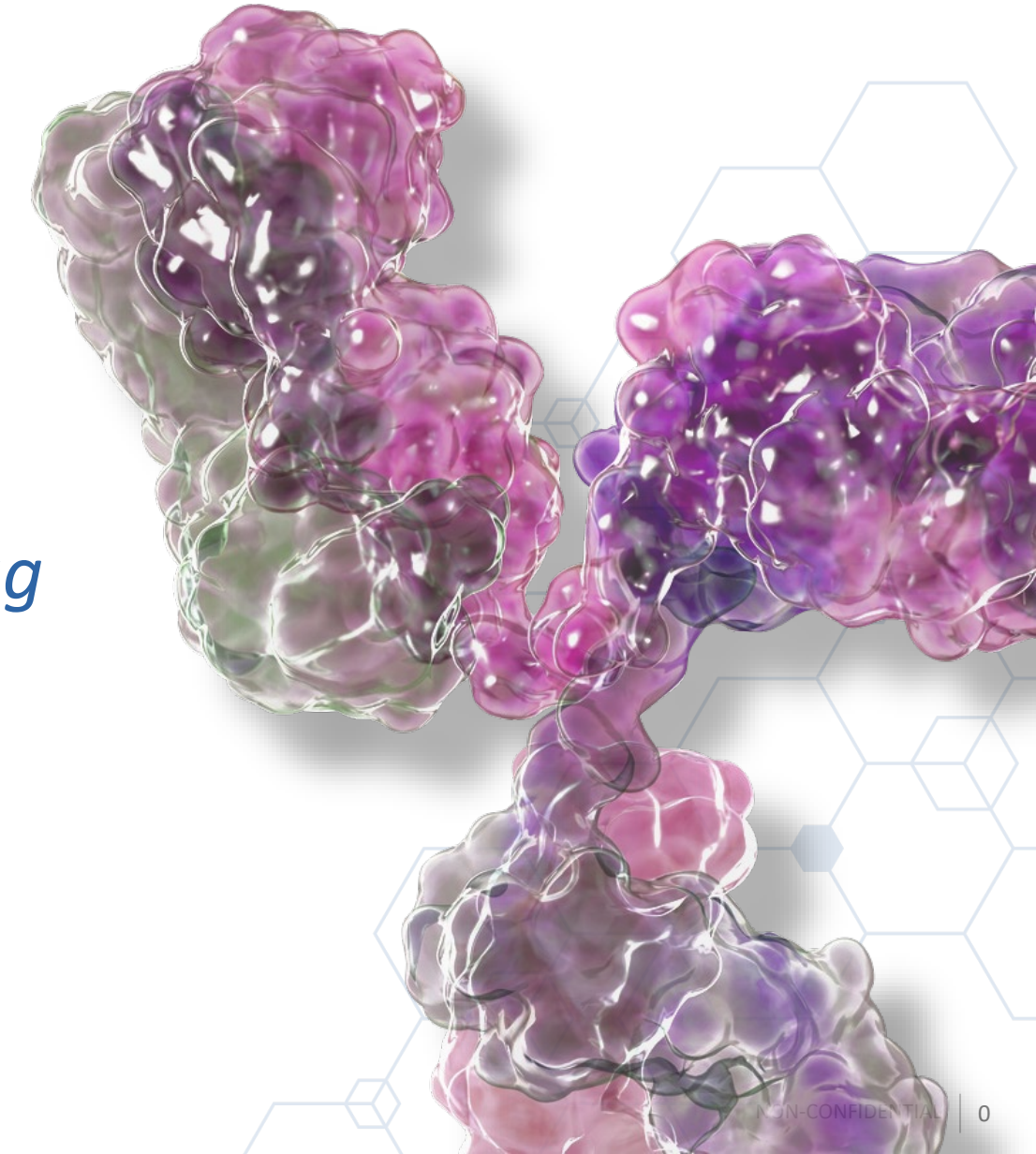
Hummingbird Bioscience

Maximizing the Promise of Precision Oncology to Address and Overcome Drug Resistance



31 JUL 2024 | Kwek Kon Yew, BM BCh, DPhil

Chief Medical Officer

Hummingbird Bioscience

Office Trial Site

Drug developer & innovator: **Developing technologies and platforms in-house** to build pipeline of biotherapeutics

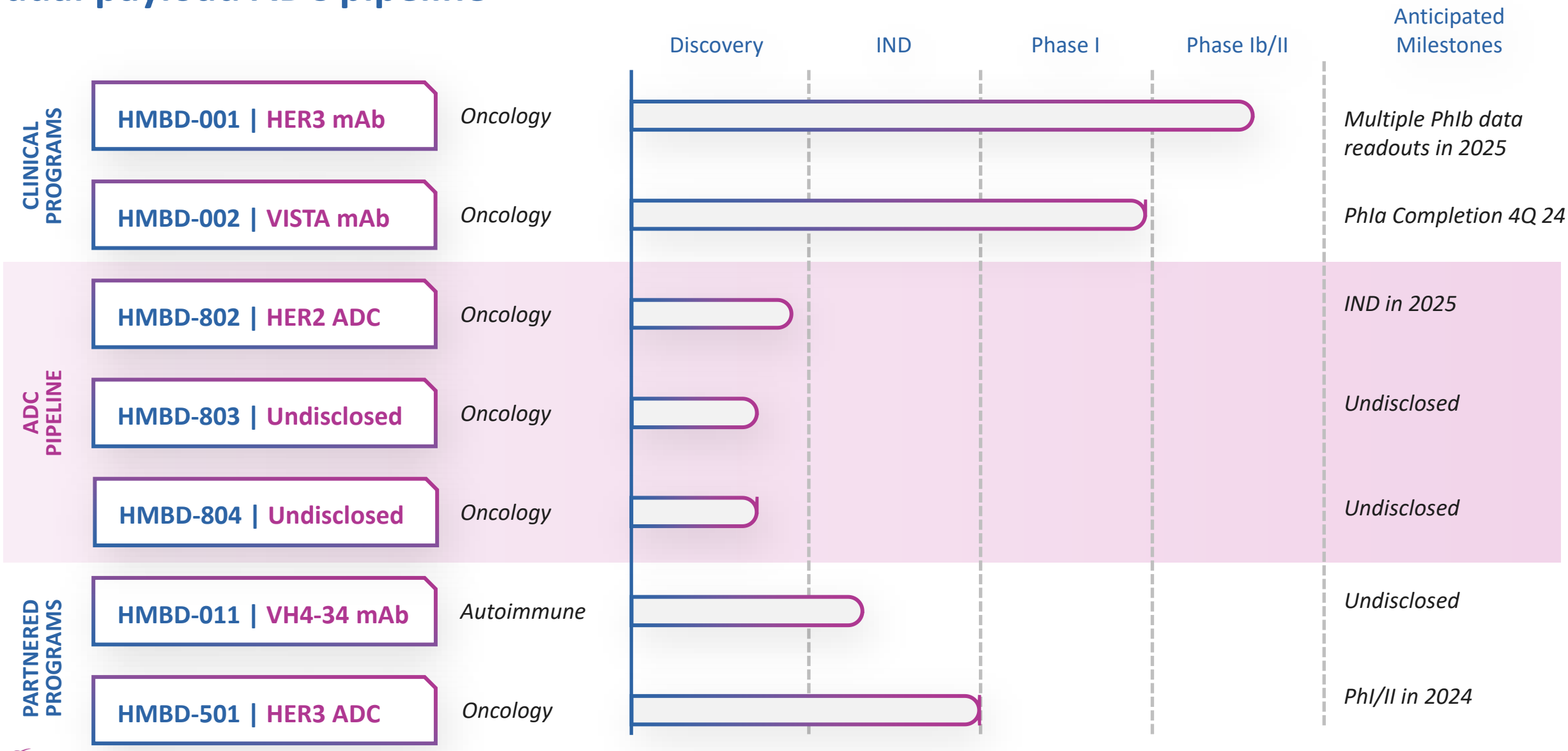
Experienced team of approximately 100 staff (mostly R&D) and based at **HQ in Singapore; CBO based in SF Bay Area**

Clinical-stage pipeline advancing toward POC for two lead programs: Best-in-class anti-HER3 (‘001) and first-in-class anti-VISTA (‘002) programs

Proprietary antibody discovery platform that enables rational epitope-directed discovery against challenging targets

Best-in-class ADC platform & pipeline: Proprietary linker and novel drug combinations, overcoming resistance with a unique dual payload

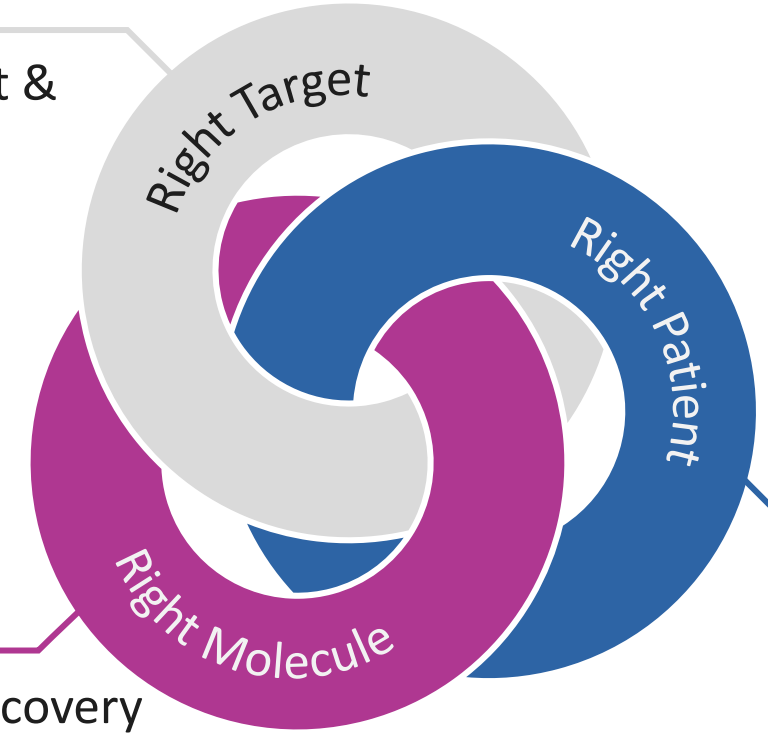
Catalyst rich calendar with clinical PoC readouts and upcoming IND for next gen dual payload ADC pipeline



Our approach | Realizing the potential of precision oncology

Right Target

- Understanding Target & Disease
- Feasibility
- Strategy



Right Molecule

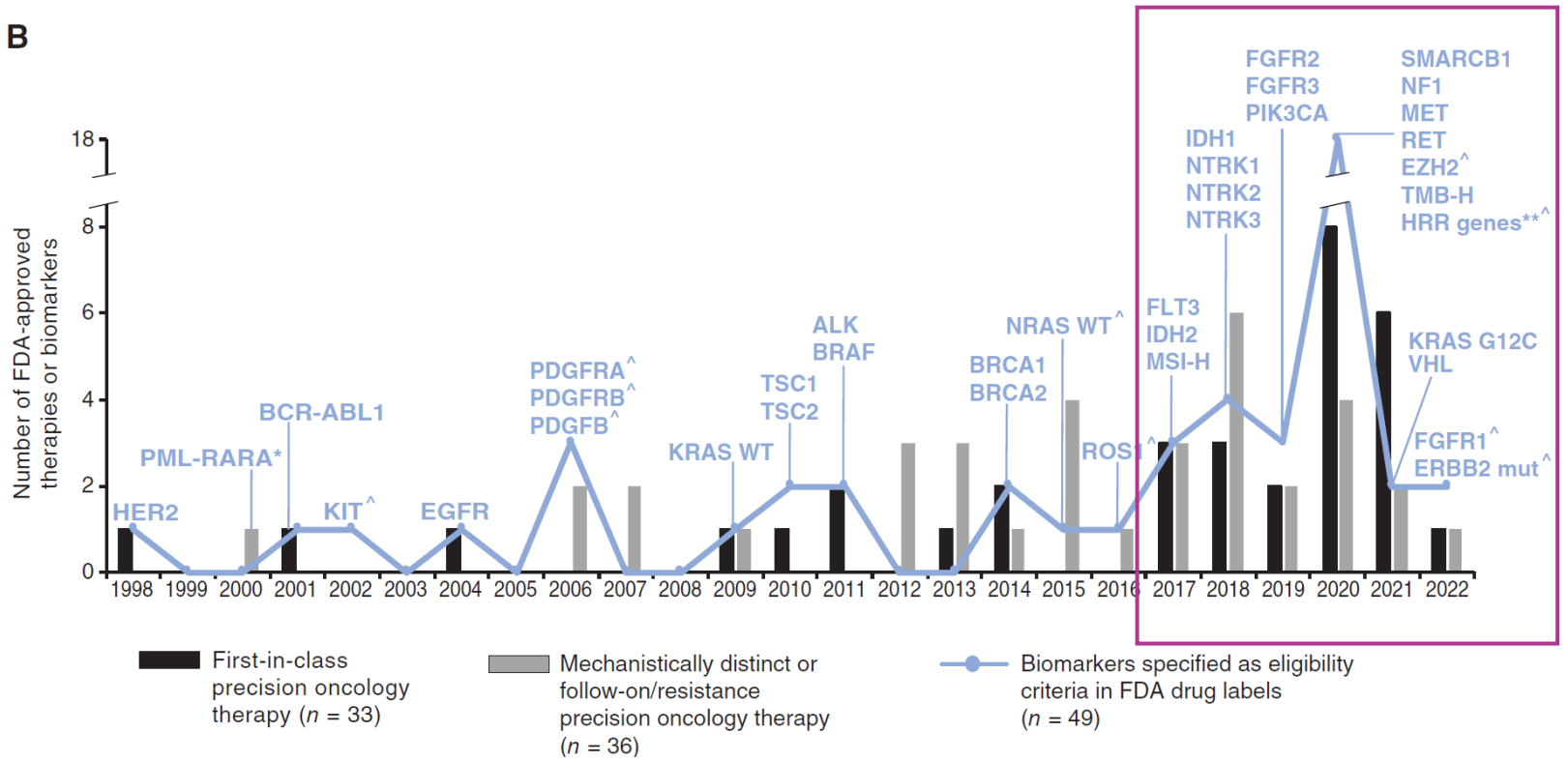
- Rational Antibody Discovery (RAD) Platform
- Pharmacology
- Developability

Right Patient

- Biomarkers
- Efficient Trial Design
- Collaborations

Increasing Relevance of Precision Oncology

Precision oncology drugs account for 43% (86/198) of new oncology drugs approved since 1998

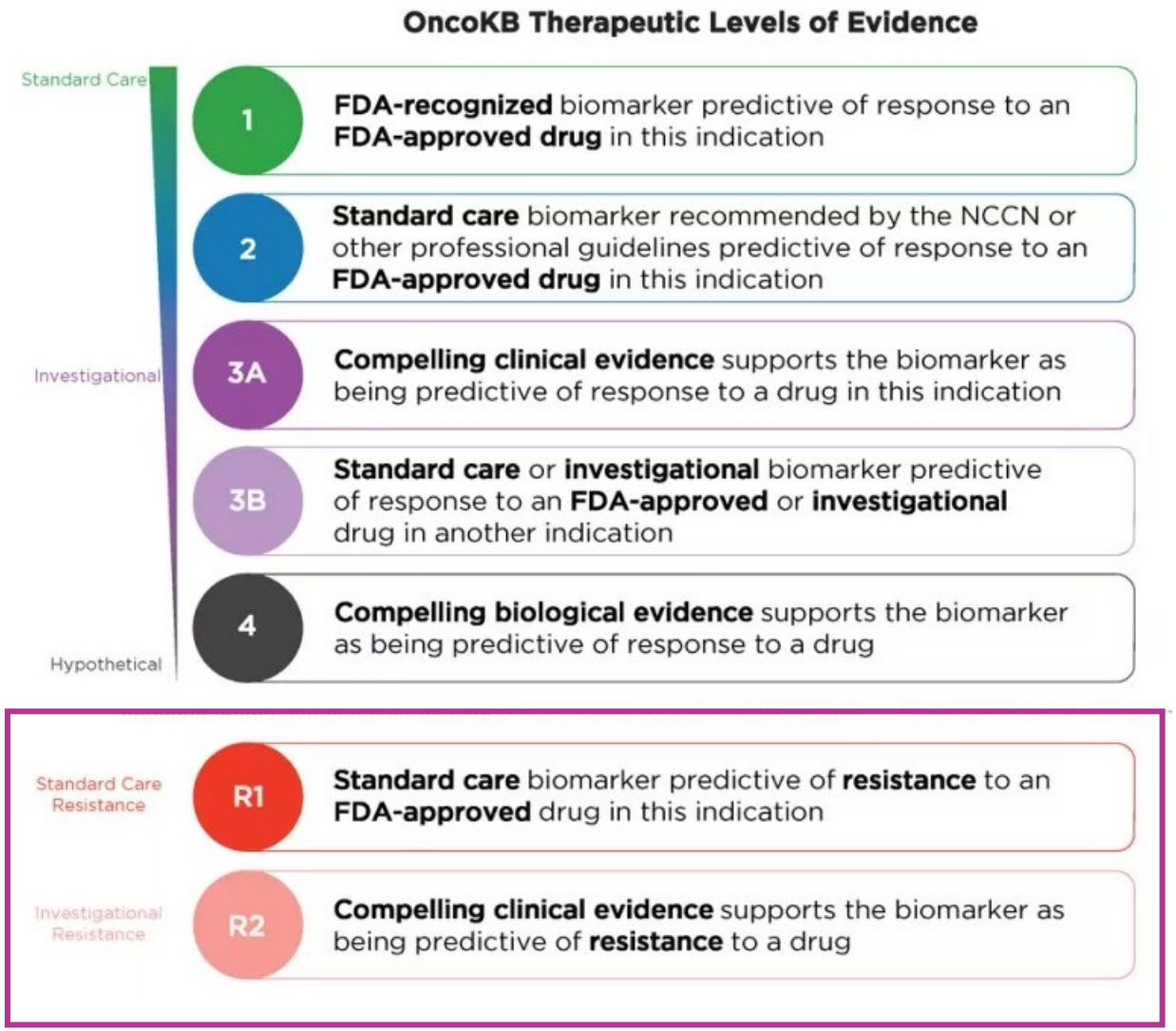


B, Number of first-in-class (black) and mechanistically distinct/follow-on/resistance (gray) FDA-approved precision oncology drugs between June 1998 and November 2022. The number of genomic biomarkers (genes and MSI-H and TMB-H) included in the "Indications and Usage" section of the FDA drug labels in drugs approved per year is shown with the blue line.

- 1998 to 2017: Annualized median of precision oncology drug approvals was 1 per year
- 2017 to 2022: Annualized median of precision oncology drug approvals was 8 per year.
- Since 1998, 69.7% (23/33) of first-in-class drugs targeting biomarker-defined patient populations were approved between 2017 to 2022
- Since 1998, 50% (18/36) of "follow on" precision oncology drugs were approved between 2017 to 2022
- The development of these drugs were largely accelerated by
  - Large scale molecular profiling studies
  - Advances in clinical trial design
  - Lower cost and better NGS-based diagnostic assays

Suehnholz SP, Nissan MH, Zhang H, et. al. Quantifying the Expanding Landscape of Clinical Actionability for Patients with Cancer. Cancer Discov. 2023

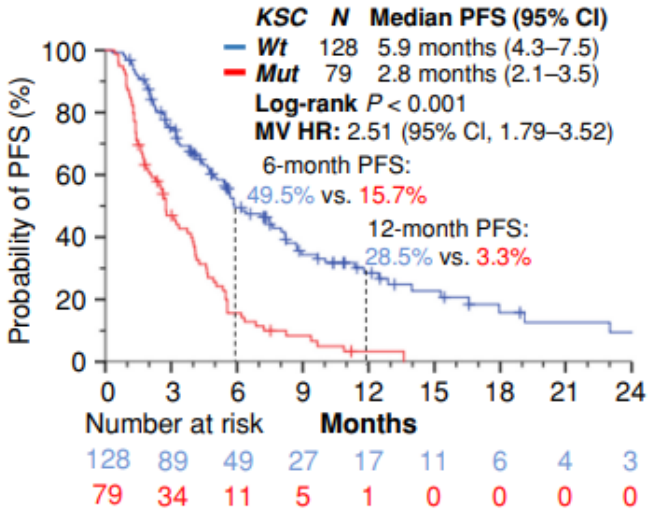
The Next Promise: Addressing Drug Resistance?

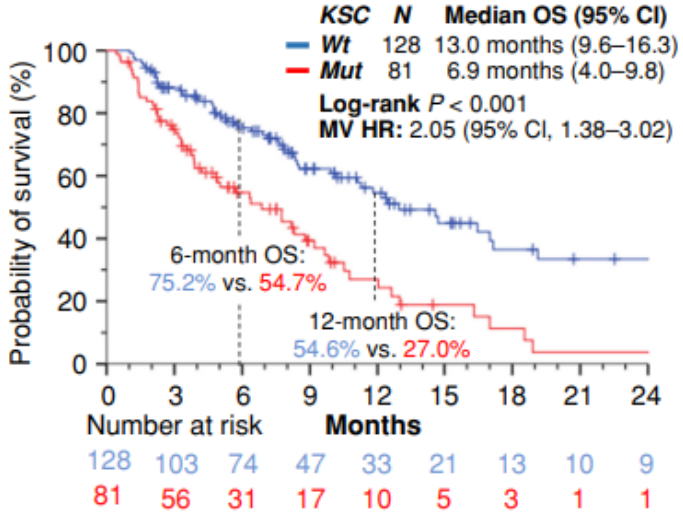


OncoKB™ Therapeutic Level of Evidence V2

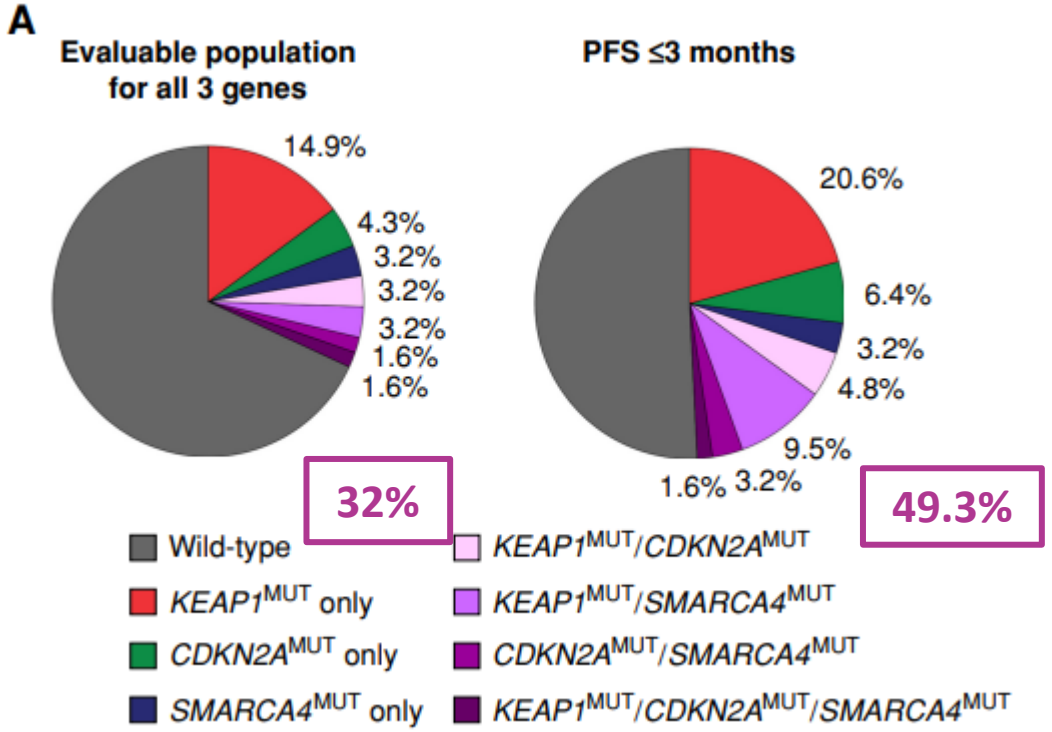
Chakravarty D, Gao J, Phillips SM, et al. OncoKB: A Precision Oncology Knowledge Base. JCO Precis Oncol. 2017;2017:PO.17.00011.

Co-mutations associated with early disease progression in patients treated with adagrasib or sotorasib





Almost 50% with early disease progression had co-mutations in KEAP1, SMARCA4 and CDKN2A[1]



Selection of patients for trials and clinical development strategies need to account for resistance mechanisms and mutations

1. Negrao MV. Cancer Discov 2023

Addressing the potential for drug resistance in the development of HMBD-001, an anti-HER3 monoclonal antibody

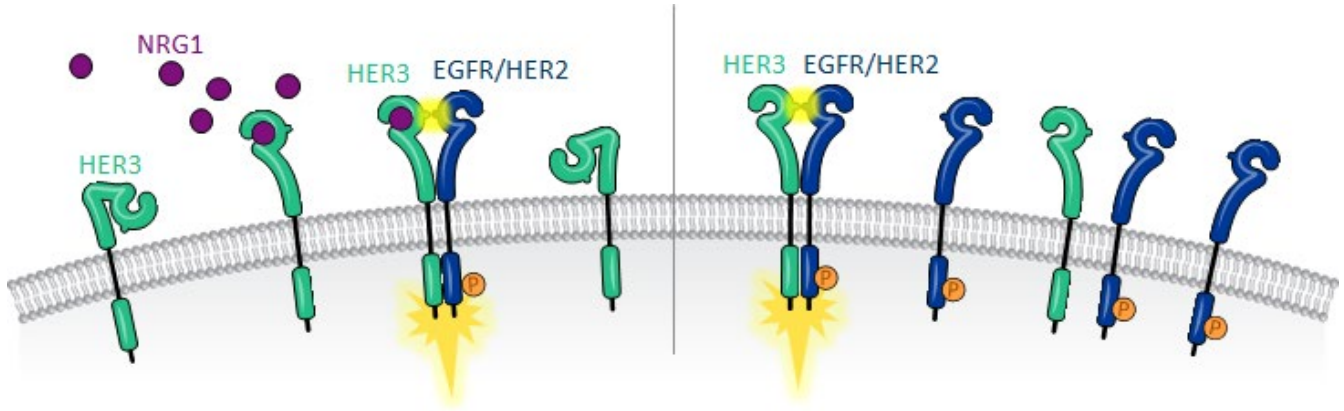
HMBD-001: Hummingbird Bioscience's novel anti-HER3 mAb
Fully blocking HER3 activation regardless of ligand binding

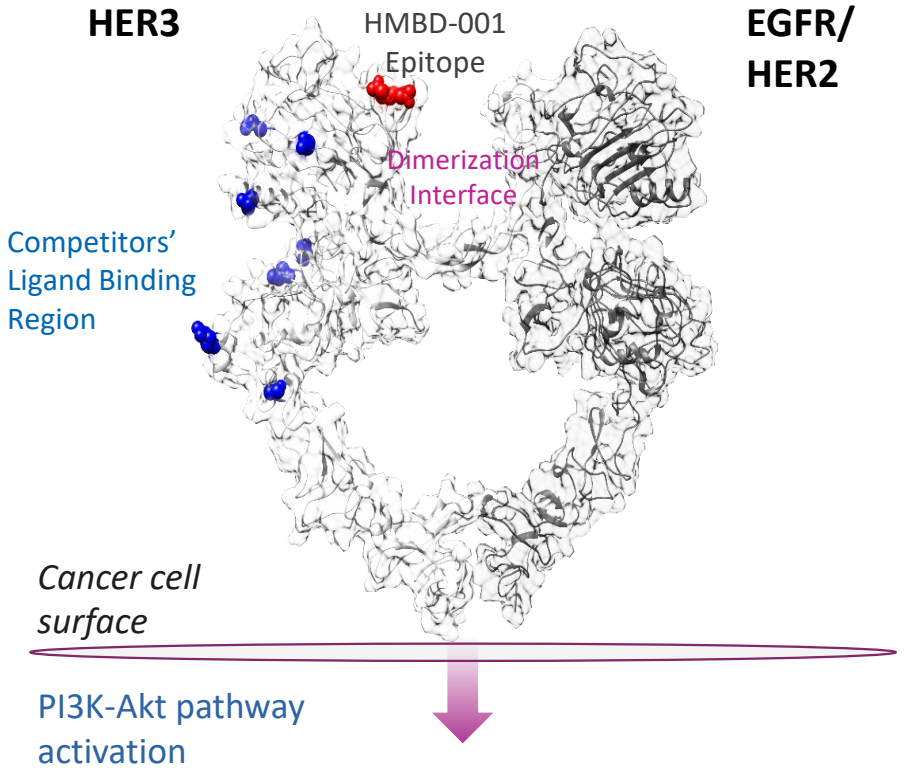
Ligand-Dependent HER3 Activation

High levels of NRG1 are needed to stabilize HER3 in an open state ready for dimerization and signaling when there are low levels of EGFR or HER2

Ligand-Independent HER3 Activation

When high levels of EGFR or HER2 are present on the cell surface NRG1 is not required as complexes can form easily with transiently open HER3



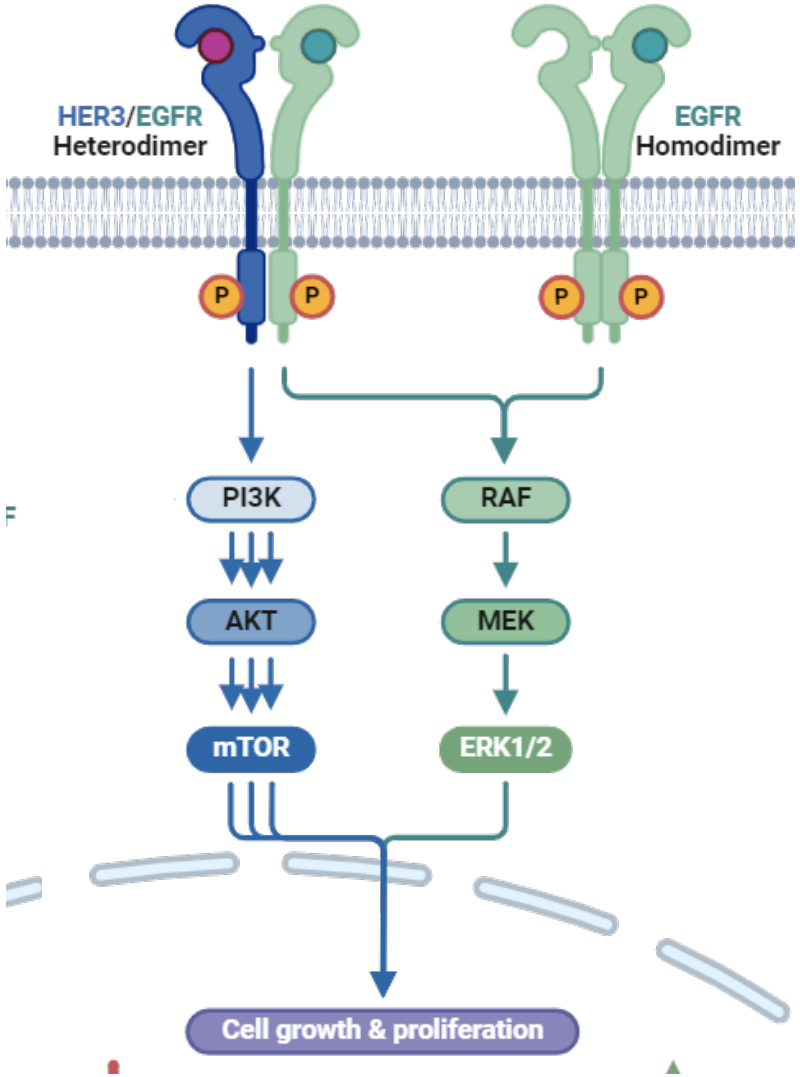


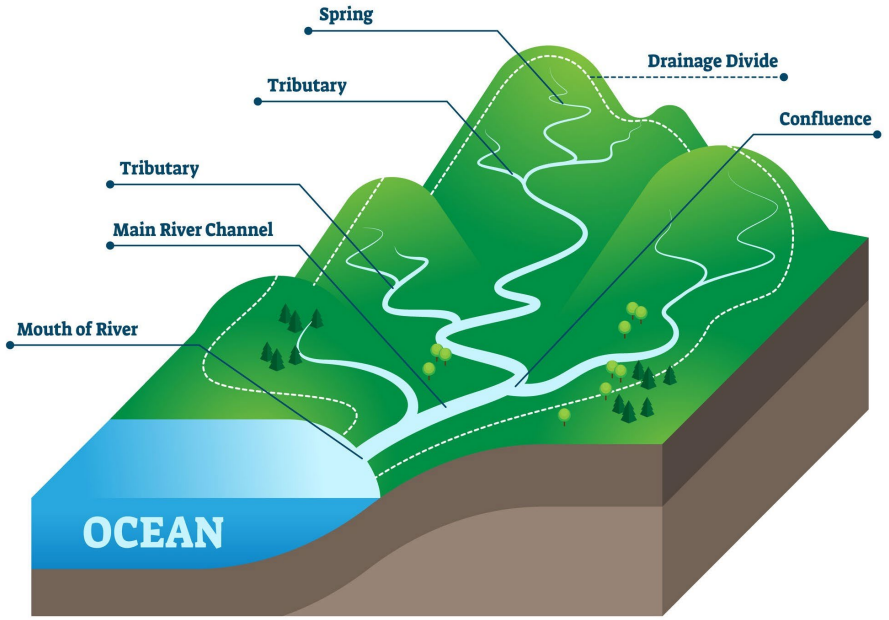
COMPETITION

10+ years of discovery efforts by Genentech, Novartis, Amgen, GSK, Merrimack and others with no successful HER3 drug approved

Source: Gala, K. and Chandarlapaty, S., 2014. Molecular Pathways: HER3 Targeted Therapy. Clinical Cancer Research, 20(6), pp.1410-1416.

HMBD-001 Development
Accounting for genomic alterations in downstream signaling pathways



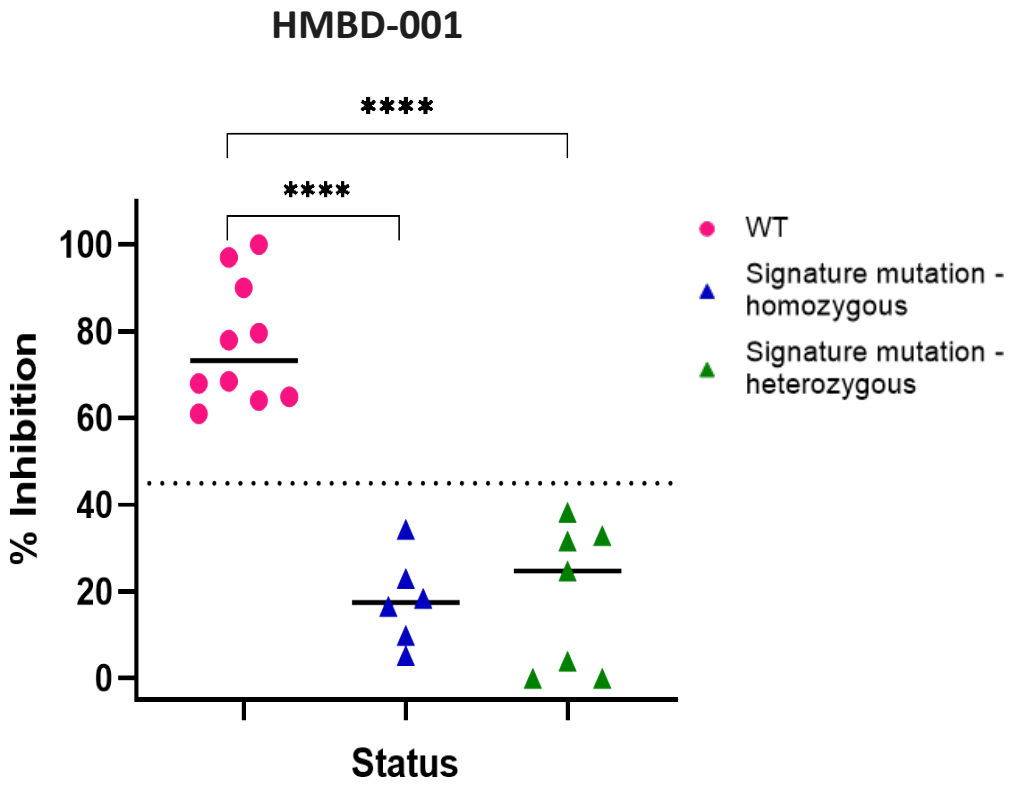


Downstream genomic alterations can cause signaling through the PI3K and/or MAPK pathways, regardless of HER3/EGFR blockade

Diagram made with BioRender.com

Proprietary WT gene signature correlates positively with clinical benefit from HMBD-001 monotherapy

Preclinical *in vivo* mouse model: Tumors that are wild-type for a select set of genes ('gene signature') are responsive to HER3 inhibition[1]



Clinical Benefit: Wild-type gene signature correlates with disease control with HMBD-001 monotherapy

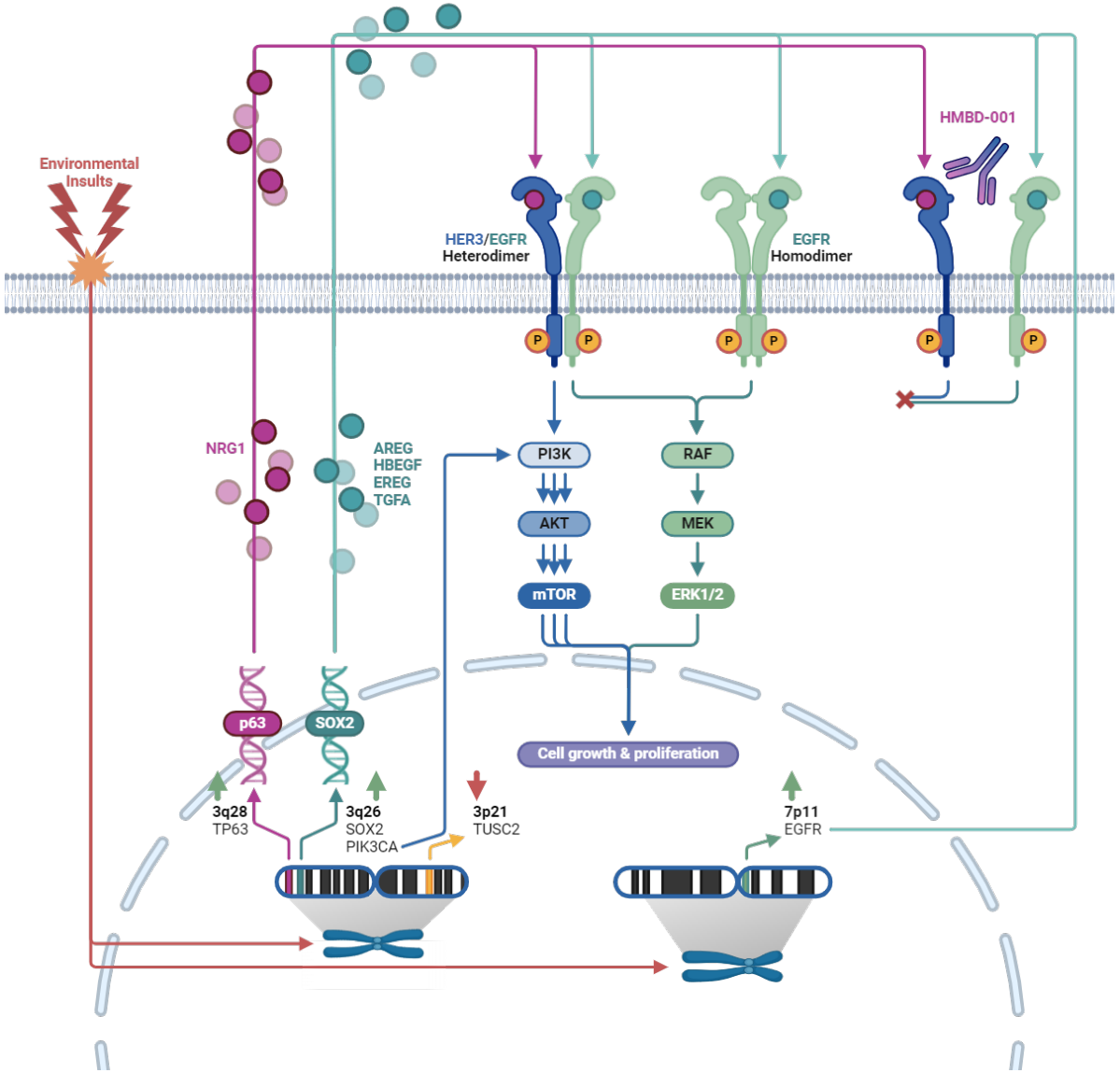
Best overall response by WT gene signature status at baseline

		Best overall response		DCR
		PD	SD/PR	
ctDNA signature	WT	1	9	90%
	Mut	10	1	9.1%

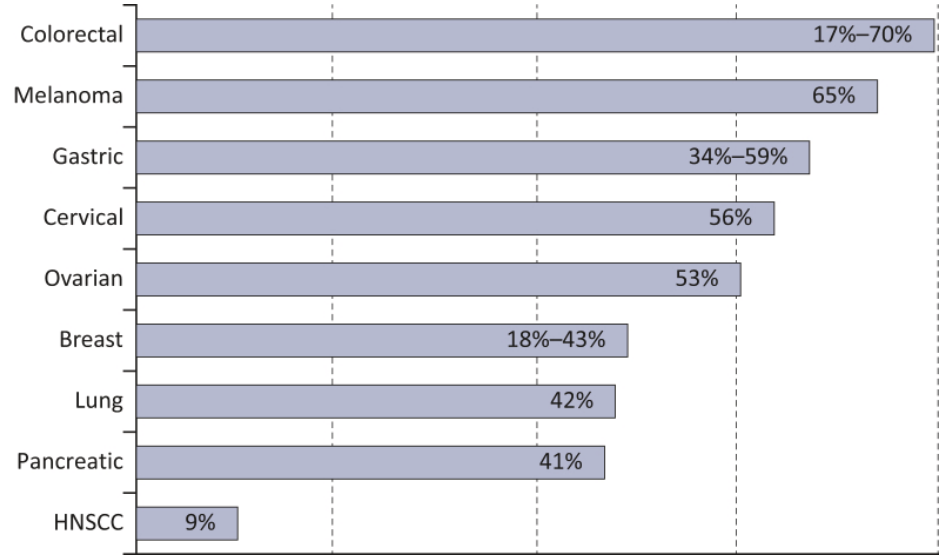
- 9 out of 10 patients harboring the WT signature at baseline had SD or PR as their best response, resulting in a disease control rate (DCR) of 90%
- Only 1 out of 9 patients with disease control (SD/PR) had a mutation in the genes of the signature
- p-value = 0.00021

1. AACR-NCI-EORTC Virtual International Conference 2021: An anti-HER3 antibody, HMBD-001, that uniquely binds to and blocks the HER3 heterodimerization interface, shows superior tumor growth inhibition in biomarker-defined preclinical cancer models including NRG1 fusion driven cancers | Hummingbird Bioscience

HMBD-001 Development | Rational combination in squamous cell carcinomas



HER3 IS HIGHLY EXPRESSED ACROSS TUMOR TYPES[1]



OPTIMAL DRUG COMBINATION STRATEGY IN SQUAMOUS NSCLC

1. HER3 inhibition to block the PI3K pathway
2. EGFR inhibition to block the MAPK pathway
3. Standard of care chemotherapy to induce cytotoxicity (at least for now)

Diagram made with BioRender.com
1. J. Uliano 2023

Patient-centric biomarker selection strategy in the development of HMBD-001

Ph Ib
Retrospective subpopulation analysis

Site-specific referral network

Principal Investigators may refer patients of their own or patients from their medical colleagues directly to sites

Phase Ib trial in patients with SCCs

HMBD-001 + cetuximab (chemo-free)

HMBD-001 + cetuximab + docetaxel

Retrospective Analysis

- "Prevalence" of propriety WT gene signature
- Correlation of clinical benefit with gene signature
- Concordance of gene signature between ctDNA and tissue

Ph II
Prospective biomarker-based pt selection

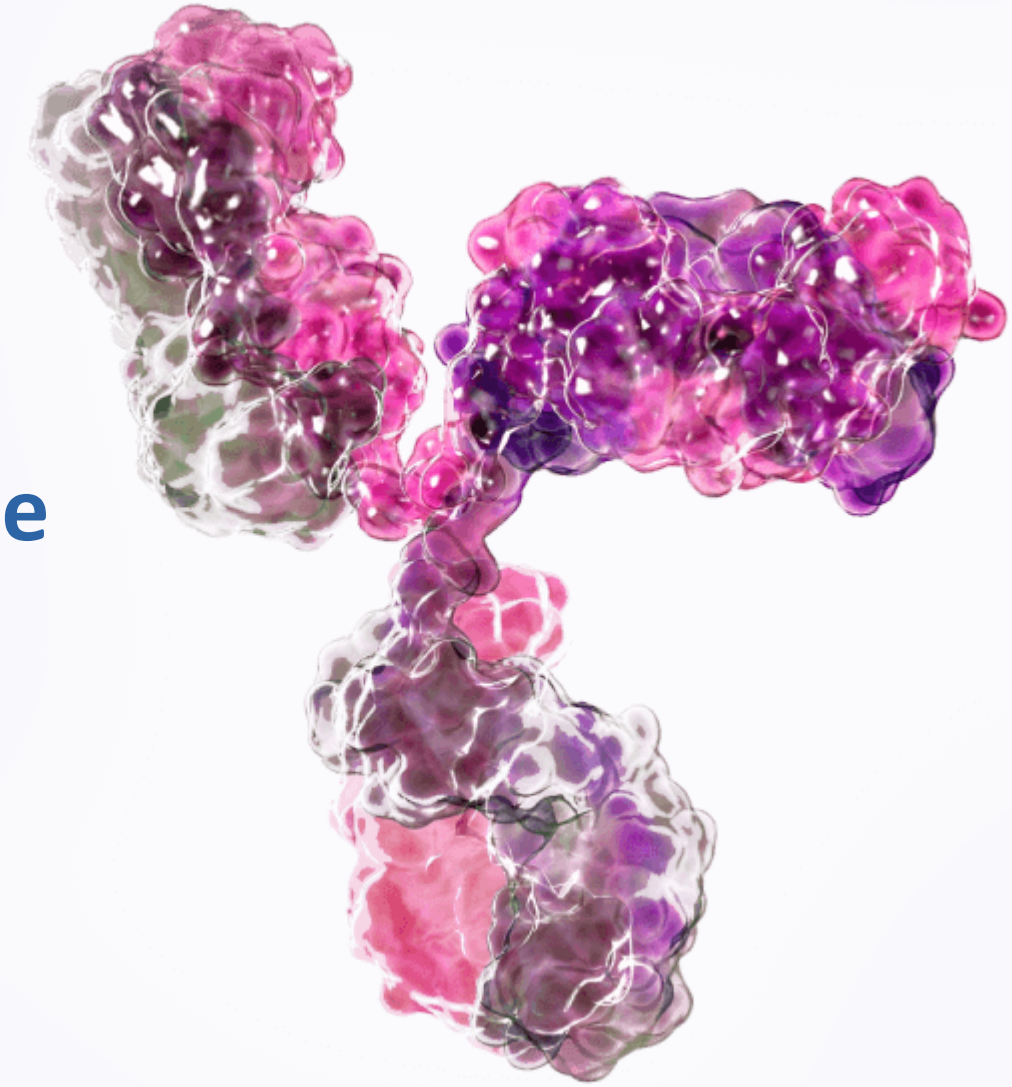
Biomarker Strategy

- Use of ctDNA /tissue/ctRNA in prospective screening
- Pre-screening with biomarkers

Country Strategy

- Countries with national precision medicine programs
- Countries with widespread NGS testing

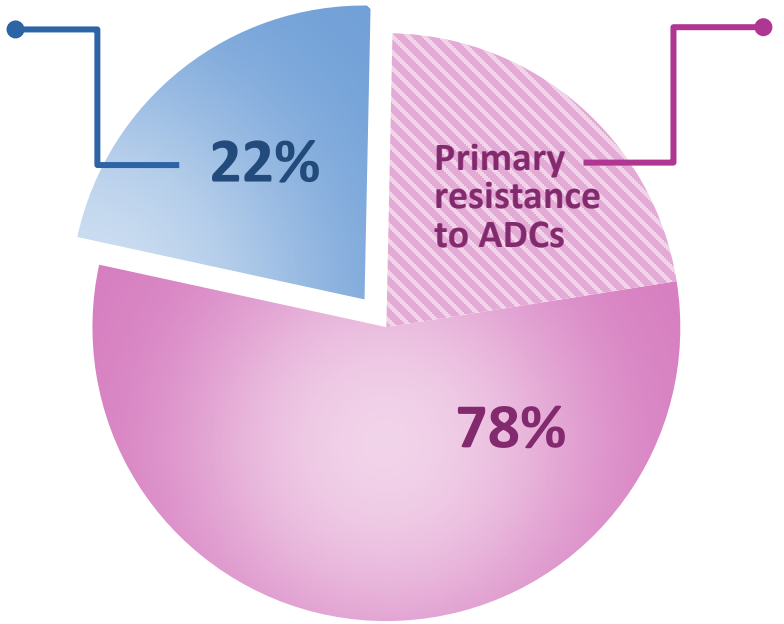
Overcoming ADC payload resistance with dual payload ADCs



Payload resistance remains a key challenge with ADC therapies
The need to understand resistance mechanisms better

ADCs have been approved for the treatment of ~1/4 of ***solid tumor patients***, however ***duration of response*** remains a key issue:

- Currently approved ADCs use topoisomerase 1 (topo1) or microtubule inhibitor payloads against 5 targets (HER2, TROP-2, Nectin-4, TF, FRα)[1]
- Majority of patients progress,[2,3] with payload resistance a primary cause
  - 65% (13/20) of patients progressing on Enhertu retained HER2 expression[3,4]
- Opportunity for improved duration of response by addressing payload resistance

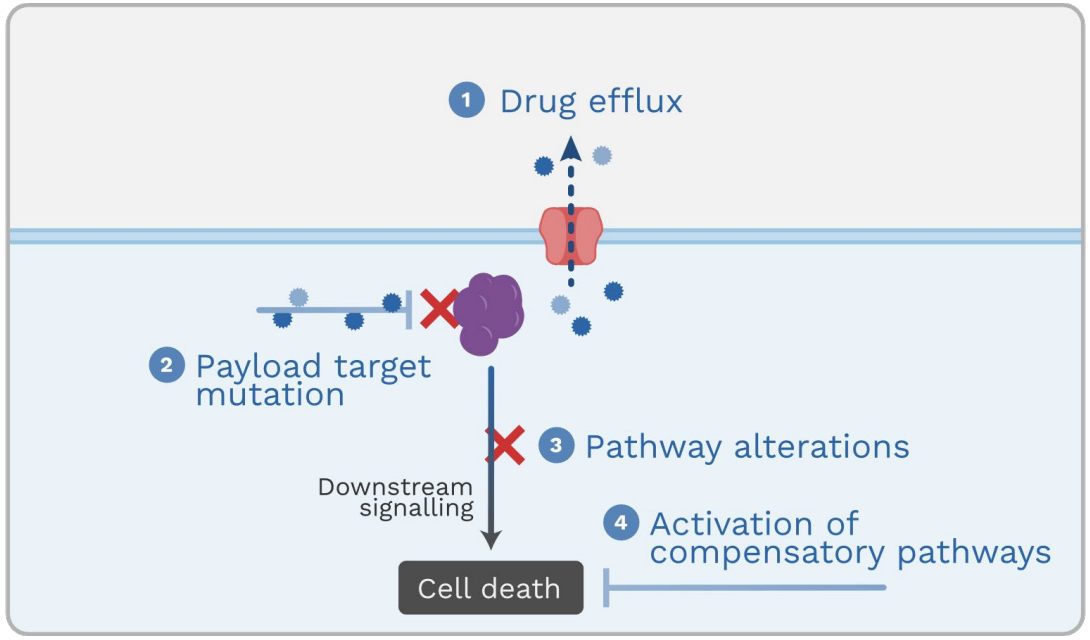


Majority of solid tumor patients do not have an approved ADC treatment:

- Primary resistance limits the patient population that can potentially be treated with an ADC
- Opportunity to maximize potential of approved ADC targets by **understanding** and addressing payload resistance

Pie chart shows percentage of 2L drug treatable patients across major solid tumors for which an ADC treatment has been approved
Sources: [1] PMID: 37631374; [2] PMID: 36831621; [3] PMID 37488289; ; [4] ESMO2022 DAISY

Payload resistance is a key driver of ADC resistance, with multiple mechanisms at play



Key mechanisms of payload resistance

1. Drug efflux	• Upregulation of drug efflux pumps (MDR1, MRP1, MRP2, BCRP) impacts drug accumulation *Reported for MMAE, DM1 (microtubule inhibitors) and SN-38 (topo1 inhibitor)*[1]
2. Payload target mutation	• Reduces ability of the payload to engage with its target *Point mutation in topo1 identified in patient resistant to Trodelvy*[2]
3. Pathway alterations	• Pathway alterations disrupting downstream signaling modulated by payload, limiting efficacy[3]
4. Activation of compensatory pathways	• Activation of parallel compensatory pathways blunt effects of payload mediated pathway modulation *Tumor cells reported to escape mitotic catastrophe by T-DM1 through defective cyclin B1*[4]

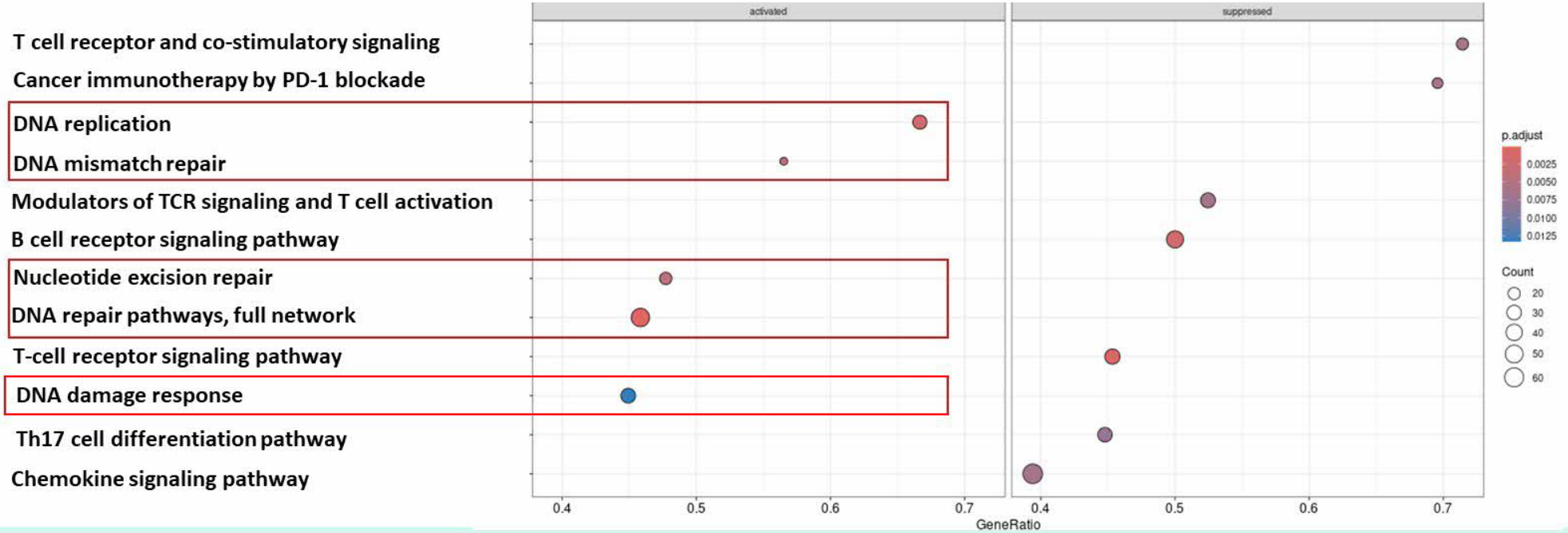
MDR: multi-drug resistance; MRP: multi-drug resistance-associated protein; BCRP: breast cancer resistance protein

Sources: [1] PMID: 36357174; [2] PMID: 34404686; [3] PMID: 32583565; [4] PMID: 28821558

DNA repair pathways are upregulated in non-responders to Dato-DXd

Gene Set Enrichment Analysis (40 pre-defined pathways of interest)

- Non-responder patients' baseline/on-treatment biopsies (14 pairs) were analyzed by bulk RNA-seq
- Upregulation of DDRi pathway



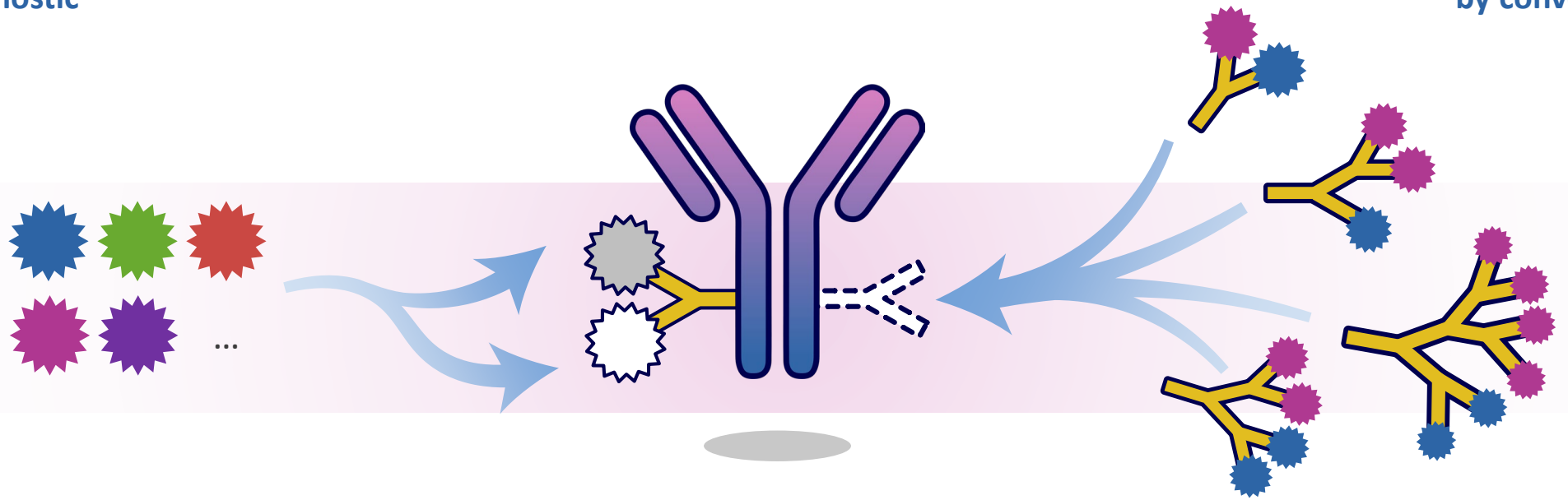
ACTIVATION OF DNA REPAIR AND SUPPRESSION OF IMMUNE RELATED PATHWAYS WITH Dato-DXd IN NON RESPONDERS (*adj p-value <0.05*)

*Samples selected by: Tumor cellularity ≥30%; Quantity >250 ng; RNA integrity number >2; Filter reads>15M; § Data on responders not presented as only 3 pairs of baseline/on-treatment biopsies were analyzable among responders

HMBD's proprietary linker-payload technology enables antibodies to connect to a broad range of payloads in a variety of DAR combinations

Dual payload-enabling linkers are payload agnostic

Combinatorial DAR can be varied by convergent synthesis



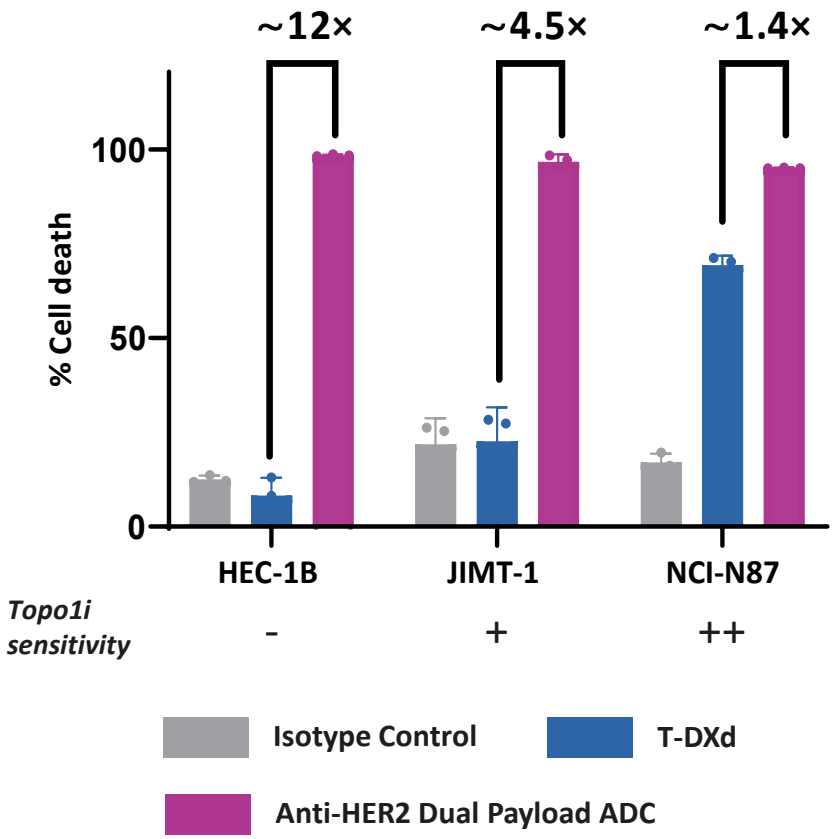
- Linker is payload agnostic – accommodates broad chemical connectivities for conjugation of different payloads
- Enables rapid evaluation of payload combinations

- Branched hydrophilic linker design to allow for DAR flexibility
- Enables rapid evaluation of combinatorial DAR

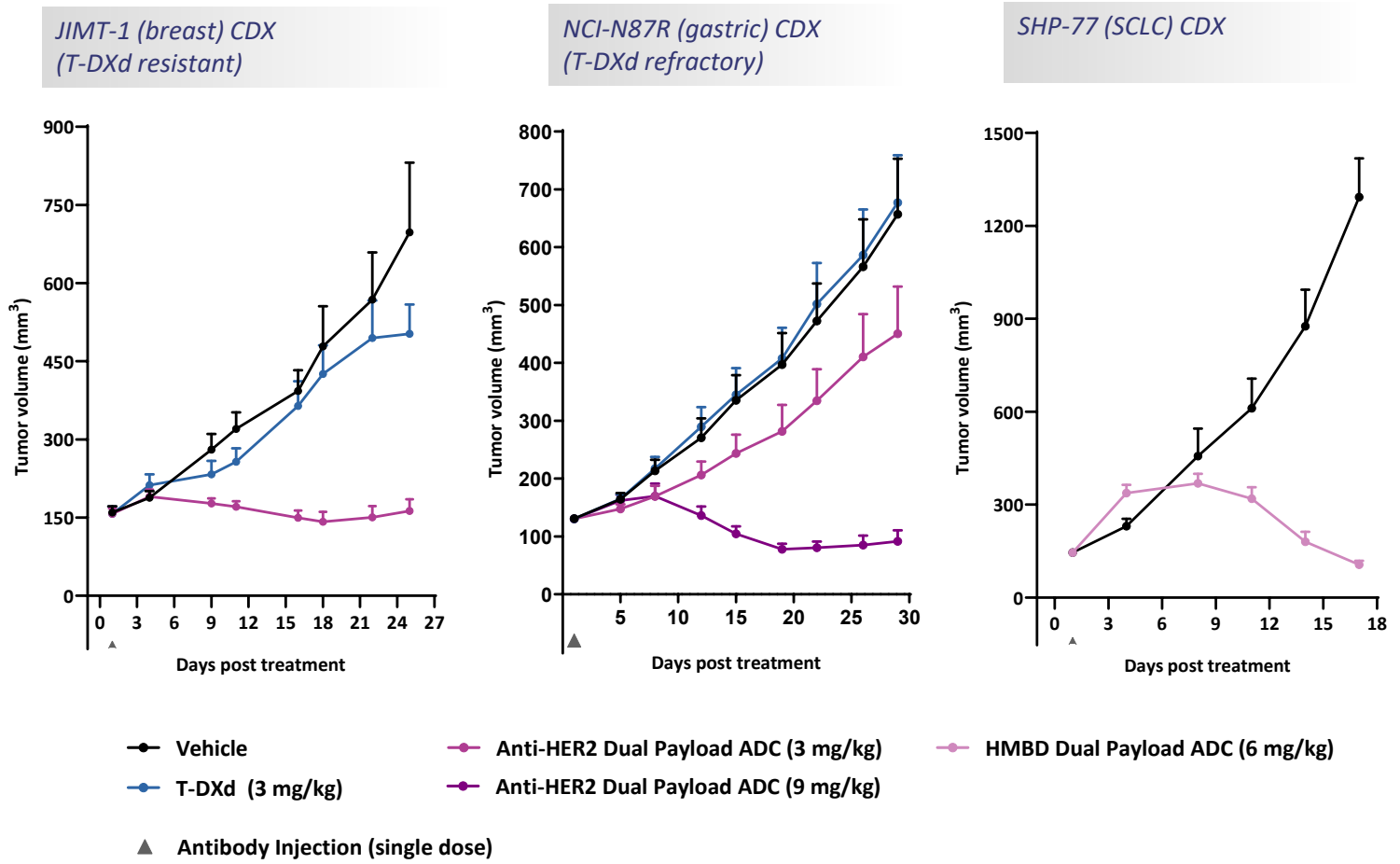
Flexibility in payload combinations and DAR allows for optimization of dual payload ADC and potential maximization of therapeutic window

HMBD dual payload ADCs show robust activity in tumors with poor response to topo1i ADCs

HMBD dual payload ADC shows superior *in vitro* efficacy to T-DXd across a range of topo1i sensitivity



HMBD dual payload ADCs are highly potent and have shown tumor regression after a single dose



Summary

- Hummingbird Bioscience continuously invests efforts in ensuring the right patients receive our precision therapies
- Precision oncology drugs are making up an increasing proportion of new drug approvals
- Genomic testing for patients with advanced cancers, regardless of the “actionability” of the results, will greatly aid in the development of new precision oncology therapies
- Genomic alterations can abrogate efficacy of drugs and development programs need to address these
- The clinical development of HMBD-001 accounts for genomic alterations in downstream signaling pathways that cause resistance to treatment
- Payload resistance is a critical challenge for ADCs and there is a need to better understand resistance mechanisms to overcome this
- Payload combinations can potentially overcome resistance arising from activation of DNA repair pathways and dual payload ADCs are an optimal therapeutic modality for targeted delivery of these combinations
- Hummingbird Bioscience is developing next-generation dual payload ADCs that demonstrate efficacy in resistant/insensitive solid tumor settings

Thank you

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