Pharmacokinetic/Biomarker Analysis of the Toll-Like Receptor 7 and 8 (TLR7/8) Agonist EIK1001 in Phase 1 Studies in Participants with Solid Tumors

ABSTRACT #7172

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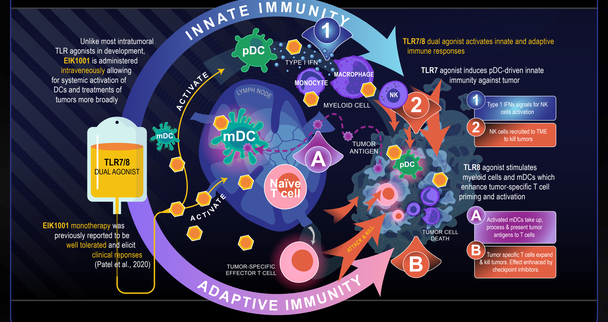
Background

- Immune checkpoint inhibitors (ICIs) relieve immunosuppression of tumor-reactive T cells and enhance antitumor immune response; however, not all patients benefit and some become refractory.
- Stimulation of both TLR7 (innate immunity) and TLR8 (adaptive immunity) provides another pathway, distinct from effects on checkpoint proteins, to enhance antitumor T-cell activity alone or in combination with ICIs.
- EIK1001 (previously known as BDB001 during development) is a TLR7/8 agonist that stimulates myeloid and plasmacytoid dendritic cells.



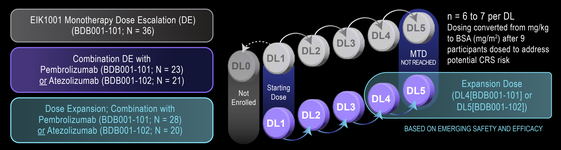
Objectives

- To characterize EIK1001 pharmacokinetics (PK) in participants with advanced solid tumors including effects of intrinsic and extrinsic factors
- To explore the relationship between EIK1001 exposure and cytokine biomarkers
- To explore the benefit-risk of EIK1001 to treat patients with solid tumors

Study Designs

- EIK1001 has been studied in Phase 1, 3 + 3 dose-escalation studies in participants with solid tumors as monotherapy (BDB001-101; NCT034863010), in combination with pembrolizumab (BDB001-101), and in combination with atezolizumab (BDB001-102; NCT04196530) (Figure 1) (Patel et al., 2020; 2021a; 2021b)
- PK sample collection: pre-dose and at 0.5, 1, 2, 4, 6, 8, 12 and 24 hr post-dose on Cycle 1 Day 1 (C1D1) and C1D8. On C2D1 and C3D1, pre-dose and 0.5 hr post-dose
- Cytokine biomarker sample collection:
  - BDB001-101: pre-dose, 4 and 8 hr post-dose on C1D1, C1D8, C2D1, C2D8, C3D1, C6D1
  - BDB001-102: pre-dose and 0.5, 1, 2, 4, 6, 8, 12, and 24 hr post-dose on C1D1, C1D8; on C3D1 and C6D1: pre-dose and 4 and 8 hr post-dose

Figure 1: Study Designs for BDB001-101 and BDB001-102



- Participants who received at least one dose of EIK1001 and who had at least one measurable EIK1001 plasma concentration were included in the analysis population
- Five dose levels were studied. No maximum tolerated dose was identified (Patel et al., 2020)
- Data extraction from June 7, 2023 included the last patient last visit May 5, 2023

Demographics & Baseline Characteristics

A total of 94 participants across 5 dose levels were analyzed (Table 1).

Participants characteristics included 23/94 patients (24%) classified as obese (BMI > 30 kg/m^2) (Table 2).

Table 1: Aggregate Number of Participants by Dose Level

	Overall (N=94)
Dose Level 1	16 (17.0%)
Dose Level 2	18 (19.1%)
Dose Level 3	24 (25.5%)
Dose Level 4	35 (37.2%)
Dose Level 5	1 (1.1%)

Table 2: Aggregate Participant Demographics and Baseline Characteristics

	Overall (N=94)
Sex	
Male	37 (39.4%)
Female	57 (60.6%)
Race	
White	85 (90.4%)
Black or African American	2 (2.1%)
Asian	2 (2.1%)
Hawaiian or Pacific Islander	1 (1.1%)
Other	4 (4.3%)
Weight Class (BMI kg/m^2)	
Underweight (BMI<18.5)	3 (3.2%)
Normal weight (BMI 18.5- 24.9)	28 (29.8%)
Overweight (BMI 25 – 29.9)	40 (42.6%)
Obese (BMI ≥ 30)	23 (24.5%)
ECOG	
0	32 (34.0%)
1	61 (64.9%)
2	1 (1.1%)

Pharmacokinetic Data Analysis

- Integrated data over the 3 treatment groups were analyzed using a population PK approach (Phoenix NLME Version 8.3, Certara, Princeton, NJ)
- The effects of intrinsic and extrinsic factors were tested using stepwise covariate modeling with significance level 0.05 for forward addition
- Empirical Bayes estimates of EIK1001 were used to generate post-hoc PK estimates of AUC and Cmax at steady state
- Data were best described by a two-compartment model (Figure 2) and fitted parameters were calculated (Table 3).

Figure 2: Schematic diagram of the two-compartment model

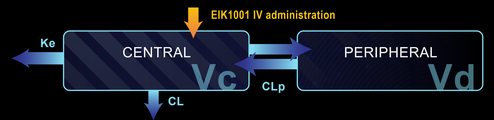


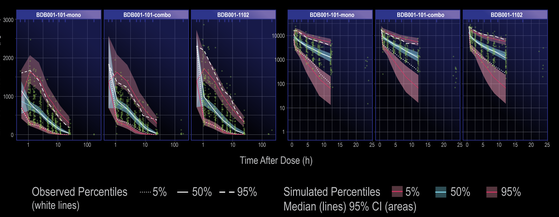
Table 3: Calculated EIK1001 Pharmacokinetic Parameters

Parameter	Estimate	RSE%	BSV% (Shrinkage%)
CL (L/h)	17.2	3.91	50.7 (28.0) IOV =79.6%
Vc (L)	116	4.55	29.8 (15.5)
CLp (L/h)	4.99	7.37	51.4 (42.6)
Vd (L)	45.7	7.80	71.7 (2.4)
Error Model			
Log-Additive Error	0.163	0.236	N/A

BSV = Between-subject variability | **CL** = Systemic clearance | **CLp** = Inter-compartment clearance | **Ke** = Elimination rate | **RSE** = Relative standard error | **Vc** = Central volume of distribution | **Vd** = Peripheral volume of distribution

Observed and predicted PK data are represented graphically in Figure 3. The observed data (green circles) are represented with median and 5th and 95th percentile values (solid white and dashed white lines) that were well reproduced by the predicted median (blue) and 5th and 95th percentiles (red) with 95%CI (shaded regions).

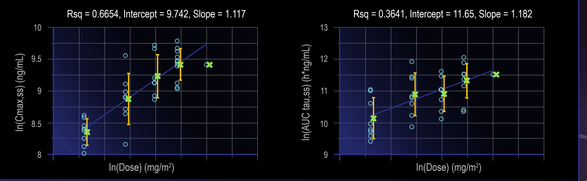
Figure 3: Observed and Predicted Pharmacokinetics of EIK1001



EIK1001 is Linear & Dose-Proportional

Linear, dose-proportional PK data are represented graphically in Figure 4. Individual estimates (open circles) of Cmax (left) and AUC (right) increase proportionally with dose over the range studied (linear parameter fits, inset).

Figure 4: EIK1001 Pharmacokinetics are Linear and Dose Proportional



PK Parameter	Slope Estimate	95%CI
AUC τ, ss	1.18	0.63 – 1.74
Cmax, ss	1.12	0.84 – 1.40

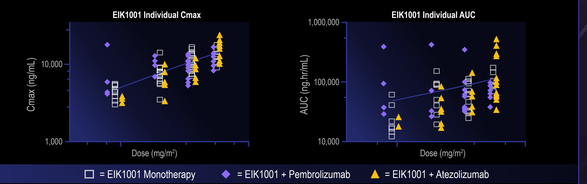
- Clearance (CL) decreases with body size (Table 4).
- Factors including age, hepatic and renal impairment, gender, race (not shown), and ECOG score (not shown) are not correlated with changes in CL.

Table 4: Effect of Intrinsic and Extrinsic Factors on EIK1001 Clearance

EIK1001 (Group 1 vs. Group 2)	Ratio (95%)
Body Size Metrics	
BSA [1.31, 1.72) m2 (N=31) vs. [1.94, 2.64] m2 (N=32)	0.703 (0.53, 0.933)
Age	
<65 (N=46) vs. >75 (N=30)	1.07 (0.878, 1.29)
<65 (N=46) vs. ≥65 (N=48)	1.01 (0.819, 1.26)
Hepatic Impairment	
BILI (mg/dL) [0.150, 0.400) (N=23) vs. [0.600, 1.74) (N=36)	0.883 (0.679, 1.15)
Renal Impairment	
Normal (N=28) vs. Mild Impairment (N=32)	0.914 (0.689, 1.21)
Normal (N=28) vs. Moderate Impairment (N=31)	1.11 (0.886, 1.39)
Normal (N=28) vs. Severe Impairment (N=2)	1.22 (0.0208, 71.9)

- EIK1001 PK is also not affected by combination with pembrolizumab or atezolizumab therapy (Figure 5).

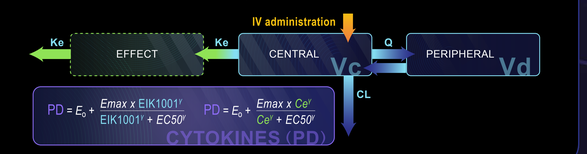
Figure 5: Effect of Combination Partner on EIK1001 Pharmacokinetics



Biomarker Data Analysis

- Nonlinear mixed-effects modeling was used to analyze time profile data of IL-6, IP-10 and IFN-γ (Figure 6).
- Post-hoc PK estimates using the actual dosing history were used to predict EIK1001 levels to match the timepoints of cytokine measurements.

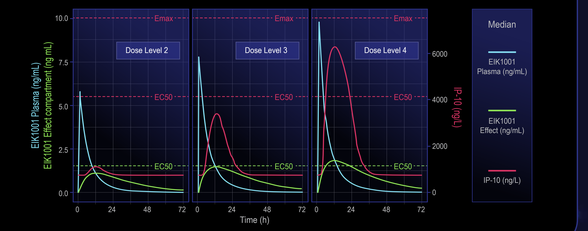
Figure 6: Direct, delayed effect of PK on cytokines with a sigmoid equation on the slope best describes the PK-PD relationship



Cytokine Response Consistent with MoA

- EIK1001 concentration-time profiles and cytokine-time profiles were simulated to estimate the maximum change from baseline of each cytokine (Figure 7).
- EIK1001 concentration in plasma *(blue, below)* as well as the site of action *(green; effect compartment)* is predicted. The concentrations predicted to cause half-maximal (EC_{50}) and maximal *(Emax)* cytokine response are indicated by horizontal dashed lines.
- IP-10 *(red, below)* is predicted to exceed EC_{50} at the highest dose *(right)*.

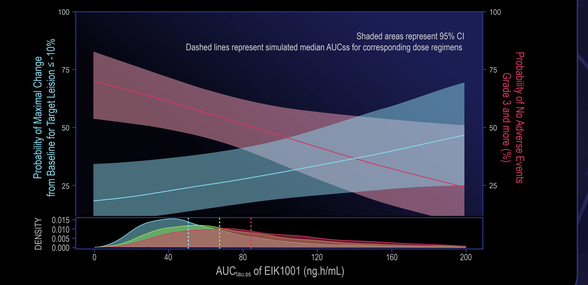
Figure 7: Simulated EIK1001 and Cytokine Concentration-Time Profiles



Benefit-risk Assessment Supports Development

- EIK1001 exposure-response relationships were explored for several measures of efficacy and safety (*described separately*).
- Simulations of these relationships were generated. A representative simulation (Figure 8) predicts the probability of decreasing tumor size with increasing dose *(blue curve and shaded region)* and of no AE Grade 3 decreasing with dose *(red curve and shaded region)*. Distributions and medians of exposures are shown *(inset below)* for Dose Level 2 *(blue shaded region and vertical dashed line, respectively)*, Dose Level 3 *(green)* and Dose Level 4 *(red)*.

Figure 8: Simulated Exposure-Response Relationships



Conclusions

- EIK1001 PK is linear in the dose range studied. Based on these preliminary analyses, patients with moderate renal and/or moderate hepatic impairment may be included in future clinical studies. BSA-based dose is planned in future studies; no other dose adjustments are indicated.
- Dose-dependent increases in IP-10 and IFN-γ (not shown) are consistent with the TLR mechanism of action.
- An increase in efficacy with increasing exposure is identified despite a heterogenous population of patients with advanced solid tumor. The balance of benefit and risk supports future study design.

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EIK1001 Modeling and Simulation Report EIKN-PMX-BDB001-5074: Population PK, Biomarker, E-R, and C-QTc Analyses BDB001 by Julie Grenier, Claudia Jomphe, Artem Uvarov, Certara

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