Zymeworks Topoisomerase 1 Inhibitor ADC Platform: From Concept to Pipeline

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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[®])

✓ Robust freeze thaw stability

• 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** pIC50 SK-BR-3 (Ag+) pIC50 MDA-MB-468 (Ag-° ADC **Benchmarks** SD ≤ 0.5 (most ≤ 0.3) T-DX

Zymeworks TOPO1i ADCs Demonstrate Potent in vivo Efficacy



Representative pIC50 in an Ag+ cell line sensitive to TOPO1i ADCs and an Ag- cell line >70 cell lines tested in 2D assays with 8 different TAA TOPO1i ADCs (~25% sensitive)

Strong Bystander Activity for Most Zymeworks TOPO1i **ADCs**



Viability of Ag- cell line determined by flow cytometry Viability of Ag+ simultaneously measured (~80-100% cytotox; not shown)

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

• Potency differences may be due to better bystander killing



-*- Vehicle -O- TAA-DXd - TAA-L1-D3

→ TAA-L2-D6 **★** TAA-L2-D4

TAA-L1-D4

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



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Murine and Rat Tolerability Studies Identified 2 Lead Drug

- Multiple pipeline programs in development

