

# Targeted alpha therapy with anti-HER2 thorium-227 antibody-chelator conjugates (HER2-TTCs) in mouse xenograft models with varying levels of HER2 expression and resistance to current state-of-the-art therapies

Targeted thorium conjugates (TTCs) represent a new class of therapeutic radiopharmaceuticals for the targeted alpha therapy (TAT) of cancer. The human epidermal growth factor receptor 2 (HER2) is overexpressed in several cancers and is a validated target for the treatment of breast and gastric cancer, also serving as a prognostic and predictive biomarker. During treatment, many patients become resistant or are not eligible for these therapies, due to low expression levels of the target (~55%). Therefore there exists a high unmet medical need for new drugs with alternative mechanisms of action targeting HER2. We describe an antibody conjugate capable of delivering thorium-227 ( $^{227}\text{Th}$ ) to cancer cells expressing the human epidermal growth factor receptor 2 (HER2). The preclinical pharmacological in vivo characterization of the HER2-TTC, with a focus on trastuzumab and T-DM1 (trastuzumab-DM1)-resistant and HER2 low expressing mouse xenograft models, are presented.

### Email Address

jenny.karlsson@bayer.com

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**Primary author:** Dr KARLSSON, Jenny (Bayer AS)

**Co-authors:** Dr CUTHBERTSON, Alan S (Bayer AS); Dr KRISTIAN, Alexandr (Bayer AS); Dr ELLINGSEN, Christine (Bayer AS); Dr SCHATZ, Christoph (Bayer AG); Dr GRANT, Derek (Bayer AS); Dr MUMBERG, Dominik (Bayer AG); Dr RYAN, Olav (Bayer AS); Dr BJERKE, Roger M (Bayer AS); Dr HAGEMANN, Urs B (Bayer AG); Dr CRUCIANI, Veronique (Bayer AS)

**Presenter:** Dr KARLSSON, Jenny (Bayer AS)