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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Background

epNECs are a heterogeneous and poorly differentiated group of aggressive cancers arising from neuroendocrine cells; they are associated with poor clinical outcomes[1]

- The heterogeneity of epNECs means that recognition, classification, and definition of the optimal treatment approach can be difficult[2,3]
- There is no current standard of care in the second line. Prospective trials for chemotherapy in this setting showed ORRs of ≈0–25%[4]
- Prognosis remains poor, with a median overall survival of <1 year in the second-line setting[5]

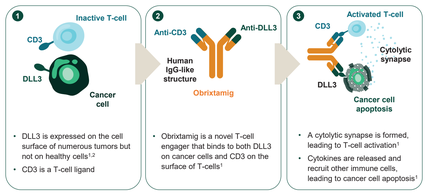
≈80% of epNEC tumors express DLL3[6]

CD3, cluster of differentiation 3; DLL3, delta-like ligand 3; epNEC, extrapulmonary neuroendocrine carcinoma; IgG, immunoglobulin G; ORR, objective response rate

Obrixtamig: a novel IgG-like DLL3-targeting T-cell engager

- Obrixtamig has potent preclinical antitumor activity against DLL3-positive cells and xenograft models[7] **(Figure 1)**

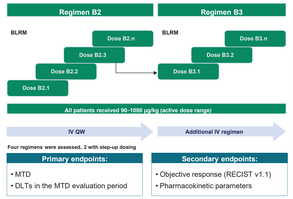
Figure 1. Overview of the mechanism of action of obrixtamig



- DLL3 is expressed on the cell surface of numerous tumors but not on healthy cells[1,2]
- CD3 is a T-cell ligand
- Obrixtamig is a novel T-cell engager that binds to both DLL3 on cancer cells and CD3 on the surface of T-cells[1]
- A cytolytic synapse is formed, leading to T-cell activation[1]
- Cytokines are released and recruit other immune cells, leading to cancer cell apoptosis[1]

Methods

First-in-human dose-escalation trial of obrixtamig in patients with SCLC, epNEC, or LCNEC-L: NCT04429087 (Figure 2)



Patients with epNEC treated with Regimens B2 and B3 are reported here

Key inclusion criteria:

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

Figure 2. NCT04429087 trial design

*DLL3 positive defined as any >0% TC staining at moderate and/or strong intensity
BLRM, Bayesian logistic regression model; DLT, dose-limiting toxicity; IV, intravenous; LCNEC-L, large cell neuroendocrine carcinoma of the lung; MTD, maximum tolerated dose; QW, every week; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SCLC, small cell lung cancer; TC, tumor cell

Patient screening and disposition by DLL3 status

- All patients were required to have DLL3-positive tumors (>0% of TC with moderate to strong staining with an investigational antibody for DLL3 [SP347; Roche Diagnostics])
- DLL3 testing was performed at the Roche CDx CAP/CLIA Laboratory (Tucson)
- Tumors were categorized as either DLL3^{high} (≥50% TC*) or DLL3^{low} (<50% TC*) **(Table 1)**

Table 1. Patient screening and treatment by DLL3 expression levels in epNEC

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*

*TC staining at moderate and/or strong intensity

Patients

Patient baseline characteristics and treatment exposure

- Baseline characteristics were mostly similar in the DLL3^{high} and DLL3^{low} subgroups **(Table 2)**

Table 2. Patient demographic and baseline disease characteristics

Characteristic	DLL3^{high} (n=30)	DLL3^{low} (n=30)
Age, median (range), years	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)†
No. of prior lines of therapy, n (%)‡		
1	10 (33)	6 (20)
2	11 (37)	8 (27)
>2	9 (30)	15 (50)

- Patients with epNEC treated in Regimens B2 and B3 were analyzed (n=60)

data cut-off: June 21, 2024
*ECOG PS data missing: n=6 (n=3 each in DLL3^{high} and DLL3^{low} subgroups); †nasal passage; ‡prior lines of therapy data missing for one patient (DLL3^{low})
CUP, cancer of unknown primary site; ECOG PS, Eastern Cooperative Oncology Group performance status; GI, gastrointestinal; GU, genitourinary

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Key findings and conclusions

- To date, this study represents the largest prospective dataset for a T-cell engager in patients with epNEC
- Obrixtamig showed a manageable safety profile in all patients with epNEC in the trial
- The ORR of 40% is promising in the context of typical response rates with chemotherapy (≈0–25%[4]) and warrants further investigation
- Obrixtamig monotherapy showed encouraging and durable responses in heavily pretreated patients with DLL3^{high} epNEC
- Clinical activity in patients with DLL3^{low} disease warrants further investigation in a combination approach
- An ongoing Phase II trial (DAREON-5) is assessing obrixtamig in patients with relapsed/refractory DLL3^{high} epNEC
- This rationale is further supported by the Orphan Drug Designations (from the European Medicines Agency and FDA) and Fast Track Designations (from the FDA) for epNEC, highlighting its strong potential as a targeted therapy in an area of high unmet need

1

- **DLL3 is widely expressed in epNEC and has been identified as a potential target[8]**
- **DLL3 is minimally expressed in normal tissues[8,9]**
- **Obrixtamig is a novel IgG-like DLL3-targeting T-cell engager**

2

- **The ongoing NCT04429087 Phase I study is assessing obrixtamig in patients with DLL3-positive SCLC, epNEC, or LCNEC-L who had failed standard treatment**
- **Here, we report the safety and efficacy of obrixtamig in patients with epNEC according to DLL3 expression**

3

- **Obrixtamig had a manageable safety profile in all patients with epNEC in the trial**
- **Obrixtamig monotherapy showed encouraging and durable response rates in patients with DLL3^{high} epNEC***

*high expression was defined as ≥50% TC staining at moderate and/or strong intensity
FDA, US Food and Drug Administration

Safety

Overall and by DLL3 expression

- Obrixtamig had a manageable safety profile in all patients with epNEC in the trial **(Table 3)**

Table 3. Treatment-related adverse events by DLL3 expression

	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 neurologic adverse events, including ICANS, n (%)	8 (13)	3 (5)	5 (17)	2 (7)	3 (10)	1 (3)

data cut-off: June 21, 2024
*those reported in ≥15% of all patients are reported
ICANS, immune effector cell–associated neurotoxicity syndrome; TRAE, treatment-related adverse event

Efficacy

Overall and by DLL3 expression

- Patients with DLL3^{high} tumors had a high ORR and DCR **(Table 4)** and greater tumor shrinkage **(Figure 3)**

Table 4. Efficacy outcomes by DLL3 expression

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)

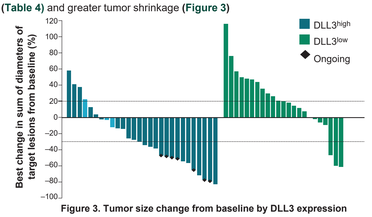


Figure 3. Tumor size change from baseline by DLL3 expression

data cut-off: June 21, 2024
*nine 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 (n=1 each)
CI, confidence interval; DCR, disease control rate; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease

Efficacy (cont)

By DLL3 expression and site of primary tumor

- Encouraging response rates were observed in patients with DLL3^{high} disease regardless of epNEC primary tumor site **(Table 5)**

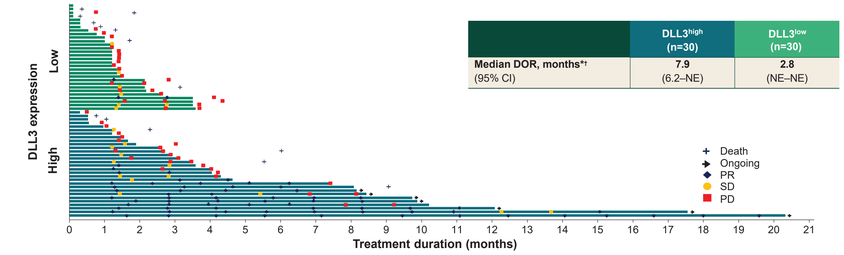
Table 5. Efficacy outcomes by DLL3 expression and primary tumor site

Confirmed response	DLL3^{high}			DLL3^{low}			
	GI (n=14)	GU (n=12)	CUP (n=4)	GI (n=18)	GU (n=8)	CUP (n=3)	Other (n=1)*
ORR, % (95% CI)	43 (21–67)	50 (25–75)	0 (0–49)	6 (1–26)	0 (0–32)	0 (0–56)	0 (0–79)
PR, n (%)	6 (43)	6 (50)	0	1 (6)	0	0	0
DCR, % (95% CI)	64 (39–84)	75 (47–91)	50 (15–85)	28 (13–51)	25 (7–59)	33 (6–79)	0 (0–79)
SD, n (%)	3 (21)	3 (25)	2 (50)	4 (22)	2 (25)	1 (33)	0
PD, n (%)	5 (36)	2 (17)	1 (25)	8 (44)	4 (50)	2 (67)	1 (100)
NE, n (%)	0	1 (8)	1 (25)	5 (28)	2 (25)	0	0

data cut-off: June 21, 2024
*primary tumor site: nasal passage

Duration of response by DLL3 expression

- Obrixtamig demonstrated durable efficacy in patients with DLL3^{high} epNEC **(Figure 4)**



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

Figure 4. Treatment duration and response status by DLL3 expression

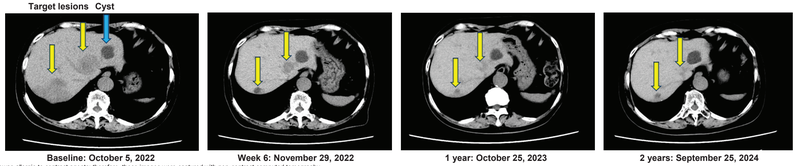
- 7 of 30 (23%) patients with DLL3^{high} disease remained on treatment at the time of data cut-off

data cut-off: June 21, 2024.
*confirmed; †median follow-up: 9.7 months (95% CI: 6.5–13.9)
DOR, duration of response

Case study

DLL3^{high} epNEC*

- A 79-year-old woman, initially diagnosed in September 2021 with neuroendocrine carcinoma of the liver (multiple lesions)
- Received first-line etoposide plus carboplatin, with a best response of SD. Discontinued in May 2022 due to poor tolerability
- Start of obrixtamig: October 2022
- PR after 6 weeks of obrixtamig
- Patient continues obrixtamig treatment with good tolerability 2.5 years later; still in PR



Baseline: October 5, 2022 | **Week 6: November 29, 2022** | **1 year: October 25, 2023** | **2 years: September 25, 2024**

patient was allergic to contrast agents; therefore, these images were captured with non-contrast computed tomography
*we thank Dr Kuboki for providing this case study

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