

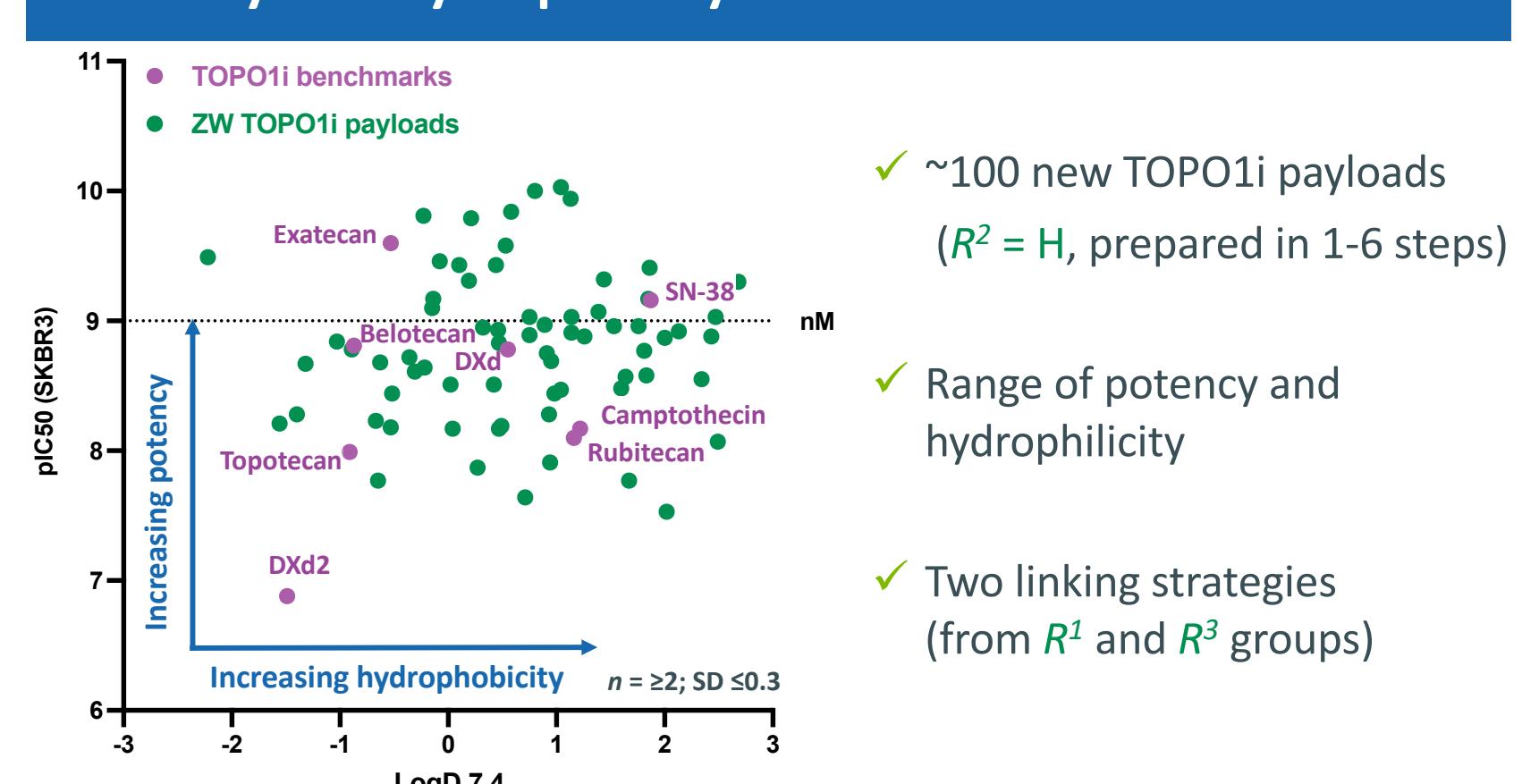
Zymeworks Topoisomerase 1 Inhibitor ADC Platform: From Concept to Pipeline

Mark Petersen, Raffaele Colombo, Michael Brant, Manuel Lasalle, Andrea Hernandez, Renee Duan, Jodi Wong, Samir Das, Vincent Fung, Sam Lawn, Daya Siddappa, Gerry Rowse, Stuart Barnscher, and Jamie Rich
Zymeworks Inc. 114 E 4th Ave Suite 800, Vancouver, BC, V5T 1G4, Canada

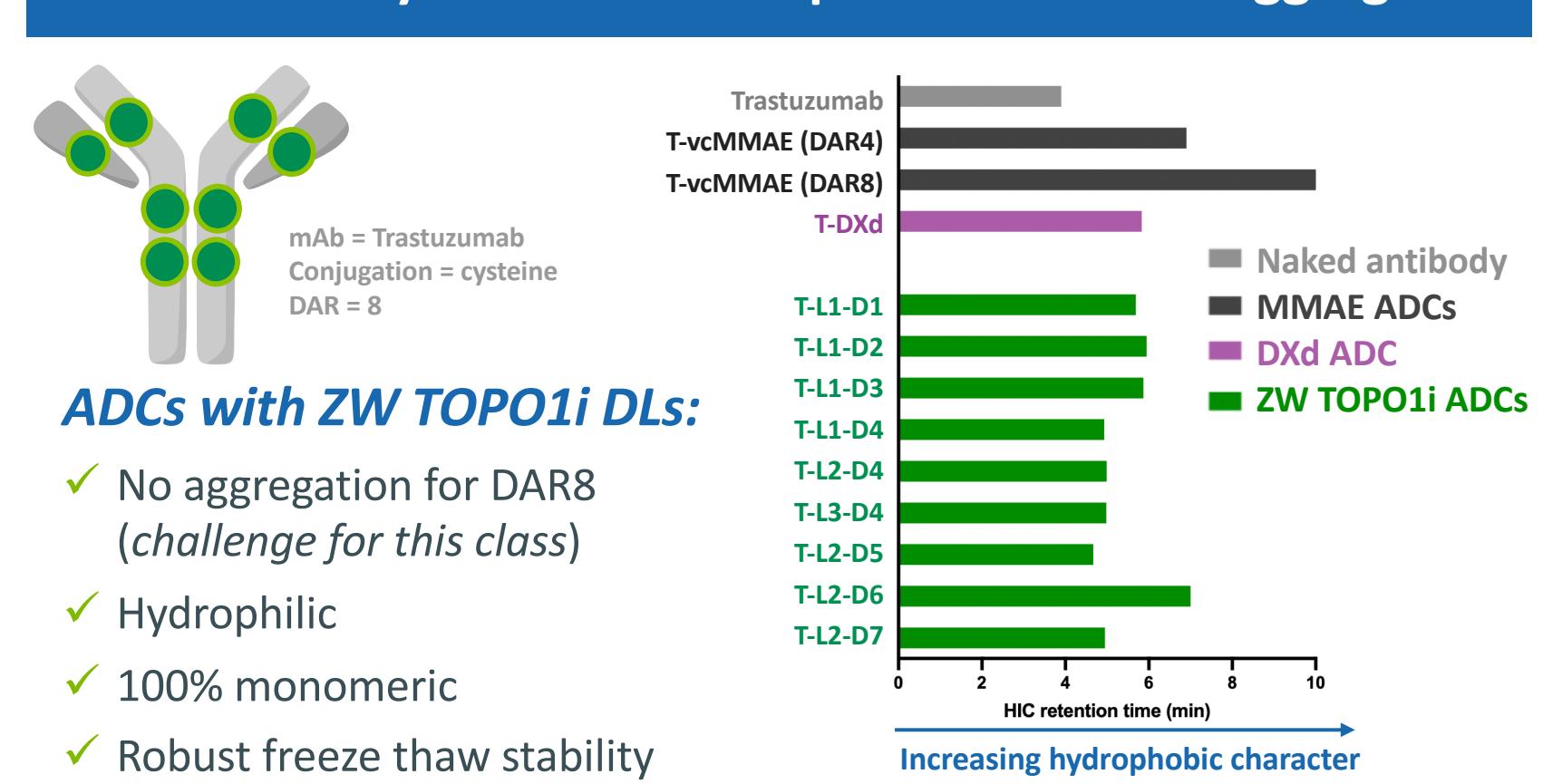
Background: Camptothecin therapeutics

- Potent inhibitors of topoisomerase I:**
- Discovered in the early 1960 by M. E. Wall and M. C. Wani of Research Triangle Institute¹
 - 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
 - 2 approved ADCs (Enhertu®, Trodelvy®)
 - Several ADCs, SMDCs, and NPs at different stages of development

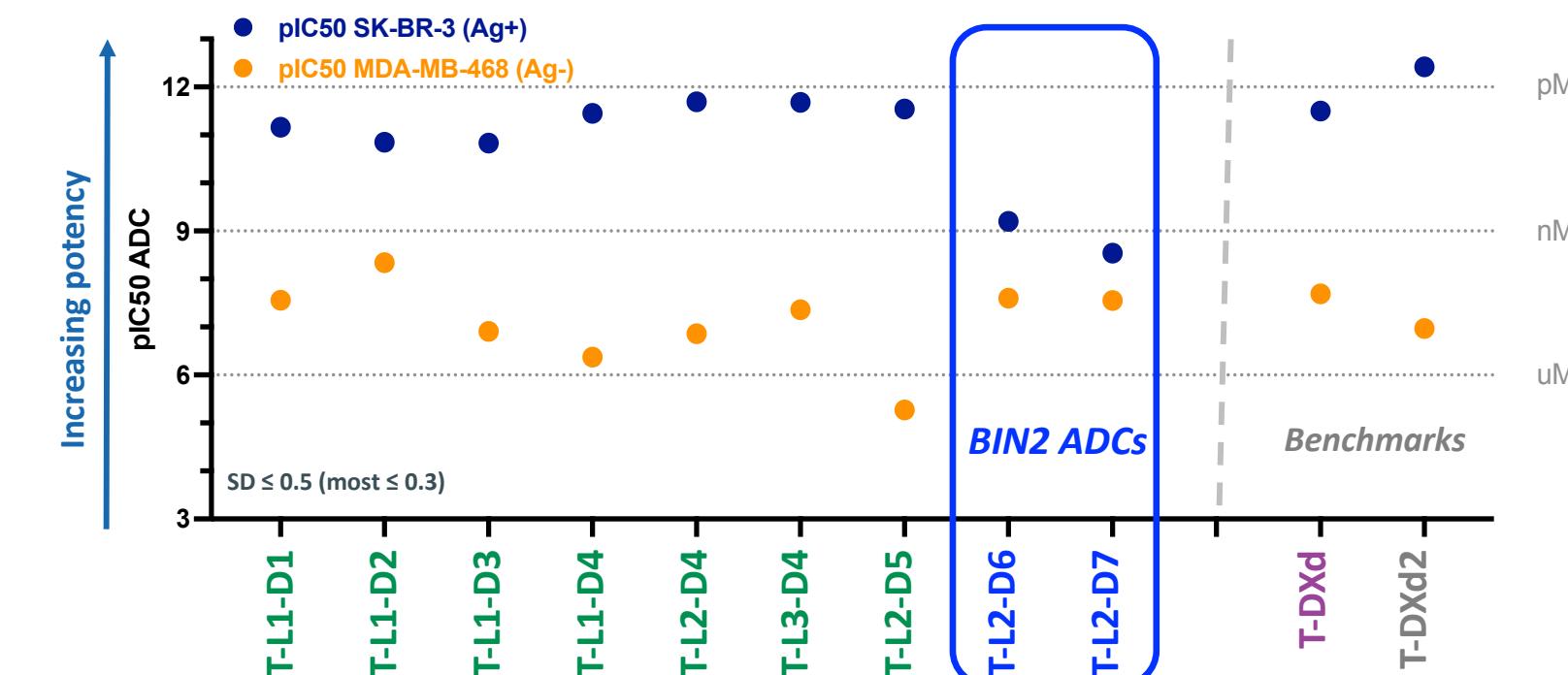
Zymeworks Camptothecin Payloads Span a Range of Potency and Hydrophilicity



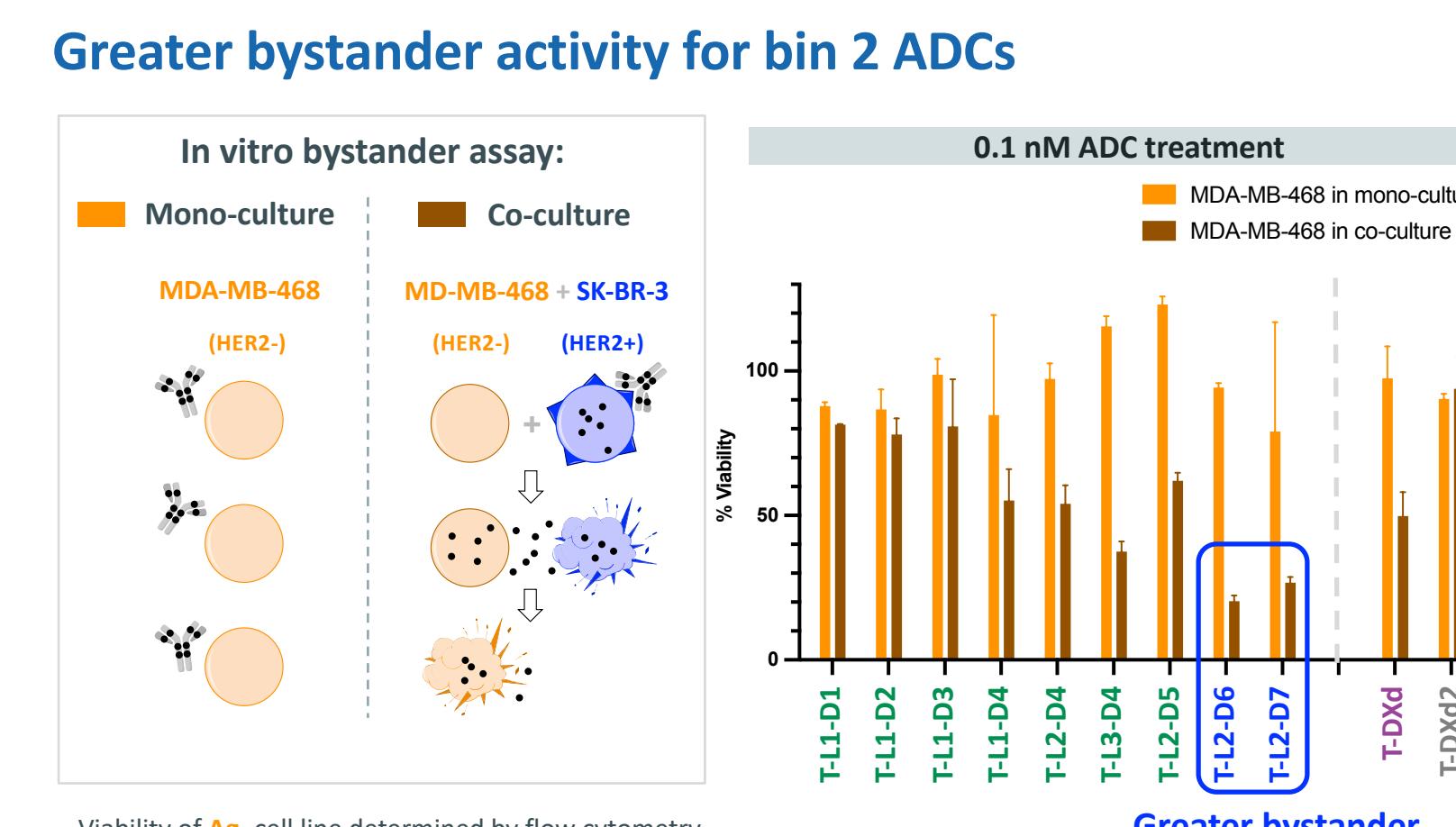
Zymeworks TOPO1i Drug-Linkers Yield ADCs with Favorable Physiochemical Properties and Low Aggregation



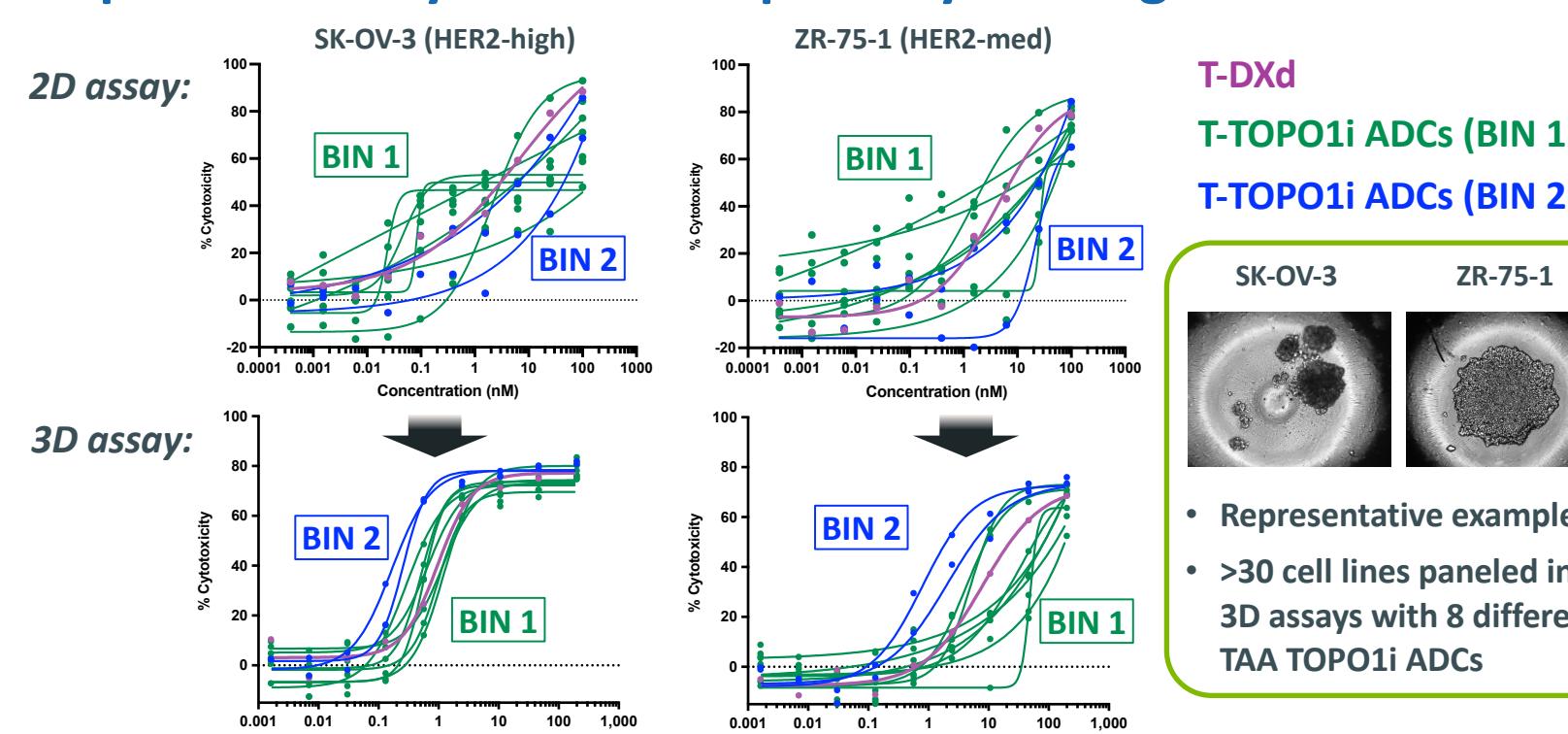
Lead ADCs Showed Good Potency and Selectivity in 2D Cytotoxicity Assays



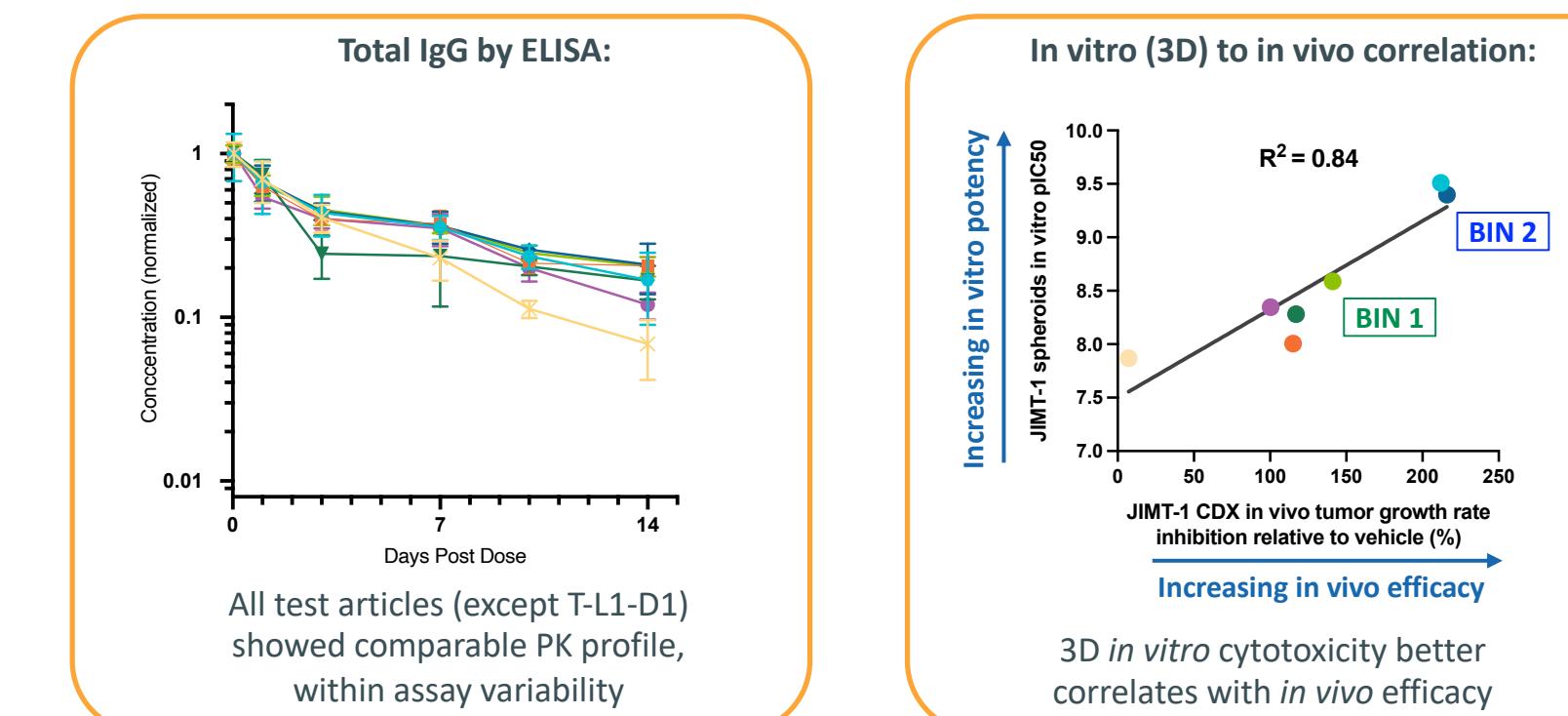
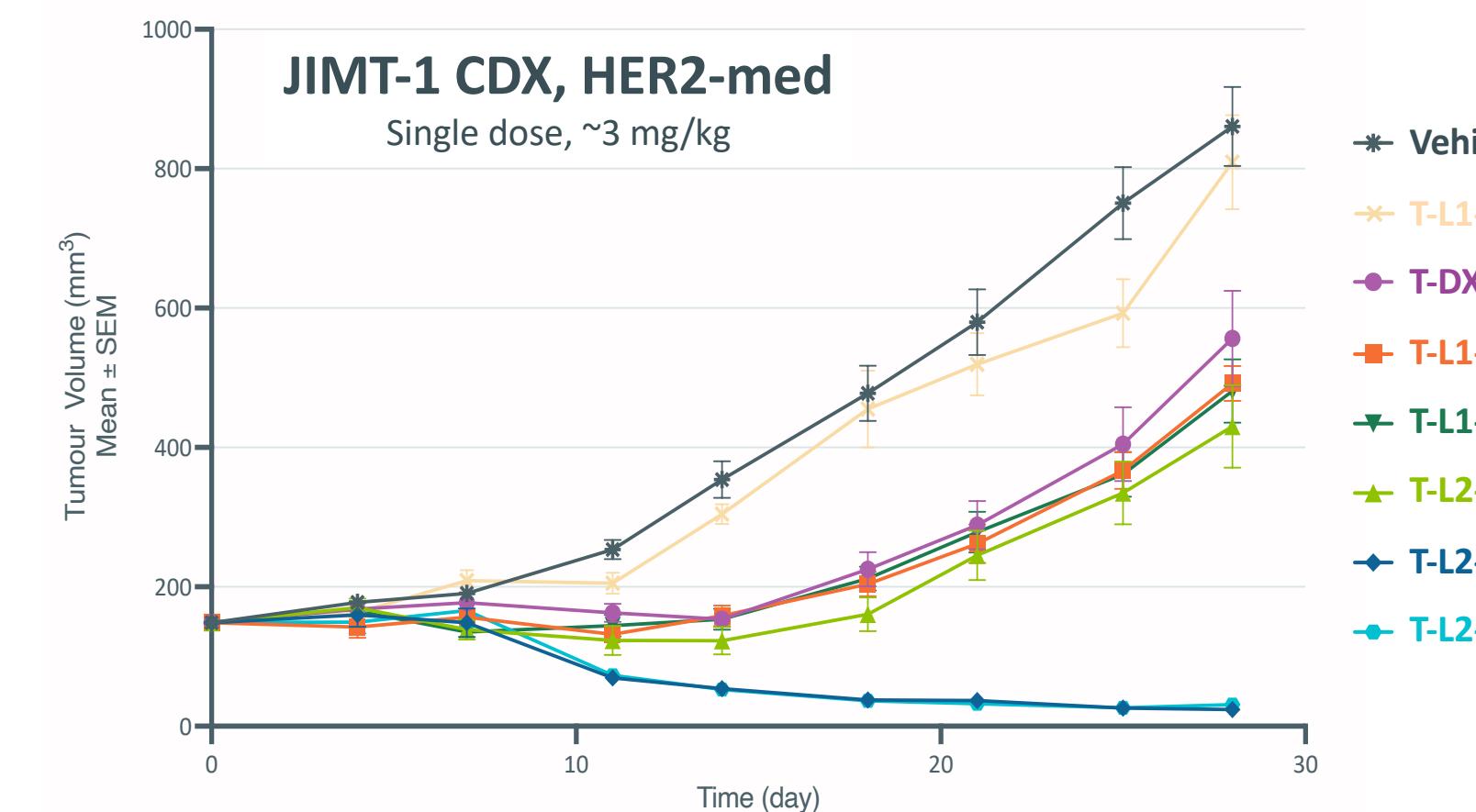
Bin 2 ADCs Demonstrate Greater Bystander Activity and Superior Potency in Spheroid Assay



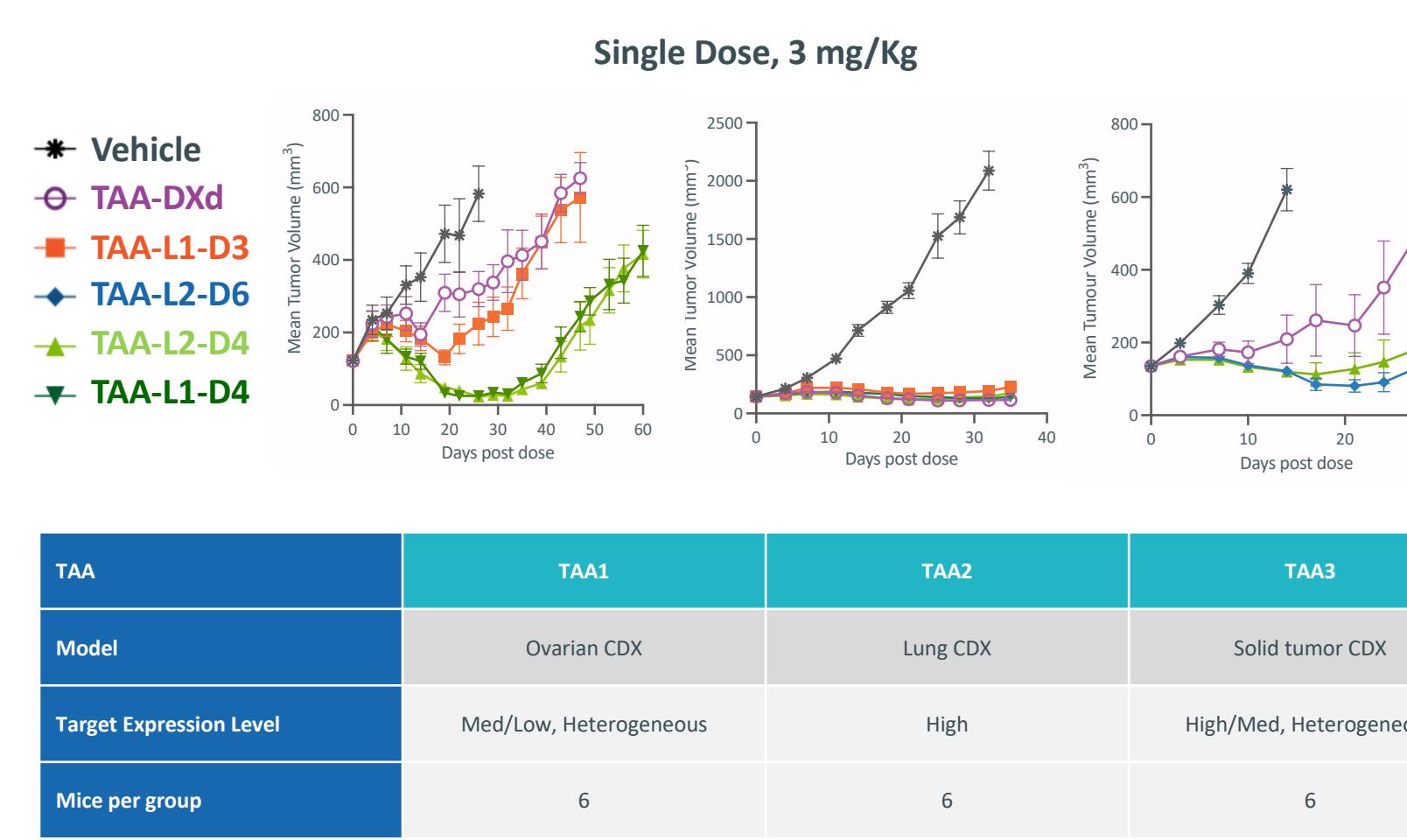
Spheroid assay altered the potency ranking of ADCs



Zymeworks TOPO1i ADCs Demonstrate Potent in vivo Efficacy

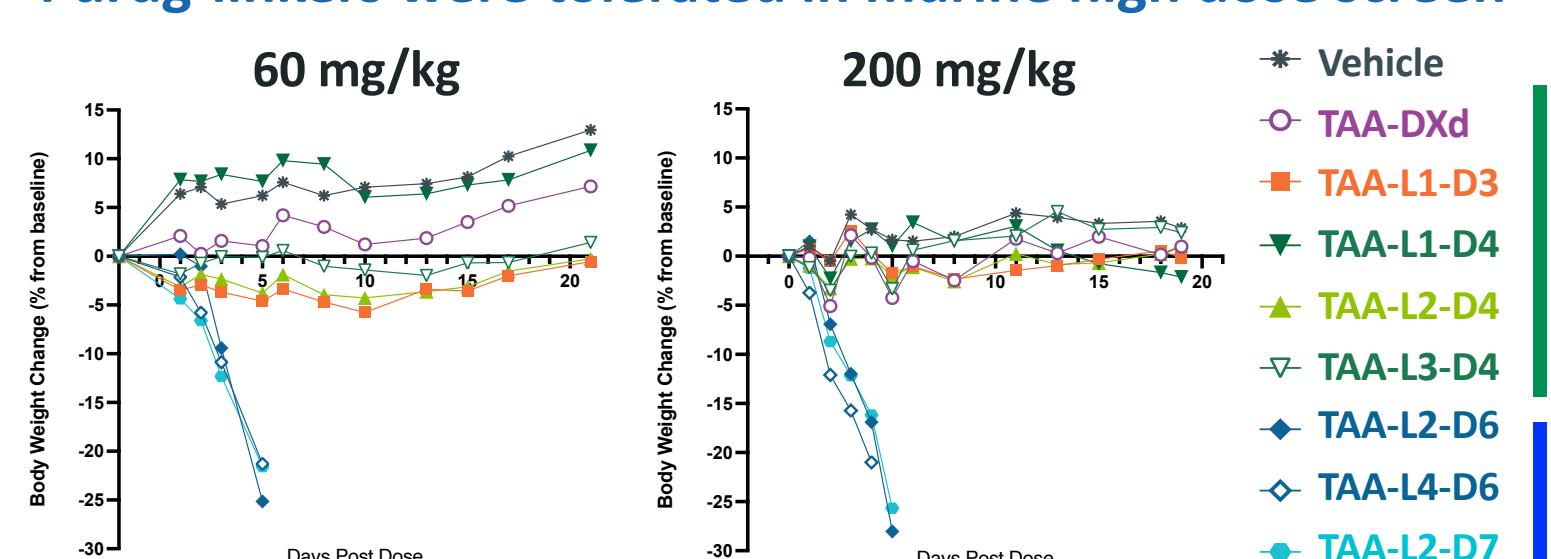


Zymeworks TOPO1i ADCs Demonstrate Anti-tumor Activity in Multiple in vivo Models

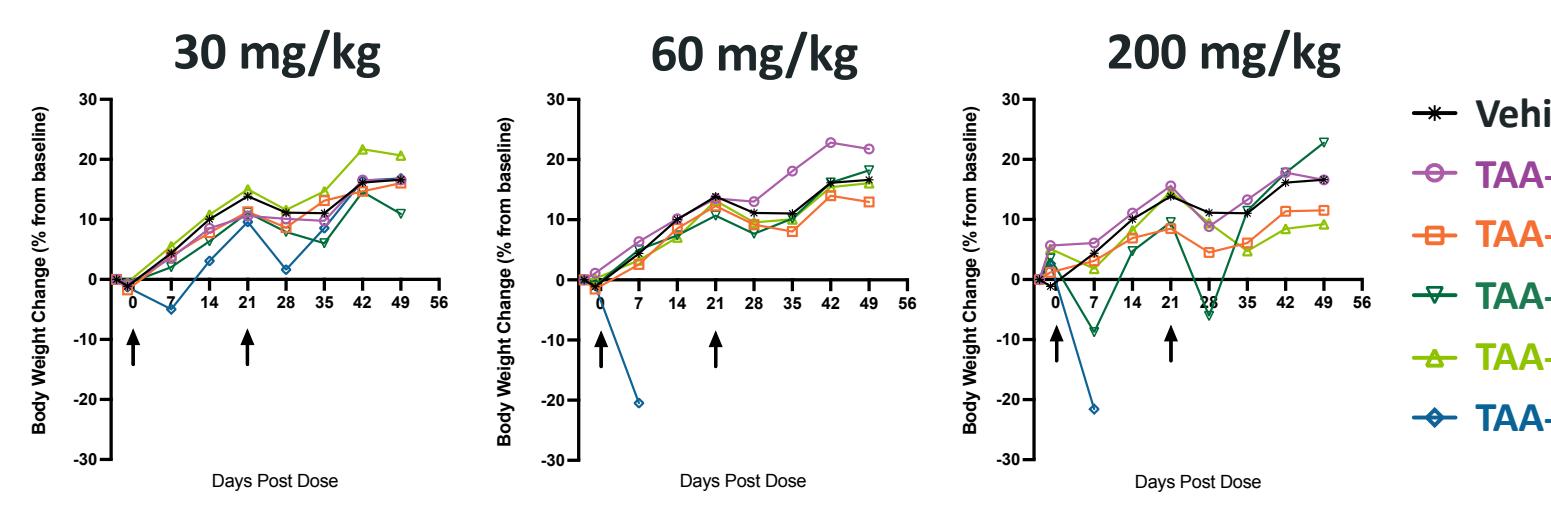


Murine and Rat Tolerability Studies Identified 2 Lead Drug Linkers

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

- Identify leads from ~100 TOPO1i payloads
- Comparable efficacy to industry leading DXd platform across different targets
- Two lead drug-linkers identified after rat tox study
- Pipeline NHP tox studies initiated
- Multiple pipeline programs in development

References

- Monroe E. Wall, M. C. Wani, C. E. Cook, Keith H. Palmer, A. T. McPhail, and G. A. Sim, *Journal of the American Chemical Society* 1966 88 (16), 3888-3890
- Irinotecan and Topotecan are FDA approved. Belotecan is approved in South Korea

Acknowledgements

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