Multistate Model to Investigate Overall Survival From Copanlisib Pivotal Trials

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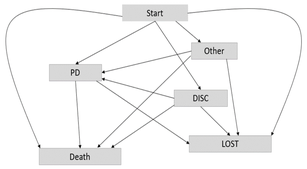
INTRODUCTION

- Copanlisib (Bayer AG) is an intravenous, potent, and highly selective pan-class I Phosphatidylinositol 3-Kinase Inhibitor (PI3K) with predominant activity against PI3K-α and -δ isoforms (inhibitory concentration [IC_{50}]:0.5 and 0.7 nM, respectively)[1]
- Preclinically, an intermittent dosing schedule enabled copanlisib concentrations in plasma and tumors to suppress tumor growth, with intervals with plasma copanlisib concentrations falling below the IC_{50}/IC_{90} for healthy tissue recovery[2]
- The phase 1 clinical study defined the maximum tolerated dose/recommended Phase 2 dose (MTD/RP2D) of copanlisib as 0.8 mg/kg on days 1, 8, and 15 of a 28-day cycle[3]
- The phase 2 CHRONOS-1 study established the initial benefit/risk profile of copanlisib monotherapy in patients with relapsed/refractory (R/R) indolent B-cell lymphoma (BCL) who previously received ≥2 therapies, demonstrating an objective response rate (ORR) of 59% and an acceptable safety profile[4]
- The phase 3 CHRONOS-3 study demonstrated superiority of copanlisib plus rituximab over placebo plus rituximab in patients with relapsed indolent non-Hodgkins lymphoma (iNHL) (iNHL; progression-free survival [PFS] hazard ratio [HR]=0.52; 95% CI, 0.39-0.69)[5]
- The phase 3 CHRONOS-4 study failed to achieve superiority of copanlisib plus immunochemotherapy over placebo plus immunochemotherapy in patients with relapsed iNHL (PFS HR=1.13; 95% CI, 0.88-1.44; p=0.83)[6]
  - Overall, copanlisib plus immunochemotherapy was associated with higher rates of serious treatment-emergent adverse events (TEAEs), grades 4 and 5 TEAEs, and treatment discontinuation[6]
- Recently, several PI3K inhibitors showed a detrimental effect on overall survival (OS)[7]
- Multistate pharmacometrics modeling has emerged as a quantitative framework that enables interrogation of intermediate events during the study period, which could contribute to OS[8-10]
- The objective of this analysis
  - Characterize copanlisib OS across CHRONOS studies using a multistate time-to-event (TTE) framework and investigate covariates on key transitions
  - Evaluate exposure-response (ER) analyses for key safety events
  - Identify subpopulations of patients who may be at increased risk of safety events with copanlisib treatment

METHODS

- Patient data from the CHRONOS studies were pooled and individual states, including baseline covariate information, reported intermediate events, and OS data, were defined in a multistate model (Figure 1; Table 1)

Figure 1: Multistate Model



DISC, discontinued; LOST, lost to follow-up; PD, progressive disease

METHODS, cont'd

Table 1. Multistate Model – Individual State Definition

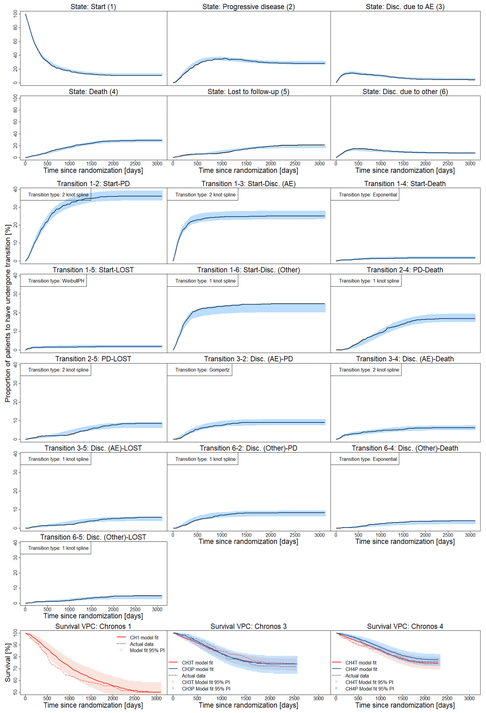
State	Description	Entry	Exit
1	Start (initial state)	Date of first copanlisib or placebo dose	Patients who receive ≥1 dose of copanlisib/placebo exit 14 days after the last dose of copanlisib or placebo or the last day of data collection that is >14 days before the right censoring date or the day of PD or death, whichever is sooner. After completing 12 months of treatment,17,833 patients that remain in state 1 are set such that transitions 1–3 and 1–6 are no longer possible.
2	Progressive disease (transient state)	Date of progressive disease	The date of last data collection that is >3 months before the right censoring date or death, whichever is sooner.
3	Discontinuation due to adverse event (transient state)	14 days after last dose of copanlisib or placebo, such that the reason for treatment discontinuation is documented as an adverse event (AE) and the patient has not experienced PD.	Date of PD, date of last data collection that is >30 days (or 3 months if specified as on survival follow-up) before the right censoring date or death.
4	Death (absorbing state)	Date of death	None
5	Lost to follow-up (absorbing state)	Patients arriving from state 1 (start) enter on the last day of data collection that is 14 days before the right censoring date. Patients arriving from state 2 (PD) enter on the date of last data collection that is >3 months before the right censoring date. Patients arriving from state 3 (DISC) or state 6 (other) enter on the date of last data collection that is >30 days or >3 months if specified as under survival follow-up before the right censoring date or death.	None
6	Discontinuation due to other reasons (transient state)	14 days after the last dose of copanlisib or placebo where no indication of an AE is present as the reason for discontinuation and the patient has not experienced PD.	Date of PD, date of last data collection that is >30 days (or 3 months, if specified as survival follow-up) before the right censoring date or death.

- The multistate model was constructed in 3 stages:
  - Stage 1: base model development for each transition between states tested exponential, Weibull, Gompertz, and spline distributions with either 1 or 2 internal knots parametric models
  - Stage 2: partial covariate search where study and treatment status (copanlisib or placebo) were tested on all model parameters for all transitions
  - Stage 3: a full covariate search on 2 transitions of specific interest: Discontinuation of treatment due to AE and the time from discontinuation of treatment due to AE to death
- Base model selection was based on the lowest Akaike information criterion (AIC) and visual inspection of the model predicted cumulative hazard against the Nelson-Aalen estimate of the cumulative hazard
- Covariates were tested in a forward inclusion (p<0.05) and backward deletion (p<0.01) procedure and were tested on both scale and shape parameters for each parametric distribution. Each covariate was tested on its own and in interaction with copanlisib treatment. This allowed for a separate covariate relationship for copanlisib treated patients vs placebo patients, to identify subgroups that may be of specific interest
- Visual predictive checks (VPCs) were done using the multistate model to simulate the full patient dataset from studies
- ER for safety evaluated TTE for time to first serious adverse event (SAE) and first grade ≥3 AE
  - Base model development and covariate analysis followed a similar approach as done for the multistate model

RESULTS

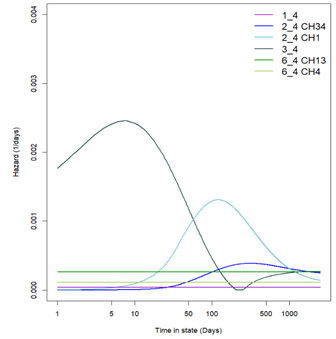
- A total of 1109 patients (copanlisib, n=707; placebo, n=402) were included in the analysis
- The multistate model adequately described patients in each state, transitions, and OS across studies and treatments (Figure 2)
- Start to discontinuation due to AE transition (transition 1-3) is dependent on treatment
  - Copanlisib treatment was associated with a 3-fold higher hazard for discontinuation due to AE compared with placebo
- Discontinuation due to AE to death (transition 3-4) was the most probable final transition to death, with the hazard peaking at approximately 8-fold higher compared with hazards for other final transitions to death (Figure 3).

Figure 2. VPCs for Final Multistate Model Describing Proportion of Patients in Each State, Transitions, and OS



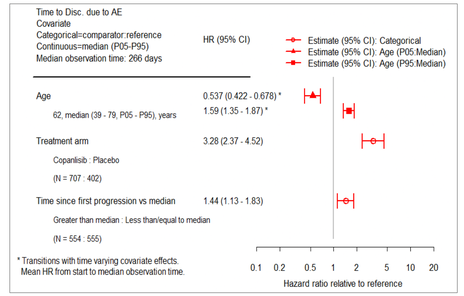
RESULTS, cont'd

Figure 3. Hazard Functions for Final Routes to Death



- Covariate analyses were conducted for:
  - Start to discontinuation of treatment due to AE (transition 1-3)
  - Discontinuation of treatment due to AE to death (transition 3-4)
  - SAEs
  - Any grade ≥3 AEs
- Start to discontinuation of treatment due to AEs: 3 covariates identified, including copanlisib treatment; however, no covariates in interaction with copanlisib treatment were significant (Figure 4)
- Discontinuation of treatment due to AE to death: 3 covariates with no covariates in interaction with copanlisib treatment (Figure 5)
- SAEs and any grade ≥3 AE: final TTE models adequately captured the distribution of events over time (Figure 6)
  - Covariate analysis identified several covariates, including copanlisib for SAE and any grade ≥3 AE (not shown)

Figure 4. Covariate Effects on Start to Discontinuation Due to AE



RESULTS, cont'd

Figure 5. Covariate effects on discontinuation due to AE to death

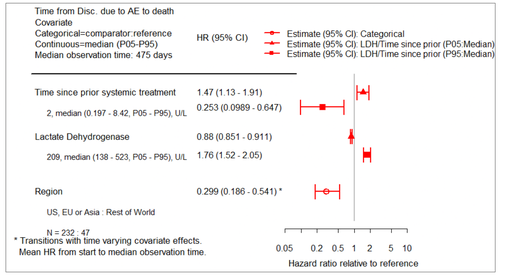
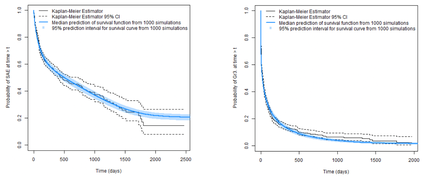


Figure 6. VPCs for final TTE models for SAEs and Any Grade ≥3 AEs



CONCLUSIONS

- The multistate model successfully captures the events across studies and can adequately distinguish between differences in patient outcomes due to study and treatment (copanlisib vs placebo) differences
- Copanlisib treatment is related to a higher risk of discontinuation of treatment due to AEs, SAEs, and any grade ≥3 AEs.
  - Although several clinical baseline covariates were identified as significant during modeling, no subset of copanlisib-treated patients had an increased risk of discontinuation of treatment due to AEs, SAEs, any grade ≥3 AE, or death

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