BT8009-100: A Phase I/II Study of Novel Bicyclic Peptide and MMAE Conjugate BT8009 in Patients (pts) with Advanced Malignancies Associated with Nectin-4 Expression, Including Urothelial Cancer (UC)

Abstract #498

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INTRODUCTION

- *Bicycles* are a novel class of chemically synthesized molecules
  - Chemical synthesis allows optimization for affinity, stability, and solubility
  - 50-100x smaller than antibodies
  - High selectivity allows more potent toxin to be delivered directly to tumor
- BT8009 is a Bicycle Toxin Conjugate (BTC™)
  - A small (~2 kDa) bicyclic peptide targeting Nectin-4 tumor antigen linked to cytotoxin MMAE via a valine-citrulline cleavable linker, with a total molecular weight of 4.2 kDa
- BTCs represent a unique therapeutic class
  - Distinct from ADCs
  - Pharmacokinetic properties analogous to small molecules
- Nectin-4 is highly expressed by tumor cells in bladder, NSCLC, upper GI, ovarian, breast, and head and neck cancers; overexpression of Nectin-4 in tumor tissue is a marker for poor prognosis
- BT8009-100 is a phase 1/2 first-in-human trial investigating the safety and efficacy of BT8009 in patients with tumors that express Nectin-4 (NCT04561362)
- Presented here are the results of the monotherapy dose escalation part of the study (Part A-1) as of 20 Sept 2022

METHODS

- Phase 1/2 first-in-human, open-label dose escalation study conducted in three parts (Figure 1)
- BT8009 administered as an IV infusion either weekly, bi-weekly, or on days 1+8 of a 21-day cycle
- Key eligibility criteria for Part A-1 include patients with advanced pure or predominant urothelial carcinoma (variant histologies are allowed if constituting <50% of the overall tumor), pancreatic, breast, NSCLC, gastric, esophageal, head and neck or ovarian cancer that have exhausted all standard treatment options, ECOG of 0 or 1, and adequate organ function
- **Primary objective:** Assess safety of the monotherapy and define maximum tolerated and recommended phase 2 dose (RP2D)
- **Secondary objectives:** Assess preliminary antitumor activity per RECIST v1.1 and determine incidence of antidrug antibodies and PK parameters

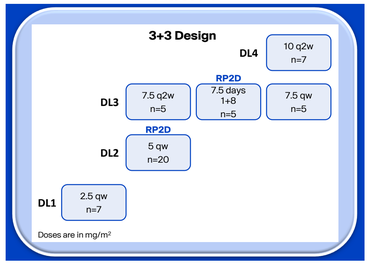

Figure 1. Study design. Number of patients in each cohort is presented.

RESULTS

- As of the data cut date, two RP2Ds were determined: 5 mg/m^2 qw and 7.5 mg/m^2 on Days 1+8 of a 21-day cycle
- Plasma pharmacokinetics of BT8009 (conjugated drug) and MMAE were both predictable and consistent
  - BT8009 exhibited rapid elimination from plasma ($t_{1/2}$ < 1 h), typically reaching undetectable levels 6 h after end of infusion
  - MMAE achieved peak concentrations within 2-3 h and has a longer half life ($t_{1/2}$ = 37-50 h)

Table 1. Baseline characteristics for the overall population and for patients with UC.

Characteristic	Overall N=49	UC N=24
Median age, yrs (range)	66 (35-83)	67 (48-81)
Sex, n (%)		
Male	29 (59)	20 (83)
Female	20 (41)	4 (17)
Race/ethnicity, n (%)		
White	30 (61)	10 (42)
Black or African American	1 (2)	0
Other	15 (31)	12 (50)
Missing	3 (6)	2 (8)
ECOG, n (%)		
0	20 (41)	12 (50)
1	29 (59)	12 (50)
Median prior lines of therapy (range)	3 (1-15)	3 (1-7)

Table 2. Primary site of diagnosis for patients with UC.

Primary diagnosis, n (%)	UC N=24
Bladder	19 (79)
Urothelial	2 (8)
Ureter	1 (4)
Urethra	2 (8)

Table 3. Types of prior therapy received by patients with UC.

Category, n (%)	UC N=24
Platinum	24 (100)
PD-(L)1 inhibitor	24 (100)
pan-FGFR inhibitor	3 (13)

RESULTS

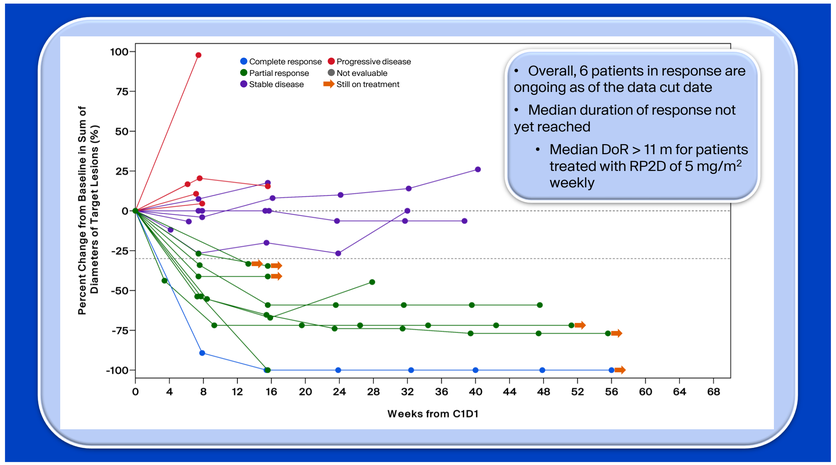

Figure 2. Change in target lesion sizes from baseline and best overall responses in patients with urothelial cancer.

Table 4. Responses in patients with urothelial cancer, per RECIST v1.1.

Best overall response, n (%)	2.5 mg/m² qw N=4	5 mg/m² qw N=8	7.5 mg/m² qw N=4	7.5 mg/m² q2w N=2	7.5 mg/m² days 1+8 N=2	10 mg/m² q2w N=4	Overall N=24
Complete Response (CR)	0	1 (13)	0	0	0	0	1 (4)
Partial Response (PR)	1 (25)	3 (38)	1 (25)	0	1 (50)	2 (50)	8* (33)
Stable Disease (SD)	2 (50)	3 (38)	1 (25)	0	1 (50)	0	7 (29)
Progressive Disease	1 (25)	0	0	2 (100)	0	2 (50)	5 (21)
Not Evaluable	0	1 (13)	2 (50)	0	0	0	3 (13)
ORR (CR+PR)	1 (25)	**4 (50)**	1 (25)	0	1 (50)	2 (50)	9 (38)
CBR (CR+PR+SD ≥16 wks)	2 (50)	**6 (75)**	2 (50)	0	1 (50)	2 (50)	13 (54)

*Includes 1 unconfirmed PR and 2 PRs that were confirmed after the data cut date. ORR=objective response rate; CBR=clinical benefit rate.

- Additional responses were observed in breast and NSCLC; details to be presented at a future congress

Table 5. Treatment-related adverse events occurring in ≥15% of patients.

Event, n (%)	Overall N=49		Patients treated with RP2D of 5 mg/m² qw N=20		Patients treated with RP2D of 7.5 mg/m² Days 1+8 N=5	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Nausea	23 (47)	1 (2)	7 (35)	0	4 (80)	1 (20)
Fatigue	18 (37)	3 (6)	5 (25)	1 (5)	3 (60)	0
Diarrhea	13 (27)	1 (2)	3 (15)	0	2 (40)	0
Decreased appetite	12 (24)	1 (2)	5 (25)	0	2 (40)	0
Asthenia	11 (22)	2 (4)	3 (15)	1 (5)	0	0
Pyrexia	11 (22)	0	4 (20)	0	2 (40)	0
Neutrophil count decreased	11 (22)	3 (6)	4 (20)	1 (5)	0	0
Alopecia	11 (22)	0	5 (25)	0	2 (40)	0
Neutropenia	8 (16)	7 (14)	1 (5)	1 (5)	3 (60)	2 (40)

RESULTS

- **DLTs**:
  - 1 Gr 3 asthenia at 7.5 mg/m^2 qw
  - 1 Gr 4 sepsis at 10 mg/m^2 q2w
- **Treatment-related SAEs** occurred in 5 patients
  - At the RP2Ds the following SAEs were observed:
    - 5 mg/m^2 qw: Vomiting (1)
    - 7.5 mg/m^2 on days 1+8 of a 21-day cycle: Nausea and neutropenia (1)
  - At doses above the RP2Ds the following SAEs were observed:
    - 10 mg/m^2 q2w: Pyrexia (1); sepsis (1); febrile neutropenia and vomiting (1)
- No patient discontinued treatment due to an AE

Table 6. Treatment-related adverse events of specific monitoring.

Event, n (%)	Overall N=49		Patients treated with RP2D of 5 mg/m² qw N=20		Patients treated with RP2D of 7.5 mg/m² Days 1+8 N=5	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Skin rash	6 (12)	0	2 (10)	0	0	0
Eye disorders	4 (8)	1 (2)	1 (5)	0	2 (40)	1 (20)
Peripheral neuropathy	13 (27)	1 (2)	6 (30)	0	2 (40)	0
Pneumonitis	0	0	0	0	0	0

Search for rash events included the following preferred terms: Eczema, photosensitivity reaction, rash, rash maculo-papular, application site rash, urticaria, blister, blood blister, conjunctivitis, dermatitis, dermatitis bullous, drug eruption, erythema, erythema multiforme, exfoliative rash, intertrigo, palmar-plantar erythrodysesthesia syndrome, rash erythematous, rash macular, rash papular, rash pruritic, rash vesicular, skin irritation, skin exfoliation, and stomatitis. Other terms represent Eye Disorders System Organ Class, Peripheral Neuropathy MedDRA SMQ (Broad), and the preferred term of 'Pneumonitis.'

- Treatment-related AEs of specific monitoring of Gr ≥3 occurred in 2 patients
  - Gr 3 eye disorder (keratitis) in patient treated with 7.5 mg/m^2 on days 1+8; resolved Gr 1, ongoing (dose reduction)
  - Gr 3 worsening neuropathy in patient treated with 7.5 mg/m^2 qw with history of Gr 1 neuropathy at Screening; resolved to Gr 2, ongoing (dose not changed)
- No Gr ≥3 rash events were observed

CONCLUSIONS

- BT8009 was shown to have preliminary **antitumor activity** in patients with locally advanced or metastatic urothelial cancer who were previously treated with platinum-based chemotherapy and an immune-checkpoint inhibitor
- Phase 1 dose escalation results show BT8009 is **well tolerated**
  - No treatment-related discontinuations occurred
  - No Grade ≥3 rash events
- Results support further expansion of the trial that is now including:
  - UC patients with renal impairment
  - Previously untreated cis-ineligible metastatic UC
  - UC with or without prior exposure to EV
  - Tumor-specific cohorts: Ovarian, TNBC, and NSCLC cancers

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- **For additional information please contact Capucine Baldini at capucine.baldini@gustaveroussy.fr**