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An ongoing phase I trial of the DLL3/CD3 IgG-like T-cell engager, BI 764532, in patients with DLL3-positive extrapulmonary neuroendocrine carcinomas

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BACKGROUND

Delta-like ligand 3 (DLL3) is highly expressed on small-cell lung cancer (SCLC) tumors and neuroendocrine carcinomas (NECs). BI 764532 is a DLL3/CD3 IgG-like T-cell engager with potent preclinical activity. NCT04429087 is an ongoing phase I dose-escalation trial of BI 764532 in adults with locally advanced/metastatic DLL3-positive (confirmed centrally) SCLC, extrapulmonary NEC, or large cell neuroendocrine lung carcinoma. Here we focus on patients with extrapulmonary NEC.

METHODS

BI 764532 was given intravenously (iv) in 3 regimens: Regimen A (RA; fixed iv dose q3w); RB1 (fixed iv dose qw); RB2 (step-in doses followed by a fixed dose). Treatment continued until progressive disease, unacceptable toxicity, other withdrawal criteria or maximum treatment duration (36 months). Main objective: maximum tolerated dose (MTD) and/or recommended dose for expansion of BI 764532. Other objectives: safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy based on investigator review (RECIST v1.1).

RESULTS

As of 26 March 2023, 107 patients received ≥1 dose (≥ 0.03 µg/kg) of BI 764532 (RA: n=24; RB1: n=10; RB2: n=73). Dose limiting toxicities: 1 patient on RA (Grade 3 confusion) and 4 patients on RB2 (Grade 4 cytokine release syndrome [CRS]; Grade 3 CRS; Grade 3 nervous system disorder and Grade 2 infusion-related reaction). MTD has not been reached and dose escalation is ongoing. 41 patients with extrapulmonary NEC have been treated. NEC baseline characteristics: male, 63%; median age, 60 (range 33–77); ECOG PS 0/1, 37/61%; prior PD1/PD-L1 treatment, 17%; ≥2 prior lines of treatment, 56%. Treatment-related adverse events (TRAEs; any/Grade ≥3): 88/20%. The most common TRAEs (any/Grade ≥3) were: CRS (76/2%); pyrexia (22/0%); dysgeusia (17/0%); fatigue (17/2%) and decreased lymphocytes (15/12%). There were no treatment discontinuations due to TRAEs.

Across all regimens and dose levels, tumor response data were available for 34 patients with extrapulmonary NEC (gastrointestinal: n=18; genitourinary: n=10; unknown origin: n=6). Overall response rate (ORR)/disease control rate (DCR) was 15/41%. In patients who received ≥ target dose of BI 764532 (90 µg/kg; n=25), 5 patients responded (all partial responses; gastrointestinal origin, n=4; genitourinary origin, n=1). ORR was 20% and DCR was 48%.

CONCLUSIONS

BI 764532 showed clinically manageable tolerability; MTD has not been reached. Promising efficacy was observed in patients with extrapulmonary NEC. The study is ongoing.

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