Analysis of Delta-Like Ligand 3 (DLL3) Expression Levels and Characteristics of Patients with Advanced Extrapulmonary Neuroendocrine Carcinomas (epNECs) from an Ongoing Phase I Trial

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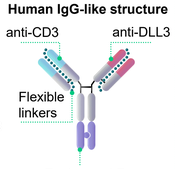
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Introduction

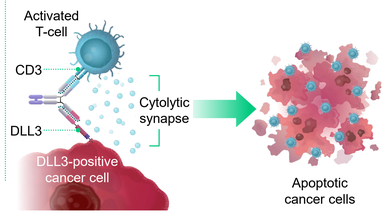
- epNECs are poorly differentiated and aggressive cancers with poor clinical outcomes; median OS is <1 year[1,2]
- Specific expression of DLL3, a Notch ligand, on the surface of epNEC tumor cells makes it a promising therapeutic target[2]
- Based on retrospective analyses, ~80% of epNECs express DLL3[2–4]
- There are a lack of prospective data on DLL3 expression patterns in epNEC and whether the DLL3 expression levels correlate with patient/disease characteristics
- Obrixtamig (BI 764532) is a novel DLL3/CD3 IgG-like T-cell engager. In a Phase I, first-in-human, dose-escalation trial (NCT04429087), it showed promising tolerability and efficacy in patients with heavily pretreated DLL3-positive SCLC, epNEC, or LCNEC-L[5]
- In a previous subanalysis in patients with epNEC, activity was greatest in patients with DLL3^{high} tumors (see Table)[6]
- Here, we provide a detailed analysis of tumor DLL3 expression levels in patients with epNEC who were screened and treated in NCT04429087

Obrixtamig

Human IgG-like structure



Mechanism of action

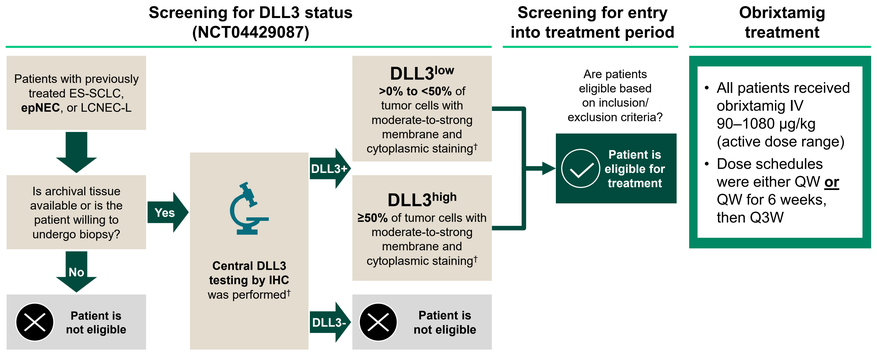


Clinical obrixtamig activity in patients with epNEC by DLL3 status[6]

	DLL3^{high} epNEC (n=30)	DLL3^{low} epNEC (n=30)
Confirmed ORR	40%	3%
DCR	67%	27%

CD3, cluster of differentiation 3; DCR, disease control rate; DLL3, delta-like ligand 3; epNEC, extrapulmonary neuroendocrine carcinoma; Fc, fragment crystallizable; IgG, immunoglobulin G; LCNEC-L, large cell neuroendocrine carcinoma of the lung; ORR, objective response rate; OS, overall survival; SCLC, small cell lung cancer

Methods



- Here we describe the DLL3 screening results for patients with epNEC, and describe the characteristics of patients with DLL3^{high} and DLL3^{low} tumors who were treated with obrixtamig

†Investigational antibody for DLL3 (SP347; Roche Diagnostics). DLL3-, DLL3-negative; DLL3+, DLL3-positive; ES-SCLC, extensive-stage small cell lung cancer; IHC, immunohistochemistry; IV, intravenous; Q3W, every 3 weeks; QW, once weekly

Plain Language Summary

Neuroendocrine carcinomas (NECs) are a diverse group of aggressive cancers found in the lungs and outside the lungs (extrapulmonary NECs [epNECs]). The current treatment option for epNECs is chemotherapy, but survival rates are low

DLL3 is a protein found at different levels on the surface of NEC cancer cells, but not on normal cells, and could be used as a drug target. This trial is testing the safety and effectiveness of a drug called obrixtamig that targets DLL3 and helps the immune system to attack and destroy tumors that have DLL3 on their surface

This analysis shows that most epNEC tumors tested (83%) expressed DLL3. About half of these tumors (51%) had high DLL3 expression levels, supporting the potential use of obrixtamig in treating epNEC

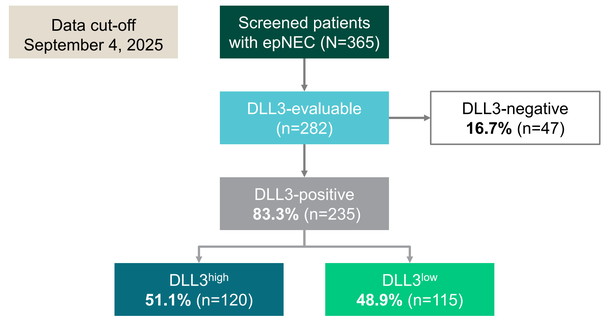
Key Findings and Conclusions

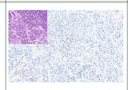
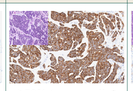
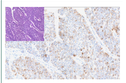
- This is the largest prospectively screened cohort of patients with heavily pretreated epNEC to be assessed for DLL3 expression
- Overall DLL3-positivity rate was 83.3%; with 51.1% of patients having DLL3^{high} tumors
- Some patient characteristics, such as primary tumor location and previous treatment, seem to have impact on DLL3 expression, warranting further analysis
- The high prevalence of DLL3 expression in patients with epNEC underscores DLL3 as a promising candidate for clinical development of targeted therapies such as obrixtamig
- Safety and efficacy of obrixtamig in patients with DLL3-expressing epNEC are being assessed in several ongoing trials, including DAREON®-5 (NCT05882058),[7] DAREON®-7 (NCT06132113),[8] and DAREON®-NEC-1 (NCT07544654)[9]

Objectives

- Assess DLL3 expression levels in a large prospectively screened cohort of patients with different heavily pretreated epNECs (n=365)
- Determine the proportion of DLL3-positive, DLL3-negative, DLL3^{high}, and DLL3^{low} tumors
- Compare the disease and patient characteristics in DLL3^{high} and DLL3^{low} subgroups

Patients



Patients with epNEC	DLL3 expression status, n (%)			
	Positive	Negative	DLL3^{high}	DLL3^{low}
Screened set N=365	235 (83.3)	47 (16.7)	120 (51.1)	115 (48.9)
Staining	 >0% tumor cells‡	 0% tumor cells‡	 ≥50% tumor cells‡	 <50% tumor cells‡

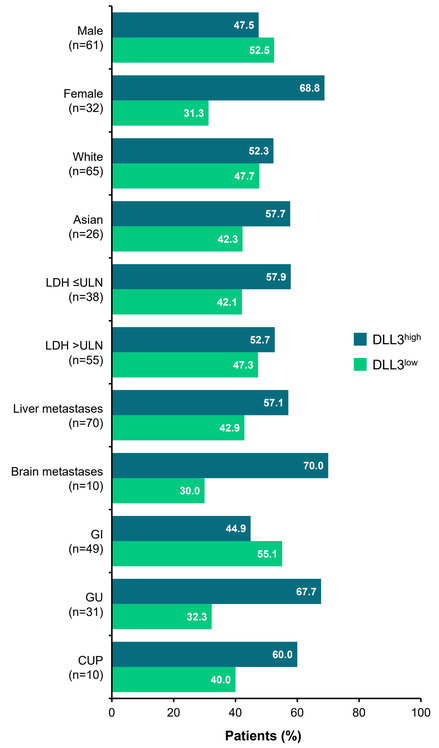
‡Moderate-to-strong membrane and cytoplasmic staining

Out of 365 screened patients with epNEC, 235 (83.3%) were DLL3-positive, broadly in line with previous retrospective analyses[3]

Comparisons of Baseline Characteristics by DLL3 Expression Status (DLL3^{high} vs DLL3^{low}) in Patients with epNEC (Treated Set, n=93§)

Patients, n (%)	DLL3^{high} (n=51)	DLL3^{low} (n=42)
Male / female	29 (56.9) / 22 (43.1)	32 (76.2) / 10 (23.8)
Median age, years (range)	64.0 (29–81)	60.5 (33–77)
Race		
White	34 (66.7)	31 (73.8)
Asian	15 (29.4)	11 (26.2)
Black or African American	2 (3.9)	0
Site of primary tumor		
GI	22 (43.1)	27 (64.3)
GU	21 (41.2)	10 (23.8)
CUP	6 (11.8)	4 (9.5)
Other	2 (3.9)	1 (2.4)
LDH ≤ULN / >ULN	22 (43.1) / 29 (56.9)	16 (38.1) / 26 (61.9)
Number of prior lines of therapy		
1	12 (23.5)	11 (26.2)
2	17 (33.3)	12 (28.6)
3	9 (17.6)	10 (23.8)
>3	13 (25.5)	9 (21.4)
Median duration of prior anticancer Tx, weeks (range)	22 (5–349)	22 (8–148)
Prior treatment		
Radiotherapy	22 (43.1)	11 (26.2)
Surgery	28 (54.9)	24 (57.1)
Anti PD-L1 or anti-PD-1	14 (27.5)	9 (21.4)
Liver / brain metastases	40 (78.4) / 7 (13.7)	30 (71.4) / 3 (7.1)
Median sum of target lesion diameters, mm (IQR)	87.5 (64.0–123.0)	117.3 (66.2–176.0)

- Differences in DLL3^{high} vs DLL3^{low} could be seen in females, patients with baseline brain metastases, and those with GU primary tumor sites



Ongoing Trials of Obrixtamig in Patients with DLL3-Expressing epNEC

DAREON®-5 (NCT05882058)[7]	DAREON®-7 (NCT06132113)[8]	DAREON®-NEC-1 (NCT07544654)[9]
Phase II expansion	Phase Ib expansion	Phase III
Obrixtamig monotherapy, 2L+	Obrixtamig + SoC, 1L	Obrixtamig + SoC vs SoC, 1L
Previously treated **epNEC**	Treatment-naïve **epNEC**, LCNEC-L, or CUP	Treatment-naïve **epNEC**¶
DLL3^{high} status by central testing required	**DLL3-positive** status by central testing required	**DLL3-positive** status by central testing required

§Patients with confirmed DLL3-positive tumors who met protocol-defined eligibility criteria were treated; ¶one mandatory cycle of platinum + etoposide must have been completed prior to randomization.
1L, first-line; 2L+, second- and later-lines; CUP, cancer of unknown primary site; GI, gastrointestinal; GU, genitourinary; IQR, interquartile range; LDH, lactate dehydrogenase; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; SoC, standard of care; Tx, treatment; ULN, upper limit of normal

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