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ANNUAL MEETING 2022 New Orleans
APRIL 8-13, 2022 • #AACR22

BT8009-100 Phase I/II Study of Novel Bicyclic Peptide and MMAE Conjugate BT8009 in Patients with Advanced Malignancies Associated with Nectin-4 Expression

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Disclosure Information

Meredith McKean

I have the following relevant financial relationships to disclose:

Employee of: Sarah Cannon Research Institute

Consultant/Advisory Role (all payments to institution): Astellas Pharma, AstraZeneca, BicycleTX Limited, Castle Biosciences, Eisai, Ideaya Biosciences, iTeos, Moderna, Pfizer, Regeneron Pharmaceuticals

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Molecular and preclinical features of Bicycle Toxin Conjugates

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BT8009 is a BTC, comprising a bicyclic peptide targeting Nectin-4 tumor antigen, linked to monomethyl auristatin E [MMAE] via a val-cit cleavable linker.

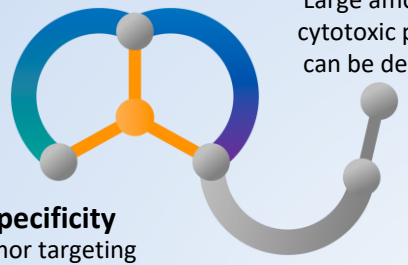
MWt of 1.5-2kDa

50-100x smaller than antibodies

High selectivity

Allows more potent toxin to be delivered directly to tumor

Bicycle® Toxin Conjugate (BTC™)

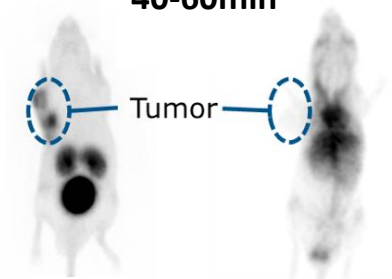


Toxin
Large amount of cytotoxic payload can be delivered

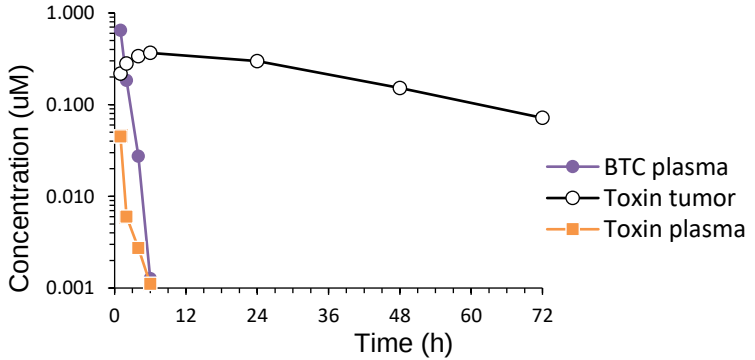
Specificity
Tumor targeting via antigen

Linker
Release of toxin directly into tumor via cleavable linker

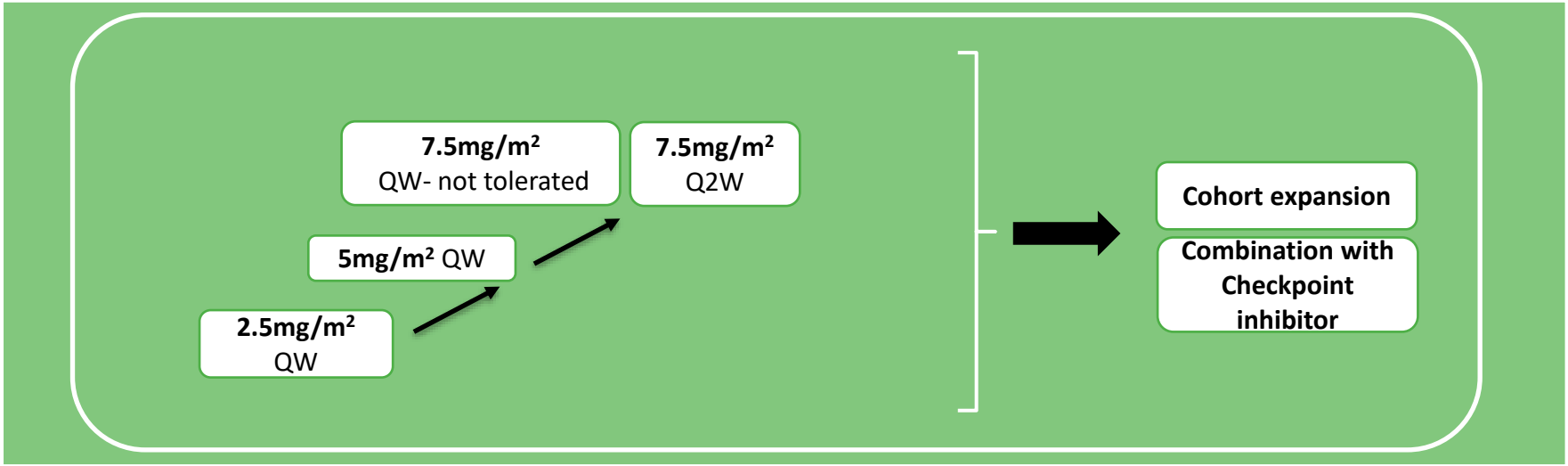
PET Imaging 40-60min



Bicycle **Antibody**



BT8009-100 FIH Study Design



Data are presented for dose cohorts listed above.

Overview of Key Demographics and Baseline Characteristics

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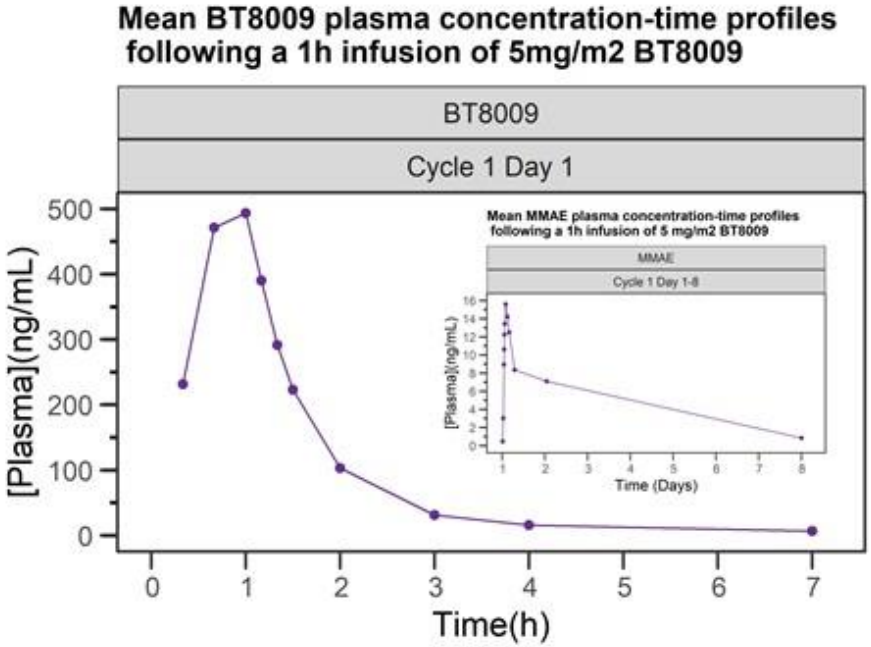
Demographics	
Total	N=37
Age median, (range)	66 (44-83)
Sex	
Male	22 (59.5%)
Female	15 (40.5%)
ECOG	
0	15 (40.5%)
1	22 (59.5%)
Median No. of Prior Lines of Treatment	3

Disease History	
Total	N=37
Tumor type	
Breast	4 (11%)
Esophageal	1 (3%)
Head/Neck	2 (5%)
Lung	5 (14%)
Ovary	1 (3%)
Pancreas	6 (16%)
Urothelial	18 (49%)

BT8009 delivers sustained systemic MMAE concentrations in contrast to short systemic exposure of parent drug



BT8009 and MMAE PK summary:

- Short terminal half-life of BT8009 (no systemic exposure after 12 h), in contrast with extended systemic exposure of ADC over 1 week
- MMAE concentrations broadly similar to those observed with ADC's

BT8009-100 – Most frequent TEAEs (>15%)

Treatment-emergent Adverse Events	N (Incidence); Total N=37
Fatigue	15 (41%)
Nausea	14 (38%)
Diarrhea	12 (32%)
Pyrexia	12 (32%)
Anemia	12 (32%)
Decreased appetite	12 (32%)
Constipation	11 (30%)
Urinary Tract Infection	10 (27%)
Neutrophil Count Decreased	9 (24%)
Asthenia	9 (24%)
Abdominal pain	8 (22%)
Pruritus	7 (19%)
Alopecia	7 (19%)
Back Pain	6 (16%)
Hypokalemia	6 (16%)
Hypomagnesemia	6 (16%)

- Uses available interim data per clinical database as of 2022-03-07
- TEAEs by preferred terms

BT8009-100 Safety Cohort

7 patients treatment-emergent serious adverse events

- UTI
- Pneumonia
- Diarrhea
- Vomiting
- Anemia
- Pyrexia
- Cementoplasty

- 2 patients with DLTs
  - Neutropenia (grade 4)
  - Asthenia (grade 3)

Uses available interim data per clinical database as of data cut 2022-03-07
*One patient with a “DLT” does not meet the protocol definition of a DLT; clinical database is expected to be updated.

BT8009-100 – Adverse Events of Interest

Toxicities	Incidence	Severity Grade ≥3	Related
Rash[a]	19%	0%	14%
Ocular toxicities[b]	3%	0%	3%
Neuropathy[c]	24%	3%	19%
Gastrointestinal Disorders:			
Nausea	38%	3%	36%
Diarrhea	32%	5%	24%
Vomiting	11%	3%	11%
Neutropenia[d]	30%	14%	30%

- Uses available interim data per clinical database as of 2022-03-07; multiple preferred terms aggregated into standardized MedDRA queries as noted in footnotes a, c-d.

A. Rash includes: eczema, photosensitivity reaction, rash, rash maculo-papular, application site rash, and urticaria.
B. Diplopia secondary to nerve palsy
C. Neuropathy[c] includes: hypoesthesia, neurotoxicity, hemiparesis, neuropathy peripheral, paresthesia, peripheral sensory neuropathy, nervous system disorders
D. Neutropenia includes: neutropenia and neutrophils decreased

BT8009-100 Dose modifications due to AEs

- Interruptions occurring in more than 1 patient
  - Fatigue: N=3, 8.1%
  - Anemia, neutropenia, asthenia, pyrexia, UTI: N=2, 5.4% each
- Reduction occurring in more than 1 patient
  - Neutropenia: N=3, 8.1%
  - Asthenia: N=2, 5.4%
- Discontinuation/disease progression
  - Pneumonia, hepatic failure/progression (both unrelated): N=1, 2.7% each

Uses available interim data per clinical database as of 2022-03-07

ENRICHMENT COHORT:

5 mg/m^2 QW Urothelial Carcinoma
Subset of the dose-escalation FIH study

Enrichment cohort : Key Demographics

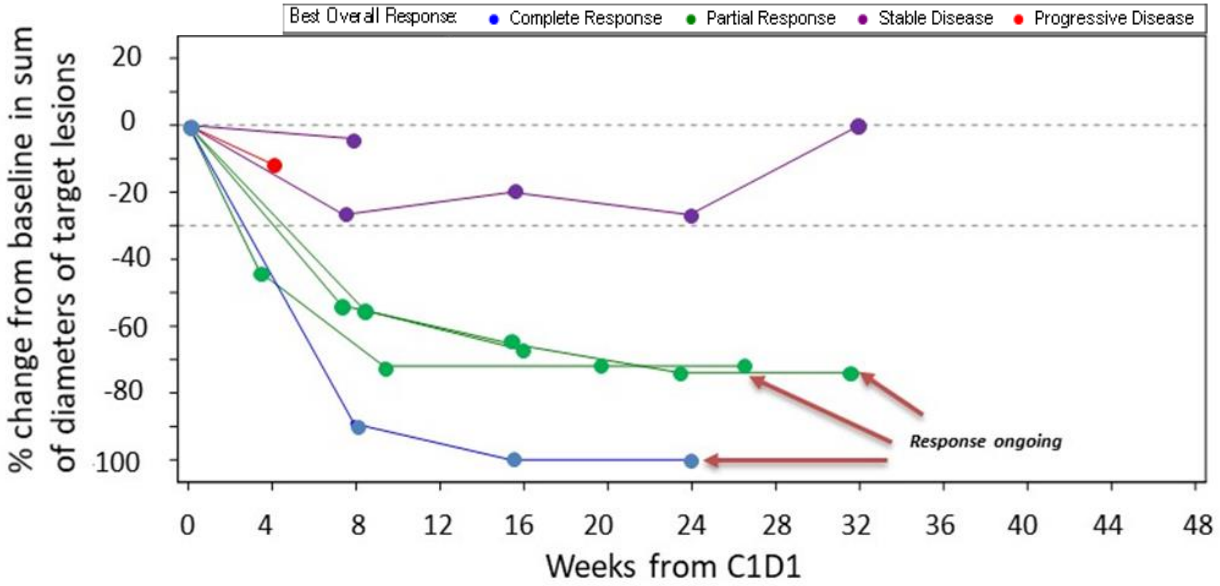
Demographics (Urothelial 5 mg/m^2 QW)	
Total	N=8
Age median (range)	67 (48-72)
Sex	
Female	2 (25%)
Male	6 (75%)
ECOG	
0	5 (62.5%)
1	3 (37.5%)
Median No. of Prior Lines of Treatment	3

Uses available interim data per clinical database as of 2022-03-07
Cohort designation references assigned cohort as of C1D1

Enrichment Cohort: Responses over Time

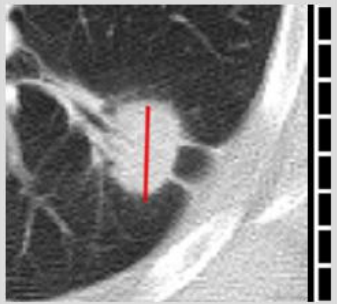
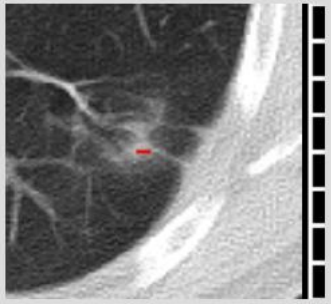
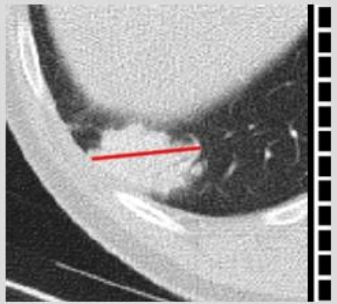
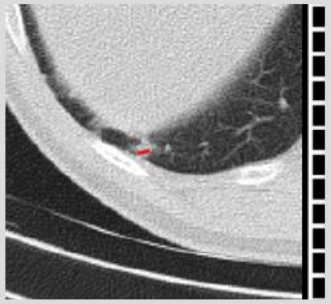
Urothelial Carcinoma Responses:

- 4 responses in 8 patients
  - 1 Complete Response
  - 3 Partial Responses
    - 71% tumor reduction
    - 65% tumor reduction
    - 54% tumor reduction
- Most responses are ongoing, with the longest responses lasting over 5 months
  - 3 responses ongoing
  - 1 progression at ~3 months
- RECIST V1.1 was used for response assessments



One subject who had clinical progression did not have post-baseline RECIST assessment data and is thereby omitted from this figure

Enrichment Cohort: Tumor Images Pre-dose & Post-dose

	Baseline	Cycle 2
Left Lung	 LA: 25.3 mm	 LA: 3.2 mm (-87.4% ΔP)
Right Lung	 LA: 40.2 mm	 LA: 4.1 mm (-89.8% ΔP)

Complete Response

- Target lesions were reduced by -100% after **four** cycles of BT8009 treatment.
- CR ongoing and maintained for over 2 months as of data cut 2022-03-07

Other tumor types across all dose levels

Tumor type	Total N=37
Breast	4 (11%)
Esophageal	1 (3%)
Head/Neck	**2 (5%)**
Lung	**5 (14%)**
Ovarian	1 (3%)
Pancreatic	6 (16%)
Urothelial	18 (49%)

- 1 SD at 7.5mg/m^2 Q2W. Disappearance of non-target lesions.

- 1 SD at 2.5mg/m^2 9+ months on therapy
- 1 SD at 7.5mg/m^2 QW. 6+ months on therapy

Will explore other tumor types during the Phase 2 expansion

Conclusions

- BT8009 exhibits promising preliminary tolerability profile with absence of significant skin and ocular toxicity
- BT8009 exhibits a robust efficacy signal in urothelial carcinoma with deep and durable responses observed
- Dose optimization is ongoing
- Phase 2 expansion is planned in monotherapy and combination with CPI

Acknowledgements

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