Concentration-QTc Analysis of Quemliclustat in Combination with/without Zimberelimab and nab-Paclitaxel/Gemcitabine in Patients with Advanced Pancreatic Cancer

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BACKGROUND

- Quemliclustat is a potent, selective, small-molecule inhibitor of soluble and membrane-bound CD73 developed with the aim of eliminating adenosine-mediated immunosuppression in the tumor microenvironment
- Study AB680CSP0002 (ARC-8) was a Phase 1, open-label, dose-escalation, and dose-expansion study, designed to evaluate the safety, tolerability, PK, pharmacodynamics, and clinical activity of quemliclustat in combination with zimberelimab (programmed cell death-1 inhibitor) and standard chemotherapy (nab-paclitaxel [NP] and gemcitabine [Gem]) in participants with advanced pancreatic cancer as first-line (1L) and second-line (2L) treatment for metastatic disease
- Dose escalation/expansion phases evaluated quemliclustat doses ranging from 25-200 mg, Q2W administered as 1-hour IV infusion

OBJECTIVES

- To evaluate the effect of single and multiple doses of quemliclustat on the QTc interval corrected for heart rate (HR) using the Fridericia method (QTcF) in cancer patients

METHODS

- Time matched pharmacokinetic samples and triplicate ECG measurements were obtained in all patients after the first dose and at steady-state
- Exploratory data tables were created to based on absolute and change-from-baseline QTc outlier categorizations and were summarized by dosing regimen on a timepoint and patient level
- Exploratory plots were used to confirm model independent assumptions which justified the use of a standardized linear mixed effect model structure
- The relationship between plasma concentrations of quemliclustat and ΔQTcF was quantified using a linear mixed-effects modeling approach and fit using NONMEM (v7.5.0)
- Additional model covariates including sex, categorical time-of-day covariates, and random effects on baseline QTcF and slope per subject were tested, significance criteria used was α=0.05 (ΔOFV = -3.8)
- The final model-predicted point estimate and its 2-sided 90% CI for ΔQTcF at the geometric mean peak steady state values at clinically relevant doses 100 mg and 200 mg Q2W were estimated
- No QTc prolongation was concluded if the upper bound of the 2-sided 90% CI (equivalent to the upper bound of the 1-sided 95% CI) of the model-predicted QTc effect (ΔQTcF) was below 10 msecs

CONCLUSION: Supported by C-QTc modeling and data analyses

- **Based on linear mixed effects modeling, the upper bound of the 90% CI of the predicted QTc effect was < 10 msecs**
- **Quemliclustat (doses up to 200 mg Q2W) was not associated with QTcF prolongation**

RESULTS: Linear mixed effect C-QTc model projections show no significant QTc prolongation at clinically relevant doses of 100 mg and 200 mg Q2W

Figure 2. Scatter plot of observed quemliclustat plasma concentrations and ΔQTcF with model-predicted ΔQTcF

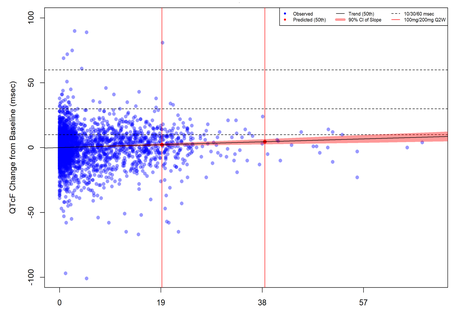


Table 4. Predicted ΔQTcF at Geometric Mean Peak Quemliclustat Concentrations

Quemliclustat Treatment	Geometric Mean Cmax of quemliclustat (µg/mL)	ΔQTcF Estimate (ms) (90% CI)
100 mg Q2W	19.2	**2.27** (1.26, **3.27**)
200 mg Q2W	38.5	**4.54** (2.52, **6.57**)

Based on a linear mixed-effects model with QTcF as the dependent variable, time-matched quemliclustat plasma concentration as an explanatory variate, and a random intercept per participant.

$$QTcF_{Predicted} = \theta_{QTcF_{base}} \cdot \exp\left(\eta_{QTcF_{base}}\right) + \theta_{Slope} \cdot Conc_{quemli,i,k}$$ **(Equation 1. C-QTc Final Model)**

$QTcF_{Predicted}$- Model predicted absolute QTcF at a given time for an individual; $\theta_{QTcF_{base}}$- Typical population mean baseline QTcF intercept value; $\eta_{QTcF_{base}}$- Random effect associated with the intercept term; θ_{Slope}- Typical population mean slope of the assumed linear association between concentration and QTcF; $Conc_{quemli}$- Concentration of quemliclustat for subject i at time k

- Observed QTcF and ΔQTcF values in other dose groups above various thresholds did not appear to be quemliclustat dose-related **(Table 1 & Table 2)**
- The final model contained baseline intercept, random intercept effect, and slope of quemliclustat concentration **(Table 3)**
- The slope of quemliclustat concentration was statistically significant, producing ΔOFV of -10.43
- The random slope effect, by timepoint correction, and sex effects did not meet convergence criteria and were removed from the model
- The estimated population slope of the concentration-QTc relationship was 0.118 msec per µg/mL (27% RSE) **(Table 4)**
- The predicted ΔQTcF at the geometric mean peak steady state quemliclustat concentrations for the 100 mg and 200 mg Q2W dosing regimens were 2.27 msecs (90%CI: 1.26, 3.27) and 4.54 msecs (90%CI: 2.52, 6.57), respectively **(Figure 2)**

RESULTS: Summary of outliers in QTcF interval values and change from baseline show no dose related trend

Table 1. Observed QTcF Outliers by Absolute Category

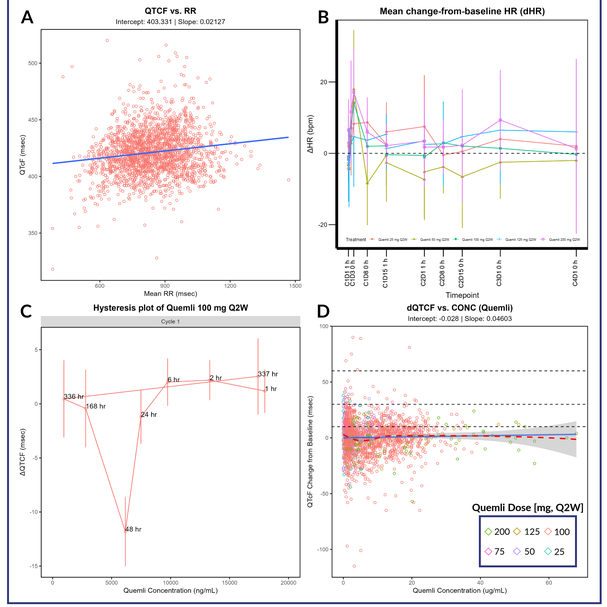
	Category	Quemli 25 mg Q2W	Quemli 50 mg Q2W	Quemli 100 mg Q2W	Quemli 125 mg Q2W	Quemli 200 mg Q2W
Patients	Total	4	6	142	3	6
	QTcF > 450 and ≤ 480 ms	2 (50%)	1 (16.7%)	41 (28.9%)	0	1 (16.7%)
	QTcF > 480 and ≤ 500 ms	0	0	7 (4.9%)	0	0
	QTcF >500 ms	0	0	6 (4.2%)	0	0
Time point	Total	52	81	1711	47	77
	QTcF > 450 and ≤ 480 ms	5 (9.6%)	1 (1.2%)	115 (6.7%)	0	1 (1.3%)
	QTcF > 480 and ≤ 500 ms	0	0	12 (0.7%)	0	0
	QTcF > 500 ms	0	0	7 (0.4%)	0	0

Table 2. Observed QTcF Outliers by Change from Baseline

	Category	Quemli 25 mg Q2W	Quemli 50 mg Q2W	Quemli 100 mg Q2W	Quemli 125 mg Q2W	Quemli 200 mg Q2W
Patients	Total	4	6	142	3	6
	ΔQTcF > 30 and ≤ 60 ms	1 (25%)	2 (33.3%)	17 (12.0%)	0	0
	ΔQTcF > 60 ms	0	0	7 (4.9%)	0	0
Time point	Total	52	81	1711	47	77
	ΔQTcF > 30 and ≤ 60 ms	3 (5.8%)	5 (6.2%)	23 (1.3%)	0	0
	ΔQTcF > 60 ms	0	0	7 (0.4%)	0	0

RESULTS

Figure 1. Exploratory Plots – Linearity Assumptions



- The correlative plot of QTcF versus RR intervals shows a minimal slope demonstrating the Fridericia method adequately corrected for heart rate within our dataset **(Figure 1.A)**
- The mean change-from-baseline HR (ΔHR) on quemliclustat showed no correlation with quemliclustat dose suggesting there is no dose-related effect on HR, additionally the observed mean ΔHR was below 10 bpm for nearly all timepoints **(Figure 1.B)**
- The time courses of mean quemliclustat plasma concentrations and arithmetic mean ΔQTcF across post-dose time-points for Cycle 1, did not show hysteresis **(Figure 1.C)**
- The scatter plot of concentrations of quemliclustat versus ΔQTcF with a linear regression line and a LOESS regression line do not diverge indicating a linear concentration-QTc model should adequately estimate the QTc effects at observed concentrations **(Figure 1.D)**

Table 3. Parameter Estimates – C-QTc Final Model

Parameter	Parameter Estimate (%RSE)
Population Baseline QTcF (msecs)	421 (0.3%)
Quemliclustat Concentration-related Slope (msecs*mL/µg)	0.118 (27%)
Random intercept effect (msecs)	12.7 (6%)
BSV Baseline QTcF (msecs)	0.00143 (14%)

REFERENCES & STATEMENTS

1. Vandenberk B, Vandael E, Robyns T, et al. Which QT Correction Formulae to Use for QT Monitoring? JAHA. 2016;5(6):e003264.
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