# Constrained peptides
# Unconstrained thinking

August 2020

bicycle
therapeutics

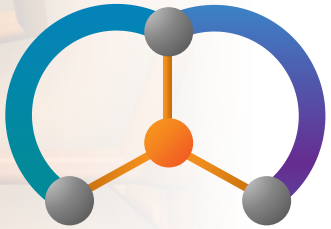
# Forward-looking statements

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 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 (SEC) on August 5, 2020, as well as in other filings Bicycle 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.

# Our goal is to create transformational medicines

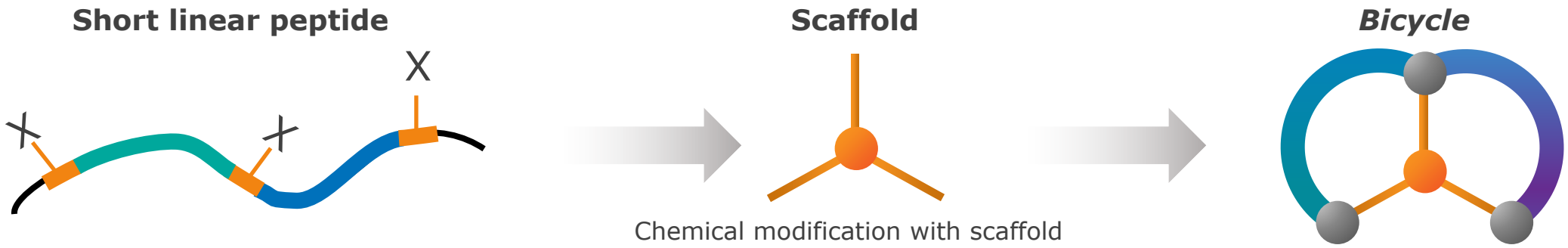
We aim to redefine what's possible for people with cancer and other serious diseases by pioneering a new and differentiated class of innovative treatments



Engineering *Bicycles*® to solve unique therapeutic challenges

- Advancing wholly-owned oncology pipeline of multiple clinical assets
- Developing world's first fully synthetic immuno-oncology (IO) platform
- Exploring broad potential beyond oncology through partnerships
- Led by world class management team, supported by strong financial foundation

# *Bicycles*® are a new therapeutic modality for addressing intractable challenges




| | Chemical synthesis | Rapid tissue distribution | Complex protein targets druggable | Route of elimination |
|---|---|---|---|---|
| Small molecules | +++ | +++ | --- | Liver |
| Antibodies | --- | + | +++ | Liver |
| *Bicycles* | +++ | +++ | +++ | Renal |

### Built-in tolerance to conjugation

- Generalizable approach
- Versatility to adopt multiple formats

### Phage-based screening platform

- Nobel Prize-winning technology
- Rapid selection from >$10^{17}$ potential candidates

### Robust patent protection

- >90 patent families
- Expiration into 2030s



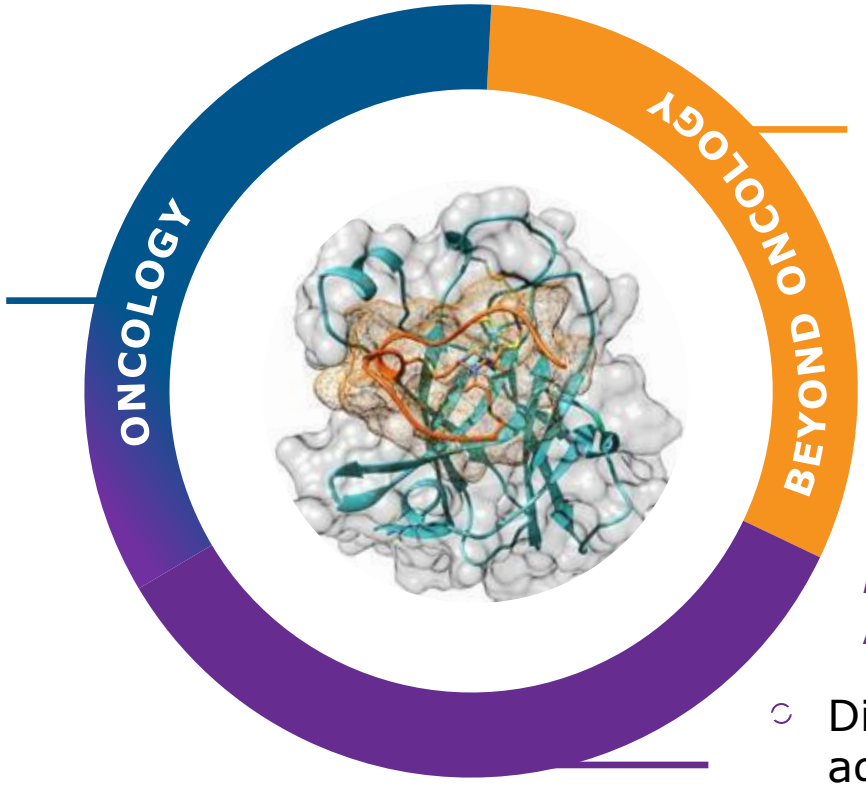


bicycle therapeutics

# Internal focus on oncology, partnerships to explore additional applications across therapeutic areas

## *Bicycle*® Toxin Conjugates

- Toxin delivery system with unique mechanism of action
- Potentially improved safety & efficacy over other modalities




- Leverage platform's versatility
- More efficiently bring novel medicines to patients

## *Bicycle* Immune Cell Agonists

- Differentiated approach to agonizing immune cells
- May overcome limitations of antibody & biologic therapies
- Multiple formats, e.g. systemic & targeted





bicycle therapeutics

# Robust proprietary and partnered pipeline

| Product/Target | Therapeutic Interest | Collaborator | Stage: Discovery/ Preclinical | Stage: Clinical |
|---|---|---|---|---|
| ***Bicycle*® Toxin Conjugates** | | | | |
| BT1718 (MT1-MMP) | Oncology | CANCER RESEARCH UK | | |
| BT5528 (EphA2) | Oncology | | | |
| BT8009 (Nectin-4) | Oncology | | | |
| **Immuno-oncology** | | | | |
| BT7480 (Nectin-4/CD137 TICA™) | Oncology | | | |
| BT7401 (multivalent CD137 systemic agonist) | Oncology | CANCER RESEARCH UK | | |
| BT7455 (EphA2/CD137 TICA) | Oncology | | | |
| Undisclosed | Oncology | Genentech | | |
| **Beyond Oncology** | | | | |
| THR-149 (Kallikrein inhibitor *Bicycle*) | Ophthalmology | OXURION | | |
| Inhaled *Bicycles* | Respiratory | AstraZeneca | | |
| Novel anti-bacterials | Anti-infectives | Innovate UK | | |
| Novel CNS targets | CNS diseases | Dementia Discovery Fund | | |





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# *Bicycle*® Toxin Conjugates

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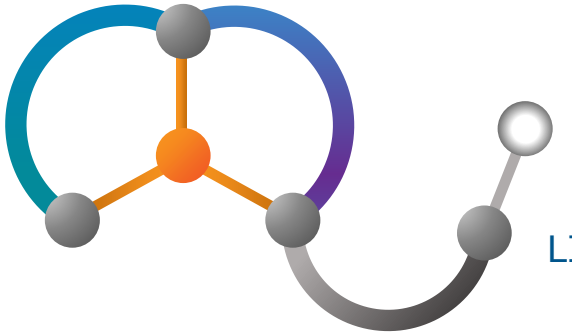
# *Bicycle*® Toxin Conjugates – designed to be selective tumor targeting therapeutics

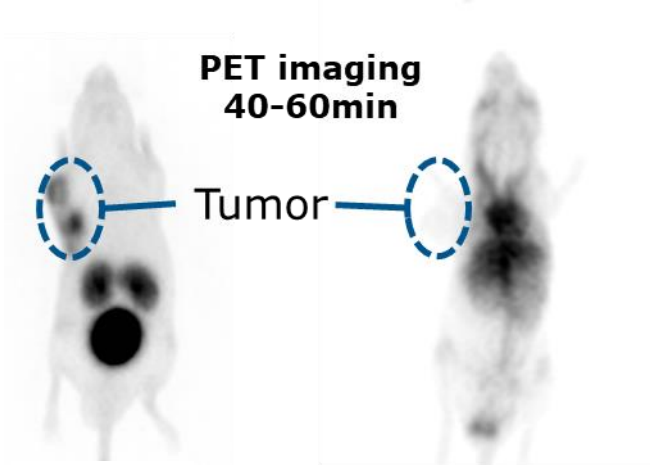
Specific tumor targeting via antigen →



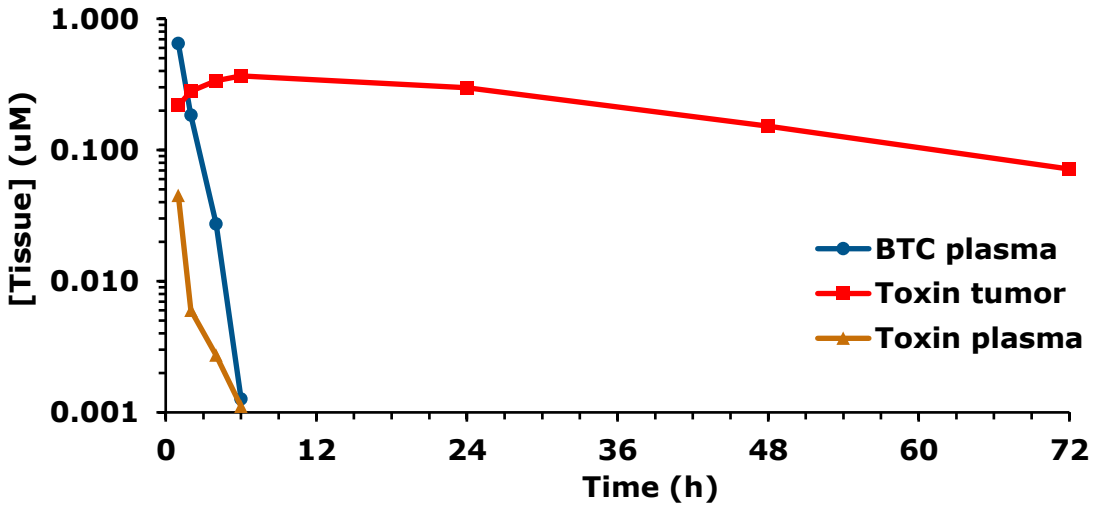
TOXIN ← Large amount of cytotoxic payload can be delivered

LINKER ← Release of toxin directly into tumor via cleavable linker

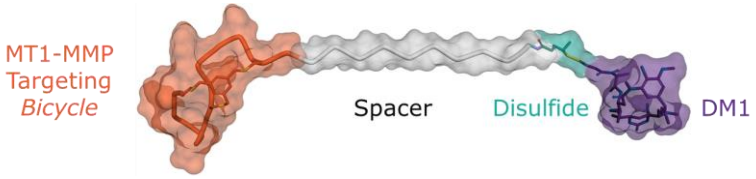
## BTCs offer advantages over antibody drug conjugate (ADC) and small molecule approaches




- MWt of 1.5-2kDa, 50-100x smaller than antibodies
- Rapid tumor penetration
- Renal elimination enhances tolerability
- Short terminal half-life
- Flexible dosing (mono or combo therapy)



# BT1718: Potential first-in-class *Bicycle*® Toxin Conjugate targeting key tumor antigen

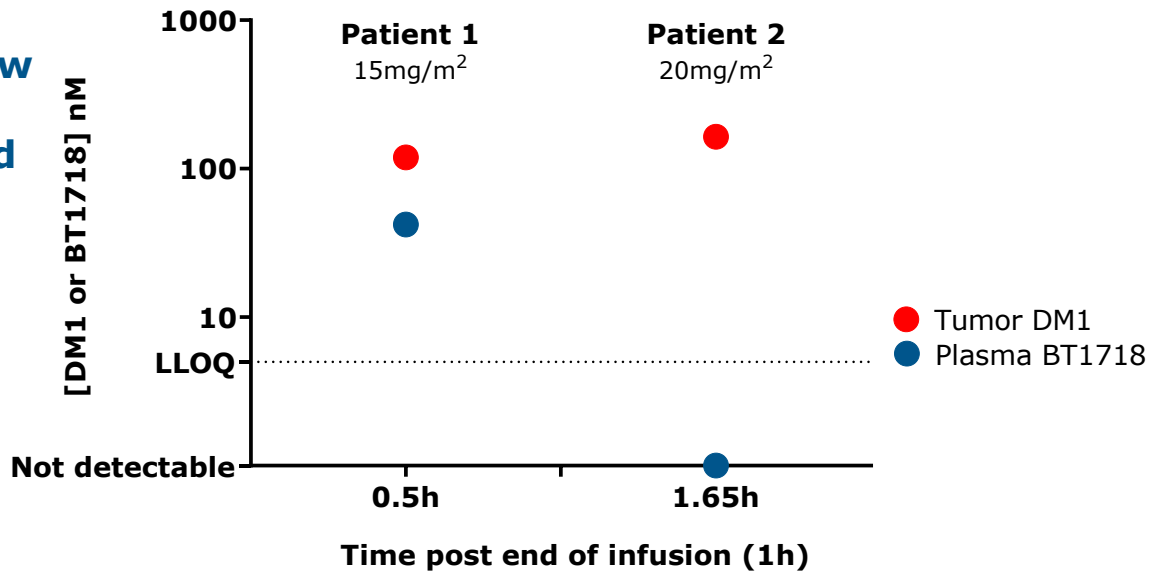



- Highly selective for MT1-MMP (MMP-14)
  - Cell-surface matrix metalloprotease
  - Established role in cell invasion and metastasis
- PhI/IIa open-label, multicenter study in patients with advanced solid tumors is ongoing

**Primary objectives of Phase I dose escalation achieved**

- BT1718 appeared tolerable, with manageable adverse events
- 20mg/m$^2$ once-weekly dose selected for Phase IIa
  - Falls within efficacious dose range predicted preclinically (equivalent doses associated with complete responses)

**Tumor biopsies show payload selectively delivered & retained in tumor**






**Reflecting a data cutoff of August 7, 2019, as reported at ESMO 2019*



CANCER RESEARCH UK

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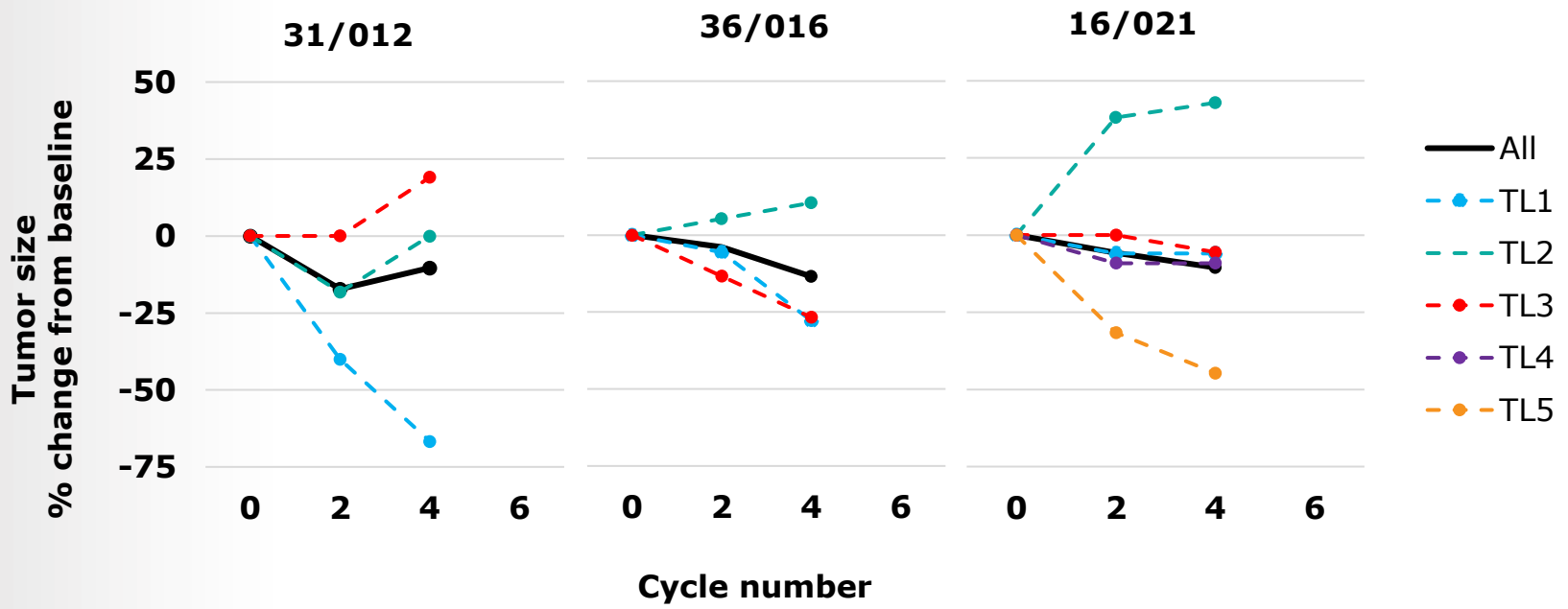
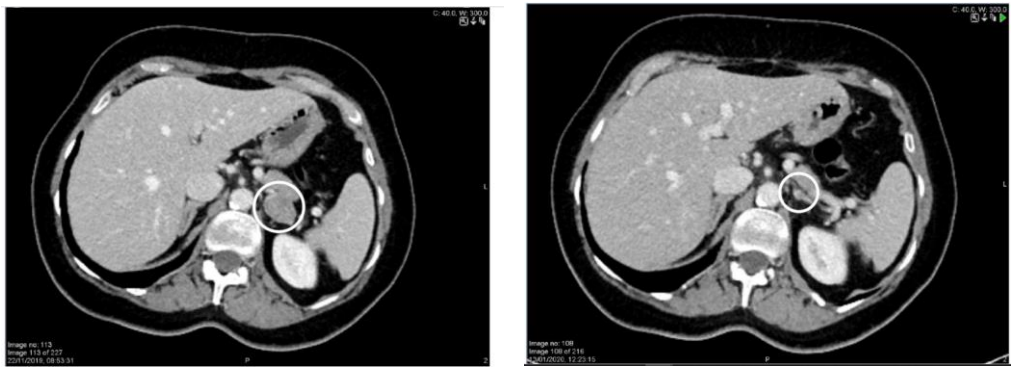
# Clinical data from BT1718 validates Bicycle platform

- **Initial analysis reported at ESMO 2019 shows stable disease in 54% of evaluable patients at 8 weeks***

**At early doses, anti-tumor activity observed in individual target lesions**



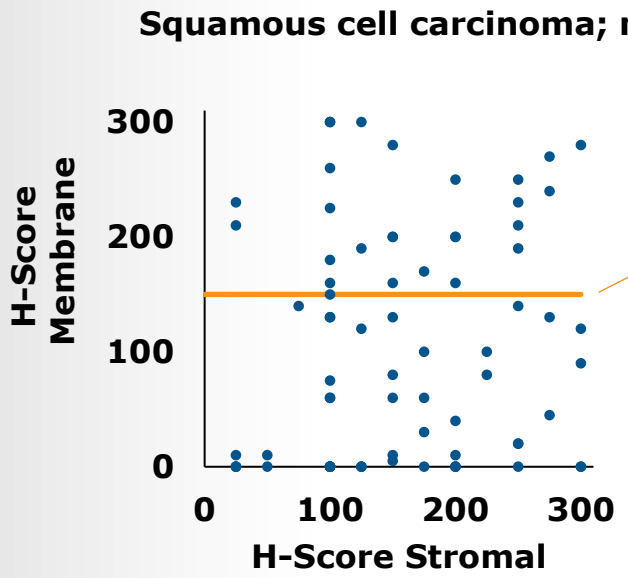

One patient with SCLC experienced a **partial response of a 68% reduction** in a target lesion



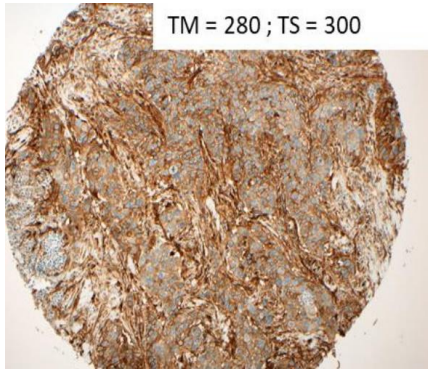
*Reflecting a data cutoff of August 7, 2019, as reported at ESMO 2019

# BT1718 Phase IIa expansion cohorts in MT1-MMP+ patients

**Analysis of historical, primary tumor micro-array (TMA) tissue series indicates squamous cancers as preferred tumor subtype for PhIIa**




Tumor membrane H-score cutoff to be used to select patients in PhIIa expansion cohorts

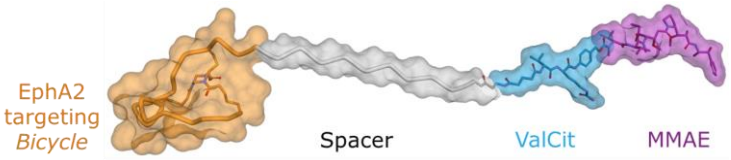



Representative image of lung cancer core with corresponding tumor membrane (TM) and tumor stroma (TS) H-scores

**Primary objectives of Phase IIa study are to evaluate safety and tolerability of BT1718, secondary objectives are to assess preliminary signals of efficacy**

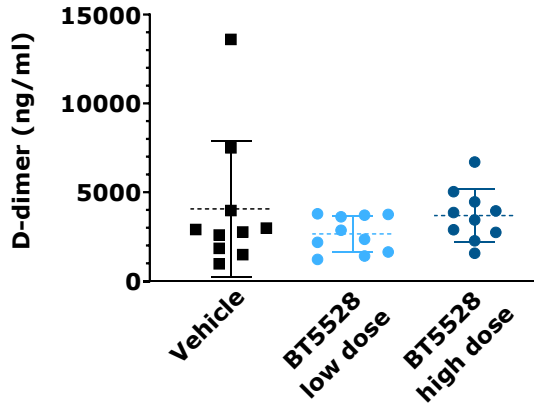

**Additional cohorts may be initiated based on response**

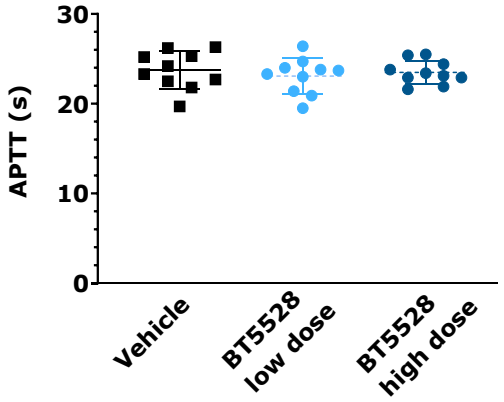
# BT5528: EphA2 BTC delivers improved preclinical safety and efficacy over comparator ADCs



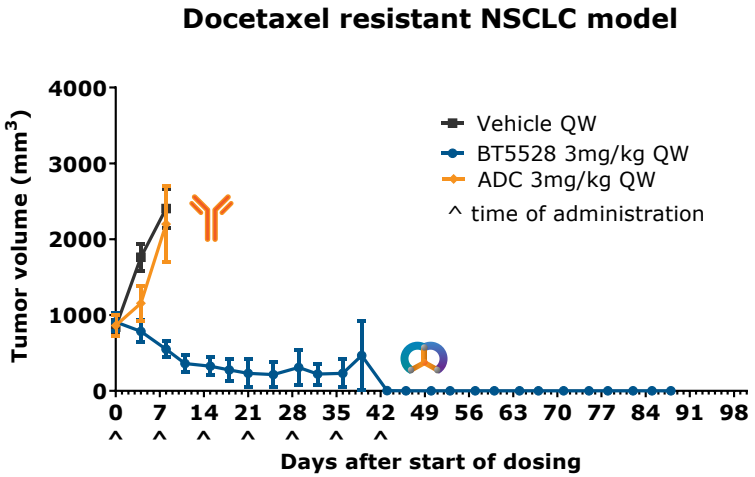

- EphA2 is overexpressed in many difficult to treat tumors
- Previous antibody drug conjugate projects, notably MEDI-547, have failed due to bleeding events
- Dosing is underway in Phase I/II study in patients with advanced solid tumors (BT5528 as monotherapy, lagging combo with nivolumab)
  - Doses administered to date appear well-tolerated with manageable adverse events
- Proprietary EphA2 IHC assay developed, demonstrates expression in high value indications including lung, pancreas and bladder

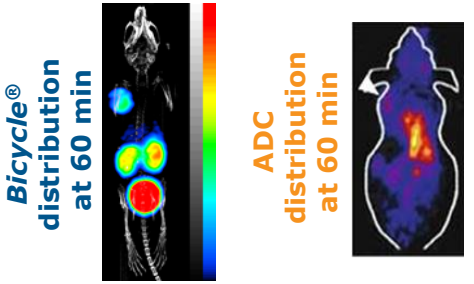
**No signs of coagulopathy or bleeding at toxin equivalent of >150x clinical dose of MEDI-547**

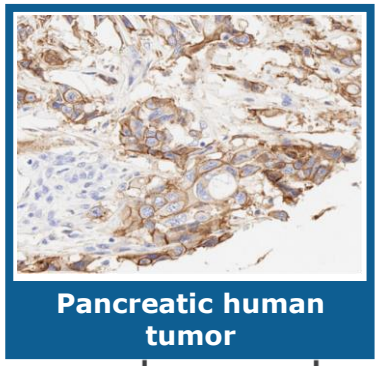



**Displayed superior activity to EphA2 ADC in large tumor xenografts**



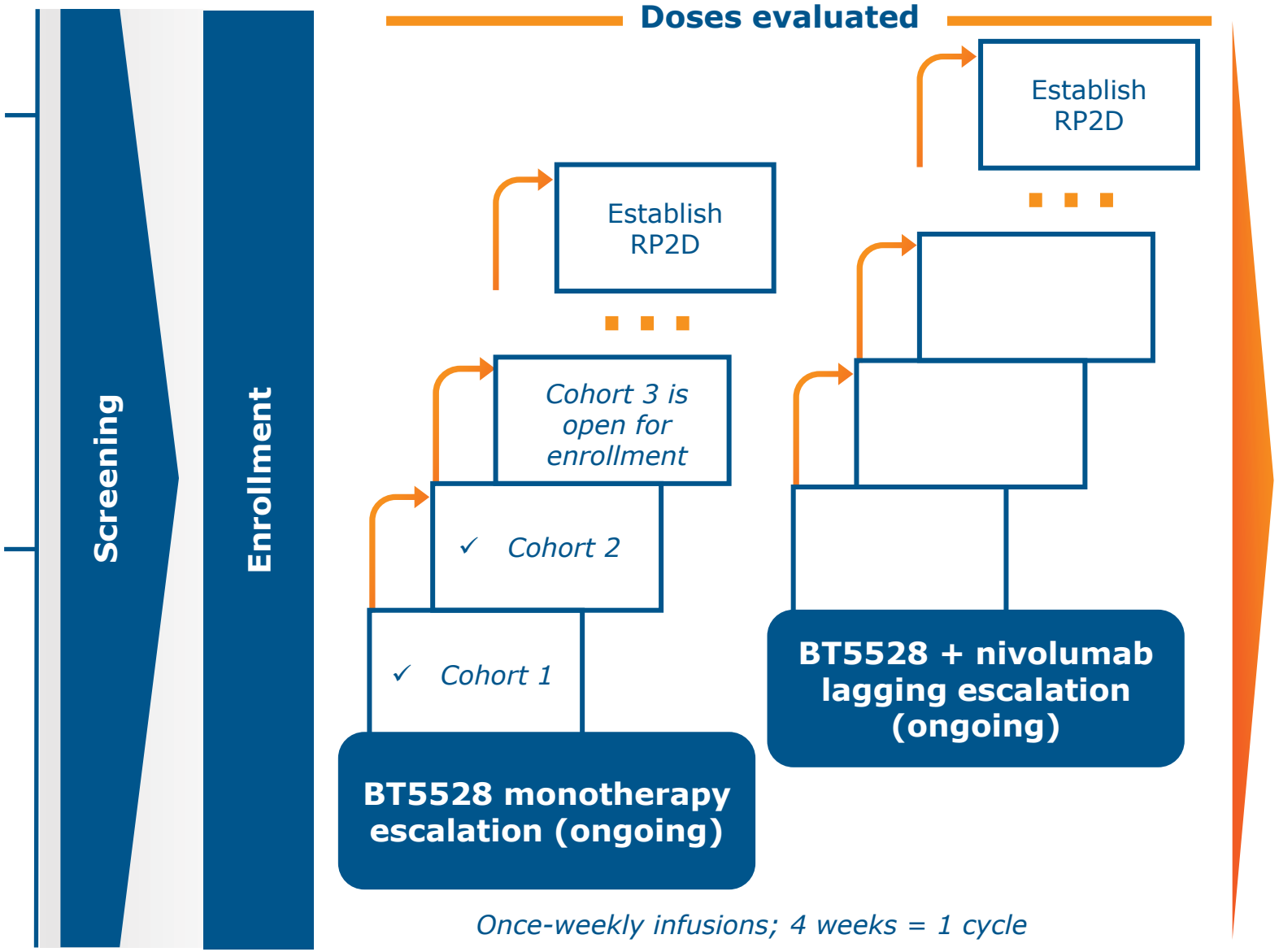



# BT5528 Phase I/II study in patients with advanced solid tumors

**Key Phase I dose escalation objectives:**

- Assess the safety and tolerability of BT5528 in patients with advanced solid tumors associated with EphA2 expression
- Determine a recommended Phase II dose (RP2D)

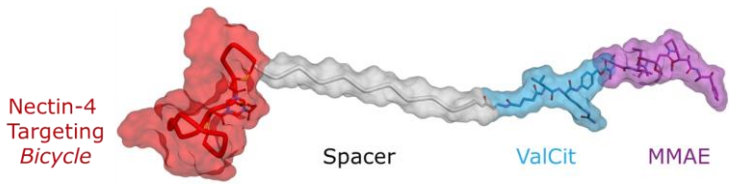
**Phase II dose expansion portion will have primary objective of evaluating the clinical activity of BT5528 in selected tumor indications**





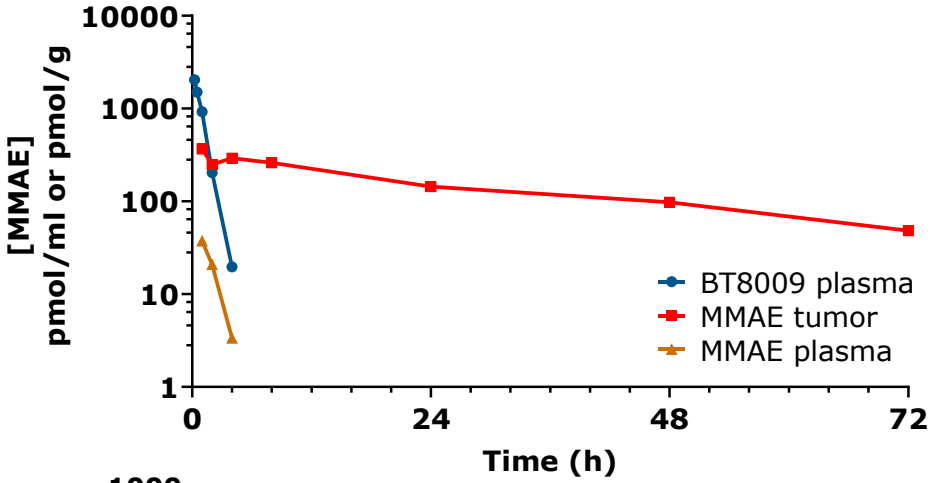

Aug-20

# BT8009: Nectin-4 BTC fast follower with differentiated profile to clinical ADC

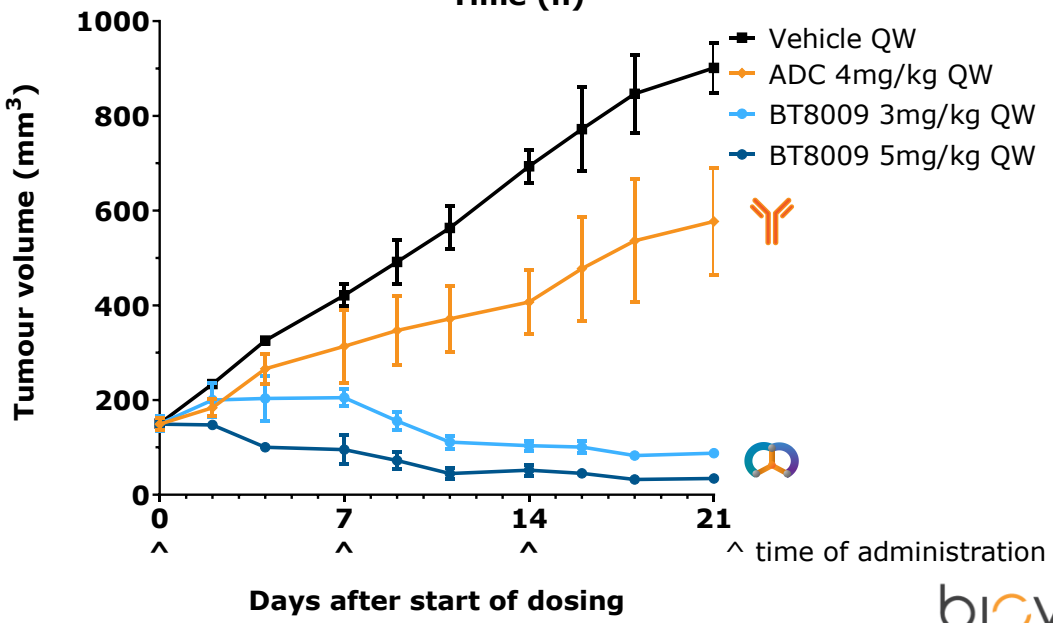



- Nectin-4 is involved in establishing cell-cell contact and tumor cell survival, overexpressed in common types of cancer (e.g. bladder, breast, gastric, lung and ovarian)
- Target validated in the clinic by enfortumab vedotin (Astellas/SeaGen)
- BT8009 designed to avoid hepatic exposure, may overcome stromal barrier in pancreatic cancer, easily manufactured
- IND-enabling studies ongoing; PhI/II initiation expected in 2020

**Impressive selective delivery of toxin to tumor**




**Improved activity over Nectin-4 ADC**








bicycle therapeutics

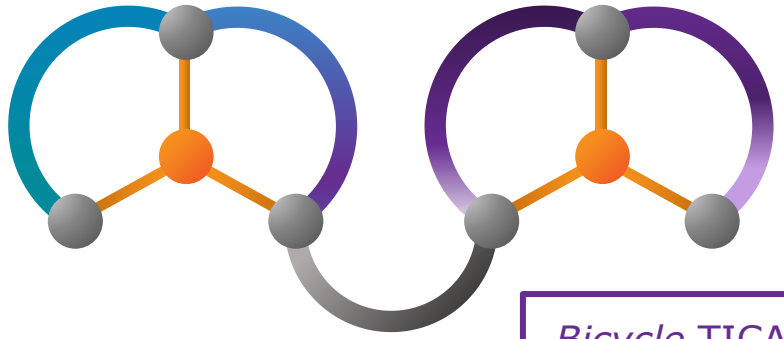
# Immuno-oncology

bicycle therapeutics

# Properties of *Bicycles*® are uniquely suited to IO modulation

Plug and play for flexible therapeutic design

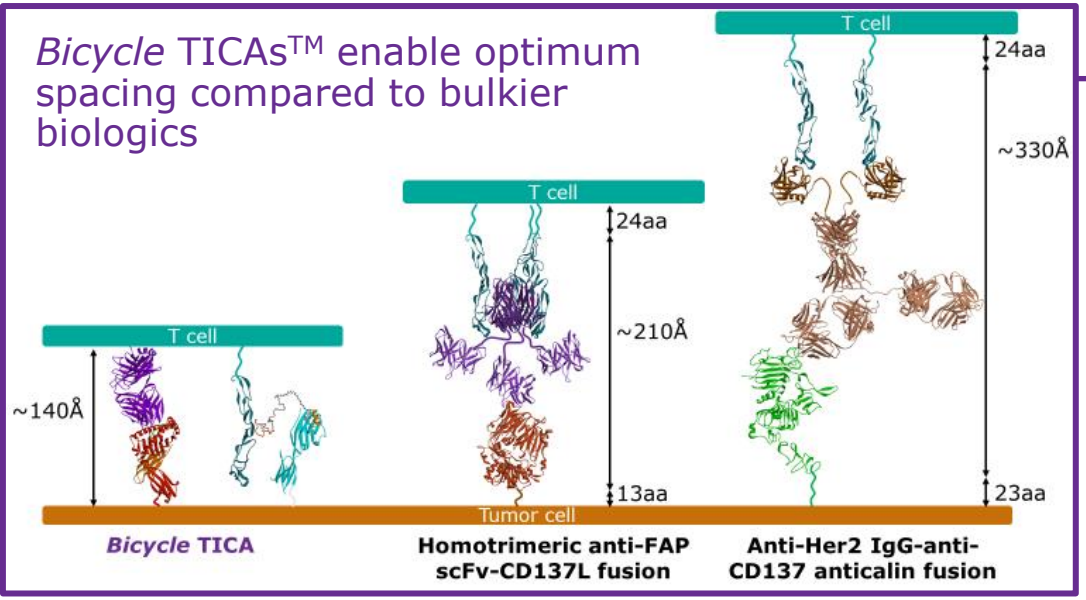
Specific tumor targeting via antigen binding *Bicycle*



*Bicycle* targeting immune cell agonist receptor

- Designed for optimal immune cell engagement
- Rapid tumor penetration
- Renal elimination avoids liver toxicity
- Small molecule COGS
- Short half-life
- Flexible dosing (mono or combo therapy)
- Tuneable PK to vary degree of activation
- Fully synthetic
- Generalizable format

*Bicycle* TICAs™ enable optimum spacing compared to bulkier biologics



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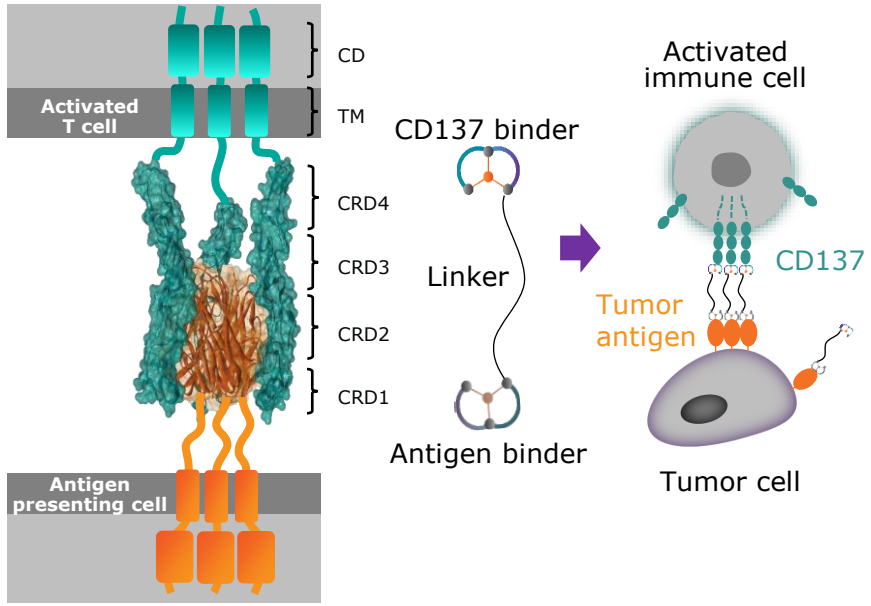
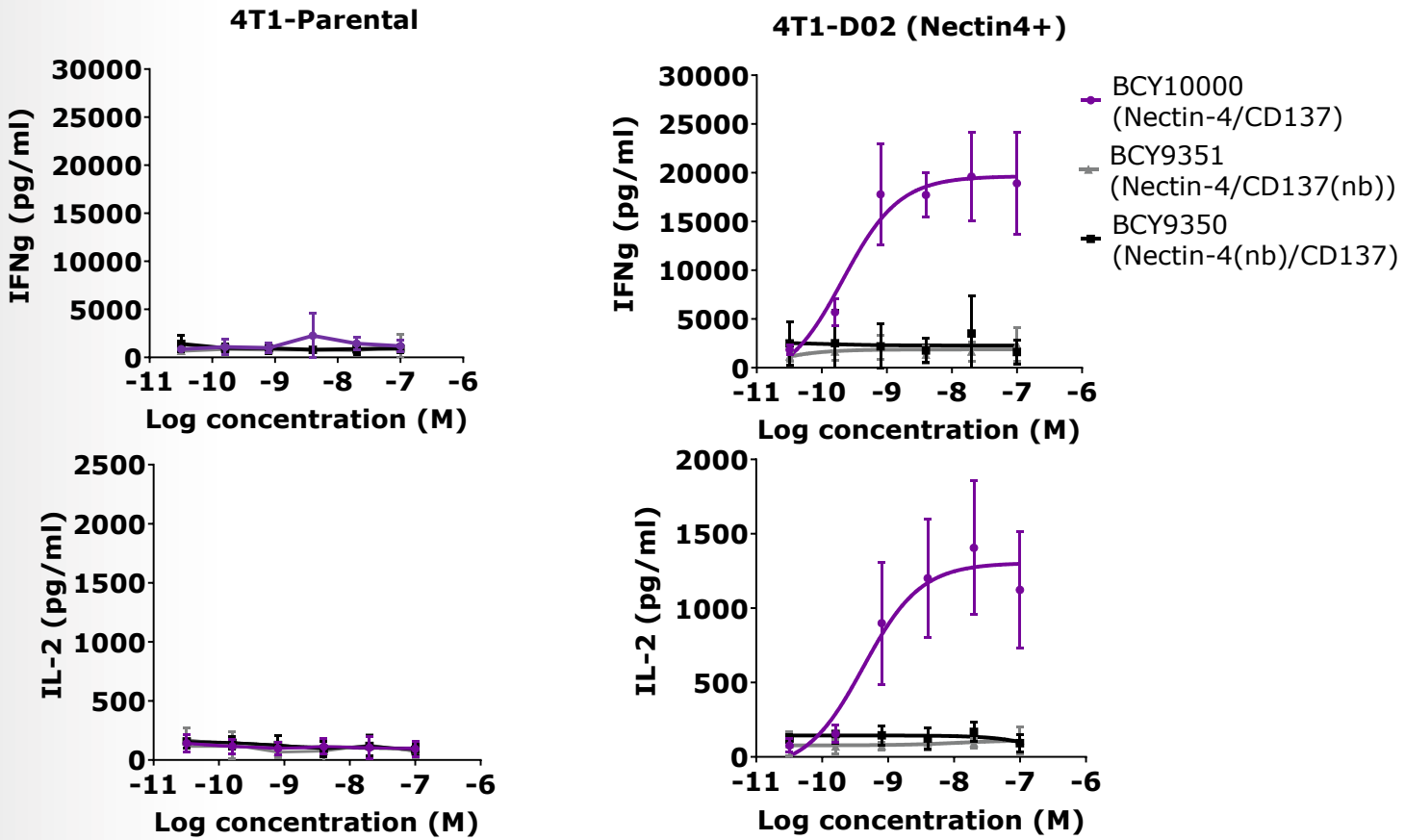
# *Bicycle*® Tumor-targeted Immune Cell Agonists are potent and selective modulators of CD137

**TICA™ molecules could achieve potent activity through receptor cross-linking across the immune synapse**

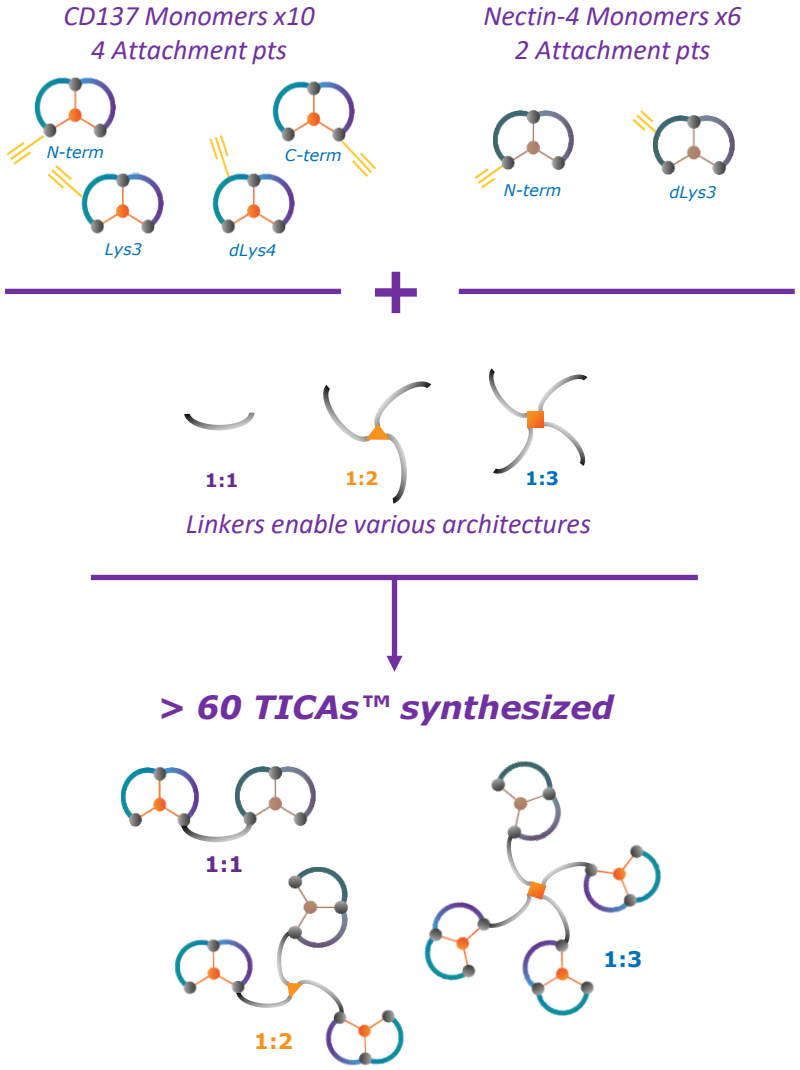



**CD137 provides robust anti-tumor T cell and NK cell effects**

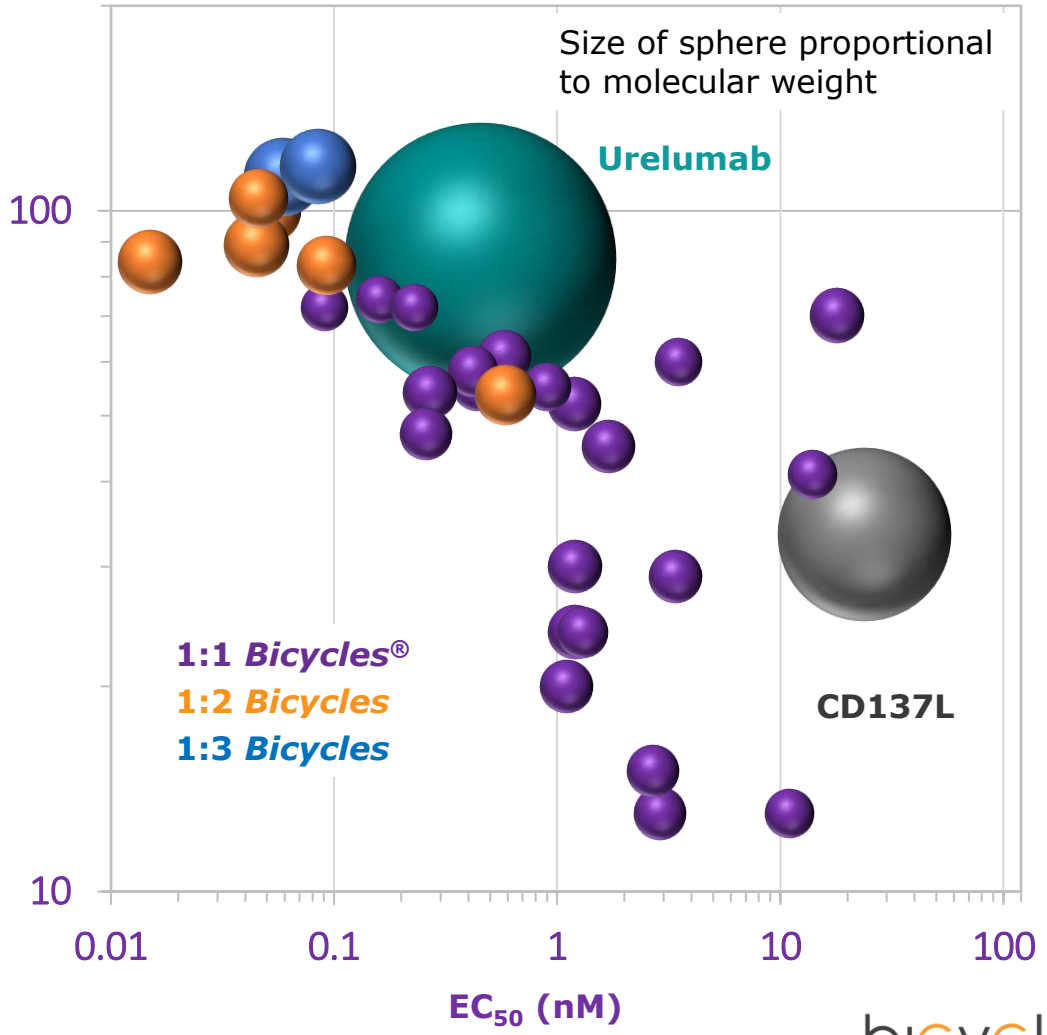




**Nectin-4/CD137 TICA molecules activate human PBMCs in a Nectin-4 dependent manner**

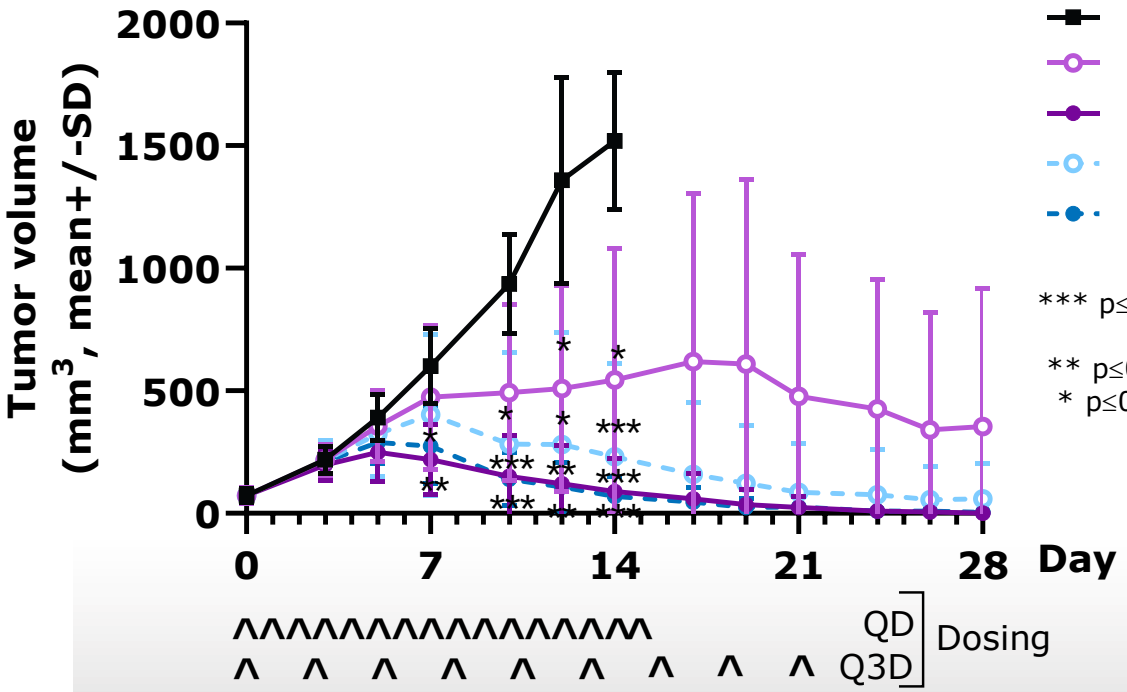
# Chemical nature of platform allows rapid "dialing in" of most desirable properties

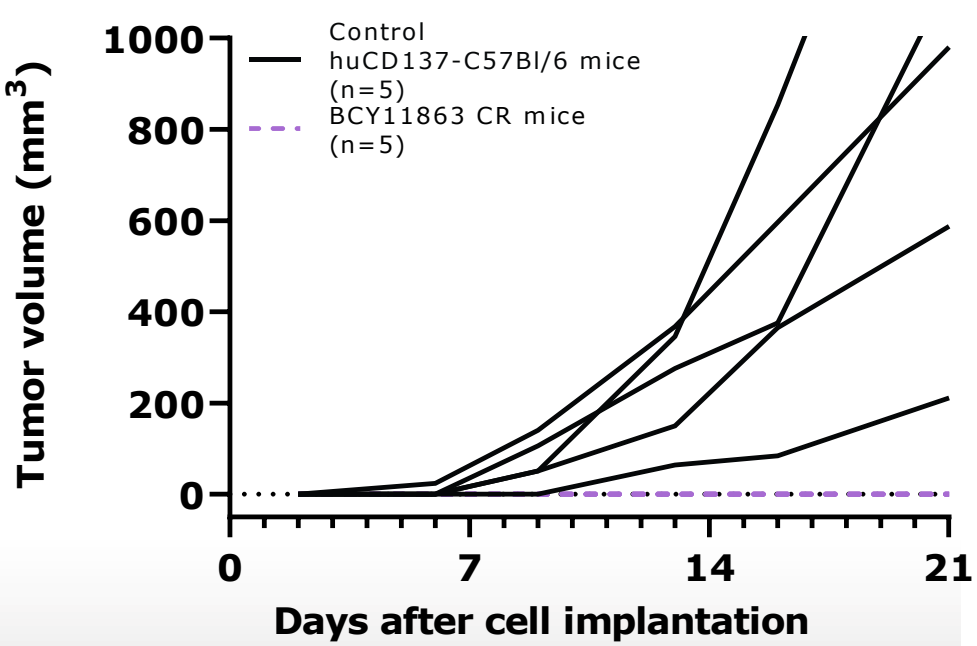



- **>90 Nectin-4 TICA molecules synthesized in combinatorial manner**
- **Reporter cell assay data for 30 Nectin-4/CD137 TICAs in co-culture with HT1376**



# BT7480 leads to robust anti-tumor activity and immune memory in a syngeneic model




**Nectin-4-CD137 TICA™ achieves rapid tumor regression**

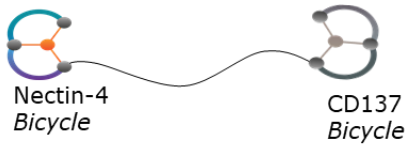
**Rechallenge of "cured" mice with tumor reimplantation shows no tumor growth, implying immunogenic memory**

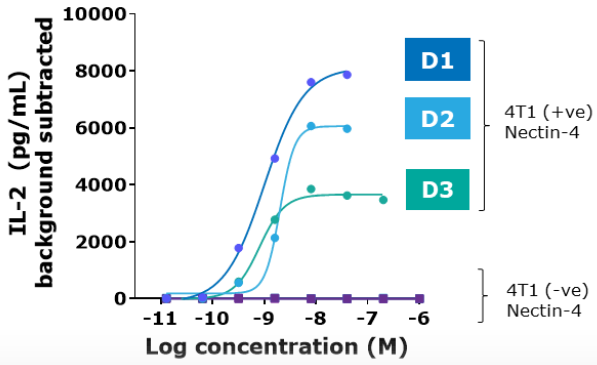


bicycle therapeutics

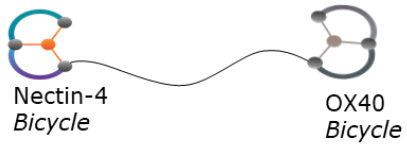
# Immune cell engaging *Bicycles*® and tumor antigen engaging *Bicycles* can be readily interchanged

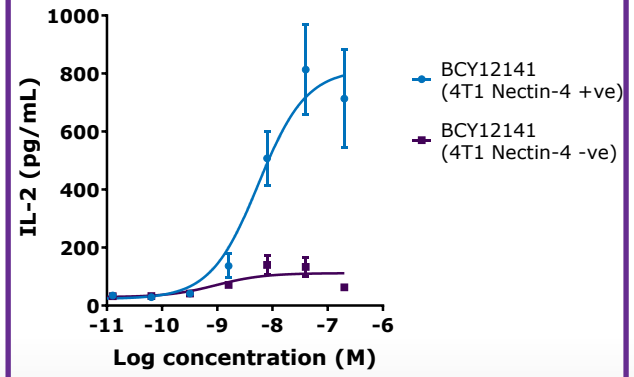
## CD137 TICA™ (BCY10000)



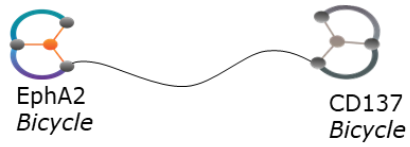



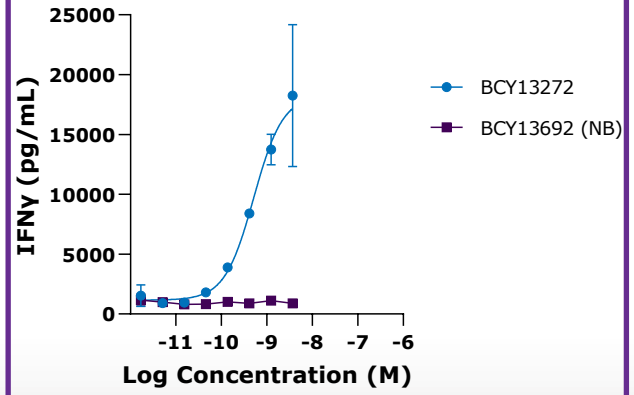

## OX40 TICA (BCY12141)




## BT7455 (EphA2 TICA)



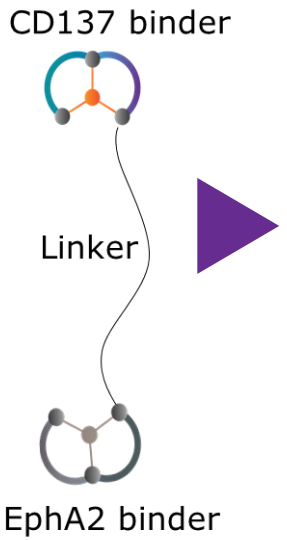



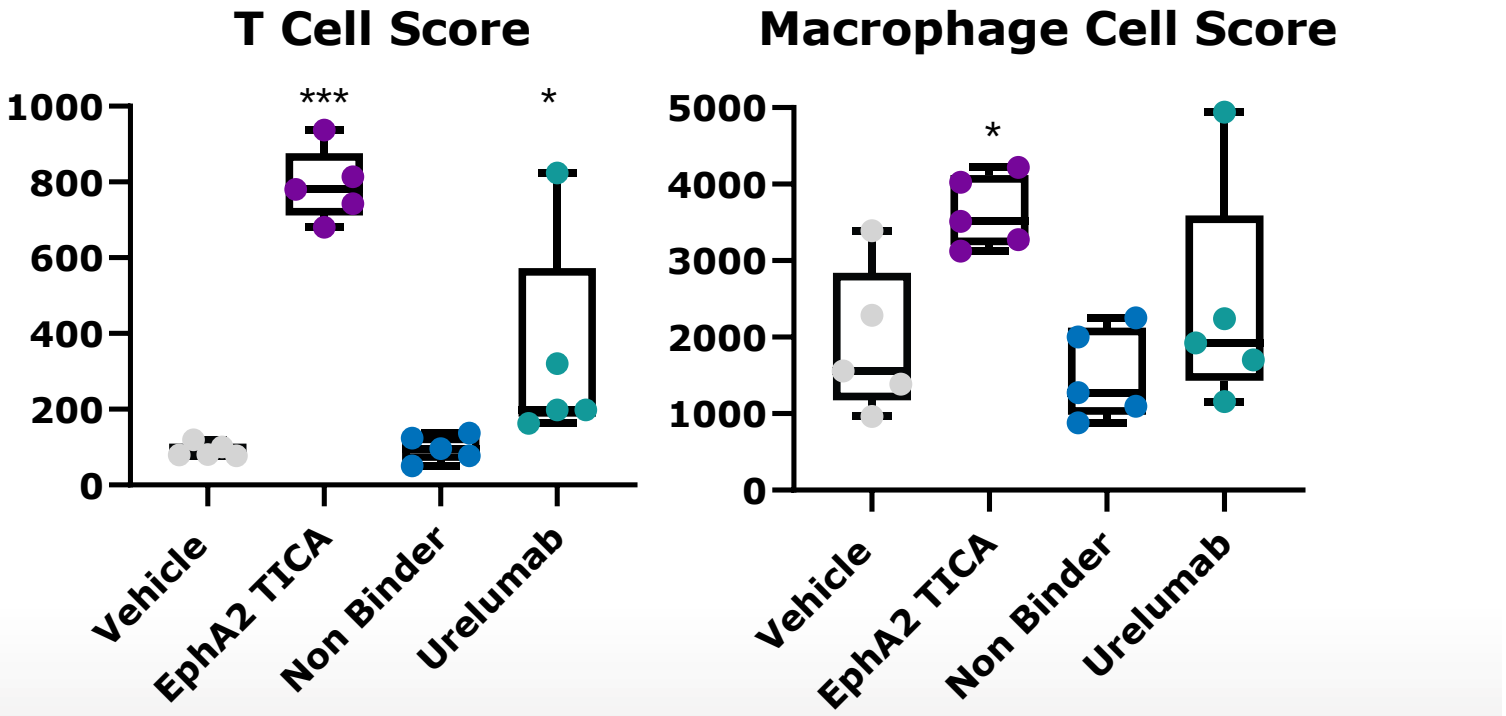

**Collaboration with Genentech builds on "plug-and-play" capability of *Bicycles* in IO field**

Genentech

**Potential to rapidly and efficiently generate multiple clinical candidates**

# EphA2 / CD137 TICA™ induces dramatic immune response in mouse tumor models



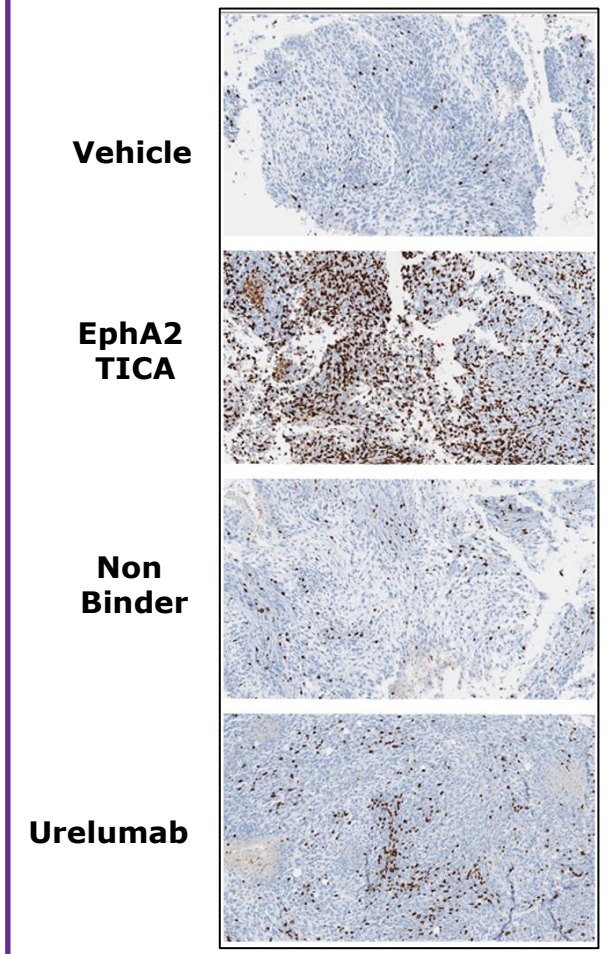




MC38 tumors (mEphA2) in hCD137-ECD transgenic mice. 15 mg/kg Q3D EphA2 TICA or control, or 2 mg/kg Q3D Urelumab

**EphA2 TICA induces a significant change in local immune cell populations when compared to a non-targeted CD137 agonist antibody**

**Significant increase in CD8+ cells and macrophage score**

**CD8+ cells in MC38 tumor tissues on D6**



# Beyond Oncology

bicycle therapeutics

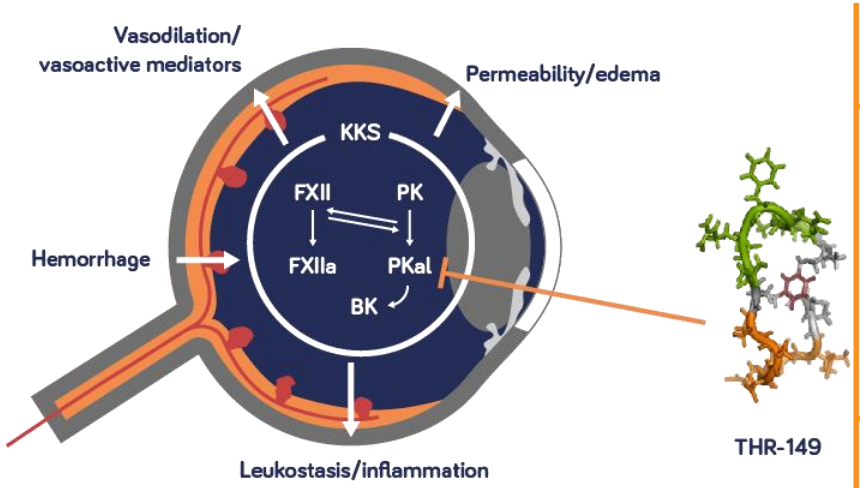
# Partnerships with leading therapeutic experts to explore broad application of *Bicycles*® beyond oncology


**Bicycle's unique technology & deep technical understanding**

**Development & therapeutic expertise**

**Differentiated treatments for diseases with high unmet need**

# THR-149: Novel Pkal inhibitor provides validation of *Bicycle*® platform for ophthalmological diseases






THR-149

Phase I trial evaluated safety of a single intravitreal injection of THR-149 at 3 ascending dose levels in 12 patients with visual impairment due to center-involved diabetic macular edema (DME)

**Topline data show that THR-149 was well-tolerated and safe**

No dose-limiting toxicities or drug-related serious adverse events reported

**Rapid onset of action starting at Day 1**

Increasing **average improvement in BCVA of up to 7.5 letters at Day 14** following a single injection of THR-149

**Activity maintained**

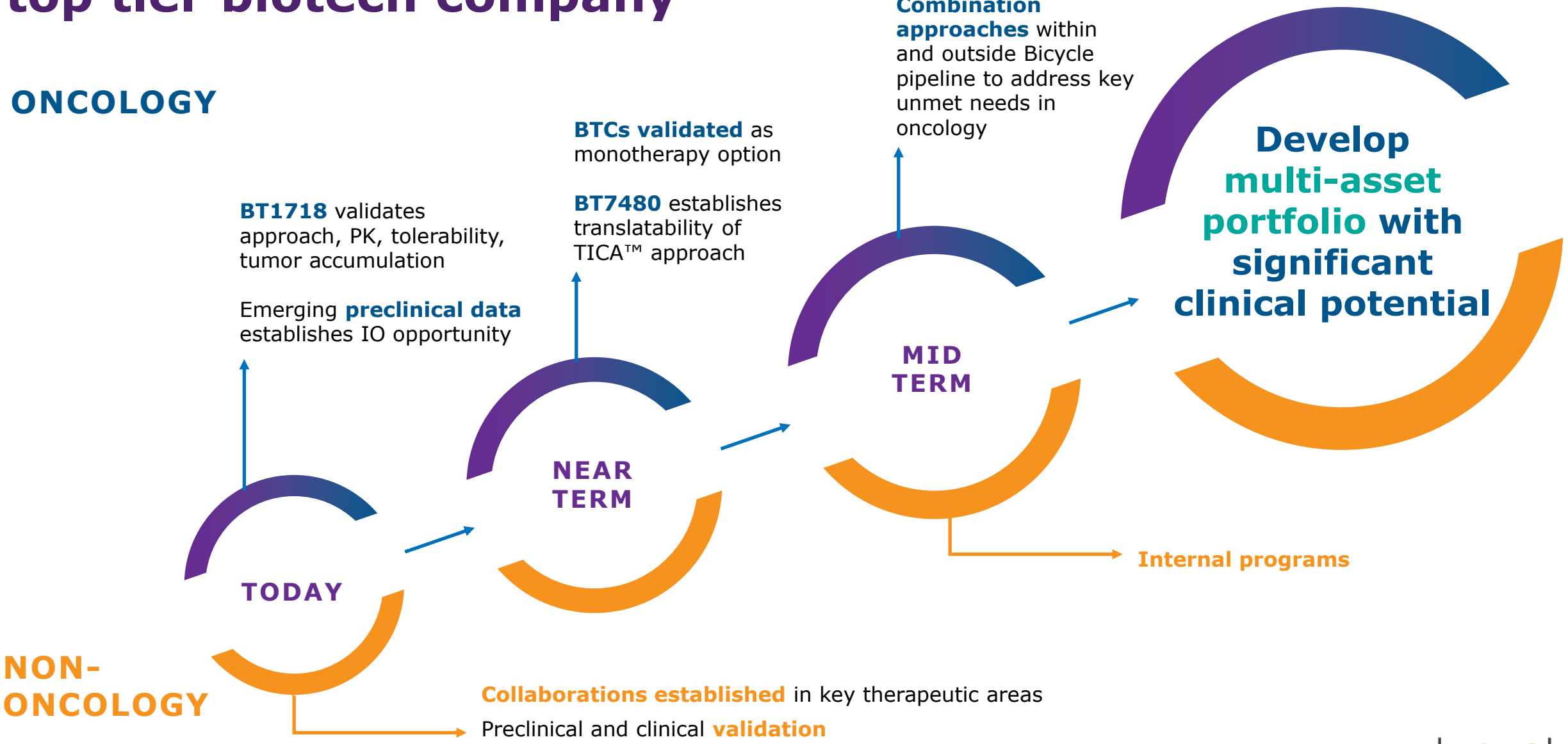
An average **improvement in BCVA of 6.5 letters at Day 90** following a single injection of THR-149

*BCVA = Best Corrected Visual Acuity



bicycle therapeutics

# Establishing Bicycle as an integrated, top tier biotech company



# Bicycle Therapeutics is led by an experienced team, growth is enabled by robust financial profile

**Experts** in drug development with executive experience at leading companies

**Clinical data** readouts at medical meetings and trial initiations expected in 2020 across BTC, IO and partnered programs

**Cash balance of $96.9M*** provides runway to support multiple clinical milestones

## 2020 Key Events

- **BT1718** PhIIa start
- **BT5528** interim PhI data
- **BT8009** PhI start
- **BT7480** IND enabling activities

**As of June 30, 2020*


bicycle
therapeutics