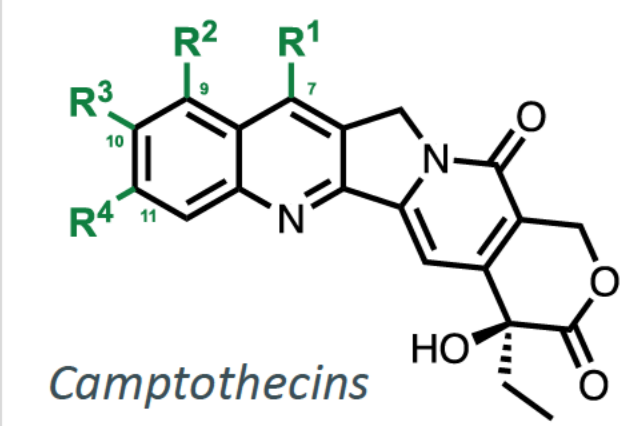


Stuart Barnscher, Raffaele Colombo, Mark Petersen, Michael Brant, Manuel Lasalle, Andrea Hernandez, Renee Duan, Jodi Wong, Samir Das, Vincent Fung, Kaylee Wu, Sam Lawn, Daya Siddappa, Gerry Rowse, and Jamie Rich

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Background: Camptothecin Therapeutics

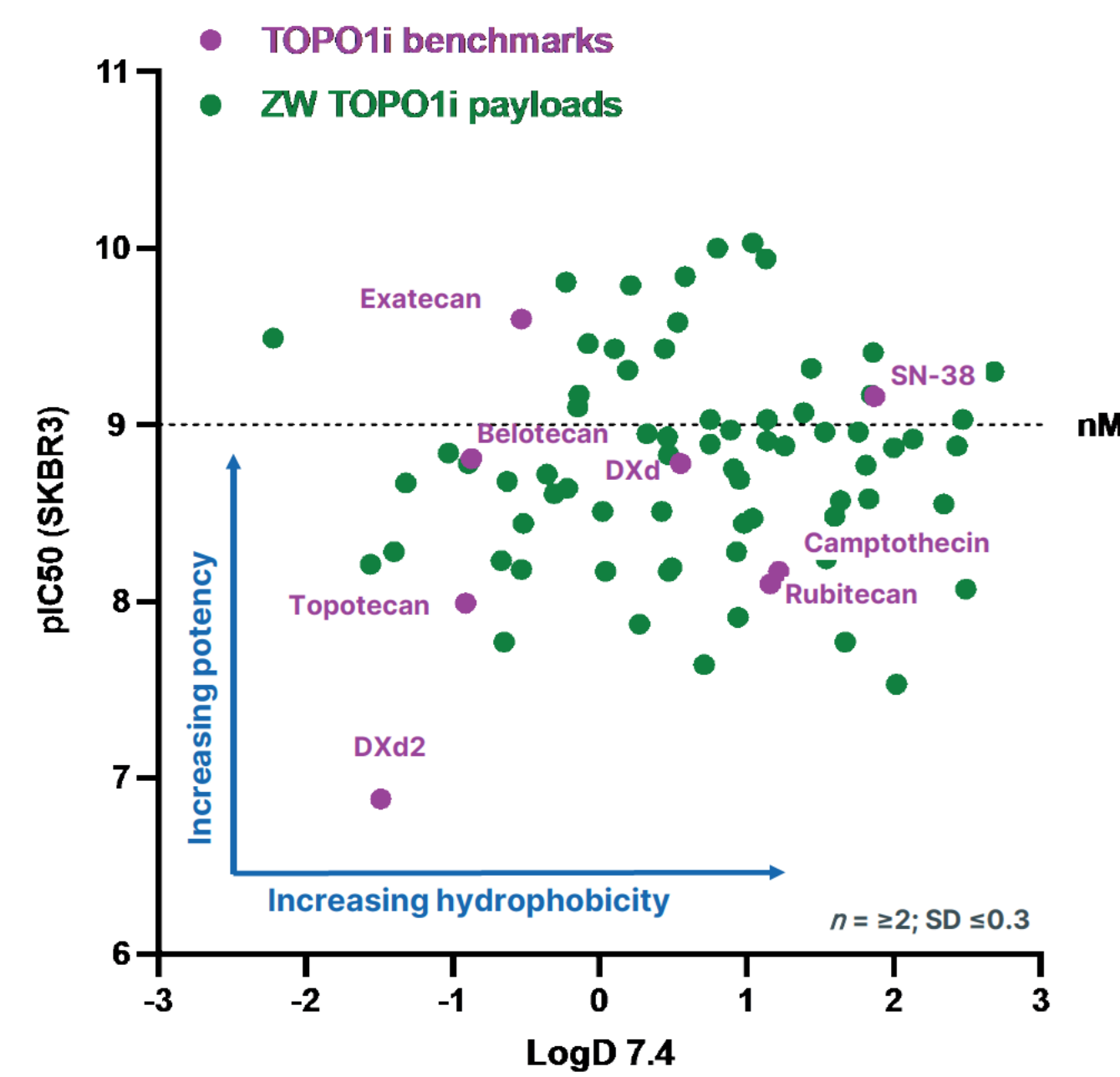
Potent inhibitors of topoisomerase I:



- Discovered in the early 1960 by M. E. Wall and M. C. Wani of Research Triangle Institute
- Isolated from *Camptotheca acuminata* (The Happy Tree)
- Prevents DNA re-ligation which results in double strand breaks and apoptosis

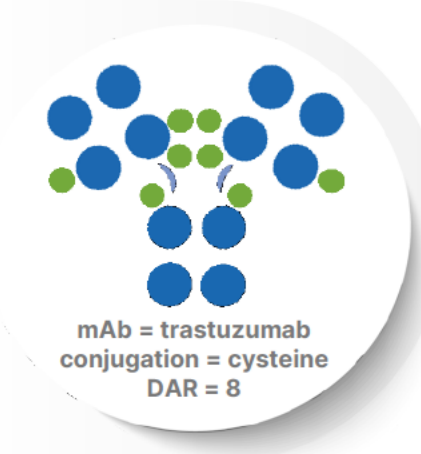
- 3 approved small molecules (Topotecan, Irinotecan, Belotecan)
- 2 approved ADCs (Enhertu®, Trodelvy®)
- Several ADCs, SMDCs, and NPs at different stages of development

Zymeworks Camptothecin Payloads Span a Range of Potency and Hydrophilicity



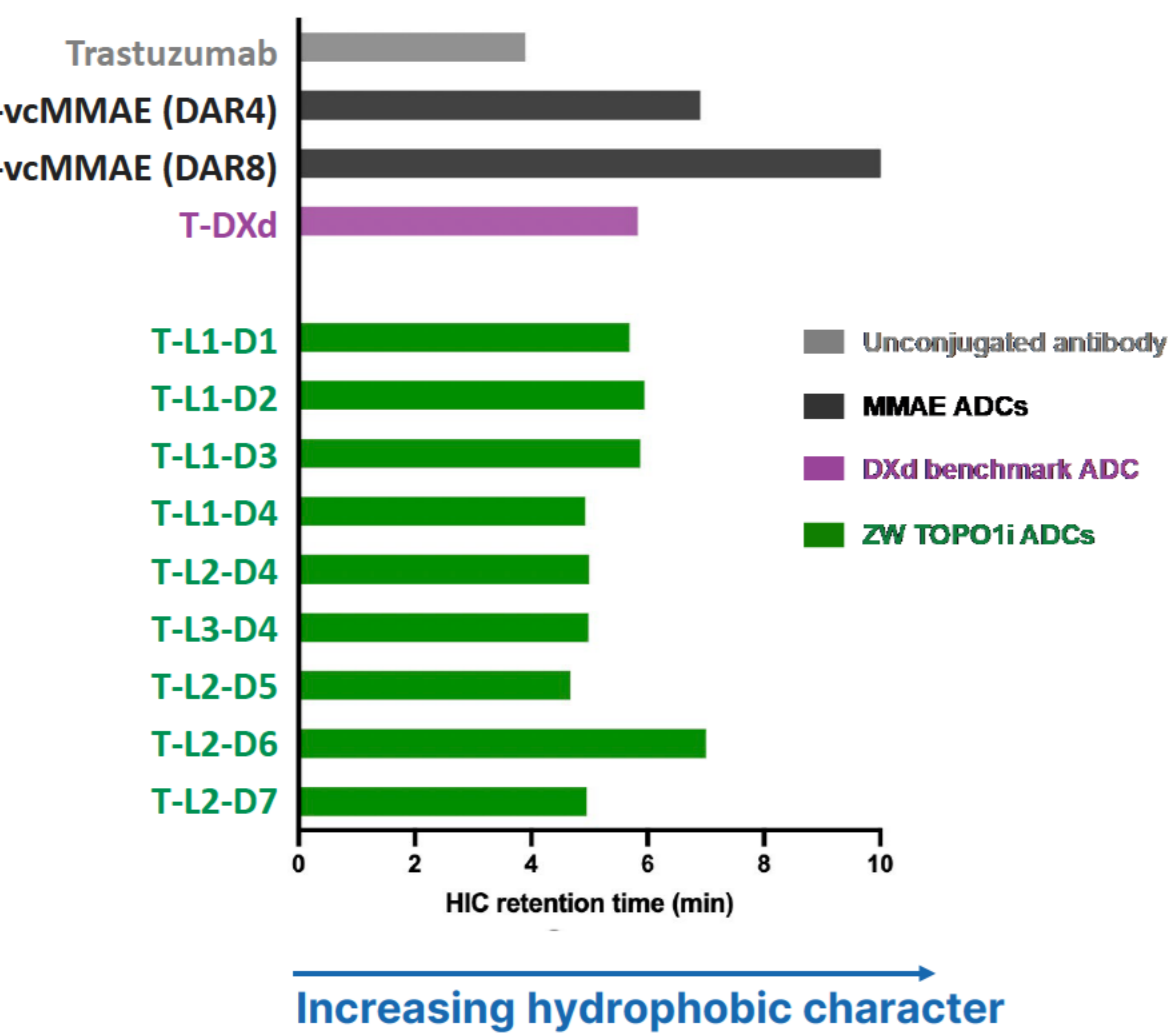
- ~100 new TOP01i payloads prepared
- Range of potency and hydrophilicity
- Two linking strategies (from R¹ and R³ groups)

Zymeworks TOP01i Drug-Linkers Yield ADCs with Favorable Physicochemical Properties and Low Aggregation

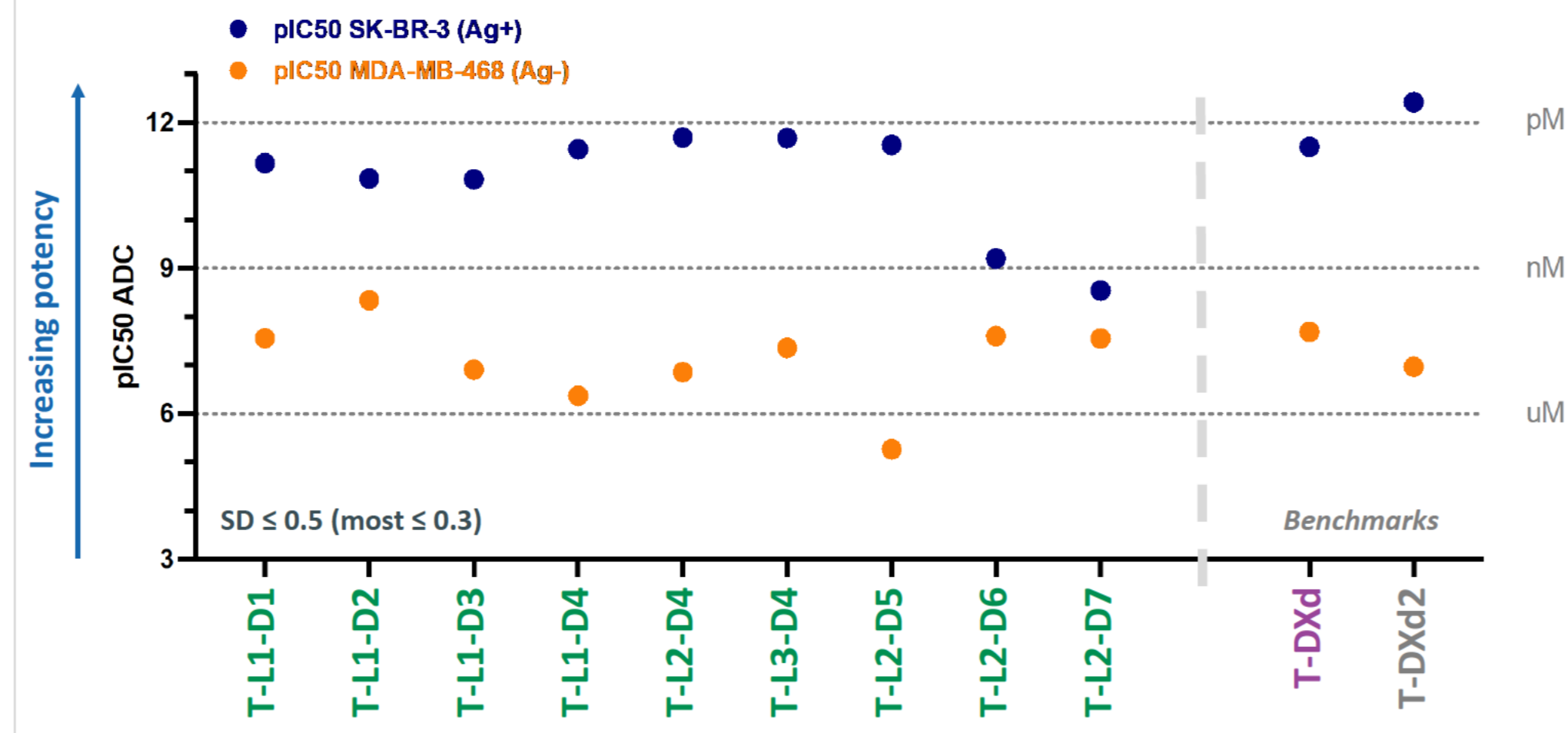


ADCs with ZW TOP01i DLs:

- No aggregation for DAR8 (challenge for this class)
- Hydrophilic
- 100% monomeric
- Robust freeze thaw stability

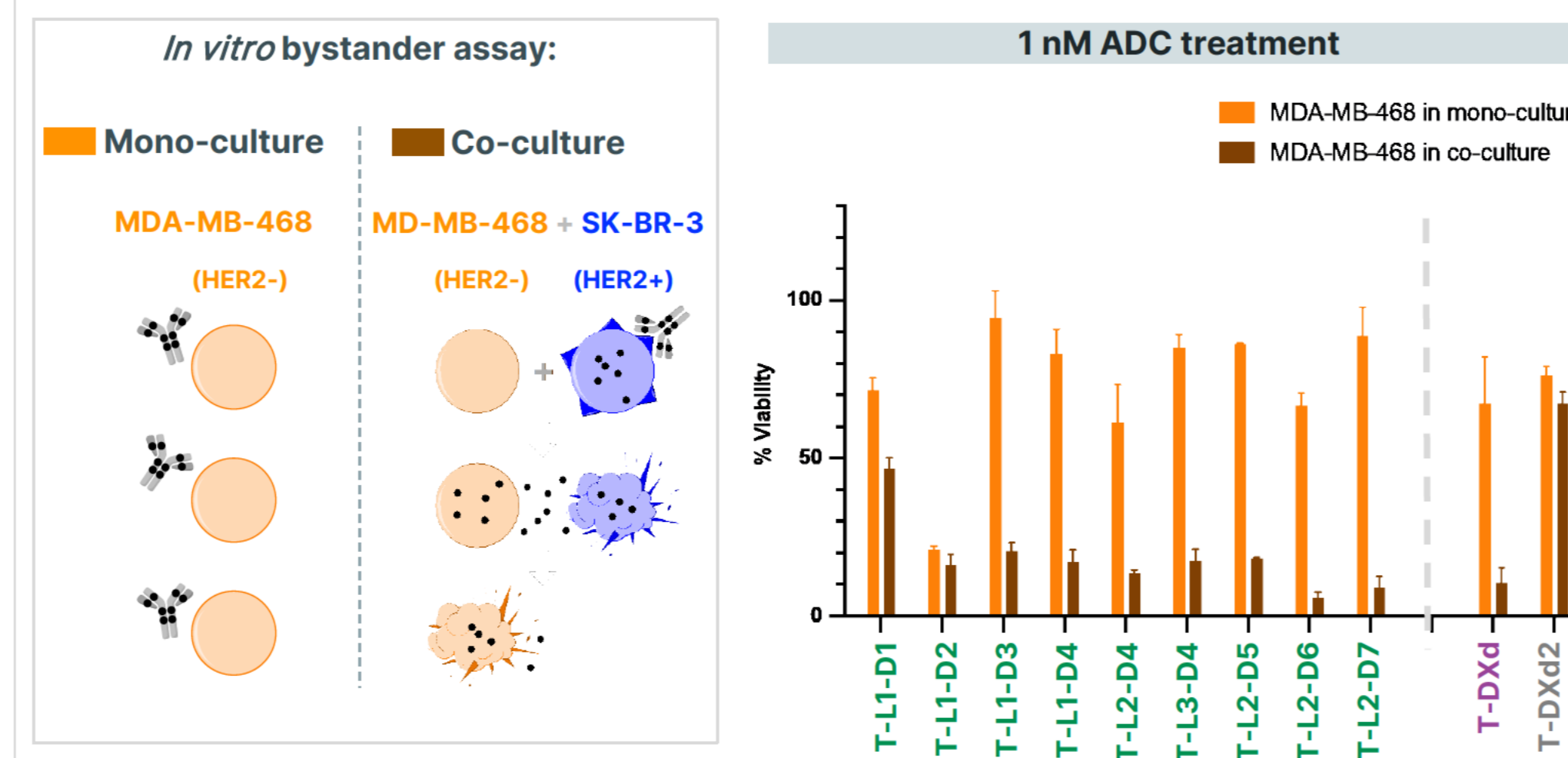


Lead ADCs Showed Good Potency and Selectivity in 2D Cytotoxicity Assays

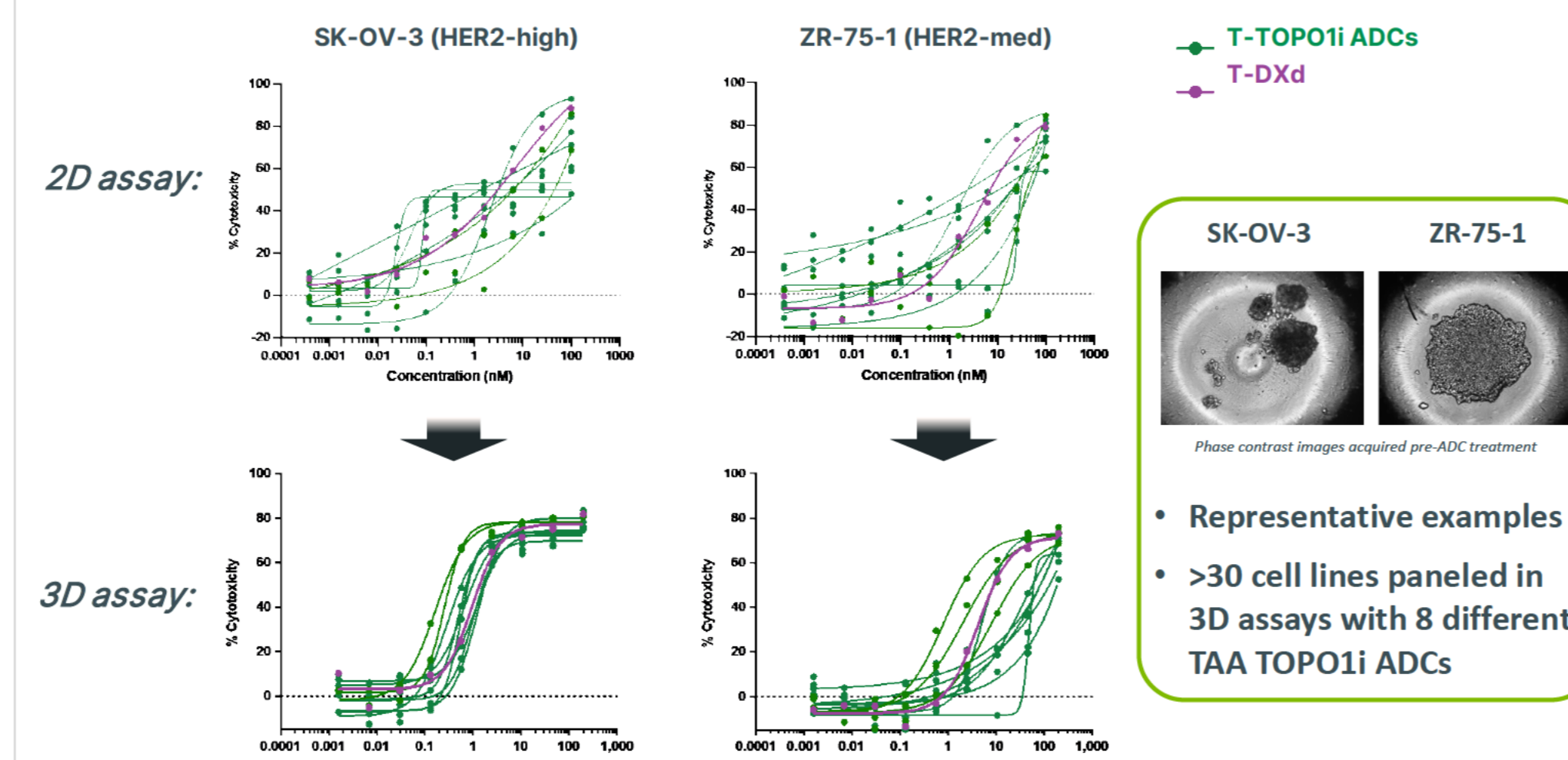


Representative pIC50 in an Ag+ cell line sensitive to TOP01i ADCs and an Ag- cell line >70 cell lines tested in 2D assays with 8 different TAA TOP01i ADCs (~25% sensitive)

Strong Bystander Activity for Most Zymeworks TOP01i ADCs

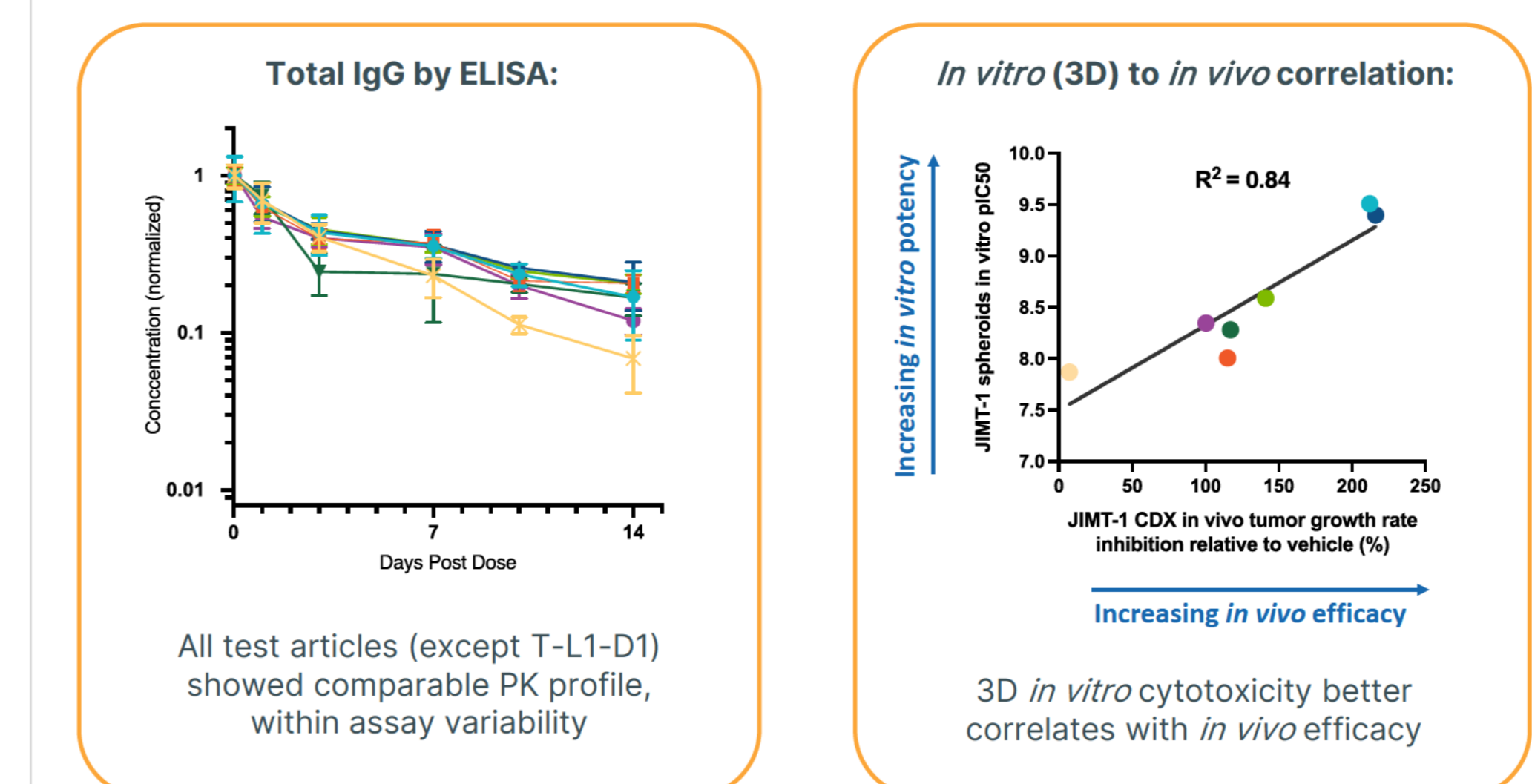
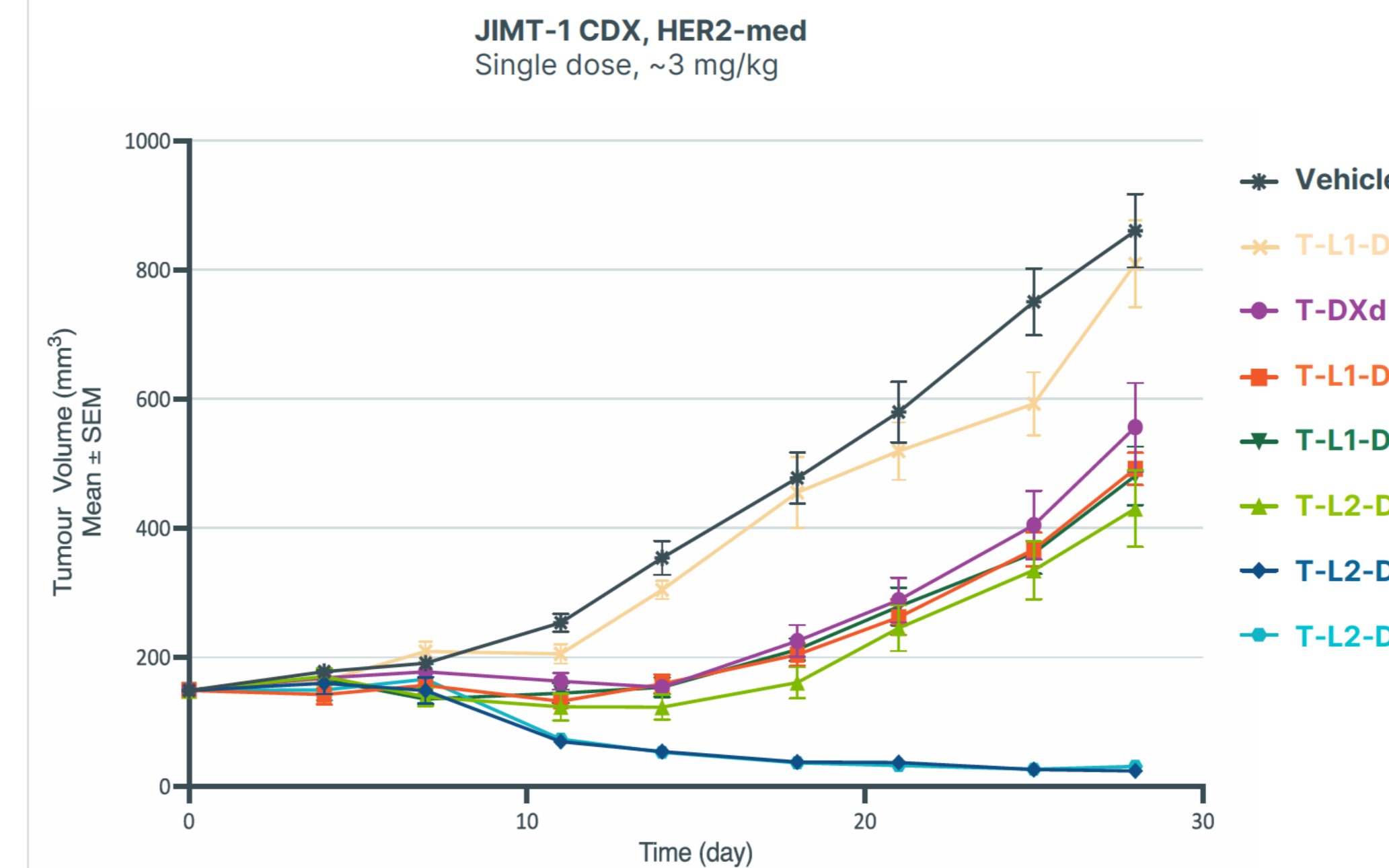


Spheroid Cytotoxicity Assay Altered Dose-Response Relationship and Relative Potency Ranking of ADCs



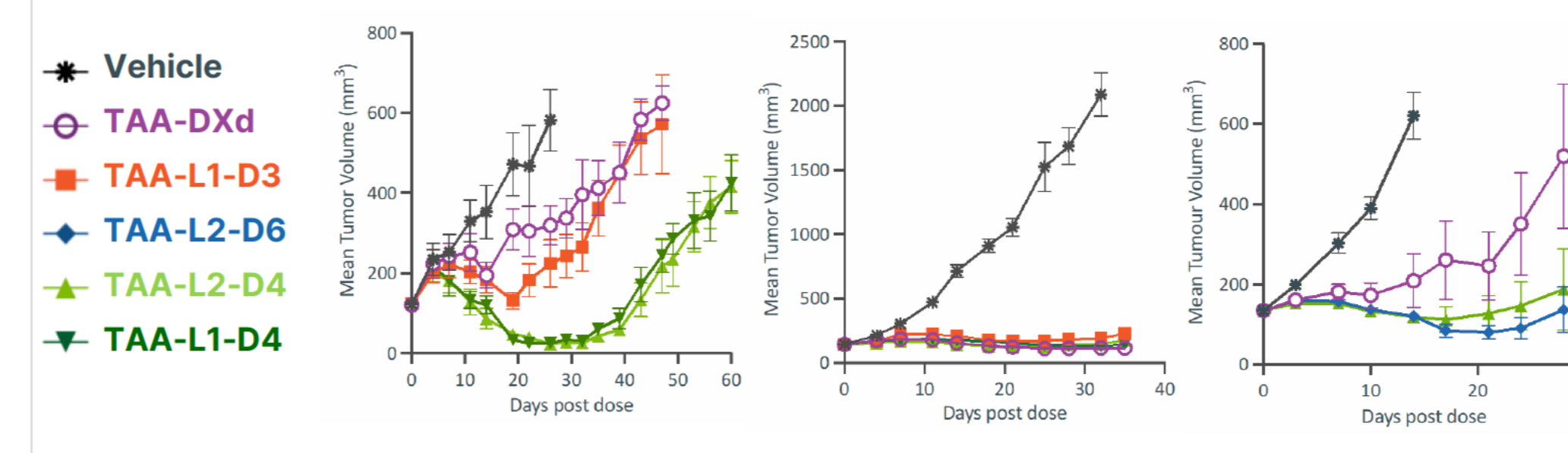
- Potency differences may be due to better bystander killing

Zymeworks TOP01i ADCs Demonstrate Potent in vivo Efficacy



Zymeworks TOP01i ADCs Demonstrate Anti-Tumor Activity in Multiple in vivo Models

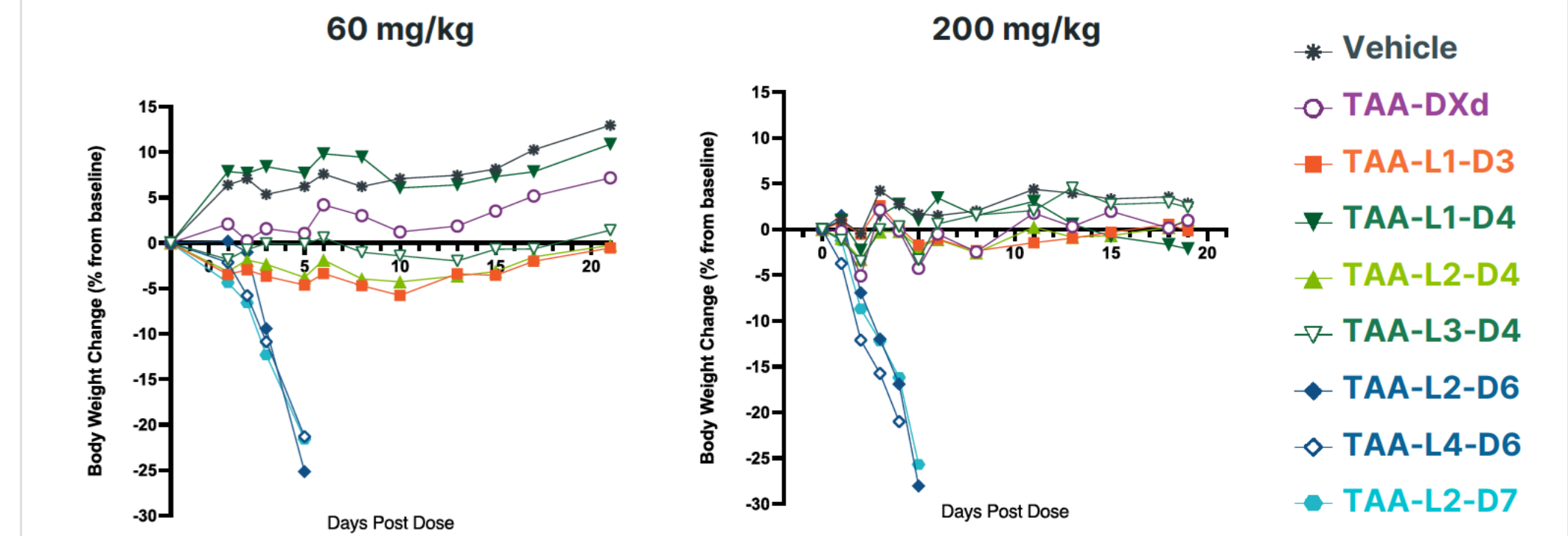
Strong anti-tumor activity for DAR8 ADCs in cell line derived xenografts models across three targets with a single dose at 3 mg/kg



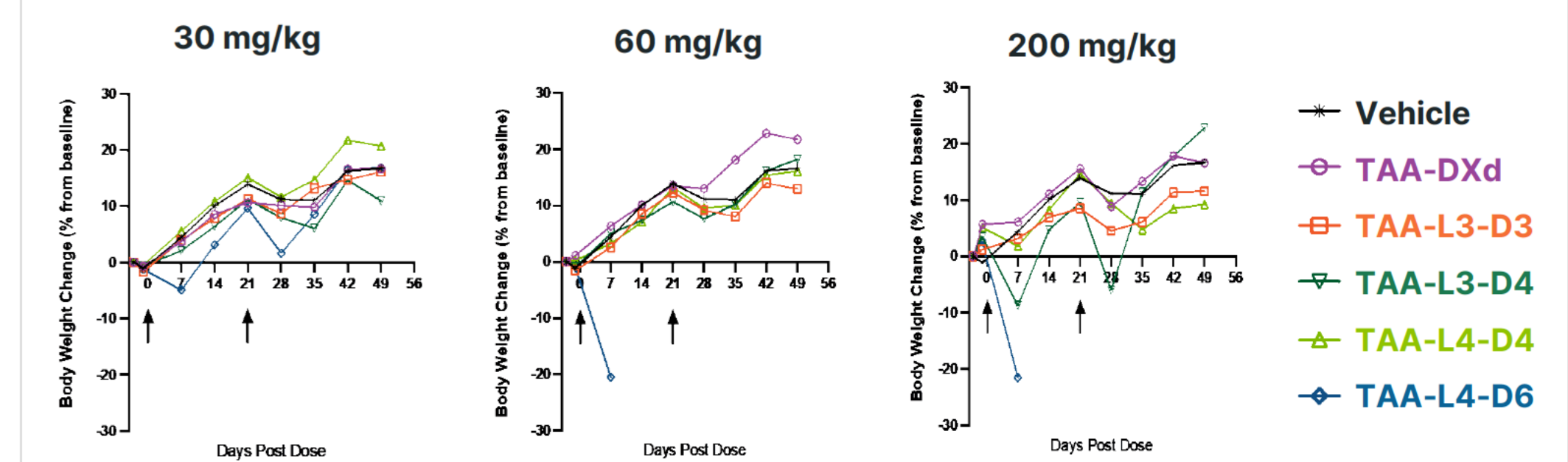
TAA	TAA1	TAA2	TAA3
Model	Ovarian CDX	Lung CDX	Solid tumor CDX
Target expression level	Med/Low, Heterogeneous	High	High/Med, Heterogeneous
Mice per group	6	6	6

Murine and Rat Tolerability Studies Identified 2 Lead Drug Linkers

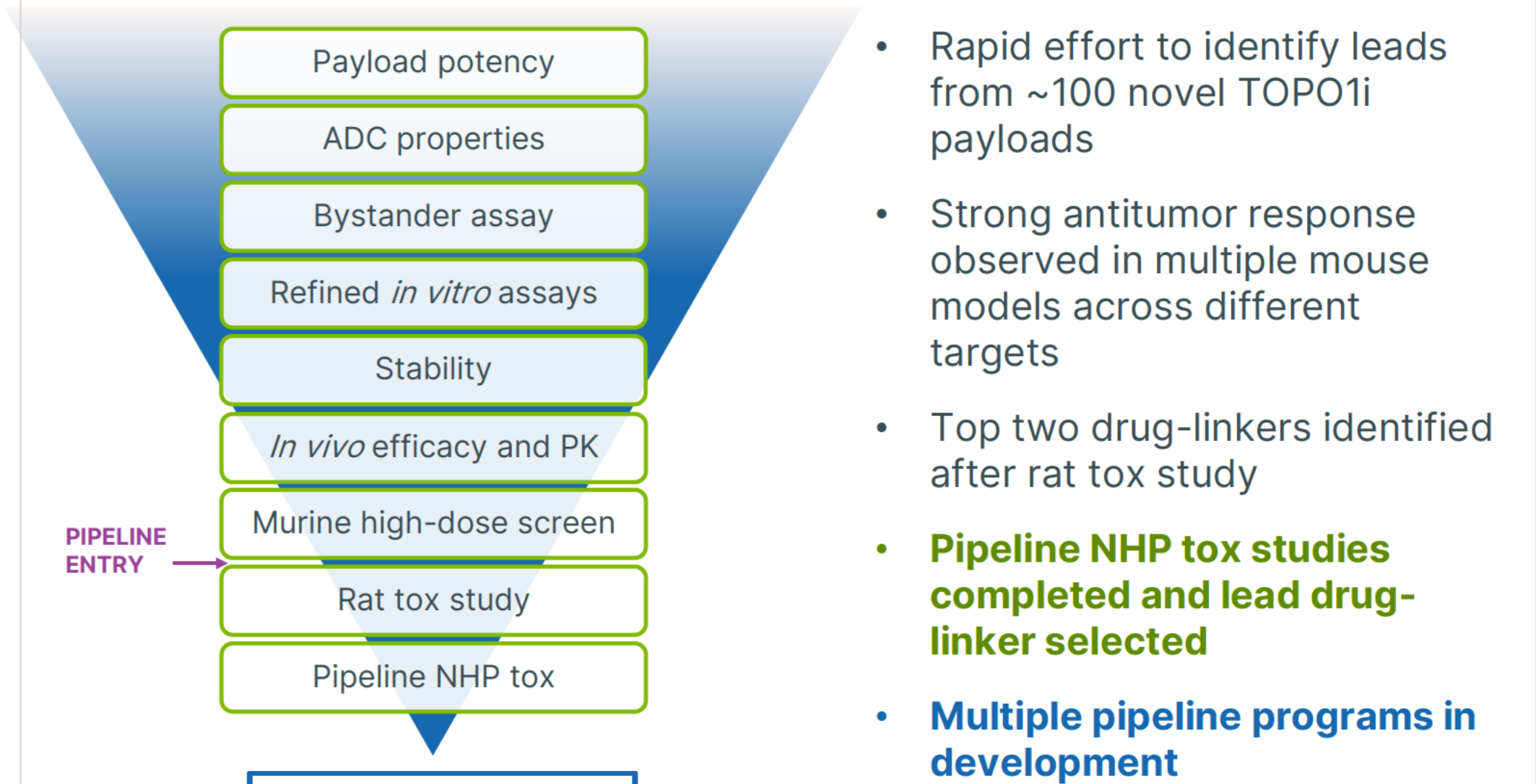
4 drug-linkers were tolerated in murine high dose screen



2 lead drug-linkers were identified in rat tox study



The Path from Concept to Pipeline



Acknowledgements

Development of this platform would not have been possible without the hard work and effort of the entire ADCTD research group at Zymeworks. Additionally, thank you to the clinical team and senior management for guidance and continued support.

