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A NOVEL BISPECIFIC ANTIBODY FOR HER2^{+} BREAST CANCER: THE BEAT GBR 1302

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While the idea of bispecific drugs was brought up over 30 years ago, the development of formats mature enough for the clinic remained for a long time a challenge. The whole field has been hampered by major problems of manufacturability (e.g. product purity and yields) and immunogenicity. With the recent arrival of new bispecific formats, either as antibody–like molecules (containing an Fc) or scFv fragments, at least 18 bispecific molecules have entered clinical trials showing very promising results. The BEAT® format has been developed as bispecific antibodies maintaining the pharmacokinetics and the low immunogenicity of human IgG with excellent manufacturability properties. In brief, the molecule is asymmetric consisting of a Hc, a Lc and a Fc-scFv. A proprietary engineered CH3 interface mimics the natural association of the heterodimeric TCRα β chains driving heterodimerization of the Hc and Fc-scFv. CHO cell lines are generated with a volumetric productivity of several g/L and a high product purity (e.g. >90% of bispecific product). Based on a built-in purification approach the BEAT molecules can be purified using a standard DSP process with yield and purity comparable to standard mAbs. The presentation will highlight a new bispecific drug targeting HER2 on tumor cells and CD3 on cytotoxic T-cells: the GBR 1302-BEAT molecule. GBR 1302-BEAT effectively recruits cytotoxic T cells against HER2 positive breast cancer cells including the trastuzumab-resistant breast cancer cell line JIMT-1. It shows strong tumor cell lysis activity with a better in vitro potential than current HER2-targeting therapies including the ADC TDM-1. The differential killing efficacy both *in vitro* and *in vivo* of HER2 overexpressing (3+) and normal, HER2 (0) cells reveals a large therapeutic window. In addition GBR 1302 does not trigger non-specific T cell activation. The excellent manufacturing attributes and the pre-clinical efficacy and safety of GBR1302 justify further clinical development as a treatment for HER2 positive cancers.