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623.MANTLE CELL, FOLLICULAR, AND OTHER INDOLENT B CELL LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

Pooled Exposure-Response (ER) and Quantitative Benefit/Risk (B/R) Analyses Support the Approved Copanlisib Intermittent Dosing Regimen

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Introduction: Copanlisib is a potent and highly selective pan-class phosphatidylinositol 3-kinase (PI3K) inhibitor with preferential activity against the p110α and p110δ isoforms. Unlike other PI3K inhibitors, copanlisib is uniquely administered intravenously using an intermittent schedule, supported by preclinical data and literature model-based analyses showing high tumor residence and time intervals enabling for recovery of normal tissue. The pivotal studies, CHRONOS-1 and CHRONOS-3, established the benefit/risk of copanlisib 60 mg on Day 1, 8, 15 of 28-day cycle as monotherapy in 3L+ relapsed follicular lymphoma and in combination with rituximab in 2L+ non-Hodgkin's lymphoma, respectively. While prior ER analyses in CHRONOS-1 suggested a positive ER trend for copanlisib safety, similar to oral continuously dosed PI3K inhibitors (2022 FDA ODAC), ER analyses from the larger Phase 3 study, CHRONOS-3, revealed no significant ER for safety (Morcos et al. *CPT Pharmacometrics Syst Pharmacol* 2023). This analysis investigates pooled ER relationships for copanlisib safety across the pivotal studies and considers them in the context of the ER for efficacy in CHRONOS-3, as part of a quantitative B/R analysis for the approved copanlisib intermittent dosing regimen.

Methods: Individual static and time-varying exposure metrics in CHRONOS-1 and CHRONOS-3 were derived from a previously established comprehensive population pharmacokinetics (popPK) analysis (Morcos et al. *CPT Pharmacometrics Syst Pharmacol* 2023). ER analyses investigated the relationship to the efficacy endpoint: progression-free survival (PFS) in CHRONOS-3 using 2-year follow-up; and to the safety endpoints: time-to-first Grade $\geq$ 3 adverse events (Gr$\geq$3 AEs) and serious adverse events (SAEs), and frequency of individual AEs associated with copanlisib treatment (hyperglycemia, diarrhea, hypertension, nausea, fatigue, neutropenia, and lung infections of any grade), pooled across CHRONOS-1 using 6-year follow-up and CHRONOS-3 using 2-year follow-up. Multivariate parametric time-to-event (TTE) and logistic regression models investigated ER relationships at a prespecified significance level of $p<0.01$ after accounting for other potentially prognostic demographic, laboratory, and disease related baseline covariates. To quantitatively assess the B/R of the copanlisib 60 mg intermittent dosing regimen, a clinical utility index (CUI) function was defined with a 1:1 weighting for efficacy and safety to consider the tradeoffs between any identified ER relationships for efficacy and safety.

Results: In CHRONOS-3, the parametric TTE ER analysis for PFS was characterized by a 2-knot spline baseline hazard function and demonstrated a statistically significant positive ER relationship ($p<0.00001$). Analysis results are consistent with a prior ER analysis using a semi-parametric Cox proportional hazards model of earlier 1-year follow-up (Morcos et al. *CPT Pharmacometrics Syst Pharmacol* 2023). Therefore, greater copanlisib exposure is associated with more prolonged PFS. Across pooled CHRONOS-1 and CHRONOS-3, parametric TTE for first Gr$\geq$3 AEs and SAEs were characterized by 2-knot spline baseline hazard functions and demonstrated a borderline significant ER for Gr$\geq$3 AEs ($p=0.014$) and no significant ER for SAEs ($p=0.26$). Multivariate logistic regression analyses showed no significant ER for individual AEs after adjusting for relevant baseline covariates. Across the range of exposures achieved with the copanlisib 60 mg intermittent dosing regimen, a steeper relationship for the hazard ratio relative to placebo in is seen for the significant ER of PFS compared with the borderline ER of Gr$\geq$3 AEs (Figure 1). The CUI accounting for the quantitative ER relationships confirmed the favorable B/R across

the range of copanlisib exposures. Thus, lower copanlisib doses may result in lower efficacy while not necessarily resulting in substantially improved safety.

Conclusions: The completed quantitative analyses substantiate the favorable B/R for the copanlisib 60 mg on days 1, 8, and 15 of a 28-day cycle dosing regimen.

Disclosures Morcos: *Bayer:* Current Employment. **Moss:** *Bayer:* Consultancy. **Phelps:** *Bayer:* Current Employment. **Hiemeyer:** *Bayer:* Current Employment. **Childs:** *Bayer:* Current Employment. **Dreyling:** *Abbvie, Astra Zeneca, Beigene, BMS/Celgene, Gilead/Kite, Janssen, Lilly/Loxo, Novartis, Roche:* Other: Scientific advisory boards; *Astra Zeneca, Beigene, Gilead/Kite, Janssen, Lilly, Novartis, Roche:* Honoraria; *Abbvie, Bayer, BMS/Celgene, Gilead/Kite, Janssen, Roche:* Research Funding. **Zinzani:** *JANSSEN-CILAG:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *CELLTRION:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *SECURA BIO:* Membership on an entity's Board of Directors or advisory committees; *GILEAD:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *SERVIER:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *BMS:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *SANDOZ:* Membership on an entity's Board of Directors or advisory committees; *MSD:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *ASTRAZENECA:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *TAKEDA:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *ROCHE:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *EUSAPHARMA:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *KYOWA KIRIN:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *NOVARTIS:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *ADC THERAPEUTICS:* Membership on an entity's Board of Directors or advisory committees; *INCYTE:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *BEIGENE:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau. **Garmann:** *Bayer:* Current Employment.

Figure 1: ER relationships of hazard ratio relative to placebo for copanlisib efficacy (PFS) from CHRONOS-3 and safety (Gr≥3 AEs) pooled from CHRONOS-1 and CHRONOS-3 at 1-year (y-axis 1) and Clinical Utility Index (CUI) function (y-axis 2) across the range of exposures (average concentration [Cavg] over prior 8 weeks) with copanlisib 60 mg on days 1, 8, and 15 of a 28-day cycle dosing regimen

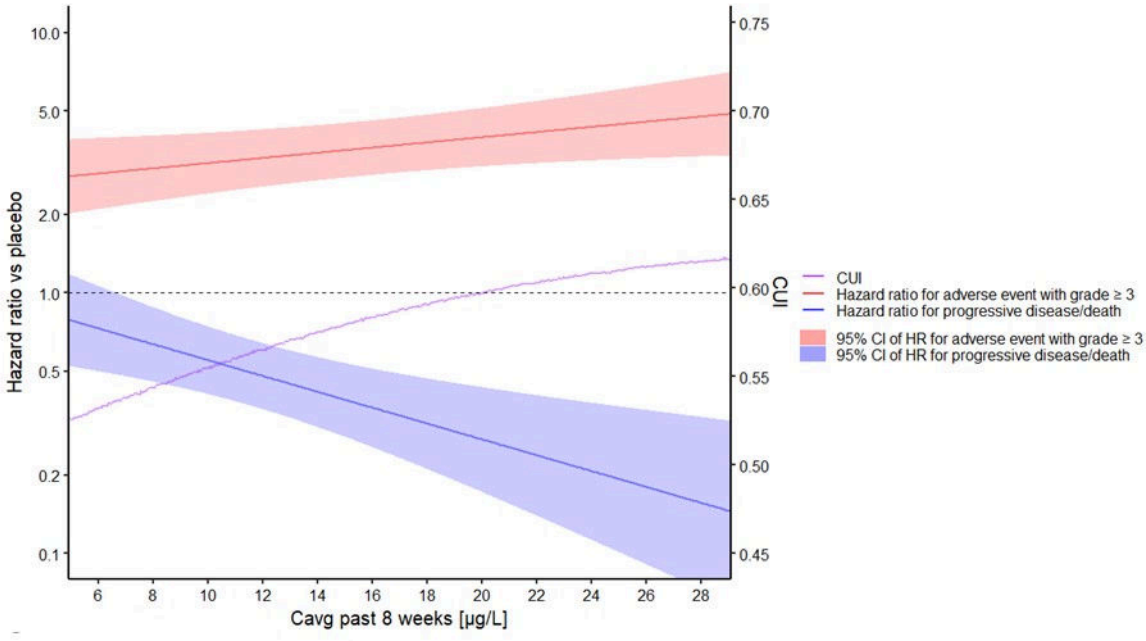

Figure 1

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