

Advancing Care in Extra-Pulmonary Neuroendocrine Carcinoma: Diagnosis, Treatment, and Emerging Therapies

Jennifer Chan, MD, MPH

*Department of Medical Oncology
Dana-Farber Cancer Institute Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts*

Disclosures

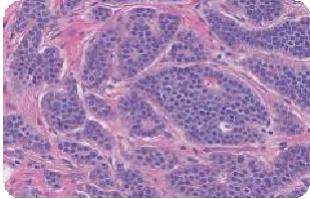
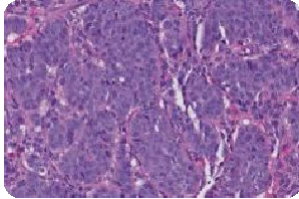
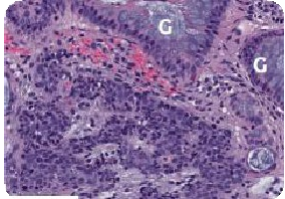
Jennifer Chan, MD, MPH: advisory board—Ipsen, Curium, Boehringer Ingelheim, Sanofi; honorarium—Ipsen, Sanofi; stock—Merck

Learning Objectives

- Differentiate neuroendocrine tumors (NETs) from neuroendocrine carcinomas (NECs), including diagnostic criteria, pathologic and molecular features, treatment guidelines, and patient outcomes
- Explain the biological significance and clinical relevance of DLL3 as an emerging therapeutic target in extrapulmonary NEC (EP-NEC)
- Assess emerging research, recent conference data, and ongoing clinical trials informing the evolving treatment landscape for EP-NEC



WHO Classification of Neuroendocrine Neoplasms

Tumor category	Neuroendocrine Neoplasia (NEN)		
<i>Family/class</i>	Well-differentiated NEN	Poorly differentiated NEN	
<i>Type</i>	Neuroendocrine tumor (NET)	Neuroendocrine carcinoma (NEC)	
<i>Subtype</i>	Variable, depending on site	Large-cell NEC	Small-cell NEC
<i>Grade</i>	G1,G2,G3	High grade (by definition)	
			

Clinicopathologic and Imaging Features of NEN



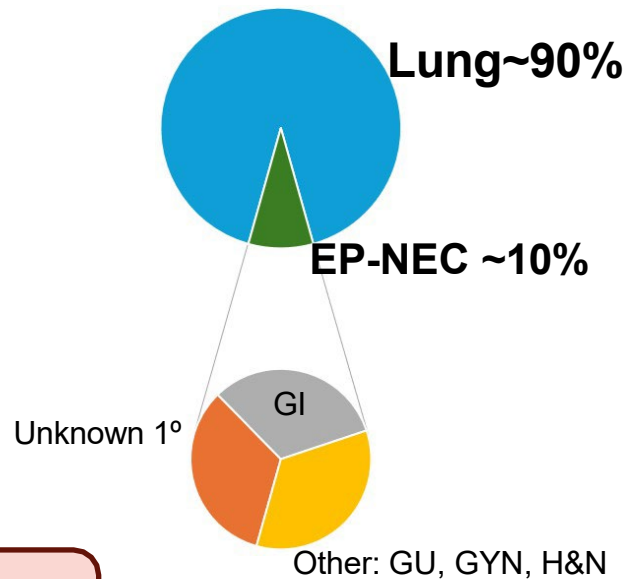
	Well-differentiated Gastroenteropancreatic NET			Poorly differentiated NEC
Grade	G1 (low)	G2 (intermediate)	G3 (high)	High grade by definition
Mitotic count	<2/2 mm ²	2-20/2 mm ²	>20/2 mm ²	
Ki-67	<3%	3-20%	>20%	Often >70%
Clinical course	Indolent	Intermediate	Intermediate-Rapid	Rapid
Nuclear Imaging Features				
Mutations	DAXX/ATRX, MEN-1, mTOR pathway (pNET) CDKN1B (SI-NET)		TP53, RB1	

FDG = fludeoxyglucose; PET = positron emission tomography; CT = computed tomography.
 Rindi G, et al. *Endocr Pathol.* 2022;33(1):115-154. Jiao Y, et al. *Science.* 2011;331(6021):1199-203. Scarpa A, et al. *Nature.* 2017;543(7643):65-71. Erratum in: *Nature.* 2017;550(7677):548. Francis JM, et al. *Nat Genet.* 2013;45(12):1483-1486.

Extrapulmonary NEC (EP-NEC)

- Outcomes for patients with advanced EP-NEC remain poor
- Limited efficacy of current therapy
 - Progression after 1st-line platinum-based chemotherapy occurs rapidly
 - Modest efficacy of 2nd-line chemotherapy
- Median overall survival <1 year

Novel targets and new treatment approaches are needed for EP-NEC.



GI = gastrointestinal; GU = genitourinary; GYN = gynecological; H&N = head and neck.
Dasari A, et al. *Cancer*. 2018;124(4):807-815.

Treatment of Advanced EP-NEC

1st-line therapy

- **Platinum-based chemotherapy remains a standard 1st-line therapy for advanced EP-NEC**
 - Cisplatin or carboplatin + etoposide : ORR 40-60%
 - mPFS 4-7 mo; mOS <12 mo
 - Radiographic responses (65% vs. 44%) and mPFS (6.4 vs 4 mo) better in small-cell NEC vs large cell NEC¹
 - Progression often happens during treatment or shortly after completion
- **TOPIC-NEC (JCOG 1213) trial²**
 - No overall survival difference between 1st-line cisplatin-etoposide (EP) vs cisplatin-irinotecan (IP) as 1st-line therapy for GEP-NEC: mOS 12.5 mo (EP) vs 10.9 mo (IP)
 - mPFS 5.6 mo for EP vs 5.1 mo for IP

ORR = objective response rate; mPFS = median progression-free survival; mOS = median overall survival.

1. Hadoux J, et al. *Eur J Cancer*. 2021;152:100-115. 2. Morizane C, et al. *JAMA Oncol*. 2022;8(10):1447-1455.

Treatment of Advanced EP-NEC

Later-line therapy

- **Chemotherapy in 2nd+ -line has only most efficacy**
 - NET-02 trial: Randomized phase II trial of docetaxel or nal-IRI/5FU/LV in EP NEC¹
 - Docetaxel 6-mo PFS only 14%
 - Nal-IRI/5FU/LV had 6-mo PFS of 31% with mPFS 3 mo; mOS 9 mo
 - **PRODIGE-41/BEVANEC trial:** 2nd-line FOLFIRI + bevacizumab vs FOLFIRI in GEP-NEC²

	Median PFS	Median OS	6-mo OS
FOLFIRI + bev	3.7	7 mo	52.5%
FOLFIRI	3.5	8.9 mo	58.2%

nal-IRI = nanoliposomal irinotecan; 5FU = 5-fluorouracil; LV = leucovorin; FOLFIRI = folinic acid, fluorouracil, irinotecan.

1. McNamara MG, et al. *EClinicalMedicine*. 2023;60:102015. 2. Walter T, et al. *Lancet Oncol*. 2023;24(3):297-306.

Treatment of Advanced EP-NEC

Should we treat EP-NEC similar to cancers arising in the same 1° site?

- **Retrospective data has shown activity of FOLFIRINOX in GEP-NEC¹**
 - ORR (all lines) 46%—including 6 of 8 patients treated in 1st line
 - mPFS: 5.4 mo; mOS: 17.8 mo
- **PRODIGE 69-FOLFIRINEC trial²**
 - **Randomized phase II of platinum (cis or carbo) + etoposide vs mFOLFIRINOX in metastatic GEP or unknown origin NEC**
 - Stratification according to center, performance status, Ki67 and pathological subtype
 - Real-time molecular profiling to inform later-line therapy (PD-L1, Rb, TP53, MLH1, NGS with TMB and MSI status)

mFOLFIRINOX = modified folinic acid, fluorouracil, irinotecan, oxaliplatin; NGS = next-generation sequencing;
TMB = tumor mutational burden; MSI = microsatellite instability.

1. Butt BP, et al. Presented at: European Society for Medical Oncology (ESMO) Congress; 2021. 2. Hadoux J, et al. *Dig Liver Dis*. 2021;53(7):824-829. ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated September 30, 2025. <https://clinicaltrials.gov/study/NCT04325425>.

Immune Checkpoint Inhibitors for Advanced EP-NEC

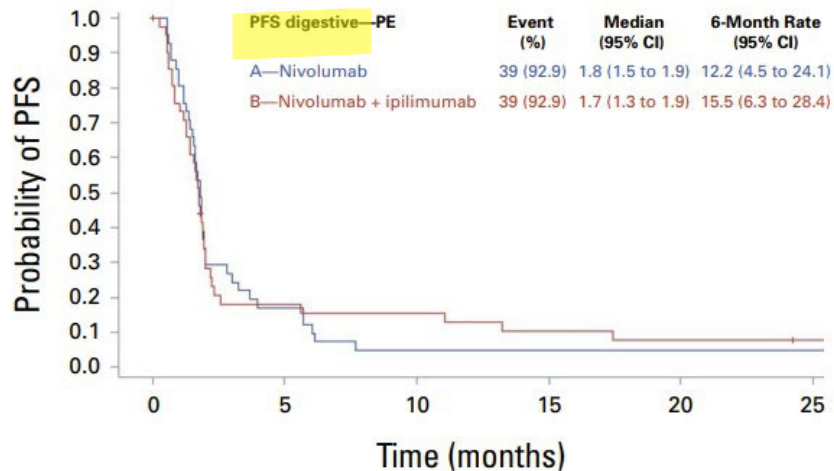
- **Minimal efficacy of single-agent anti PD-1 and PD-L1 agents in biomarker unselected EP-NEC¹⁻⁷**
 - Very low response rates to pembrolizumab, avelumab, spartalizumab, nivolumab
- **Dual immune checkpoint inhibition with anti-PD-(L)1 + anti-CTLA4 blockade may benefit some patients⁸⁻¹²**

1. Vijayvergia N, et al. *Br J Cancer*. 2020;122(9):1309-1314. 2. Raj N, et al. *Br J Cancer*. 2023;129(2):291-300. 3. Frumovitz M, et al. *Gynecol Oncol*. 2020;158(3):570-575. 4. DL Chan, et al. *Eur J Cancer*. 2022;169:74-81. 5. Fottner C, et al. *Clin Cancer Res*. 2025;31(5):860-867. 6. Yao JC, et al. *Endocr Relat Cancer*. 2021;28(3):161-172. 7. Walter TP, et al. *J Clin Oncol*. 2026;44(12):1120-1129. 8. Klein O, et al. *Clin Cancer Res*. 2020;26(17):4454-4459. 9. Patel SP, et al. *Clin Cancer Res*. 2020;26(10):2290-2296. 10. Patel SP, et al. *Cancer*. 2021;127(17):3194-3201. 11. Walter TP, et al. *J Clin Oncol*. 2026;44(12):1120-1129. 12. Capdevila J, et al. *Nat Commun*. 2023;14(1):2973.

Immune Checkpoint Inhibitors for Advanced EP-NEC

GCO-001 NIPINEC Trial

Nivolumab ± Ipilimumab in Previously Treated Digestive NEC and Large-Cell Lung NEC



Morphological Response Criteria	Digestive	
	N (n = 42)	N-I (n = 42)
Morphologic response at 8 weeks, No. (%)		
Objective response	3 (7.1)	4 (9.5)
Stable disease	9 (21.4)	6 (14.3)
Progressive disease	25 (59.5)	25 (59.5)
Not evaluable/missing	5 (11.9)	7 (16.7)
Best objective response, No. (%)	3 (7.1)	6 (14.3)
Response duration, months, median (IC 95%)	NR (3.7 to NR)	22.3 (3.3 to NR)

NR = not reached.

Walter TP, et al. *J Clin Oncol.* 2026;44(12):1120-1129.

1st-Line Immunotherapy + Chemo for EP-NEC

NICE-NEC (GETNE-T1913) Phase II Trial

Nivolumab + Platinum-Doublet in G3 GEP/Unknown 1°-NEN

Induction Phase

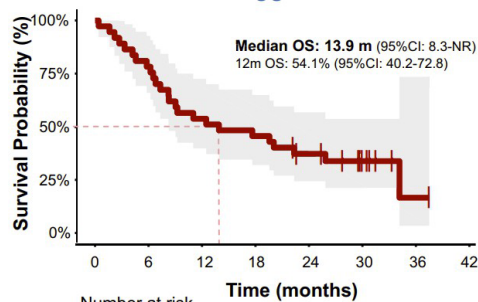
Nivolumab +
Carboplatin +
Etoposide

6 cycles



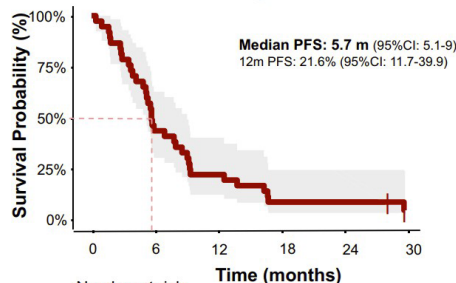
Maintenance Phase

Nivolumab every 4 weeks



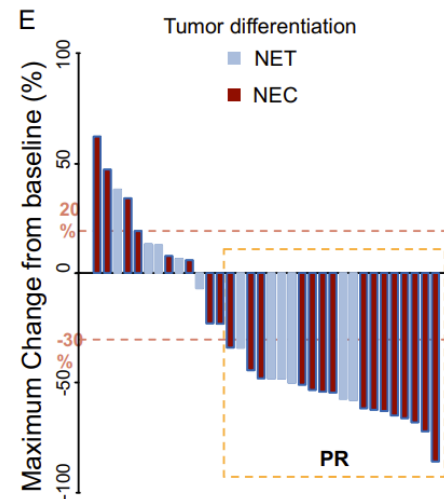
Number at risk

Time (months)	0	6	12	18	24	30	36	42
37	37	29	20	17	12	6	1	0



Number at risk

Time (months)	0	6	12	18	24	30
37	37	16	8	3	3	0



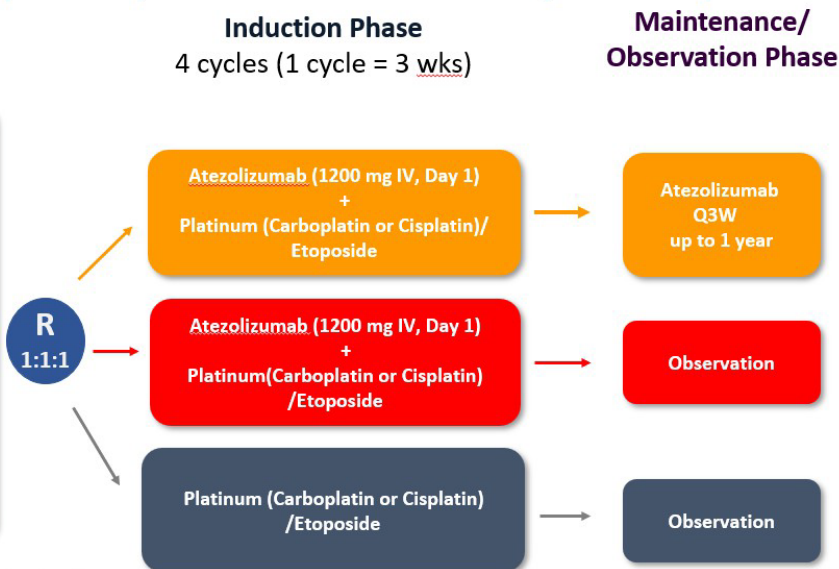
	ORR, n (%)	
NET	N = 12	6 (50.0)
NEC	N = 25	15 (60.0)

1st-Line Immunotherapy + Chemo for EP-NEC

SWOG S2012: Randomized Ph 2/3 Trial of First Line Platinum/Etoposide +/- Atezolizumab for Extrapulmonary NEC

Key Eligibility: **N=189**

- Metastatic poorly-differentiated extrapulmonary (i.e. exclude lung) NEC with Ki-67 ≥ 55%
- Evaluable, measurable and non-measurable disease
- Zubrod PS 0-2
- No prior treatment EXCEPT one cycle of platinum/etoposide allowed
- Asymptomatic brain metastases eligible
- Stratification factors:
 - ❑ 1) PS 0-1 vs 2
 - ❑ 2) Known prostate vs GI vs other origin



Primary endpoint: OS (from time of randomization)

Secondary endpoints: OS (from time of maintenance/observation), PFS, ORR, DOR

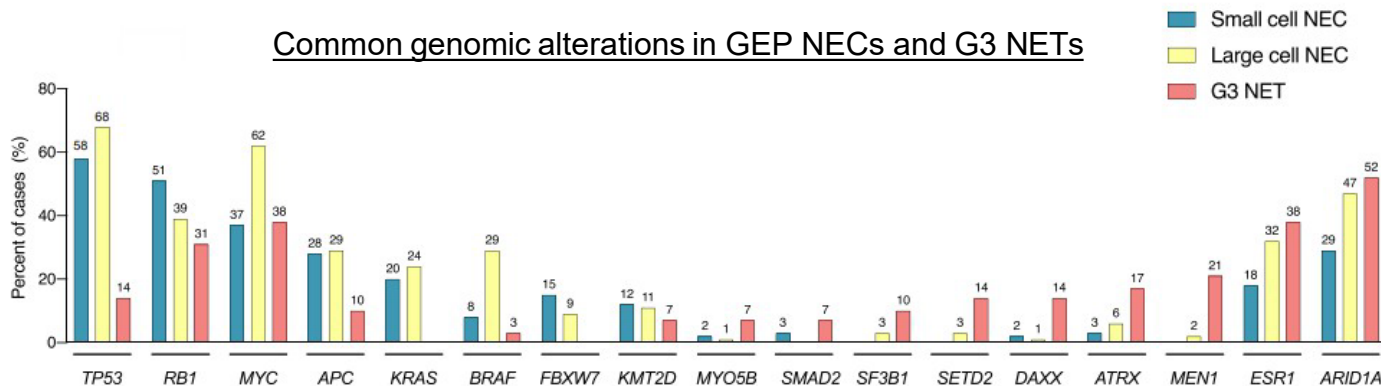
Translational analyses: Banking tissue and blood for future biomarker analyses

PS = performance status; DOR = duration of response.

ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated July 31, 2026. <https://clinicaltrials.gov/study/NCT05058651>.

Genomic Alterations in NEC

- EP-NEC are genomically different from small cell lung cancer (SCLC)
 - SCLC: nearly universal inactivation of *TP53* and *RB1*
 - EP-NEC: *TP53* and *RB1* alterations (although not ubiquitous), but also have typical alterations of non-neuroendocrine cancers arising at same primary tumor site



Molecularly Targeted Therapy for EP-NEC

- Potentially targetable molecular alterations are seen in up to ~60% of advanced digestive NEC
- Molecular alterations of note include
 - MSI-H in ~5% → marker of benefit for immunotherapy
 - TMB-H in ~5% → marker of benefit for immunotherapy
 - *BRAF* V600 mutations in up to 40% of colon NEC → encorafenib + cetuximab (+ FOLFOX/FOLFIRI) or dabrafenib + trametinib or if *BRAF* V600E mutation-positive
 - *KRAS* mutations
 - Other rare targetable alterations in NEC
 - NTRK gene fusion (entrectinib, larotrectinib)
 - RET gene fusion (selpercatinib)

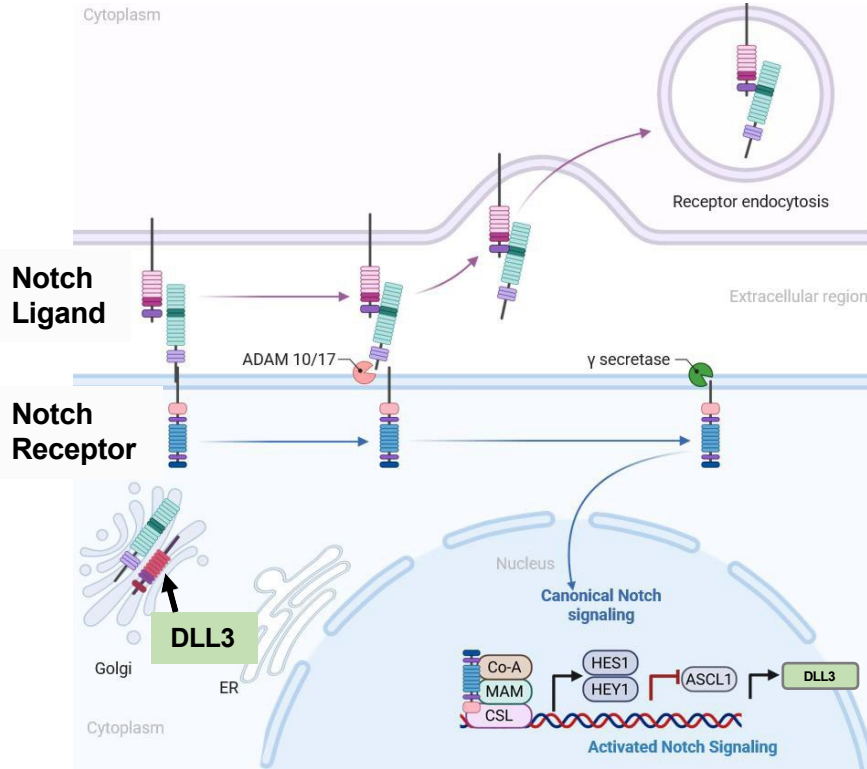
MSI-H = high MSI; TMB-H = high TMB.

Venizelos A, et al. *Endocr Relat Cancer*. 2021;29(1):1-14. Puccini A, et al. *Clin Cancer Res*. 2020;26(22):5943-5951.

Sigal DS, et al. *Oncotarget*. 2018;9(88):35809-35812.



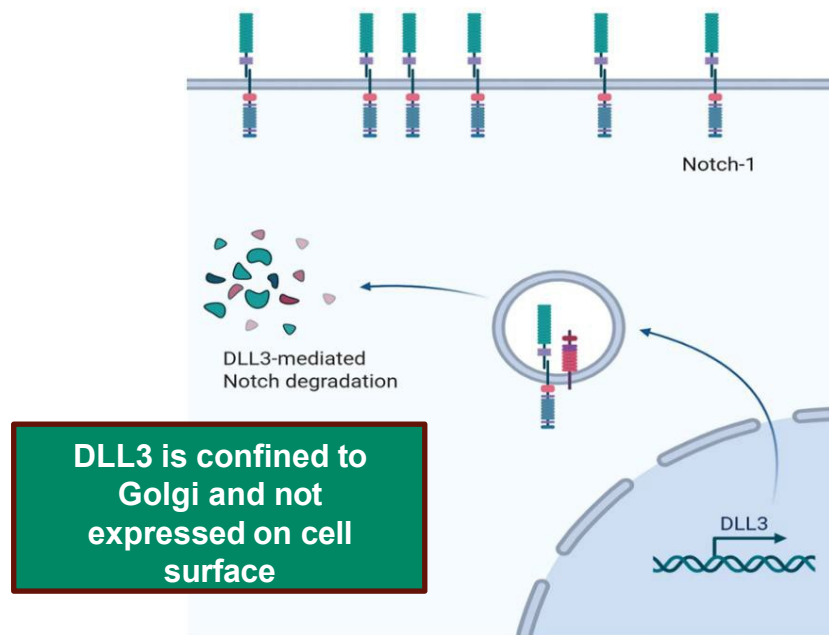
Emerging Role of DLL3 in EP-NEC



- Notch signaling is involved in cell fate and differentiation, proliferation, angiogenesis
- **Dysregulation of Notch signaling is implicated in various cancers, particularly neuroendocrine malignancies**
 - Notch inhibition → ASCL1 expression
- **DLL3** is an inhibitory ligand of Notch

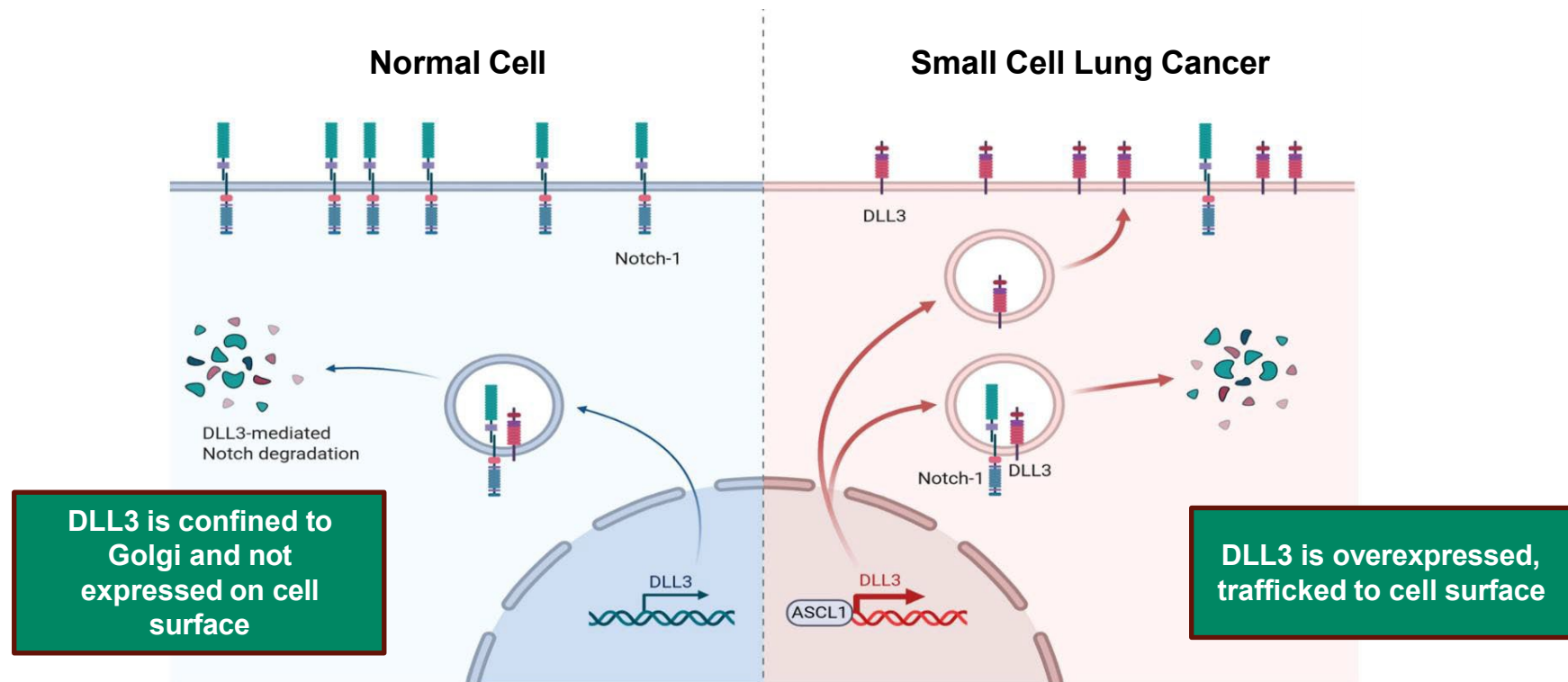
Adapted from Shi Q, et al. *Signal Transduct Target Ther.* 2024;9(1):128.

DLL3 Expression in Neuroendocrine Carcinomas



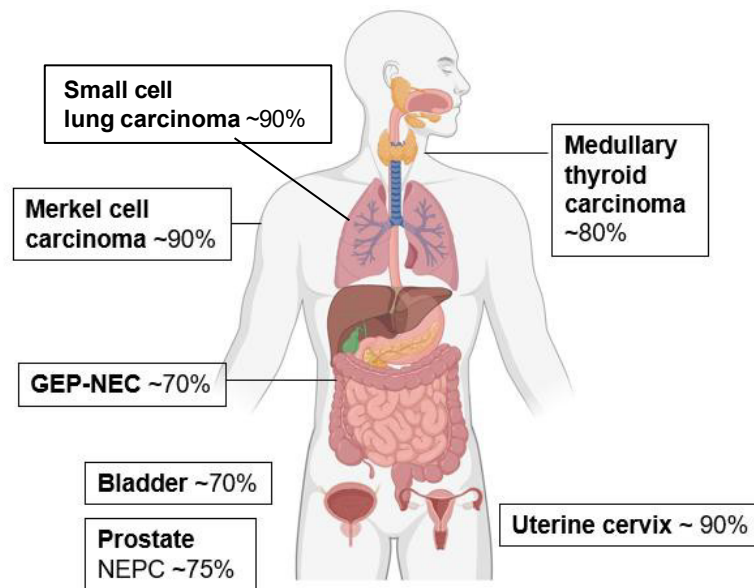
Denninghoff V, et al. *Cancers (Basel)*. 2021;13(7):1723.

DLL3 Expression in Neuroendocrine Carcinomas

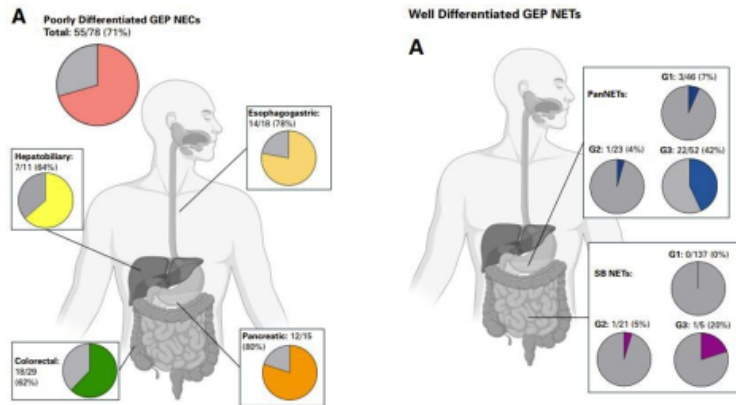


DLL3 Expression in Neuroendocrine Neoplasms

- DLL3 is expressed in NENs from many primary sites of origin
- DLL3 expression is strongest in poorly differentiated NEC; less common in well-differentiated NET



Delta-Like Ligand 3 Expression and Functional Imaging in Gastroenteropancreatic Neuroendocrine Neoplasms



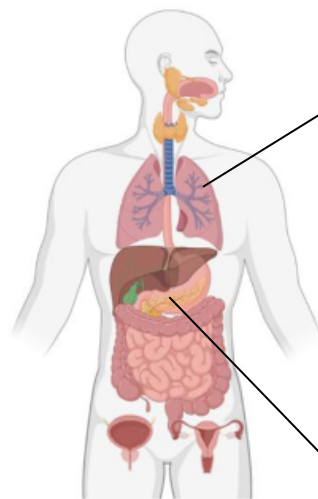
GEP-NEC (N=78)

- **DLL3+: 71%**
- Median H-score higher for small-cell vs large-cell histology

GEP-NET (N=301)

- **DLL3+**
 - G1-G2 NET: 2% (5/235)
 - G3 Pan-NET: 43% (22/52)
 - G3 SI-NET: 20% (1/5)

DLL3 Expression in Neuroendocrine Carcinomas and Neuroendocrine Tumours: Insights From a Multicentric Cohort of 1294 Pulmonary and Extrapulmonary Neuroendocrine Neoplasms



SCLC (n=91): 83.5%

Strong 58.2%

Large Cell NEC (n=62): 75.8%

Strong 53.2%

Atypical Carcinoid (n=39): 48.7%

Strong 30.8%

Typical Carcinoid (n=96): 39.5%

Strong 18.8%

GEP-NEC (n=133)

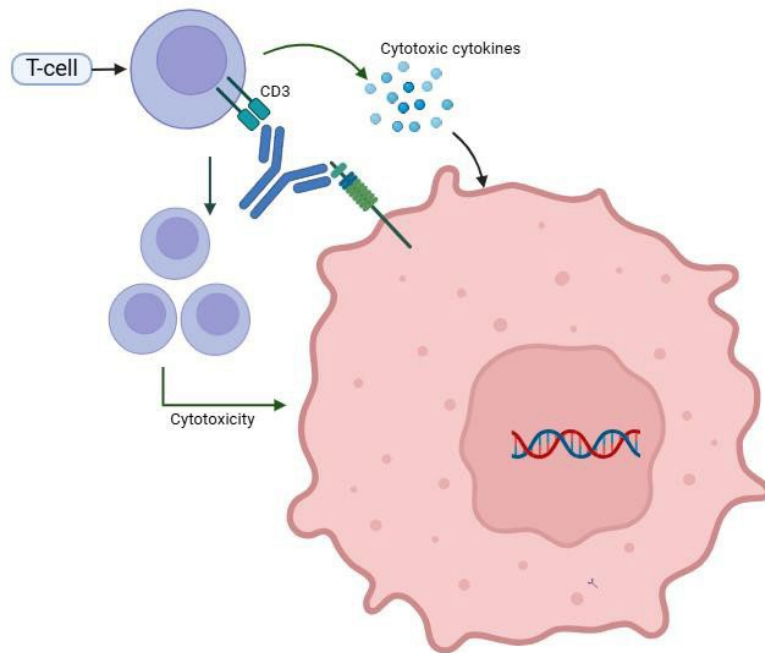
- **DLL3+: 43.6%**

Pan = pancreas; SI = small intestine.

Thummalapalli R, et al. *JCO Precis Oncol.* 2025;9:e2500724. Schmitt M, et al. *Endocr Pathol.* 2025;36(1):9.

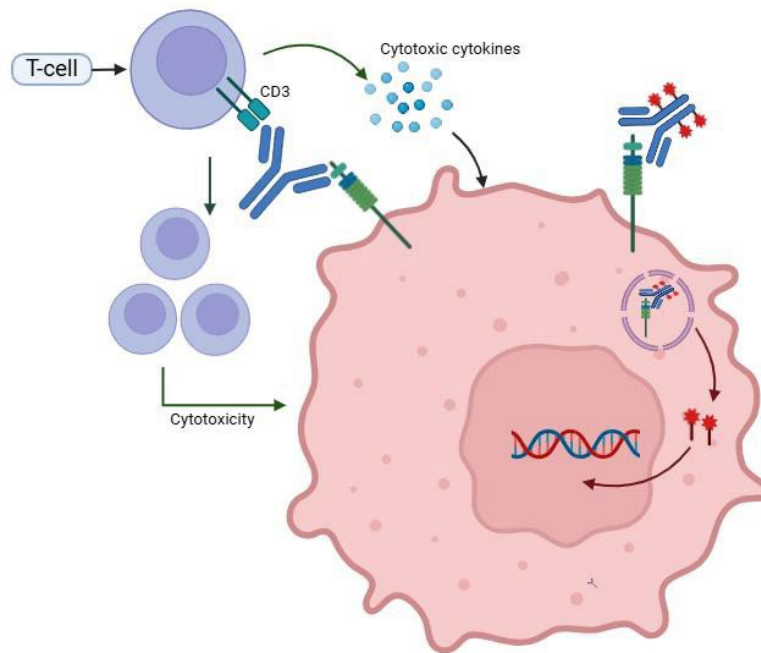
DLL3-Targeting Treatment Strategies

DLL-3-Targeting T-Cell Engager



DLL3-Targeting Treatment Strategies

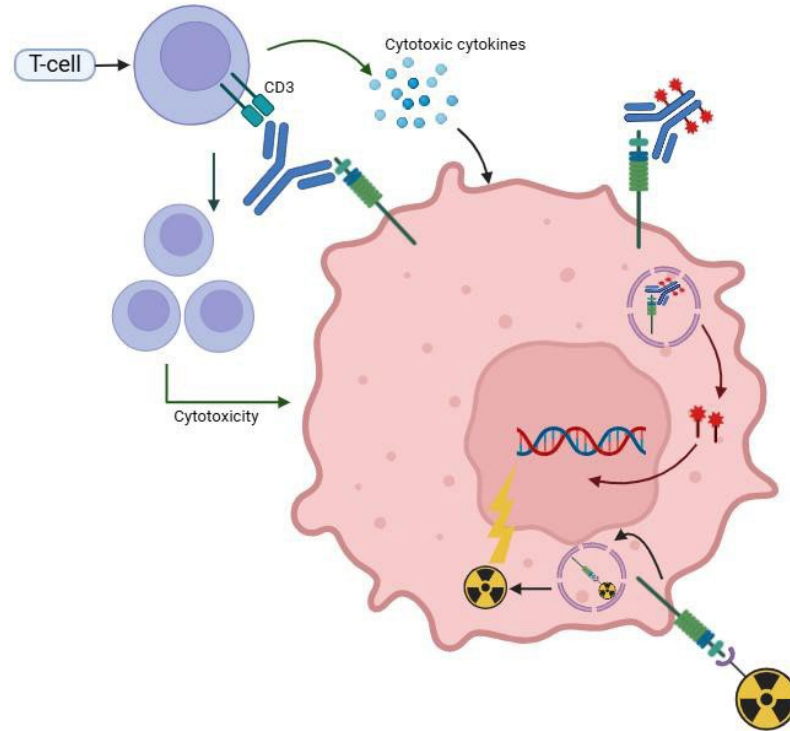
**DLL3-Targeting
T-Cell Engager**



**DLL3-Targeting
Antibody-Drug
Conjugate**

DLL3-Targeting Treatment Strategies

**DLL3-Targeting
T-Cell Engager**



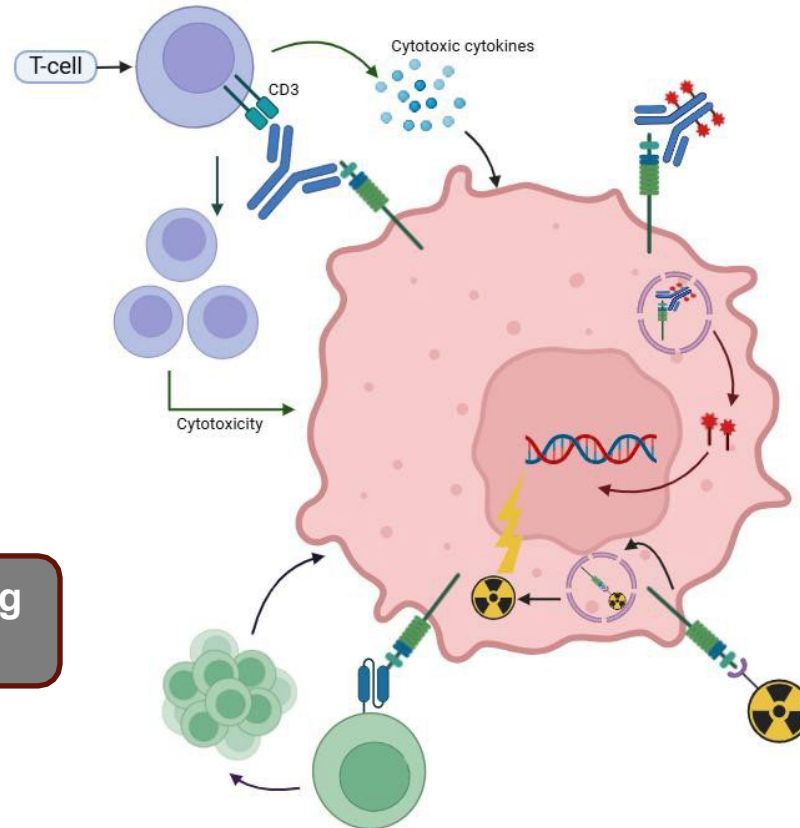
**DLL3-Targeting
Antibody-Drug
Conjugate**

**DLL3-Targeting
Radioligand
Therapy**

DLL3-Targeting Treatment Strategies

**DLL3-Targeting
T-Cell Engager**

**DLL3-Targeting
CAR T-cell**



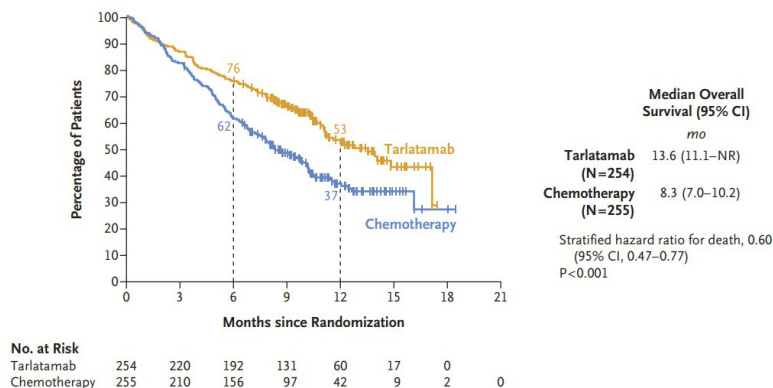
**DLL3-Targeting
Antibody-Drug
Conjugate**

**DLL3-Targeting
Radioligand
Therapy**

Targeting DLL3 in SCLC with Tarlatamab

ORIGINAL ARTICLE

Tarlatamab for Patients with Previously Treated Small-Cell Lung Cancer



- Tarlatamab = bispecific T-cell engager targeting **DLL3** and **CD3**
- Significant overall survival benefit in SCLC compared to SOC chemotherapy after platinum-based chemotherapy
- Tarlatamab is now standard of care for extensive-stage SCLC in the 2nd-line setting

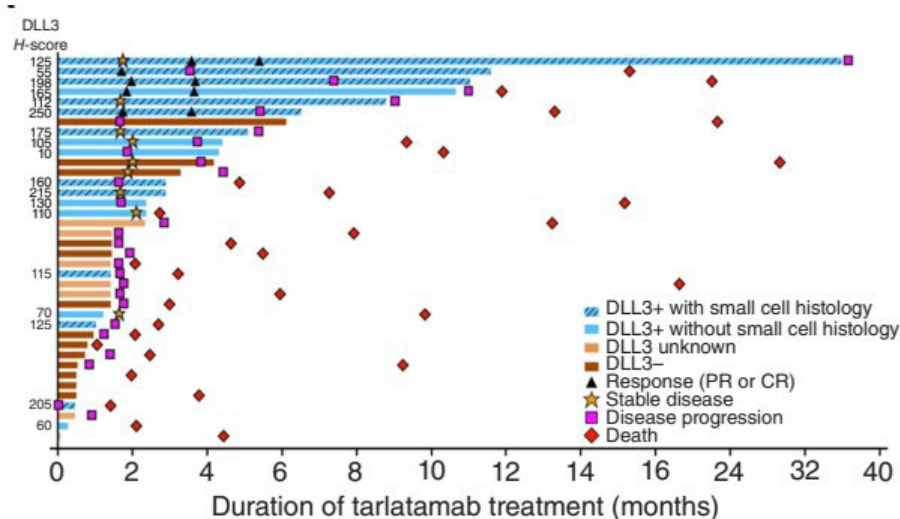
SOC = standard of care.

ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated January 5, 2026.

<https://clinicaltrials.gov/study/NCT05740566>. Mountzios G, et al. *N Engl J Med*. 2025;393(4):349-361.

Tarlatamab in Neuroendocrine Prostate Cancer

- **Phase 1b DeLLpro-300 Study**
- De novo or treatment-emergent neuroendocrine prostate cancer (NEPC)
- **Overall ORR 10.5%**
 - DLL3+ (n=18): 22.5%
 - DLL3-/unknown (n=20): 0%
- Most NEPC is treatment-emergent, arising from a non-neuroendocrine state; DLL3 expression dynamics in NEPC may differ from SCLC



Obrixtamig in Previously Treated DLL3+ EP-NEC



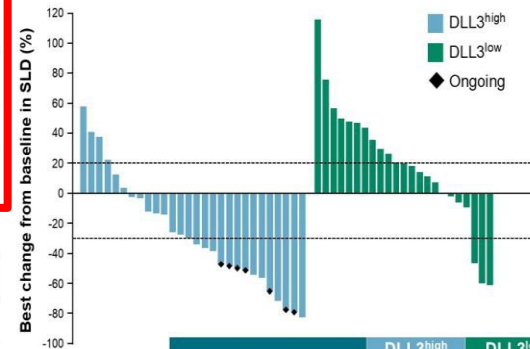
- Obrixtamig = IgG-like bispecific T-cell engager targeting **DLL3** and **CD3**
- In EP-NEC: obrixtamig has higher ORR, DCR and longer median duration of response in DLL3-high tumors
 - DLL3-high: $\geq 50\%$ tumor cells staining with strong or moderate intensity
- Phase 2 DAREON-5 expansion cohort is evaluating obrixtamig in patients with DLL3-high EP-NEC after prior platinum-based chemotherapy (NCT05882058)

Phase 1 obrixtamig dose escalation trial: EP-NEC results

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)



Enrolled patients (n):

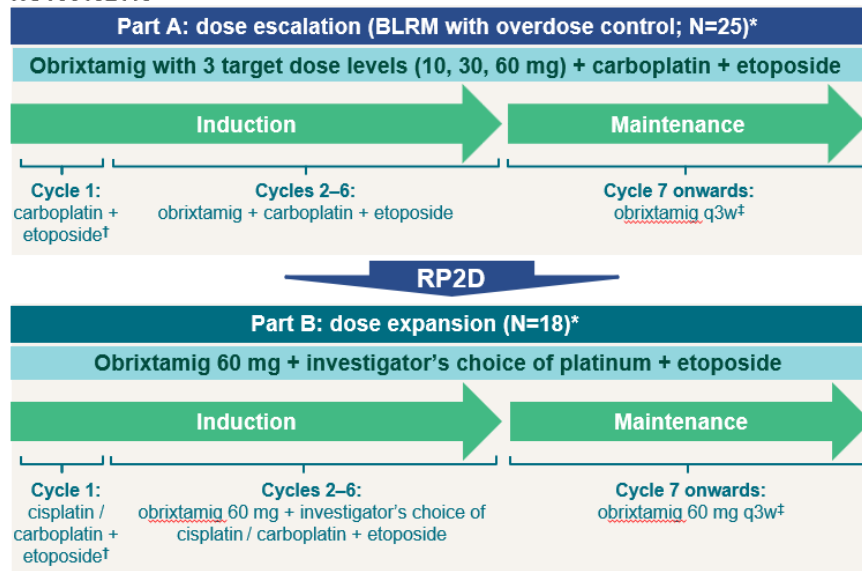
GI=32; GU=20; Unknown 1°=7; Other=1

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

DAREON-7: Obixtamig with Platinum + Etoposide as 1st-Line Therapy in NEC



NCT06132113¹



Key inclusion criteria

- Locally advanced/metastatic DLL3-positive NEC (by central testing)
 - EP-NEC, unknown primary NEC, large-cell NEC-lung
- Eligible to continue platinum + etoposide as 1L treatment
- Adequate liver, bone marrow, and renal function

Endpoints

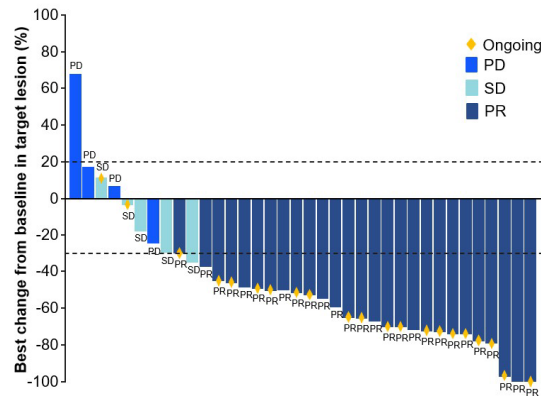
- **Primary:** DLTs
- **Secondary**
 - **Part A:** AEs and DLTs during the on-treatment period
 - **Part B:** ORR and DoR by RECIST v1.1 (investigator-assessed)
- **Further:** PFS by RECIST v1.1 (investigator-assessed)

RP2D = recommended phase 2 dose; 1L = first-line; DLT = dose-limiting toxicity; AE = adverse event; RECIST = response evaluation criteria in solid tumors.

Capdevila J, et al. Presented at: Annual European Neuroendocrine Tumor Society (ENETS) Conference; 2026.

DAREON-7: Obixtamig with Platinum + Etoposide as 1st-Line Therapy in NEC

- Obixtamig with platinum + etoposide demonstrated encouraging ORR (75%), duration of response and PFS
- Randomized phase 3 DAREON NEC-1 trial will evaluate obixtamig with carboplatin + etoposide as 1st-line treatment vs carboplatin + etoposide for patients with DLL3+ EP-NEC (NCT07544654)



*Investigator-assessed; †efficacy-evaluable population; ‡per Kaplan-Meier estimates

Enrolled patients

EP-NEC (n=38 mostly GI)

Lung LC-NEC (n=2)

Unknown 1° NEC (n=3)

Best confirmed response*	N=36†
ORR, % (95% CI)	75 (59–86)
Complete response, n (%)	0
Partial response, n (%)	27 (75)
DCR, % (95% CI)	89 (75–96)
Stable disease, n (%)	5 (14)
Progressive disease, n (%)	4 (11)

Median DoR: 8.8 months (95% CI: 5.5–NC)

6-month DoR rate:‡ 70% (95% CI: 47–92)

Median PFS:
7.7 months (95% CI: 5.8–NC)

6-mo PFS: 66%

9-mo PFS: 46%

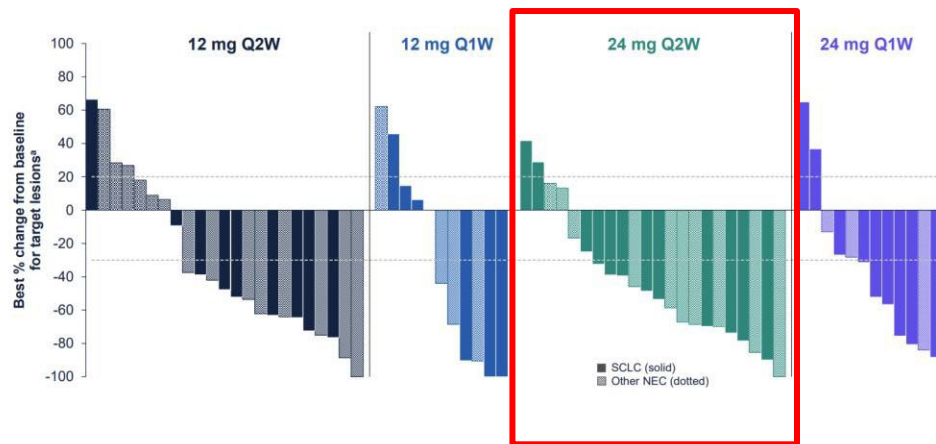
LC-NEC = large-cell NEC; NC = not calculable; DCR = duration of complete response.

Capdevila J, et al. Presented at: Annual ENETS Conference; 2026.

Gocatamig in SCLC or DLL3+ NEC

- **Gocatamig = Tri-specific T-cell engager targeting **DLL3** and **CD3** and **albumin** for half-life extension**
- Updated phase 1 results from 73 pts (39 SCLC, 29 other NEC, 5 high-grade NET)
 - ORR 44% in all cohorts
 - Median DOR 10.8 mo; 53% of responses ongoing

Phase 1/2 trial in patients with relapsed/refractory SCLC, other DLL3+ NEC



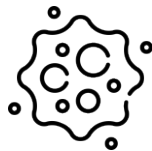
Preferred monotherapy dose
24 mg Q2W: SCLC ORR = 46%, other NEC = 50%

DLL3-Targeting Immune Cell Engagers in NEC

Drug	Targets	Indication	Phase	NCT Trial Number
Tarlatamab	DLL3/CD3	SCLC Poorly differentiated NEC	II	NCT07016230 (France)
Tarlatamab	DLL3/CD3	EP-NEC	II	NCT06893783 (South Korea)
Tarlatamab	DLL3/CD3	EP-NEC	II	NCT06816394 (Taiwan)
Tarlatamab	DLL3/CD3	DLL3+ tumors (except SCLC and neuroendocrine prostate cancer)	II	NCT06788938 (University of California system)
Peluntamig (PT217)	DLL3/CD47	SCLC LCNEC EP-NEC	I/II	NCT05652686
ZG006	DLL3/DLL3/CD3	EP-NEC	I	NCT05978284
HLX3901	DLL3/DLL3/CD3/CD28	SCLC NEC	I	NCT07416695

NCT = National Clinical Trial.

Adverse Events with DLL3-Targeting T-Cell Engagers



Cytokine Release Syndrome (CRS)

- Occurs early in the majority of patients (~60%), mostly low grade
- Step-in dosing
- Admission for initial infusions
- Anti-IL6 drugs
- No grade ≥ 3 CRS in combination with chemo in DAREON-7



Immune effector cell-associated neurotoxicity syndrome (ICANS)

- Occurs in ~10%
- Supportive care, steroids if grade 2
- No ≥ 2 ICANS in combination with chemo in DAREON-7

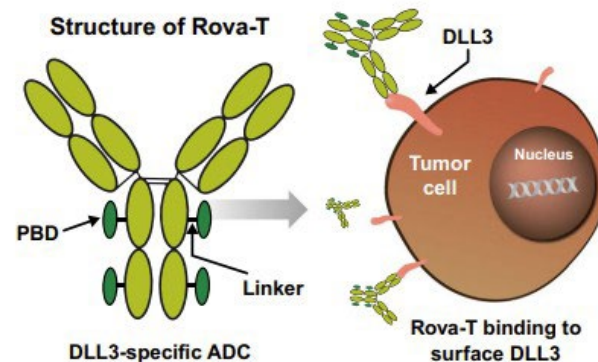


Other

- Fever
- Dysgeusia
- Decreased appetite
- Asthenia, fatigue
- Tumor flare

DLL3-Targeting Antibody Drug Conjugates (ADCs)

- **Rovalpituzumab tesirine (Rova-T):** 1st-generation DLL3-targeted ADC with pyrrolobenzodiazepine (PBD) payload
- Failed in later-line trials in SCLC due to toxicity and lack of efficacy/worse outcomes compared to SOC
- Challenges with Rova-T related: unstable linker leading to off-target toxicity and reduced payload delivery to tumor



ADC = antibody-drug conjugate.

Rudin CM, et al. *J Hematol Oncol.* 2023;16(1):66. Blackhall F, et al. *J Thorac Oncol.* 2021;16(9):1547-1558. Johnson ML, et al. *J Thorac Oncol.* 2021;16(9):1570-1581.

DLL3-Targeting ADCs in NEC

Agent	Payload	Linker	Indication	Phase	Sponsor	NCT
Zocilurtatug pelitecan (ZL-1310)	DNA topoisomerase I inhibitor (YL0010014)	Cleavable	NECs excluding SCLC	Ib/II	Zai Lab	NCT06885281
BL-M14D1	DNA topoisomerase I inhibitor (Ed-04)	Cleavable	SCLC NEC	I	SystImmune Inc.	NCT07080242
IDE849	DNA topoisomerase I inhibitor	Cleavable	SCLC High-grade NEC Other DLL3+ tumors	I/II	IDEAYA Biosciences	NCT07174583

Early Results from DLL3 Targeting ADCs in EP-NEC

Zocilurtatug pelitecan (ZL-1310) Phase 1b

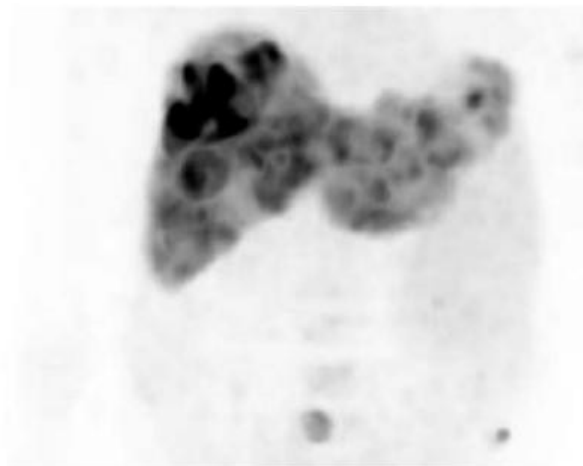
- **Total (n=34): ORR 38.2%**
 - **GEP-NEC (n=18): ORR 33%**
 - **Other DLL3+NEC (n=16): ORR 43.8%**
- No clear association between response and DLL-3 expression
- Gr ≥ 3 TEAEs in 30.4% (mostly hematologic)
- Study is ongoing, expansion into phase 2
- FDA fast-track designation for treatment of EP-NEC following progression on 1st-line Tx

BL-M14D1—Phase 1 in SCLC, NEC

- **Enrolled 40 pts with NEC, 87 with SCLC**
- Efficacy at 4.0 and 4.5 mg/kg presented
- **In 22 evaluable pts with NEC: ORR 40.9%; cORR 27.3%**
- Gr ≥ 3 TRAEs: thrombocytopenia (54.3%), neutropenia (53.5%), leukopenia (46.5%), anemia (32.3%).
- Gr 3 ILD in 1; 1 treatment-related death

TEAE = treatment-emergent AE; Tx = treatment; cORR = confirmed ORR; ILD = interstitial lung disease.
Thummalapalli R, et al. Presented at: American Association for Cancer Research (AACR) Annual Meeting; 2026.
Li W, et al. *J Clin Oncol*. 2026;44(16 Suppl):3001.

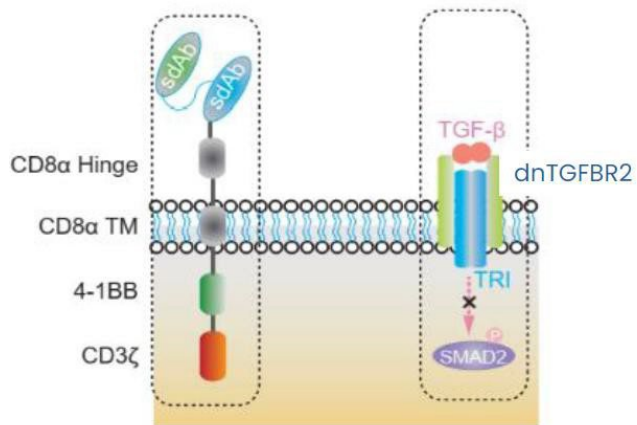
DLL3-Directed Imaging and Radioligand Therapy



[⁸⁹Zr]Zr-DFO-SC16.56 immunoPET/CT
Identifies DLL3+ NEC

Agent	Indication	Phase	NCT
[²¹²Pb]Pb-DOTAM-MAM279	SCLC DLL3+ NEC	I/IIa	NCT07278479
[²²⁵Ac]Ac-ETN029	SCLC LCNEC-lung GEP-NEC Neuroendocrine prostate cancer	I	NCT07006727
²²⁵Ac-ABD147	SCLC LCNEC-lung	Ia/b	NCT06736418
¹⁷⁷Lu-DTPA-SC16.56	SCLC Neuroendocrine prostate cancer	I	NCT06941480

DLL3-Directed CAR T-Cell Therapy

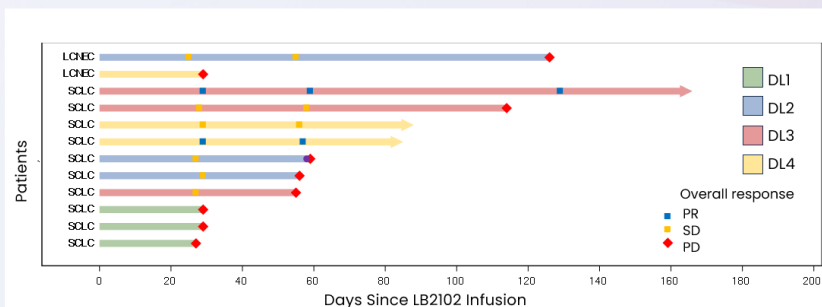


**LB2102—DLL3-targeting CAR T cell
with dominant negative TGFβ receptor**

Phase 1 Trial (NCT05680922)

- Prelim data from 15 patients (13 with SCLC) treated with LB2102
- Early signal of efficacy with PRs at DL3 or higher

Figure 3. Disease Response at Different Dose Levels



Arrowheads indicate patients (n=3) still on study follow up, without progression or anti-cancer therapy as of their last visit. The purple circle indicates when the patient received subsequent anti-cancer therapy.

PR = partial response; DL = dose level; SD = stable disease; PD = progressive disease.

Schoenfeld AJ, et al. Presented at: International Association for the Study of Lung Cancer (IASLC) 2025 World Conference on Lung Cancer (WCLC); 2025.



Key Learning Points

- Extrapulmonary NECs are poorly differentiated neuroendocrine malignancies with aggressive biology and poor outcomes with standard chemotherapy
- A subset of patients with EP-NEC may have genomic alterations that can be targeted
- DLL3 is an inhibitory Notch ligand expressed on the cell surface of most NECs. Tumor testing is needed to identify patients likely to benefit from DLL3-targeted treatment.
- T-cell engagers targeting DLL3 and CD3 have shown activity against extrapulmonary NEC
- Participation in clinical trials evaluating DLL3 targeting strategies and other novel approaches is encouraged