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Preliminary population pharmacokinetic co-variates and exposure response assessment of QT for RP-3500, a highly potent and specific inhibitor of ataxia telangiectasia and Rad3-related protein kinase

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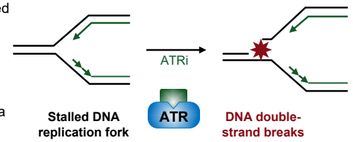
Introduction

- Ataxia telangiectasia and Rad3-related (ATR) is a key mediator of cellular DNA damage response (DDR) that is activated in response to DNA replication stress[1,2]
- Specific genes encoding DNA repair proteins, such as ataxia telangiectasia mutated (ATM), represent synthetic lethal (SL) interactions with ATR[1,2]
  - Perturbation of either of two SL genes is tolerated, but simultaneous perturbation causes cell death, making ATR inhibition (ATRi) an attractive target for the treatment of patients with specific genetic lesions
- Pre-clinical CRISPR-based Synthetic Lethal Interactions for Precision Diagnostics (SNiPDx) screening identifies SL genomic alterations that predict sensitivity to ATRi (STEP[2] genes)
  - *ATM, ATRIP, BRCA1/2, CHEK2, CDK12, CHTF8, FZR1, MRE11, NBN, PALB2, RAD17, RAD50, RAD51B/C/D, REV3L, RNASEH2A/B, SETD2*
- RP-3500 is a potent and highly selective ATRi which has demonstrated efficacy in both pre-clinical xenograft models as well as in early clinical trials[3,4]
- The ongoing TRESR study (NCT04497116) is a phase 1/2a study of patients with advanced cancer whose tumors harbor STEP[2] gene alterations



Objective

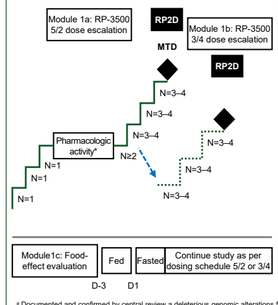
- The objective of this analysis was to develop a population pharmacokinetic (popPK) model of RP-3500 from the dose-escalation portion of the on-going Phase 1/2a TRESR study
- Additionally, an initial analysis of changes in QT and exposure-response for changes in QT in patients administered RP-3500 in the dose escalation phase was conducted

Methods

Study Design

- TRESR is an exploratory, modular, phase 1/2a, first-in-human, multicenter, open-label dose-escalation and dose-expansion study (**Figure 1**)

Figure 1. TRESR study design



Inclusion criteria:
- Male or female patients ages ≥18 years
- ECOG-PS score of 0 or 1
- Histologically confirmed solid tumors resistant or refractory to standard treatment and/or patients who are intolerant to standard therapy
- Existing biomarker profile (tumor tissue or plasma) reported from a local test obtained in a CAP/CLIA, ISO or equivalent lab per institutional guidelines[a]
- Acceptable organ function at Screening, as evidenced by laboratory data[b]

Exclusion criteria:
- Chemotherapy, small molecule anticancer or biologic anticancer therapy given within 14 days prior to first dose of study drug
- Prior therapy with an ATR or DNA-PK inhibitor
- Uncontrolled, symptomatic brain metastases
- Moderate or severe hepatic impairment (ie, Child-Pugh class B or C)
- Current treatment with medications that are well-known to prolong QT interval
- Patients who are receiving strong CYP3A inhibitors or inducers, P-glycoprotein inhibitors and/or breast cancer resistant protein inhibitors within 14 days prior to first dose of study drug

[a] Documented and confirmed by central review a deleterious genomic alterations for at least 1 of the following genes: *ATM, ATRIP, BRCA1, BRCA2, CDK12, CHTF8, FZR1, MRE11, NBN, PALB2, RAD17, RAD50, RAD51B, REV3L, RNASeH2A, RNAseH2B, SETD2* or other genes decided upon between the sponsor and investigators.
[b] Serum creatinine ≤1.5 × upper limit of normal (ULN) or calculated creatinine clearance ≥60 mL/min using the Cockcroft-Gault equation or by 24-hour urine collection; Total bilirubin ≤1.5 × ULN or <3.0 × ULN if known Gilbert's disease; Serum albumin ≥2.5 g/dL; Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN unless liver metastases are present and thought to be a reason for AST/ALT elevation, in which case they must be ≤5 × ULN
ATR, ataxia telangiectasia and Rad3-related; CAP, College of Pathology; CLIA, Clinical Laboratory Improvement Amendments; DNA-PK: DNA-dependent protein kinase; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; ISO, International Organization for Standardization.

- Patients received RP-3500 either once daily (QD) or twice daily (BID) on a schedule of 5 days on/2 days off (Module 1a) or 3 days on/4 days off (Module 1b) for a 21-day cycle (**Table 1**)
  - This data set consisted of 2360 measurable RP-3500 concentrations from 121 patients

Table 1. Summary of study modules

Module	Fed/Fasted	Day 1 Dose
1a: 5 days on/2 days off (N=22)	Fasted	5, 10, 20, 40, 80, 100, 120, or 160 mg QD 40 or 80 mg BID
1b: 3 days on/4 days off (N=86)	Fasted	120, 160, or 200 mg QD 40 or 60 mg BID
1c: Food Effect (N=12)	Day -3, high fat meal (~1000 kcal, ~50% fat): day 1, fasted	100, 120, or 160 mg QD

BID, twice daily; QD, once daily.

Study Endpoints

- The primary study endpoint of the TRESR study was safety and tolerability of RP-3500 as well as identification of the maximum tolerated dose and the recommended phase 2 dose and schedule
- Secondary endpoints included characterization of the PK of RP-3500 as well as evaluation of the impact of treatment with RP-3500 on the QT/QTc interval

Study Assessments

- Population PK and co-variate analysis
  - Pharmacokinetic (PK) sampling occurred for 24 hours post dose on cycle 1/day 1, and either cycle 1/ day 3 or 5, or cycle 2/day 3 or 5, depending on the dosing schedule
  - RP-3500 plasma concentrations were measured using a validated liquid chromatography–mass spectrometry assay
  - The popPK parameters model and co-variate analysis was performed in Phoenix® WinNonlin® 8.3 (Certara USA, Inc., Princeton, NJ)
  - Analysis of covariates of PK included age, sex, body weight (BW), body mass index, body surface area (BSA), race, Eastern Cooperative Oncology Group (ECOG) performance status, hepatic function (alanine aminotransferase, aspartate aminotransferase, albumin), and renal function (creatine clearance and glomerular filtration rate)
  - Missing co-variate data were imputed with median values from the respective data sets
- Electrocardiograms (ECG) measurement and RP-3500 exposure response analysis
  - Triplicate ECG samples were collected for each patient during the screening period, at cycle 1/day 1 (pre-dose, and 1, 2, and 4 hrs post dose), and at either cycle 1/day 3 or day 5, depending on enrollment module (pre-dose, and 1, 2, and 4 hrs post dose)
  - Corrected QT intervals (QTc) were performed using Fridericia's correction (QTcF), QTc = QT / $\sqrt[3]{RR}$
  - The exposure response analysis for QTc prolongation was performed in R version 4.0.2 with statistical analysis performed using lme function with method "ML" from the nlme package

Patient Baseline Characteristics

- Patient baseline characteristics are presented in **Table 2**

Table 2. Patient Baseline Characteristics

	All Patients (N=121)
Sex, n (%)	
Male	49 (40.5)
Female	72 (59.5)
Race, n (%)	
White	83 (68.6)
African American	5 (4.1)
Asian	6 (5.0)
Other	2 (1.7)
Unknown	25 (20.7)
Ethnicity, n (%)	
Hispanic or Latino	6 (5.0)
Nor Hispanic or Latino	90 (74.4)
Unknown	25 (20.7)
ECOG performance status, n (%)	
0	58 (47.9)
1	63 (52.1)
Hepatic function, n (%)	
Normal	89 (73.6)
Mild	21 (17.4)
Moderate	1 (0.8)
Severe	2 (1.7)
Pending	8 (6.6)
Renal function (CrCL), n (%)	
Normal	57 (47.1)
Mild	48 (39.7)
Moderate	13 (10.7)
Pending	3 (2.5)
Renal function (eGFR), n (%)	
Normal	38 (31.4)
Mild	63 (52.1)
Moderate	18 (14.9)
Pending	2 (1.7)

CrCL, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate.

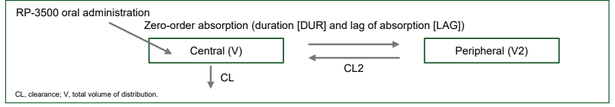
		All Patients (N=121)
Age, years	Mean (CV%) Median (min, max)	61.2 (17.8) 63.0 (30.0, 77.0)
Body weight, kg	Mean (CV%) Median (min, max) Pending, n (%)	76.0 (25.1) 76.5 (43.8, 147) 1 (0.8)
Height, m	Mean (CV%) Median (min, max) Pending, n (%)	1.68 (5.9) 1.68 (1.41, 1.98) 9 (7.4)
BSA, m^2	Mean (CV%) Median (min, max) Pending, n (%)	1.85 (13.2) 1.85 (1.40, 2.64) 10 (8.3)
BMI, kg/m^2	Mean (CV%) Median (min, max) Pending, n (%)	26.8 (22.7) 26.6 (16.2, 45.5) 10 (8.3)
Albumin, g/dL	Mean (CV%) Median (min, max) Pending, n (%)	3.95 (12.7) 4.00 (2.40, 5.10) 2 (1.7)
ALT, U/L	Mean (CV%) Median (min, max) Pending, n (%)	24.3 (93.9) 18.0 (0, 218) 2 (1.7)
AST, U/L	Mean (CV%) Median (min, max) Pending, n (%)	30.5 (62.8) 24.0 (9.00, 116) 2 (1.7)
Bilirubin, mg/dL	Mean (CV%) Median (min, max) Pending, n (%)	1.48 (203.1) 0.200 (0, 27.0) 8 (6.6%)
Serum creatinine, mg/dL	Mean (CV%) Median (min, max) Pending, n (%)	0.862 (23.7) 0.820 (0.440, 1.48) 2 (1.7)
CrCL[a], mL/min	Mean (CV%) Median (min, max) Pending, n (%)	92.0 (34.3) 87.6 (39.5, 233) 3 (2.5)

[a]Assessed using the Cockcroft-Gault equation.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BSA, body surface area; CrCL, creatinine clearance; CV, coefficient of variation; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

RP-3500 PopPK Model Scheme

- The PK of RP-3500 was described using a two-compartment model with linear elimination, a zero-order oral absorption, along with a lag time of absorption (**Figure 2**)

Figure 2. RP-3500 PopPK Model Scheme



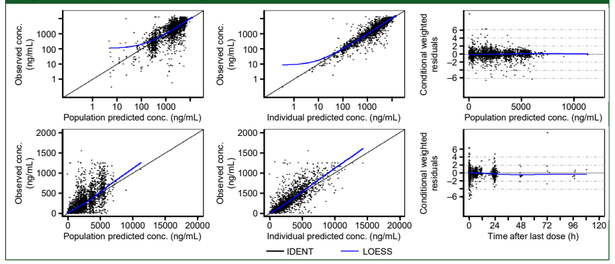
CL, clearance; V, total volume of distribution.

Table 3. PopPK model parameters

Parameters	Typical Values	CV (%)	2.5% CI	97.5% CI	Units	BSV (%)	Shrinkage (%)
tvDUR	1.07	7.42	0.915	1.23	h	41.7	12.2
tvLAG	0.221	0.0459	0.221	0.221	h	62.5	13.8
tvV	23.4	5.09	21.0	25.7	L	62.7	8.7
tvCL	3.80	5.01	3.42	4.17	L/h	54.8	4
tvV2	16.1	14.1	11.7	20.6	L	88.5	34.7
tvCL2	1.09	10.8	0.861	1.32	L/h	19.4	32.8
Log-Additive Error	0.621	0.588	0.614	0.629			

BSV, between-subject variability; CI, confidence interval; CV, coefficient of variance; CL, clearance; DUR, duration of absorption; h, hours; L/h, liters per hour; LAG, lag of absorption; tv, typical value; V, total volume of distribution.

Figure 3. popPK model diagnostic plots



- Of the co-variates examined, only BSA and BW were found to have significant effects on any PK parameters (**Figure 4**)
- To better understand the effect of BSA and BW on the PK of RP-3500, rich concentration-time profiles were simulated with the individual posterior Bayes PK parameter obtained from the final PK model
  - Non-compartmental analysis (NCA) was used on rich concentration profile derived following a single 160 mg dose of RP-3500 to derive the following PK parameters of interest on Day 1:
    - Area under the concentration-time curve for a dosing interval ($AUC_{0\text{-}24}$)
    - Maximum concentration (C_{max})
    - Concentration at 24 hours post-dose (C_{24})
- In the co-variate analysis, a trend of an effect of creatine clearance (CrCL) with clearance was observed, however the number of missing CrCL values complicate this interpretation

Figure 4. Co-variate effect on NCA parameters

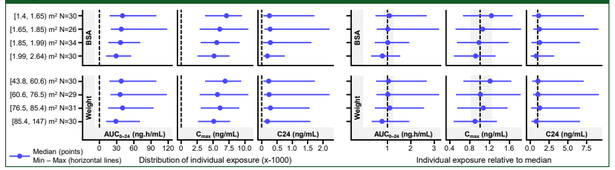
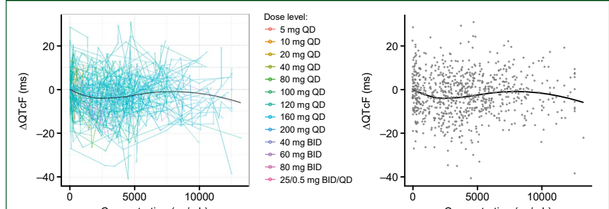
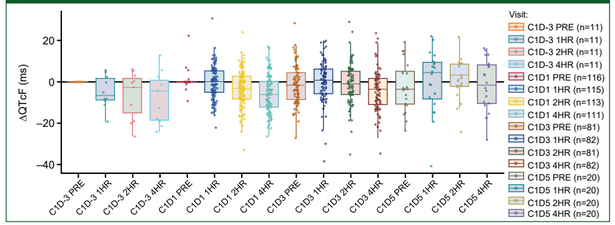


Figure 5. QTcF Exposure Response



Black bold lines: locally weighted scatter plot smoothing (LOESS)

Figure 6. Change from Baseline of QTcF Stratified by Visit



Conclusions

- A total of 121 patients were included in the population PK analysis; the majority were dosed at RP-3500 160 mg QD (n=64) or 120 mg QD (n=31)
- The PK of RP-3500 was described using a two-compartment model with linear elimination, a zero-order oral absorption, and a lag time of absorption
- No changes in the CL of RP-3500 over-time was observed
- Both BW and BSA were identified co-variates of total clearance and total volume of distribution
  - BSA better explained the uncertainty of clearance and volume parameters than BW
  - There was a trend for renal clearance to impact the CL of RP-3500
- There was no significant correlation between RP-3500 concentrations and ΔQTcF
  - The ECG analysis revealed a statistically significant effect of RP-3500 on ΔQTcF at cycle 1/day 1, 4 hours post-dose, only time point where a clinically insignificant reduction of the QT interval of 6 ms was observed
- The results indicate RP-3500 presents a very low risk for clinically impacting QT at therapeutically relevant doses (120 mg or 160 mg QD)

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