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PRECLINICAL IN VIVO EVALUATION OF A ZR-89 LABELED ANTI-CD44 ANTIBODY AS PRELUDE TO CLINICAL IMMUNO-PET STUDIESD.J. Vugts¹, D.A. Heuveling¹, M. Stigter-van Walsum¹, S. Weigand², M. Bergstrom³, T. Nayak³, G.A.M.S. Van Dongen¹¹VU University Medical Center, Amsterdam, Netherlands Pharma Research and Early Development, Roche Diagnostics GmbH, Penzberg, Germany ²Imaging Sciences, Pharma Res. and Early Development, F. Hoffmann-La Roche Ltd, Basel, Switzerland (dvugts@rnc.vu.nl)

Introduction: CD44 is a single-chain, single-pass, transmembrane glycoprotein, which is widely expressed in healthy tissues as well as in many hematological malignancies and solid tumor types. Interestingly, CD44 is associated with cancer stemcellness, and therefore an appealing target for antibody-based therapy. The investigational drug RO5429083 is a recombinant humanized mAb that specifically binds to the constant region of the extracellular domain of CD44. RO5429083 inhibits the binding of hyaluronic acid to CD44, and was shown to inhibit several CD44⁺ xenografts in vivo, while toxicology studies with high dose RO5429083 in cynomolgous monkeys did not reveal adverse effects. Therefore, CD44 might have a more critical role in malignant growth than in normal tissue maintenance and we hypothesize that despite the broad expression of CD44 in normal tissues, therapy with RO5429083 might be feasible. However, for obtaining optimal efficacy the dosing of the antibody might be very critical, and immuno-PET is considered to be a powerful tool to get insight in dose-response relationships. Past years we have developed GMP-compliant radiolabelling procedures for clinical immuno-PET studies with ⁸⁹Zr and ¹²⁴I-labeled monoclonal antibodies. As prelude to clinical trials ⁸⁹Zr-RO5429083 was GMP produced and evaluated for specific and measurable uptake in nude mice bearing CD44-expressing tumor.

Methods: ⁸⁹Zr-RO5429083 was prepared according to Verel et al [1]. 1 mg/kg ⁸⁹Zr-RO5429083 was evaluated in MDA-MB231 (CD44⁺, responder), PL45 (CD44⁺, non-responder) and HepG2 (CD44⁻)-tumor bearing mice. In addition, a dose escalation study was performed in MDA-MB231 tumor bearing mice at 2, 8, 20 and 40 mg/kg (predose) ⁸⁹Zr-RO5429083.

Results: ⁸⁹Zr-RO5429083 was prepared with >99% radiochemical purity and optimal immunoreactivity. Tumor uptake in MDA-MB231 tumor bearing mice was high (32.4 ± 6.8 %ID/g) and uptake in HepG2 tumor bearing mice low (5.7 ± 1.2 %ID/g) at 6 days post injection (p.i.). In addition, decreased blood levels were observed for CD44⁺ tumor bearing mice (5.8 ± 3.6 %ID/g vs 14.7 ± 2.6 %ID/g). PL45 tumor bearing mice showed comparable tumor uptake and blood levels as MDA-MB231 tumor bearing mice. A dose escalation study revealed that tumor uptake and tumor-to-blood ratios at 48, 72 and 144 p.i. decreased at higher antibody dose, indicating saturation of the CD44 target.

Conclusions: An efficient method for the labeling of RO5429083 with ⁸⁹Zr has been developed, resulting in an optimal quality conjugate. ⁸⁹Zr-RO5429083 at a low dose of 1 mg/kg showed high and specific uptake in CD44⁺ xenograft models, while uptake became less at higher antibody dose. With this method selective targeting and target saturation can be confirmed in patients with CD44⁺ tumors. However, as shown herein with xenograft PL45, efficient targeting does not guarantee antitumor effects, and therefore early response monitoring with e.g. ¹⁸F-FDG is recommendable in clinical studies.

References: [1] Verel I. et al. (2003), J Nucl Med 44, 1271-1281.