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Analysis of DLL3 expression levels and characteristics of patients with advanced extrapulmonary neuroendocrine carcinomas from an ongoing phase I trial

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BACKGROUND

Specific delta-like ligand 3 (DLL3) surface expression in extrapulmonary neuroendocrine carcinomas (epNECs) makes it a promising therapeutic target, but prospective data on DLL3 expression patterns in epNEC are lacking. Obrixtamig (BI 764532) is a DLL3/CD3 IgG-like T-cell engager. The first-in-human Phase I trial (NCT04429087) showed obrixtamig activity in DLL3-positive epNEC, especially in DLL3^{high} tumors. We report updated DLL3 expression data and patient/tumor characteristics in epNEC from NCT04429087.

METHODS

DLL3 immunohistochemistry was performed with an investigational DLL3 antibody (SP347) at the Roche CDx CAP/CLIA Laboratory. DLL3 expression was categorized as: negative (absent or weak tumor cell [TC] membrane/cytoplasm staining), positive

(moderate-to-strong staining in any TCs), high (≥50% moderate-to-strong TC staining), or low (<50% moderate-to-strong TC staining).

RESULTS

As of September 4, 2025, 282/365 screened patients with epNEC were DLL3-evaluable, of whom 235 (83.3%) had DLL3-positive tumors (DLL3^{high}: n=120 [42.6%], DLL3^{low}: n=115 [40.8%]); 47 (16.7%) were DLL3-negative. Of 93 DLL3-positive treated patients, 51 (54.8%) had DLL3^{high} and 42 (45.2%) had DLL3^{low} tumors. The prevalence of DLL3^{high} tumors was 47.5%/68.8% in males/females, and 57.1%/70.0% in patients with liver/brain metastases. DLL3^{high} prevalence by primary tumor site, gastrointestinal (GI)/genitourinary (GU)/cancer of unknown primary site (CUP), was 44.9%/67.7%/60.0%. Patient characteristics in obrixtamig-treated DLL3^{high} and DLL3^{low} epNEC subgroups are in Table 1.

Table 1. Baseline characteristics in obrixtamig-treated DLL3^{high}/DLL3^{low} subgroups.

	DLL3^{high} (n=51)	**DLL3^{low} (n=42)**
Male/female, n(%)	29 (56.9)/22 (43.1)	32 (76.2)/10 (23.8)
Primary tumor site: GI/GU/CUP, n(%)	22 (43.1)/21 (41.2)/ 6 (11.8)	27 (64.3)/10 (23.8)/ 4 (9.5)
Lactate dehydrogenase ≤ULN/>ULN, n(%)	22 (43.1)/29 (56.9)	16 (38.1)/26 (61.9)
Prior lines of therapy: 1/2/3/>3, n(%)	12 (23.5)/17 (33.3)/ 9 (17.6)/13 (25.5)	11 (26.2)/12 (28.6)/ 10 (23.8)/9 (21.4)
Median duration of prior anticancer treatment, weeks(range)	22 (5-349)	22 (8-148)
Prior radiotherapy/surgery/anti PD-(L)1, n(%)	22 (43.1)/28 (54.9)/ 14 (27.5)	11 (26.2)/24 (57.1)/ 9 (21.4)
Liver/brain metastases, n(%)	40 (78.4)/7 (13.7)	30 (71.4)/3 (7.1)
Median sum of diameters of target lesions, mm(IQR)	87.5 (64.0-123.0)	117.3 (66.2-176.0)

CONCLUSIONS

In the largest prospectively screened epNEC cohort, high (83.3%) prevalence of DLL3 expression was seen, underscoring DLL3 as a promising target for clinical development of DLL3-targeted therapies, including obrixtamig. Obrixtamig safety/efficacy in patients with DLL3-positive epNEC are being assessed in several ongoing trials, including DAREON®-5 (NCT05882058), DAREON®-7 (NCT06132113), and DAREON®-NEC-1 (NCT07544654), with data expected to inform/support further development.

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