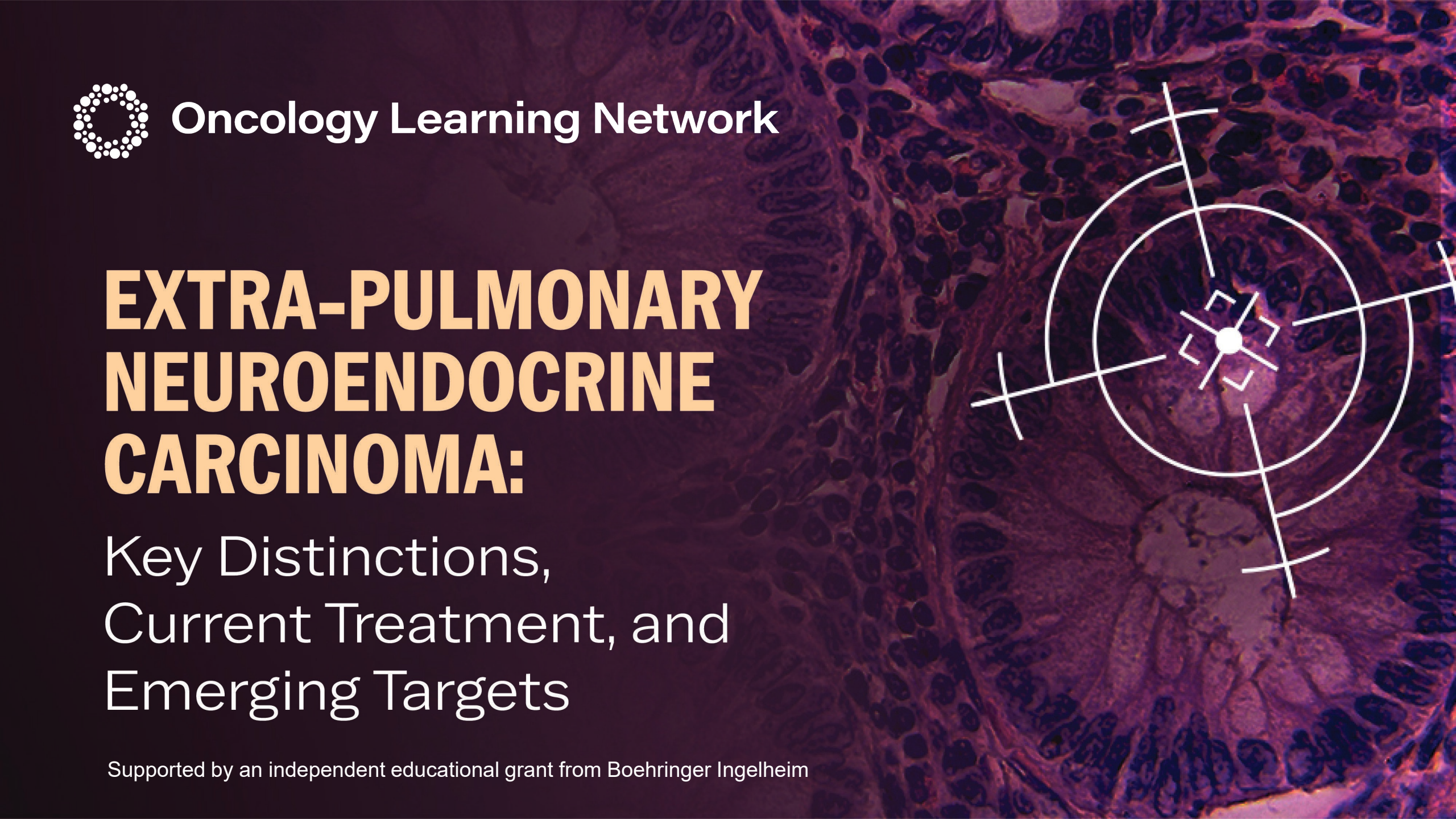
Oncology Learning Network

EXTRA-PULMONARY NEUROENDOCRINE CARCINOMA:

Key Distinctions, Current Treatment, and Emerging Targets

Supported by an independent educational grant from Boehringer Ingelheim



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Faculty Disclosures

- **Jonathan Strosberg, MD:** Advisory Board—Exelixis, ITM, Boehringer Ingelheim
- **Namrata (Neena) Vijayvergia, MD, FACP:** Advisory Board—Exelixis, Pfizer, Boehringer Ingelheim

Program Information

- Provided by HMP Education, LLC, an HMP Global Company
- Supported by an educational grant from Boehringer Ingelheim

Learning Objectives

- Delineate the key differences between NETs and NECs, including their respective pathologic features, diagnostic criteria, treatment guidelines, and prognostic implications
- Describe the role of DLL3 as an emerging target in the progression and prognosis of EP-NEC
- Evaluate the current treatment landscape, most recent clinical trial data, and innovative advancements associated with available and emerging therapies for EP-NEC

NET = neuroendocrine tumor; NEC = neuroendocrine carcinoma; EP-NEC = extra-pulmonary NEC.

Diagnostic Criteria and Standard Treatment Approaches for Poorly Differentiated, Extra-Pulmonary Neuroendocrine Carcinoma (NEC)

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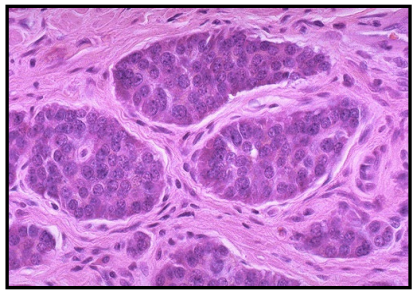
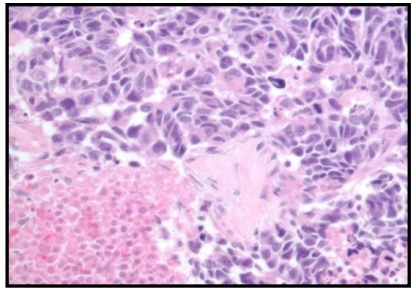
Definitions: Neuroendocrine Tumors

Differentiation	Grade	WHO grading	WHO nomenclature
Well differentiated	**Low (G1)**	<2 mitoses/10 HPF and <3% Ki67 index	NET grade 1
	Intermediate (G2)	2 to 20 mitoses/10 HPF or 3%-20% Ki67 index	NET grade 2
	High (G3)	>20 mitoses/10 HPF or >20% ki-67 index	NET grade 3
Poorly differentiated	**High**	>20 mitoses/10 HPF or >20% Ki67 index	Neuroendocrine carcinoma, grade 3 (large-cell or small-cell type)



Well-Differentiated NET



Poorly-Differentiated NEC

- Well-differentiated neuroendocrine tumors resemble endocrine tissues of origin: well-organized nests or trabeculae. Cells with typical “salt and pepper” chromatin pattern. Ki-67 index rarely above 55%.
- Poorly differentiated neuroendocrine carcinomas exhibit poor morphologic differentiation: sheets of cells, often pleomorphic with high nuclear to cytoplasmic ratio. Can distinguish between small and large cell. Ki-67 typically >60%.

WHO = World Health Organization; HPF = high-power field.

Rindi G, et al. *Endocr Pathol*. 2022;33(1):115-154.

Extra-Pulmonary NEC

- Can originate in various primary sites including GI, GU, and gyn organs
- Distribution of primary sites differs from NETs; common sites include
  - Colorectal (vary rare for NETs except for cecum and rectum)
  - Esophagus (very rare for NETs)
  - Gastric
  - Gallbladder (very rare for NETs)
  - Pancreas
  - Cervix (very rare for NETs)
  - Bladder (very rare for NETs)
  - Prostate (typically evolves from adenocarcinoma)
  - Unknown primary

GI = gastrointestinal; GU = genitourinary.
Stumpo S, et al. *J Clin Med*. 2023;12(24):7715.

Distinguishing NET from NEC

- May be ambiguous in some cases
- Mutations in p53, Rb, and SMAD 4 characteristic of NEC (IHC staining for P53 and Rb available)
- GI NEC may express mutations typical of the corresponding adenocarcinomas of same organ (eg, KRAS, BRAF)
- Mutations typical of NETs (eg, DAXX/ATRX, MEN1) indicate NET
- Positive somatostatin receptor imaging (eg, dotatate PET) correlates with NET diagnosis but not definitively

IHC = immunohistochemistry; PET = positron emission tomography.

La Rosa S, Uccella S. *Rev Endocr Metab Disord*. 2020;22(3):527-538. Uccella S. *Endocr Pathol*. 2024;35(2):91-106.

MINEN (Mixed Neuroendocrine/ Non-Neuroendocrine Neoplasm)

- Formerly called MANEC (mixed adenoneuroendocrine carcinoma)
- Strictly requires at least 30% component of neuroendocrine (typically NEC) and non-neuroendocrine (typically adenocarcinoma)
- Reflects the fact that many NEC may originate from similar precancerous cells to adenocarcinomas and acquire neuroendocrine differentiation; needle biopsies may identify only one of the two lineages

Díaz-López S, et al. *World J Gastrointest Oncol*. 2024;16(4):1166-1179.

Prognosis

- Extra-pulmonary NECs are highly aggressive neoplasms, usually identified in the metastatic stage
- Performance status often too poor at diagnosis to initiate treatment
- Median survival is <12 months

Stumpo S, et al. *J Clin Med*. 2023;12(24):7715.

Standard Treatment for Metastatic Disease

- Extra-pulmonary NEC is typically treated similarly to small-cell lung cancer
- Platinum (either cisplatin or carboplatin) with etoposide is common first-line treatment
  - Response rates typically 30-50%
  - Optimal number of cycles is unclear; may benefit from administering >4 cycles if tolerated
  - Benefit of adding checkpoint inhibitor (eg, atezolizumab) demonstrated only in SCLC
    - NICE-NEC trial was single-arm study of platinum-etoposide plus nivolumab in G3 NET/NEC, median OS was only 13.9 months but approximately 38% survived >2 years
    - Randomized phase II study in extra-pulmonary NEC currently ongoing

SCLC = small-cell lung cancer; OS = overall survival.

Riesco-Martinez MC, et al. *Nat Commun*. 2024;15(1):6753. Bongiovanni A, et al. *Onco Targets Ther*. 2015;8:3613-3619.

Other Frontline Chemotherapy Regimens

- Cisplatin plus irinotecan shows equivalent outcomes to cisplatin plus etoposide
- Retrospective study of 5-fluoruracil, oxaliplatin and irinotecan (FOLFIRINOX) shows encouraging outcomes in GI NEC; randomized phase II study is comparing this regimen to platinum/etoposide

Second Line and Beyond

- Platinum-based chemo can be repeated if >3-6 months PFS after first-line treatment
- Outcomes are equally poor for various second-line regimens including FOLFOX, FOLFIRI, and capecitabine/temozolomide
- NET-02 study showed median PFS of only 3 months with Nal-iri/5-FU
- BEVANEC trial showed no benefit to adding bevacizumab to FOLFIRI backbone; outcomes with FOLFIRI (53% 6-month PFS rate) were mildly encouraging compared to alternatives
- Case reports suggest some benefit from targeted treatments in select patients (eg, BRAF mutations)

PFS = progression-free survival.

Walter T, et al. *Lancet Oncol*. 2023;24(3):297-306. Bongiovanni A, et al. *Eur J Cancer*. 2024:208:114129. McNamara MG, et al. *EClinicalMedicine*. 2023:60:102015.

Role of Checkpoint Inhibitors in Second Line and Beyond

- Prospective and retrospective trials have shown mixed results
- Prospective trial in small cohort of EP-NEC showed response rate of 26% with ipilimumab/nivolumab
- DUNE study of G3 NET/NEC showed response rate of only 9% with durvalumab and tremelimumab
- NIPINEC study or nivolumab vs nivolumab plus ipilimumab showed response rate of only 15% with the combination vs 7.5% with nivo monotherapy; median OS was only 5.8 months with the combination
- Retrospective studies have shown response rates of about 15% with ipilimumab/nivolumab
- Some guidelines (eg, NCCN) indicate that checkpoint inhibitors are an option whereas others (eg, ENETS) discourage their use in unselected patients

NCCN = National Comprehensive Cancer Network; ENETS = European Neuroendocrine Tumor Society.

Patel SP, et al. *Cancer*. 2021;127(17):3194-3201. Capdevila J, et al. *Nat Commun*. 2023;14:2973. Girard N, et al. *Ann Oncol*. 2021;32(Suppl 5):S1318. NCCN [www.nccn.org]. Last updated Feburary 2025. https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Sorbye H, et al. *J Neuroendocrinol*. 2023;35(3):e13249.

Management of Early-Stage Extra-Pulmonary NEC

- Data is very limited
- Guidelines generally recommend multimodal therapy with neoadjuvant or adjuvant chemotherapy as a component of treatment
- Surgical resection can be considered, particularly in locations that are relatively resectable (eg, colon, cervix). Definitive chemoradiation appropriate for esophagus and can be considered for distal rectal and anal, even if technically resectable. Trimodality treatment may be appropriate in some cases.

Stumpo S, et al. *J Clin Med*. 2023;12(24):7715.

Key Learning Points

- Extra-pulmonary NECs are highly aggressive neoplasms, usually identified in the metastatic stage, and performance status can be too poor at diagnosis to initiate treatment
- NECs exhibit poor morphologic differentiation characterized by sheets of cells, often pleomorphic with a high nuclear to cytoplasmic ratio, and a Ki-67 index typically >60%
- Thus far, progress in management of extra-pulmonary NECs has been very limited
- Standard of care for stage IV disease remains platinum/etoposide chemotherapy; role of checkpoint inhibitors in unselected patients is debatable
- There is an urgent unmet need for new therapies; DLL 3 targeting bispecific engagers may represent a new option for patients who progress after first-line therapy

Extra-Pulmonary Neuroendocrine Carcinomas: Novel Agents and Future Directions

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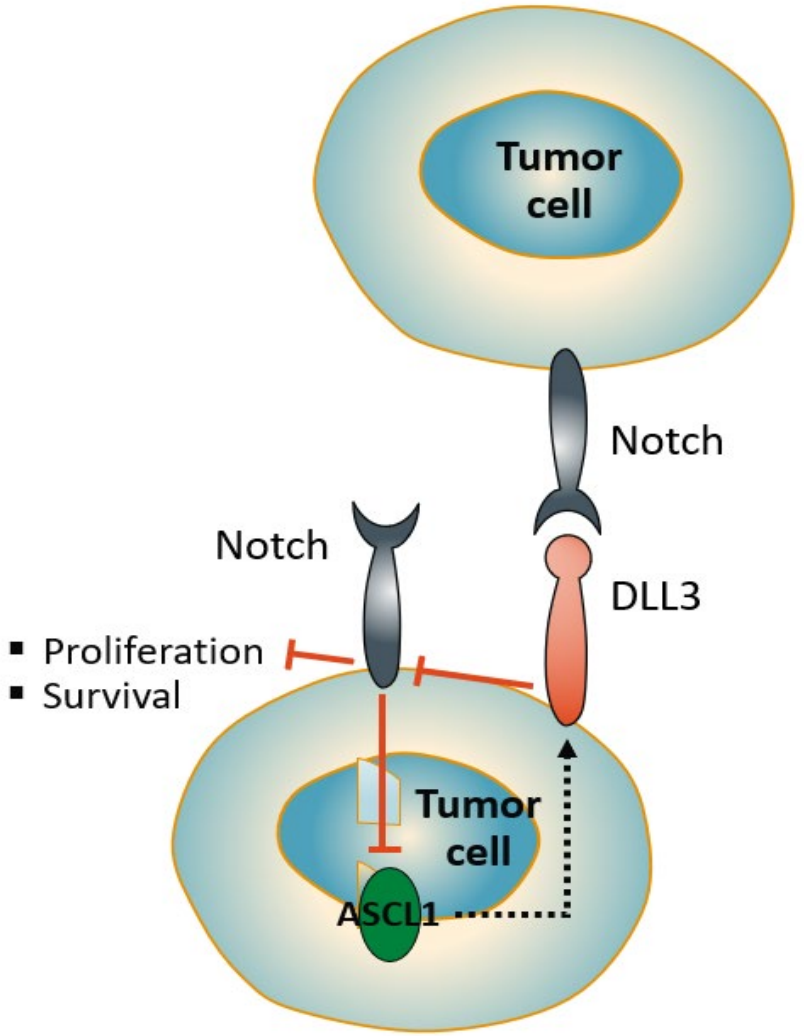
What Is DLL3?

- DLL3 is an inhibitory ligand of the Notch signaling pathway
- The Notch pathway promotes pro-cancerous events
- DLL3 expression modifies neuroendocrine transcription factor ASCL1



Yao J, et al. *Oncologist*. 2022;27(11):940-951. Leonetti A, et al. *Cell Oncol (Dordr)*. 2019;42(3):261-273. Sahlgren C, Lendahl U. *Regen Med*. 2006;1(2):195-205. Gay CM [www.clinicaloptions.com]. Last updated November 7, 2024. https://clinicaloptions.com/activity/ecase/50C2BE64-50CB-464E-87E2-C695DEDEC3C7/1.

Expression of DLL3 outside of Lung

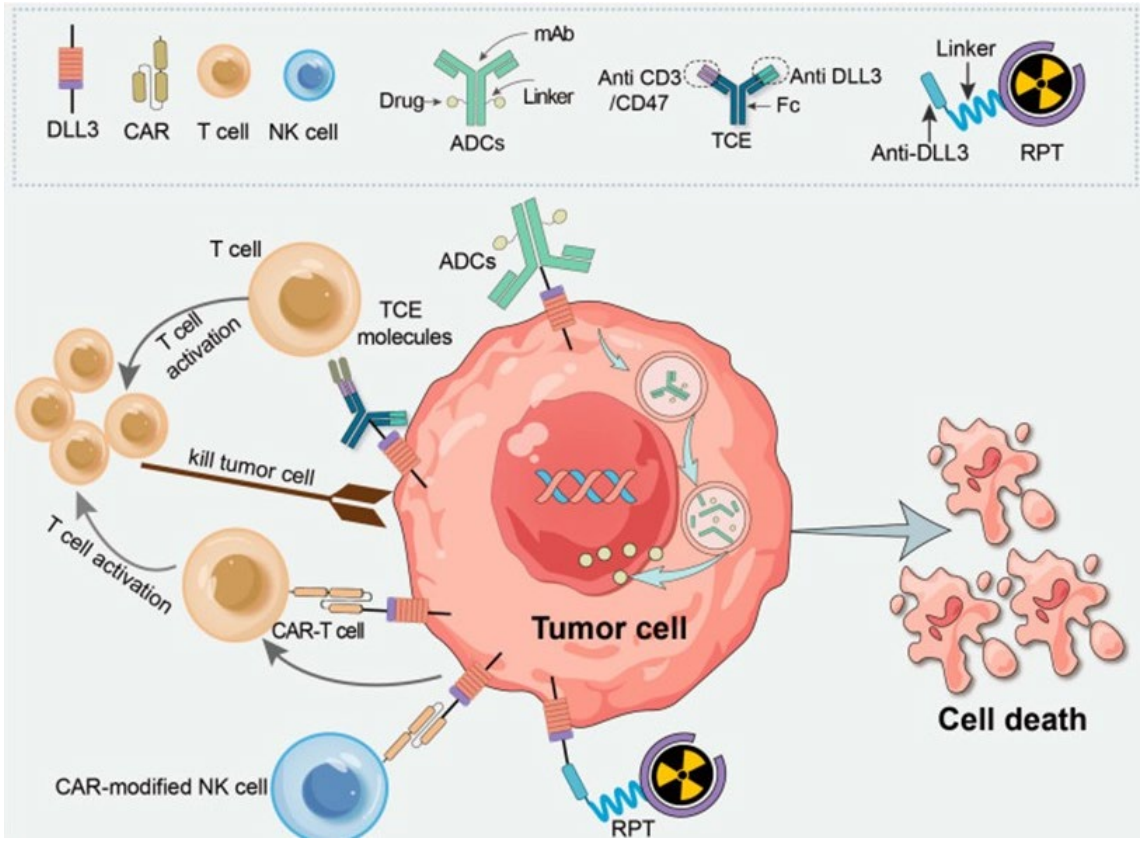
- NECs of the cervix (81%)
- Poorly differentiated gastroenteropancreatic cancer (76.9%)
- Castration-resistant NEPC (76.6%)
- Neuroendocrine bladder cancer (68.0%)

NEPC = neuroendocrine prostate cancer.

Yao J, et al. *Oncologist*. 2022;27(11):940-951. Hermans BCM, et.al. *Lung Cancer*. 2019:138:102-108. Puca et.al., Sci Transl Med. 2019;11:eaav0891. Koshkin et.al., Clin Cancer Res. 2019;25:210–221.

Mechanisms to Target DLL3

- T cell engagers
- Antibody drug conjugate
- CAR-T cell
- DLL3-targeted radioligand therapy



Wang H, et.al. *Pharmaceutics*. 2025;17(4):520.

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

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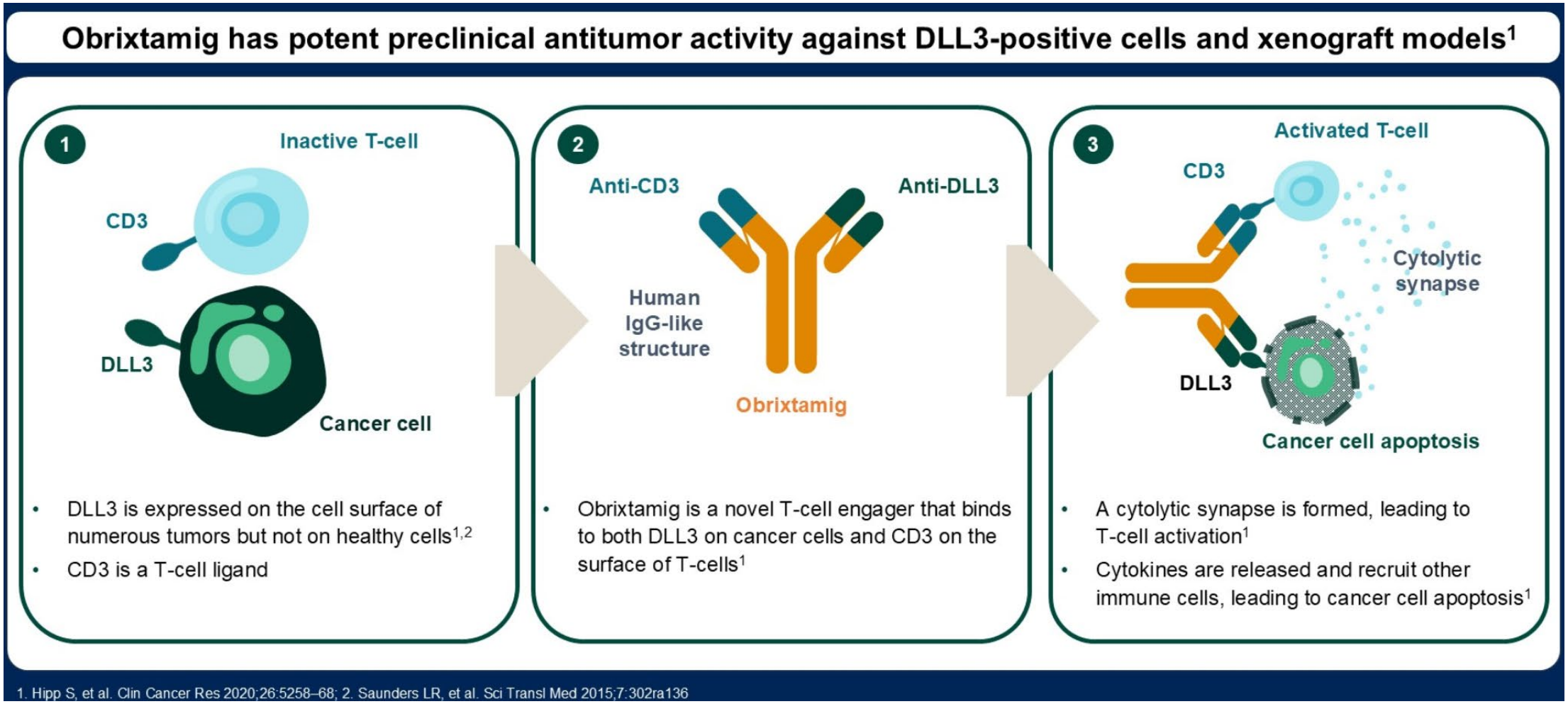
Capdevila J, et al. Presented at: American Society for Clinical Oncology (ASCO) Annual Meeting; May 30-June 3, 2025; Chicago, Illinois. Abstract 3004.

Obrixtamig: A Novel IgG-Like DLL3-Targeting T Cell Engager

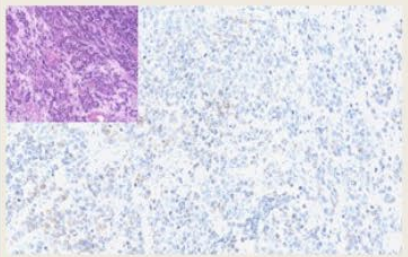
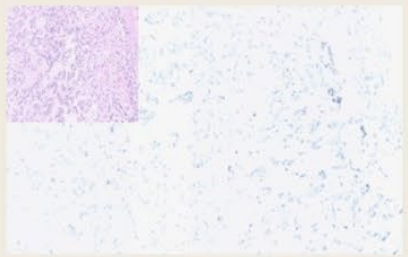
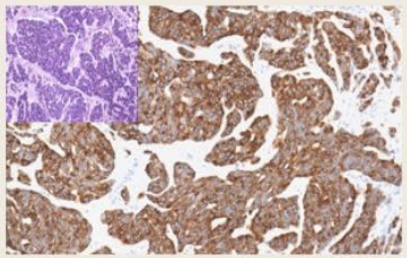
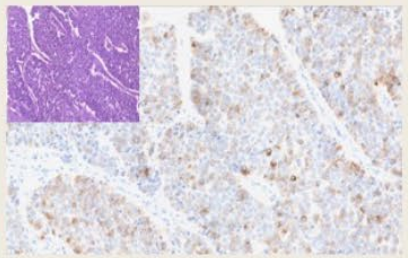


CD = cluster of differentiation; DLL = delta-like ligand; IgG = immunoglobulin G

Capdevila J, et al. Presented at: ASCO Annual Meeting; May 30-June 3, 2025; Chicago, Illinois. Abstract 3004.

Screening and Disposition by DLL3 Status

- DLL3 positivity was called
  - DLL^{high} (≥50% tumor cells or TC)
  - DLL^{low} (< 50% TC)

Patients with epNEC	DLL3 expression levels, n (%)			
	Positive	Negative	DLL3^{high}	DLL3^{low}
Screened N=200	165 (83)	35 (18)	78 (39)	87 (44)
Treated N=60	60 (100)	0	30 (50)	30 (50)
Staining	 >0% TC*	 0% TC*	 ≥50% TC*	 <50% TC*

Capdevila J, et al. Presented at: ASCO Annual Meeting; May 30-June 3, 2025; Chicago, Illinois. Abstract 3004.

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

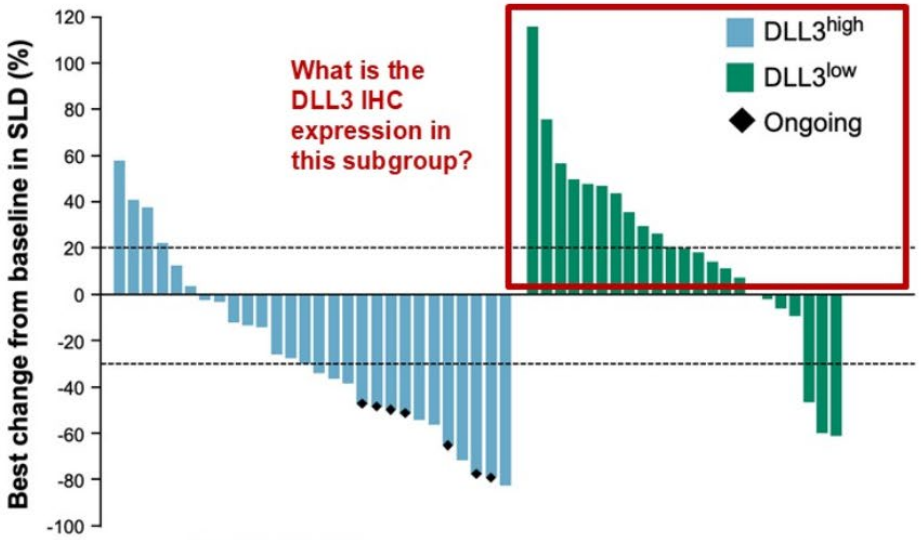
	All N=60		DLL3^{high} n=30		DLL3^{low} n=30	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TRAE, n (%)*	57 (95)	13 (22)	30 (100)	7 (23)	27 (90)	6 (20)
Cytokine release syndrome	39 (65)	2 (3)	21 (70)	1 (3)	18 (60)	1 (3)
Pyrexia	19 (32)	0	12 (40)	0	7 (23)	0
Dysgeusia	15 (25)	0	11 (37)	0	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)

ECOG PS = Eastern Cooperative Oncology Group performance status; CUP = cancer of unknown primary; TRAE = treatment-related adverse event; ICANS = immune effector cell-associated neurotoxicity syndrome.

Capdevila J, et al. Presented at: ASCO Annual Meeting; May 30-June 3, 2025; Chicago, Illinois. Abstract 3004.

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)



Confirmed response	DLL3^{high} GI n=14	GU n=12	CUP n=4
ORR, % (95% CI)	43 (21–67)	50 (25–75)	0 (0–49)
PR, n (%)	6 (43)	6 (50)	0
DCR, % (95% CI)	64 (39–84)	75 (47–91)	50 (15–85)
SD, n (%)	3 (21)	3 (25)	2 (50)
PD, n (%)	5 (36)	2 (17)	1 (25)
NE, n (%)	0	1 (8)	1 (25)

ORR = objective response rate; DCR = disease control rate; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable.

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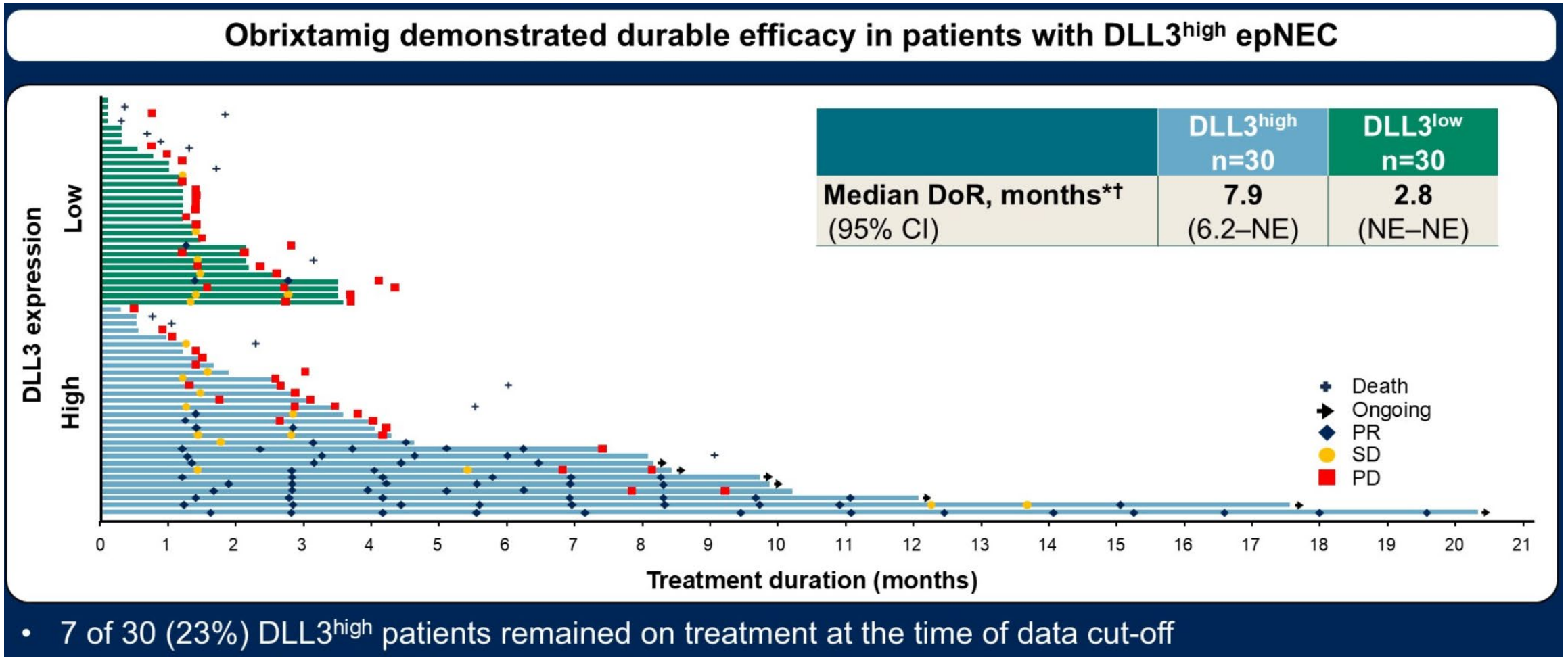
Duration of Response by DLL3 Expression



	DLL3high n=30	DLL3low n=30
Median DoR, months*† (95% CI)	**7.9** (6.2–NE)	**2.8** (NE–NE)

Data cutoff: June 21, 2024.
***Confirmed; †median follow-up: 9.7 months (95%CI; 6.5-13.9)**
DoR = duration of response
Capdevila J, et al. Presented at: ASCO Annual Meeting; May 30-June 3, 2025; Chicago, Illinois. Abstract 3004.

Ongoing Trials of DLL3 Targeting Therapies for Extra-Pulmonary NENs

NCT ID	Title	Drug
NCT02709889	An Open-Label Study of Rovalpituzumab Tesirine in Subjects With Delta-Like Protein 3-Expressing Advanced Solid Tumors **Terminated**	Rovalpituzumab tesirine
NCT06893783	A Phase II Trial of Tarlatamab, a DLL3-targeted Bispecific T-cell Engager, in Patients With Advanced Extrapulmonary Neuroendocrine Carcinoma (DeLLight) Not recruiting yet	Tarlatamab
NCT06788938	Tarlatamab in Advanced DLL3-Expressing Tumors Including Neuroendocrine Neoplasms	Tarlatamab
NCT06816394	Tarlatamab for Patients With Previously Treated Advanced Extrapulmonary Small Cell Carcinoma and Neuroendocrine Carcinoma	Tarlatamab
NCT05882058	DAREON™-5: An Open-label, Multi-center Phase II Dose Selection Trial of Intravenous BI 764532, a DLL3-targeting T Cell Engager, in Patients With Relapsed/Refractory Extensive-stage Small Cell Lung Cancer and in Patients With Other Relapsed/Refractory Neuroendocrine Carcinomas	Obrixtamig
*NCT06736418 (*LUNG)*	*Phase 1a/b, Open-label, Dose-escalation Study of the Safety, Pharmacokinetics, and Initial Efficacy of 225Ac-ABD147 in Patients With Small Cell Lung Cancer and Large Cell Neuroendocrine Carcinoma of the Lung Following Platinum-based Chemotherapy*	*225Ac-ABD147*

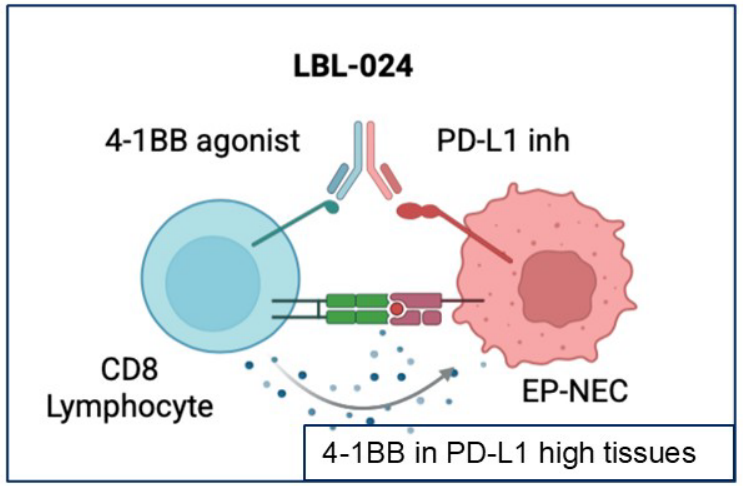
Soares H. Presented at: ASCO Annual Meeting; May 30-June 3, 2025; Chicago, Illinois.

Phase 1b/2 Study LBL-024 + Platinum/VP16 in Front-Line Extra-Pulmonary Neuroendocrine Carcinoma (EP NEC)

- LBL-024 binds to **PD-L1 in the tumor** or immune infiltrates and **4-1BB in effector T-cells**.

- 4-1BB is a very potent co-stimulatory receptor for T-Cells.
  -Induces lymphocyte survival and replication
  -Increases cytokine production

- However, **4-1BB is expressed in Kupffer** cells and agonistic drugs typically cause severe **hepatitis** .



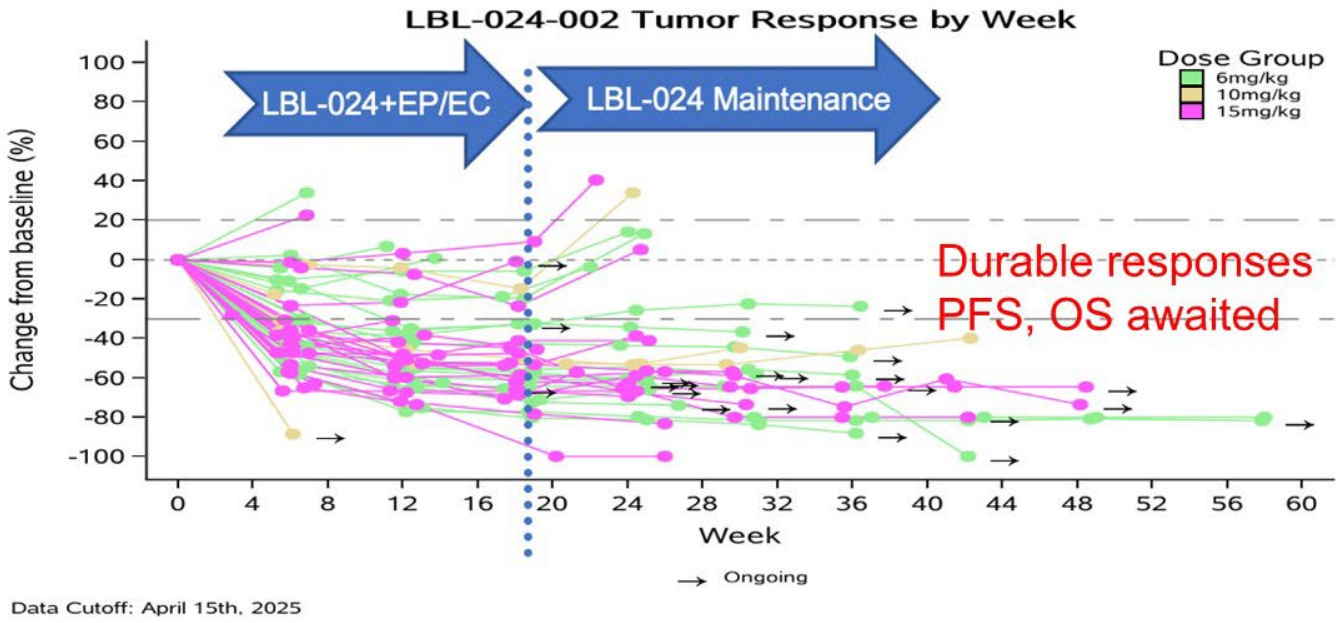
-LBL-024 targets PD-L1 positive epithelia, **skipping the liver.**
-LBL-024 cannot induce immune response in non-immunogenic tumors (lack of CD3 engagement)

1. Pampan et al. ASCO 2024.
2. Singh et al Exp. Mol. Med. 2024.
3. Bartkowiak et al Cin Can Res 2018.

Argilés G. Presented at: ASCO Annual Meeting; May 30-June 3, 2025; Chicago, Illinois. Abstract 2500.

Discussing Points: Efficacy

1. The combo showed promising early efficacy
   - **75% ORR at 15 mg/kg (RP2D).**



Numbers are low!

	ORR, n (%)	DCR, n (%)
Esophagus (N=9)	7 (77.8)	8 (88.9)
Gallbladder (N=3)	2 (66.7)	3 (100.0)
Gastric (N=15)	9 (60.0)	14 (93.3)
Genitourinary# (N=3)	3 (100.0)	3 (100.0)
Lung (N=2)	2 (100.0)	2 (100.0)
Pancreas (N=6)	5 (83.3)	6 (100.0)
Colorectal (N=2)	1 (50.0)	1 (50.0)
Primary unknown (N=3)	2 (66.7)	3 (100.0)
Others‡ (N=9)	8 (88.9)	8 (88.9)

Argilés G. Presented at: ASCO Annual Meeting; May 30-June 3, 2025; Chicago, Illinois. Abstract 2500.

Discussing Points: Safety

- LBL-024 / Platinum-VP16 **showed no DLTs** and **RP2D combination = RP2D single agent.**
  - **LBL-024 drug design was able to minimize 4-1BB liver toxicity.**
  - **Hematologic toxicity was numerically high.**

Preferred Terms, n (%)	Total, n=55	
	Any grade	≥Grade 3
Leukopenia	44 (80.0)	20 (36.4)
Neutropenia	44 (80.0)	34 (61.8)
Anemia	41 (74.5)	12 (21.8)
Thrombopenia	36 (65.5)	14 (25.5)
Nausea	29 (52.7)	2 (3.6)
AST increased	20 (36.4)	2 (3.6)
Asthenia	19 (34.5)	0
Alopecia	19 (34.5)	0
Proteinuria	18 (32.7)	0
ALT increased	16 (29.1)	1 (1.8)
Constipation	16 (29.1)	0

Managed with dose-delays

G-CSF were permitted as secondary prophylaxis

irAE (Grade ≥3)	
Preferred Terms, n (%)	Total, n=55
Immune-mediated myocarditis	2 (3.6)
AST increased	1 (1.8)
Diabetes mellitus	1 (1.8)
Myasthenia	1 (1.8)
Acute kidney injury	1 (1.8)
Cytokine release syndrome	1 (1.8)

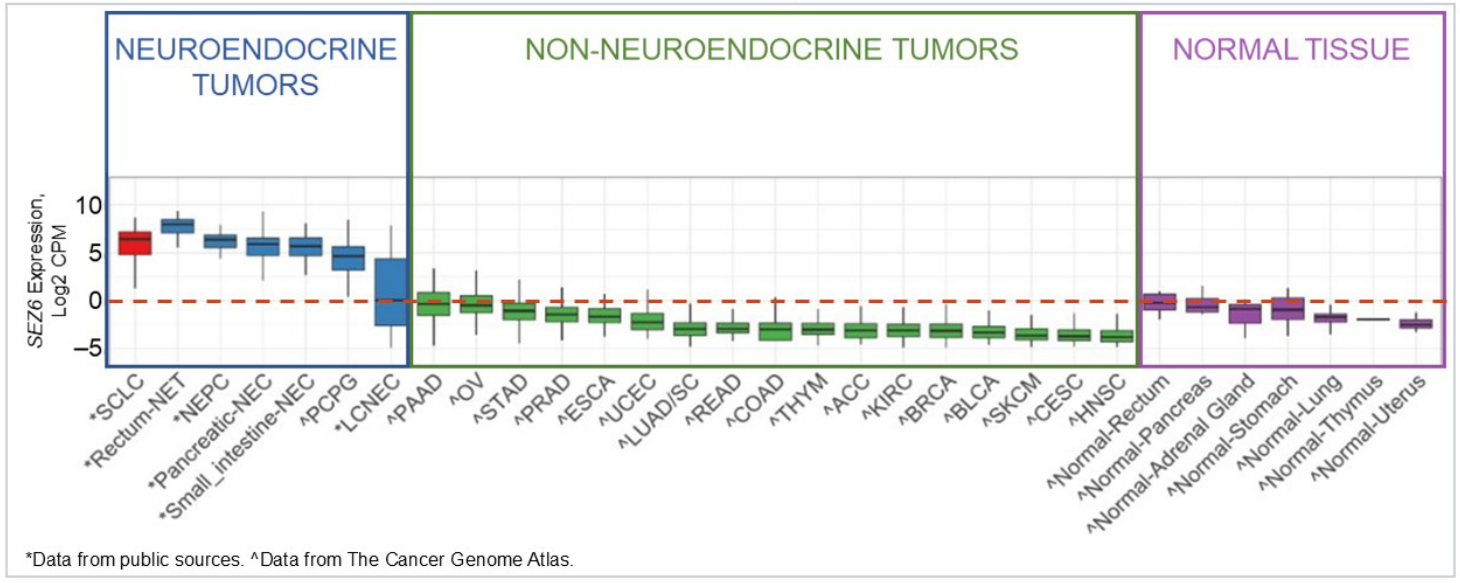
Myocarditis remains as AE of special interest.

Data cutoff: April 15, 2025. Data from China.
DLT = dose-limiting toxicity; RP2D = recommended phase 2 dose; irAE = immune-related adverse event; AST = aspartate aminotransferase; ALT = alanine aminotransferase; G-CSF = granulocyte colony-stimulating factor.
Argilés G. Presented at: ASCO Annual Meeting; May 30-June 3, 2025; Chicago, Illinois. Abstract 2500.

SEZ6 Is Highly Expressed in Neuroendocrine Neoplasms (NENs) and Is the Target of the ADC ABBV-706

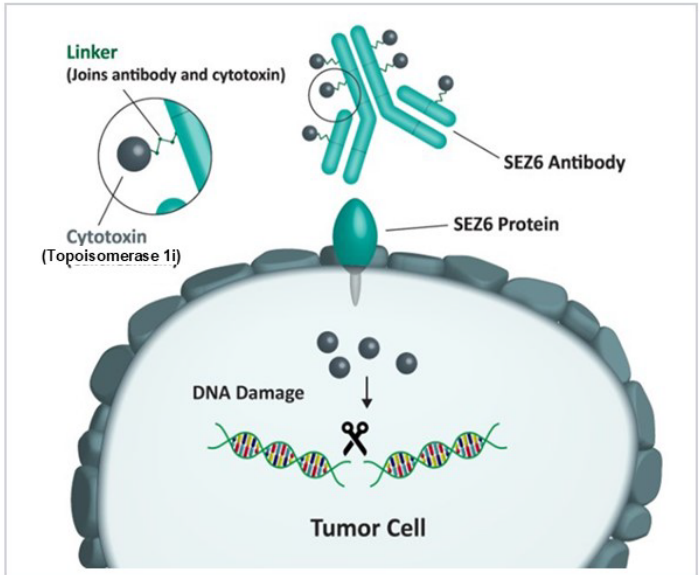
- SEZ6 is a neuroendocrine lineage marker specifically expressed in SCLC and high-grade NENs[1]
- ABBV-706 is a first-in-class ADC composed of a potent Top1i attached via a stable linker to a SEZ6-directed monoclonal antibody, delivering the cytotoxic payload specifically to SEZ6-expressing tumor cells
- Preliminary data of ABBV-706 monotherapy showed manageable safety and promising activity in SCLC and NENs[2]

SEZ6 Gene Expression



*Data from public sources. ^Data from The Cancer Genome Atlas.

ABBV-706 Mechanism of Action



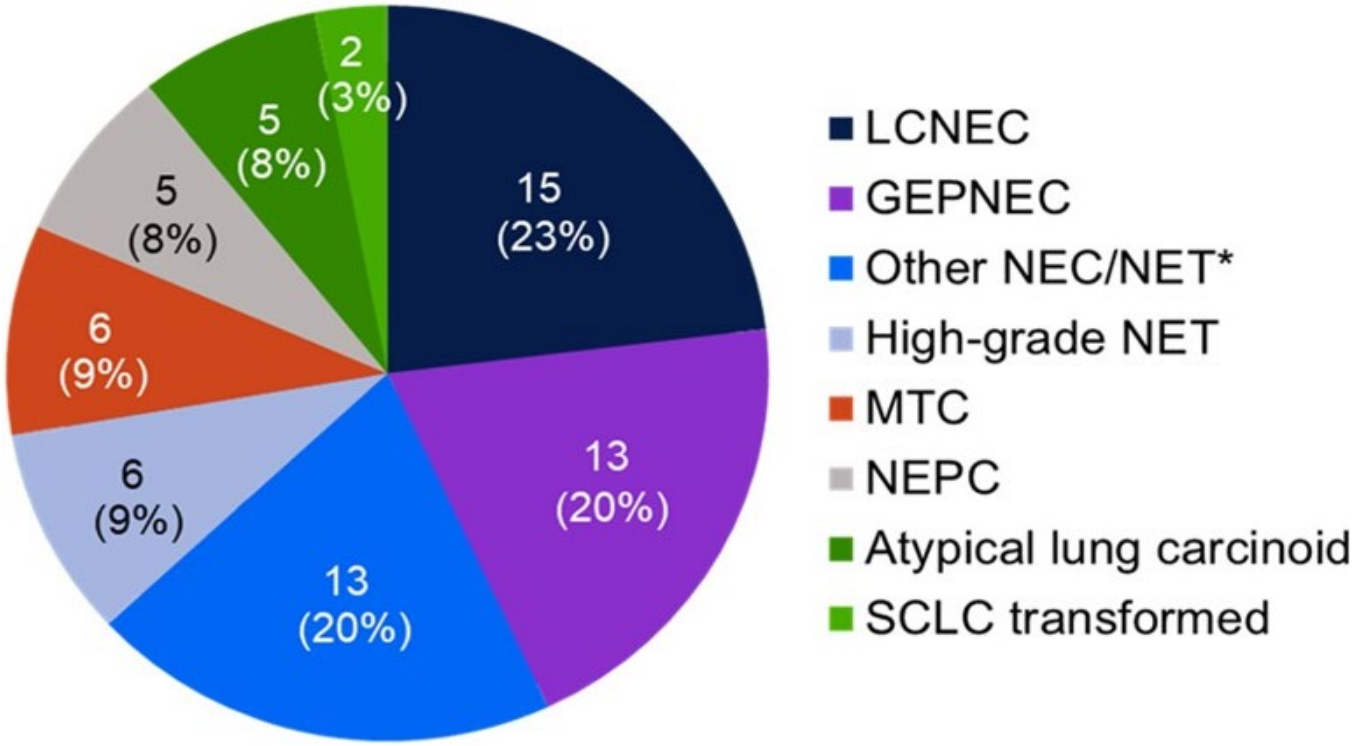
1. Wiedemeyer WR, et al. *Mol Cancer Ther.* 2022;21:986-998. 2. Chandana S, et al. ASCO 2024. Abstract 3001 (oral presentation).

ADC = antibody-drug conjugate; LCNEC = large-cell NEC; SEZ = seizure-related homolog protein; Top1i = topoisomerase 1 inhibitor; PCPG = pheochromocytoma and paraganglioma; PAAD = pancreatic adenocarcinoma; OV = ovarian serous cystadenocarcinoma; STAD = stomach adenocarcinoma; PRAD = prostate adenocarcinoma; ESCA = esophageal carcinoma; UCEC = uterine corpus endometrial carcinoma; LUAD/SC = lung adenocarcinoma/lung squamous cell carcinoma; READ = rectum adenocarcinoma; COAD = colon adenocarcinoma; THYM = thymoma; ACC = adrenocortical carcinoma; KIRC = kidney renal clear cell carcinoma; BRCA = breast invasive carcinoma; BLCA = bladder urothelial carcinoma; SKCM = skin cutaneous melanoma; CESC = cervical squamous cell carcinoma and endocervical adenocarcinoma; HNSC = head and neck squamous cell carcinoma.

Cooper AJ, et al. *J Clin Oncol*. 2025;43(16 Suppl):105.

Safety and Efficacy of ABBV-706, a SEZ6-Targeting ADC, in High-Grade Neuroendocrine Neoplasms

- High-grade NEN cohort dose expansion
- N=65

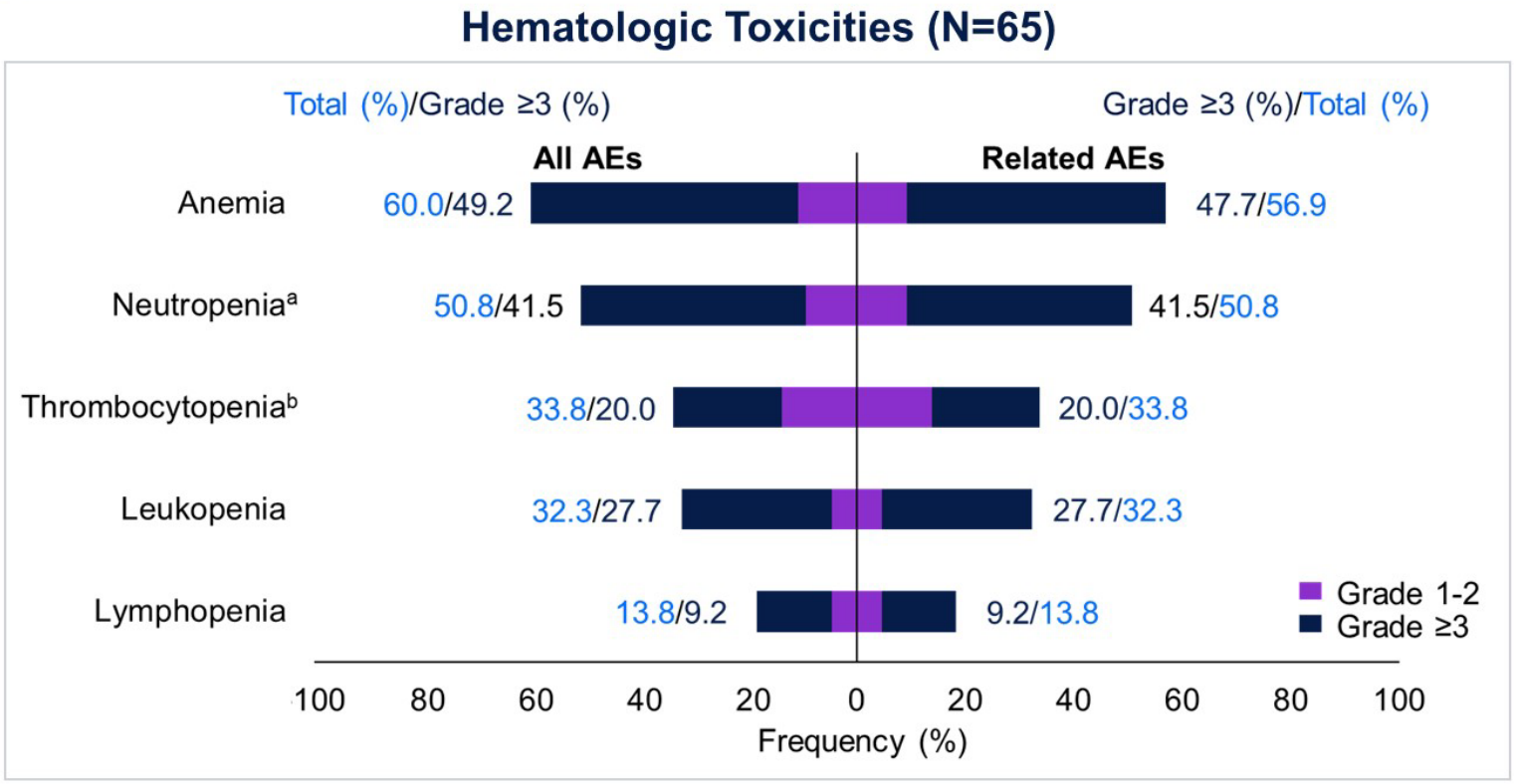


**Other NEC/NET: NEC GU (n=4; bladder 3, kidney 1), NEC cervix (n=3), high-grade NEN unspecified (n=4), MINEN (n=1), NEC parathyroid (n=1).*

GEPNEC = gastroenteropancreatic NEC; MTC = medullary thyroid cancer.

Cooper AJ, et al. *J Clin Oncol*. 2025;43(16 Suppl):105.

Most Common High-Grade TEAEs Are Hematologic



- Cytopenias were dose dependent and manageable with supportive care

- Gastrointestinal toxicity was mostly G1/2; G≥3 events, 5%
- All-grade pneumonitis/ILD (unadjudicated[c]) for patients with NENs: n=2 (3%); both events at 2.5 mg/kg; G≥3, n=1 (2%)
- Febrile neutropenia: n=2 (3%); both events at 2.5 mg/kg: G≥3, n=2

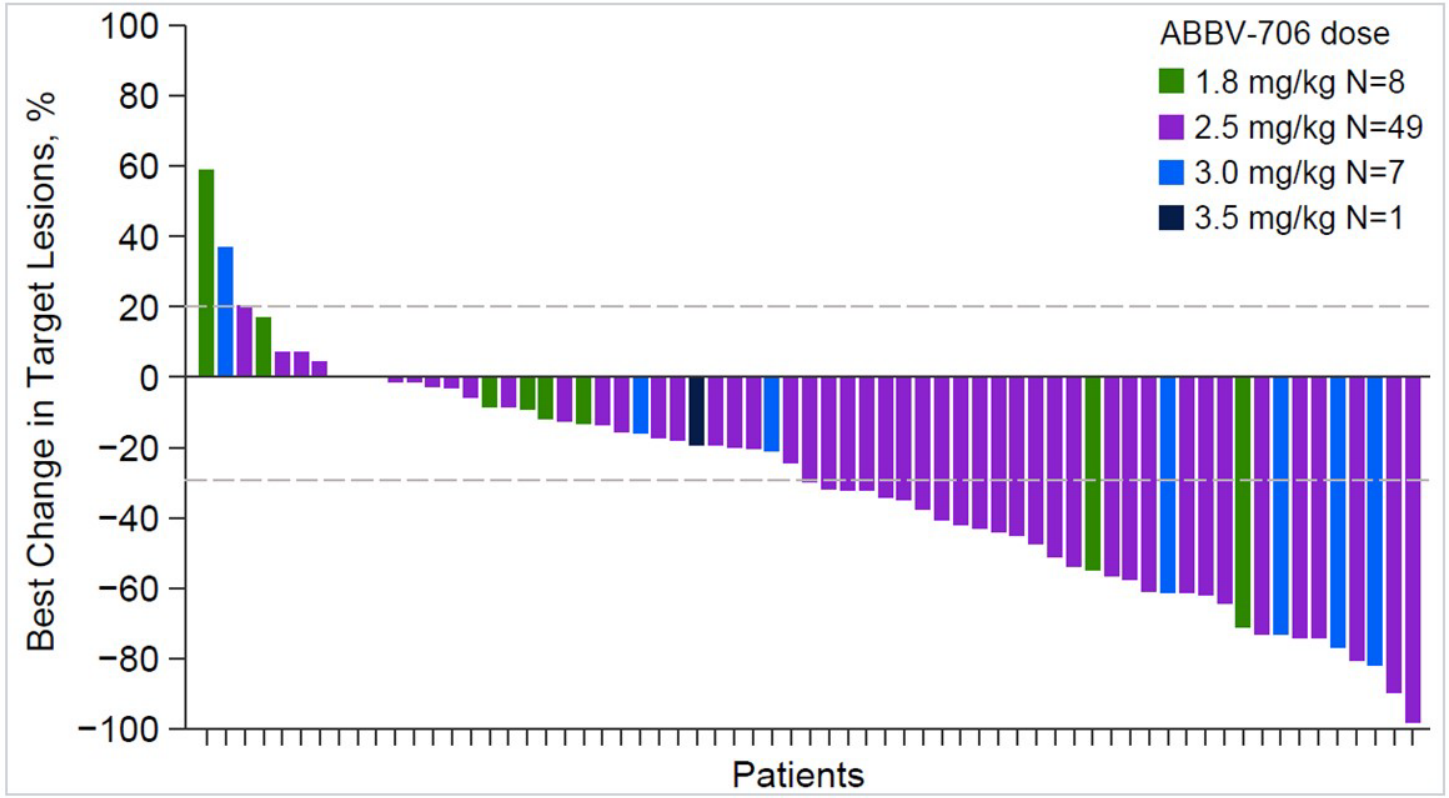
[a]Includes the terms "neutrophil count decreased" and "neutropenia." [b]Includes the terms "platelet count decreased" and "thrombocytopenia."
[c]Currently being adjudicated.

G = grade; ILD = interstitial lung disease; TEAE = treatment-emergent adverse event.

Cooper AJ, et al. *J Clin Oncol*. 2025;43(16 Suppl):105.

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 (%) [95% exact CI]	**24 (36.9)** [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 [95% CI]	6.37 [4.44, 9.46]
Median PFS, months [95% CI]	7.62 [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.

RECIST = Response Evaluation Criteria in Solid Tumors.

Cooper AJ, et al. *J Clin Oncol*. 2025;43(16 Suppl):105.

Key Learning Points

- DLL3-targeted radioligand therapy, bispecific antibody treatment, and SEZ-6-targeting antibody-drug conjugates all show efficacy in the management of extra-pulmonary NEC
- DLL3 contributes to EP-NEC progression primarily through inhibiting Notch signaling
- Cytokine release syndrome is the most frequently associated adverse event with DLL3-targeted T-cell engagers in extra-pulmonary NECs

Thank You!