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Activity of BNT327/PM8002 (PD-L1 x VEGF-A bispecific antibody) in combination with BNT325/DB-1305 (TROP2 ADC) in solid tumors: Early preclinical and clinical evidence to support BNT327 + ADC combinations

Erika P. Hamilton[1], Jianqing Zhu[2], Wu Zhuang,[3] Ying Cheng,[4] Jianhua Shi,[5] Harshad Amin[6], Kathleen Moore[7], Hua Yang[8], Yuping Sun[9], Keith A. Lerro[10], Kuan Sheng[11], Yang Qiu[11], Xi Li[11], Chenggang Li[11], Yi Luo[12], Andy Tsun[12], Weifeng Huang[13], Shaogang Peng[13], Ping Wang[13], Friederike Gieseke[14], Sascha Tillmanns[15], Darlington Akahara[16], Secil Koseoglu[16], Aurora M. O'Brate[17], Claudia-Nanette Gann[14], Michael Wenger[14], Ilhan Celik[14], Özlem Türeci[14], Ugur Sahin[14]

[1]Sarah Cannon Research Institute, Nashville, TN, USA; [2]Zhejiang Cancer Hospital, Hangzhou, China; [3]Fujian Cancer Hospital, Fuzhou, China; [4]Jilin Provincial Cancer Hospital, Changchun, China; [5]Linyi Cancer Hospital, Linyi, China; [6]BRCR GLOBAL, Plantation, FL, USA; [7]Stephenson Cancer Center at the University of Oklahoma Medical Center, Oklahoma City, OK, USA; [8]Affiliated Hospital of Hebei University, Baoding, China;[9]Shandong Cancer Hospital and Institute, Jinan, China; [10]Regional Medical Oncology Center, Wilson, NC, USA; [11]Duality Biologics, Shanghai, China; [12]Biotheus Inc., Zhuhai City, Guangdong Province, China; [13]Biotheus (Suzhou) Co., Ltd., Suzhou, China; [14]BioNTech SE, Mainz, Germany; [15]BioNTech SE, Munich, Germany; [16]BioNTech US Inc., Cambridge, MA, USA; [17]BioNTech Pharmaceuticals Spain, S.L., Barcelona, Spain

Background and rationale

Combination of BNT327 with ADCs

- **BNT327/PM8002** is an investigational anti-PD-L1 x VEGF-A bispecific antibody (**Figure 1**) with encouraging early efficacy results and safety profile across tumor types, including 'cold' tumors not generally responsive to immunotherapy (e.g., low PD-L1 levels)[1–3]

BNT327 is designed to:
- restore effector T-cell function by binding to PD-L1, *while*
- localizing VEGF-A neutralization within the TME, *thereby*
- reversing the negative impact of VEGF signaling on immune-cell infiltration and activation, *and*
- normalizing tumor vasculature
- leading to tumor growth inhibition

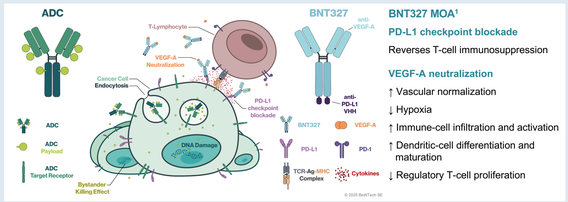
Dual targeting of PD-L1 and VEGF-A combines two complementary modalities, aiming to improve efficacy and safety.

Learn more about BNT327 at poster #6061 by Miao X on 29 April: Dual PD-L1 blockade and VEGF-A neutralization with the bispecific antibody BNT327/PM8002 shows potent antitumor activity in preclinical models

- The following investigational topoisomerase I inhibitor-based ADCs have shown manageable safety and encouraging early clinical activity
  - **BNT325/DB-1305**, a TROP2 ADC with DAR 4, in ovarian cancer or NSCLC[4–6]
  - **BNT324/DB-1311**, a B7H3 ADC with DAR 6, in SCLC or NSCLC[7,8]
  - **BNT323/DB-1303**, a HER2 ADC with DAR 8, in endometrial or breast cancer[9–11]
  - **BNT326/YL202**, a HER3 ADC with DAR 8, in NSCLC or breast cancer[12,13]
- We hypothesize that **combining BNT327 with ADCs** could improve efficacy (**Figure 1**).[14–16] Targeting VEGF-A may facilitate ADC penetration, which in turn could stimulate tumor immunity and increase sensitivity to PD-L1 inhibition

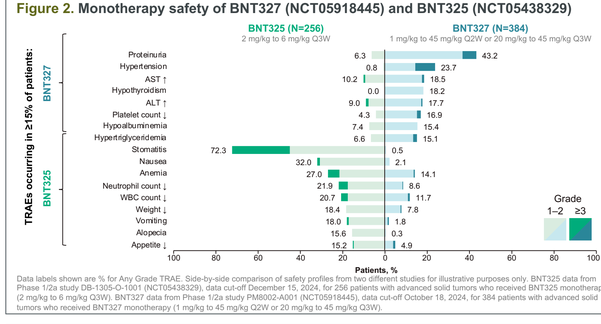
Figure 1. Potential mechanisms for efficacy of BNT327 + ADCs[14–16]

- Induction of immunogenic cell death
- Maturation of dendritic cells
- Increase in T-cell infiltration
- Improved immunological memory and expression of immune-regulatory proteins such as PD-L1 and MHC
- The antiangiogenic function of BNT327 could facilitate ADC penetration and the exposure of tumor cells



- The combination of anti-PD(L)1 + ADCs has shown promising clinical activity in breast and lung cancer[17,18] and has significantly improved outcomes in patients with urothelial cancer[19]
- Based on monotherapy data from early clinical trials of BNT327[20] or the abovementioned ADCs,[4,5,8,11,13] their combination may allow for improved efficacy while maintaining a manageable safety profile with few overlapping toxicities
- The safety profile of BNT327[17] is mainly characterized by low-grade proteinuria, hypertension, and elevated transaminases, while the safety profile of BNT325[4,5] is mainly characterized by stomatitis (**Figure 2**)

Figure 2. Monotherapy safety of BNT327 (NCT05918445) and BNT325 (NCT05438329)



Data labels shown are % for Any Grade TRAE. Side-by-side comparison of safety profiles from two different studies for illustrative purposes only. BNT325 data from Phase 1/2a study DB-1305-O-1001 (NCT05438329), data cut-off December 15, 2024, for 256 patients with advanced solid tumors who received BNT325 monotherapy (2 mg/kg to 6 mg/kg Q3W). BNT327 data from Phase 1/2a study PM8002-A001 (NCT05918445), data cut-off October 18, 2024, for 384 patients with advanced solid tumors who received BNT327 monotherapy (1 mg/kg to 45 mg/kg Q2W or 20 mg/kg to 45 mg/kg Q3W).

Herein we provide first evidence of early preclinical and clinical data to support the novel combination of BNT327, an anti-PD-L1 x VEGF-A bispecific antibody, with ADCs

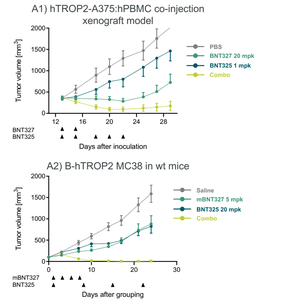
Preclinical evidence

Preclinical *in vivo* models testing the combination of BNT327 with ADCs showed superior tumor growth inhibition compared with each treatment alone

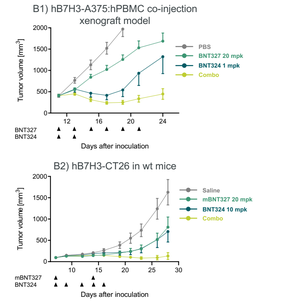
- The combination of BNT327 and BNT325/DB-1305 (TROP2), BNT324/DB-1311 (B7H3), BNT323/DB-1303 (HER2), and BNT326/YL202 (HER3) ADCs was explored in different *in vivo* models (xenograft and syngeneic)
- The combination of BNT327 and ADCs resulted in tumor regression and tumor control, and significantly lower tumor volume compared with monotherapy (**Figure 3** and **Table 1**)

Figure 3. *In vivo* models testing the combination of BNT327+ BNT325 (TROP2) (A), BNT327 + BNT324 (B7H3) (B), BNT327 + BNT323 (HER2) (C), BNT327 + BNT326 (HER3) (D)

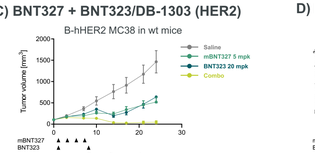
A) BNT327 + BNT325/DB-1305 (TROP2)



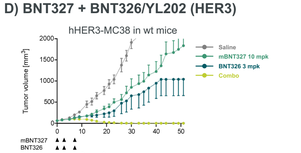
B) BNT327 + BNT324/DB-1311 (B7H3)



C) BNT327 + BNT323/DB-1303 (HER2)



D) BNT327 + BNT326/YL202 (HER3)



mBNT327 refers to the total mouse surrogate BNT327 antibody that binds murine VEGF-A/PD-L1 targets (B20-ATE-SCFV); Data shown represents mean±SEM. Across all preclinical experiments, no body weight loss or obvious adverse effects were observed.
Xenograft models: subcutaneous inoculation of A375 human melanoma cancer and human PBMCs in B-NDG B2M KO Plus mice.
Syngeneic models: subcutaneous inoculation of highly expressing human TROP2, HER2, or HER3 MC38 (murine colon carcinoma cell line) in C57BL/6 mice, or subcutaneous inoculation of B7H3 overexpressing CT26 (murine colon carcinoma cell line) in BALB/c mice

Table 1. TGI (%)

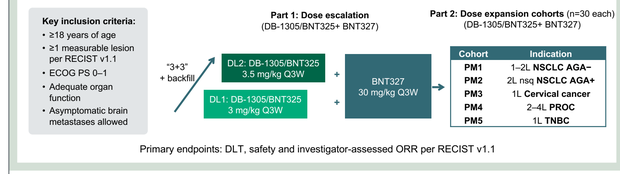
Model	Figure 3 panel	(m)BNT327 TGI (%)	ADC TGI (%)	ADC + (m)BNT327 TGI (%)	Significance level vs ADC control	Significance level vs ADC mono	Significance level vs BNT327 mono
BNT325/DB-1305							
Xenograft	A1	78.2	33.6	111.3	****	###	Δ
Syngeneic	A2 (20 mpk not shown)	47.6 (5 mpk) 71.4 (20 mpk)	51.4	106.1 (5 mpk) 106.9 (20 mpk)	**** ****	## ##	ΔΔΔ ΔΔΔ
BNT324/DB-1311							
Xenograft	B1	45.7	91.4	110.0	****	ns	ΔΔΔΔ
Syngeneic	B2	53	60	98	***	#	Δ
BNT323/DB-1303							
Xenograft	Not shown	45	53	74	****	#	ΔΔ
Syngeneic	C (20 mpk not shown)	69.5 (5 mpk) 88.1 (20 mpk)	60.7	104.3 (5 mpk) 106.7 (20 mpk)	**** ****	### ###	ΔΔ ΔΔ
BNT326/YL202†	Syngeneic	D	59.2	65.4	99.7	***	###	ΔΔΔΔ

TGI (%) on last day of study where saline/PBS control was still alive. †Xenograft data not yet available.
Statistical significance when compared with PBS/saline (*), with ADC monotherapy (#) or with (m)BNT327-monotherapy (Δ).
*, # ,Δ p<0.05; **, ##, ΔΔ p<0.01; ***, ###, ΔΔΔ p<0.001; ****, ####, ΔΔΔΔ p<0.0001.

Clinical evidence

DB-1305-O-1001 study (NCT05438329): Cohorts of DB-1305/BNT325 + BNT327

- Ongoing, first-in-human Phase 1/2a study evaluating BNT325 plus BNT327 in patients with advanced/metastatic solid tumors. Recruitment to PM Cohorts is ongoing



- As of March 03, 2025, 67 patients have received BNT325 + BNT327 Q3W (21 in Part 1 and 46 in Part 2); 53 are still on treatment (**Table 2**)

Table 2. Baseline patient and disease characteristics

		BNT325 3 mg/kg + BNT327 30 mg/kg N=25	BNT325 3.5 mg/kg + BNT327 30 mg/kg N=42	Overall N=67
Age	Median (range), years	57 (35–72)	58.5 (34–85)	58 (34–85)
Sex, n (%)	Female	24 (96.0)	23 (54.8)	47 (70.1)
	Male	1 (4.0)	19 (45.2)	20 (29.9)
Race, n (%)	Chinese	17 (68.0)	28 (66.7)	45 (67.2)
	White	5 (20.0)	11 (26.2)	16 (23.9)
	Black or African American	2 (8.0)	1 (2.4)	3 (4.5)
	American Indian or Alaska Native	1 (4.0)	1 (2.4)	2 (3.0)
	Other Asian	0	1 (2.4)	1 (1.5)
Region, n (%)	China	17 (68.0)	27 (64.3)	44 (65.7)
	USA	8 (32.0)	15 (35.7)	23 (34.3)
ECOG PS,* n (%)	0	10 (40.0)	10 (23.8)	20 (29.9)
	1	15 (60.0)	31 (73.8)	46 (68.7)
Tumor,† n (%)	NSCLC	0	23 (54.8)	23 (34.3)
	Ovarian cancer	22 (88.0)	0	22 (32.8)
	TNBC	1 (4.0)	9 (21.4)	10 (14.9)
	Cervical cancer	0	7 (16.7)	7 (10.4)
No prior treatment,‡ n (%)		0	5	5 (7.5)
Prior lines‡	Median (range), number	2 (1–3)	1 (1–10)	2 (1–10)

*ECOG PS missing for one patient. †Other tumors included: HR+HER2− breast cancer, colon cancer, soft tissue sarcoma, gallbladder. ‡For advanced/metastatic disease.

- No DLTs were reported in the DLT-evaluable period (first six patients)
- The safety profile (**Table 3**) was manageable with low rate of Grade 3 TRAEs (32.8%) or TRAEs leading to discontinuation (n=3, 4.5%; one patient with Grade 3 stomatitis, one with Grade 2 ILD, one with Grade 5 pneumonia)

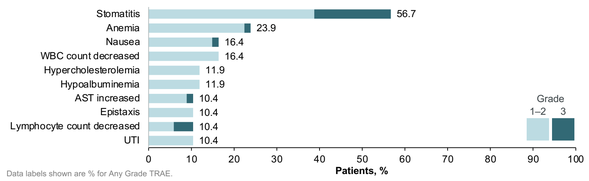
Table 3. Safety overview, n (%)

	BNT325 3 mg/kg + BNT327 30 mg/kg N=25	BNT325 3.5 mg/kg + BNT327 30 mg/kg N=42	Overall N=67
Any TRAE	22 (88.0)	32 (76.2)	54 (80.6)
Grade ≥3 TRAE	11 (44.0)	11 (26.2)	22 (32.8)
TRAEs leading to BNT325 dose reduction*	5 (20.0)	7 (16.7)	12 (17.9)
TRAEs leading to dose interruption	6 (24.0)	8 (19.0)	14 (20.9)
BNT325	4 (16.0)	6 (14.3)	10 (14.9)
BNT327	4 (16.0)	5 (11.9)	9 (13.4)
TRAEs leading to discontinuation	1 (4.0)	2 (4.8)	3 (4.5)
BNT325	1 (4.0)	2 (4.8)	3 (4.5)
BNT327	0	1 (2.4)	1 (1.5)
TRAEs leading to death†	1 (4.0)	0	1 (1.5)

*Per protocol, dose reduction was only allowed for BNT325.
†Infectious pneumonia in a patient with 4L PROC, considered by investigator to be potentially related to study treatment.

- Treatment with BNT325 + BNT327 (**Figure 4**) did not lead to an increase in TRAEs that have been previously reported with BNT327 or BNT325 alone (see **Figure 2**)
- Stomatitis was reported in 38 (56.7%) patients (Grade 3 in 12 [17.9%]) and led to a dose reduction of BNT325 in 12 (17.9%) patients

Figure 4. TRAEs occurring in ≥10% of patients receiving BNT325 + BNT327 Q3W (N=67)

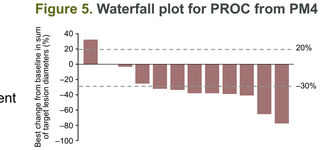


Data labels shown are % for Any Grade TRAE.

- Other TRAEs commonly associated with BNT327 monotherapy occurred infrequently: proteinuria (n=2, 3.0%), hypertension (n=1, 1.5%), ALT increased (n=3, 4.5%)

- Tumor response analyses are ongoing
- In early efficacy data from Cohort PM4* (2L–4L PROC), amongst 13 evaluable patients, 7 had a PR and 3 had SD (**Figure 5**). Ten patients are still on treatment
- Responses were also observed in patients with NSCLC or TNBC

Figure 5. Waterfall plot for PROC from PM4



*Efficacy-evaluable patients included those with ≥1 post-baseline assessment. At the DCO, Cohort PM4 had the most patients as it was the first PM Cohort to start enrolling. Cohort PM4 is expected to enroll 30 patients. One patient is not included in waterfall plot as she died before the first tumor assessment.

Conclusions

BNT327 plus ADCs against TROP2 (BNT325/DB-1305), B7H3 (BNT324/DB-1311), HER2 (BNT323/DB-1303), and HER3 (BNT326/YL202) demonstrated superior anti-tumor effects preclinically compared to each drug alone.

Preliminary clinical data suggests that BNT327 plus BNT325 had a manageable safety profile with few overlapping toxicities and signs of activity in PROC.

Ongoing studies of BNT327 + ADCs

Further evaluation is ongoing of BNT327 with ADCs, with a focus on tumors where early monotherapy efficacy has been observed with these ADCs.

- BNT327 + BNT325: DB-1305-O-1001 (NCT05438329), continues to enroll patients with NSCLC, cervical cancer, PROC and TNBC
- BNT327 + BNT323: BNT323-03 (NCT06827236) in breast cancer
- BNT327 + BNT324: BNT324-01 (NCT06892548) in lung cancer (SCLC and NSCLC± AGA)
- BNT327 + BNT324: DB-1311-201 in HNSCC, HCC, melanoma, cervical cancer
- Studies are also planned for BNT327 + BNT326

Abbreviations:
1L, first line; **2L**, second line; **ADC**, antibody-drug conjugate, **AE**, adverse event; **AGA**, actionable oncogenic alteration; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **B7H3**, B7 homolog 3; **bsAb**, bispecific antibody; **DAR**, drug-antibody ratio; **DCO**, data cut-off; **DL**, dose level; **DLT**, dose-limiting toxicity; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **HCC**, hepatocellular cancer; **HER**, human epidermal growth receptor; **HNSCC**, head and neck squamous-cell carcinoma; **ILD**, interstitial lung disease; **MOA**, mechanism of action; **MHC**, major histocompatibility complex; **mpk**, mg/kg; **ns**, not significant; **NSCLC**, non-small cell lung cancer; **nsq**, non-squamous; **ORR**, objective response rate; **PBMC**, peripheral blood mononuclear cells; **PBS**, phosphate-buffered saline; **PD-1**, programmed cell death protein 1; **PD-L1**, PD-1 ligand 1; **PR**, partial response; **PROC**, platinum-resistant ovarian cancer; **Q2W**, every 2 weeks; **Q3W**, every 3 weeks; **RECIST**, Response Evaluation Criteria in Solid Tumors; **SCLC**, small cell lung cancer; **SD**, stable disease; **SEM**, standard error of the mean; **TCR**, T-cell receptor; **TGI**, tumor growth inhibition; **TME**, tumor microenvironment; **TNBC**, triple-negative breast cancer; **TRAE**, treatment-related AE; **TROP2**, targeting trophoblast cell surface antigen 2; **UTI**, urinary tract infection; **VEGF-A**, vascular endothelial growth factor A; **WBC**, white blood cell; **WT**, wildtype.

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Corresponding author:
Dr Sascha Tillmanns
sascha.tillmanns@biontech.de

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