286 TUMOR TARGETING AND TISSUE BIODISTRIBUTION OF RO7122290, A NOVEL FAP-TARGETED 4–1BB (CD137) AGONIST, IN PATIENTS WITH ADVANCED SOLID TUMORS, USING [89ZR]-RO7122290 AS A PET TRACER

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Background RO7122290 (RO) is a potent next generation 4-1BB agonist simultaneously targeting fibroblast activation protein (FAP). FAP is highly expressed on cancer-associated fibroblasts in many solid tumors, while expression in healthy tissue is low. 4 1BB stimulation via FAP mediated cross linking augments the cytotoxicity, proliferation, and longevity of immune effector cells in FAP-positive tumors. RO was labelled with Zirconium-89 (89Zr) to visualize FAP-dependent tumor accumulation and assess the biodistribution in patients (pts) after successful proof of principle of 89Zr-based PET in preclinical pilot studies.

Methods Pts with advanced and/or metastatic solid tumors were eligible for this sub-study of an ongoing Phase 1/1b trial (EUDRACT 2017-003961-83). RO was administered intravenously once at a total dose of 5, 45, 200 or 500 mg consisting of RO (cold) + 5 mg 89Zr-RO (hot, 37.0 [± 3.4] MBq). Up to three 89Zr-PET scans were performed over a period of nine days followed by a single tumor biopsy before pts could switch to Part A (single agent) and subsequently to Part B (combination with atezolizumab) of the main study to continue treatment. Tracer uptake was calculated as peak standardized uptake value (SUVPeak) of the lesion with the highest uptake.

Results 14 pts were exposed to a total dose of 5, 45, 200 (all n=3) or 500 mg (n=5); median age was 60 years (range 26–74) with seven male and female pts each. Primary tumor sites included colon (n=4), lung (n=3), thymus (n=2), anus (n=1), breast (n=1), bile duct (n=1), pleura (n=1), and uvea (n=1). In healthy tissues, uptake of 89Zr-RO was predominantly observed in the liver and spleen across all doses and in non-malignant lymph nodes in 2/3 patients at 5 mg. Consistent with the target expression, tracer uptake was detected in FAP-positive scarring tissue and tissues with ongoing remodeling. Intra-tumoral accumulation of 89Zr-RO was observed at all doses. 96 hours p.i., SUVPeak values were 12.1 [± 4.1], 10.0 [± 4.9], and 7.0 [± 3.7] for the 5, 45 and 200 mg cohorts, respectively, while SUVPeak for the 500 mg cohort was even lower at 4.9 [± 0.5].

Conclusions 89Zr-PET confirmed tumor-specific uptake and expected biodistribution pattern of 89Zr-RO. The decrease in SUV with increasing doses suggest that more cold antibodies saturated FAP binding sites in the tumor. 89Zr-PET results supported together with clinical PK, PD, safety and response data the selection of the recommended phase 2 dose and schedule of RO in combination with atezolizumab.

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287 SAFETY AND ANTITUMOR ACTIVITY OF INDOLEAMINE 2,3-DIOXYGENASE 1 (IDO-1) INHIBITOR KHK2455 IN COMBINATION WITH ANTI-CCR4 MONOCLONAL ANTIBODY MOGAMULIZUMAB IN PATIENTS WITH ADVANCED SOLID TUMORS

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Background IDO-1 inhibitors have shown antitumor activity in combination with immunotherapeutic agents in multiple cancers. KHK2455 is a novel and selective oral IDO-1 inhibitor. KHK2455 inhibits IDO-1 apo-enzyme, with long-lasting and potent activity. Mogamulizumab is an anti-C-C chemokine receptor 4 (CCR4) monoclonal antibody that has shown synergy with KHK2455 in preclinical models. Mogamulizumab is approved in the US and EU for treatment of mycosis fungoides and Sézary syndrome.

Methods In this first-in-human study, patients with advanced solid tumors received escalating oral doses of KHK2455 alone (0.3, 1, 3, 10, 30 and 100 mg once daily) for 4 weeks (Cycle 0), followed by combination with 1 mg/kg weekly of IV mogamulizumab for 4 weeks (Cycle 1), and then on Days 1 and 15 (from Cycle 2 onward) in a standard 3+3 Phase I design. Safety, tolerability, pharmacokinetics and IDO activity (kynurenine [Kyn] and tryptophan [Trp] levels and ex vivo Kyn production) were evaluated.

Results Thirty-six patients were enrolled across all cohorts. One patient with lower esophageal cancer in the 100 mg cohort exhibited dose-limiting toxicity (Grade 3 gastrointestinal necrosis). The most frequent (≥10%) treatment-emergent adverse events (TEAEs) are presented in table 1. Overall numbers of TEAEs, ≥Grade 3 TEAEs, and serious TEAEs related to KHK2455 and mogamulizumab are presented in table 2. Serious KHK2455-related TEAEs included gastrointestinal necrosis (KHK2455 monotherapy), and nausea and drug eruption (combination therapy). In addition, five drug-related TEAEs in combination therapy led to discontinuation; there were no fatal outcomes related to either study drug. Plasma KHK2455 concentrations reached steady state by Day 8 (Cycle 0) and increased dose-dependently. Potent dose-dependent inhibition of IDO activity was demonstrated by plasma Kyn concentration and Kyn/Trp ratio (median inhibition 70.5% and 70.8%, respectively, at 100 mg dose on Day 15, compared to baseline) and ex vivo Kyn production (>95% inhibition at ≥10 mg KHK2455), confirming target modulation. Six of 26 evaluable patients from all dosing groups achieved durable disease stabilization (≥6 months, RECIST 1.1), and one patient with bevacizumab-resistant glioblastoma demonstrated confirmed partial response (43.5% tumor reduction over a 2-year observation period). Median overall survival was 13.4 months, with 30% of subjects surviving for 2 years or longer (figure 1).