



16th
CONGRESS
Lung ON
CANCER

BARCELONA
27 / 28
NOVEMBER 2025

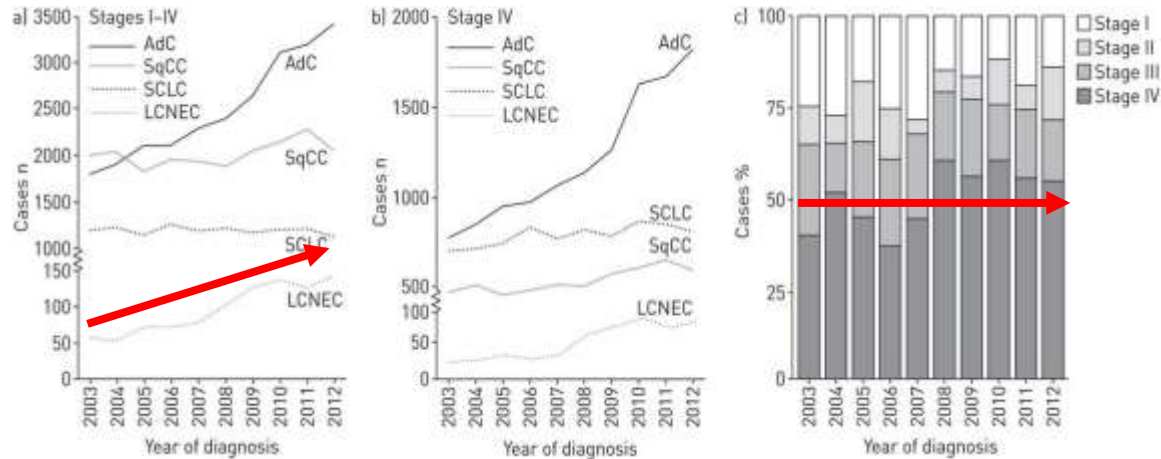
Large Cell Neuroendocrine Carcinoma: New Insights

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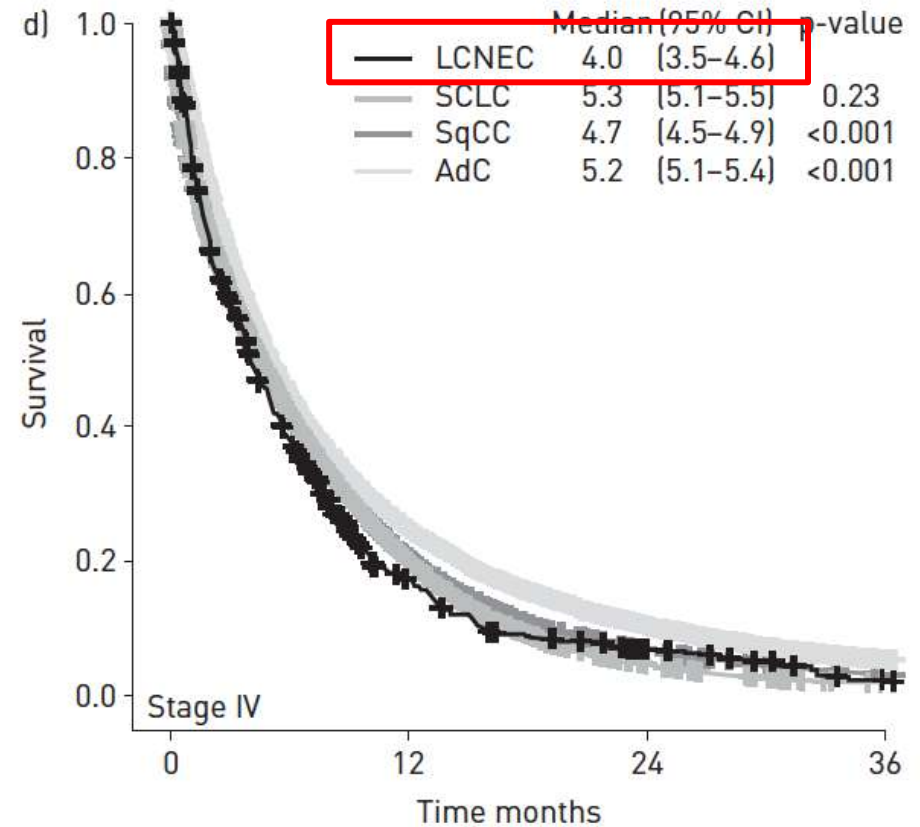
Declaration of Interest

Commercial Interest	Relationship(s)
Speaker/Consultancy/Advisory/Travel (self)	AbbVie, Amgen, Astra-Zeneca, Bayer, BMS, GILEAD, Boehringer Ingelheim, J&J, Merck, MSD, Novartis, Pfizer, Roche, Takeda, Lilly, PharmaMar, Gilead Sciences, Regeneron, Revolution Medicines, Tubulis, Summit Therapeutics, Harpoon Therapeutics, BeOne Medicines, Daiichi Sankyo, ArriVent Biopharma
Clinical and Research Funding (self)	MSD (IIT), Amgen (IIS)
Institutional Financial Interests	Related to clinical trials and patient recruitment

LCNEC: Trends and Outcomes (NCR)

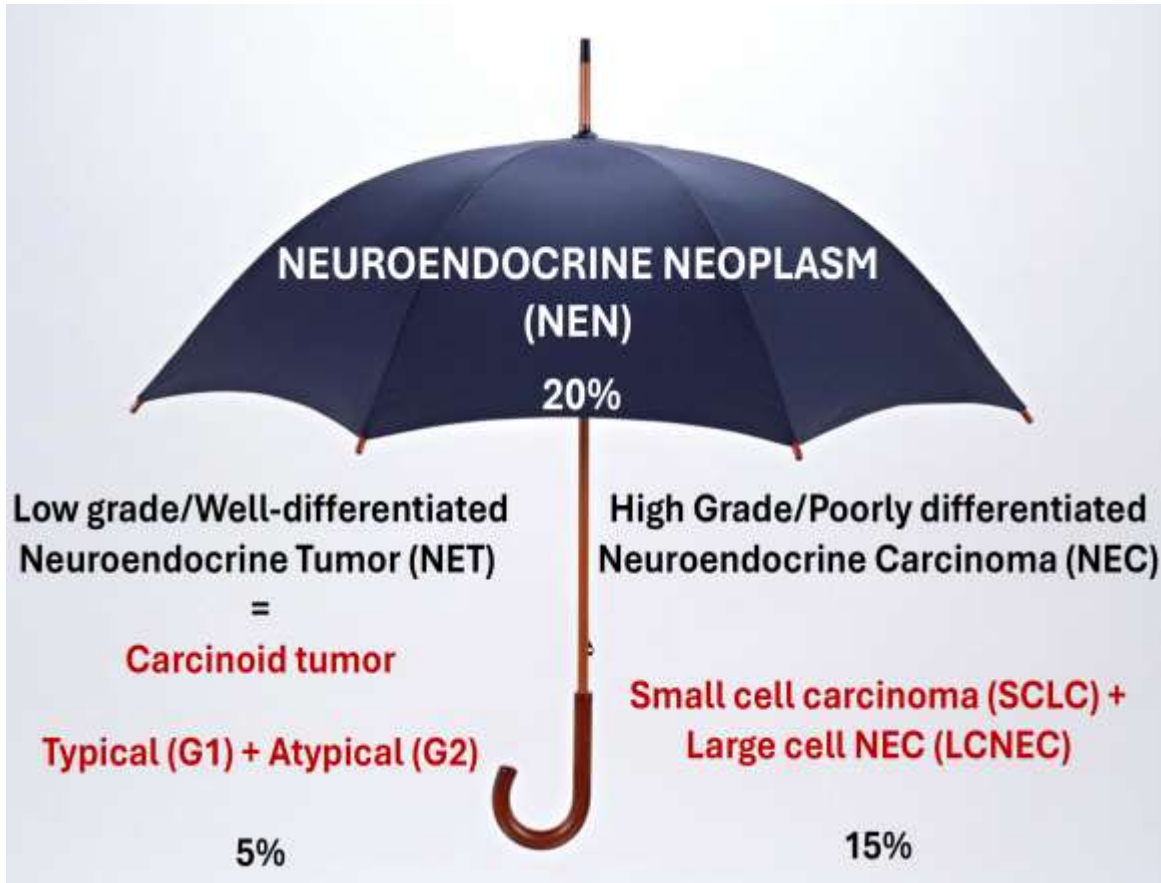


Stage IV (N = 25.845)



- Incidence increasing
- >50% de novo metastatic disease
- Poor outcomes

PATHOLOGIC CLASSIFICATION



WHO 2021 Classification Of Pulmonary NENs²

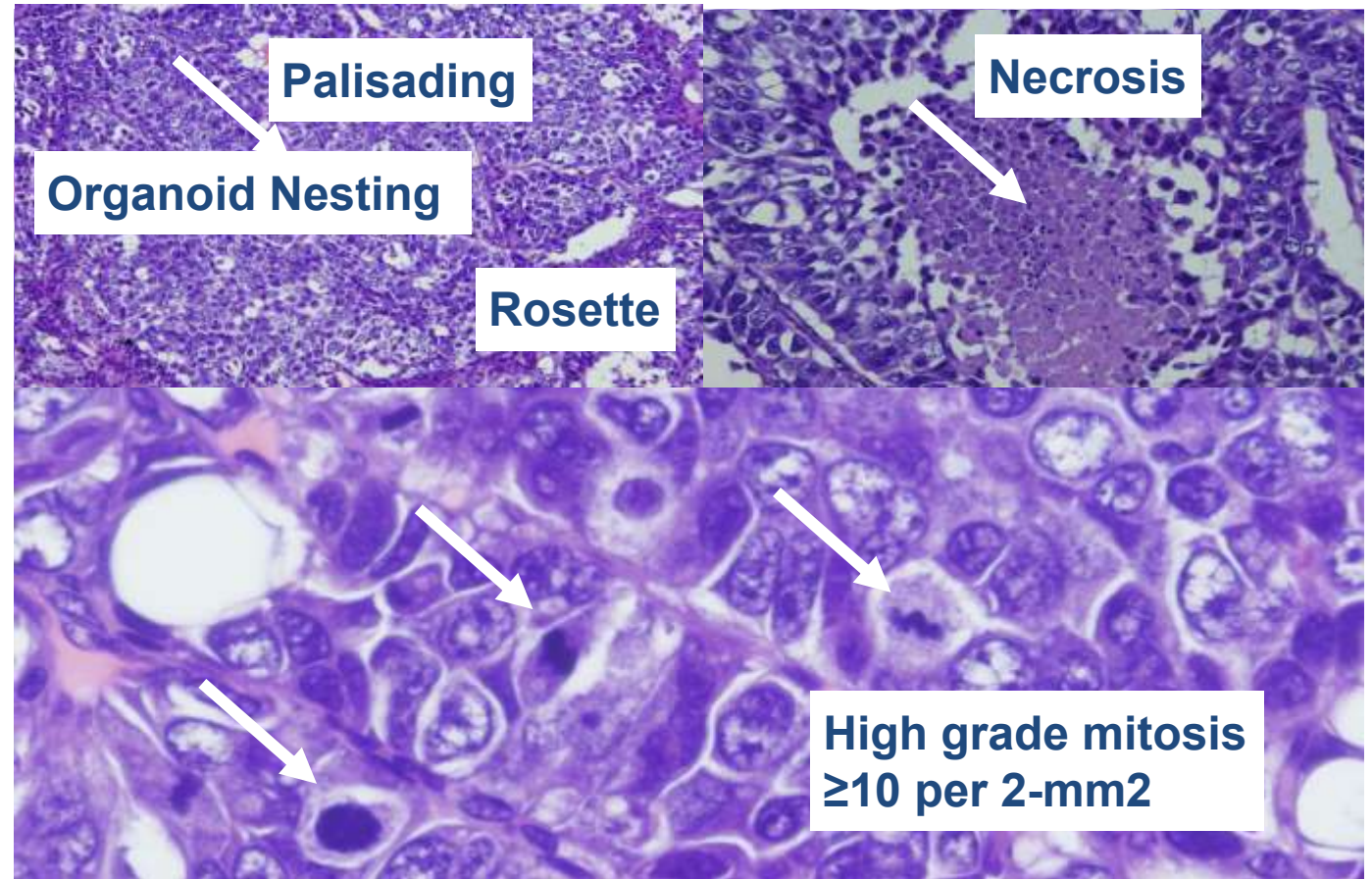
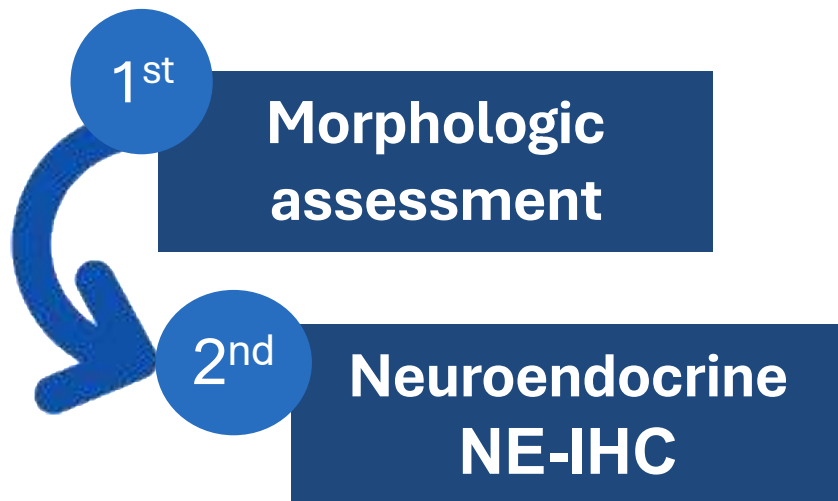
<i>LOW GRADE</i> ($<10 \times 2\text{-mm}^2$)	<i>HIGH GRADE</i> ($>10 \times 2\text{-mm}^2$, Typically: $>60\%$)	
<i>Carcinoid (TC/AC)</i>	<i>SCLC</i>	<i>LCNEC</i>

IHC¹

Synaptophysin	Chromogranin	CD56	INSM1

Categorization of high-grade NETs (WHO 2021 Edition)

- Diagnosis of **LARGE CELL CARCINOMA** cannot be made in small biopsy/cytology².
- **Neuroendocrine IHC markers** should be used **ONLY** where there is morphologic evidence of neuroendocrine morphology².



An unmet need: specific markers to separate SCLC of LCNEC

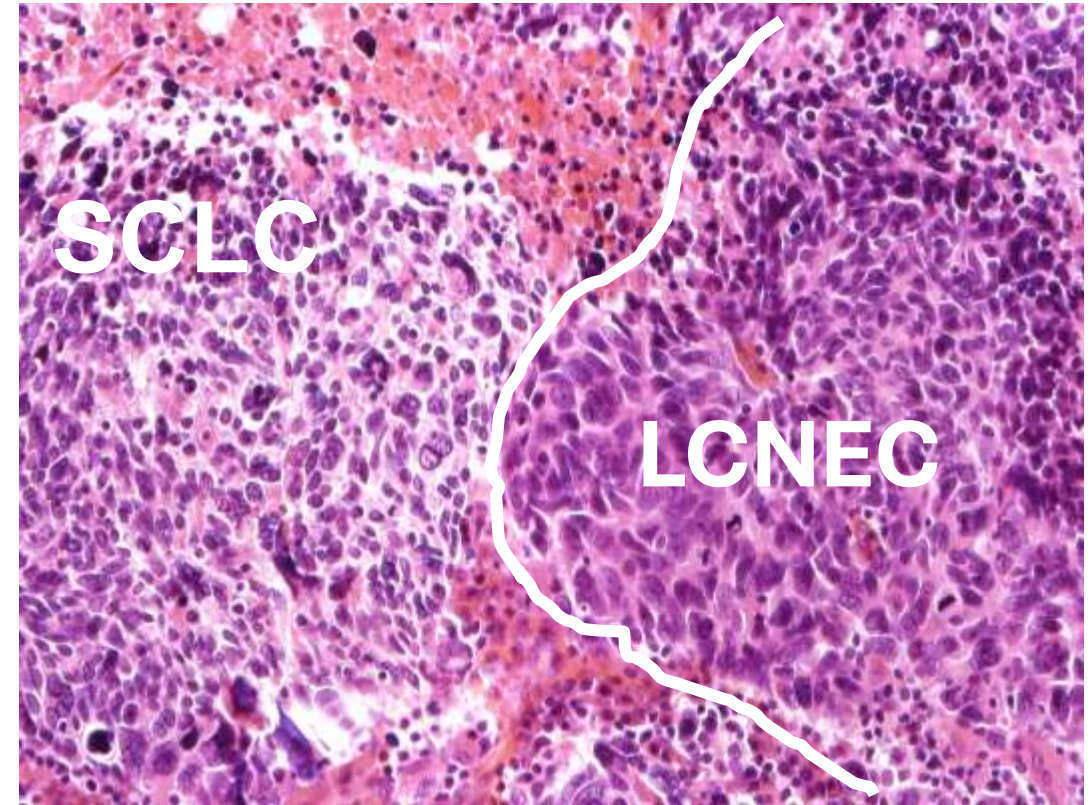
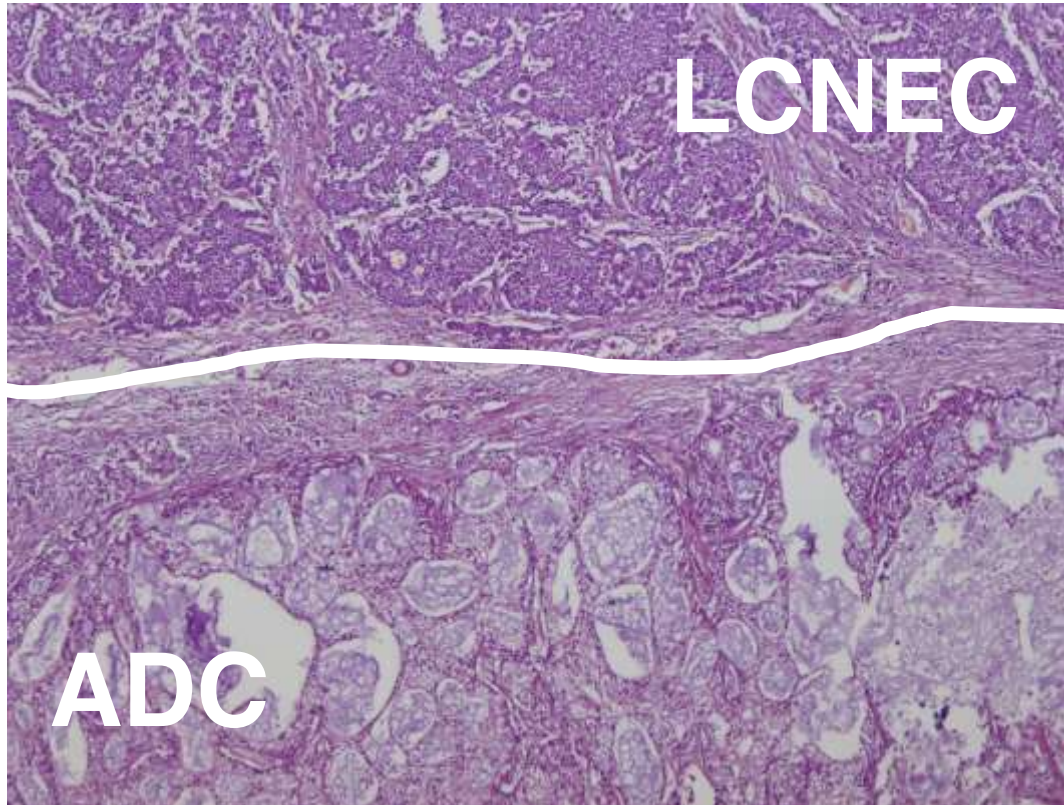
**Poorly-differentiated LCNEC ->
May fall into NOS classification¹**



**SCLC with large cell appearance->
May be diagnosed as LCNEC²**



To complicate it further.....Combined Histologies Can Exist



HOW DO WE TREAT LCNEC?

After all these years the debate is still ongoing

Chemotherapy for pulmonary large cell neuroendocrine carcinoma: Similar to that for small cell lung cancer or non-small cell lung cancer?

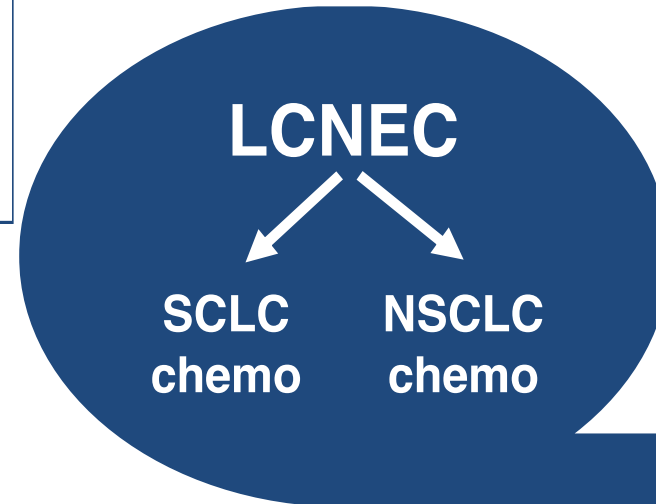
Jong-Mu Sun^a, Myung-Ju Ahn^a, Jin Seok Ahn^a, Sang-Won Um^b, Hojoong Kim^b, Hong Kwan Kim^c, Young Soo Choi^c, Jounggho Han^d, Jhingook Kim^c, O Jung Kwon^b, Young Mog Shim^c, Keunchil Park^{a,*}

Should Large Cell Neuroendocrine Lung Carcinoma be Classified and Treated as a Small Cell Lung Cancer or with Other Large Cell Carcinomas?

John M. Varlotto, MD, Laura Nyshel Medford-Davis, BA,† Abram Recht, MD,‡
John C. Flickinger, MD,§ Eric Schaefer, MS,|| Dani S. Zander, MD,¶ and Malcolm M. DeCamp, MD#*

Chemotherapy for pulmonary large cell neuroendocrine carcinomas: does the regimen matter?

Jules L. Derks¹, Robert Jan van Suylen², Erik Thunnissen³, Michael A. den Bakker^{4,5}, Harry J. Groen⁶, Egbert F. Smit^{7,8}, Ronald A. Damhuis⁹, Esther C. van den Broek¹⁰, Ernst-Jan M. Speel^{11,13}, Anne-Marie C. Dingemans^{1,13} and PALGA group¹²



NO CONSENSUS ON THE OPTIMAL SYSTEMIC TREATMENT



MOST APPROPRIATE TREATMENT NOT DEFINED

GUIDELINES do not provide much help this time



Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update



Neuroendocrine bronchial and thymic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]



National Comprehensive Cancer Network[®]

- **Platinum-etoposide** or the same as **non-squamous carcinoma** (evidence LOW; weak recommendation)¹
- **Platinum-etoposide** is mainly used in high proliferating tumors (III, B)².
- **Treatment according to NSCLC guidelines**

HETEROGENEOUS OUTCOMES WITH CHEMOTHERAPY

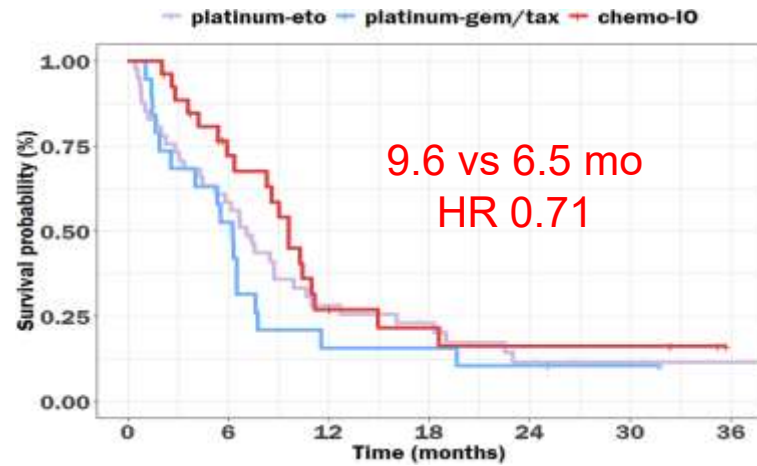
Chemotherapy Type

				NSCLC-type	SCLC-type	
Author	Design	Path Review	N	OS (months)		Ref
Christopoulos <i>et al.</i>	Phase 2	YES	49	10	-	<i>Ann Oncol 2017</i>
Le Treut <i>et al.</i> GFPC 0302	Phase 2	YES	29	-	5	<i>Ann Oncol 2013</i>
Niho S <i>et al.</i>	Phase 2	YES	30	-	13	<i>JTO 2013</i>
Metro G <i>et al.</i>	RWD	NO	37	-	8	<i>Lung Cancer 2016</i>
Sun JM, <i>et al.</i>	RWD	YES	45	9	16.5	<i>Lung Cancer 2012</i>
Naidoo J, <i>et al.</i>	RWD	YES	37	19.5	8	<i>Clin Lung Cancer 2016</i>
Derks JL, <i>et al.</i>	RWD	YES	128	8.5	7	<i>ERJ 2017</i>
Heijboer F WJ <i>et al.</i>	RWD	YES	88	~6	~6	<i>Lung Cancer 2025</i>

WHAT ABOUT IO?

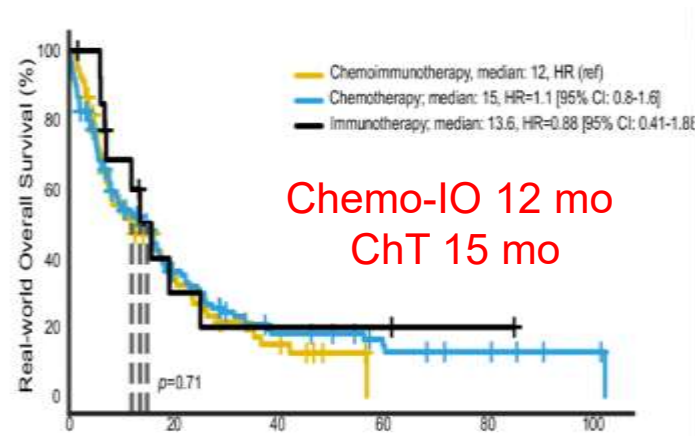


Front-Line ICIs
Panel reviewed (pRB+, N = 88)



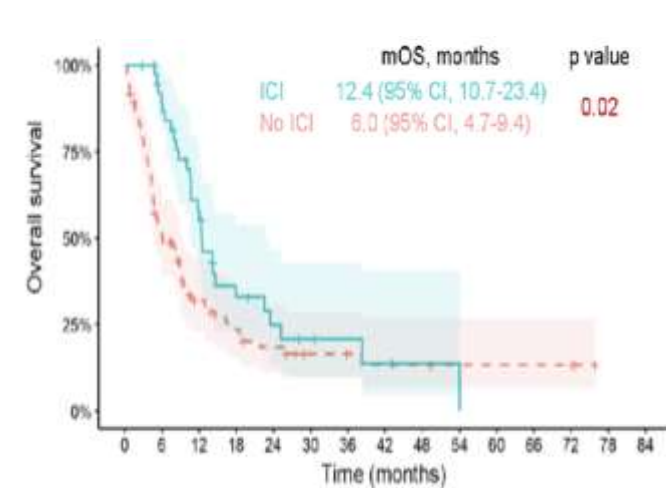
Integrated molecular and clinical characterization of pulmonary large cell neuroendocrine carcinoma

Front-Line ICIs
(N = 590)



Real-world survival outcomes with immune checkpoint inhibitors in large-cell neuroendocrine tumors of lung

ICIs after front-line therapy
(N = 125)

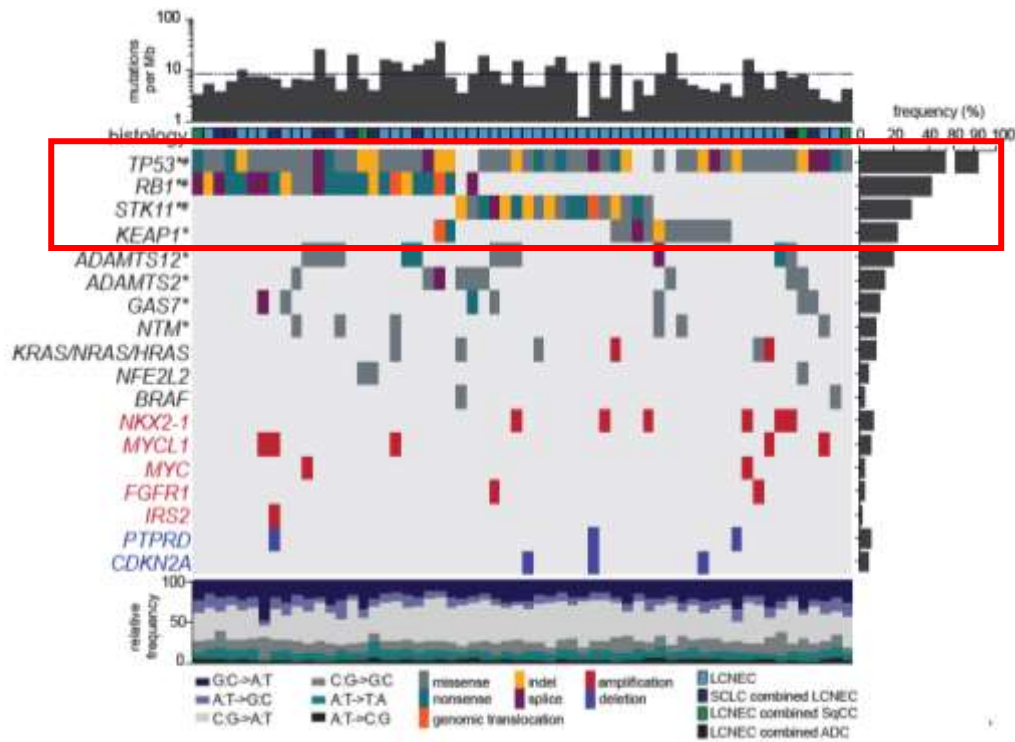


Poor outcomes, NO prospective data, role of IO remains uncertain

Genomic Profiling of LCNEC

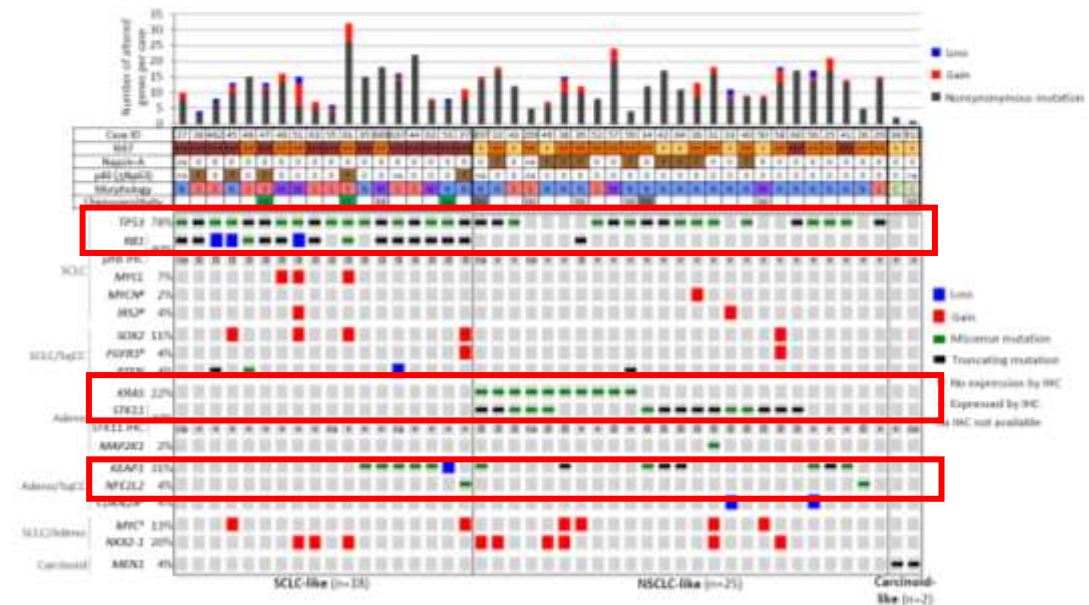


Integrative genomic profiling of large-cell neuroendocrine carcinomas reveals distinct subtypes of high-grade neuroendocrine lung tumors



Next-Generation Sequencing of Pulmonary Large Cell Neuroendocrine Carcinoma Reveals Small Cell Carcinoma-like and Non-Small Cell Carcinoma-like Subsets

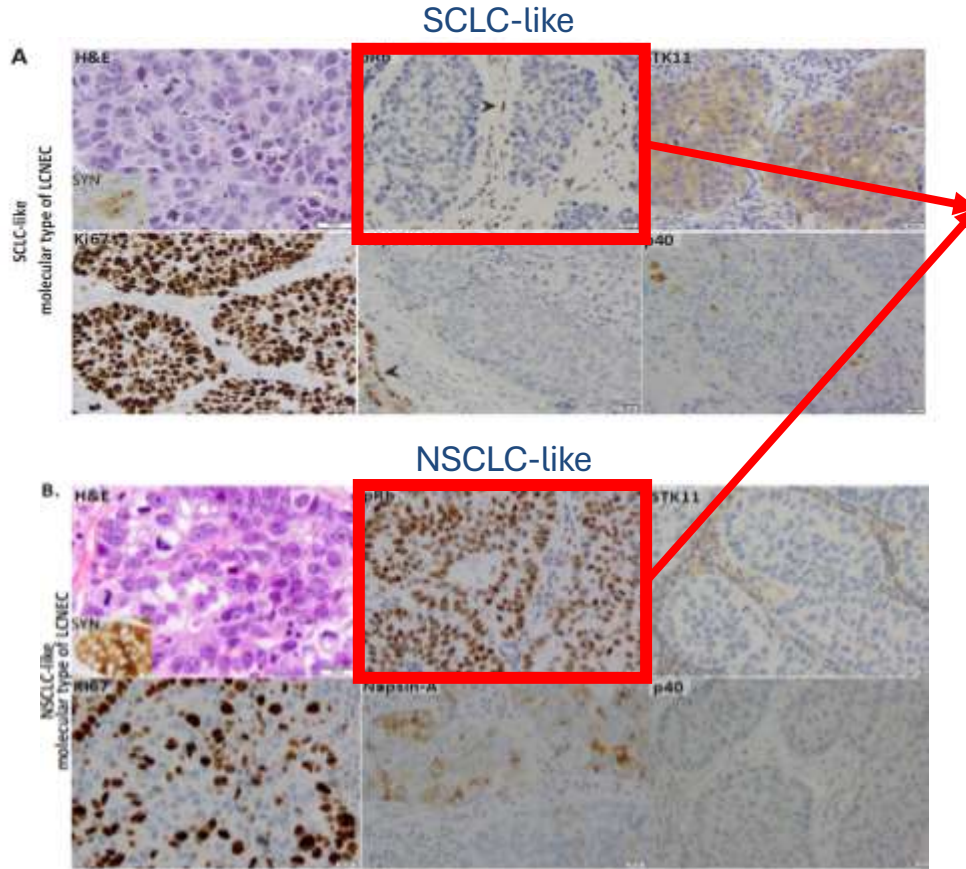
N=45



**Both (TP53-RB1) ~ 50%
KRAS/STK11 and RB exclusive
KEAP1-NFE2L2 common (~ 40%)**

Genomic Profiling of LCNEC and Treatment Outcomes

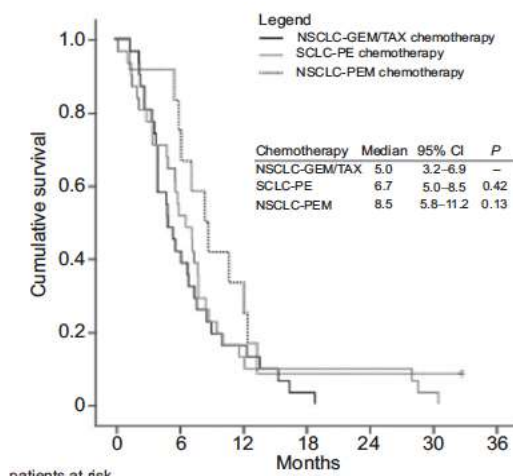
NSCLC-Like Subtype ($RB1^{WT}$) retains pRB expression → potential biomarker



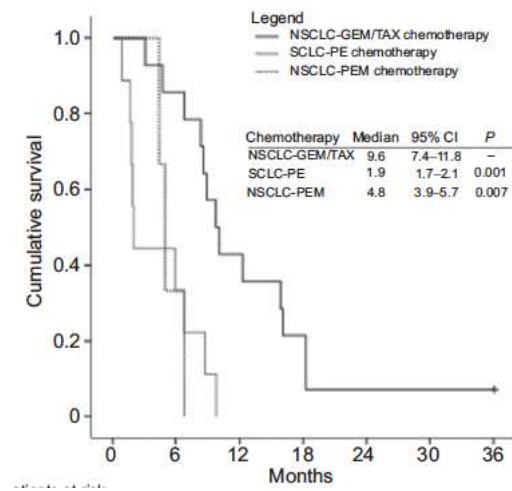
		RB1 gene	
		Mut/lost	Wild Type
pRB protein	Lost	16	2
	Expressed	0	24

Rb-IHC expression as a marker of NSCLC-like subtype¹⁻²

LCNEC with RB1 H-score < 50



LCNEC with RB1 H-score ≥ 50



A Case Experience

75-year-old woman, former light smoker | **Medical history:** No relevant comorbidities

LCNEC stage IVB (cT2aN1M1c1)

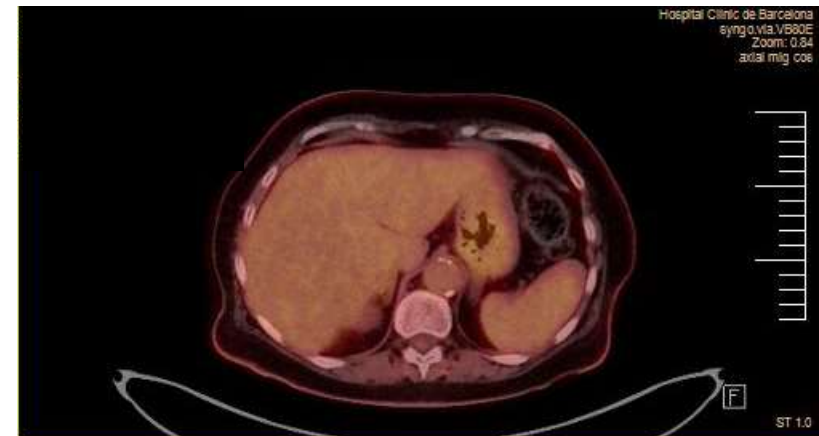
Synaptophysin +, P40 and TTF-1 –
KRAS mut (Q61H, FA 70%), TP53 mut
PD-L1 negative



RB-IHC + (WT)
NSCLC-type

1 L CBCDA-TAX-IO

PR after 2 cycles



Integrative Genomic/Transcriptomic Profiling of LCNEC



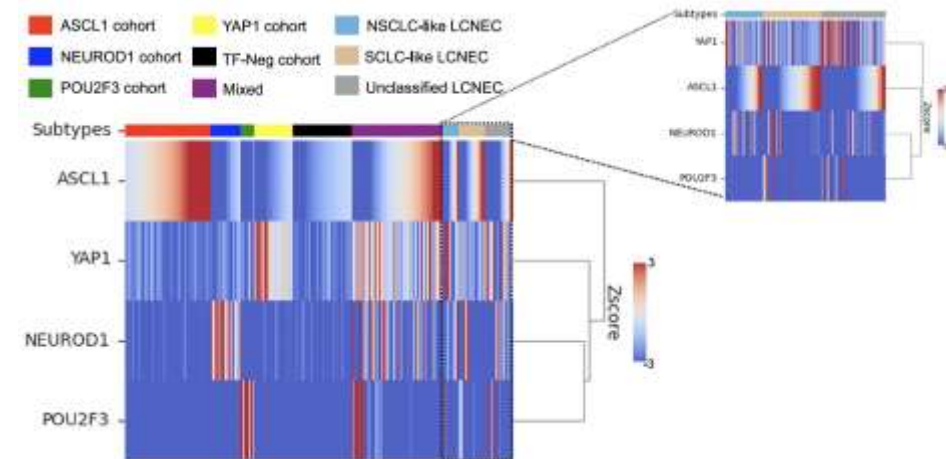
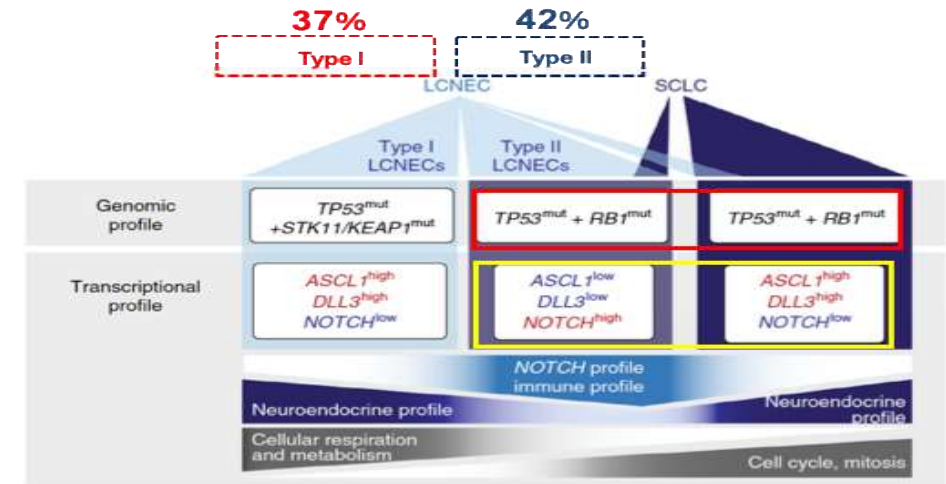
Two major LCNEC subtypes:

Type I: $TP53^{mut} + STK11/KEAP1^{mut}$

Type II: $TP53^{mut} + RB^{mut}$

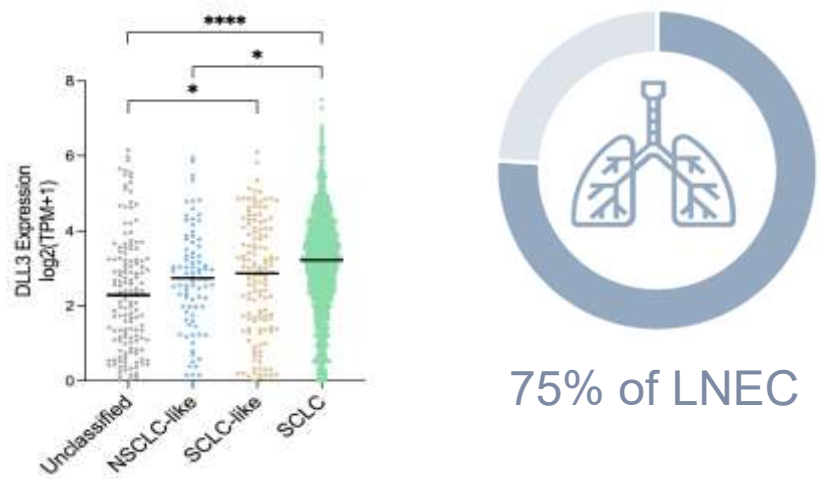
Integrative genomic profiling of large-cell neuroendocrine carcinomas reveals distinct subtypes of high-grade neuroendocrine lung tumors ⁽¹⁾

Integrated molecular and clinical characterization of pulmonary large cell neuroendocrine carcinoma ⁽²⁾



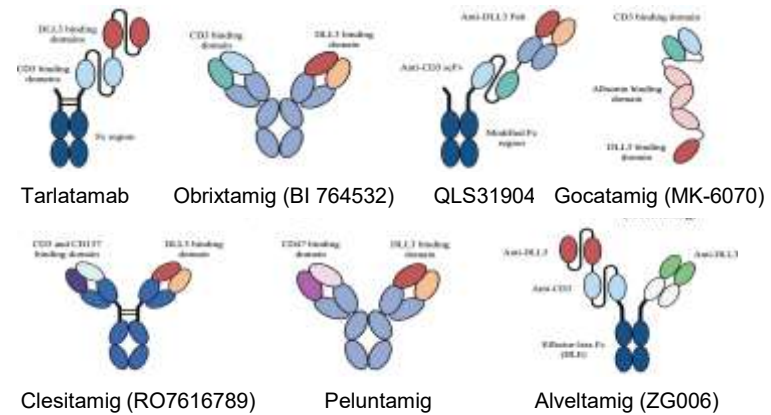
TARGETING DLL3 AS A THERAPEUTIC STRATEGY

DLL3 expression

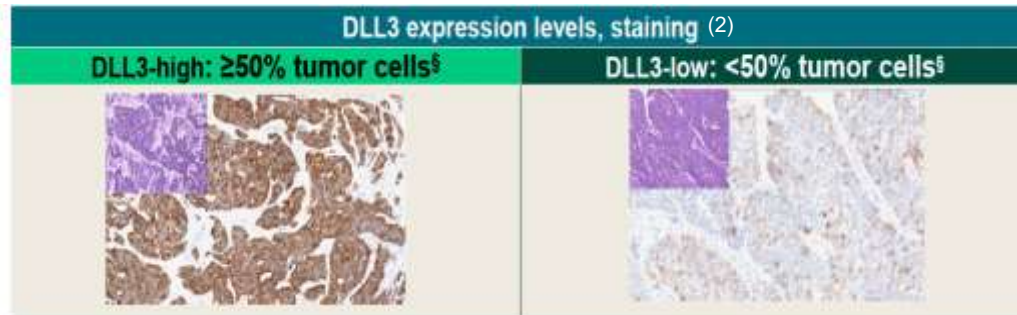
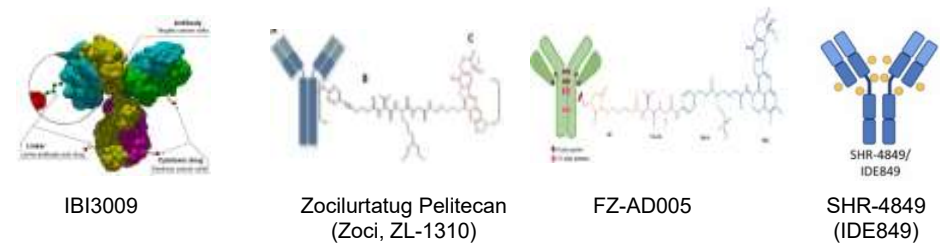


DLL3-directed agents⁴

T-Cell Engagers



DLL-3 ADCs



Images from: 1.- Nassar AH et al. Nature Communications 2025; 2. Hermans BCM, et al. Lung Cancer 2019; 3.- Pavel ME, ESMO 2025; 4.- Aijaz A, et al ASCO Book 2025

TARLATAMAB: CASE REPORTS OF EFFICACY IN LCNEC

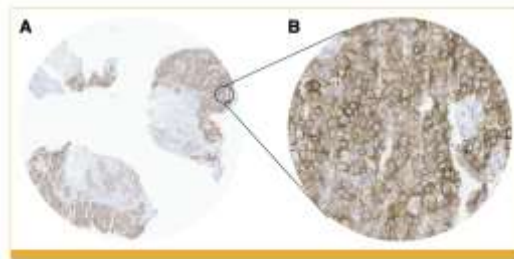
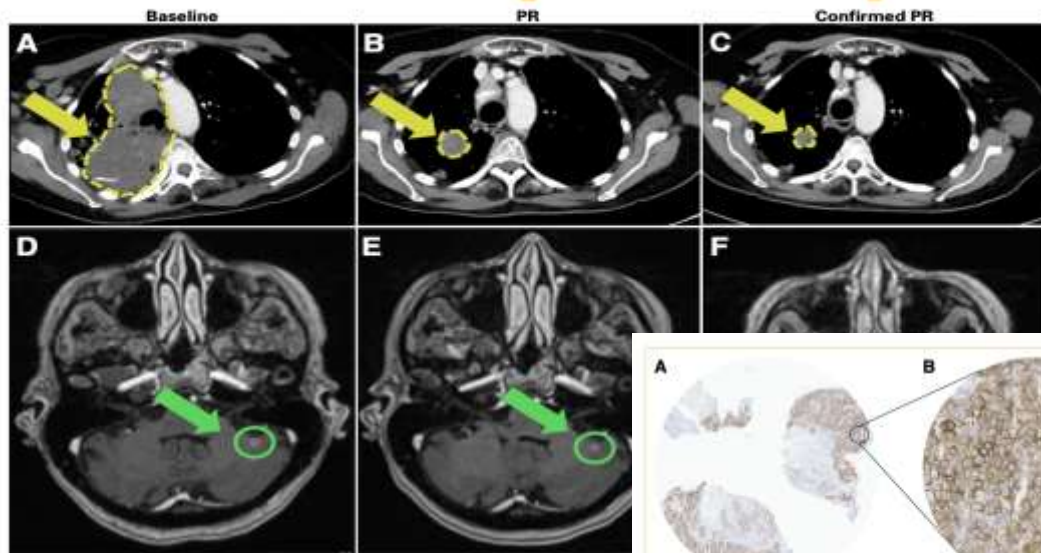
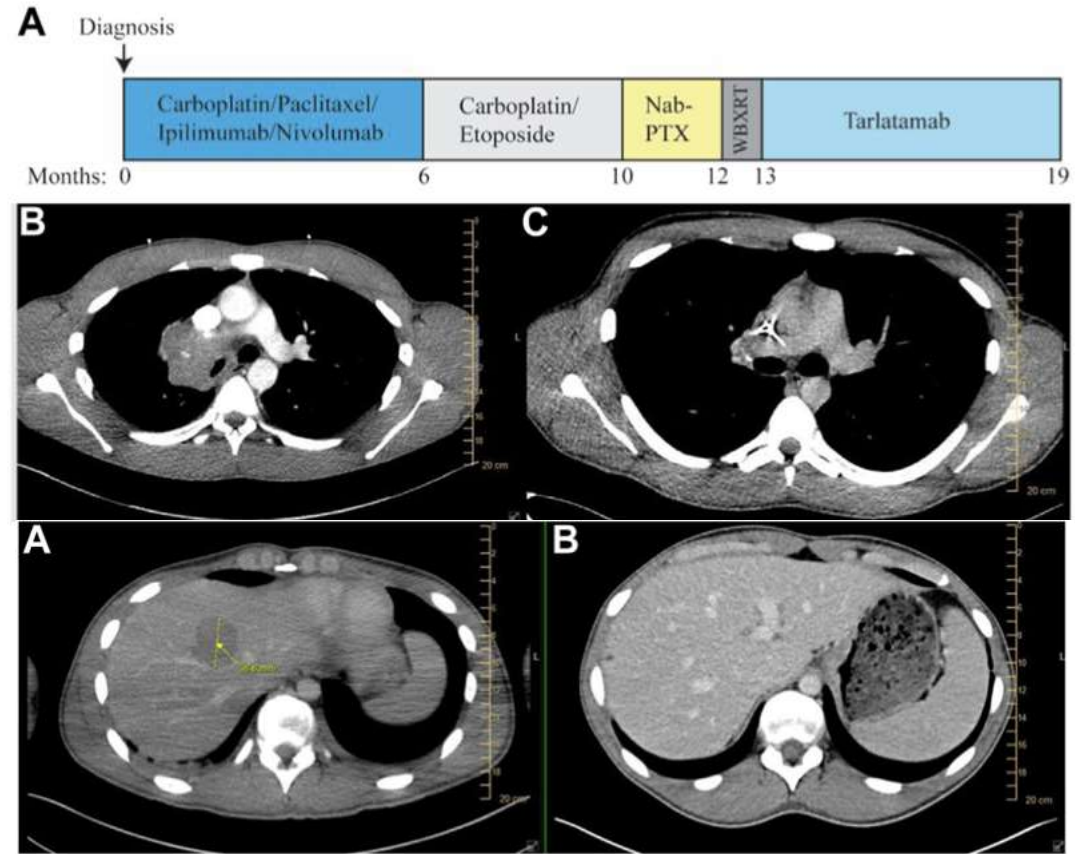


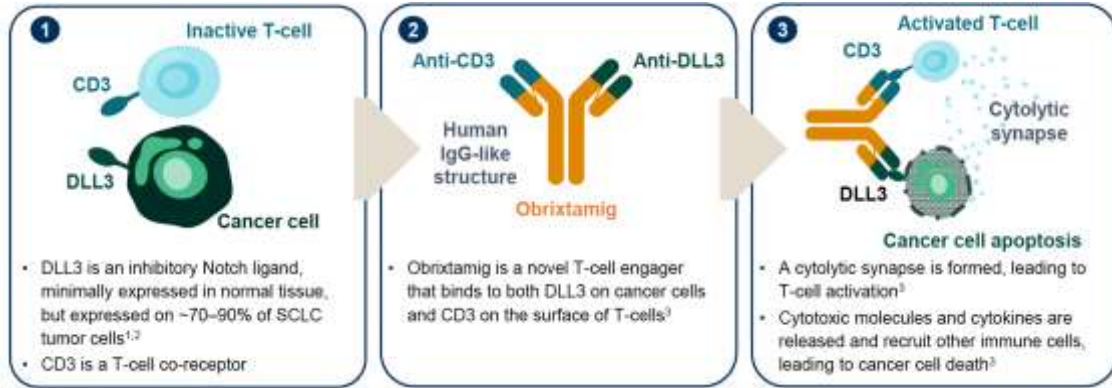
FIG 1. DLL3 immunohistochemical expression on patient's tumor samples, using rabbit anti-DLL3 antibody (clone E3J53; Cell Signaling Technology, Inc, Danvers, MA). Overview of the (A) entire sample tumor and (B) magnified view at 20x.



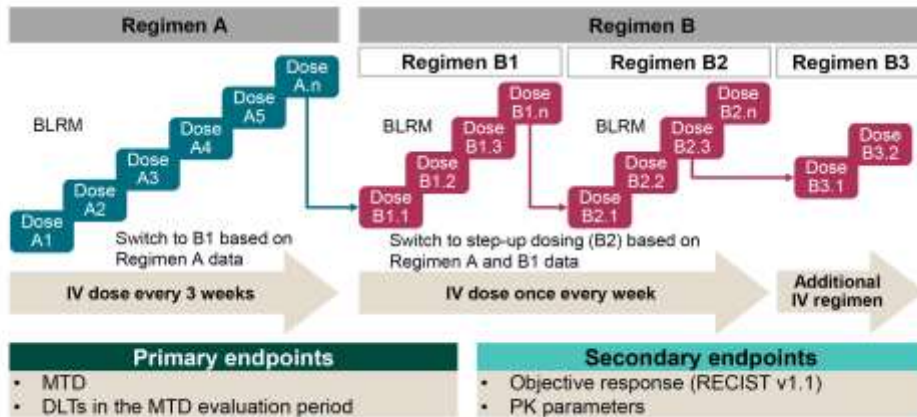
OTHER
NENs

Tarlatamab for Advanced Extrapulmonary Small Cell Carcinoma and NECs (TAURUS) (NCT06816394)
Tarlatamab in Advanced Delta-like 3 (DLL3)-Expressing Tumors Including NENs (NCT06788938)

OBRIXTAMIG (BI 764532): FIH DOSE-ESCALATION TRIAL IN DLL3-EXPRESSING NECs



First-in-human dose-escalation trial of obrixtamig in patients with SCLC, epNECs, or LCNEC-L: NCT04429087



- Key inclusion criteria
Advanced SCLC, epNEC, or LCNEC-L
- DLL3-positive (archived tissue or in-study biopsy) according to central review
- Failed/ineligible for available standard therapies (≥1 line of platinum-based chemotherapy)
- Adequate liver, bone marrow, and renal function
- ECOG PS 0/1

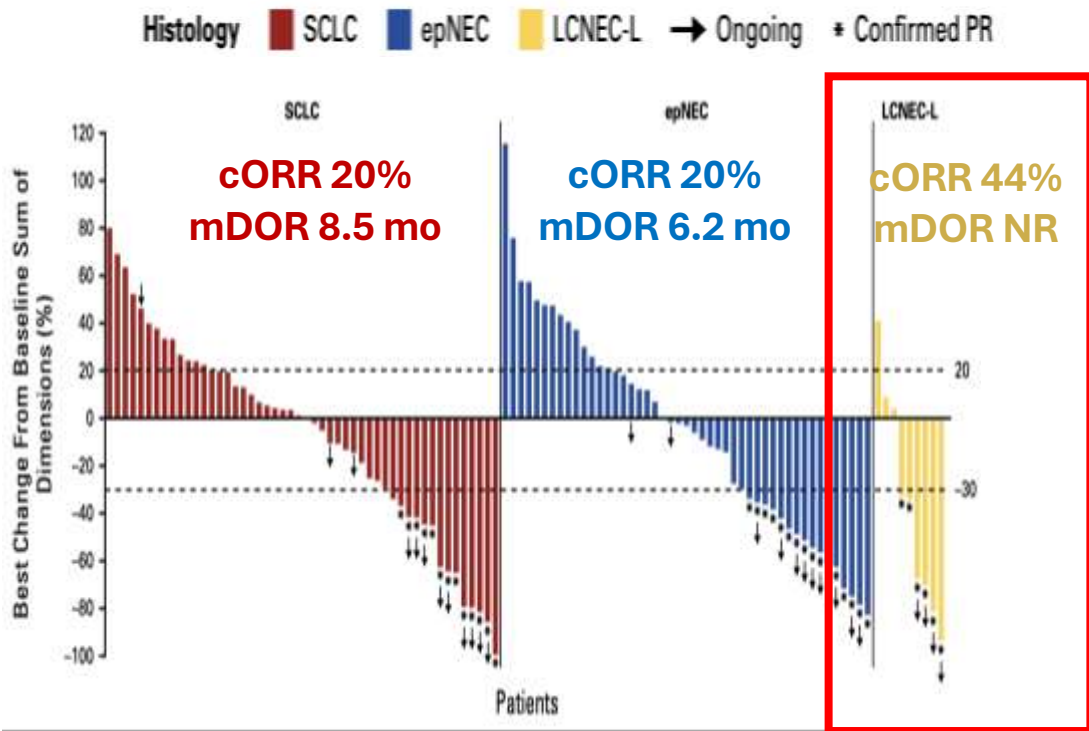
NCT04429087

Treated patients as of 21 February 2024	All N = 168	LCNEC-L n = 14
Median age, years (range)	61 (32–81)	58 (32–79)
Male, n (%)	103 (61)	10 (71)
Prior lines of therapy, n (%) [*]		
1	45 (27)	3 (21)
2	66 (39)	6 (43)
≥3	55 (33)	4 (29)
ECOG PS 0/1, n (%) [†]	46 (27) 13 (67)	2 (14) 11 (79)
Prior anti-PD-1/PD-L1, n (%)	85 (51)	10 (71)
Brain/liver metastases, n (%)	56 (33) 99 (59)	7 (50) 5 (36)

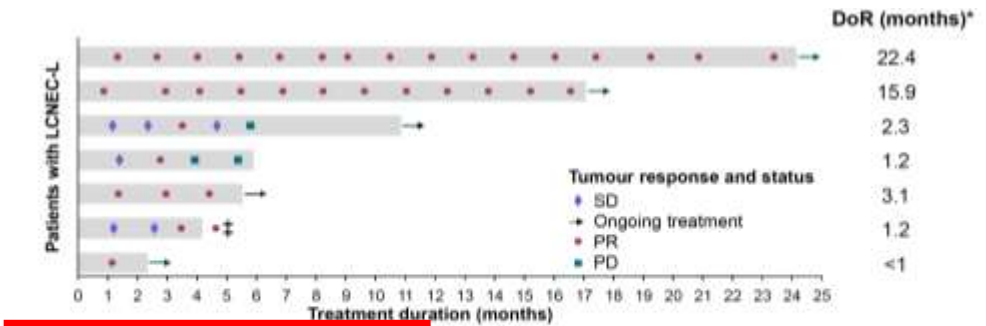
^{*}Not available for 2 patients; [†]Not available for 9 patients

OBRIXTAMIG (BI 764532) IN LCNEC-L

Best ORR by Tumor Type in Patients Treated With Regimens $\geq 90 \mu\text{g/kg}$



Duration of Response in LCNEC Cohort (N = 10)



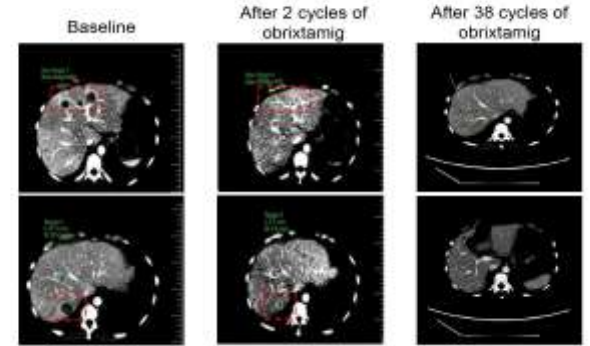
• Five patients (71%) are ongoing treatment

* Data are immature
 *Duration of objective response is defined as the time from first documented CR or PR until the earliest of disease progression or death among patients with objective response according to RECIST v1.1
 † Patient discontinued treatment due to an AE
 Data cutoff: 21 Feb. 2024
 AE: adverse event; CR, complete response; DoR, duration of response; LCNEC-L, large-cell neuroendocrine carcinoma of the lung; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

LCNEC-L case study: current DoR of 22.1 months and ongoing

59-year-old female:

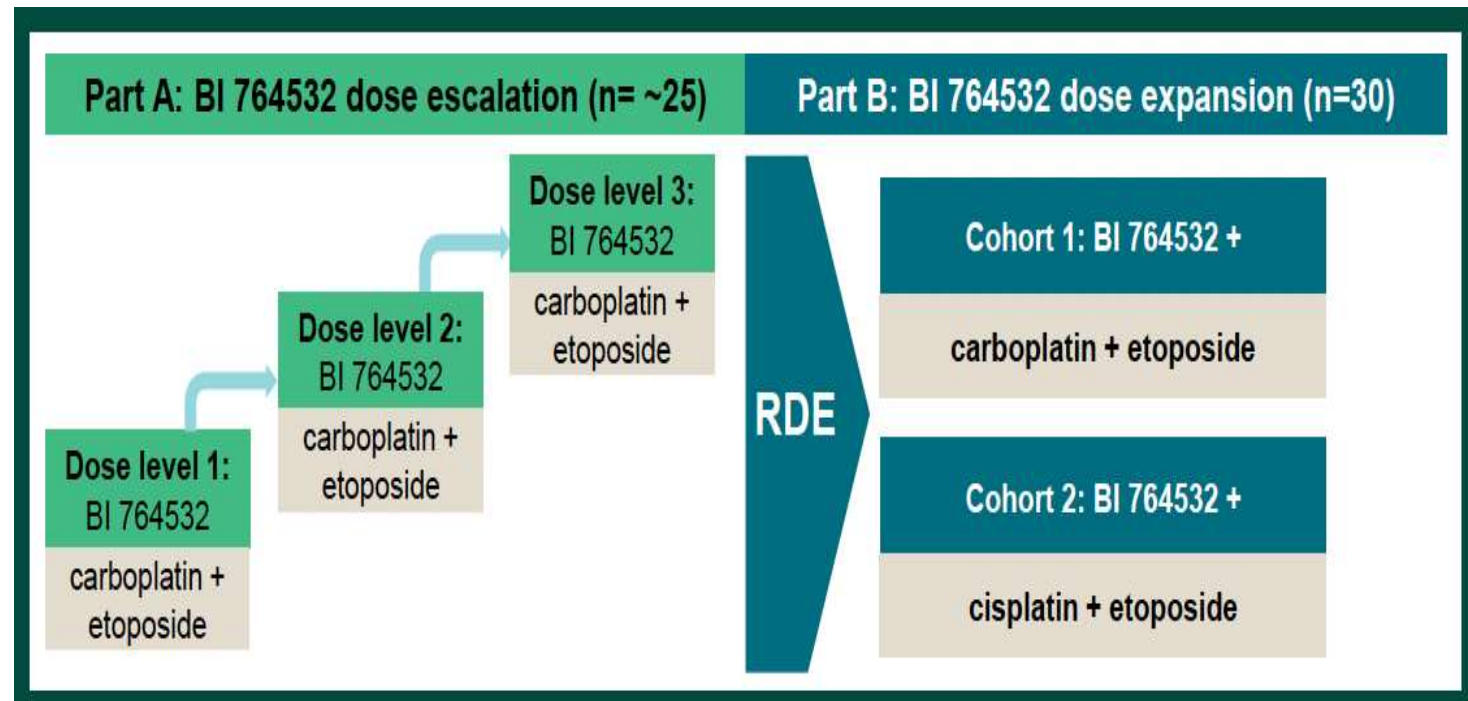
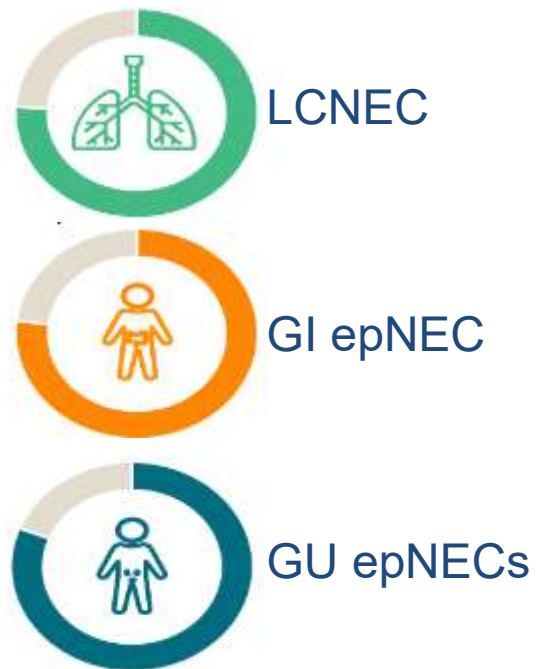
- Initial diagnosis (August 2019)
- 1L: cisplatin + etoposide (until April 2020)
- 2L: carboplatin + etoposide + atezolizumab (until April 2021)
- Mediastinal radiotherapy (April 2021)
- Start of obixtamig (February 2022; see CT imaging)



Responses at $\geq 90 \text{ mg/kg}$ once weekly or once every 3 weeks

New Frontline Combinations with OBRIXTAMIG in DLL3+ NECs

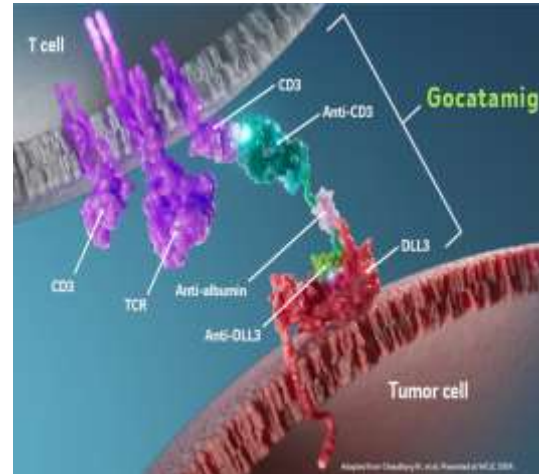
DAREON[®]-7: OBRIXTAMIG + PE (PHASE I), 1L



NCT06132113

GOCATAMIG (MK-6070/HPN328): PHASE I/II IN SCLC AND DLL3-EXPRESSING NECs

- **Gocatamig (MK-6070/HPN328)** is a TriTAC binding **DLL3n T-cell engager**¹
 - **Small size** (~50kDa)
 - **Prolonged half-life** (13.8 days)
- Initial results from the phase 1/2 study promising efficacy at target doses of **12 mg and 24 mg** (N = 41)¹
- Updated results in **SCLC and other NECs** (N = 73)²



Baseline Characteristics

	12 mg Q2W (n=25)	12 mg Q1W (n=11)	24 mg Q2W (n=25)	24 mg Q1W (n=12)	All Cohorts (N=73)
Median age (range), years	62.0 (42-79)	62.0 (48-77)	61.0 (37-75)	64.0 (43-77)	61.5 (37-79)
Male / female, %	60 / 40	55 / 45	36 / 64	75 / 25	53 / 47
ECOG PS 0 / 1, %	44 / 56	55 / 45	36 / 64	58 / 42	45 / 55
Tumor type: SCLC / other NEC, %	40 / 60	64 / 36	52 / 48	75 / 25	53 / 47
Median prior lines of therapy (range)	2.0 (1-6)	2.0 (1-3)	2.0 (1-6)	2.5 (1-5)	2.0 (1-6)
≥3 prior lines of therapy, %	28	45	36	50	37
Prior anti-PD-(L)1 therapy, %	76	82	80	83	79
Prior platinum therapy, %	92	100	92	100	95
Brain / liver metastases, %	52 / 56	45 / 27	44 / 48	50 / 58	48 / 49

Phase 1/2 6070-001 Gocatamig Monotherapy in SCLC and Other NEC

Key eligibility criteria

- Age ≥18 years
- SCLC relapsed/refractory to ≥1 prior line of platinum-based chemotherapy OR
- **Other DLL3-expressing NEC relapsed/refractory to standard therapy (or standard therapy does not exist or is considered inappropriate)**
- ECOG PS 0 or 1

Gocatamig monotherapy dosing

- 12 mg or 24 mg IV Q1W or Q2W with step-up dosing^a

Key study objectives

- Safety and tolerability: AEs, DLTs
- Preliminary antitumor activity: ORR assessed by investigator per RECIST v1.1

Participants with SCLC or other NEC treated in a 12-mg or 24-mg Q1W or Q2W target dose cohort (N=73)^a

12 mg Q2W (n=25)

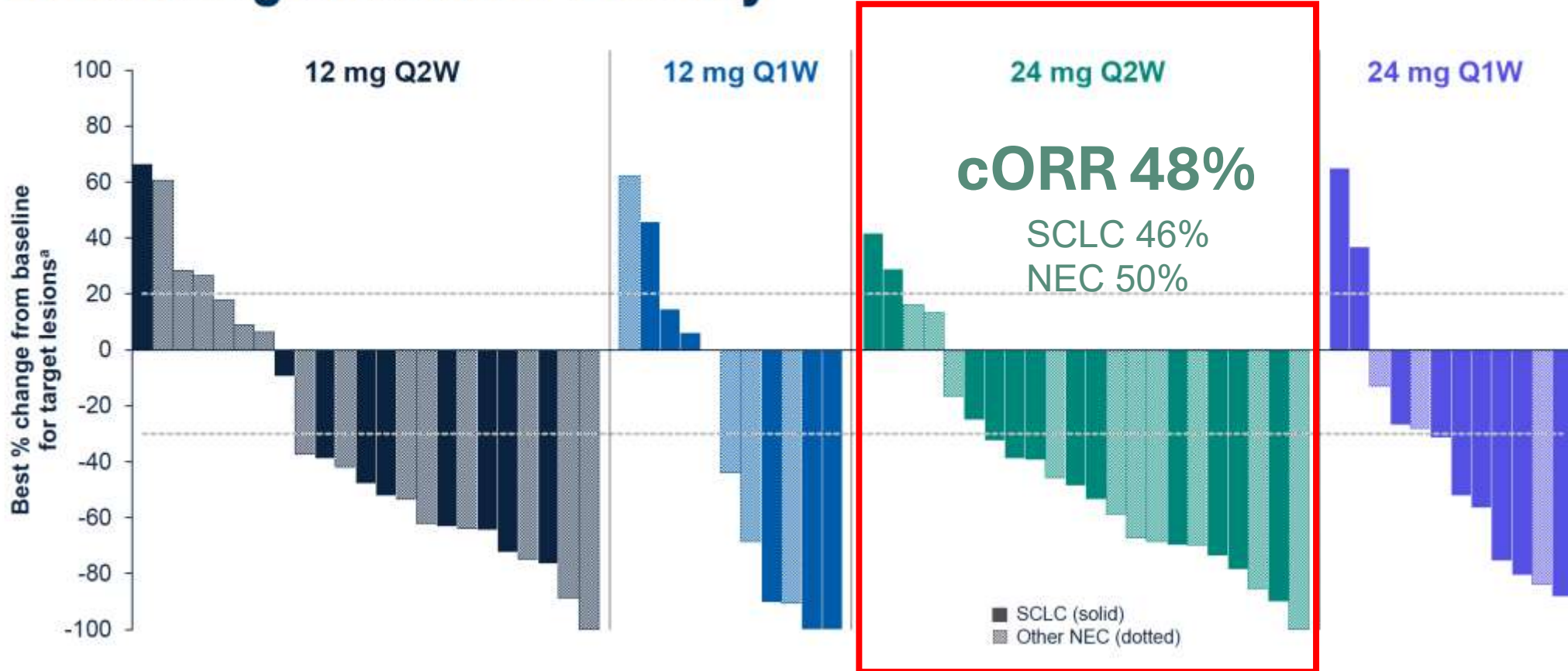
12 mg Q1W (n=11)

24 mg Q2W (n=25)

24 mg Q1W (n=12)

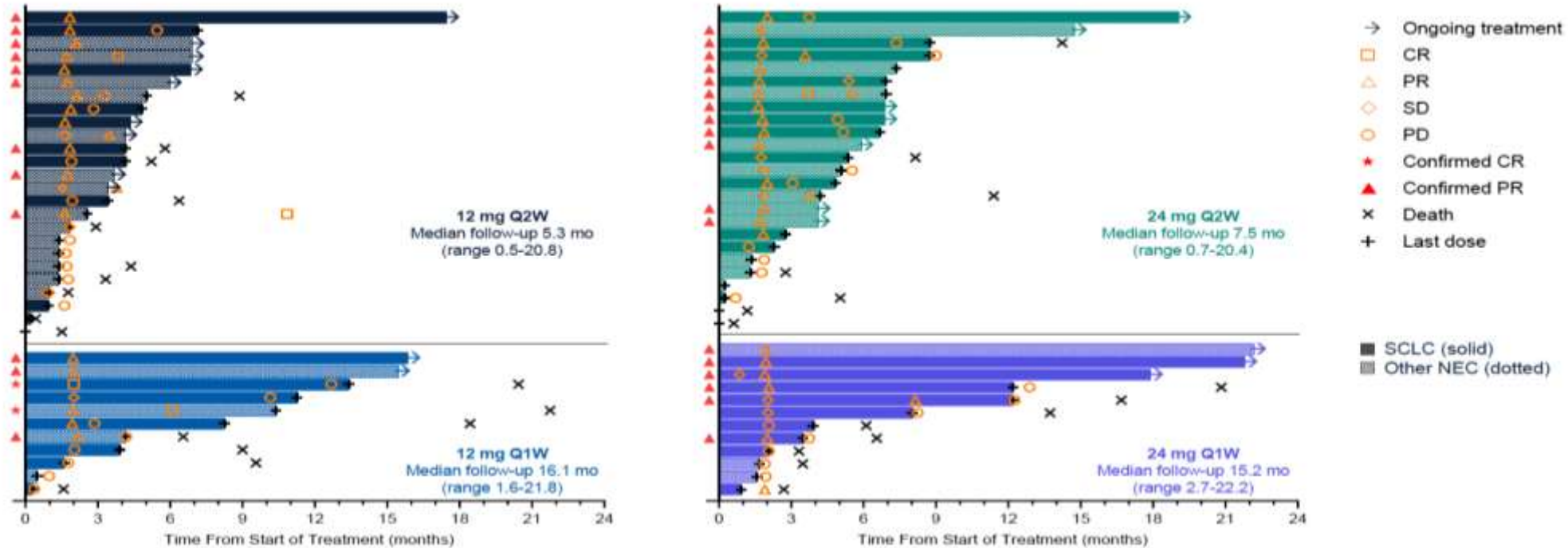
GOCATAMIG (MK-6070/HPN328): PHASE I/II IN SCLC AND DLL3-EXPRESSING NECs

Gocatamig Antitumor Activity



GOCATAMIG (MK-6070/HPN328): PHASE I/II IN SCLC AND DLL3-EXPRESSING NECs

Duration of Treatment and Response^a



Median DOR was 10.8 months (range 1.8-19.8 months) with 17/32 (53%) of responses ongoing at data cutoff

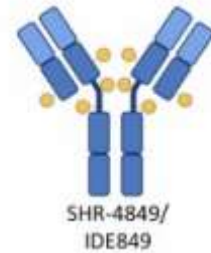
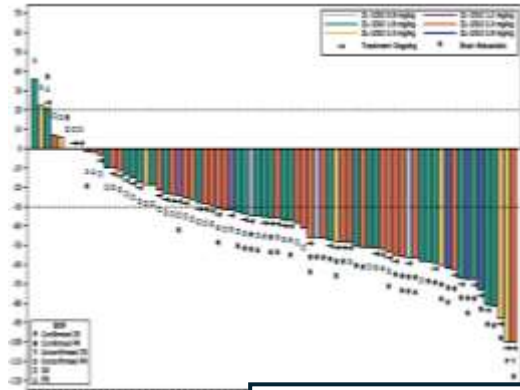
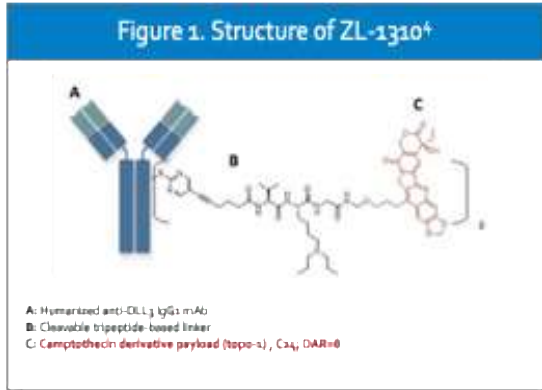
OTHER
NENs

Phase 1/2 HPN328 monotherapy and in combination with IO or I-DXd in DLL3-expressing tumors (NCT04471727)

SEVERAL STUDIES WITH DLL-3 BITES ONGOING IN NECs

NCT05879978	I/II	Obixtamig (BI 764532)	DLL3/CD3 BiTE	Advanced, metastatic, or relapsed SCLC and other NECs expressing DLL3	Obixtamig (BI 764532) in combination with ezabenlimab	Safety	Recruiting
NCT04429087	I	BI 764532	DLL3/CD3 BiTE	Locally advanced or metastatic SCLC, pulmonary LCNEC, and other NECs expressing DLL3	BI 764532 administered by parenteral route	MTD, safety	Recruiting
NCT05916313	I	BI 764532	DLL3/CD3 BiTE	Primary progressive diffuse glioma expressing DLL3	BI 764532 monotherapy administered by repeated IV infusions	Safety	Recruiting
NCT04471727	I/II	MK-6070 (HPN 328)	TriTAC binding DLL3, CD3, and albumin	Relapsed/refractory SCLC, NEPC, high-grade NECs, and other advanced DLL3-expressing malignancies	MK-6070 monotherapy and MK-6070 with atezolizumab or ifinatamab deruxtecan	MTD, RDE, PK, PD, safety	Recruiting
NCT06780137	I/II	Gocatumig (MK-6070)	TriTAC binding DLL3, CD3 and albumin	ES-SCLC after at least one previous line of systemic therapy that included platinum-based chemotherapy	MK-6070 monotherapy and MK-6070 with ifinatamab deruxtecan	Safety, ORR	Recruiting
NCT05461287	I	QLS31904	Bispecific antibody targeting DLL3 and CD3	Advanced solid DLL3-expressing tumors including SCLC and other NECs	QLS31904 IV monotherapy	Safety, MTD, RP2D	Recruiting
NCT05619744	I	RO7616789	Multispecific antibody targeting DLL3 and CD3/CD137	Relapsed ES-SCLC or high-grade NEC of any other origin	RO7616789 IV infusion + tocilizumab rescue therapy for CRS	Safety, ORR, DOR, PFS, OS	Completed
SKYBRIDGE (NCT05652686)	I/II	Peluntamig (PT217)	Bispecific antibody targeting DLL3 and CD47	Unresectable advanced or metastatic SCLC, pulmonary LCNEC, EP-NEC	PT217 monotherapy and in combination with chemotherapy (carboplatin + etoposide) and/or ICI combination (atezolizumab)	MTD, RDE, safety	Recruiting
NCT05978284	I/II	ZG006	Trispecific TCE targeting two distinct DLL3 epitopes and CD3	SCLC and NEC with no standard treatment available/intolerant to standard treatments	ZG006 administered as an IV infusion	MTD, RP2D, safety	Recruiting

OPPORTUNITIES WITH NOVEL DLL3-ADCs ZOCI (ZL-1310) and IDE849 (SHR-4849) IN SCLC



Tumor response in SCLC

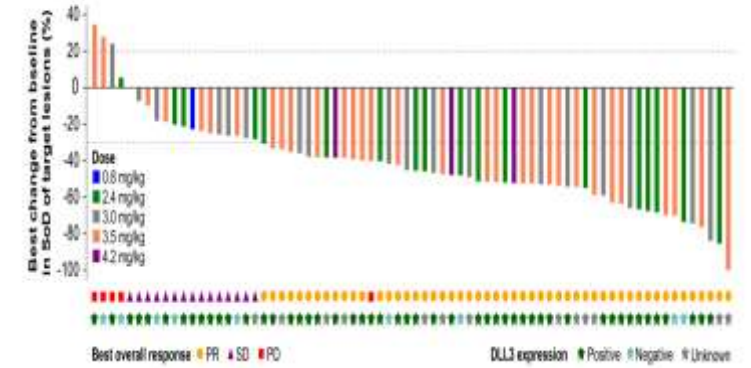


Table 4. Best Overall Response in Dose Escalation

	0.8 mg/kg (N=4)	1.6 mg/kg (N=8)	2.0 mg/kg (N=6)	2.4 mg/kg (N=7)	Total (N=25)
Best Overall Response – n(%)					
Confirmed CR	0	0	0	1 (14%)	1 (4%)
Confirmed PR	3 (75%)	5 (63%)	4 (67%)	3 (43%)	15 (64%)
Stable Disease	0	3 (38%)	2 (33%)	2 (29%)	7 (28%)
Progressive Disease	1 (25%)	0	0	1 (14%)	2 (8%)
ORR – n(%)	3 (75%)	5 (63%)	4 (67%)	4 (57%)	16 (64%)
Disease Control Rate –n(%)	3 (75%)	8 (100%)	6 (100%)	6 (86%)	23 (92%)

Evaluated in SCLC
Reproducible in NEC?
Phase I/II ongoing

	(n=19)	All (n=19)	3.0 mg/kg 2L Setting (n=8)	All (n=18)	3.5 mg/kg 2L Setting (n=16)	All (n=31)	4.2 mg/kg 2L Setting (n=1)	All (n=3)	Total (>2.4 mg/kg) 2L Setting (n=35)	All (n=71)
ORR, n (%)	8 (80.0%)	14 (73.7%)	6 (75.0%)	12 (66.7%)	12 (75.0%)	23 (74.2%)	1 (100.0%)	3 (100.0%)	27 (77.1%)	52 (73.2%)
95% CI	44.4-97.5	48.8-90.9	34.9-96.8	41.0-86.7	47.6-92.7	55.4-88.1	2.5-100.0	29.2-100.0	59.9-89.6	61.4-83.1
Confirmed ORR, n (%)	7 (70.0%)	11 (57.9%)	2 (25.0%)	4 (22.2%)	11 (68.8%)	16 (51.6%)	1 (100.0%)	3 (100.0%)	21 (60.0%)	34 (47.9%)
95% CI	34.8-93.3	33.5-79.7	3.2-65.1	6.4-47.6	41.3-89.0	33.1-69.8	2.5-100.0	29.2-100.0	42.1-76.1	35.9-60.1
Response pending confirmation, n (%)	0	1 (5.3%)	4 (50.0%)	8 (44.4%)	0	1 (3.2%)	0	0	4 (11.4%)	10 (14.1%)
DCR, n (%)	10 (100.0%)	18 (94.7%)	8 (100.0%)	17 (94.4%)	15 (93.8%)	28 (90.3%)	1 (100.0%)	3 (100.0%)	34 (97.1%)	66 (93.0%)
95% CI	69.2-100.0	74.0-99.9	63.1-100.0	72.7-99.9	69.8-99.8	74.2-98.0	2.5-100.0	29.2-100.0	85.1-99.9	84.3-97.7

OPPORTUNITIES WITH DLL3-ADCs: ZL-1310 IN SCLC (PHASE 1)

ADCs							
NCT06179069	I	ZL-1310	DLL3-targeted ADC	Metastatic/ES-SCLC	ZL-1310 as monotherapy, in combination with atezolizumab, and in combination with atezolizumab + carboplatin	Safety	Recruiting
NCT06613009	I	IBI3009	DLL3-targeted ADC	Unresectable/metastatic/ES-SCLC	IBI3009 as monotherapy	Safety	Recruiting
NCT06443489	I	SH-4849	DLL3-targeted ADC	Advanced solid tumors	SH-4849 as monotherapy	Safety, MTD, RP2D	Recruiting
NCT06424665	I	FZ-AD005	DLL3-targeted ADC	Advanced solid tumors (especially SCLC or LCNEC)	FZ-AD005 as monotherapy	Safety, ORR	Recruiting

FINAL REMARKS

- LCNEC has **poor outcomes** with current SoC (chemo +/- IO).
- Both NSCLC(others than pemetrexed)- and SCLC-type chemotherapy are possible: **no consensus**.
- **DLL3** emerging as potential biomarker in LCNEC for targeted therapies (BiTES, ADCs).
- Encouraging preliminary activity with **DLL3 T-Cell engagers**.
- Opportunity to explore **DLL3-ADCs** and novel **combinations** (chemot, IO, ADCs, BiTES).
- Correlative IHC and genomic/transcriptomic characterization required to optimize their clinical use.

THANK YOU

16th
CONGRESS
Lung ON
CANCER
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