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An ongoing phase 1 trial of obrixtamig in patients with extrapulmonary neuroendocrine carcinomas with high or low DLL3 expression

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BACKGROUND

Delta-like ligand 3 (DLL3) is highly expressed in neuroendocrine carcinomas (NEC). Obrixtamig (BI 764532) is a DLL3/CD3 IgG-like T-cell engager that targets DLL3-positive tumors. NCT04429087 is an ongoing, phase 1, dose-escalation trial of obrixtamig in patients with DLL3-positive pulmonary and extrapulmonary NEC (epNEC) who failed to respond to standard treatment.

METHODS

Obrixtamig was given intravenously in 4 dose-escalation regimens (R): RA (fixed dose every 3 weeks [q3w]); RB1 (fixed dose weekly [qw]); RB2 (step-up dose, then qw); and RB3 (step-up dose, then qw for 3 weeks, then q3w). Efficacy was assessed through objective response rate (ORR) and disease control rate (DCR) using RECIST v1.1. Results are reported for patients who received obrixtamig RB2 or RB3, categorized as having high versus low DLL3, using a threshold of ≥50% of tumor cells stained with an investigational antibody for DLL3 (SP347, Roche Diagnostics).

RESULTS

As of June 21, 2024, 60 patients with epNEC were included (gastroenteropancreatic: 45.0%, genitourinary: 30.0%, other/unknown primary site: 25.0%); 30 each DLL3-high and DLL3-low. Mean age: 63.9 years (DLL3-high), 59.1 (DLL3-low). Baseline characteristics were well-balanced across DLL3 groups. All patients had received prior systemic therapy; 30.0% of DLL3-high and 50.0% of DLL3-low patients had received >2 lines of prior treatment. Efficacy data are shown in the Table. After obrixtamig treatment, patients with high DLL3 expression had greater ORR, DCR, and duration of response (DoR) than DLL3-low patients. Responses were seen most frequently among patients with DLL3-high

gastroenteropancreatic (50.0%) or genitourinary (60.0%) epNECs. Seven DLL3-high patients are still receiving treatment. Most treatment-related adverse events (TRAEs) were mild to moderate for both groups **(Table).**

	DLL3-high (n=30)	DLL3-low (n=30)
ORR, % (95% CI)	40.0 (24.6–57.7)	3.3 (0.6–16.7)
DCR, % (95% CI)	66.7 (48.8–80.8)	26.7 (14.2–44.4)
Median DoR (95% CI), months	7.9 (6.2–NC)	2.8 (NC–NC)
TRAEs, all grade/grade ≥3, (%)	100.0/23.3	90.0/20.0
Cytokine release syndrome, all grade/grade ≥3, (%)	70.0/3.3	60.0/3.3
Neurotoxicity, including immune effector cell–associated neurotoxicity syndrome*, all grade/grade ≥3, (%)	16.7/6.7	10.0/3.3

*Evaluated with a customized MedDRA query
CI, confidence interval; NC, not calculable

CONCLUSIONS

Analyses showed greater obrixtamig efficacy in patients with DLL3-high versus DLL3-low epNEC. The safety profile was manageable and comparable across both groups. The ORR of 40.0% and median DoR of 7.9 months in heavily pretreated epNEC tumors with high DLL3 expression are encouraging and support further development of obrixtamig for this subgroup.

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