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CHRONOS-3: RANDOMIZED PHASE III STUDY OF COPANLISIB PLUS RITUXIMAB VS RITUXIMAB/PLACEBO IN RELAPSED INDOLENT NON-HODGKIN LYMPHOMA

Topic: 18. Indolent and mantle-cell non-Hodgkin lymphoma - Clinical

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Pier Luigi Zinzani[1], Marcelo Capra[2], Muhit Özcan[3], Fangfang Lv[4], Wei Li[5], Eduardo Yañez[6], Katya Sapunarova[7], Tongyu Lin[8], Jie Jin[9], Wojciech Jurczak[10], Aryan Hamed[11], Ming-Chung Wang[12], Ross Baker[13], Igor Bondarenko[14], Qingyuan Zhang[15], Jifeng Feng[16], Klaus Geissler[17], Mihaela Lazaroiu[18], Guray Saydam[19], Árpád Szomor[20], Krimo Bouabdallah[21], Rinat Galiulin[22], Toshiki Uchida[23], Lidia Mongay Soler[24], Anjun Cao[24], Florian Hiemeyer[25], Aruna Mehra[24], Barrett H Childs[24], Yuankai Shi[26], Matthew J Matasar[27]

[1] IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli" and Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy
[2] Centro de Hematologia e Oncologia, Hospital Mãe de Deus, Porto Alegre, Brazil
[3] Ankara University School of Medicine, Ankara, Turkey
[4] Fudan University Shanghai Cancer Center, Shanghai, China
[5] The First Hospital of Jilin University, Changchun, China
[6] Department of Internal Medicine, Oncology-Hematology Unit, University of La Frontera, Temuco, Chile
[7] Medical University, Plovdiv, Bulgaria
[8] Sun Yat-sen University Cancer Center, Guangzhou, China
[9] The First Affiliated Hospital of Zhejiang University College of Medicine, Hangzhou, China
[10] Maria Skłodowska Curie National Research Institute of Oncology, Krakow, Poland
[11] Petz Aladár Megyei Oktató Kórház, Gyor, Hungary
[12] Chang Gung Memorial Hospital Kaohsiung, Kaohsiung, Taiwan, Province of China
[13] Perth Blood Institute, Murdoch University, Perth, Australia
[14] Chemotherapy Department, City Dnipropetrovsk Multi-field Clinical Hospital, 4 DSMA, Dnipro, Ukraine
[15] Harbin Medical University Cancer Hospital, Harbin, China
[16] Jiangsu Cancer Hospital, Nanjing, China
[17] Sigmund Freud University, Vienna, Austria
[18] S.C. Policlinica de Diagnostic Rapid S.A., Brasov, Romania
[19] Ege Üniversitesi Tıp Fakültesi, Izmir, Turkey
[20] Pécsi Tudományegyetem Klinikai Központ, Pécs, Hungary
[21] Hematology and Cellular Therapy Department, University Hospital of Bordeaux, Bordeaux, France
[22] Department of Chemotherapy for Children and Adults, Clinical Oncological Dispensary of Omsk Region, Omsk, Russian Federation
[23] Hematology and Oncology, Japanese Red Cross Nagoya Daini Hospital, Nagoya, Japan
[24] Bayer HealthCare Pharmaceuticals, Inc., Whippany, United States
[25] Pharmaceuticals Division, Bayer AG, Berlin, Germany
[26] Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China
[27] Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, United States

Background: Rituximab (R)-based therapies are standard for patients (pts) with relapsed advanced indolent non-Hodgkin lymphoma (iNHL). Copanlisib (C) is a PI3K inhibitor approved as monotherapy for relapsed follicular lymphoma (FL) in pts who have had ≥2 prior systemic therapies.

Aims: We report primary data from the Phase III CHRONOS-3 study of treatment with C+R *vs* placebo (P)+R in relapsed iNHL (NCT02367040).

Methods: Pts with relapsed iNHL who were progression-free and treatment-free for ≥12 months (mo) after last R-

based therapy or unwilling/unfit to receive chemotherapy were randomized 2:1 to receive C+R or P+R. C 60 mg/P was given i.v. on days 1, 8, and 15 (28-day cycle); R 375 mg/m^2 was given i.v. on days 1, 8, 15, and 22 during cycle 1 and on day 1 of cycles 3, 5, 7, and 9. Primary endpoint: centrally assessed progression-free survival (PFS). Secondary endpoints: objective response rate (ORR), duration of response, complete response rate (CRR), overall survival (OS), and treatment-emergent adverse events (TEAEs). The data cut-off date was August 31, 2020. All pts provided informed consent.

Results: 307 pts were randomized to C+R and 151 to P+R. FL was the most common lymphoma histology subtype (60.0%), followed by marginal zone (MZL, 20.7%), small lymphocytic (SLL, 10.9%), and lymphoplasmacytic/Waldenström macroglobulinemia (LPL/WM, 8.3%). Median age was 63 years (range 28-91). With a median follow-up of 19.2 mo, the primary study endpoint was met: C+R significantly reduced the risk of disease progression/death *vs* P+R (hazard ratio [HR] 0.52 [95% CI 0.39, 0.69]; 1-sided p=0.000002); median PFS was 21.5 mo (95% CI 17.8, 33.0) *vs* 13.8 mo (95% CI 10.2, 17.5), respectively. Reductions in risk of progression/death were seen across all histology subtypes (HR [95% CI]): FL 0.580 [0.404, 0.833]; MZL 0.475 [0.245, 0.923]; SLL 0.243 [0.111, 0.530]; LPL/WM 0.443 [0.160, 1.231]. ORRs were 80.8% (CRR 33.9%) for C+R and 47.7% (CRR 14.6%) for P+R. Higher ORRs and CRRs were seen across all iNHL subtypes with C+R treatment. Median OS was not estimable. Most common TEAEs (all grades [G]/G3+) in pts receiving C+R were hyperglycemia (69.4%/56.4%), hypertension (49.2%/39.7% [all G3]), and diarrhea (33.6%/4.9% [all G3]). For pts receiving P+R, hyperglycemia (23.3%/8.2% [all G3]), hypertension (19.2%/8.9% [all G3]), neutropenia (16.4%/12.3%), and upper respiratory tract infection (16.4%/0%) were the most common TEAEs. Serious adverse events were higher with C+R (47.2%) *vs* P+R (18.5%). G5 TEAEs occurred in 6 pts (2.0%) receiving C+R (1 [0.3%] deemed treatment-related; pneumonitis) and 1 (0.7%) receiving P+R.

Summary/Conclusion: C+R demonstrated broad and superior efficacy *vs* P+R in pts with relapsed iNHL. The safety profile of C+R was manageable and consistent with C and R as monotherapy. Copanlisib is the first PI3K inhibitor to be safely combined with R in relapsed iNHL, representing a potential new therapy option for relapsed iNHL across all subtypes.

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