Interim Phase I Update on BT5528 and Preliminary Findings from BT8009 Program

October 7, 2021

bicycle therapeutics

Forward-looking statements

This presentation may contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. These statements may be identified by words such as "aims," "anticipates," "believes," "could," "estimates," "expects," "forecasts", "goal," "intends," "may" "plans," "possible," "potential," "seeks," "will," and variations of these words or similar expressions that are intended to identify forward-looking statements. All statements other than statements of historical facts contained in this presentation are forward-looking statements, including statements regarding our future financial or business performance, conditions, plans, prospects, trends or strategies and other financial and business matters; our current and prospective product candidates, planned clinical trials and preclinical activities, current and prospective collaborations and the timing and success of our development of our anticipated product candidates.

Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based on our current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, our development plans, our preclinical and clinical results, our plans to initiate clinical trials and the designs of the planned trials and other future conditions, and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to, risks related to the ongoing COVID-19 pandemic, the risk that any one or more of our product candidates will not be successfully developed or commercialized, the risk of cessation or delay of any ongoing or planned clinical trials, the risk that we may not realize the intended benefits of our technology, including that we may not identify and develop additional product candidates for our pipeline, the risk that we may not maintain our current collaborations or enter into new collaborations in the future, or that we may not realize the intended benefits of these collaborations, the risk that our product candidates or procedures in connection with the administration thereof will not have the safety or efficacy profile that we anticipate, the risk that prior results will not be replicated or will not continue in ongoing or future studies or trials, the risk that we will be unable to obtain and maintain regulatory approval for our product candidates, the risk that the size and potential of the market for our product candidates will not materialize as expected, risks associated with our dependence on third-parties, risks regarding the accuracy of our estimates of expenses, risks relating to our capital requirements and needs for additional financing, and risks relating to our ability to obtain and maintain intellectual property protection for our product candidates. For a discussion of these and other risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the section entitled "Risk Factors" in our Quarterly Report on Form 10-Q, filed with the Securities and Exchange Commission on August 5, 2021, as well as in other filings we may make with the SEC in the future, as well as discussions of potential risks, uncertainties and other important factors in our subsequent filings with the Securities and Exchange Commission. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

Agenda

Introduction	**Kevin Lee** Chief Executive Officer
Review monotherapy trials to date: **BT5528** **BT8009**	**Dominic Smethurst** Chief Medical Officer
Beyond BT5528 and BT8009	**Nick Keen** Chief Scientific Officer
Closing remarks	**Lee Kalowski** President and Chief Financial Officer
Q&A	**Executive Management Team**

Robust proprietary and partnered pipeline

Target / Product	Partner / Sponsor	Indication	Modality	Pre-clinical	IND-enabling	Phase I	Phase II
Internal programs							
BT5528 (EphA2)		Oncology	Bicycle® Toxin Conjugate				
BT8009 (Nectin-4)		Oncology	Bicycle® Toxin Conjugate				
BT7480 (Nectin-4/CD137)		Immuno-oncology	Bicycle TICA™				
BT7455 (EphA2/CD137)		Immuno-oncology	Bicycle TICA™				
Partnered programs							
THR-149 (Kallikrein inhibitor Bicycle)	OXURION	Ophthalmology					
BT1718 (MT1-MMP)	CANCER RESEARCH UK	Oncology	Bicycle® Toxin Conjugate				
BT7401 (multivalent CD137 systemic agonist)	CANCER RESEARCH UK	Immuno-oncology					
Undisclosed	Genentech A Member of the Roche Group	Immuno-oncology					
Inhaled Bicycles	AstraZeneca	Respiratory					
Novel anti-infectives	Innovate UK	Anti-infectives					
Novel CNS targets	Dementia Discovery Fund IONIS	CNS					
Novel neuromuscular targets	IONIS	Neuromuscular					

BT5528 Monotherapy

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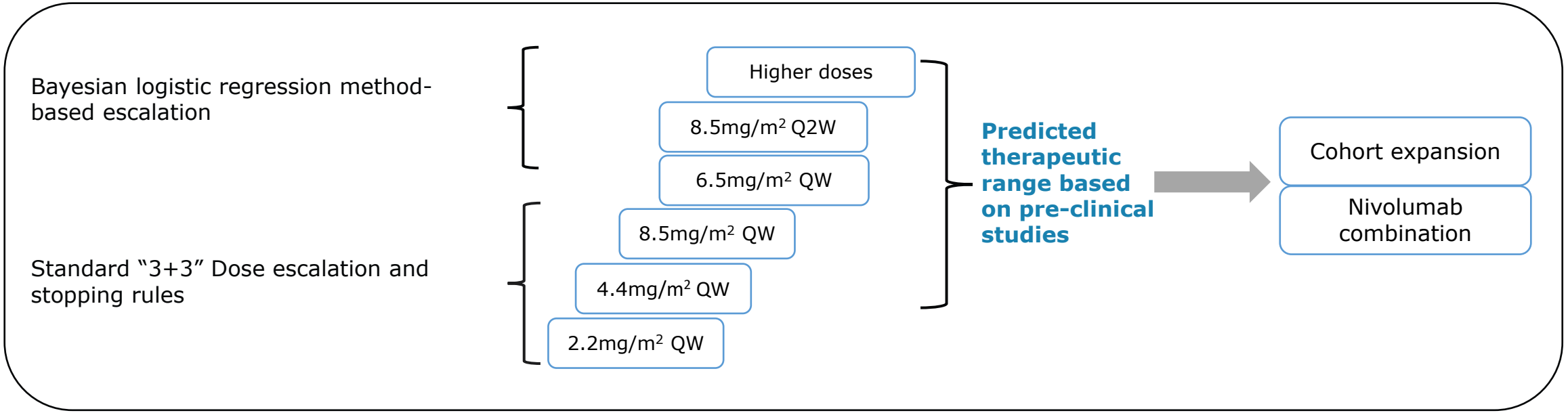
Background to BT5528 and ADC target: EphA2

- 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."[1]

1. 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 phase I dose escalation: trial design



Inclusion/Exclusion criteria:

- Standard first-in-human criteria
- **Prior neuropathy must have returned to ≤Grade 1**
- IHC based enrichment for EphA2(+) tumors introduced mid-trial

Objectives:

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

ClinicalTrials.gov Identifier: NCT04180371

Overview of key demographics for patients enrolled in BT5528 phase I dose escalation trial

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

Data as of 14Jul21, not fully QCed

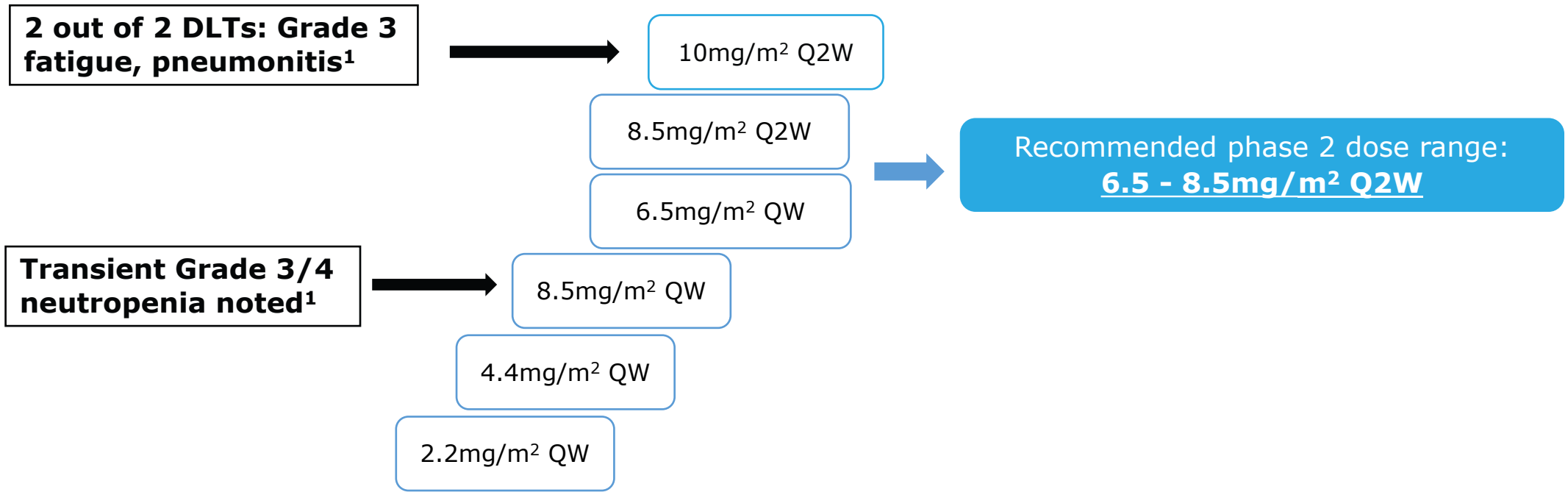
Overview of key adverse events observed in BT5528 phase I dose escalation trial

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

- Total number of adverse events: 235[1]
- Adverse events related to BT5528: 101[1]
- Other toxicities (<Gr 3) were predominantly hematological and GI[1]
- Two Gr 5 events observed, one following data cut-off

1. Data as of 14Jul21, not fully QCed

BT5528 phase I dose escalation – establishment of RP2D range



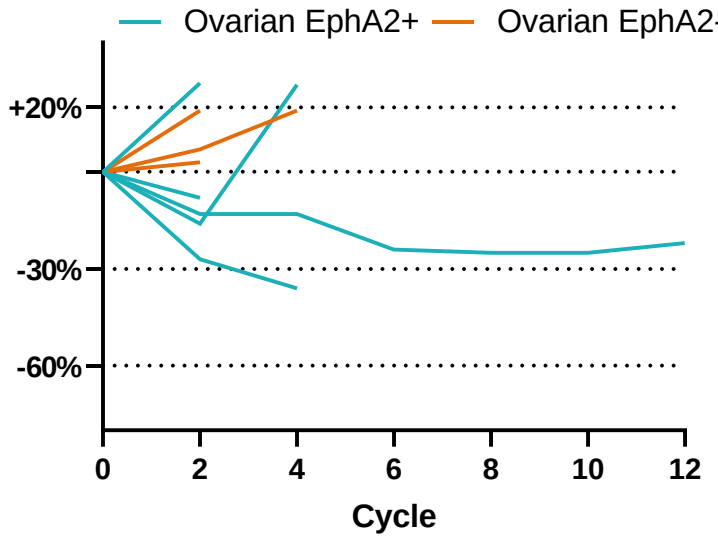
1. Data as of 14Jul21, not fully QCed

BT5528: Preliminary responses observed during phase I dose escalation trial

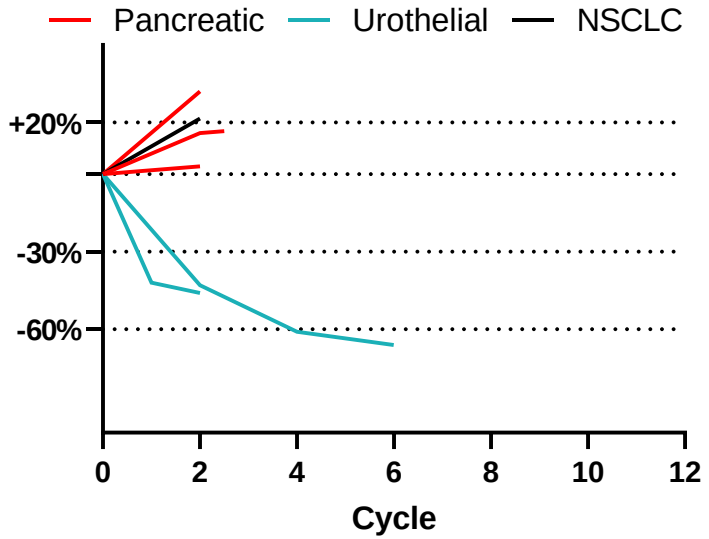
Responses observed:

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

Change in target lesion size relative to baseline



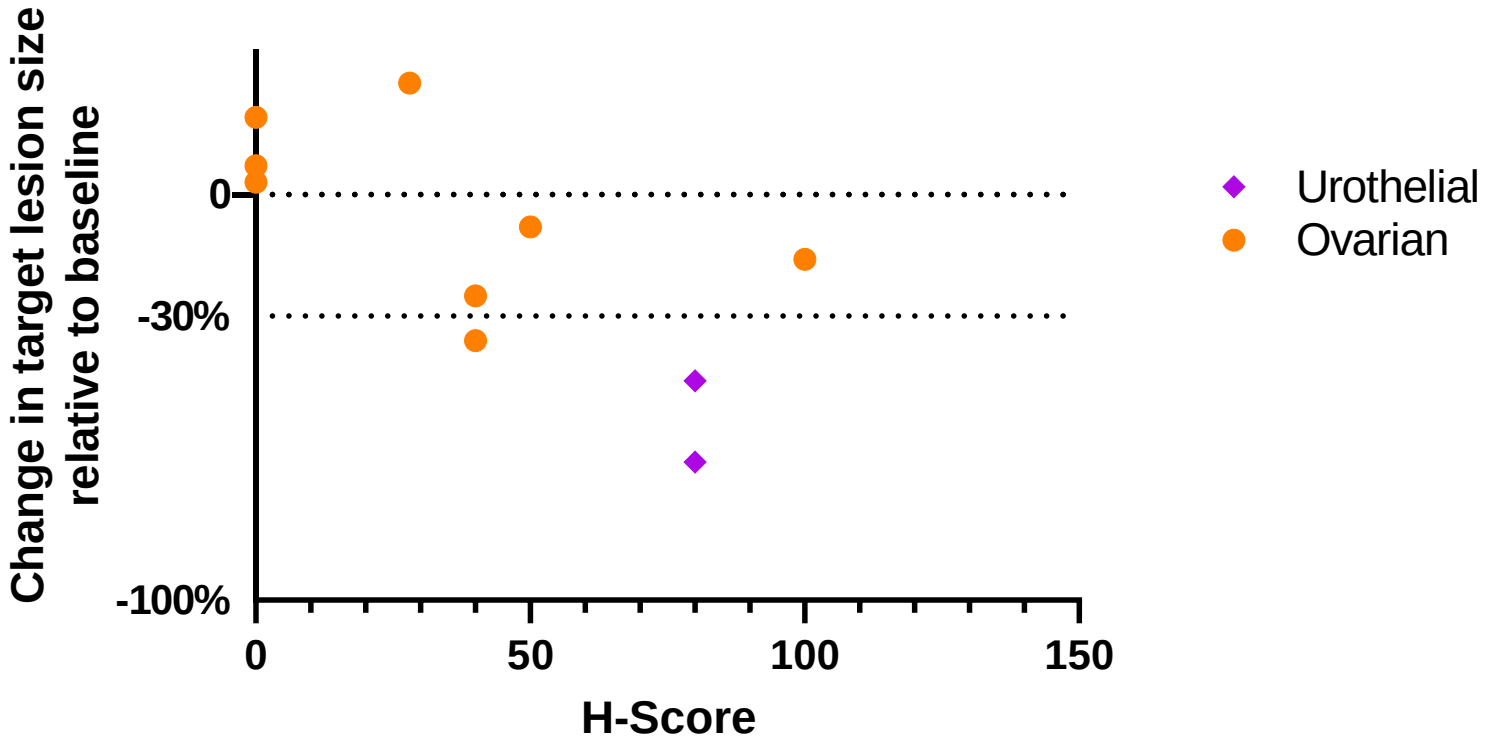
- **Urothelial**
  - 2 of 2 PRs[1], both at 2 months
  - Both responses by first scan



1. Partial responses under response evaluation criteria in solid tumors (RECIST) version 1.1.
Data as of 14Jul21, not fully QCed

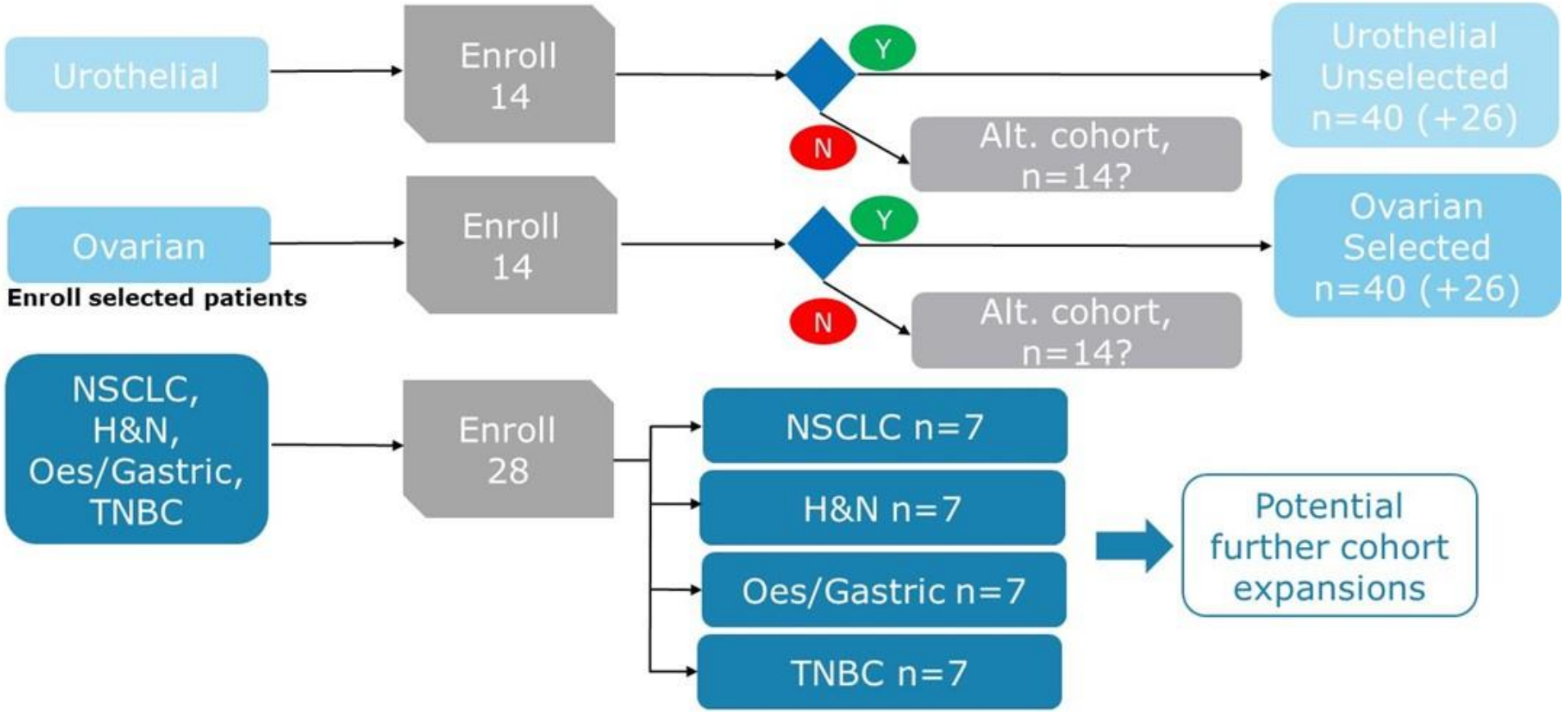
Emerging observed relationship between EphA2 staining and responses

- More EphA2 staining = more tumor shrinkage
- Early relationship with low numbers



Data as of 14Jul21, not fully QCed

BT5528 expansion: overall trial design



BT5528 – Phase I dose escalation preliminary conclusions and next steps

- BT5528 is a first-in-class *Bicycle*® toxin conjugate
- No evidence of BT5528 clotting abnormalities vs multiple disseminated intravascular coagulation events for MEDI-547 ADC
- Doses tolerated within expected therapeutic range; preliminary anti-tumor activity observed in two tumor types (ovarian and urothelial)
- Additional potential points of differentiation: to date, neuropathy, eye and skin toxicities not observed in BT5528 clinical trial
- Preliminary findings indicate activity associated with tumor expression
- Preparations underway for expansion cohorts in multiple tumor types

BT8009 Monotherapy

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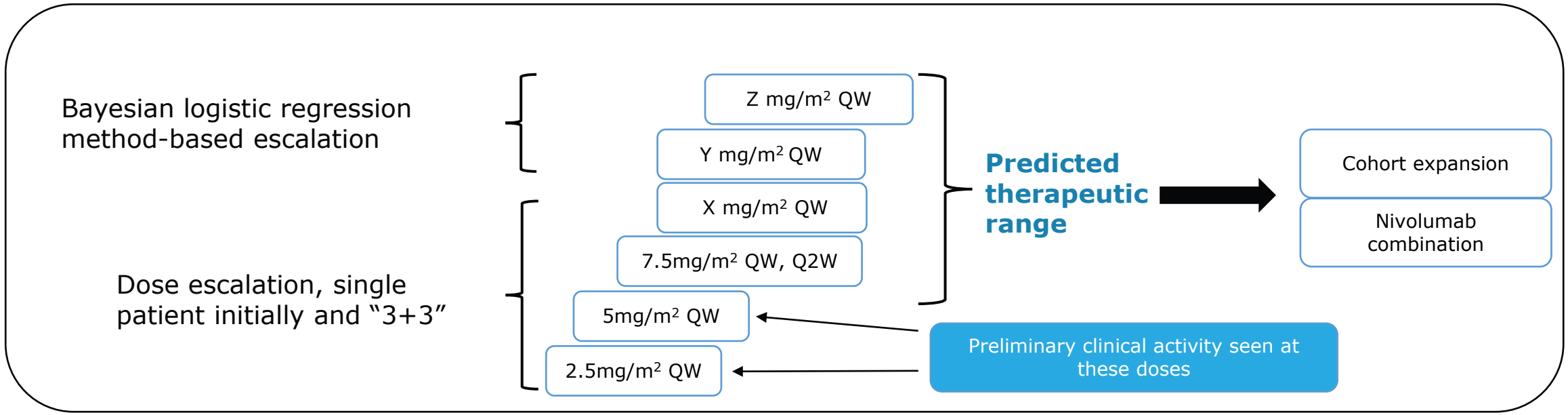
Background to BT8009 and ADC target: Nectin-4

- A cell adhesion molecule and one of four members of the nectin family
- All nectins share the same overall structure defined by three extracellular immunoglobulin domains, a single transmembrane helix and an intracellular domain
- Overexpressed in human cancers and correlated with tumor progression
- Solid tumors with high levels of Nectin-4 expression are urothelial, TNBC, ovarian, head & neck and NSCLC
- Target for Padcev (enfortumab vedotin), an FDA approved ADC

BT8009 phase I dose escalation trial design – currently escalating to 7.5mg/m² QW and Q2W



Inclusion/Exclusion criteria:

- Standard first-in-human criteria
- Any prior Nectin-4 target therapy excluded
- Urothelial patients were not IHC screened for Nectin-4

Objectives:

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

ClinicalTrials.gov Identifier: NCT04561362

Overview of key demographics for evaluable patients enrolled in BT8009 phase I dose escalation trial

Demographics	
Total	26 (100%)
Age, years, median (range)	66 (44-81)
Sex, n (%)	
Male	15 (58%)
Female	11 (42%)
ECOG, n (%)	
0 (Good performance status)	11 (42%)
1	15 (58%)
2+	0
Prior therapies, median (range)	**5 (2-12)**

Data as of 30Sept21, not fully QCed

BT8009 phase I dose escalation trial: evaluable patients enrolled by tumor type

Demographics	
Total	26 (100%)
By tumor type:	
Urothelial	11 (42%)
Pancreatic	6 (23%)
NSCLC	4 (15%)
TNBC	3 (12%)
Head & Neck	1 (4%)
Ovarian	1 (4%)

Data as of 30Sept21, not fully QCed

Key demographics of evaluable urothelial cancer patients participating in BT8009 phase I dose escalation trial

Demographics	
Total	11 (100%)
Age, years, median (range)	69 (54-81)
Sex, n (%)	
Male	9 (82%)
Female	2 (18%)
ECOG, n (%)	
0 (Good performance status)	7 (64%)
1	4 (36%)
2+	0
Prior therapies, median (range)	2 (2-6)

Data as of 30Sept21, not fully QCed

Overview of key adverse events observed in BT8009 phase I dose escalation trial across all patients (N=27)

Adverse Events	Related Gr ≥3 AE N=10 events
Anemia	N=4
Neutropenia	N=3
Hypertension	N=1
Hypokalemia	N=1
Asthenia	N=1

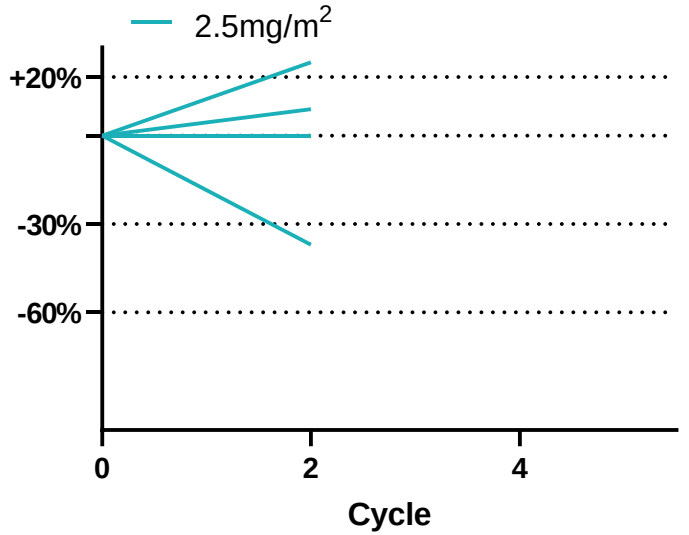
Data as of 30Sept21, not fully QCed

BT8009: preliminary responses observed in phase I dose escalation by dose in response evaluable urothelial cancer patients

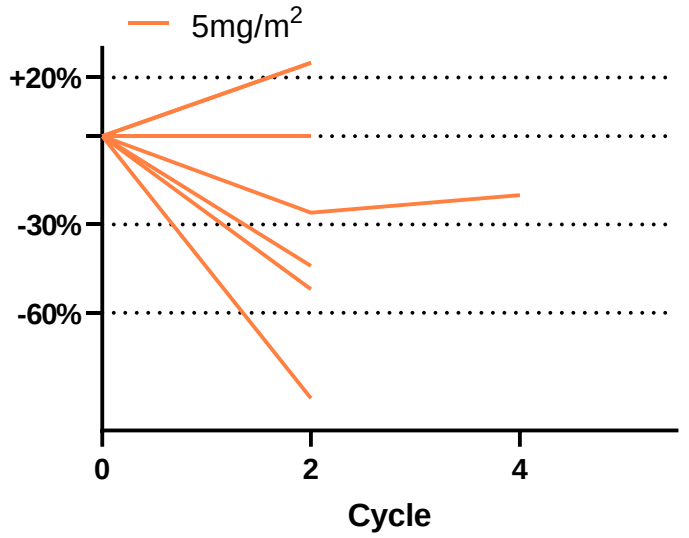
Responses observed:

- **2.5mg/m²**
  - 1 of 4 PR[1]: -37% tumor reduction
  - 2 of 4 SD
  - 75% disease control

Change in target lesion size relative to baseline



- **5mg/m²**
  - 3 of 7 PR[1]
    - -89% tumor reduction
    - -52% tumor reduction
    - -44% tumor reduction
  - 2 of 7 SD
  - 71% disease control



1. Partial responses under response evaluation criteria in solid tumors (RECIST) version 1
Data as of 30Sept21, not fully QCed

Comparison of BT8009 to enfortumab vedotin (Padcev©) phase I dose escalation – urothelial cancer

Comparison*	BT8009 2.5mg/m²	BT8009 5mg/m²	BT8009 both cohorts	Enfortumab (1mg/kg and below)**	Enfortumab (All cohorts)**
No of patients	4	7	11	26	33
Median age	75	68	69	67	67
≥2 prior lines (%)	4 (100%)	7 (100%)	11 (100%)	N/A	25 (60%)
IHC pre-screen (%)	0	0	0	26 (100%)	33 (100%)
Partial or Complete Response (ORR %)	1 (25%)	3 (43%)	4 (36%)	6 (23%)	10 (30%)
Stable Disease or better (DCR %)	3 (75%)	5 (71%)	8 (73%)	N/A	N/A
Adverse event commentary			No eye tox, no DLTs		21% had Gr1/2 eye tox, 6% had DLTs

BT8009 data as of 30Sept21, not fully QCed

* This comparison is for illustrative purposes only. This table does not depict a head-to-head trial.

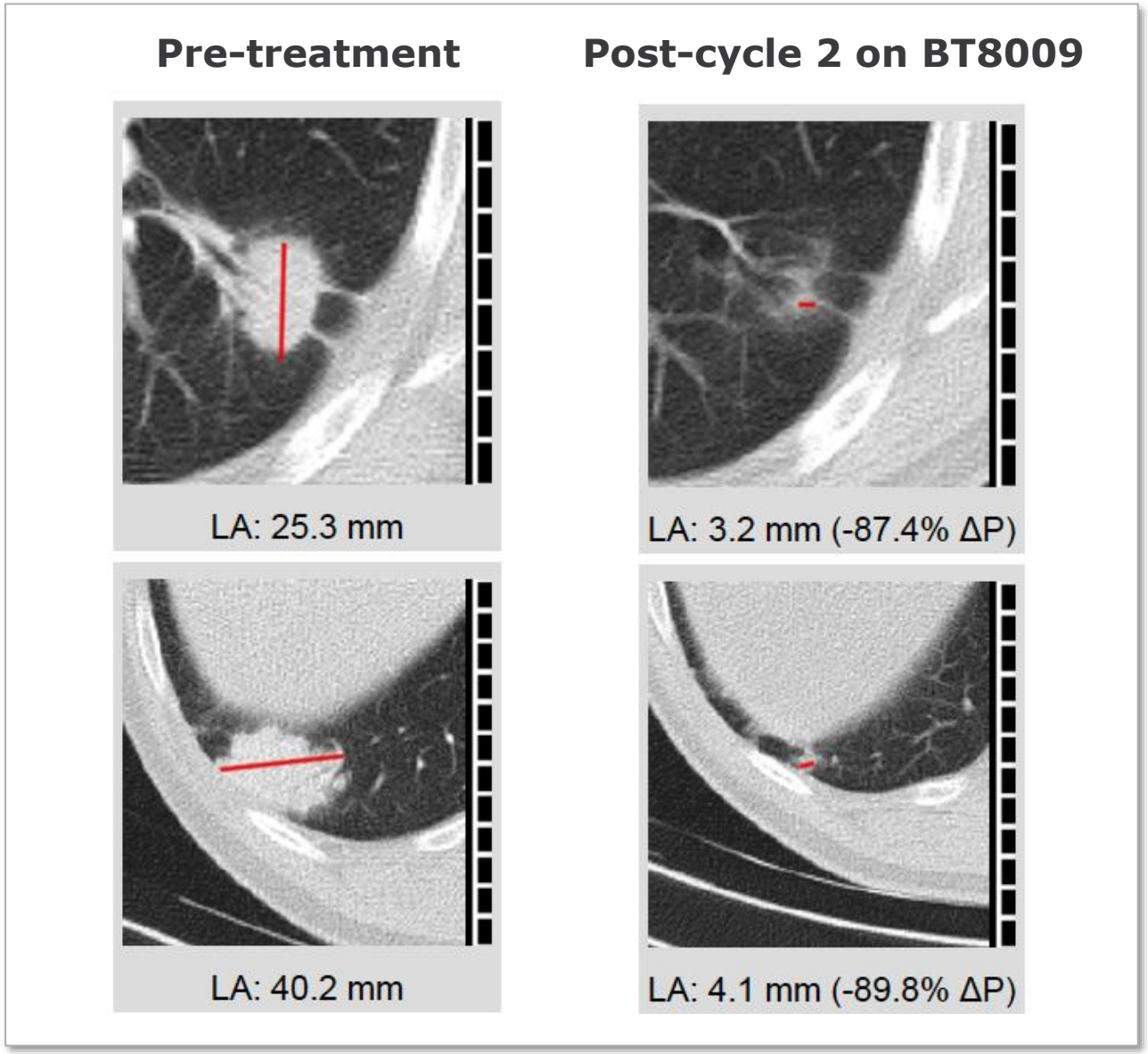
** Rosenberg, Jonathan, et al. "Interim analysis of a phase I dose escalation trial of ASG-22CE (ASG-22ME; enfortumab vedotin), an antibody drug conjugate (ADC), in patients (Pts) with metastatic urothelial cancer (mUC)" *Annals of Oncology 27 (Supplement 6): vi266-vi295*, 2016

More information on preliminary responses observed for urothelial cancer patients in BT8009 phase I dose escalation trial

	Patient A	Patient B	Patient C	Patient D
Dose (mg/m^2)	2.5	5.0	5.0	5.0
Age	81	68	66	62
Sex	M	M	M	M
Prior lines of therapy	2	2	2	2
Partial response	-37%	-89%	-44%	-52%

Data as of 30Sept21, not fully QCed

Comparison of Patient B pre-dose tumor images with tumor images after 2 months treatment (5mg/m² QW)



Target lesions were reduced by -89% after two cycles of BT8009 treatment

BT8009 phase 1 dose escalation summary as of Sept 30

- No DLTs observed and escalation remains ongoing, with patients currently being enrolled in 7.5 mg/m^2 weekly and every-other-week cohorts
- BT8009 anti-tumor activity observed in pre-treated, urothelial cancer patients in both cohorts
- Doses tolerated within the expected therapeutic range; most common side effects GI-related
- Expect to present additional Phase I data in 2022

Beyond BT5528 and BT8009

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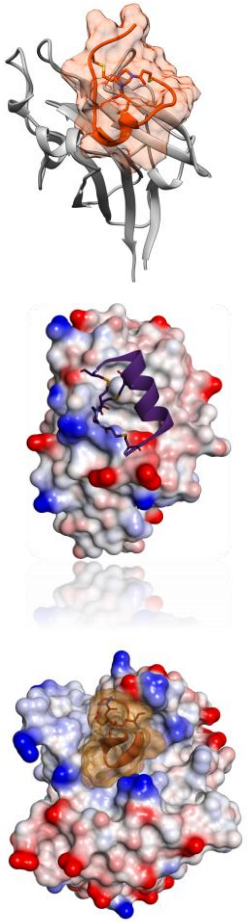
We believe we are well positioned to be the next generation of targeted oncology therapeutics

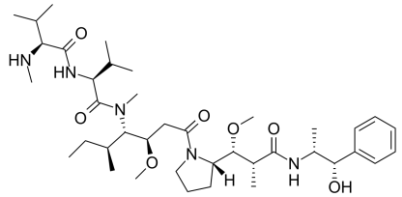
Tumor targeting *Bicycles*



DEPTH

Building depth in internal library of tumor antigen binding Bicycles

Bicycle Toxin Conjugates®

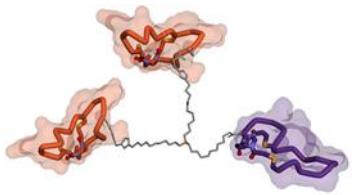


- Clinical signal observed
- Generalizable to other payloads
- Intend to build on current clinical trial observations with "wave" of 3rd Gen molecules

3rd Gen BTCs

- Broaden indications with additional targets and payloads

Bicycle® TICAs



- BT7480 expected to enter phase I 4Q21
- BT7455 in IND enabling studies
- We believe our platform uniquely suited to tumor specific IO modulation
- Generalizable to multiple receptor classes

2nd Gen IO

- Tumor cell specific NK cell engagers in optimization
- Multi-targeted molecules in discovery

Internal & external pipeline combinations

- Short $t_{1/2}$ critical for sequencing
- Current data provides compelling biological rationale for combination of cytotoxic BTC with TICAs and / or PD1

BREADTH

Looking forward

- Plan to initiate BT5528 expansion cohorts in 2022
- BT8009 dose escalation to 7.5 mg/m^2 will continue during Q4. Expect to present additional Phase I data in 2022
- BT7480 - a Nectin-4-CD137 Bicycle TICA® - anticipate dosing first patient by year end 2021
- Third generation Bicycle Toxin Conjugates® and NK cell engagers are in development

Question and Answer

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