VERAXA

Abstract # 1762, AACR Annual Meeting 2026

VERAXA Biotech GmbH, Heidelberg, Germany www.veraxa.com info@veraxa.com

An avidity-driven, dual-targeting ADC with superior tumor selectivity for the treatment of solid tumors

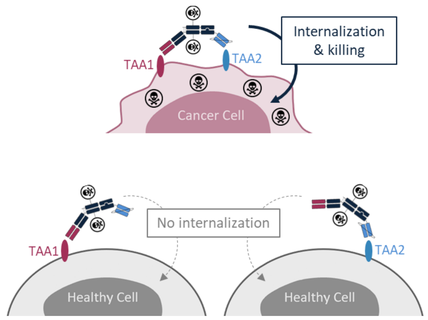
Steffen Runz, Paul Sauter, Sebastian Latwiel, Jennifer Volkind, Jawad Iqbal, Wilma Neumann, Helga Groetsch, Dina Osmanovic, Abdul-Habib Maag, Anja Schreiber, Christine Köhler, Tatjana Schneidt, Anna Pryszlak, Christoph Erkel, Richard J. Austin

Abstract

Toxicities as consequence of antigen expression in healthy tissues (on-target) and instable conjugation technology (off-target) have hampered the application of highly potent pyrrolobenzodiazepine (PBD) payloads in ADCs. To address these safety liabilities, we have developed an AND-gate bispecific ADC (bsADC) which preferentially kills tumor cells expressing two tumor-associated antigens (TAAs), while sparing healthy cells expressing only one TAA. Our proprietary site-specific, click-based glycan-conjugation platform minimizes off-target toxicities by using a highly stable tumor-selective linker and a hydrophilic chemistry that reduces target-independent uptake. The beneficial safety profile and conjugation technology enables the use of a PBD dimer as cytotoxic payload. With our AND-gate approach, *in vitro* we show more potent binding to and killing of double target positive cells compared to single target positive or target negative cells. *In vivo*, our bsADC demonstrates promising efficacy, tolerability, and pharmacokinetics.

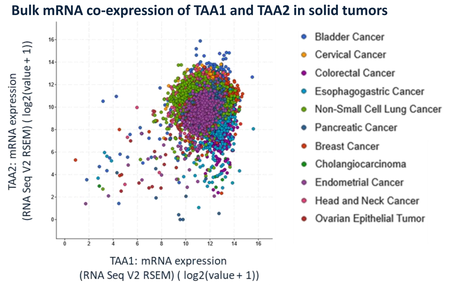
1 AND-gate bispecific ADCs kill tumor cells upon simultaneous binding of both targets

By restricting their function to target pair co-expressing tumor cells and sparing healthy cells, AND-gate bispecific ADCs are expected to result in a superior safety profile, as on-target/off-tumor toxicity will be significantly reduced.



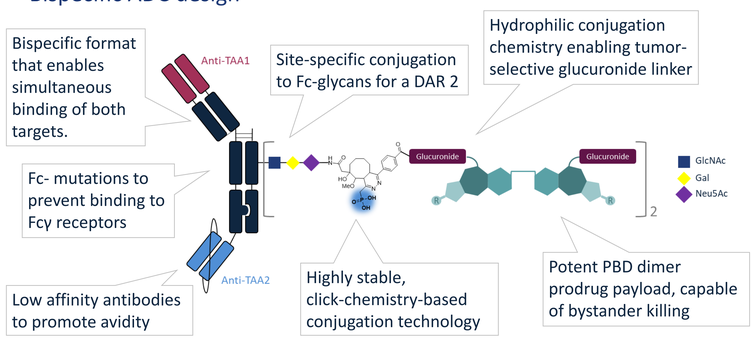
2 Co-expression profile of TAA1 and TAA2 supports AND-gate approach

- Broad co-expression of TAA1 and TAA2 in multiple solid tumor indications
- Limited co-expression in healthy tissues (not shown)
- Combination will reduce on-target liabilities described for clinical-stage monospecific ADCs

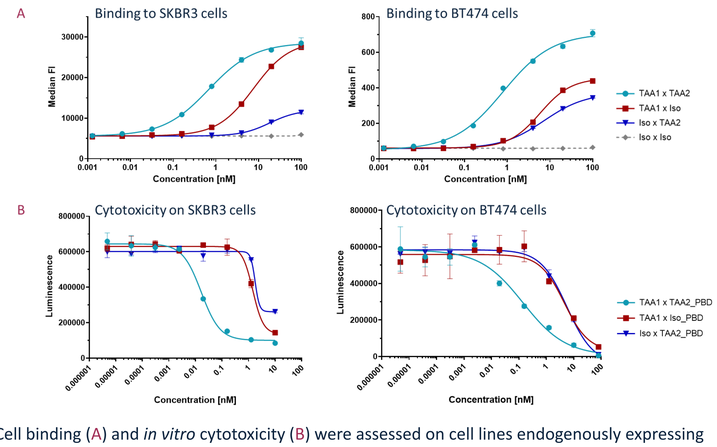


TCGA Firehouse Legacy datasets of indicated tumor types were analyzed using the cBioPortal platform (Cerami et al., Cancer Discovery, 2012; Gao et al., Sci. Signal, 2013; de Bruijn et al., Cancer Res, 2023)

3 Bispecific ADC design



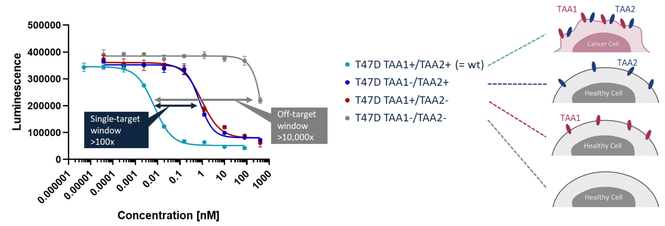
4 Avidity-mediated binding of TAA1 x TAA2 bispecific antibody translates to superior *in vitro* cytotoxicity of bsADC



Cell binding (A) and *in vitro* cytotoxicity (B) were assessed on cell lines endogenously expressing TAA1 and TAA2. Isotype-paired control constructs mimic single target-expressing cells.

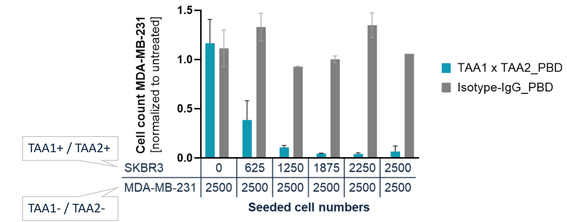
Cell binding: Flow cytometry | Alexa488-conjugated anti-human IgG detection antibody
Cytotoxicity assay: SKBR3: 7 days, BT474: 14 days | CellTiterGlo (Promega)

AND-gate approach supports the preferential killing of TAA1+/TAA2+ cells



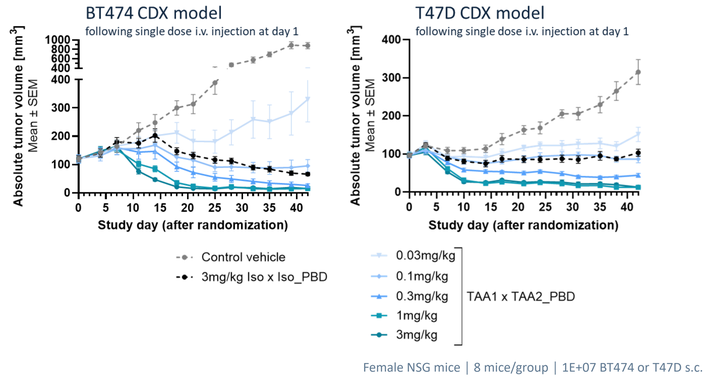
7 days | CellTiterGlo (Promega)

TAA1 x TAA2_PBD induces bystander killing of target-negative cells in co-culture with target-expressing cells



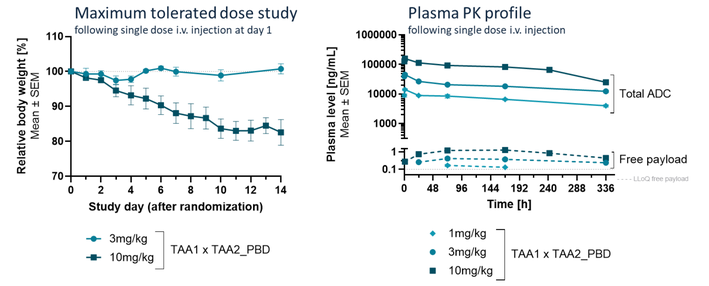
10nM ADC | 5 days | Flow cytometry: cell line discrimination via anti-human CD340 (BioLegend) staining; viability assessment via Zombie R718 (BioLegend); numbers of viable MDA-MD-231 cells were normalized to the untreated control

5 TAA1 x TAA2_PBD shows strong dose-dependent efficacy in breast cancer-derived CDX mouse models



Female NSG mice | 8 mice/group | 1E+07 BT474 or T47D s.c.

Promising tolerability and pharmacokinetics in tumor-free NSG mice



Female NSG mice | 3 mice/group

Female NSG mice | 3 mice/timepoint | LC-MS/MS

Summary & Conclusion

- Avidity-driven dual targeting enables a true logic AND-gate
  - Strong potency *in vitro* and in mouse tumor models
  - Significant safety advantage expected due to a 100-10,000-fold therapeutic index *in vitro*
- PBD payload and cleavable linker enable bystander killing to address tumor heterogeneity
- Promising efficacy in breast cancer CDX mouse models; minimum efficacious dose of ≤0.1 mg/kg and maximum tolerated dose of ≤10 mg/kg indicate a safety margin that is substantially wider than the industry standard for PBD-carrying ADCs
- Current program status: Lead optimization; preclinical readiness envisioned for H2/2026
- **TAA1 x TAA2_PBD is a promising candidate for the safe and efficacious treatment of solid tumor indications**