## 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).

**Abstract 287 Table 1** Study 2455-001: Treatment-Emergent Adverse Events (≥10% by Preferred Term)

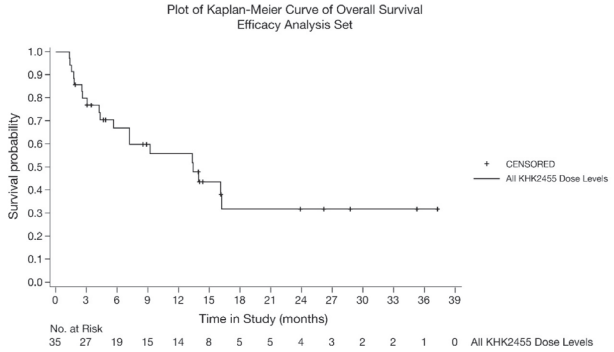
| System Organ Class<br>Preferred Term | Any Cycle[a]<br>N=36<br>n (%) |
|---|---|
| **Patients with any TEAE** | **36 (100.0)** |
| **Gastrointestinal disorders** | **27 (75.0)** |
| Nausea | 14 (38.9) |
| Vomiting | 11 (30.6) |
| Diarrhoea | 8 (22.2) |
| Abdominal pain | 6 (16.7) |
| Constipation | 4 (11.1) |
| **General disorders and administration site disorders** | **22 (61.1)** |
| Fatigue | 12 (33.3) |
| Pyrexia | 4 (11.1) |
| **Metabolism and nutrition disorders** | **21 (58.3)** |
| Hypoalbuminaemia | 8 (22.2) |
| Hyponatraemia | 7 (19.4) |
| Decreased appetite | 5 (13.9) |
| Hypokalaemia | 5 (13.9) |
| Hyperglycaemia | 4 (11.1) |
| **Skin and subcutaneous tissue disorders** | **21 (58.3)** |
| Drug eruption | 20 (55.6) |
| **Investigations** | **20 (55.6)** |
| Aspartate aminotransferase increased | 8 (22.2) |
| Alanine aminotransferase increased | 6 (16.7) |
| Blood alkaline phosphatase increased | 5 (13.9) |
| Blood creatinine increased | 4 (11.1) |
| Activated partial thromboplastin time prolonged | 4 (11.1) |
| Weight decreased | 4 (11.1) |
| **Injury, poisoning and procedural complications** | **17 (47.2)** |
| Infusion related reaction | 14 (38.9) |
| **Nervous system disorders** | **16 (44.4)** |
| Headache | 12 (33.3) |
| **Blood and lymphatic system disorders** | **15 (41.7)** |
| Anaemia | 9 (25.0) |
| Lymphopenia | 8 (22.2) |
| **Musculoskeletal and connective tissue disorders** | **15 (41.7)** |
| Back pain | 6 (16.7) |
| **Respiratory, thoracic and mediastinal disorders** | **12 (33.3)** |
| Dyspnoea | 8 (22.2) |
| **Vascular disorders** | **11 (30.6)** |
| Hypertension | 5 (13.9) |

a: Includes both KHK2455 monotherapy and KHK2455 + mogamulizumab combination therapy cycles.

**Abstract 287 Table 2**

| Adverse Event Category | Cycle 0[a]<br>N=36 | Any Cycle[b]<br>N=36 |
|---|---|---|
| **Any treatment-emergent adverse event (TEAE)** (n, %) | **33 (91.7)** | **36 (100.0)** |
| Any IMP-related | 12 (33.3) | 31 ( 86.1) |
| KHK2455-related | 12 (33.3) | 27 (75.0) |
| Mogamulizumab-related | 0 | 29 (80.6) |
| **Any ≥Grade 3 TEAE** (n, %) | **8 (22.2)** | **22 (61.1)** |
| Any IMP-related ≥Grade 3 | 1 (2.8) | 11 (30.6) |
| KHK2455-related ≥Grade 3 | 1 (2.8) | 8 (22.2) |
| Mogamulizumab -related ≥Grade 3 | 0 | 9 (25.0) |
| **Any serious TEAE (SAE)** (n, %) | **1 (2.8)** | **14 (38.9)** |
| Any Serious IMP-related | 1 (2.8) | 6 (16.7) |
| Serious KHK2455-related | 1 (2.8) | 3 (8.3) |
| Serious Mogamulizumab -related | 0 | 5 (13.9) |

a: KHK2455 monotherapy
b: Includes both KHK2455 monotherapy and KHK2455 + mogamulizumab combination therapy cycles
IMP=investigational medicinal product




**Abstract 287 Figure 1** Study 2455-001: Overall Survival

**Conclusions** KHK2455 in combination with mogamulizumab was well-tolerated and manageable at all doses tested, suppressed Kyn production in a dose-dependent and sustained manner, and demonstrated signals of antitumor activity. These data support the continued development of this combination.

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**Trial Registration** NCT02867007 (www.clinicaltrials.gov)
**Ethics Approval** This study was approved by Ethics Committees at all participating study institutions.

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## 288 A PHASE 1 STUDY OF IMC-001, A PD-L1 BLOCKER, IN PATIENTS WITH METASTATIC OR LOCALLY ADVANCED SOLID TUMORS

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**Background** IMC-001 is a fully human IgG1 monoclonal antibody that binds to human PD-L1 and mediate the antibody-dependent cell-mediated cytotoxicity. The main objectives of this study were to evaluate the safety, pharmacokinetics, and pharmacodynamics of IMC-001 in patients with advanced solid tumors. Here, we report final result of the phase 1 study of IMC-001.
**Methods** This open-labeled phase 1 study used standard 3+3 dose-escalation design, dose ranging from 2 to 20 mg. IMC-001 was administered intravenously every two weeks until disease progression or unacceptable toxicity. Dose limiting toxicity (DLT) window was defined as 21 days from the first dose. Adverse events (AEs) were assessed using CTCAE v4.03, and tumor response was assessed by and the Response Evaluation Criteria In Solid Tumors (RECIST) version v1.1.
**Results** Fifteen subjects (8 Male, 7 Female; Median age : 58 [range 39–69]) were included in 5 dose escalation cohorts. No DLT was observed and the maximum tolerated dose was not reached. Most common AEs were general weakness, decreased appetite, fever, and cough. No Grade 4 or 5 treatment emergent AEs (TEAEs) were reported during the study and no TEAE or serious AE led to treatment discontinuation or death. There were no infusion-related reactions during this study. Grade 2 immune-induced thyroiditis and diabetes mellitus suspected to be related to IMC-001 were seen in one subject at 2 mg/kg cohort. Over the dose range of 2 to 20 mg/kg IMC-001, AUC 0-14d, AUC 0—∞, and Cmax generally appeared to increase in a dose proportional manner for each step of dose escalation. Of the 15 enrolled patients, one subject with colon cancer showed partial response, and disease control rate was 33.3%. There were total 3 biliary tract cancer patients (1 GB cancer, 2 Cholangiocarcinoma) who received ≥3 lines of systemic therapies prior to this trial. They all had stable disease during IMC-001 treatment, and one cholangiocarcinoma subject received the treatment for 434 days.
**Conclusions** IMC-001 demonstrated a favorable safety profile up to 20 mg/kg given IV every 2 weeks and showed encouraging preliminary efficacy in patients with advanced solid tumors. Based on PK and PD data, 20 mg/kg was selected as recommended Phase 2 dose (RP2D).
**Ethics Approval** This study was approved by Institutional Review Board; approval number SMC 2018-01-007-001 and H-1801-042-913.

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