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## News Release

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Plenary Session at AACR Annual Meeting 2021:

### **Combination of copanlisib and rituximab significantly increases progression-free survival in patients with relapsed indolent non-Hodgkin's Lymphoma**

- Copanlisib is the first and only PI3K inhibitor to demonstrate broad and superior efficacy in combination with rituximab in patients with relapsed indolent non-Hodgkin's Lymphoma (iNHL) compared to rituximab and placebo
  - Phase III trial CHRONOS-3 showed the combination of copanlisib and rituximab resulted in a 48% reduction in the risk of disease progression or death in patients with iNHL
  - The strong reduction in risk of progression or death was observed across all prespecified iNHL subtypes
  - The adverse event (AE) profile of the copanlisib and rituximab combination was manageable and generally consistent with previous data on copanlisib and rituximab as individual therapies
  - Bayer is discussing the data from CHRONOS-3 with health authorities worldwide
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#### **Abstract: CT001**

**Berlin, April 10, 2021** – Results from the randomized, double-blind, placebo-controlled Phase III trial CHRONOS-3 show a significant progression-free survival (PFS) benefit for the combination of copanlisib, the only pan class I phosphatidylinositol-3-kinase (PI3K) inhibitor, and rituximab in patients with relapsed indolent non-Hodgkin's Lymphoma (iNHL). Patients treated with this combination had a decrease in risk of disease progression or death by 48% (HR=0.52, p=0.000002) compared to patients treated with placebo and rituximab, with a median PFS of 21.5 months versus 13.8 months. The strong reduction in risk of progression or death was observed across all prespecified iNHL subtypes including follicular lymphoma (FL; HR=0.580), marginal zone lymphoma (MZL; HR=0.475), small lymphocytic lymphoma (SLL; HR=0.243) and lymphoplasmacytoid

lymphoma/Waldenström macroglobulinemia (LPL/WM; HR=0.443). The adverse event (AE) profile of the combination was generally consistent with previously published data on the individual components of the combination and no new safety signals were identified. This data will be presented in a Clinical Trials Plenary Session on April 10 at the virtual [American Association for Cancer Research \(AACR\) Annual Meeting 2021](#) and simultaneously published in *The Lancet Oncology*.

Copanlisib is already approved as a monotherapy in the U.S. under the accelerated approval pathway for the treatment of adult patients with relapsed FL who have received at least two prior systemic therapies. Continued approval for this indication is contingent upon verification and description of clinical benefit in a confirmatory trial.

“The CHRONOS-3 data signals a much-needed advancement in the iNHL treatment paradigm,” said Pier Luigi Zinzani, M.D., Ph.D., Institute of Hematology and Medical Oncology at the University of Bologna in Italy. “The significant reduction in risk of death with the copanlisib and rituximab combination is key to addressing unmet needs in the relapsed setting.”

“Copanlisib is the first PI3K inhibitor to demonstrate broad and superior efficacy in combination with rituximab with a manageable safety profile in patients with relapsed iNHL across all pre-specified subtypes compared to rituximab and placebo,” said Dr. Scott Z. Fields, Senior Vice President and Head of Oncology Development at Bayer. “In addition to the superior efficacy observed in CHRONOS-3, treatment-limiting side effects commonly associated with existing oral PI3K inhibitors, such as severe gastrointestinal toxicities and immune-mediated events, are infrequent with the combination of copanlisib and rituximab. Bayer is committed to putting patients’ needs first and delivering innovative treatment options and these data highlight the potential of copanlisib and rituximab as a new strategy for treating these patients and we look forward to advancing regulatory discussions.”

### **Additional CHRONOS-3 Data Being Presented at AACR**

In addition to the primary endpoint of PFS, data on the secondary endpoints of overall response rate (ORR) and complete response rate (CRR) will also be presented. ORR for the combination of copanlisib and rituximab was 80.8% versus 47.7% for rituximab and placebo, with 33.9% and 14.6% of patients achieving CR, respectively.

Of the relapsed iNHL patients included in the trial, 60% had FL, 20.7% MZL, 10.9% SLL and 8.3% LPL/WM. Further analyses of the subtypes presented at AACR and published in *The Lancet Oncology* showed that the combination of copanlisib and rituximab provided a significant improvement in clinical response across all prespecified iNHL subtypes. Patients treated with the combination of copanlisib and rituximab also showed early and durable clinical benefit compared to rituximab monotherapy.

All-grade treatment-emergent adverse events (TEAEs) observed with the copanlisib and rituximab combination that occurred in more than 20% of the patients included hyperglycemia (69.4%) and hypertension (49.2%), both of which were infusion-related, transient and manageable, as well as diarrhea (33.6%), neutropenia (20.8%), nausea (22.5%) and pyrexia (20.5%). Discontinuation due to all-grade TEAEs in CHRONOS-3 for copanlisib and rituximab was 32% versus 8% for rituximab and placebo, which is consistent with the safety previously reported for copanlisib and rituximab as monotherapies and suggests that copanlisib can be combined with rituximab for the treatment of patients with relapsed iNHL without affecting the overall safety profile of the individual products.

### **About CHRONOS-3**

CHRONOS-3 (NCT02367040)<sup>1</sup> is a Phase III randomized, double-blind, placebo-controlled study which enrolled 458 patients. The study evaluates the efficacy and safety of copanlisib in combination with rituximab versus placebo in combination with rituximab in patients with relapsed indolent NHL who have received at least one or more lines of prior treatment. Patients were randomized at a 2:1 ratio. Histological subtypes included in the trial were follicular lymphoma (FL), small lymphocytic lymphoma (SLL), lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia (LPL/WM), and marginal zone lymphoma (MZL).

Patients must have relapsed after the last rituximab-, rituximab biosimilars-, or anti-CD20 monoclonal antibody (e.g., obinutuzumab)-containing therapy (other previous treatment lines after rituximab were allowed) and either had a treatment-free interval of  $\geq 12$  months after completion of the last rituximab-containing treatment, or had been unwilling to receive chemotherapy, or for whom chemotherapy was contraindicated on reason of age, comorbidities, and/or residual toxicity. Copanlisib was administered on days 1, 8 and 15

of each 28-day cycle in addition to rituximab given weekly during Cycle 1 on days 1, 8, 15 and 22, and then on day 1 of Cycles 3, 5, 7 and 9.

### **About non-Hodgkin's Lymphoma**

Non-Hodgkin's Lymphoma (NHL) comprises a highly heterogeneous group of chronic diseases with poor prognosis. NHL is the most common hematologic malignancy and the tenth most common cancer worldwide, with about 510,000 new cases diagnosed in 2018. It accounts for about 250,000 deaths per year worldwide.

Indolent NHL consists of multiple subtypes, including follicular lymphoma (FL), marginal zone lymphoma (MZL), small lymphocytic lymphoma (SLL), lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia (LPL/WM). While the disease is typically slow growing, it can become more aggressive over time. Despite treatment advances, there remains a need for improved treatment options for the relapsed or refractory stage of the disease. After response to initial therapy, response rates and duration of response decline with subsequent lines of therapy, underscoring the need for patients whose disease has already progressed.

### **About Copanlisib**

Developed by Bayer, copanlisib is the only pan class I PI3K inhibitor with inhibitory activity against all four isoforms including the PI3K-alpha and PI3K-delta isoforms expressed in malignant B cells. It is also the only PI3K inhibitor administered intravenously on an intermittent schedule, allowing effective inhibition of the PI3K pathway in tumor cells while limiting toxicity to healthy cells. The PI3K pathway is involved in cell growth, survival and metabolism, and aberrant activation of it is occurring across different solid and hematological tumor types, including all subtypes of iNHL. Its dysregulation plays an important role in lymphoma.

Copanlisib is currently approved in the U.S., Israel and Taiwan under the brand name Aliqopa™. Approvals were based on an overall response rate (ORR) of 59%, including 14% of complete responses (CRs) from the open-label, single-arm Phase II CHRONOS-1 (NCT01660451) trial of copanlisib monotherapy in 104 adult patients with follicular B-cell NHL who had relapsed disease following at least two prior systemic therapies.<sup>2</sup> Updated data for CHRONOS-1, published in the *American Journal of Hematology* in 2020, showed an ORR of 59% including 20% of CRs in patients with follicular B-cell NHL.<sup>3</sup> The compound has also received a breakthrough therapy designation in the U.S. and China

for marginal zone lymphoma (MZL) based on clinical data of MZL patients enrolled in the CHRONOS-1 study.

Bayer is in discussions with health authorities worldwide regarding the data from CHRONOS-3.

### **About Oncology at Bayer**

Bayer is committed to delivering science for a better life by advancing a portfolio of innovative treatments. The company has the passion and determination to develop innovative medicines that help improve and extend the lives of people living with cancer. The oncology franchise at Bayer includes six marketed products across various indications and several compounds in different stages of clinical development. Bayer focuses its research activities on first-in-class innovations across the following scientific platforms: Oncogenic Signaling, Targeted Alpha Therapies, and Immuno-Oncology. Across the areas of focus, we have several prostate cancer treatments on the market or in development, with the goal of extending survival while limiting side effects of treatment throughout the different stages of the disease. Another key focus at Bayer is on innovative precision oncology treatments, with an approved TRK inhibitor exclusively designed to treat tumors that have an *NTRK* gene fusion, the oncogenic driver of tumor growth and spread, and another TRK inhibitor advancing through the pipeline. The company's approach to research prioritizes targets and pathways with the potential to impact the way that cancer is treated.

### **About Bayer**

Bayer is a global enterprise with core competencies in the life science fields of health care and nutrition. Its products and services are designed to help people and planet thrive by supporting efforts to master the major challenges presented by a growing and aging global population. Bayer is committed to drive sustainable development and generate a positive impact with its businesses. At the same time, the Group aims to increase its earning power and create value through innovation and growth. The Bayer brand stands for trust, reliability and quality throughout the world. In fiscal 2020, the Group employed around 100,000 people and had sales of 41.4 billion euros. R&D expenses before special items amounted to 4.9 billion euros. For more information, go to [www.bayer.com](http://www.bayer.com).

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**Forward-Looking Statements**

This release may contain forward-looking statements based on current assumptions and forecasts made by Bayer management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the Bayer website at [www.bayer.com](http://www.bayer.com). The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

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<sup>1</sup> ClinicalTrials.gov. Copanlisib and Rituximab in Relapsed Indolent B-cell Non-Hodgkin's Lymphoma (iNHL) (CHRONOS-3). Available online: <https://clinicaltrials.gov/ct2/show/NCT02367040>. Last Accessed: March 2021.

<sup>2</sup> ClinicalTrials.gov. Open-label, Uncontrolled Phase II Trial of Intravenous PI3K Inhibitor BAY80-6946 in Patients With Relapsed, Indolent or Aggressive Non-Hodgkin's Lymphomas. Available online: <https://clinicaltrials.gov/ct2/show/NCT01660451>. Last Accessed: March 2021.

<sup>3</sup> Dreyling, M.; Santoro, A.; Mollica, L.; Leppa, S.; Follows, G.; Lenz, G.; Kim, W.S.; Nagler, A.; Dimou, M.; Demeter, J.; Ozcan, M.; Kosinova, M.; Bouabdallah, K.; Morschhauser, F.; Stevens, D.A.; Trevarthen, D.; Munoz, J.; Rodrigues, L.; Hiemeyer, F.; Miriyala, A.; Garcia-Vargas, J.; Childs, B.H.; Zinzani, P.L. Am. J. Hematol. 2020, 95, 362-371. Long-term safety and efficacy of the PI3K inhibitor copanlisib in patients with relapsed or refractory indolent lymphoma: 2-year follow-up of the CHRONOS-1 study.