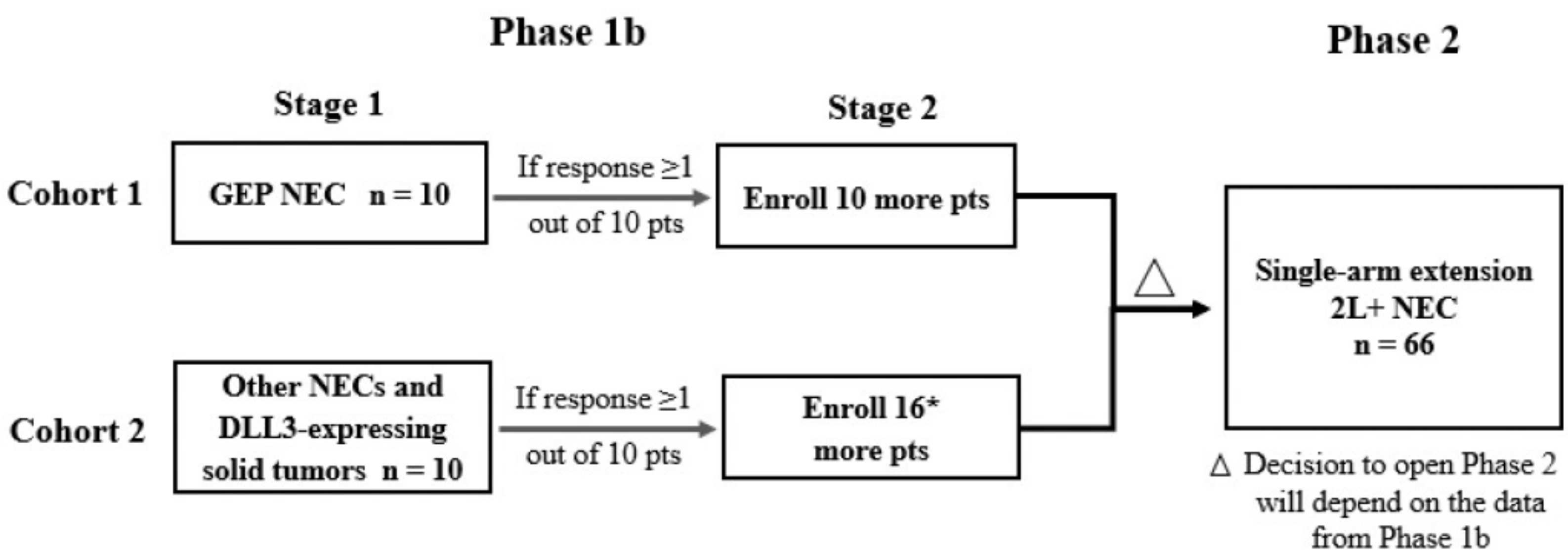



EORTC | NIH NATIONAL CANCER INSTITUTE | AACR American Association for Cancer Research

DLL3: delta-like ligand 3; DAR: drug-to-antibody ratio Ig: immunoglobulin; mAb: monoclonal antibody; mpk: milligrams per kilograms; nM: nanomolar; PDX: patient-derived xenograft; Q1W: once weekly; SCLC: small cell lung cancer; TGI: tumor growth inhibition.

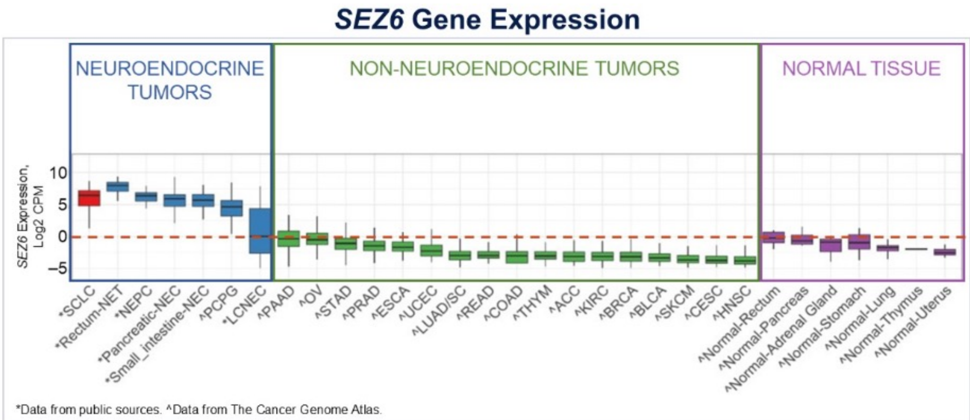

1. Sabari JK, et al. Nat Rev Clin Oncol. 2017;14(9):549–61. 2. Saunders LR, et al. Sci Transl Med. 2015;7(302):302ra136. 3. Petrelli F, et al. Mol Clin Oncol. 2021;15(4):218. 4. Liu LN, et al. Poster presented at: ELCC; March 22, 2024; Prague, Czech Republic.

# ZL-1310-002 (DLL3 ADC): planned for phase 2 expansion in NECs

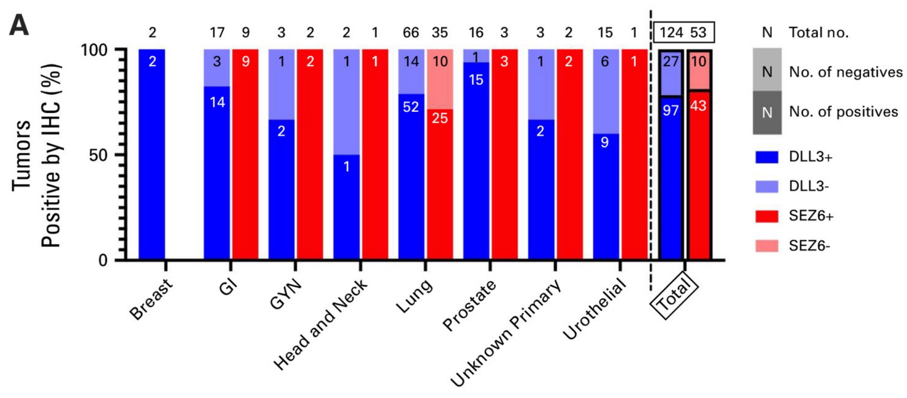



- NCT06885281 (phase 2 open, recruiting)

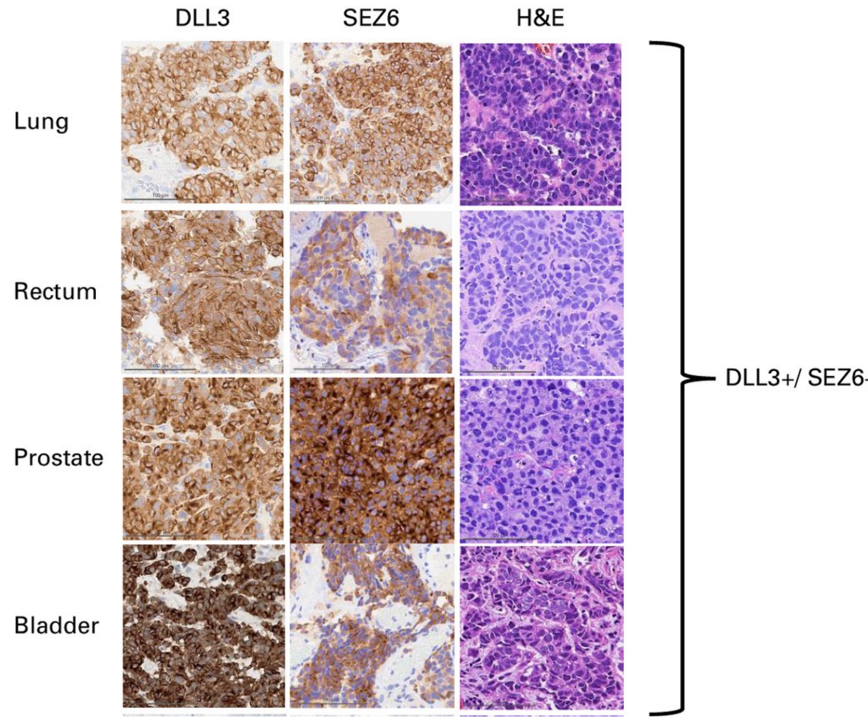
# SEZ6 is expressed on a majority of NECs (and likely high grade NETs)




Wiedemeyer, et al. *Mol Cancer Ther* 2022



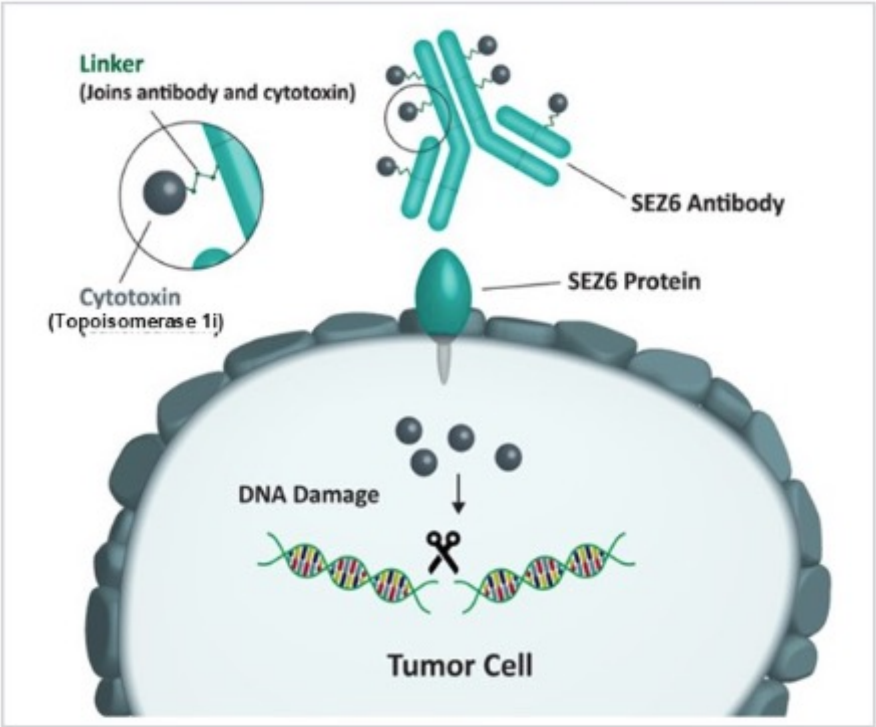

Ross, et al. *JCO PO* 2025



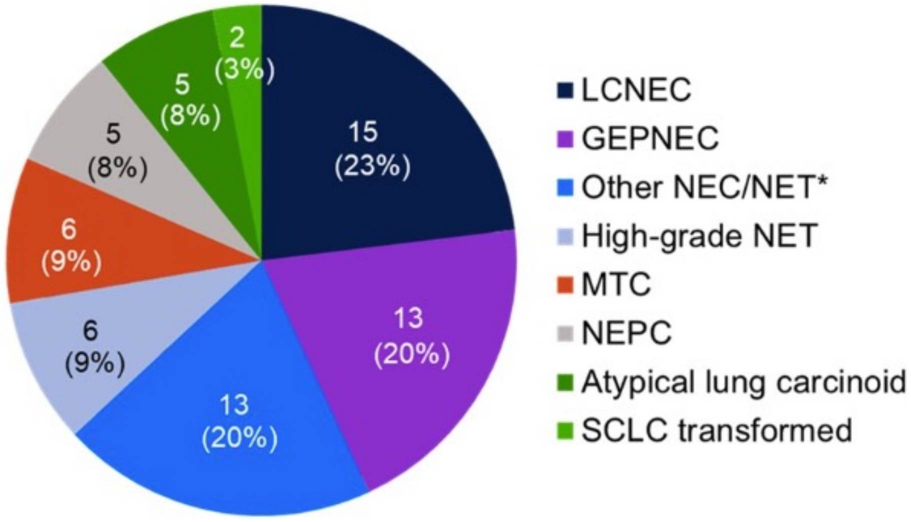

Ross, et al. *JCO PO* 2025

# Activity of ABBV-706 (SEZ6 ADC) in high grade NENs

ABBV-706 Mechanism of Action




NEN Types (N=65)

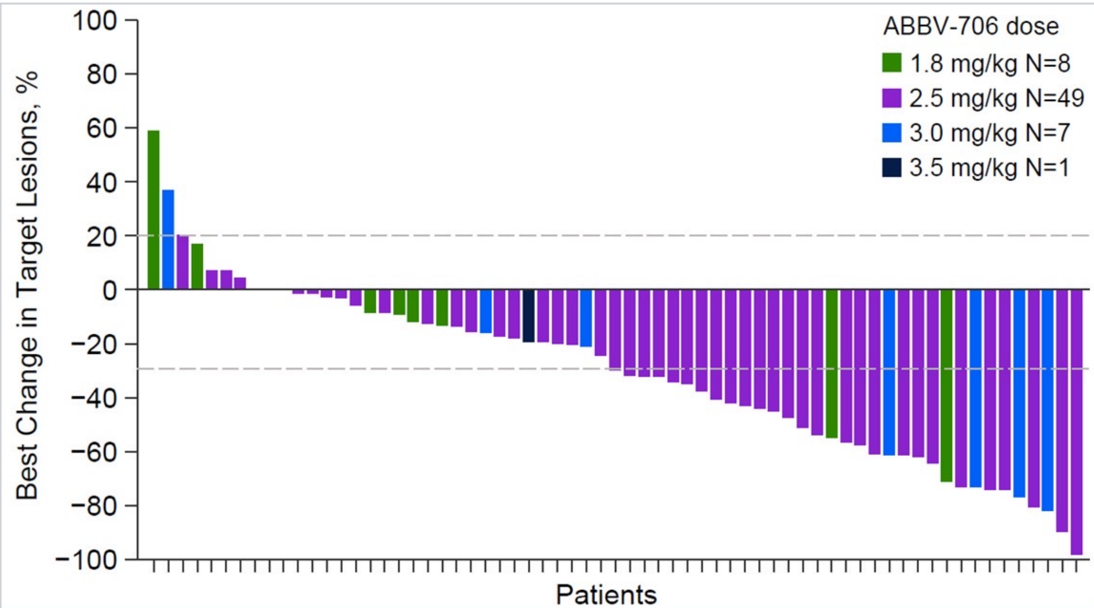



**Other NEC/NET: NEC GU (n=4; bladder 3, kidney 1), NEC cervix (n=3), high-grade NEN unspecified (n=4), MINEN (n=1), NEC parathyroid (n=1).*

Cooper, et al. ASCO 2025

## ABBV-706 has promising antitumor activity in NENs

### Change in Target Lesion Size by Dose (N=65)



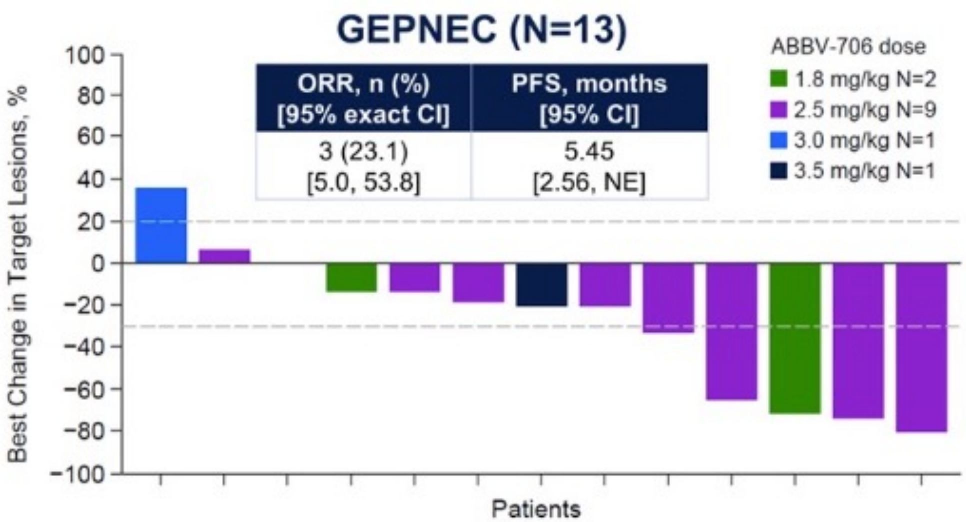

| Outcome | Total NEN (N=65)[a,b] |
|---|---|
| ORR,[c] n (%)<br>[95% exact CI] | **24 (36.9)**<br>[25.3, 49.8] |
| Best response, n (%) | |
| *CR* | 1 (1.5) |
| *PR* | 23 (35.4) |
| *SD* | 37 (56.9) |
| *PD* | 4 (6.2) |
| Median DOR, months<br>[95% CI] | 6.37<br>[4.44, 9.46] |
| Median PFS, months<br>[95% CI] | 7.62<br>[5.52, 8.31] |

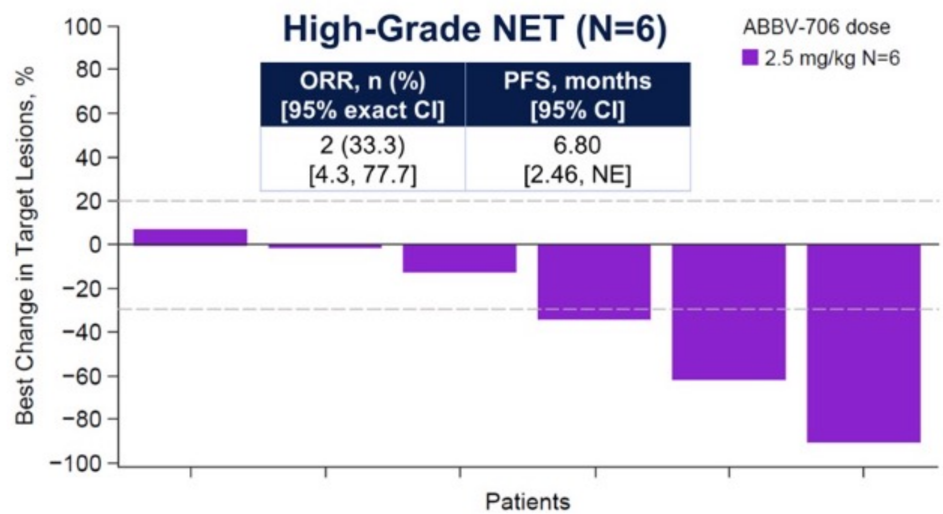
- As of January 3, 2025, cutoff, 17/65 (26%) patients remain on treatment
- Median follow-up was 8.67 months for the 2.5-mg/kg cohort (n=49/65, 75%)

[a]Patients with response evaluation per RECIST v1.1. [b]49 of 65 (75%) patients received ABBV-706 at 2.5 mg/kg. [c]Requires a CR or PR confirmed ≥4 weeks later.
CI, confidence interval; CR, complete response; DOR, duration of response; NEN, neuroendocrine neoplasm; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Cooper, et al. ASCO 2025

# Preliminary activity of ABBV-706 in GEP NECs and high grade NETs




Cooper, et al. ASCO 2025

# DLK1 is widely expressed in adrenal cancers, and to a lesser extent in pancreatic and GI NETs

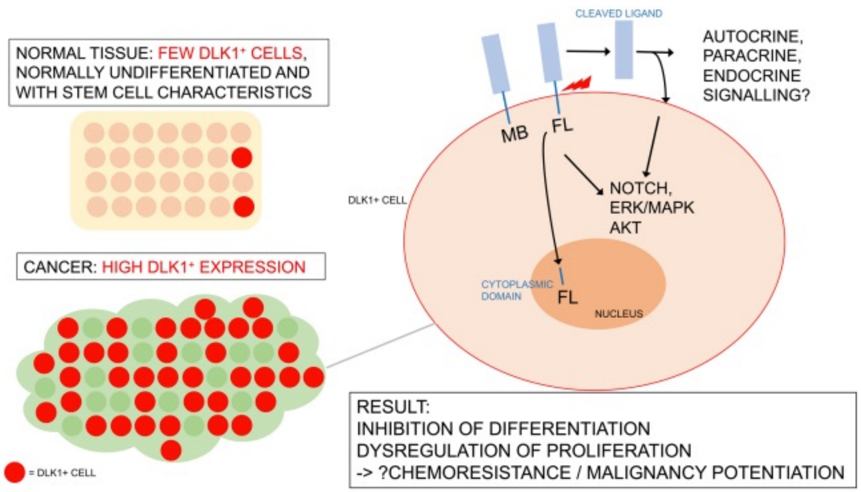


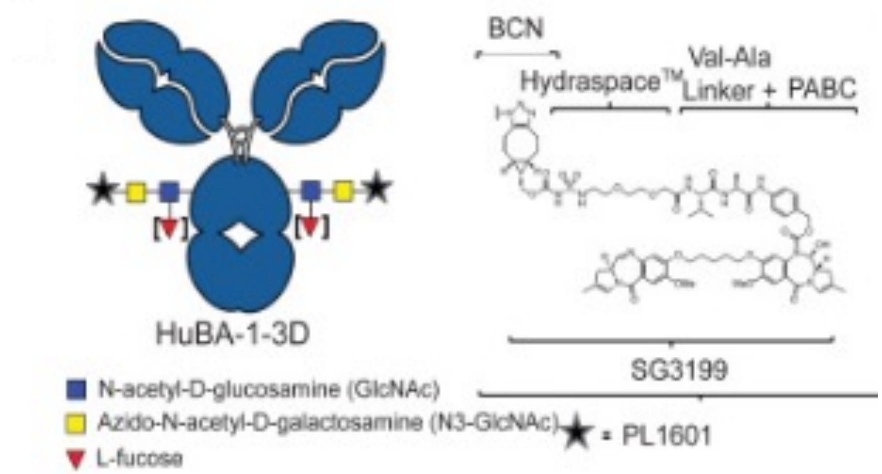

**Table 1** The expression of DLK1 in cancer.

| Tumour | Paper | Expression | Frequency | Cases |
|---|---|---|---|---|
| **Endocrine and neuroendocrine** | | | | |
| Adrenocortical carcinoma | (Hadjidemetriou *et al.* 2019) | Protein IHC | 100% | 9 |
| | (Hadjidemetriou *et al.* 2019) | Protein lysate | 100% | 5 |
| | (Turányi *et al.* 2009) | Protein IHC | 100% | 5 |
| Medullary thyroid carcinoma | (Araujo *et al.* 2021) | Protein IHC | 93% | 27 |
| | (Turányi *et al.* 2009) | Protein IHC | 45% | 11 |
| Ovarian | (Huang *et al.* 2019*a*) | Protein IHC | 67% | 221 |
| Pancreatic islet cell carcinoma | (Yanai *et al.* 2010) | Protein IHC | 50% | 6 |
| Carcinoid lung | (Jensen *et al.* 1994) | Protein IHC | 83% | 6 |
| Gastrointestinal carcinoid | (Turányi *et al.* 2009) | Protein IHC | 10% | 20 |
| Phaeochromocytoma | (Turányi *et al.* 2009) | Protein IHC | 100% | 13 |
| Paraganglioma | (Turányi *et al.* 2009) | Protein IHC | 100% | 4 |
| Testicular adrenal rest tumour | (Lottrup *et al.* 2014) | Protein IHC | 100% | 8 |
| Somatotroph pituitary tumours | (Altenberger *et al.* 2006) | mRNA | 100% | 5 |
| Lactotroph pituitary tumours | (Altenberger *et al.* 2006) | mRNA | 50% | 2 |

Pittaway, et al. *Endocrine Related Cancer* 2021

# Phase 1, first-in-human trial of ADCT-701, DLK1-targeted ADC, in patients with neuroendocrine neoplasms

- Eligibility: patients with NETs, NECs, SCLC, neuroblastoma, PPGLs, and adrenal cancers
- Primary objective: to determine the maximum tolerated dose (MTD) in patients with NENs
- 3+3 dose escalation trial, with expansion cohorts planned
- NCT06041516 (recruiting)
- PI: Dr. Jaydira Del Rivero at NCI



# Thank you!