BDB001, A TOLL-LIKE RECEPTOR 7 AND 8 (TLR7/8) AGONIST, CAN BE SAFELY ADMINISTERED INTRAVENOUSLY AND SHOWS CLINICAL RESPONSES IN ADVANCED SOLID TUMORS

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Background TLR agonists mediate antitumor activity through dendritic cell (DC) activation. Most TLR agonists in development are administered intratumorally allowing for less than 30% of advanced solid tumor to be treated. BDB001 is an intravenously administered novel TLR7/8 agonist that activates plasmacytoid and myeloid DCs and has shown to have activity in preclinical studies. Here we report on BDB001 administration in patients with advanced solid tumors.

Methods BDB001-101 is a Phase 1, open label, dose escalation/expansion trial of BDB001 administered intravenously weekly in patients with advanced solid tumors. The primary endpoint was safety and tolerability. Secondary endpoints included efficacy, pharmacokinetics and pharmacodynamic profiling of immune activation.

Results Thirty-six subjects with 16 different tumor types were enrolled across 5 dose levels. Seventy seven percent were female, median age was 66 years (range, 38–88), median number of prior therapies was 4 (range, 0–12), and 61% of tumors had progressed on prior anti-PD-(L)1 therapy. BDB001 was well tolerated and a maximum tolerated dose was not reached. Eleven (30.5%) subjects had no treatment related adverse events (AEs) and the majority of AEs were Grade 1 or 2. Three (8.3%) subjects had Grade 3 AEs, including 2 with a cytokine release syndrome, both of whom were clinically stable and had symptoms fully resolved within 2 to 5 days. There were no Grade 4 or 5 AEs. The most common AEs included chills/rigor (19.4%), fever (19.4%), fatigue (11.1%), nausea (11.1%) and pruritus (11.1%). Of 32 subjects evaluable for efficacy, best overall response rate was: 6% durable partial response, 12% partial response, 56% stable disease, 38% progressive disease, for a disease control rate of 62%. Durable responses were seen in renal cell carcinoma and non-small cell lung cancer. Interestingly, clinical activity favored subjects with tumors that had progressed on prior anti-PD-(L)1 therapy, compared to prior DNA-damaging chemotherapy, within 6 months of BDB001 initiation. Median time on treatment was 12.1 weeks (range, 3.1 – 68.0). Transcriptional profiling showed up-regulation of interferon inducible genes, activation of dendritic cells and macrophages. BDB001 also significantly increased serum levels of interferon gamma and interferon inducible protein-10 (IP-10).

Conclusions Intravenously administered BDB001 monotherapy was well tolerated. Clinical responses were achieved, supported by BDB001-induced immune activation. Preliminary findings suggest that BDB001 is a promising therapeutic option for patients with tumors that progress on anti-PD-(L)1 therapy. BDB001 is also being evaluated in combination with pembrolizumab (anti-PD-1, NCT03486301) and with atezolizumab (anti-PD-L1, NCT04196530).

Trial Registration NCT03486301

Ethics Approval This study was approved by the institutional review boards at the four participating institutions. All subjects signed informed consent before enrolling in the clinical trial.