A first in class phase I/II study of the novel bicyclic peptide and MMAE conjugate, BT5528, in patients with advanced malignancies associated with EphA2 expression

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Meredith McKean MD, MPH.

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Employee of: Sarah Cannon
Background: Ephrin A2 (EphA2)

Erythropoietin-producing hepatocellular A2 receptor: member of Eph subfamily of receptor tyrosine kinases

Regulates cell migration, adhesion, proliferation and differentiation

Overexpressed in human cancers and correlates with tumor progression

Development of MEDI-547 (MedImmune) in ovarian cancer was halted following serious bleeding events in phase I.

“The bleeding and coagulation events observed in humans showed similarities to those evident in rats and monkeys. In all three species, increased activated partial thromboplastin time, increased fibrinogen/fibrin degradation product, and increased fibrin D-dimer were reported. Monkeys had red/blood discharge from the nose, mouth, gums.”


BT5528: A bicycle toxin conjugate

- Ephrin A2 protein
- Highly specific and high avidity Bicycle Binder
- Spacer
- Val-cit linker
- MMAE
Bicycle toxin conjugates – engineered to penetrate and remain in tumors but not the circulation

Pre-clinical toxicology and efficacy models

No bleeding events seen in BT5528 toxicology studies

- Dosing to toxin equivalent doses >100x dose of MEDI-547 used in patients
- No significant effect on clotting parameters
- No evidence of abnormal liver function
Multiple pre-clinical models showed target presence robustly parallels efficacy

Trial design

Bayesian logistic regression method-based escalation

Standard ‘3+3’ Dose escalation and stopping rules

Predicted efficacious range

Cohort expansion

Nivolumab combination

Inclusion/Exclusion criteria:
Standard first-in-human criteria

Prior Neuropathy must have returned to ≤Grade 1
Pre-existing eye conditions were not excluded per se nor were patients with diabetes

IHC based enrichment for EphA2+ve tumors introduced mid-trial

Objectives:
Primary – Safety and tolerability
Secondary – PK, PD and preliminary signs of efficacy

ClinicalTrials.gov Identifier: NCT04180371
### Results: Overview of key demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>24 (100%)</td>
</tr>
<tr>
<td><strong>Age, years, median (range)</strong></td>
<td>65.5 (49-76)</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7 (29%)</td>
</tr>
<tr>
<td>Female</td>
<td>17 (71%)</td>
</tr>
<tr>
<td><strong>ECOG, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11 (46%)</td>
</tr>
<tr>
<td>1</td>
<td>13 (54%)</td>
</tr>
<tr>
<td>2+</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Prior Therapies, median, (range)</strong></td>
<td>7 (range 1-16)</td>
</tr>
</tbody>
</table>

Data as of 14Jul21, preliminary/emerging data
## Overview of key adverse events

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Related Gr ≥ 3 AE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=13 events</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>N=8</td>
</tr>
<tr>
<td>Anemia</td>
<td>N=2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>N=1</td>
</tr>
<tr>
<td>Ileus</td>
<td>N=1</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>N=2</td>
</tr>
<tr>
<td>Tumor Lysis Syndrome</td>
<td>N=1</td>
</tr>
<tr>
<td>Bleeding disorders</td>
<td>N=0</td>
</tr>
<tr>
<td>Conjunctival disorders</td>
<td>N=0</td>
</tr>
<tr>
<td>Cutaneous events</td>
<td>N=0</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>N=0</td>
</tr>
</tbody>
</table>

- Total number of adverse events: 235
- Adverse events related to BT5528: 101
- Other toxicities (<Gr 3) were predominantly hematological and gastrointestinal

Data at 14Jul21, emerging/preliminary data
Dose escalation on study

2 out of 2 DLTs: Grade 3 Fatigue, Pneumonitis

Transient Grade 3/4 neutropenia, GI disturbances noted led to Q2W dosing exploration

Pending phase 2 dose recommendation: 6.5-8.5 mg/m² Q2W

2.2 mg/m² QW
4.4 mg/m² QW
6.5 mg/m² QW
8.5 mg/m² Q2W
10 mg/m² Q2W
BT5528 and MMAE Clinical PK

Mean ± SD (n=13) plasma concentration-time profiles following an IV infusion of 4.4 mg/m² BT5528

Parent conjugate (BT5528)

Free plasma payload (MMAE)

BT5528 clinical pk predicted from preclinical data

No difference D1 vs D15
Linear over the dose range 2.2 to 8.5 mg/m² (limited data)
Patients dosed at 6.5mg/m2 and above are presented here.

At various doses the following tumors were recruited:

- Pancreatic, Ovarian, Ewing’s, NSCLC, Urothelial
- Urothelial and Ovarian carcinomas showed significant signs of clinical activity

### Summary of efficacy

<table>
<thead>
<tr>
<th>Group</th>
<th>Preliminary unconfirmed responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>All comers, all doses</td>
<td>3/24 response rate (12.5%)</td>
</tr>
<tr>
<td>Ovarian Cancer all comers</td>
<td>1/8 response rate (12.5%)</td>
</tr>
<tr>
<td>Ovarian Cancer IHC positive</td>
<td>1/5 response rate (20%)</td>
</tr>
<tr>
<td></td>
<td>4/5 disease control (80%)</td>
</tr>
<tr>
<td>Urothelial Cancer</td>
<td>2/2 response rate (100%)</td>
</tr>
</tbody>
</table>
Efficacy: Patient with urothelial bladder cancer Partial response

Pre-treatment BT5528

2 months post first dose

ABSENT
Same patient: Larger lesion

Pre-treatment BT5528

2 months post first dose
Responses:

- **Ovarian**
  - 1 out of 8 ovarian cancer patients
  - 4 out of 5 patients with EphA2 staining showed some shrinkage
  - 1 PR by month 4

- **Urothelial**
  - 2/2, PRs both at 2 months
  - Both responses by first scan
  - 1 PR ongoing
  - 1 PR sustained systemically but with pre-existing CNS lesion progression at 7 months
Among selected tumor types EphA2 staining and RECIST nadirs appear to correlate

- More EphA2 staining = more tumor shrinkage
- Early relationship with low numbers
Conclusions and next steps

- BT5528 is a first in class, small, and tumor penetrant, bicyclic peptide conjugated to MMAE
- A tolerable and effective dose has been outlined with activity in at least two tumor types (Ovarian and Urothelial)
- Some toxicities (bone marrow, GI, alopecia) overlap with ADC profiles
- No evidence of BT5528 clotting abnormalities versus multiple DIC events for MEDI-547 ADC
- Salient differences may also exist – lack of neuropathy, eye and skin tox (early data, etc.)
- Correlation between target presence and efficacy appears to be more pronounced than with ADCs
- Meaningful PD and PK observations suggest impactful tumor penetration with short systemic vascular compartment half-life
- Formal cohort expansion in multiple tumor types is in planning
- Other Bicyclic peptides are also being tested in the clinic
  - 2 PRs and 2 SDs out of 5 bladder cancer patients at the 5mg/m² dose with BT8009 (Nectin-4 targeted MMAE conjugate which is still in Phase 1 dose escalation)
  - Further dose escalations will be watched closely
Thank you to patients, their caregivers, family, friends and sites.