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DAREON®-NEC-1: Phase III trial of first-line obrixtamig plus carboplatin and etoposide (SoC) vs SoC in patients with DLL3-positive epNEC

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BACKGROUND

Extrapulmonary neuroendocrine carcinomas (epNECs) are heterogeneous, highly aggressive neoplasms. The current first-line standard of care (SoC) is platinum-based chemotherapy, but prognosis remains poor despite early treatment, indicating an urgent unmet medical need for better treatment options. Delta-like ligand 3 (DLL3) is widely expressed in epNECs. Obrixtamig (BI 764532) is a DLL3/CD3 IgG-like T-cell engager that binds simultaneously to DLL3 on tumor cells and CD3 on T-cells, leading to tumor cell lysis. In the Phase Ib DAREON®-7 trial (NCT06132113), first-line obrixtamig + SoC showed encouraging clinical outcomes and manageable safety in patients with DLL3-positive epNEC. DAREON®-NEC-1 (NCT07544654) is an ongoing Phase III, multicenter, open-label, randomized trial evaluating first-line obrixtamig + carboplatin/etoposide (SoC) vs SoC in patients with DLL3-positive epNEC.

METHODS

Patients with poorly differentiated, unresectable, locally advanced or metastatic epNEC, including neuroendocrine carcinoma (NEC) of unknown primary site, are eligible. Patients must be treatment-naïve except for one mandatory cycle of platinum/etoposide before

randomization and have adequate archival FFPE tumor tissue with DLL3-positive expression status. Patients with asymptomatic CNS metastases are eligible if neurologically stable and radiotherapy is completed more than 14 days prior to randomization. Mixed histologies are permitted if the NEC component is >70% of the tumor tissue. Patients with leptomeningeal disease, carcinomatous meningitis, Merkel cell carcinoma, medullary thyroid carcinoma, or neuroendocrine prostate cancer are not eligible. Patients are randomized 1:1 to SoC with or without obrixtamig; stratification includes by DLL3 expression status ($DLL3^{high}$: ≥50% of tumor cells with moderate-to-strong staining; $DLL3^{low}$: <50%), assessed centrally using an investigational antibody for DLL3 (SP347; Roche Diagnostics). After one cycle of SoC, patients in the obrixtamig + SoC arm receive obrixtamig in a step-up dosing regimen, followed by target dose with SoC treatment for up to 5 cycles, followed by obrixtamig maintenance treatment every three weeks until disease progression, unacceptable toxicity, or other protocol-defined discontinuation criteria, for up to 36 months. SoC is administered per label. Cross-over is not permitted. The primary endpoint is overall survival. Secondary endpoints include progression-free survival (RECIST v1.1; investigator assessed), patient-reported outcomes (EORTC QLQ-C30), and safety. Planned enrolment is approximately 390 patients across 150 sites in North America, South America, Europe, Asia and Oceania.

RESULTS

N/A

CONCLUSIONS

N/A

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