Haematologica HAEMATOL/2018/206433 Version 3

Asparagine levels in the cerebrospinal fluid of children with acute lymphoblastic leukemia treated with PEG-Asparaginase in the induction phase of the AIEOP-BFM ALL 2009 study.

Carmelo Rizzari, Claudia Lanvers-Kaminsky, Maria Grazia Valsecchi, Andrea Ballerini, Cristina Matteo, Joachim Gerss, Gudrun Wuerthwein, Daniela Silvestri, Antonella Colombini, Valentino Conter, Andrea Biondi, Martin Schrappe, Anja Moericke, Martin Zimmermann, Arend Von Stackelberg, Christin Linderkamp, Michael C. Frühwald, Sabine Legien, Andishe Attarbaschi, Bettina Reismüller, David Kasper, Petr Smisek, Jan Stary, Luciana Vinti, Elena Barisone, Rosanna Parasole, Concetta Micalizzi, Massimo Zucchetti, and Joachim Boos

Disclosures: This study was supported by Comitato M. L. Verga and Fondazione Tettamanti (Monza) and by Stiftung Deutsche Krebshilfe (Bonn). The TDM program performed in the international AIEOP-BFM ALL 2009 study has been supported by an unrestricted grant from the company Shire (and previously from medac GmBH, Sigma-Tau, Baxalta that have marketed the drug during the present study period). Carmelo Rizzari received institutional grants for asparaginase pharmacological studies, fees for participation to advisory boards and invited lectures for the companies involved in marketing different asparaginase products Claudia Lanvers-Kaminsky held invited talks for Sigma-Tau and Erytech and received honoraria for consultancy from Erytech. Anja Moericke participated in an advisory board for Baxalta/Shire and received personal honoraria from Jazz Pharmaceuticals and Baxalta/Shire. Arend von Stackelberg is in the advisory boards and performed invited lectures for Jazz and Shire Andishe Attarbaschi received funding by the "Children's Cancer Research Institute (CCRI) - St. Anna Kinderkrebsforschung". He also has consulting or advisory Role with Jazz Pharmaceuticals and received travel, accommodations expenses from Jazz Pharmaceuticals, Amgen, and Pfizer declares no conflict of interest Bettina Reissmueller participated in an advisory board for and received travel support from Jazz Pharmaceuticals J. Boos served personally as a consultant and participated in advisory and safety boards for the medac GmbH. He received support for travel from Eusa Pharma, Jázz Pharmaceuticals, Baxalta, and Shire. For medac GmbH, Eusa Pharma, Jazz Pharmaceuticals, Baxalta, Shire, and Sigma-Tau, he held invited lectures. In addition, institutional grants in the context of ASNase drug monitoring from more or less all ASNase providers contributed to the therapeutic drug monitoring program, including the medac GmbH, Eusa Pharma, Jazz Pharmaceuticals, Baxalta, Shire, and Sigma-Tau (all representing the varying marketing authorization holders of E. coli ASNase, PEG-ASNase, and Erwinase) Maria Grazia Valsecchi Andrea Ballerini, Cristina Matteo, Joachim Gerss, Gudrun Wuerthwein, Daniela Silvestri, Antonella Colombini, Valentino Conter, Andrea Biondi, Martin Schrappe, Martin Zimmermann, Christin Linderkamp, Michael C. Frühwald, Sabine Legien, David Kasper, Petr Smisek, Jan Stary, Luciana Vinti, Elena Barisone, Rosanna Parasole, Concetta Micalizzi, and Massimo Zucchetti declare no conflict of interest.

Haematologica HAEMATOL/2018/206433 Version 3

Contributions: Experimental design and data analysis: CR, CLK, MGV, AB, DS, VC, AC, MZ, JB Patient enrollment and sample collection: CR, JG, GW, AC, VC, AB, MS, AS, CK, MF, SB, AA, BR, DK, PS, JS, LV, EB, RP, CM, JB Sample analysis: CLK, AB, CM, MZ, JB, BR, DK Statistical analysis: MGV, DS, AM, MZ Writing the manuscript: CR, CLK, MGV, AB, MZ, JB Supervision: CR, CLK, VC, AB, MS, MZ, JB