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POSTER ABSTRACTS

616.ACUTE MYELOID LEUKEMIAS: INVESTIGATIONAL THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Dose Escalation of HLA-A2-WT1 CD3 T-Cell Bispecific Antibody in a Phase I Study in Patients with Relapsed/Refractory Acute Myeloid Leukemia (AML)

Martin Hutchings, MD PhD[1], *Pau Montesinos, PhDMD*[2], *Armando Santoro, MD*[3], *Hsin-An Hou*[4], *Maria Pilar Martinez-Sanchez, MD*[5], *Susana Vives*[6], *Sara Galimberti, MD PhD*[7], *Tsai-Yun Chen, MD*[8], *Marco Frigeni, MD*[9], *Sylvain Garciaz*[10], *Olga Salamero, MD*[11], *Su-Peng Yeh, MD*[12], *Karen Yee, MD*[13], *Gabriel Schnetzler, MD*[14], *Teresa Barata*[15], *Silke Simon, PharmD, PhD*[16], *Heather Hinton*[17], *Koorosh Korfi, PhD*[18], *Muriel Richard, PharmD, PhD*[18], *Nino Keshelava, MD*[18], *Marion Subklewe, MD*[19]

[1] Department of Hematology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
[2] Hematology Department, Hospital Universitari i Politècnic La Fe, Valencia, Spain
[3] Humanitas University, Pieve Emanuele, Milan, Italy
[4] National Taiwan University Hospital, Taipei, TWN
[5] hospital universitario 12 de octubre, Madrid, Spain
[6] Hospital Germans Trias i Pujol, Badalona, ESP
[7] Department of Clinical and Experimental Medicine, Hematology, University of Pisa, Pisa, Italy
[8] National Cheng-Kung Univ. Hospital, Tainan, TWN
[9] Hematology and Bone Marrow Transplant Unit, ASST Papa Giovanni XXIII, Bergamo, Italy, Bergamo, Italy
[10] Aix-Marseille University, INSERM U1068, CNRS, Institut Paoli-Calmettes, CRCM, Marseille, France
[11] Hospital Vall d'Hebron, Barcelona, Barcelona, ESP
[12] Department of Internal Medicine, China Medical University Hospital, Taichung City, TWN
[13] Princess Margaret Cancer Center (PMCC), Toronto, CAN
[14] Roche Pharma Research and Early Development, Discovery & Translational Area Oncology, Roche Innovation Center, Basel, Switzerland
[15] 15 Roche Product Development, Data Science, Roche Innovation Center, Basel, Switzerland
[16] Pharmaceutical Sciences, Roche Innovation Center, Basel, Switzerland
[17] Pharma Development, Roche Innovation Center Basel, Switzerland, Basel, Switzerland
[18] Roche Pharma Research and Early Development, Discovery & Translational Area Oncology, Roche Innovation Center Zurich, Schlieren, Switzerland
[19] Department of Medicine III, LMU University Hospital, LMU Munich, Muenchen, Germany

Background: RO7283420 (RG6007) is a 2+1 TCR-like (TCR-L) T-cell bispecific (TCB) antibody targeting CD3 and the RMFP-NAPYL peptide of Wilms Tumor 1 (WT1) protein presented by the major histocompatibility complex-I HLA-A*02 on acute myeloid leukemia (AML) blasts and other antigen presenting cells. The pre-clinical evaluation of RO7283420 in our *in vivo* humanized AML xenografts and *ex vivo* AML co-culture models showed strong T-cell mediated AML cell killing (Augsberger C, et al. *Blood* 2021). A Phase 1 dose-escalation (DE) study (NCT04580121) evaluated the safety, tolerability, pharmacokinetics, anti-drug antibodies (ADAs), and anti-leukemic activity of RO7283420 in patients with relapsed/refractory (R/R) AML.
Methods: In this open-label, multi-center study, DE was performed using a 3+3 design. Patients received RO7283420 every 3 weeks (Q3W, n=46), or every week (QW, n=4) as intravenous (IV) infusions. Preliminary anti-leukemic activity included response assessment according to European Leukemia Net (ELN) response categories (adapted from Döhner H, et al. *Blood* 2017).
Results: As of 13 April 2023, 50 HLA-A2+ R/R AML patients received at least one dose of RO7283420. Patients had a median age of 65.5 years (range 35-84), presented with ECOG of 0 (56%) or 1 (38%) or 2 (6%), and 58% were male. Median prior line of therapy was 2 (range 1-5). Overall, 58% of patients had relapsed and 42% had primary refractory disease. According to the ELN 2017 risk stratification, patients were of adverse (48%), intermediate (38%) or favorable (8%) risk category, for 6% of patients the risk category missing. The most common genetic abnormalities reported were *RUNX1* (21%), *ASXL1* (17%), *TP53* (10.6%), *FLT3*-ITD (6.4%) and *NPM1* (6.4%) of the 47 patients tested. Median bone marrow blast percentage at baseline was

35% (range 3-90%), while the median of circulating blast was 17% (range 0-88%). Study patients received RO7283420 IV at 13 different dose levels, ranging from a Minimum Anticipated Biological Effect Level (MABEL) of 0.15 mg (flat) to 18 mg Q3W (with a preceding weekly 1/3 mg 'double step-up' during Cycle 1) and one QW dose level with 9 mg preceded by a 1/3 mg step-up. Maximum tolerated dose was reached at 1/3/12 mg double step-up Q3W. Explored alternative QW schedule was not tolerable at 1/3/9 mg.

The most common (≥20%) adverse events (AEs) were cytokine release syndrome (CRS) occurring in 34 (68%), pneumonia 14 (28%), pyrexia 13 (26%), febrile neutropenia 13 (26%), hyperglycemia 12 (24%), hypokalemia 11 (22%), and nausea 10 (20%) of patients. Eight dose limiting toxicities (DLTs) were reported: five G3 CRS (at 1/3, 2/12, 1/6/12 mg dose levels), G3 stomatitis (at 1/3/12 mg), G3 myositis (at 1/3/18 mg), and G4 thrombocytopenia (at 1/3/18 mg). Eleven patients (22%) experienced Grade 5 AEs with pneumonia, sepsis, and hemophagocytic lymphohistiocytosis (HLH) reported in >1 patient; all Grade 5 events were considered unrelated to RO728342 except 1 (at 1/3/9 mg) of 2 HLH events.

IV PK has been overall dose-linear and characterized by a terminal half-life of 29 to 84 hours and a clearance of 58 to 92 mL/h. Preliminary ADA incidence within the study population was 19%. In the dose ranges tested, a trend for study drug exposure-dependent blast reduction was observed in blood, while a clear exposure-response relationship could not be established with BM blast reduction. Furthermore, our preliminary pharmacodynamic analysis identified expansion of naive and memory CD8 T cells in blood and activated CD8+ T cells in bone marrow, in line with the expected mode of action (MoA) of RO7283420. Preliminary efficacy signals were observed with 3 complete responses (CR), including 1 CR with incomplete blood count recovery.

Conclusions: RO7283420 is the first TCR-L TCB antibody evaluated in AML. We observed pharmacodynamic evidence of T-cell activation and expansion in the clinic, in line with the expected MoA of TCBs, however, at the explored doses, no clear exposure-response relationship and only a modest clinical activity were observed. The safety profile was shown to be consistent with the other TCBs and R/R AML population. Based on the totality of data, the study was discontinued.

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