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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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Employee of: Sarah Cannon

Background: Ephrin A2 (EphA2)

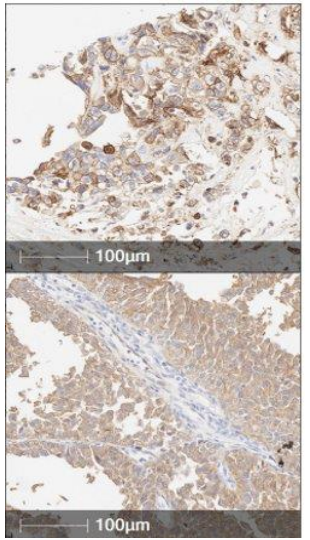
Erythropoietin-producing hepatocellular A2 receptor: member of Eph subfamily of receptor tyrosine kinases

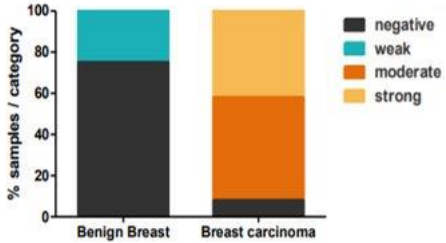
Regulates cell migration, adhesion, proliferation and differentiation

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.

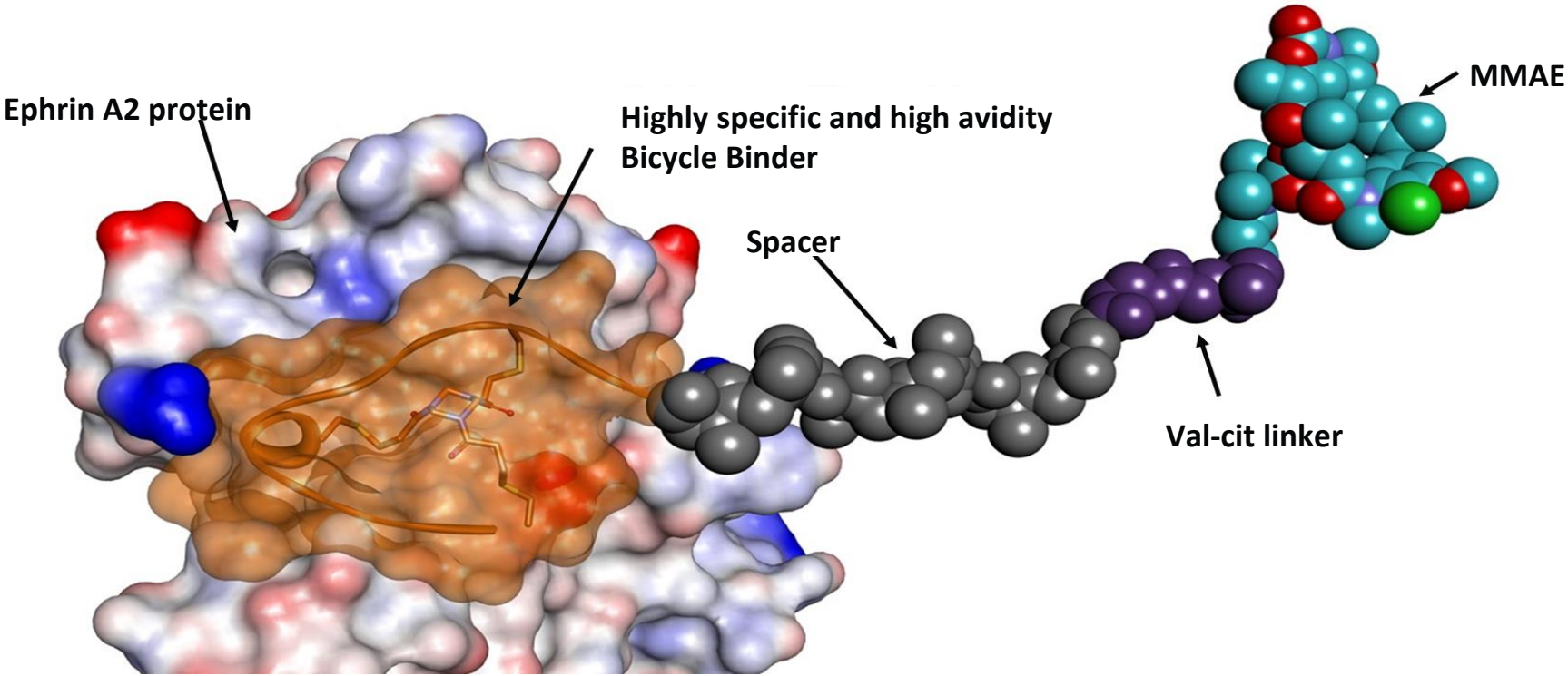
> "The bleeding and coagulation events observed in humans showed similarities to those evident in rats and monkeys. In all three species, increased activated partial thromboplastin time, increased fibrinogen/fibrin degradation product, and increased fibrin D-dimer were reported. Monkeys had red/ blood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



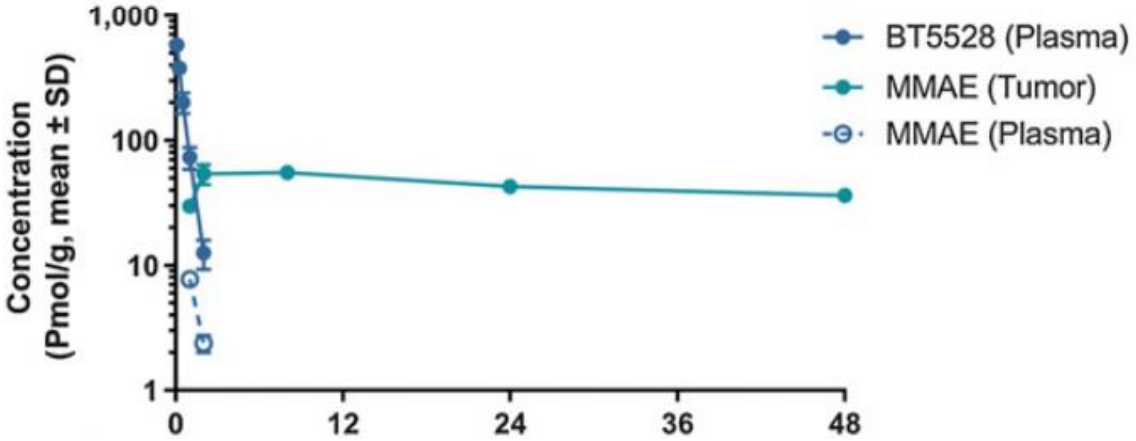


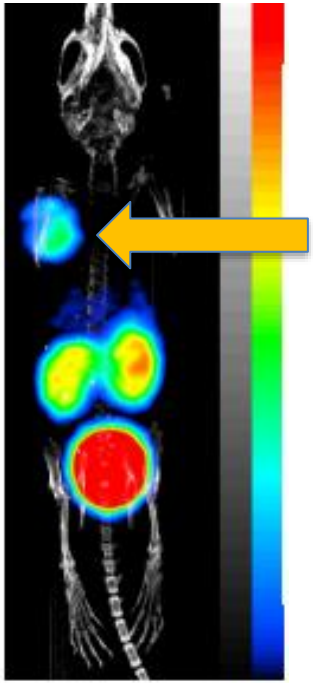
Annunziata, Christina M., et al. "Phase 1, open-label study of MEDI-547 in patients with relapsed or refractory solid tumors." *Investigational new drugs* 31.1 (2013): 77-84.
Zelinski, Daniel P., et al. "EphA2 overexpression causes tumorigenesis of mammary epithelial cells." *Cancer research* 61.5 (2001): 2301-2306.

BT5528: A bicycle toxin conjugate



Bicycle toxin conjugates – engineered to penetrate and remain in tumors but not the circulation





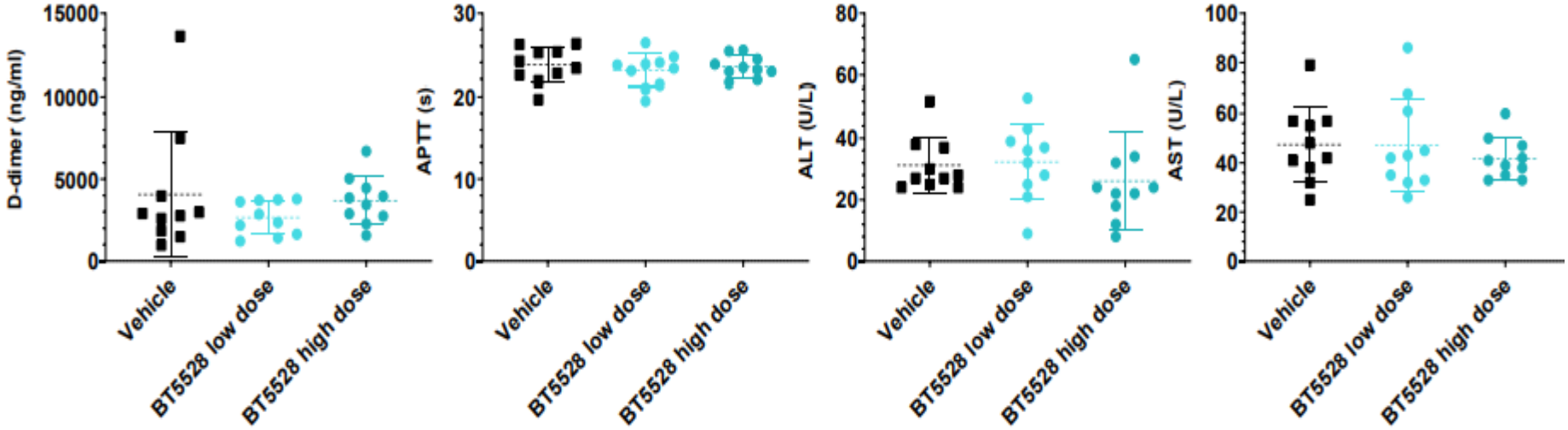
Tumor penetration after 45 minutes of dosing

Bennett, Gavin, et al. "MMAE delivery using the Bicycle toxin conjugate BT5528." *Molecular cancer therapeutics* 19.7 (2020): 1385-1394.

Pre-clinical toxicology and efficacy models

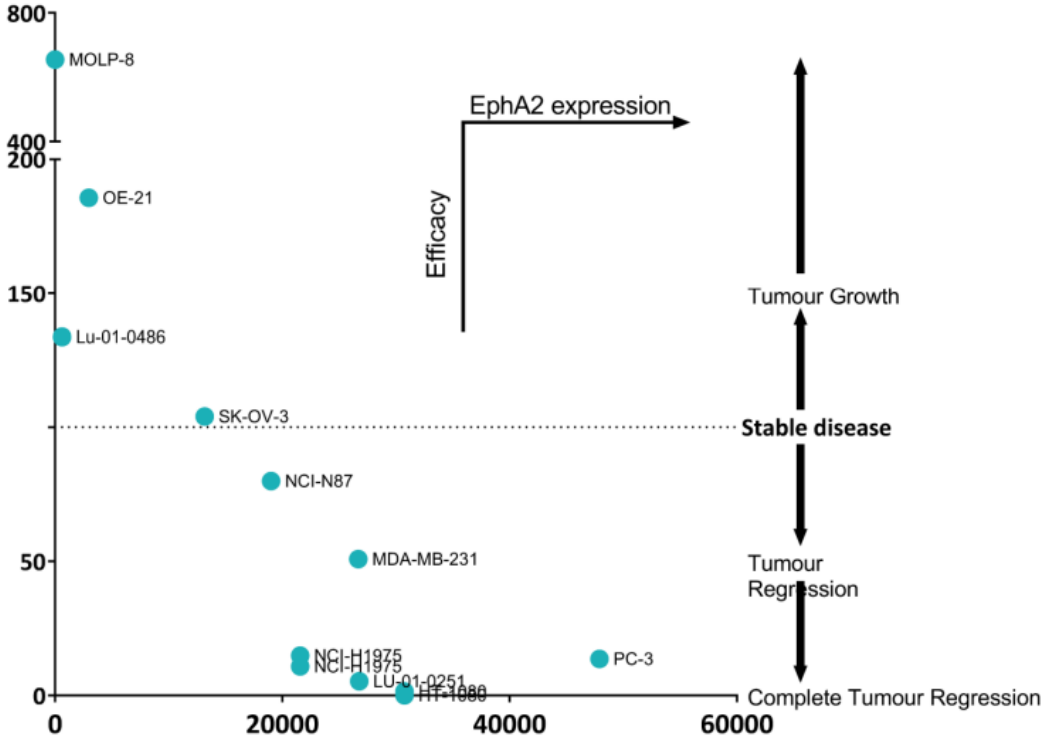
No bleeding events seen in BT5528 toxicology studies

- 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



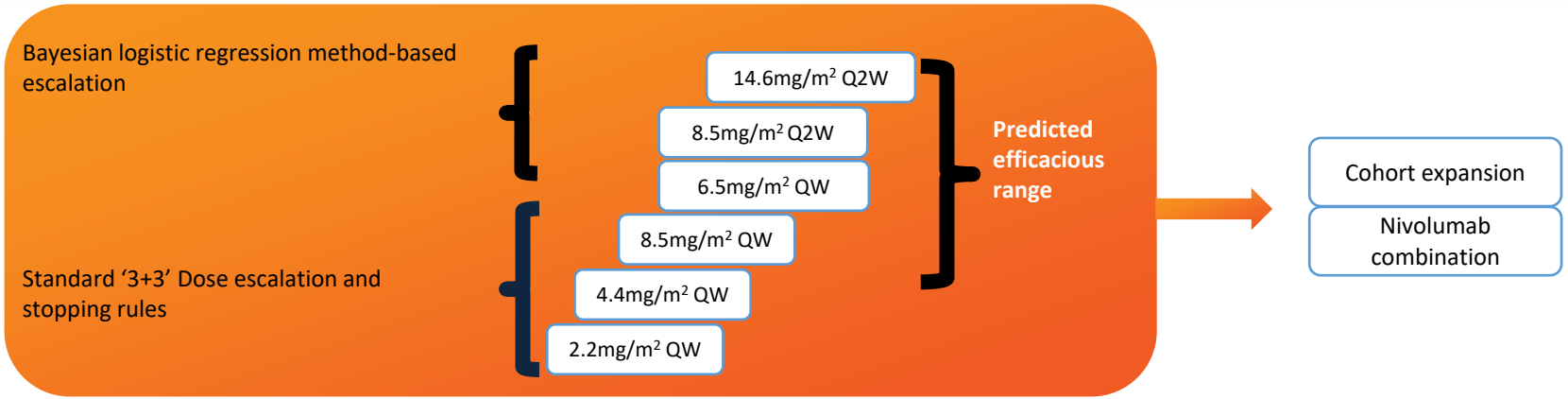
Multiple pre-clinical models showed target presence robustly parallels efficacy

Xenograft tumor volume
% reduction versus baseline



Bennett, Gavin, et al. "MMAE delivery using the Bicycle toxin conjugate BT5528." *Molecular cancer therapeutics* 19.7 (2020): 1385-1394.

Trial design



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

Demographics	
Total	24 (100%)
Age, years, median (range)	65.5 (49-76)
Sex, n (%)	
Male	7 (29%)
Female	17 (71%)
ECOG, n (%)	
0	11 (46%)
1	13 (54%)
2+	0 (0%)
Prior Therapies, median, (range)	**7 (range 1-16)**

Data as of 14Jul21, preliminary/emerging data

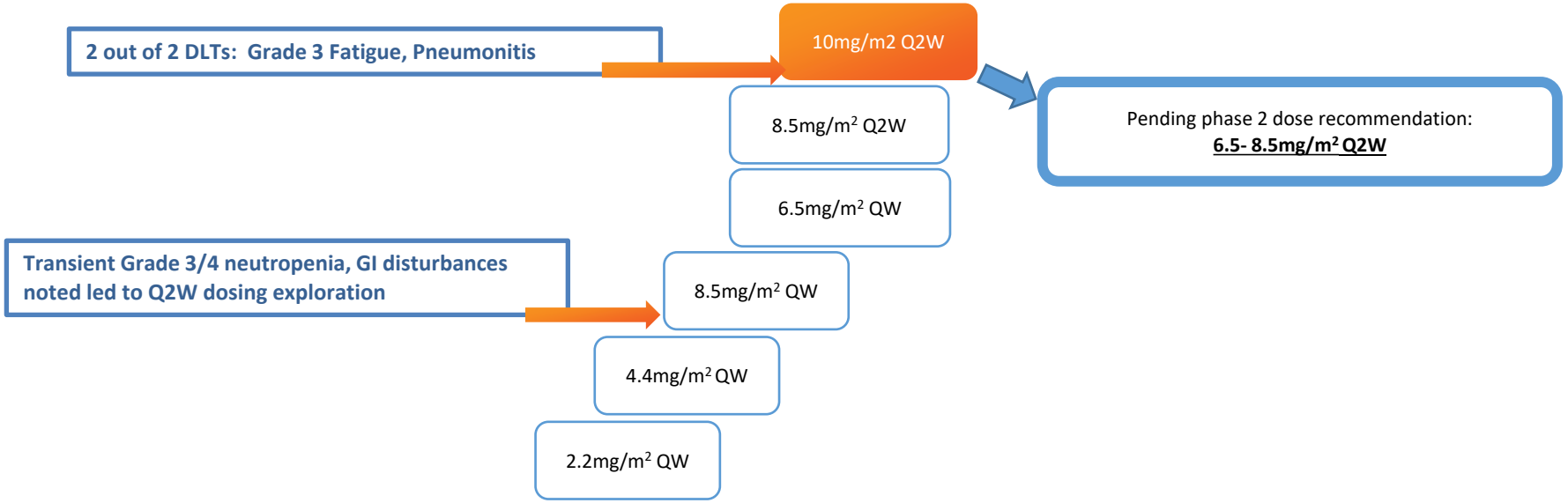
Overview of key adverse events

Adverse Events	Related Gr ≥ 3 AE N=13 events
Neutropenia	N=8
Anemia	N=2
Fatigue	N=1
Ileus	N=1
Pneumonitis	N=2
Tumor Lysis Syndrome	N=1
Bleeding disorders	N=0
Conjunctival disorders	N=0
Cutaneous events	N=0
Neuropathy	N=0

Data at 14Jul21, emerging/preliminary data

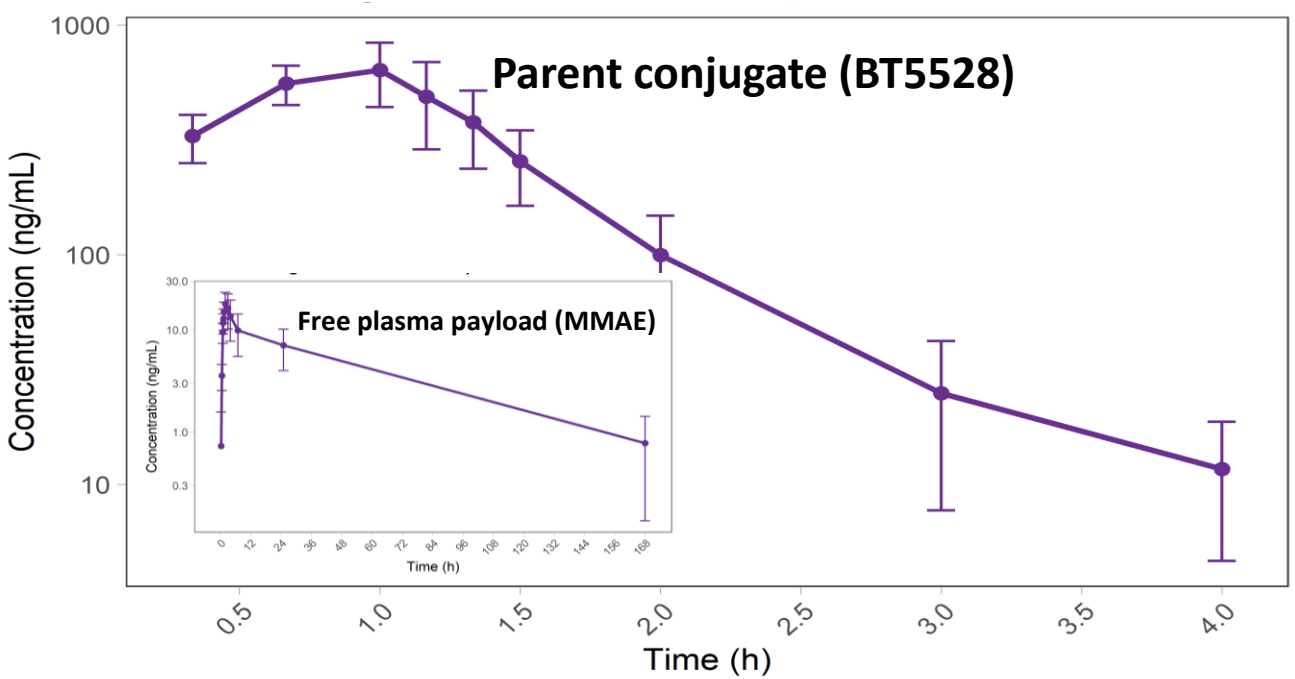
- Total number of adverse events: 235
- Adverse events related to BT5528: 101
- Other toxicities (<Gr 3) were predominantly hematological and gastrointestinal

Dose escalation on study



BT5528 and MMAE Clinical PK

Mean ± SD (n=13) plasma concentration-time profiles following an IV infusion of 4.4 mg/m^2 BT5528



BT5528 clinical pk predicted from preclinical data

- No difference D1 vs D15
- Linear over the dose range 2.2 to 8.5 mg/m^2 (limited data)

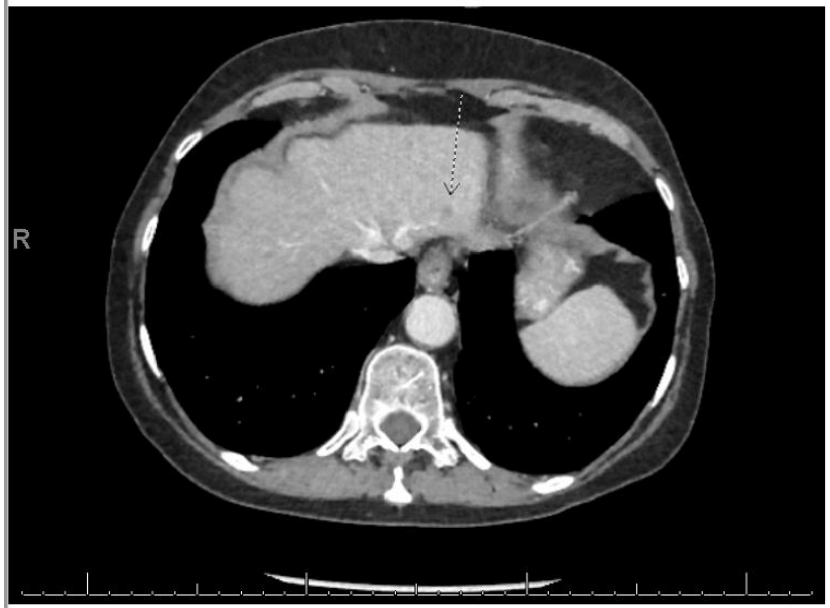
Summary of efficacy

- 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

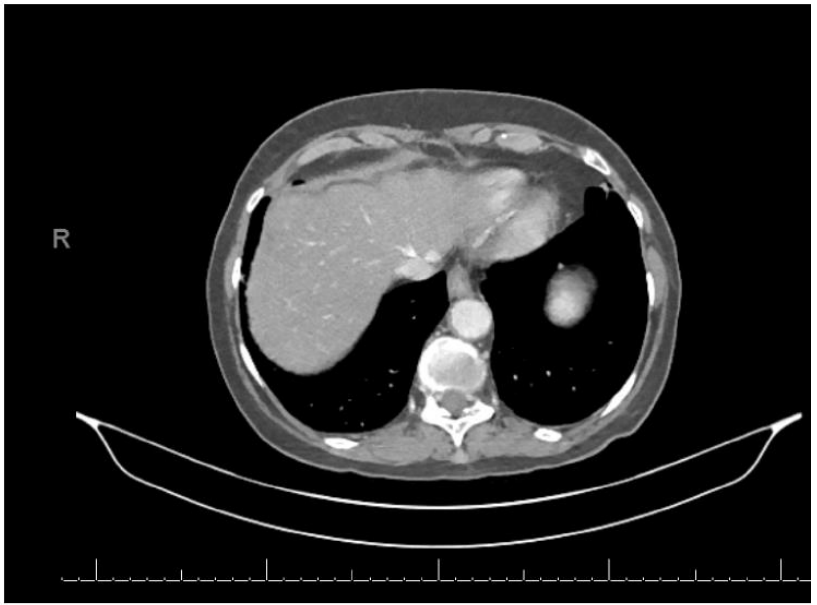
Group	Preliminary unconfirmed responses
All comers, all doses	3/24 response rate (12.5%)
Ovarian Cancer all comers	1/8 response rate (12.5%)
Ovarian Cancer IHC positive	1/5 response rate (20%) 4/5 disease control (80%)
Urothelial Cancer	2/2 response rate (100%)

Efficacy: Patient with urothelial bladder cancer Partial response

Pre-treatment BT5528



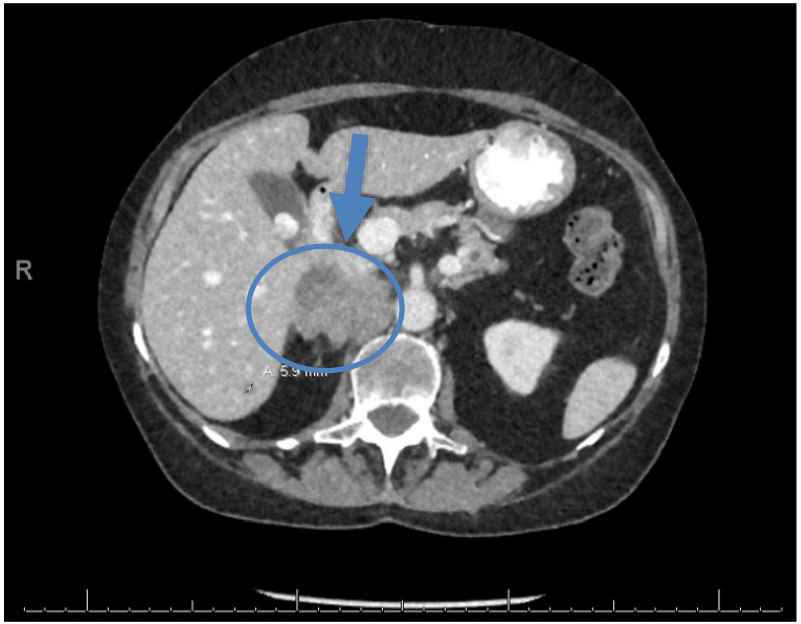
2 months post first dose



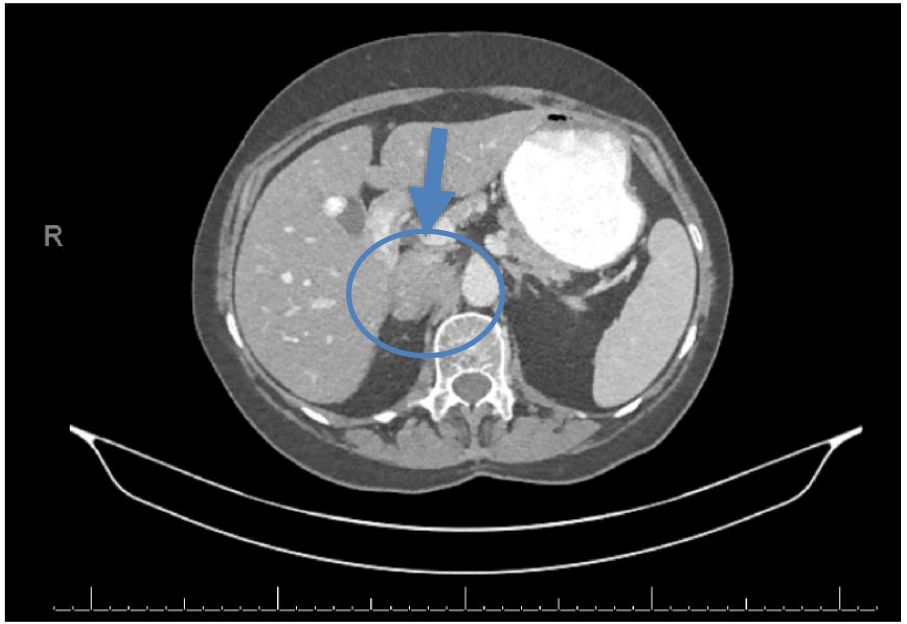
ABSENT

Same patient: Larger lesion

Pre-treatment BT5528



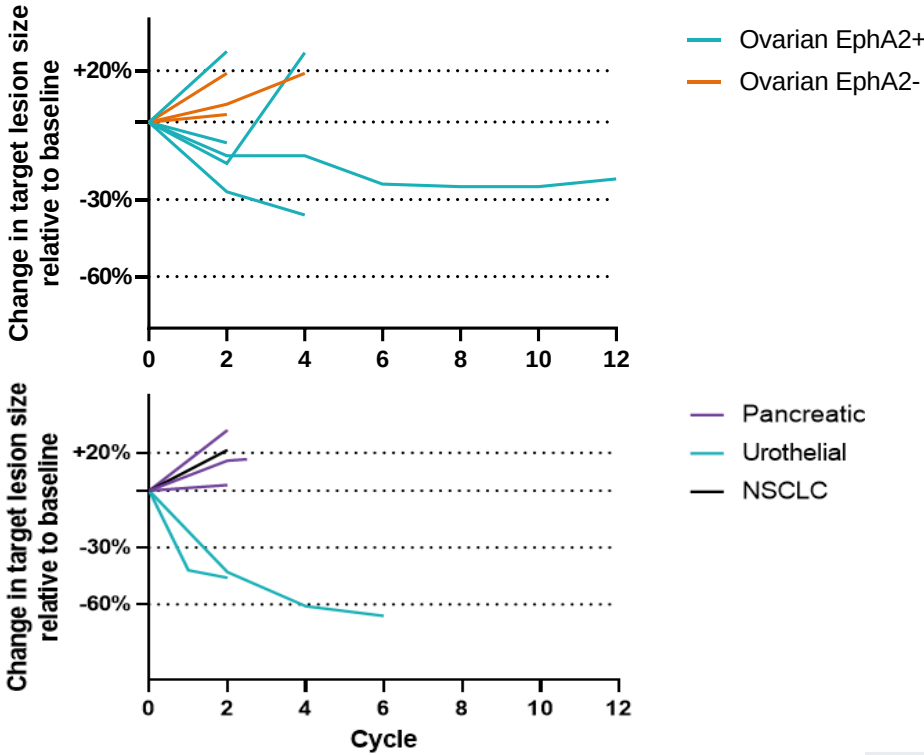
2 months post first dose



BT5528: Efficacy over time

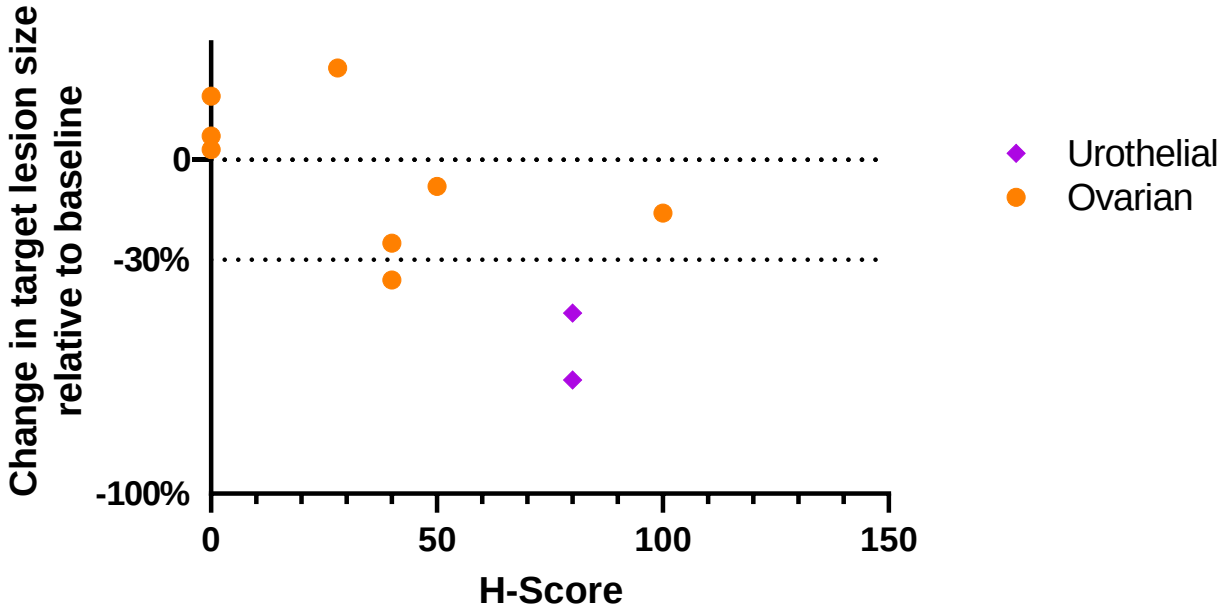
Responses:

- 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/m^2 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

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