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 I/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 following the injection of 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). High in healthy tissues, uptake of 89Zr-RO was predominantly observed in the liver and spleen across all doses and in nonmalignant 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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