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Updated Phase 1 data for the DLL3/CD3 IgG-like T-cell engager BI 764532 in DLL3-positive tumors: focus on extrapulmonary neuroendocrine carcinomas

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BACKGROUND

Delta-like ligand 3 (DLL3) is expressed on several cancers including extrapulmonary neuroendocrine carcinomas (epNECs). BI 764532 is a DLL3/CD3 immunoglobulin G (IgG)-like T-cell engager. This ongoing phase 1 trial (NCT04429087) aims to determine the maximum tolerated dose (MTD) and/or recommended dose for expansion of BI 764532 in patients with locally advanced/metastatic DLL3-positive small cell lung cancer, epNEC, or large cell neuroendocrine lung carcinoma. Other objectives include safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy (investigator review per Response Evaluation Criteria in Solid Tumors v1.1). Here, we focus on patients with epNEC.

METHODS

BI 764532 was given intravenously in four regimens: Regimen A (RA; fixed dose Q3W); Regimen B1 (RB1; fixed dose QW); and Regimens B2 and B3 (RB2 and RB3; step-in dose, followed by target dose). Treatment continued until disease progression, unacceptable toxicity, other withdrawal criteria, or maximum treatment duration (36 months).

RESULTS

As of August 14, 2023, 132 patients had received ≥1 dose of BI 764532 (RA: n=24; RB1: n=10; RB2: n=79; RB3: n=19). Most patients (60%) were male, median (range) age was 60 (32–81) years, and 28% and 71% had ECOG performance status of 0 and 1, respectively. Around half (48%) of patients had prior PD1/PD-L1 treatment, and 70% had ≥2 prior lines of treatment.

Dose-limiting toxicities were observed in one patient on RA (Grade 3 confusion) and five patients on RB2 (Grade 4 cytokine release syndrome [CRS], Grade 3 CRS, Grade 3 immune effector cell-associated neurotoxicity syndrome [ICANS], Grade 3 nervous system disorder, Grade 2 infusion-related reaction). MTD was not reached. Fifty-four patients with epNEC have been treated (gastrointestinal [GI]: n=28; genitourinary [GU]: n=18; unknown origin: n=7; missing: n=1). Treatment-related adverse events (TRAEs) were observed in 94% of patients (GI: 93%; GU: 94%), with 19% experiencing Grade ≥3 TRAEs (GI: 21%; GU: 17%). The most common TRAEs (any/Grade ≥3) were CRS (72%/4%), pyrexia (30%/0%), and dysgeusia (19%/0%). There was one Grade 5 TRAE (ICANS). Objective response rate/disease control rate in patients who received clinically active doses of BI 764532 was: overall (n=98): 28%/54%; epNEC group (n=41): 29%/49% (GI [n=21]: 29%/43%; GU [n=14]: 36/57%; unknown origin [n=6]: 17%/50%). Seven (58%) of the responding patients with epNEC were still on treatment.

CONCLUSIONS

BI 764532 showed clinically manageable tolerability; MTD was not reached. Promising efficacy was observed in patients with epNEC. The study is ongoing, and updated efficacy and safety data will be presented.

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