BDB001, a Toll-Like Receptor 7 and 8 (TLR 7/8) agonist, can be safely administered intravenously and shows clinical responses in advanced solid tumors

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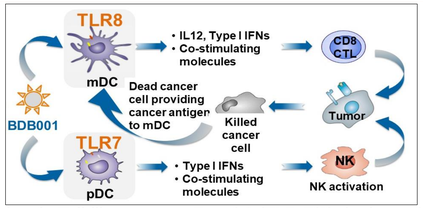
Background / Study Design

BDB001 is an immune modulator capable of generating both innate and adaptive immunity against tumors



- BDB001 is a small molecule Toll-like receptor 7 and 8 (TLR 7/8) dual agonist capable of activating dendritic cells (DCs).
- Activation of TLR 7 (plasmacytoid DC) and TLR 8 (myeloid DC) results in induction of type I interferon (IFN) inducible pathways, critical steps for initiating both innate and adaptive immunity against tumors.
- Unlike most intratumoral TLR agonists in development, BDB001 is administered intravenously allowing for systemic activation of DCs and treatments of tumors more broadly.

A multi-center, open-label, dose escalation / dose expansion Phase 1 study of BDB001 monotherapy

Subjects with histologically-confirmed, unresectable or metastatic solid tumors that have relapsed or are refractory to SoC

❖ Monotherapy dose escalation phase has been completed

Dose Level 5
Dose Level 4
Dose Level 3
Dose Level 2
Dose Level 1

- BSA dosing based on the Mosteller formula
- DLT period = Cycle 1 (21 days)

BDB001 (IV qweek in 3-week cycles) (n=36)

Primary Endpoints

- Safety and tolerability of BDB001 monotherapy

Secondary Endpoints

- Dose-limiting toxicity (DLT) or maximum tolerated dose (MTD) for BDB001 monotherapy
- Pharmacokinetic parameters of BDB001
- Pharmacodynamic (PDy) effects of BDB001 monotherapy
- Correlation between PDy effects and activity of BDB001 monotherapy
- Objective response rate as defined by irRECIST

Patient Characteristics	No.
Gender	
Female	24 (67%)
Male	12 (33%)
Age median, range	**66 yrs (38-88)**
Tumor type	
NSCLC	7
Uterine	6
Ovarian	4
Head and Neck squamous cell carcinoma	3
Pancreas	3
Breast cancer	2
Melanoma	2
Renal cell carcinoma	2
Carcinoid	1
Cholangiocarcinoma	1
Colorectal	1
Esophageal	1
Liposarcoma	1
Small cell lung cancer	1
Urothelial carcinoma	1
Prior lines of systemic therapy median, range	**4 (0-13)**
Prior anti-PD-1/PD-L1 therapy	**22 (61%)**

Safety and Efficacy Results

BDB001 was well tolerated and MTD was not reached

Treatment related AEs occurring in > 5% of subjects or ≥ Grade 2, (N=36)				
Adverse events (AEs)	Subjects with AEs, n (n/N, %)			
	All grades	Grade 1	Grade 2	Grade 3
All AEs	25 (69.4)			
Fever	7 (19.4)	4 (11.1)	2 (5.6)	1 (2.8)
Chills/Rigors	7 (19.4)	5 (13.9)	1 (2.8)	1 (2.8)
Fatigue	4 (11.1)	2 (5.6)	2 (5.6)	
Nausea	4 (11.1)	3 (8.3)	1 (2.8)	
Pruritus	4 (11.1)	3 (8.3)	1 (2.8)	
Cytokine Release Syndrome (CRS)	3 (8.3)		1 (2.8)	2 (5.6)
Dyspnea	3 (8.3)	1 (2.8)	2 (5.6)	
Infusion Related Reaction	3 (8.3)	1 (2.8)	2 (5.6)	
Vomiting	3 (8.3)	1 (2.8)	2 (5.6)	
Diarrhea	3 (8.3)	2 (5.6)	1 (2.8)	
Rash	3 (8.3)	3 (8.3)		
Headache	2 (5.6)	2 (5.6)		
Diabetic Ketoacidosis	1 (2.8)			1 (2.8)¶

¶ Subject with diabetes had a Grade 3 diabetic ketoacidosis 7 weeks after discontinuing BDB001 treatment

As of June 17, 2020

Dose levels	Patients (N)	BDB001-related AE			
		None n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)*
1	8	2 (25)	5 (63)	3 (38)	1 (13)
2	8	2 (25)	3 (38)	4 (50)	0 (0)
3	7	2 (29)	4 (57)	2 (29)	0 (0)
4	11	5 (42)	4 (33)	5 (42)	0 (0)
5	2	0 (0)	1 (50)	1 (50)	2 (100)
Total	36	11 (31)	17 (47)	15 (42)	3 (8)

- Over 30% of the subject did not experience any treatment-related AE's (TRAE's) and there were no Grade 4 or 5 TRAE's.
- Most common TRAE's were immune-related (fever, chills/rigors, fatigue, nausea, and pruritus).
- 2 subjects (Dose Level 5) had a grade 3 CRS – one had Grade 3 fever and chills associated with CRS.
  - Both subjects did not require vasopressors and were clinically stable on standard supportive care – fully resolved within 2-5 days.
- No dose-dependent increase in toxicity observed, MTD was not reached.

BDB001 as monotherapy induces clinical responses especially in subjects with anti-PD-(L)1 refractory tumors

Responses in evaluable subjects (N=32)

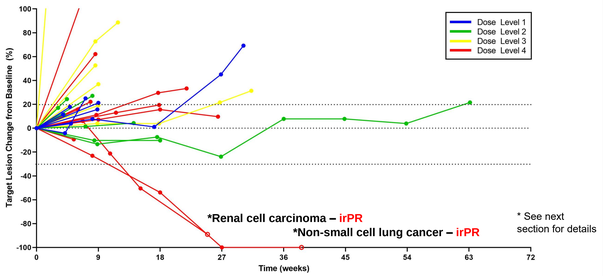
Best Overall Response (BOR)	Subjects (%)
Complete response (irCR)	0 (0)
Partial response (irPR)	2 (6) ¶
Stable disease (irSD)	18 (56) *
Progressive disease (irPD)	12 (38)
Disease control rate, DCR (irCR+irPR+irSD)	20 (62)

As of June 17, 2020

¶ Durable partial responses in NSCLC and RCC subjects

* 7 subjects with prolonged stable disease (> 18 weeks)

The 2 DLT subjects and 2 subjects who did not complete the DLT period for non-treatment related reasons were not evaluable for efficacy



* See next section for details

BDB001 Monotherapy at Dose Level 4

BOR	Subjects (%) N=11
Complete response (irCR)	0 (0)
Partial response (irPR)	2 (18) ¶
Stable disease (irSD)	5 (45) *
Progressive disease (irPD)	4 (36)
Disease control rate, DCR (irCR+irPR+irSD)	7 (64)

¶ Durable partial responses in NSCLC and RCC subjects

* 3 subjects with prolonged stable disease (> 18 weeks)

Subjects with anti-PD-(L)1 refractory tumors

BOR	Subjects (%) N=22
Complete response (irCR)	0 (0)
Partial response (irPR)	2 (9)
Stable disease (irSD)	12 (55) *
Progressive disease (irPD)	8 (36) †
Disease control rate, DCR (irCR+irPR+irSD)	14 (64)

* 4 subjects with prolonged stable disease (> 18 weeks)

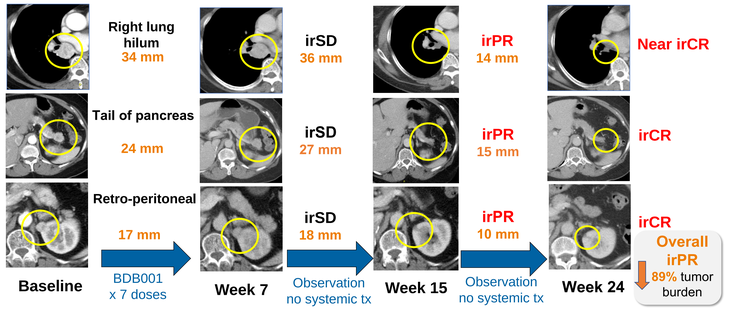
† **No irPD** in subjects whose tumors progressed on anti-PD-(L)1 within 6 months of BDB001 initiation (DCR of 100%)

- At **BDB001 Dose Level 4**
  - **Durable irPR 18% (2/11)**
  - **DCR** of **64%**
- **Clinical responses favored subjects with tumors that progressed on anti-PD-(L)1** within 6 months prior to BDB001 initiation

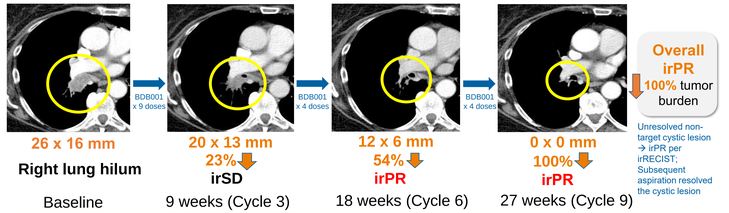
Efficacy and Pharmacodynamic Results

BDB001 shows clinical activities as a single agent

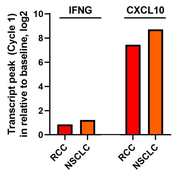
- **Metastatic Renal Cell Carcinoma**: 76-year-old female – **BDB001 at Dose Level 4**
- Progressed on 5 previous lines of systemic therapy, including nivolumab for 9 months prior to starting BDB001



- **Metastatic NSCLC adenocarcinoma**: 72-year-old female, prior smoker – **BDB001 at Dose Level 4**
- Progressed on atezolizumab +/- TIGIT mAb prior to starting BDB001



BDB001 induces robust immune activation



- Whole-blood transcription analysis showed upregulation of CXCL10 (interferon-inducible protein 10) in both responders (RCC and NSCLC).
- BDB001 induced DC activation and upregulation of IFN-mediated genes (not shown).

Discussion / Conclusions

- Seven and Eight Biopharma's systemic delivery of TLR 7/8 dual agonist BDB001 is first-in-class
- BDB001 was delivered safely intravenously and a therapeutic window was established
- BDB001 monotherapy resulted in clinical responses in subjects with renal cell carcinoma and non-small cell lung cancer and showed evidence of robust immune activation
- Dose escalation of BDB001 in combination with pembrolizumab (NCT03486301) and atezolizumab (NCT04196530) is ongoing
- Phase 2 trial of BDB001 monotherapy at Dose Level 4 is planned in subjects with anti-PD-(L)1 refractory tumors

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