BT8009 Regulatory Update

- September 2023

Bicycle®

Speakers

Kevin Lee, Ph.D., MBA

Chief Executive Officer

Santiago Arroyo, M.D., Ph.D.

Chief Development Officer

Jennifer Perry, Pharm.D.

SVP, Head of Commercial

Alethia Young

Chief Financial Officer

Nick Keen, Ph.D.

Chief Scientific Officer

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Agenda

- Welcome
- BT8009 regulatory update
- Metastatic bladder cancer landscape
- Q&A

Bicycle Therapeutics: A clinical-stage company pioneering a new, differentiated class of innovative medicines

Unique Platform

Developing Bicycles – a novel synthetic peptide modality that enables the drugging of complex targets

Bicycle® modular format platform based on Nobel Prize science

Strong intellectual property portfolio

Internal Programs

Focused on oncology, with multiple Phase I/II clinical assets (BT5528, BT8009 and BT7480)

BT5528 and BT8009 have shown signs of anti-tumor activity

Trial updates for BT5528, BT8009 and BT7480 in 2H23

Validating Partnerships

Extending use of Bicycle® platform into diverse range of therapeutic areas like radiopharmaceuticals and neurology

Genentech – A Member of the Roche Group
NOVARTIS
Bayer
IONIS
OXURION
Innovate UK
dkfz.
CANCER RESEARCH UK

Ambitious Company

Deeply experienced team

Located in Cambridge, UK and Cambridge, MA

NASDAQ: BCYC

Pro forma cash balance of $600.9M as of Aug. 3, 2023

Broad range of programs supports robust nature of Bicycle® platform

Target / Product	Partner/Sponsor	Indication	Modality	Preclinical	IND-enabling	Phase I	Phase II/ Expansion	Phase III
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™					
Undisclosed	dkfz.	Radiopharmaceutical	Bicycle® Radio Conjugate					
Partnered Programs								
THR-149 (Kallikrein inhibitor)	OXURION	Ophthalmology						
BT1718 (MT1-MMP)	CANCER RESEARCH UK	Oncology	Bicycle® Toxin Conjugate					
BT7401 (multivalent CD137 system agonist)	CANCER RESEARCH UK	Immuno-oncology						
Undisclosed	Genentech A Member of the Roche Group	Immuno-oncology						
Novel anti-infectives	Innovate UK	Anti-infectives						
Novel CNS targets	IONIS	CNS						
Novel neuromuscular targets	IONIS	Neuromuscular						
Undisclosed	NOVARTIS	Radiopharmaceutical	Bicycle® Radio Conjugate					
Undisclosed	Bayer	Radiopharmaceutical	Bicycle® Radio Conjugate					

BT8009 regulatory update

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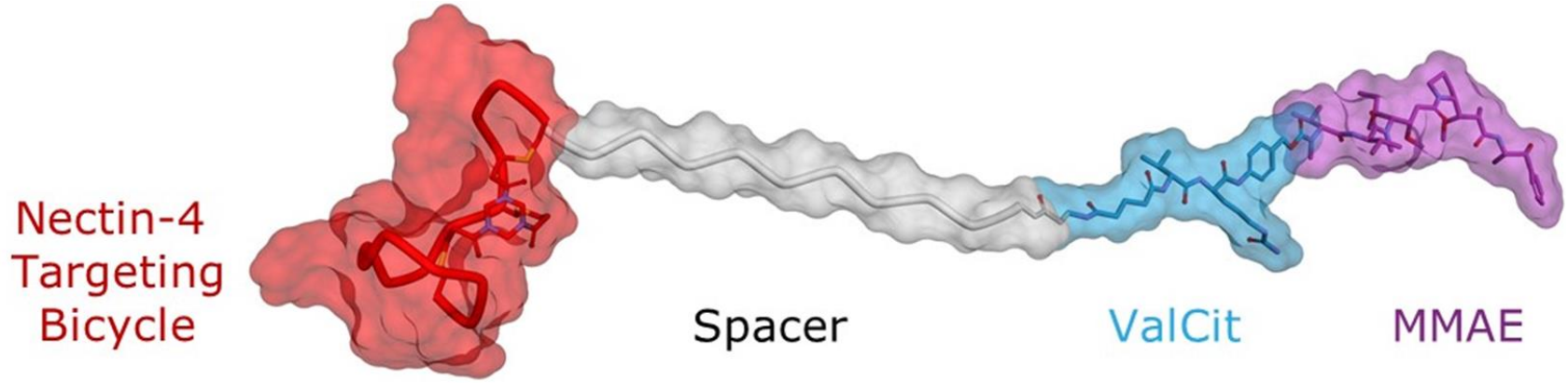
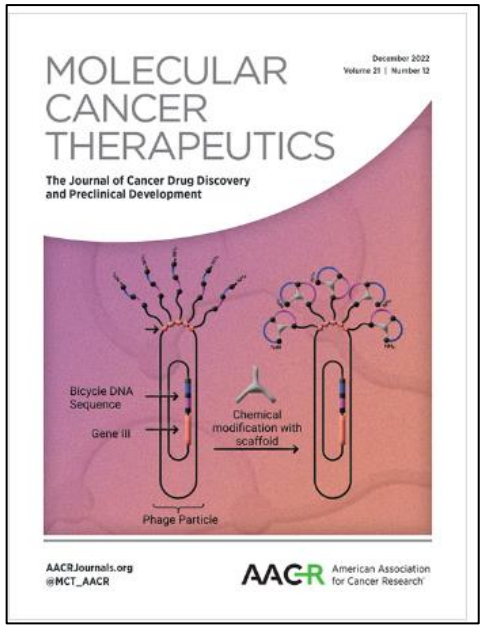
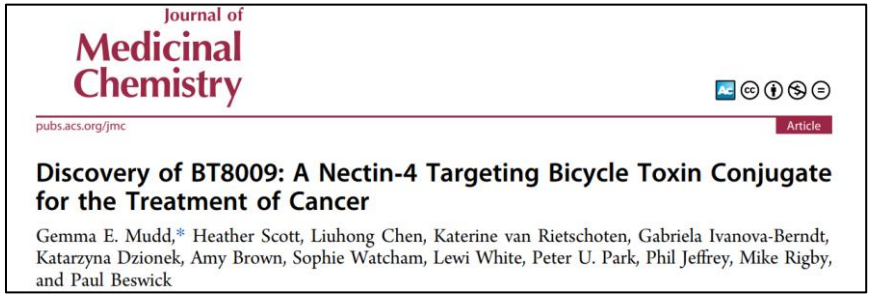
BT8009, a Nectin-4 targeting BTC™ with excellent preclinical performance





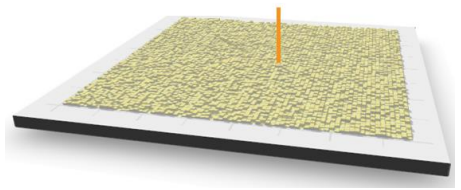


- Fully synthetic molecule
- 4kDa (vs >150kDa for mAb)
- Defined synthetic route
- Homogeneous product, single molecular species
- Cost of goods much lower than comparator biologics
- Highly stable with excellent pharmaceutical properties

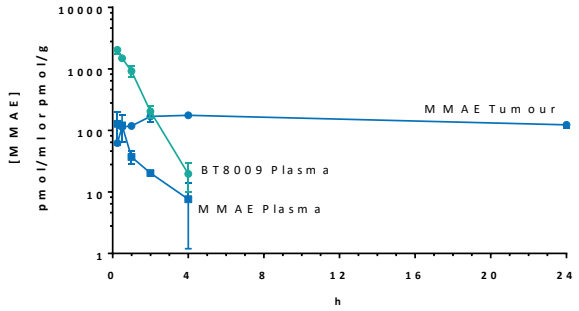
Bicycle conjugates exhibit superior preclinical performance

Selectivity

- Antibodies bind to multiple receptors (Fc, c-type lectin receptors and others)
- In internal comparator studies, Bicycles are completely selective for their biological target while mAbs can bind to more than 6 additional proteins

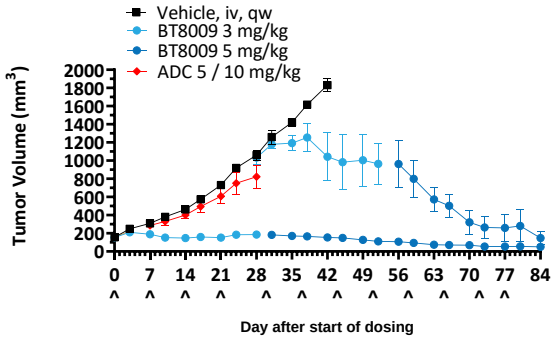


Unique and advantageous PK profile



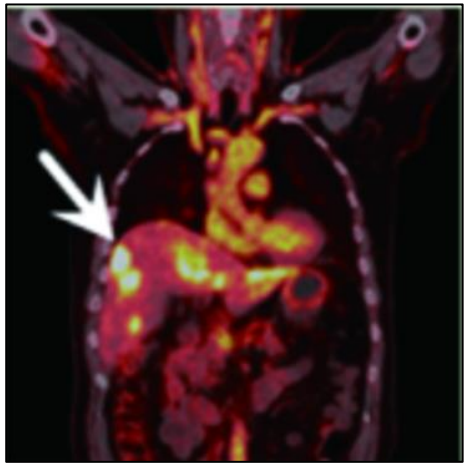
- Efficient and durable tumor MMAE delivery
- Minimal exposure to parent drug minimizes off target delivery

Potent anti-tumor activity



- Significant anti-tumor effects in multiple preclinical models including patient derived tissue
- Superiority to EV observed in preclinical patient derived xenografts

Validated tumor penetration



Duan *et al.* Clin Cancer Res. 2023 Apr 24

- Imaging shows Nectin-4 Binding Bicycle rapidly penetrates human tumors (15 mins) and is selectively retained

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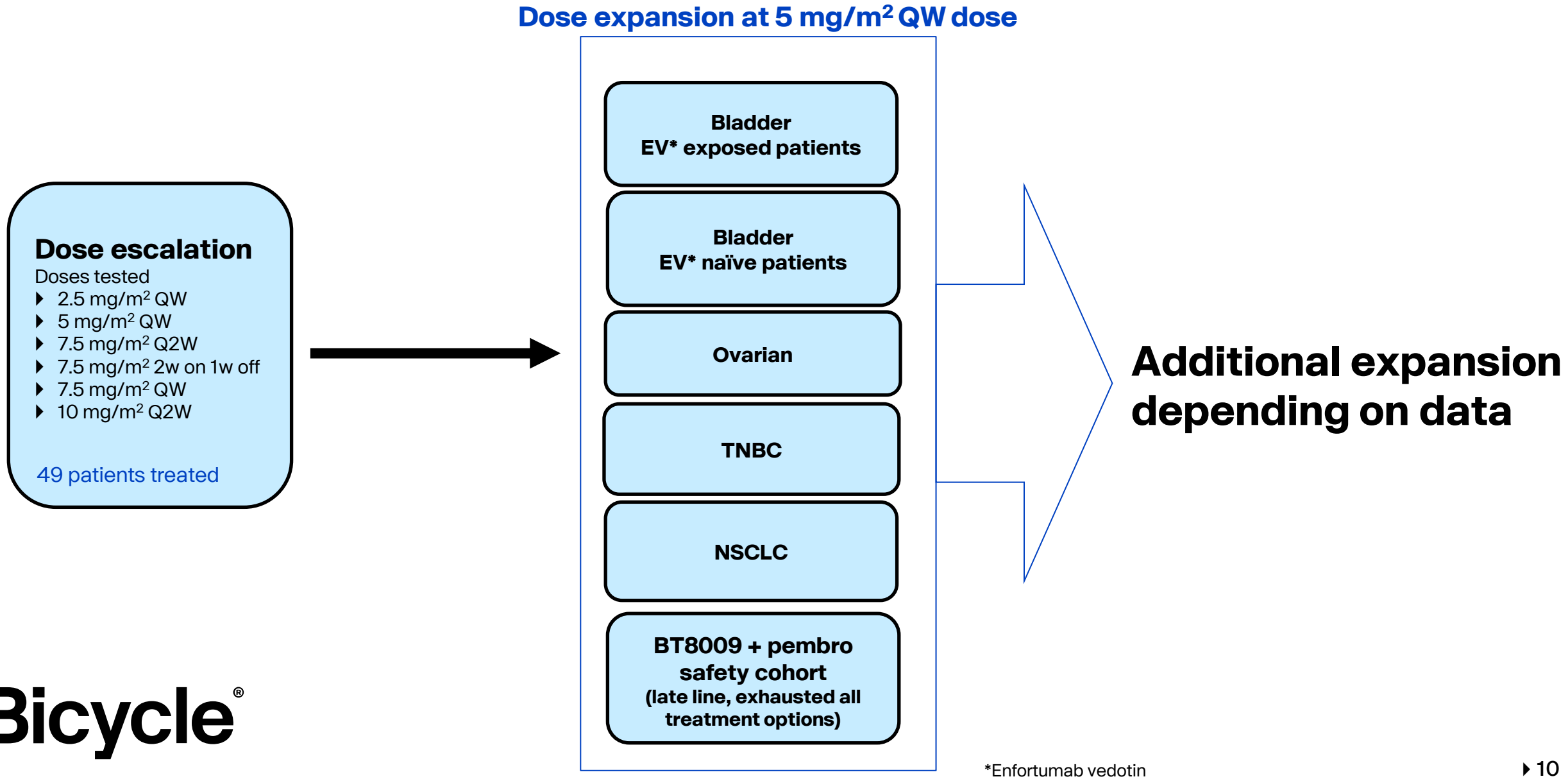
Phase 1/2 study is currently in dose expansion phase, combination BT8009 dose with anti-PD1 being assessed in parallel



*Enfortumab vedotin

Data from BT8009 dose escalation studies support a differentiated profile

- ORR data in line with ADCs
  - EV data in previously treated patients: **~40% ORR**
- Differentiated safety profile compared to ADCs
  - **ADC-mediated events:** Severe skin reactions, peripheral neuropathy, ocular toxicity
  - **BT8009:** Low discontinuation due to adverse events
- Potentially longer duration of response (DOR)

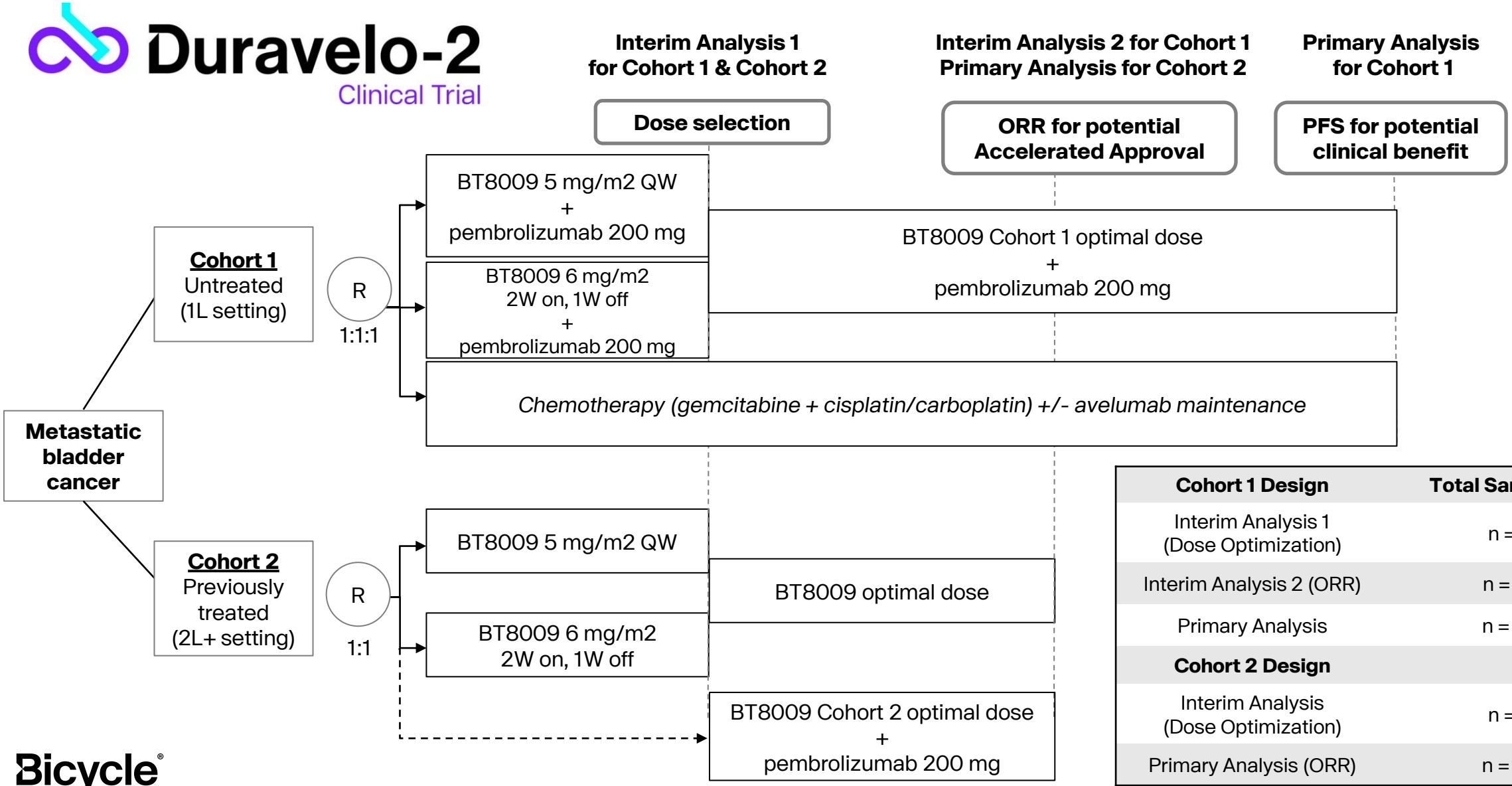
EV-101 study and Padcev label from EV-301

Expediting development of BT8009 for metastatic bladder cancer

- **January 2023:** Announced Fast Track designation in previously treated metastatic bladder cancer
- **Today:** Announced alignment with FDA on regulatory path and Phase 2/3 trial design
  - Innovative study design allows for **potential accelerated approval in 1L and 2L+ metastatic bladder cancer**
  - **1L in combination with pembrolizumab vs. chemotherapy:** Objective response rate (ORR) for potential accelerated approval; progression-free survival (PFS) to confirm clinical benefit
  - **2L+ monotherapy and in combination with pembrolizumab vs. historical control data:** ORR for potential accelerated approval; discussions on confirmatory trial design ongoing

Innovative trial design allows for efficient path-to-market

Duravelo-2
Clinical Trial



Cohort 1 Design	Total Sample Size
Interim Analysis 1 (Dose Optimization)	n = 60
Interim Analysis 2 (ORR)	n = 292
Primary Analysis	n = 566
Cohort 2 Design	
Interim Analysis (Dose Optimization)	n = 60
Primary Analysis (ORR)	n = 240

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Summary: BT8009 Regulatory Update

- **Robust and innovative clinical development plan for BT8009** that is in line with the philosophy of the FDA's Project FrontRunner and follows the agency's recent draft guidance on accelerated approval of oncology therapeutics
- Alignment with the FDA on the registrational trial design, dose selection and clinical trial endpoints that could support **potential accelerated approval in a broad metastatic bladder cancer population**
- Clinical infrastructure established, allowing **registrational trial start in 1Q 2024**
- **Our goal: Get this much-needed therapy to patients as quickly as possible**

Metastatic bladder cancer landscape

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Overview of bladder cancer

Annual Incidence (Stages 0-IV)[1]

573,000 Worldwide
85,503 United States

Rank among all cancers (Incidence)

10 Worldwide
6 United States

Median age at diagnosis

73

Male : Female Ratio

3.3:1

5-year Survival

63% / 12%

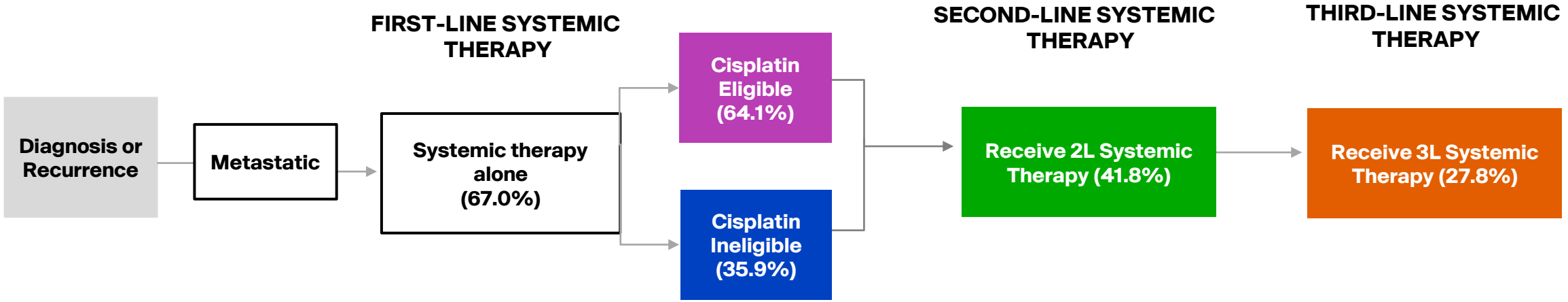
Stages 0-IV Stage IV

- Bladder cancer is the 10th most common cancer in the world and the 6th most common in the US(1)
- Tobacco use, especially smoking cigarettes, continues to be a major risk factor(1)
- 50% of patients who undergo surgery for their bladder cancer will experience disease progression and recurrence within two to three years after surgery(2)
- Approximately 20-25% of patients with bladder cancer will develop metastatic disease(1)
- Poor durability of response with treatments in the first line setting for metastatic disease remains challenging and limits treatment options in the second-line setting for patients with advanced disease

1 Cerner Enviza CancerMPact, Treatment Architecture US Bladder Cancer, Nov 2022. Sources: Based on CancerMPact® Patient Metrics U.S., accessed February 2022. Ranking is based on relative incidence of 31 tumors; Risk factors from National Cancer Institute (cancer.gov), NCCN Guidelines *Bladder Cancer* v2.2022, ASCO's patient information website (Cancer.Net), American Cancer Society (cancer.org)

2 Journal of Urology, Adult Urology, Late Recurrences Following Radical Cystectomy Have Distinct Prognostic and Management Considerations, Sept'20

Metastatic bladder cancer treatment journey can be complex due to disease progression and the need for retreatment



1L Utilization: Cisplatin Eligible

- **Chemotherapy use: ~80-90%** regardless of PD-L1 status

Top 3 modalities:

gemcitabine, cisplatin
gemcitabine, carboplatin
MVAC

1L Utilization: Cisplatin Ineligible

- **Chemotherapy use: ~50-60%** regardless of PD-L1 status
- **CPI use: ~50%** if PD-L1 positive

Top 3 modalities:

gemcitabine, carboplatin
pembrolizumab
atezolizumab

2L Utilization

- **CPI use: ~40%**
- **Targeted agent use: ~30%**

Top 3 modalities:

pembrolizumab	**23.8%**
enfortumab vedotin	20.0%
avelumab	9.0%

3L Utilization

- **Targeted agent use: ~50%**
- **CPI use: ~20%**

Top 3 modalities:

sacituzumab	**24.3%**
enfortumab vedotin	19.4%
Investigational drug	11.7%

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Cerner Enviza CancerMPact Treatment Architecture Nov 2022, US Bladder Cancer, Source: survey 103 physicians treating 3,920 bladder cancer patients
Only top 3 active modalities are shown for first-line therapy. Regimen boxes refer to use of systemic therapy when given alone or combined with other therapies
CPI = checkpoint inhibitors

Significant opportunity to displace approved targeted therapies by addressing ADC shortcomings

Limitations to enfortumab vedotin (EV) use:

- Neuropathy, skin toxicity and other ADC concerns can limit utilization
- Significant increase in **AEs in combination** with pembrolizumab
  - Adverse reactions in the EV-103 Study[1], led to
    - **69%** of patients requiring a **dose interruption**
    - **45%** of patients requiring a **dose reduction**
    - **36%** of patients **discontinuing EV**
  - **Dose interruptions, delays and discontinuations** may impact long term efficacy for patients as well as impact the overall opportunity

Dana-Farber Cancer Institute

"Association of EV Toxicity with Baseline Parameters and Clinical Outcomes in Patients with mUC"
Semaan et al, Abstract e16585 ASCO 2023

Stony Brook Medicine

"Incidence and Risk of Peripheral Sensory Neuropathy (PSN) with EV in Advanced UC: Systematic Review and Meta-Analysis"
Shah et al, Abstract e16556 ASCO 2023

Perelman School of Medicine University of Pennsylvania

"Real-world Use, Dose Intensity, and Adherence to EV in Locally Advanced or Metastatic Urothelial Carcinoma (la/mUC)"
Tsingas et al, Abstract e16567 ASCO 2023

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1 PADCEV Full Prescribing Information, https://astellas.us/docs/PADCEV_label.pdf, Warnings and Precautions, Updated Apr'23
American Society of Clinical Oncology 2023 abstract references noted in text, www.asco.org, 2023 meeting abstracts accessed Sept 2023

Positive early feedback from experts supports BT8009 as a potentially differentiated advancement

KOL views on efficacy

"If this drug maintains a **DoR beyond 9-12 months**, it could be **given more chronically** and be better tolerated"

"In metastatic, **long DoR matters along with stable disease and partial responses** especially when combined with a **true improvement in quality of life**"

KOL views on safety

"Tolerability matters in all lines of treatment because patients become frail as they progress... **and this drug could be used before more challenging drugs"**

"If you have developed a less toxic EV **with at least a 20-30% improvement in rash and neuropathy**, people will jump on it"

Thought leaders are excited for a new treatment that potentially improves upon current therapies and could be moved into earlier lines of treatment

ASCO GU February 2023, ASCO June 2023 Bladder Cancer Key Opinion Leader Meetings
DOR = duration of response, EV = enfortumab vedotin

BT8009 combination and monotherapy has potential to be a best-in-class treatment for metastatic bladder cancer

PRODUCT VISION

- Best-in-class *Bicycle*® technology to be indicated for 1L and 2L+
- Powerful and durable responses as combination and monotherapy
- Better tolerability allowing for longer treatment, improved efficacy and a better patient experience

Key areas of opportunity

1. **Standard of care in first line combination**
2. **Standard of care in previously treated**
3. **Expand beyond metastatic disease***

BT8009 has potential to become the preferred and 'next generation' treatment for metastatic bladder cancer

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*eg: MIBC, NMIBC

Closing

BT8009

- Data show **robust anti-tumor activity and differentiated safety profile,** potentially making it the **partner of choice** for PD1s/PDL1s and **novel combinations** in metastatic bladder cancer and other Nectin-4 expressing tumors
- **Fast Track designation** in previously treated metastatic bladder cancer
- Positive interaction with FDA aligns on expedited clinical development plan and path-to-market **in 1L and 2L+ metastatic bladder cancer**
- Evaluation of BT8009 advancing in **other cancers** (lung, ovarian, breast)

Pipeline

- Clinical data updates for BT8009, BT5528 and BT7480 planned in **2H 2023**

Q&A

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Thank you

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