A PHASE I, FIRST-IN-HUMAN CLINICAL TRIAL OF THE GDF-15 NEUTRALIZING ANTIBODY CTL-002 IN SUBJECTS WITH ADVANCED STAGE SOLID TUMORS (ACRONYM: GDFATHER)

¹Ignacio Melero*, ²Emiliano Calvo, ³Maria-Elisabeth Goebeler, ⁴Elena Garraza, ⁵Reinhard Dummer, ⁶Maria Rodríguez-Ruiz, ⁷Maria de Miguel, ⁸Cyrus Michael Sayehli, ⁹Guzman Alonso Casal, ¹⁰Egle Ramelyte, ¹¹Martin Schuler, ¹²Tanja Gromke, ¹³Miguel Sanmamed, ¹⁴Irene Moreno, ¹⁵Ralf Bargou, ¹⁶Maria Lostes, ¹⁷Julia-Tatjana Maul, ¹⁸Corinne Eggenschwiler, ¹⁹Heike Richly, ²⁰Petra Fettes, ²¹Kathrin Klar, ²²Christine Schuberth-Wagner, ²³Markus Haake, ²⁴Jörg Wischhusen, ²⁵Eugen Leo. ¹Universidad de Navarra, Navarra, Spain; ²START Madrid-Centro Integral Oncológico Clara Campal, Madrid, Spain; ³University Hospital Würzburg, Würzburg, Germany; ⁴Hospital Universitari Vall d'Hebron, Barcelona, Spain; ⁵University Hospital Zürich, Zurich, Switzerland; ⁶Clinica Universidad de Navarra, Pamplona, Spain; ⁷Hospital Universitari Vall d'Hebron, Barcelona, Spain; ⁸University Hospital Zurich, Zürich, Switzerland; ⁹University Hospital Essen, Essen, Germany; ¹⁰University Hospital Zürich, Zürich, Switzerland; ¹¹CatalYm GmbH, Planegg, Germany; ¹²University of Würzburg, Würzburg, Germany

Background Growth and differentiation factor 15 (GDF-15) is a TGF- β superfamily member physiologically expressed mainly in placenta and linked to feto-maternal tolerance. Under pathophysiologic conditions, prevention of excessive immune cell infiltration during tissue damage and cachexia induction have been ascribed to GDF-15. Recent research has though indicated a prominent role in modulation of the tumor microenvironment and the immune synapse, too^{1 2} indicating that GDF-15 may be a major tumor-derived immunosuppressant. Importantly, several cancer entities secrete high levels of GDF-15, correlating with poor prognosis and reduced overall survival [Front Immunol 2020 May 19;11:951]. To block this effect the GDF-15 neutralizing antibody CTL-002 was generated. In preclinical models CTL-002 demonstrated potent effector T cell shifting into tumor tissue by neutralizing GDF-15.

Methods This is a phase 1, first-in-human (FIH), two-part, open-label clinical trial of intravenous (IV) administration of CTL-002 given as monotherapy and in combination with an anti-PD-1 antibody in subjects with advanced-stage, relapsed/refractory solid tumors who relapsed or were refractory to a prior anti-PD-1/PD-L1 therapy. Eligible subjects have exhausted all available approved standard treatments, including prior anti-PD1/PD-L1 treatment, and present with a biopsy-accessible tumor for serial biopsy taking. The trial is termed GDFATHER, for "GDF-15 Antibody-mediaTed Effector cell Relocation". Main endpoints are safety of CTL-002 monotherapy and CTL-002 combination with an anti-PD-1 antibody, pharmacokinetics, pharmacodynamics (e.g. degree of GDF-15 neutralization achieved and change in immune-cell number and composition in the tumor tissue) as well as preliminary clinical efficacy (tumor mass reduction; anticachexia effect). In part A of the trial (dose escalation) up to 24 subjects will receive escalating doses of CTL-002 IV (0.3 – 20 mg/kg) in a "mono-followed-by-combination"-design with CTL-002 given as monotherapy and followed by combination with an anti-PD-1 checkpoint inhibitor. In part B (expansion) up to 5 cohorts with up to 25 subjects per cohort with defined tumor entities expected to be GDF-15 dependent will be treated to determine the recommended phase 2 dose (RP2D) and further evaluate safety and preliminary efficacy of CTL-002 monotherapy and the combination. The study was initiated in December 2020 and enrolled the first patient on Dec 09, 2020. Cohort 4 is ongoing at time of submission (07/2021) and so far no DLT has occurred. Updated safety, biomarker and response assessments will be reported at the meeting. The ClinicalTrials.

gov Identifier is NCT04725474. For more information please contact info@catalym.com.

Trial Registration NCT04725474

REFERENCES

1. Wischhusen J, Wistuba-Hamprecht K, Harter PN, Cheng P, Martens A, Gogolla F, Nonomura Y, Romer P, Koch SD, Haake M, Schuberth-Wagner C, Rudiger M, Leo E, Mittelbronn M, Levesque MP, Hackl H, Dummer R, Weide B. Identifying GDF-15 as potential novel immunotherapeutic target linked to immune cell exclusion in tumors and resistance to anti-PD-1 treatment [abstract]. In: Proceedings of the Annual Meeting of the American Association for Cancer Research 2020; 2020 Apr 27–28 and Jun 22–24. Philadelphia (PA): AACR; *Cancer Res* 2020;**80**(16 Suppl): Abstract nr 2161.
2. Hurt E, Thomas S, Mulgrew K, Blackmore S, Moynihan J, Cusdin F, Dodd R, Car-iuk P, Sigurdardottir A, Brannigan E, Dobson C, Kumar R, Cobbold M. AZD8853: A novel antibody targeting GDF15 for immunotherapy refractory tumors [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2021; 2021 Apr 10–15 and May 17–21. Philadelphia (PA): AACR; *Cancer Res* 2021;**81**(13_Suppl): Abstract nr 1828.

Ethics Approval All participants gave informed consent prior to participation. EC approval by Gobierno de Navarra, Departamento de Salud, EC_2020/30, Dated: Oct 13, 2020 in Pamplona, Spain. Respective additional national lead EC approvals for Germany (Ethikkommission der Universität Würzburg, 203–20ff of Oct 26, 2020) and Switzerland (Kantonale Ethikkommission Zürich, 2020–02308 of Nov 24, 2020).

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.504>