The Multibody Drug Conjugate (MDC) BD200 Mediates Anti-tumor Activity Through a Novel Dual-Targeting Mode

Michael Oberst[1], Dror Luger[1], Michael Kebede[1], Devi Gunasekera[1], Meital Gadrich[2], Yonit Ben David[2], Leah Asulin[2], Noam Grossman[2], Reut Fuchs[2], Hezi Sasson[2], Yael Diesendruck[2], Guy Nimrod[2], Tim Wyant[1], Ronald Herbst[1], Yanay Ofran[2,3] and Inbar Amit[2]

[1]Biolojic Design, LLC Washington, DC,[2]Biolojic Design, Ltd. Rehovot, Israel, [3]The Goodman Faculty of Life Sciences, Bar Ilan University, Israel.

AACR Annual Meeting 2026
Poster 438

INTRODUCTION

- Biolojic Design uses an AI-guided antibody engineering platform to design antibodies with novel therapeutic mechanisms[1].
- BD200 is an example of an antibody-drug conjugate designed using the 'Multibody' platform.
- Multibodies retain the standard symmetrical IgG architecture but are engineered to bind more than one target on the same Fab. These antibodies are designed for high affinity and specificity while maintaining the optimal developability properties of a standard human IgG.
- BD200 is a multibody-drug conjugate (MDC) carrying a potent topoisomerase inhibitor payload conjugated to the multibody via a cleavable linker at a Drug-to-Antibody Ratio (DAR) of 4. The MDC is formatted as an IgG antibody that can bind Trop2 with both arms; Nectin-4 with both arms; or Trop2 with one arm and Nectin-4 with a second arm (**Figure 1**).
- The absence of target at treatment, heterogeneity of target antigen or the loss of target expression under drug selective pressure remains a major barrier to the efficacy of ADCs and may be overcome by dual antigen targeting[2].
- BD200 addresses tumor antigen absence, heterogeneity and drug-induced target loss by targeting two tumor-associated antigens without the liabilities of non-standard antibody formats as well as by using a stable linker-payload design. BD200's Topo1 inhibitor payload demonstrates strong anti-tumor activity and is resistant to multi-drug resistance (MDR) pumps which represent clinically relevant resistance mechanisms[3].

RESULTS

- **Internalization and Cytotoxicity**
  - BD2 (unconjugated Ab) internalizes into the Trop2/Nectin-4 dual-expressing T47D HR+ breast cancer cell line with superiority over antibodies that bind only to Trop2 (Sacituzumab) or to Nectin-4 (Enfortumab) alone (**Figure 2**). Likewise, enhanced cytotoxic activity in T47D cells or HCC1806 TNBC cell line engineered to over-express multi-drug resistance pumps and Nectin-4 is observed for BD200 compared to ADCs that bind only to Trop2 (Dato-Dxd/ Datroway®) or to Nectin-4 (Enfortumab vedotin/Padcev®).
- **Anti-tumor Activity in Human Cancer CDX Models**
  - BD200 demonstrates potent anti-tumor activity in the NCI-N87 gastric and MDA-MB-468 TNBC cell line-derived (CDX) tumor models with superiority over Trodelvy®, an FDA-approved therapy for TNBC (**Figure 3**). These results may reflect the Topo1i activity in an MMAE resistant setting as well as broadening activity beyond Nectin-4 engagement by targeting Trop2.
- **Efficacy in Drug-Resistant Settings**
  - In a setting of Padcev® or Enfortumab Topo1i ADC resistance in the NCI-N87 model, switch to BD200 restores potent anti-tumor activity whereas a higher (MTD) dose of Padcev® or Enfortumab Topo1i ADCs does not (**Figure 4**).
- **Deep and Durable Anti-tumor Activity in Clinically-relevant PDX Models**
  - BD200 demonstrates strong anti-tumor responses across PDX models of triple negative breast cancer (TNBC), bladder, cervical and esophageal cancer (**Figure 5**).
  - Enhanced mPFS in a TNBC PDX model vs ADCs with FDA approval or promising clinical activity in TNBC (**Figure 6**).
- **High Serum Stability and Favorable PK Properties**
  - BD200 exhibits strong serum stability and PK properties similar or superior to that of other FDA-approved anti-Trop2 or Nectin-4 ADCs[4] (**Figure 7**).

Anti-Tumor Activity of the Multibody-Drug Conjugate BD200

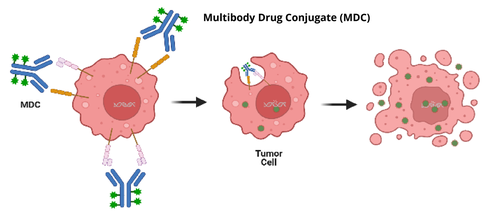


Figure 1. Schematic Illustration of the binding, internalization and tumor cell cytotoxicity mediated by BD200. Lavender receptor, TROP2; brown receptor, Nectin-4. Green, topoisomerase-1 inhibitor payload.

Internalization and Cytotoxic Activity of BD200 in Human Cancer Cells

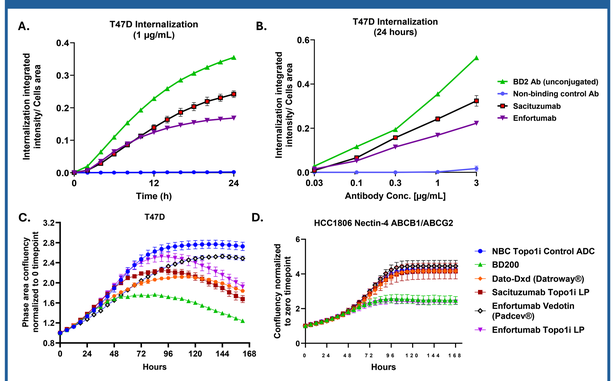


Figure 2. Cellular internalization and cytotoxicity of BD200 in cultured human cancer cell lines. Internalization kinetics of BD2 Ab (BD200 unconjugated Ab) in T47D HR+ breast cancer cells measured over time (A) or as an endpoint at 24h at various concentrations (B) using Incucyte® cell imaging. Cellular cytotoxicity was measured using Incucyte® cell imaging of RFP labeled T47D cells (C) or HCC1806 TNBC cells transfected with Nectin-4 and multi-drug resistance (MDR) pumps ABCB1 (Pgp) & ABCG2 (BCRP).

In vivo activity of BD200 in NCI-N87 and MDA-MB-468 CDX models

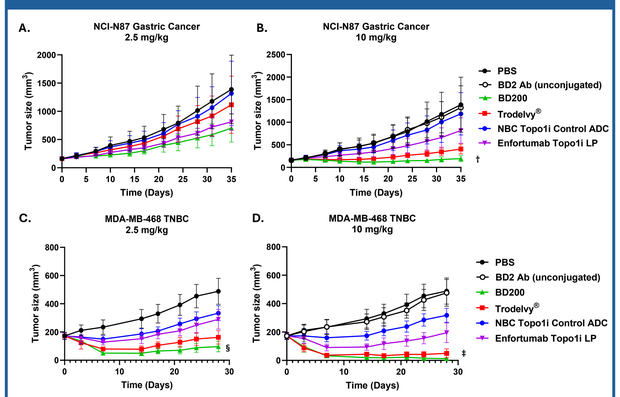


Figure 3. Anti-tumor activity in the NCI-N87 and MDA-MB-468 CDX models. Mice were engrafted with NCI-N87 gastric cancer (A, B) or MDA-MB-468 TNBC (C, D) cell lines and treated when tumors reached a median volume of ~150-200 mm³ with a single intravenous dose of test articles at 2.5 or 10 mg/kg, as indicated. †, p<0.05 BD200 vs other test articles Day14+; §, p<0.05 BD200 vs other test articles Day 7+; ‡, p<0.05 BD200 vs other test articles except Trodelvy® Day 3+ and vs Trodelvy® Day 24+ using one-way ANOVA with Dunnett's post-test for multiple comparisons.

BD200 anti-tumor activity in Padcev®- and Enfortumab Topo1i ADC-resistant tumors

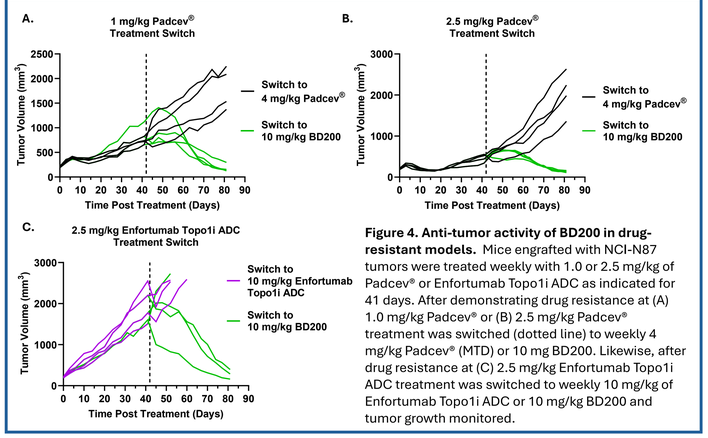


Figure 4. Anti-tumor activity of BD200 in drug-resistant models. Mice engrafted with NCI-N87 tumors were treated weekly with 1.0 or 2.5 mg/kg of Padcev® or Enfortumab Topo1i ADC as indicated for 41 days. After demonstrating drug resistance at (A) 1.0 mg/kg Padcev® or (B) 2.5 mg/kg Padcev® treatment was switched (dotted line) to weekly 4 mg/kg Padcev® (MTD) or 10 mg BD200. Likewise, after drug resistance at (C) 2.5 mg/kg Enfortumab Topo1i ADC treatment was switched to weekly 10 mg/kg of Enfortumab Topo1i ADC or 10 mg/kg BD200 and tumor growth monitored.

Anti-tumor Activity of BD200 in human PDX models

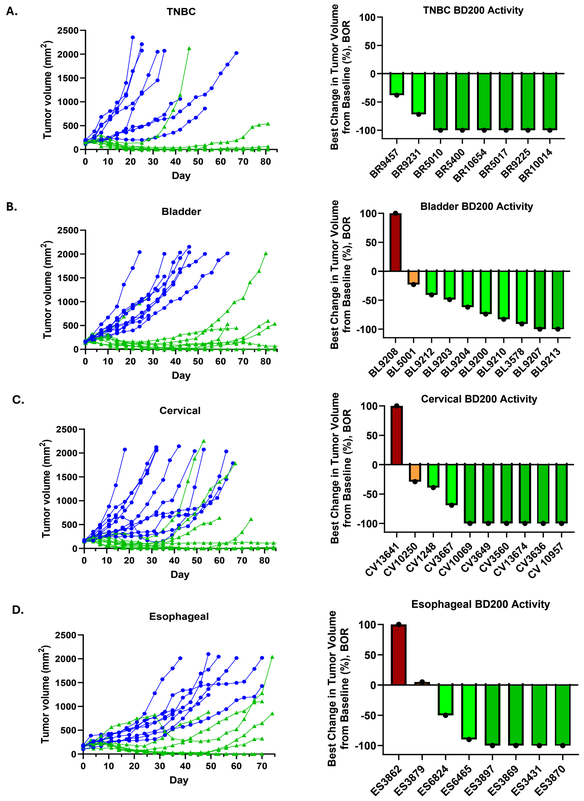
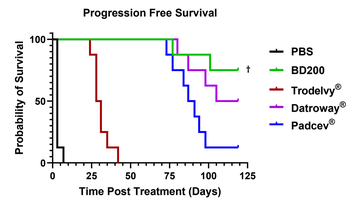


Figure 5. Anti-tumor activity of BD200 vs NBC Topo1i ADC control. Mice engrafted with (A) TNBC, (B) bladder, (C) cervical, or (D) esophageal PDX tumors were tested in an n=1 HuTrial™ study (CrownBio) with a single mouse receiving 10 mg/kg BD200 (green) or NBC Topo1i ADC control (Blue) QWx3 and tumor volume measured (matched pairs not indicated for simplicity). Spider (left) & BOR waterfall plots (right) are shown.

Progression-Free Survival of BD200 vs Benchmarks in the BR5400 TNBC PDX model



Group (n=8)	mPFS
PBS	3
BD200	NR
Trodelvy®	30
Datroway®	89
Padcev®	68

Figure 6. Progression-free survival in a TNBC PDX. Mice engrafted with the BR5400 TNBC PDX model (Crown Bioscience, San Diego, CA) were treated intravenously with 3 weekly doses of PBS, BD200, Trodelvy®, Dato-Dxd (Datroway®) at 10 mg/kg or Padcev® at 4 mg/kg (MTD) and tumor growth monitored. A PFS event was defined as tumor volume >20% of volume at time of treatment and analyzed by Kaplan-Meier plot. †, p<0.05 for BD200 compared to PBS, Trodelvy®, and Padcev® by Mantel-Cox log-rank test.

Serum Stability (Cyno) and NHP Pharmacokinetics of BD200

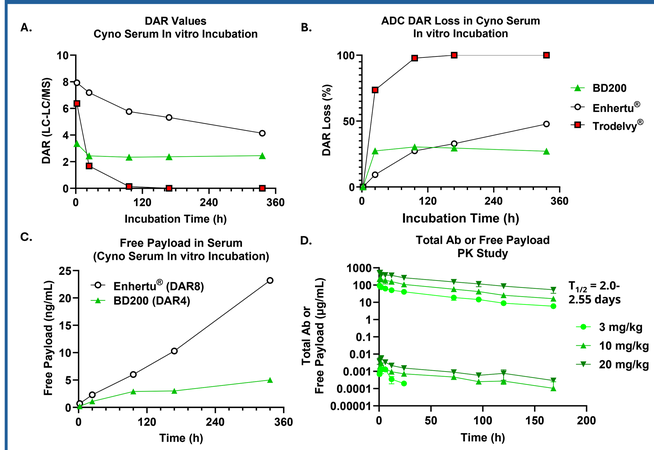


Figure 7. Serum stability and cyno PK. The MDC BD200, Trastuzumab deruxtecan (Enhertu®), or Sacituzumab govitecan (Trodelvy®) were incubated in cynomolgus monkey serum at 1 mg/mL for up to 14 days. At various time points, serum was collected for measurement of the drug-to-antibody ratio (DAR) and free payload by tandem LC-LC/MS. (A) Median DAR values of test articles over time, (B) percentage loss in DAR value and (C) free payload over time. (D) PK profiles of BD200 total antibody (top curves) or free payload (bottom curves) after intravenous administration of 3, 10, or 20 mg/kg.

SUMMARY & CONCLUSIONS

- **BD200 is a multibody drug conjugate that demonstrates superior internalization and cellular cytotoxicity through dual antigen-targeting of Trop2 and Nectin-4**
- **In drug resistant tumor models, BD200 is efficacious where other ADCs are inactive**
- **BD200 shows strong anti-tumor activity across clinically-relevant human tumor PDX models that express Trop2 and/or Nectin-4, including deep and durable responses**
- **BD200 has stable linker-payload and PK characteristics favorable for clinical development**

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